Neurobiology of Stress 1 (2015) 89–99

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder

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ARTICLE INFO

Article history:
Received 1 August 2014
Received in revised form
15 October 2014
Accepted 15 October 2014
Available online 27 October 2014

Keywords:
Norepinephrine
Dopamine
Pediatric
Prazosin
Guanfacine
Clonidine

ABSTRACT

Research on the neurobiology of the stress response in animals has led to successful new treatments for Post-Traumatic Stress Disorder (PTSD) in humans. Basic research has found that high levels of catecholamine release during stress rapidly impair the top-down cognitive functions of the prefrontal cortex (PFC), while strengthening the emotional and habitual responses of the amygdala and basal ganglia. Chronic stress exposure leads to dendritic atrophy in PFC, dendritic extension in the amygdala, and strengthening of the noradrenergic (NE) system. High levels of NE release during stress engage low affinity alpha-1 adrenoceptors, (and likely beta-1 adrenoceptors), which rapidly reduce the firing of PFC neurons, but strengthen amygdala function. In contrast, moderate levels of NE release during nonstress conditions engage higher affinity alpha-2A receptors, which strengthen PFC, weaken amygdala, and regulate NE cell firing. Thus, either alpha-1 receptor blockade or alpha-2A receptor stimulation can protect PFC function during stress. Patients with PTSD have signs of PFC dysfunction. Clinical studies have found that blocking alpha-1 receptors with prazosin, or stimulating alpha-2A receptors with guanfacine or clonidine can be useful in reducing the symptoms of PTSD. Placebo-controlled trials have shown that prazosin is helpful in veterans, active duty soldiers and civilians with PTSD, including improvement of PFC symptoms such as impaired concentration and impulse control. Open label studies suggest that guanfacine may be especially helpful in treating children and adolescents who have experienced trauma. Thus, understanding the neurobiology of the stress response has begun to help patients with stress disorders.

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a debilitating condition affecting soldiers, veterans and civilians alike, often leading to substance abuse, loss of work and erosion of family life. Trauma during childhood can be particularly devastating, and can have lifelong debilitating consequences. Over the last 25 years, studies in animals have begun to reveal how stress alters brain physiology, providing new strategies for treatment. Exposure to stress markedly impairs the executive functions of the highly evolved prefrontal association cortex (PFC), while simultaneously strengthening the primitive emotional responses of the amygdala and the tonic firing of the noradrenergic (NE) locus coeruleus (LC), three brain regions that are intimately interconnected. Understanding the effects of stress on these brain circuits has led to successful medications for stress-related disorders in humans, as described in the following review.

2. The prefrontal cortex vs. the amygdala

2.1. The highly evolved prefrontal cortex

The PFC provides top-down regulation of behavior, thought and emotion, generating the mental representations needed for flexible, goal-directed behavior, including the ability to inhibit inappropriate impulses, regulation of attention, reality testing, and

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http://dx.doi.org/10.1016/j.ynstr.2014.10.002

insight about one's own and others' actions (Fig. 1; Robbins, 1996; Goldman-Rakic, 1996; Blakemore and Robbins, 2012).

The ability to use mental representations to guide behavior is often tested in working memory paradigms, and is a fundamental building block of abstract thought. The PFC has expanded greatly in brain evolution, making up over a third of the human cortex (Elston et al., 2006). Thus, the PFC plays a major role in governing human behavior.

In primates, the dorsolateral PFC (dlPFC) guides thoughts, attention and actions using working memory (Goldman-Rakic, 1995), while the orbital and ventromedial PFC (vmPFC) use mental representations to regulate emotion (Ongür and Price, 2000). These two general regions interconnect, e.g. allowing the dlPFC to regulate the vmPFC (Barbas and Pandya, 1989). The PFC has extensive connections that position it to either accentuate or inhibit actions in other brain regions e.g. (Barbas et al., 2005; Ghashghaei and Barbas, 2002; Neafsey, 1990), including inhibiting the fear responses of the amygdala (Quirk and Mueller, 2008). Of special relevance to the symptoms of PTSD, lesions to the PFC impair the ability to concentrate or focus attention (Wilkins et al., 1987; Chao and Knight, 1995), and can weaken impulse control and produce reckless behavior (Aron, 2011). Bilateral lesions to the vmPFC impair modulation of emotional reactions, including increased irritability, impaired decision-making, and lack of insight (Barrash et al., 2000). PFC lesions can also impair the ability to inhibit cognitive interference, e.g. inhibiting inappropriate memories (Thompson-Schill et al., 2002), or inappropriate dimensions as tested by the Stroop interference task (Golden, 1976). The dorsal PFC is needed for reality testing (Simons et al., 2008), a property important for distinguishing a vivid memory from an actual event, i.e. the flashbacks that occur in PTSD. Finally, the PFC can regulate our state of arousal, e.g. through projections to the NE neurons where it can inhibit LC firing (Sara and Herve-Minvielle, 1995), and reduce the stress response (Amat et al., 2006). Thus, the PFC can provide widespread orchestration of brain physiology needed for calm, rational and flexible responding.

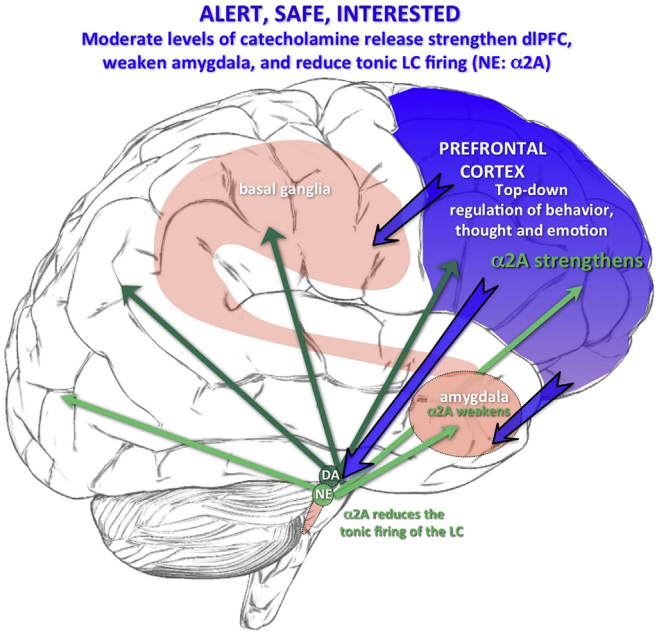

Fig. 1. During nonstressed arousal conditions when the subject is alert, safe and interested, the highly evolved prefrontal cortex (highlight in blue) provides top-down regulation of behavior, thought and emotion. It orchestrates behavioral response through extensive connections, e.g. to the amygdala, basal ganglia and brainstem, including the catecholamine neurons. Under these arousal conditions, there are moderate levels of catecholamine release, and phasic firing of LC neurons to appropriate stimuli (Rajkowski et al., 1998). Moderate levels of NE engage high affinity alpha-2A receptors, which strengthen PFC, but weaken amygdala (Arnsten, 2000). Alpha-2A receptors also reduce the tonic firing of LC neurons. All of these actions promote thoughtful PFC regulation of brain and behavior. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. The primitive amygdala

The amygdala also has extensive connections through much of the brain, and is positioned to initiate and coordinate an unconscious, primitive stress reaction throughout the brain and body (Fig. 2; reviewed in Davis, 1992; Price and Amaral, 1981).

The amygdala can activate the traditional HPA axis (hypothalamus–pituitary–adrenal gland) via projections to the hypothalamus, and the sympathetic nervous system through projections to hypothalamus and brainstem (Davis, 1992). It can rapidly alter behavior as well, e.g. inducing the freezing response through projections to the peri-aqueductal gray, and increasing the startle response through parallel brainstem projections (Davis, 1992). Amygdala projections to striatum strengthen habitual responses (Elliott and Packard, 2008), while those to hippocampus can strengthen the consolidation of emotionally-charged memories (Roozendaal and McGaugh, 2011) (although with severe stress the hippocampus may also be weakened, perhaps contributing to amnesia (Kim and Yoon, 1998)). Importantly, the amygdala mediates fear conditioning, whereby a previously neutral stimulus (e.g. a hot day), can trigger a fear response after it is paired with a traumatic event (Phelps and LeDoux, 2005). Thus, the amygdala can perpetuate a stress response long after a trauma is over. In contrast, circuits within the PFC are needed to extinguish a conditioned response to a traumatic event and return to normative behavior (Quirk and Mueller, 2008).

The amygdala also drives the arousal systems, e.g. increasing the firing of the NE neurons of the LC (Van Bockstaele et al., 1998), and dopaminergic (DA) neurons in the midbrain (Phillipson, 1979). For example, the amygdala is critical for increasing catecholamine

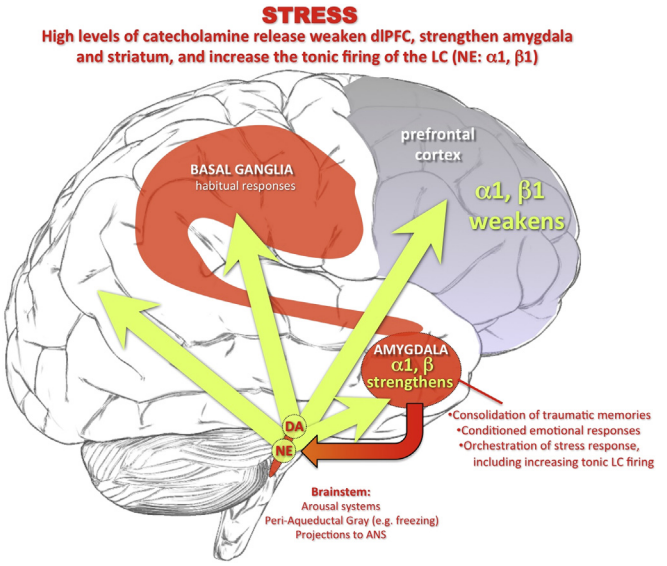

Fig. 2. Under conditions of uncontrollable stress, there are high levels of catecholamine release in brain, which weaken PFC function but strengthen the affective responses of the amygdala and the habitual responses of the basal ganglia. The amygdala activates the catecholamine under conditions of psychological stress, in addition to coordinating other aspects of the stress response (e.g. projections to the peri-aqueductal gray). Amygdala activation of the locus coeruleus via CRF increases tonic firing. High levels of NE release engage lower affinity alpha-1 and beta receptors, which enhance amygdala and weaken PFC function, thus producing a vicious cycle that maintains primitive circuits in control of behavior.

release in the PFC in response to psychological stressors (Goldstein et al., 1996). These increases in catecholamine release can have rapid and pervasive effects on brain physiology, impairing the functions of the PFC while further strengthening amygdala actions, thus setting up a vicious cycle (reviewed below).

3. The effects of stress exposure on brain functioning

3.1. Acute stress weakens dlPFC and strengthens amygdala

Early studies in animals showed that exposure to even a mild uncontrollable stressor, e.g. loud white noise, can rapidly impair the working memory functions of the PFC in monkeys and rodents (Fig. 2; Arnsten and Goldman-Rakic, 1998; Arnsten, 1998). A key aspect of this effect of stress is that the subject feels that they do not have control over the stressor (Amat et al., 2006). Intriguingly, the PFC can turn off the stress response if it considers that the subject has control over the situation (Amat et al., 2006).

Loss of dlPFC working memory function during uncontrollable stress also can be seen in humans, e.g. where exposure to an upsetting, violent film impaired working memory performance and reduced the dlPFC BOLD response (Qin et al., 2009) and theta band activity (Gärtner et al., 2014). Impairments in working memory have even been seen in Special Forces soldiers under conditions of stress exposure (Morgan et al., 2006). Acute uncontrollable stress exposure also weakens PFC self-control and contributes to substance abuse (Sinha and Li, 2007). In contrast to the PFC, uncontrollable stressors such as upsetting images increase the ability of the amygdala to enhance consolidation of the memory of the stressful event, a mechanism that has been documented in both animals and humans (Cahill and McGaugh, 1996). Stress may also accentuate the fear-conditioning operations of the amygdala (Rodrigues et al., 2009). This flip from reflective (PFC) to reflexive (amygdala) brain state has to be very rapid, e.g. in response to a sudden danger. However, prolonged stress can have even more marked effects on brain physiology.

3.2. Chronic stress accentuates these actions

With chronic stress, there are additional architectural changes that further exaggerate the switch from highly evolved to more primitive brain circuits.

Studies in rodents have shown that sustained stress exposure induces loss of dendrites and spines in the PFC (Seib and Wellman, 2003; Liston et al., 2006; Radley et al., 2005; Shansky et al., 2009). The loss of spines and/or dendrites correlates with impaired working memory (Hains et al., 2009) and weaker attentional flexibility (Liston et al., 2006), suggesting that there are functional consequences to loss of dendrites and their connections. In young rodents, PFC dendrites can regrow with sufficient time spent under safe conditions, but there is less plasticity in the aged PFC (Bloss et al., 2011). In contrast to the PFC, chronic stress increases dendritic growth in the amygdala (Vyas et al., 2002), thus accentuating the imbalance of amygdala over PFC function. The molecular basis for these opposing architectural reactions to stress are not known, and will be an important arena for further research.

The loss of PFC gray matter with chronic stress has also been seen in humans. Structural imaging has shown that the number of adverse events a person has been exposed to correlates with smaller PFC gray matter (Ansell et al., 2012). Chronic stress in humans also weakens PFC functional connectivity (Liston et al., 2009), and PFC regulation of the amygdala (Kim et al., 2013). Thus, sustained stress exposure leads to more persistent changes in brain circuits regulating behavior and emotion, maintaining the brain in a more primitive, reactive state.

4. Role of dlPFC dysfunction in PTSD

4.1. Symptoms of PTSD in adults

PTSD is typically characterized by intrusive memories of a traumatic event, and may take the form of nightmares or flashbacks, sometimes accompanied by frank hallucinations.

During flashbacks, reality testing is impaired and the past is literally re-experienced and reenacted. In this sense, PTSD-related intrusive memories are a crossroads of the 'then-and-there' and the 'here-and-now' in which the feeling becomes the fact and the thought becomes the act. This complete loss of touch with reality may represent PFC dysfunction in its most extreme.

Many other core symptoms of PTSD mirror behavior changes associated with weakened PFC and strengthened amygdala activity as discussed in preceding sections. According to the fifth edition of the Diagnostic and Statistical Manual (DSM-V), for PTSD symptoms to develop, an initial exposure to a psychic trauma must have occurred: "The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence." This occurs in the context of an eyewitness or an accomplice. These exposure criteria have recently been revised to also include certain indirect exposures such as: "Learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental." Or: "Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties." First responders on scene or other professionals such as firemen and doctors, are included. However, the DSM-V specifies that "This does not include indirect non-professional exposure through electronic media, television, movies, or pictures."

The DSM-V divides the symptoms of PTSD into four basic categories, which are often assessed using the Clinician Administered Post-traumatic Stress (CAPS) rating scale. The first category, "intrusive symptoms", refers to unbidden, distressing nightmares, memories, and flashbacks of trauma-relevant events. Importantly, these recollections may involve any or all of the five senses, smells often being the most disturbing, perhaps because the sense of smell is less subject to PFC modulation (Vermetten et al., 2007). Flashbacks can be so vivid that the individuals so afflicted may reenact the trauma.

The second category, "avoidance symptoms", includes all behaviors involving the avoidance of trauma-related thoughts, feelings, or external reminders, such as people, places, or things. These avoidance behaviors may take many forms including substance abuse, as a way to escape intrusive internal and external reminders of the trauma. Substance abuse can further compromise PFC function, thus exacerbating the problem.

"Negative alterations in cognitions and mood", is a category that includes distorted and negative views of oneself and others. There may be a diminished interest in daily activities and an alienation from others, even loved ones. Affect and emotions may be increasingly limited to trauma-relevant events including anger, guilt, or shame, all associated with the trauma.

"Alterations in arousal and reactivity" is the broad fourth category. In addition to signs of hyperarousal and hypervigilance, ratings from this category capture increased irritability and/or aggression, recklessness, and impaired concentration, all of which are associated with impaired PFC function. An exaggerated startle response and insomnia are also common symptoms associated with increased arousal.

4.2. Symptoms of PTSD in children and adolescents

In contrast to adults with PTSD, symptoms of distress following exposure to traumatic stress can be quite varied in exposed children and adolescents.

Factors influencing reaction to traumatic stress include characteristics of the child such as age, gender, and previous psychiatric history, characteristics of the trauma including type, chronicity, frequency, and proximity, and the availability of supportive relationships with caregivers that serve to buffer the effects of toxic stress (Shonkoff and Garner, 2012). The DSM 5 diagnosis of PTSD highlights fear and anxiety-based symptoms including intrusion symptoms associated with the traumatic event(s), dissociative reactions, marked physiological reactions upon exposure to cues that symbolize or resemble an aspect of the traumatic event, avoidance of stimuli that are reminders of the trauma, negative alterations in mood or cognitions associated with the event, and symptoms of physiological overarousal. Associated depression and anxiety disorders may co-occur (Ford et al., 2011). In younger traumatized children symptoms may include loss of previously established developmental milestones and/or repetitive posttraumatic play.

Traumatic stress symptoms of overarousal may include aggressive and irritable behaviors, outbursts of temper, reckless behavior, problems with concentration on tasks requiring vigilance such as schoolwork, and sleep disturbances. Many of these symptoms arise from PFC dysfunction, and may be clinically mistaken as criteria for impulse-control disorders such as oppositional defiant disorder (ODD), conduct disorder (CD), or attention deficit/hyperactivity disorder (ADHD), which also involve impaired PFC abilities. Indeed, studies of clinically referred child psychiatry outpatient admissions with ODD find high rates of traumatic stress (Ford et al., 2000), and studies of conduct disorder in adolescents find high rates of PTSD (Connor et al., 2007). In contrast, PFC dysfunction in ADHD is likely genetic, and arises from slowed or impaired development of the PFC, particularly in the right hemisphere (Shaw et al., 2009). Risk may be bi-directional such that antecedent impulse-control disorders may increase involvement in high-risk activities that may lead to traumatic events, and/or overarousal symptoms of PTSD may clinically mimic signs of impulse-control disorders. It is not surprising that PTSD and ADHD symptoms frequently co-occur in clinically referred children and adolescents since both disorders involve PFC dysfunction.

4.3. Evidence for PFC and LC-NE dysfunction in PTSD

Imaging and post-mortem studies have shown consistent signs of PFC dysfunction in patients with PTSD.

For example, functional imaging studies of PTSD subjects vs. healthy controls have shown reduced BOLD response over the dlPFC during memory retrieval (Tian et al., 2014), and patients have deficits performing tasks that depend on the PFC (Koenen et al., 2001). Similarly, reduced vmPFC activation in subjects with PTSD correlated with impaired inhibition of the fear response (Jovanovic et al., 2013). Structural imaging studies have shown thinner dlPFC, thinner vmPFC, a smaller subgenual PFC, as well as thinner temporal association cortex (Mollica et al., 2009; Herringa et al., 2012; Kühn and Gallinat, 2013). Gene array analyses of post-mortem tissue show dysregulated mitochondrial function in the dlPFC of patients with PTSD (Su et al., 2008). Preliminary evidence suggests that rTMS to strengthen left dlPFC may aid treatment of PTSD, at least in those with depression (Nakama et al., 2014). Functional imaging has also shown altered patterns of PFC activity to emotional charged words in abused women with PTSD (Bremner et al., 2003), although the pattern of changes was more complex.

In addition to changes in the PFC, there is extensive evidence of elevated NE responsiveness in PTSD. For example, veterans with PTSD show elevated NE levels in CSF (Geracioti et al., 2001). They also show greater response to the alpha-2 receptor blocker, yohimbine, which increases the firing of the LC and increases NE release through actions at pre-synaptic alpha-2 receptors. Patients with PTSD given yohimbine showed greater NE metabolite levels in plasma than healthy controls, and yohimbine induced panic attacks and PTSD symptoms such as flashbacks in patients as well (Southwick et al., 1993). Yohimbine also decreased metabolism in the PFC of subjects with PTSD compared to healthy controls (Bremner et al., 1997). All of these changes are consistent with data from animal models showing weaker dlPFC and increased tonic firing of the LC following stress exposure.

5. Mechanisms learned from basic research – how stress takes PFC "off-line"

Research has begun to reveal how stress exposure can rapidly impair PFC function through intracellular signaling events that open ion channels and weaken dlPFC network connections (Arnsten, 2009). In brief, high levels of NE and DA release drive feedforward, Ca^{2+}-cAMP-signaling in spines near network synapses, which in turn opens nearby K^+ channels (schematically illustrated in Fig. 3A). This weakens the effectiveness of the nearby synaptic connection, and reduces the firing of neurons that generate the mental representations needed for top-down control. In contrast, high levels of catecholamines strengthen the affective responses of the amygdala, the habitual responses of the striatum, and primary sensory cortical function. Cortisol has been shown to accentuate the effects of catecholamines in the PFC and the amygdala (Barsegyan et al., 2010), thus creating a coordinated

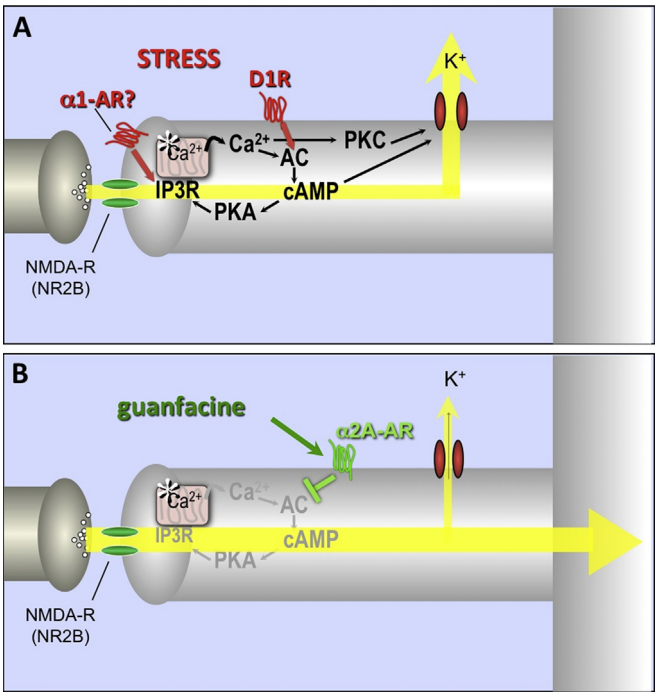

Fig. 3. The strength of dlPFC glutamate NMDA receptor connections on spines is dynamically modulated by arousal state. A. During stress, high levels of DA D1 receptor stimulation activate feedforward, cAMP- calcium (Ca^{2+}) signaling, which opens nearby potassium (K^+) channels to rapidly weaken connections and reduce PFC neuronal firing. NE stimulation of alpha-1 receptors also reduces PFC neuronal firing through IP3- Ca^{2+}-protein kinase C (PKC) mechanisms (the ultrastructural localization of alpha-1 receptors in primate PFC is not yet known). Calcium is stored in the spine apparatus (indicated by asterisk), the endoplasmic reticulum in the spine. B. Guanfacine stimulation of post-synaptic alpha-2A receptors on PFC spines strengthens network connections, increases PFC neuronal firing and improves working memory by inhibiting feedforward cAMP- Ca^{2+} signaling and closing K^+ channels on spines near the synapse. These actions likely contribute to guanfacine's therapeutic effects in patients. Additional abbreviations: AC = adenylyl cyclase; IP3R = inositol triphosphate receptors; PKA = protein kinase A.

stress response. The following reviews catecholamine actions in the PFC and amygdala, and the effects of stress on NE and DA neurons.

5.1. Dynamic modulation of dlPFC network synapses

Pyramidal cell circuits in the dlPFC interconnect on dendritic spines through glutamatergic, NMDA receptor synapses (Fig. 3; Wang et al., 2013).

The functional strength of these synapses is dynamically modulated to rapidly enhance or weaken connections, and thus help to shape the contents and strength of working memory. These very rapid changes in synapse strength, called Dynamic Network Connectivity, are mediated by feedforward, cAMP-Ca^{2+} signaling events, which open K^+ channels near the synapse to weaken the connection (Fig. 3A; Arnsten et al., 2012). Catecholamines can either inhibit or activate these signaling events to strengthen (e.g. when we are safe) or weaken (e.g. when we are stressed) PFC network function. This contrasts with cAMP-Ca^{2+} signaling actions in more primitive circuits, where increases in cAMP-Ca^{2+} generally strengthen synaptic connections, e.g. via long-term potentiation. These opposing actions in different brain circuits may help begin to explain why dendrites retract in PFC, but hypertrophy in amygdala, in response to chronic stress. Thus, understanding the cellular effects of the catecholamines may be especially important for treatment strategies. The following provides a brief review of DA and NE actions in the PFC.

5.2. The role of dopamine

Initial studies of stress effects on PFC function focused on the role of DA, revealing that increased DA stimulation of D1 receptors in the PFC impaired working memory (Arnsten, 1998; Murphy et al., 1996).

Mild stress preferentially increases DA release in the PFC but not in striatum (Deutch and Roth, 1990), likely involving release from "salience" DA neurons that fire to aversive as well as rewarding events (Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010). Indeed, even a very mild stress such as receiving water instead of juice increases DA release in the primate dlPFC (Kodama et al., 2014). Studies in rats showed that the levels of DA release in PFC during stress exposure correlated with the degree of working memory impairment (Murphy et al., 1996), and that treatments that blocked DA D1 receptors or reduced DA release protected cognitive performance from the detrimental effects of stress in both rats and monkeys (Arnsten and Goldman-Rakic, 1998; Murphy et al., 1996). These studies uncovered an inverted U dose–response, where either too little or too much D1 receptor stimulation impaired working memory (Arnsten, 1998; Arnsten et al., 1994; Zahrt et al., 1997). An inverted U was also seen in physiological recordings from dlPFC neurons in monkeys performing a working memory task, where high levels of DA D1 receptor stimulation suppressed dlPFC neuronal firing and impaired working performance by increasing cAMP-PKA signaling (Vijayraghavan et al., 2007), which opens K^+ (HCN, KCNQ) channels on dendritic spines (Fig. 3A; Arnsten et al., 2012; Gamo et al., 2014). Although blocking D1R can protect dlPFC neuronal firing and restore working memory abilities, D1R antagonists may not be appropriate agents for clinical use, as the inverted U makes it difficult to find a dosage that is helpful across a range of arousal conditions. Thus, the remaining review focuses on NE mechanisms, where the separation of beneficial (alpha-2A) vs. detrimental (alpha-1) receptor actions has facilitated clinical utility.

5.3. The role of norepinephrine

Stress exposure increases NE as well as DA release in rat PFC (Goldstein et al., 1996; Finlay et al., 1995).

As with DA neurons, recent studies show that just a subset of LC neurons project selectively to PFC (Chandler et al., 2014), which may accentuate the stress response within this region. Differing levels of NE provide a "molecular switch" for whether the PFC is engaged or weakened: moderate levels of norepinephrine release during alert, nonstress conditions engage high affinity, alpha-2A receptors which strengthen PFC function, while high levels of NE release during stress engage low affinity adrenoceptors (alpha-1 and likely beta-1 receptors) that impair PFC function (Li and Mei, 1994; Arnsten, 2000; Ramos et al., 2005).

Under optimal arousal conditions (Fig. 1), moderate levels of NE release engage alpha-2A receptors that are localized on dlPFC spines near the synapse. Alpha-2A receptor stimulation, e.g. with guanfacine, inhibits cAMP signaling, closes the K^+ channels, strengthens connectivity, increases task-related neuronal firing, and improves top-down control of behavior (Fig. 3B; Wang et al., 2007; Arnsten and Jin, 2014).

In contrast, high levels of NE release during stress exposure impairs PFC function via actions at alpha-1 receptors. Stimulation of alpha-1 receptors reduces dlPFC neuronal firing and impairs working memory by activating Ca^{2+}-PKC signaling mechanisms (Mao et al., 1999; Birnbaum et al., 2004). Although the location of alpha-1 receptors within dlPFC neurons is not yet known, it is possible that they increase the release of Ca^{2+} from the spine apparatus near the synapse, as shown in Fig. 3A. Importantly, alpha-1 receptor antagonists such as prazosin, urapidil or HEAT, protect PFC function from the detrimental effects of stress exposure (Arnsten and Jentsch, 1997; Birnbaum et al., 1999). The detrimental effects of alpha-1 receptor stimulation may be especially important with chronic stress, when NE axons increase their synthetic capacity (see below). Interestingly, increases in alpha-1 receptor stimulation in PFC also occur during traumatic brain injury (Kobori et al., 2011), which is known to be a risk factor for PTSD (Bryant, 2011). Thus alpha-1 receptors are a rational therapeutic target for treating PTSD.

5.4. Rapid switch in brain circuits controlling behavior

The high levels of catecholamine release during acute stress not only impair PFC function, but strengthen amygdala function, switching control of behavior to more primitive circuits.

There are feedforward interactions that set up "vicious vs. delicious cycles" to maintain the orchestration of brain circuits in fundamentally different states. As shown in Fig. 1, there is a "Delicious cycle" during nonstress conditions where moderate levels of phasic NE release engage high affinity alpha-2A receptors which strengthen PFC (see above), weaken amygdala (DeBock et al., 2003), and normalize tonic firing of LC neurons (Svensson et al., 1975; Nestler and Alreja, 1999) and NE release (Engberg and Eriksson, 1991). This enhances PFC function, providing intelligent regulation of the LC and amygdala. Thus, these interactive mechanisms maintain a state that promotes top-down regulation of brain and behavior. In contrast, stress exposure rapidly switches brain orchestration of behavior to primitive circuits, as summarized in Fig. 2. Stress activates feed-forward vicious cycles whereby the amygdala activates the LC and VTA to increase catecholamine release (Goldstein et al., 1996; Valentino et al., 1998), which in turn takes PFC "off-line" through alpha-1 receptor activation. Loss of PFC function further erodes regulatory control of the amygdala, striatum and brainstem (Arnsten, 2009), while the high levels of catecholamine release strengthen amygdala function via alpha-1AR, beta-AR and DA receptors (Ferry et al., 1999; Nader and LeDoux, 1999). Increased amygdala activity continues to drive the LC, thus maintaining the vicious cycle. Higher catecholamine levels have been linked to PFC impairments during stress in humans as well (Qin et al., 2012), suggesting that these mechanisms holds across species.

5.5. Changes with chronic stress

With sustained stress, there are both chemical and architectural changes that exacerbate the effects of stress on brain function. The mechanisms underlying spine loss are just beginning to be understood, with data suggesting that inhibiting alpha-1-protein kinase C signaling (Hains et al., 2009), stimulating alpha-2A receptors (unpublished data), or promoting growth factors such as FGF-2 (Elsayed et al., 2012) can protect PFC spines from sustained stress exposure. There are also alterations in the catecholamine systems themselves with prolonged stress exposure. Studies in rodents suggest that the DA system depletes with chronic stress (Mizoguchi et al., 2000), while the NE system is strengthened. Most studies show that chronic stress increases the tonic and/or evoked firing of LC neurons (Nestler and Alreja, 1999; Jedema and Grace, 2003); increases in tonic firing appear to arise from increased CRF-PKA activation of pacemaker cation channels (Nestler et al., 1999). (However, some chronic stress paradigms may produce a "giving up" pattern of stress response, reducing CRF receptor expression and instead inducing opioid inhibition of LC firing (Chaijale et al., 2013) – see Valentino and Van Bockstaele, 2015). Chronic stress also increases the expression of the NE synthetic enzymes tyrosine hydroxylase and dopamine beta hydroxylase within NE neurons and axons both rat (Melia et al., 1992; Miner et al., 2006; Fan et al., 2013) and primate (Bethea et al., 2013). This strengthening of the NE system with chronic stress likely leads to the exacerbation of detrimental alpha-1 receptor actions in the stressed PFC.

Increased NE release in other brain regions may also contribute to symptoms of PTSD such as hypervigilance and altered sleep, e.g. via alpha-1 receptor stimulation in thalamus (McCormick et al., 1991). NE alpha-1 receptor stimulation also increases acetylcholine release (Tzavara et al., 2006), which drives REM sleep (Hobson, 1992), that may contribute to increased nightmares in PTSD. Thus normalizing NE actions and restoring the alpha-2A vs. alpha-1 receptor balance may be especially important for treating stress disorders in humans.

6. Catecholamines influence risk/resilience to PTSD

Underlying differences in catecholamines appear to predispose individuals for PTSD vs. resilience when faced with a traumatic stress. The relationship between genotype and stress reactivity has been seen most clearly with the catecholamine catabolic enzyme, COMT (catechol-O-methyltransferase), where a common polymorphism at amino acid 158 substitutes native valine (Val) for methionine (Met), weakening enzyme activity and increasing catecholamine availability. As mentioned above, laboratory studies of stress reactivity have shown that subjects with higher baseline catecholamine availability (i.e. those with COMT Met–Met genotype) show impaired dlPFC function under conditions of acute, moderate stress, while those with lower baseline catecholamines (i.e. those with COMT Val genotype) can actually perform better than control conditions following acute modest stress (Qin et al., 2012), thus demonstrating the catecholamine "inverted-U" dose–response (Arnsten et al., 2012). This relationship can also be seen clinically, with increased incidence of PTSD in those with the COMT Met genotype, including the incidence of PTSD in those exposed to genocide (Kolassa et al., 2010; Boscarino et al., 2012). The Met158 COMT genotype has been related to greater fear response, and to increased epigenetic changes in the gene that may further reduce enzyme availability and compound the effects of stress (Norrholm et al., 2013). Similar effects have been seen with nontraumatic stressors, where gene alterations that increase catecholamine availability have been related to increased rates of distress (Desmeules et al., 2012) and depression or anxiety (Lacerda-Pinheiro et al., 2014).

The risk of PTSD has also been related to polymorphisms in the gene encoding for PKCα (de Quervain et al., 2012). Animal studies have shown that PKCα signaling is increased in the PFC in response to an acute stress, where it weakens PFC function (Birnbaum et al., 2004) and drives stress-induced loss of PFC gray matter (Hains et al., 2009). In contrast, PKC signaling strengthens amygdala function (Bonini et al., 2005). Thus, the link to risk of PTSD is particularly intriguing.

Another important risk factor for PTSD and depression appears to be sex, and specifically the presence of estrogen, as females of cycling age are at greater risk for illness than noncyling women/girls or men (Breslau et al., 1999; Weissman et al., 1991). Studies in animals suggest that some of this increased risk may be due to estrogen's effects on catecholamines and on spine morphology in medial PFC neurons. Animal studies have shown that estrogen promotes catecholamine production, including more DA in the dlPFC (Kritzer and Kohama, 1998). In rodents, estrogen exaggerates stress-induced dendritic changes in medial PFC neurons that drive the amygdala and increase the stress response (Shansky et al., 2009). In humans, sex appears to interact with COMT genotype in influencing emotional responsivity (Chen et al., 2011), and there are likely numerous other biological and nonbiological (e.g. cultural) factors that contribute as well. For example, perceived control over a stressor is a key factor in alleviating stress-induced PFC dysfunction (Bland et al., 2003), and women traditionally have less control over their lives than men. In the face of uncontrollable trauma, treatment may be needed to restore PFC function and allow the person to better help themselves.

7. Treatment of PTSD in adults

The data discussed so far indicate that an important goal for treatment of PTSD should be to strengthen PFC regulation, allowing the patient to better regulate their emotions, thoughts and actions. In other words, the animal data suggest that a stronger PFC should help patients to extinguish fear responses (via PFC regulation of amygdala), to calm themselves and reduce hyperarousal (e.g. via PFC regulation of brainstem), and reduce flashbacks and intrusive memories (via PFC regulation of posterior cortex and hippocampus). It is likely that many behavioral therapies act at least in part by strengthening PFC. For example, exposure therapy may work in part by creating a safe context where the PFC can increasingly come "on-line" to regulate the amygdala, breaking the vicious cycle of primitive brain responses and extinguishing the traumatic response. However, many patients are stuck in a vicious cycle where the PFC remains dysfunctional and primitive circuits dominate, and for these patients, medication may be essential to normalize brain physiology and allow the return to health. As described above, animal research has shown that NE alpha-1 receptor stimulation weakens, while alpha-2A receptor stimulation strengthens the PFC, while the converse is true for the amygdala. Based on this work, the alpha-1 receptor antagonist, prazosin, and the alpha-2A agonist, guanfacine, are now being tested and used to treat PTSD. The following reviews this emerging clinical research.

7.1. The use of the alpha-1 receptor antagonist, prazosin, for adults with PTSD

The alpha-1 adrenoceptor blocker, prazosin, proved a logical choice for human experimentation because of its clinical availability and it being the most lipid soluble of the alpha-1 antagonists, facilitating CNS penetration following oral administration.

Prazosin trials in PTSD were initiated in both military and civilian cohorts in parallel, in part based on the research in animals described above. The military studies will be addressed first.

7.1.1. Military studies

Four combat-related PTSD prazosin efficacy studies have been completed and published, all randomized controlled trials (RCTs), all demonstrating significant and substantial efficacy of prazosin for reducing nighttime PTSD symptoms, reducing daytime hyperarousal symptoms and improving global clinical status. It is noteworthy that the hyperarousal scale includes many PFC-related symptoms (e.g. impaired concentration, impaired regulation of mood and aggression), in addition to alterations in sleep-wakefulness. The first three trials focused on prazosin for the treatment of nightmares and only administered prazosin at night; the fourth study including a morning dose to extend observations more meaningfully into daytime experience.

The participants in the first two RCTs were Vietnam War combat veterans with decades of treatment resistant chronic PTSD. Prazosin was administered as a single evening dose specifically to target persistent and distressing trauma-related nightmares and sleep disruption as primary outcome measures. The Clinical Global Impression of Change (CGIC) also was assessed to determine the impact of nightmare reduction and sleep improvement in global clinical status anchored to function at home and work.

The first RCT was a double-blind placebo-controlled crossover study performed in 10 veterans (Raskind et al., 2003). Prazosin or placebo in random order were begun at an initial dose of 1 mg at bedtime and titrated upward for 3 weeks to a dose that eliminated trauma nightmares or to a maximum dose of 10 mg HS. The achieved maintenance dose was maintained for 6 weeks. Following a one-week washout period, participants were crossed over to the other treatment condition, again for 3 weeks titration and 6 weeks maintenance. At a mean achieved maintenance prazosin dose of 9.6 mg, prazosin was significantly and substantially superior to placebo for reducing nightmares (CAPS "recurrent distressing dreams of the event" item) and sleep disturbance (CAPS "sleep difficulty" item) and improving global clinical status. Change in total CAPS score and all three CAPS PTSD symptom clusters (reexperiencing, avoidance and hyperarousal) also significantly favored prazosin.

The second RCT was a parallel group study on forty veterans randomized to prazosin or placebo (Raskind et al., 2007). A four-week dose titration of prazosin or placebo was followed by 8 weeks of maintenance medication (maximum bedtime dose = 15 mg; mean maintenance bedtime prazosin dose = 13.3 mg). Prazosin was significantly and substantially superior to placebo for reducing nightmares and sleep disturbance and improving global clinical status. Dream content was assessed using the PTSD Dream Rating Scale (Tian et al., 2014), demonstrating a change from those typical of trauma nightmares toward those typical of normal dreaming.

The third RCT was performed by Germain and colleagues (Germain et al., 2012) in which 50 PTSD veterans with chronic sleep disturbance were randomized to one of three conditions: prazosin (mean dose = 9 mg at night); a behavioral sleep intervention (BSI) that included imagery rehearsal therapy, stimulus control and sleep restriction; or placebo pill treatment. Both prazosin and BSI were significantly more effective than placebo for sleep improvement, reduction in both nocturnal and daytime PTSD symptoms and improvement of global function.

The fourth RCT was performed in active duty American soldiers returned from combat deployments in Iraq and Afghanistan (Raskind et al., 2013). Because prazosin duration of action is approximately 6–10 h, a midmorning prazosin dose was included as well as a larger bedtime prazosin dose to address daytime PTSD symptoms. Maintenance prazosin doses were 4.0 ± 1.2 mg midmorning and 15.6 ± 6.0 mg bedtime for men; and 2.0 ± 0.0 mg midmorning and 7.0 ± 3.5 mg bedtime for women. Prazosin was significantly more effective than placebo for reducing CAPS "recurrent distressing dreams of the event" item scores; Pittsburgh Sleep Quality Index scores; and total 17 item CAPS scores (reduction from baseline = 25.1 ± 3.4 prazosin group and 13.8 ± 3.3 placebo group [($p = 0.02$]). Total CAPS score decrease remained significantly greater in the prazosin group ($p = 0.04$) even after removing the nightmare item. Similar open label prazosin beneficial effects with good tolerability have been reported in soldiers performing combat operations in the dehydrating Iraq desert warfare environment (Calohan et al., 2010), and in elderly World War II Veterans and Holocaust survivors (Peskind et al., 2003).

7.1.2. Civilian studies

Studies of civilians with PTSD have examined nighttime as well as daytime administration of prazosin. A double-blind placebo crossover design study found that nighttime prazosin significantly reduced subjective PTSD symptoms of trauma-relevant nightmares and insomnia while preserving normal dreaming (Taylor et al., 2008). Subjective measures of sleep were also recorded using a portable monitoring device allowing participants to sleep in their own homes thus avoiding confounding variables associated with sleep lab monitoring. Compared with placebo, prazosin significantly increased total sleep time, REM sleep time, and mean REM period duration in the absence of a sedative-like effect on sleep onset latency (Taylor et al., 2008). It seems paradoxical that alpha-1 adrenergic blockade could both increase total REM sleep time and decrease trauma-relevant nightmares, since most dreaming occurs during REM sleep. It is therefore possible that trauma-relevant nightmares are peculiar in that they do *not* occur during REM sleep. This is in keeping with study subject reports that even with PTSD nightmare reduction, normal dreaming was preserved or even restored following the prazosin treatment arm.

Another double-blind placebo-controlled crossover study of civilians addressed whether daytime-only prazosin treatment reduced PTSD symptoms during a trauma-relevant stress paradigm that simultaneously measured PFC-related executive function (Taylor et al., 2006). The Stroop Color-Word Interference Test (Golden, 1976), has been used for decades to assess cognitive function, and shown to involve PFC activity in humans (Milham et al., 2003). The E-Stroop is a modification developed to study the cognitive effects of increased emotional arousal in PTSD in a controlled laboratory setting (McNally et al., 1990). In brief, it is a timed task that requires the participant to read a list of trauma-relevant words and name the color of ink that each word is printed in. The experimental trauma-related word list consisted of five words chosen by each participant from their personal narrative of their etiologic trauma event (e.g., "fire" and "9/11" for a World Trade Center occupant who survived the September 11, 2001, terrorist attack). Time to completion, errors of omission and commission, as well as subjective distress were all recorded. At doses averaging 3.2 ± 1.3 mg, prazosin simultaneously reduced subjective stress and improved cognitive performance over the placebo condition, suggesting that alpha 1 adrenergic blockade improved PFC function in PTSD individuals under duress (Taylor et al., 2006).

Together, these clinical trials support the role of alpha-1 adrenergic blockade in reducing PTSD symptoms. These studies showed a reduction in daytime symptoms of PTSD, even when only dosed at night. Several studies report a reduction of the hyperarousal category of PTSD symptoms as measured by the CAPS. It is interesting that most of the symptoms in this category are those associated with PFC deficits including irritability, aggression, recklessness, and impaired concentration. In the trauma-relevant stress paradigm study, prazosin's simultaneous reduction of both

subjective stress and objective measures of cognitive function further support preclinical findings that alpha-1 receptor stimulation impairs PFC function, and that blockade of these receptors can restore function. A recent case report cites high doses of prazosin, up to 30 or 40 mg, as efficacious and well-tolerated in the treatment of daytime PTSD symptoms, (Koola et al., 2014) underscoring the need for further studies on the use of higher doses of prazosin to treat daytime PTSD symptoms. Higher doses of prazosin may be needed in daytime, as levels of LC firing and NE release are higher during waking (Foote et al., 1983). It will be of particular interest to see whether prolonged prazosin use can restore PFC gray matter in patients with PTSD.

Prazosin may also be helpful in reducing substance abuse, which is common in those with PTSD. Preliminary trials suggest that prazosin can reduce craving and use of alcohol (Simpson et al., 2009), including stress-induced craving of alcohol (Fox et al., 2012a), in subjects without PTSD. Based on these initial trials, prazosin RCTs for alcohol use disorders with and without comorbid PTSD are underway in civilians, military Veterans and active duty military service members.

Finally, there is anecdotal evidence that prazosin may enhance the effectiveness and utility of exposure therapy. Therapists have speculated that Veterans with PTSD who would have been "drop-outs" during the early anxiety-increasing stages of exposure therapy may have been able to complete their course of therapy successfully because they were taking prazosin; the prazosin appeared to allow them to tolerate (or not develop) the intensely dysphoric hyperarousal and reexperiencing symptoms that often occur early in the course of exposure therapy prior to therapeutic reductions. These positive effects of prazosin may involve its ability to strengthen PFC and weaken amygdala, thus facilitating the process of extinction and enhancing the therapeutic response.

7.2. The use of the alpha-2A receptor agonist, guanfacine, for adults with PTSD

There have only been two published studies of the effects of guanfacine in adults with PTSD.

These experiments examined the effects of 8 weeks of guanfacine in subjects with long-established PTSD, and found no effect of treatment (Neylan et al., 2006; Davis and Ward, 2008). The negative effects in this cohort may be due to a loss of substrate for drug actions, e.g. due to spine loss with chronic illness. Guanfacine has been shown to ameliorate stress-induced substance abuse in adults (Fox et al., 2012b; Fox and Sinha, 2014), and thus may be helpful in patients for whom the PTSD is more recently initiated.

8. Treatment of PTSD in children and adolescents

Supported by pre-clinical and clinical studies that demonstrate dysregulated CNS noradrenergic functioning and PFC underfunctioning, adrenergic medications are increasingly being used in the treatment of trauma in children. Centrally acting α_2-agonists including guanfacine, guanfacine extended release (GXR), and clonidine appear effective in diminishing the intensity of trauma-induced hyperarousal symptoms, including impaired concentration, poor impulse control, hypervigilance, nightmares and insomnia, and exaggerated startle response in children and adolescents. Although there are no controlled trials of these agents in pediatric PTSD, case reports and open trials suggest that clonidine may reduce flashbacks and traumatic repetitive play in children and that guanfacine may reduce trauma-induced nightmares (Harmon and Riggs, 1996; Horrigan, 1996). Presently, there are no reports of clonidine extended release use in pediatric PTSD.

A once-daily preparation of guanfacine (guanfacine extended release; Intuniv®) is available and is currently FDA approved for use in ADHD in 6–17 year old children. An open label study of GXR suggests effectiveness for symptoms of traumatic stress and PTSD in children (Connor et al., 2013). In an 8-week open-label design, and using an average GXR daily dose of 1.19 mg ± 0.35 mg and an average weight adjusted daily dose of 0.03 mg/kg ± 0.01 mg/kg significant improvement was found in reexperiencing, avoidant, and overarousal rating scale child trauma symptoms. Of study completers, 71% met a priori criteria for response. This open-label study suggests that the α_{2A}-adrenoceptor agonist GXR may have therapeutic effects in the treatment of PTSD symptoms in traumatically stressed children and adolescents and that the effective dose may be lower than that found for ADHD (Connor et al., 2013).

As described above, the α_1-antagonist, prazosin, has been shown to be effective in treating PTSD in controlled trials of adult subjects. At present, the data on the use of prazosin for symptoms of traumatic stress in the pediatric years is limited to open case reports, generally describing use in adolescents (Brkanac et al., 2003; Fraleigh et al., 2009; Oluwabusi et al., 2012; Strawn et al., 2009). There is one case report of successful treatment of a seven-year-old child with PTSD using 1 mg of prazosin (Strawn and Keeshin, 2011). Case reports suggest that in daily doses between 1 mg and 4 mg prazosin appears helpful in reducing trauma nightmares in adolescents and possibly in children with PTSD. Although prazosin is used in doses up to 15 mg/day to treat pediatric hypertension, these case reports suggest possible PTSD effectiveness at lower doses. However, conclusions on the suggested efficacy of prazosin for symptoms of PTSD and traumatic stress await data from more controlled clinical trials.

It is especially important to assay and develop treatments for childhood PTSD, as it can have such far-reaching effects. The epidemiology of pediatric trauma exposure reveals that outcomes vary, from resilience to psychopathology, and early death. Influencing outcomes are child specific factors such as antecedent mental health vulnerabilities, family factors such as intact caregiving relationships that serve to buffer stress, and characteristics of the trauma such as proximity, presence of injury, chronicity, and characteristics of the agent (natural disaster versus caregiver inflicted). When psychopathology is an outcome, comorbidity is the rule. The sequelae of childhood traumatic stress include a range of possible outcomes encompassing persistence of post-traumatic symptoms, alterations in developmental trajectories with subsequent impairment in emotional and behavioral control, learning disabilities, persistent aggression and/or violence which increases risk for juvenile justice involvement, substance abuse, and early death (Deans et al., 2013; Stoddard, 2014; Subica et al., 2012). Thus, there is an imperative need for effective treatments for childhood PTSD.

9. Closing

This review highlights one of the few examples where research in animals has helped lead to treatments for human brain disorders. Since the PFC expands greatly in evolution, work in nonhuman primates has been particularly important for revealing the molecular mechanisms to protect and normalize PFC physiology in humans. Continued research is needed to help develop treatments that alleviate the suffering of patients exposed to trauma.

Acknowledgments

AFTA is supported by an NIH Director's Pioneer Award DP1AG047744-01. The research described in this review has been funded by a wide variety of sources.

Disclosures: AFTA and Yale University receive royalties from Shire Pharmaceuticals from the sales of Intuniv™ (extended release guanfacine) for the treatment of pediatric ADHD.

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