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

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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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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.

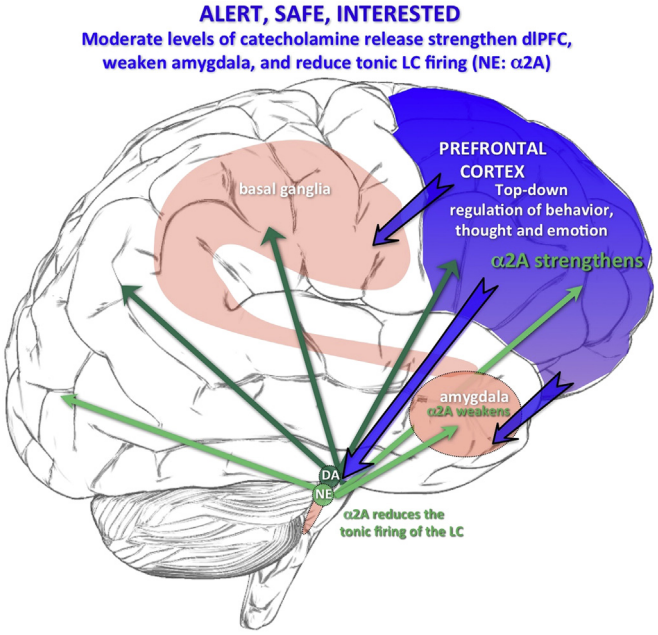

Fig. 1. During nonstressed arousal conditions when the subject is alert, safe and interested, the highly evolved prefrontal cortex (highlight in blue) provides top-down regulation of behavior, thought and emotion. It orchestrates behavioral response through extensive connections, e.g. to the amygdala, 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

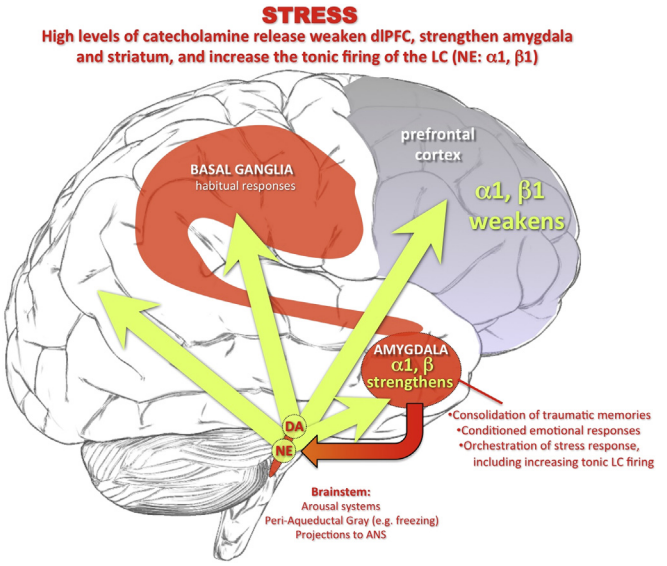

Fig. 2. Under conditions of uncontrollable stress, there are high levels of catecholamine release in brain, which weaken PFC function but strengthen the affective responses of the amygdala and the habitual responses of the basal ganglia. The amygdala activates the catecholamine under conditions of psychological 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.