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A Review of the Effects of Prolonged Exposure to Cortisol on the Regulation of the HPA Axis: Implications for the Development and Maintenance of Posttraumatic Stress Disorder

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The present review examines the extant literature in both human and animal experiments of the stress response. Specifically, this paper aims to demonstrate that the prolonged release, and subsequent higher basal levels of cortisol results in altered functioning of the regulatory systems that modulate the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, the intent is to show that these alterations in neural circuitry and neuroendocrines play a substantial role in the development and maintenance of posttraumatic stress disorder (PTSD). A review of the literature was conducted and summarized according to the three major regulatory systems that interact to facilitate the functioning of the HPA axis (i.e., hippocampus, amygdala, and prefrontal cortex). Finally, the author integrates the findings and provides a theoretical rationale for the development and maintenance of PTSD. Discussions of limitations and future directions are offered throughout.

Keywords: trauma, hormone exposure, stress, neurobiology, neuroplasticity, hypothalamic-pituitary-adrenal axis, translational research, glucocorticoid

Cortisol, also called hydrocortisone, is an endogenous steroid hormone classified as a glucocorticoid and is one of the endocrines produced by the adrenal glands (i.e., endocrine organs located superior to the kidneys). When mammals experience stress, the hypothalamic-pituitary-adrenal (HPA) axis mediates the release of cortisol (De Kloet & Rinne, 2007). The areas of the brain that comprise the HPA axis include the hypothalamus, pituitary gland, and projections to the adrenal cortex. Excitatory inputs converge on neurons located in the hypothalamic paraventricular nucleus, where corticotropin-releasing hormone (a peptide hormone often referred to as the stress hormone) is synthesized. Under stressful conditions the amygdala stimulates the paraventricular nucleus. This results in the release of corticotropin-releasing hormone into the portal circulation, which signals the anterior pituitary gland to release adrenocorticotropic hormone (ACTH, also known as corticotropin; Cullinan, Herman, Helmreich, & Watson, 1995; Franklin, Saab, & Mansuy, 2012). Release of ACTH then stimulates the adrenal cortex, which results in cortisol release into the bloodstream (Jovanovic et al., 2011).

Once released, cortisol, like other glucocorticoids, acts throughout the body and mediates changes in various processes such as inflammatory reactions, immune function, and metabolic regulation by interacting with mineralocorticoid and glucocorticoid receptors. While in the brain, glucocorticoids increase these stress responses and serve to contain or regulate the responses, thus facilitating recovery and behavioral adaptation (Franklin et al., 2012). Containment and regulation are important as a number of sites in the brain can be negatively affected by increased and prolonged exposure to cortisol (e.g., hippocampal dysfunction results in deficits in declarative memory function, reduced neural survival and plasticity, and promotion of inflammatory cascades; Bremner, 1999; Franklin et al., 2012). Although moderate levels of these hormones are responsible for mediation of normal cell functioning, glucocorticoids must be maintained at appropriate levels to preserve homeostatic function of systems (Franklin et al., 2012).

Through negative feedback inhibition, cortisol attenuates the stress response by acting on the hypothalamus, pituitary gland, hippocampus, and medial prefrontal cortex, which suppresses the HPA axis (DeBellis, 2010; van der Kolk, 1996). The negative feedback regulation of the HPA axis is facilitated by the rapid inhibition of corticotropin-releasing

hormone release, as well as a more prolonged down-regulation of corticotropin-releasing hormone and vasopressin expression in the neurons of the paraventricular nucleus (Di, Malcher-Lopes, Halmos, & Tasker, 2003; Franklin et al., 2012). By suppressing the HPA axis, basal cortisol levels are restored and the brain returns to homeostasis (DeBellis, 2010).

However, these reactions can be altered following intensely distressing, psychologically traumatic events. Under chronic, persistent stressors the effectiveness of the stress response is inhibited. Over sustained periods of stress, the negative feedback loop ultimately reduces resting glucocorticoid levels and their secretion in response to subsequent stressors (van der Kolk, 1996). These functional alterations have been observed in individuals diagnosed with posttraumatic stress disorder (PTSD) following a psychologically traumatic event (Southwick, Rasmusson, Barron, & Arnsten, 2005).

Posttraumatic Stress Disorder

PTSD is a mental health diagnosis that results from one or more traumatic events in a person's life whereby the person experiences intense fear, helplessness, and/or horror (American Psychiatric Association, 2013). The disorder is characterized by symptoms of re-experiencing the event (e.g., intrusive recollection of disturbing memories, distressing dreams or nightmares), behavioral avoidance and emotional numbing (e.g., avoidance of people, places, and events that serve as reminders of the event, loss or blunting of primary emotions), and hypervigilance (e.g., increased startle response, diminished concentration; APA, 2013; Roth & Fonagy, 2005). Epidemiological studies suggest that over half of all adults in the United States will experience traumatic stress at some point in their lives (Friedman, Resick, & Keane, 2007).

Although the behavioral manifestations and impact of psychological trauma are subject to individual differences, and the construct of PTSD is broad (particularly in light of recent updates to the criteria set forth in the DSM-5; Galatzer-Levy & Bryant, 2013), about one-third of the individuals who experience a trauma will go on to receive a PTSD diagnosis. Indeed, these individual differences may result from differential functioning of the HPA axis among those who are able to recover following a traumatic event (with little or no impairment from subjective psychological symptoms) compared to those who develop PTSD (Franklin et al., 2012; Southwick et al., 2005).

Although results from studies examining basal urinary cortisol levels among individuals with PTSD have been mixed though often finding lower baseline cortisol levels (Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998), studies examining cerebrospinal fluid (CSF) have shown that basal cortisol levels are higher among PTSD-diagnosed individuals than compared healthy controls (Baker et al., 1999; Baker et al., 2005). Furthermore, the CSF levels were shown to be higher compared to within-subject urinary levels. This suggests that urinary measurements may not reflect the actual level of cortisol within the central nervous system (Southwick et al., 2005). Moreover, studies that examined cortisol levels in individuals within the acute aftermath of trauma found that cortisol levels are increased and prolonged just after a traumatic event and in the face of acute stress (Bremner et al., 2003; Lemieux & Coe, 1995; Pitman & Orr, 1990). Thus, it has been suggested that immediate and prolonged exposure to cortisol results in HPA adaptation over time, which may in turn explain later reductions in cortisol levels and the resultant inefficiency in the normal HPA suppression and behavioral adaptation processes (Bremner, 2001; Handwerger, 2009).

Another reason for mixed findings may lie in the comorbidity between PTSD and depression (Morris, Compas, & Garber, 2012). Indeed, this has been suggested by studies that have found reduced activity of intracellular cortisol-deactivating enzymes 5alpha-reductase and 11beta-HSD2, resulting in high amounts of circulating cortisol (hypercortisolemia) among clinically depressed individuals in comparison to healthy controls (Romer et al., 2009). Similar findings have emerged in individuals with PTSD, demonstrating a three-fold less hepatic 5alpha-reductase presence and a deficiency of 11beta-HSD2 in the kidneys. These deficiencies slow the body's ability to clear cortisol, thus increasing the amount of bioavailable cortisol (Yehuda & Seckl, 2011). Ultimately, research in this area of PTSD is relatively young and, as a result, will likely be subject to debate until more methodologically sound studies are available.

At this time, there is sufficient evidence to suggest that cortisol levels are increased and prolonged in individuals who experience a traumatic event and that such exposure to higher levels of cortisol can result in changes to the neural circuits that mediate the fear and stress response, as well as emotional and memory processing. For the purposes of the present review, the focus will be on alterations in neurobiological functioning in the presence of PTSD. Specifically, the intent is to demonstrate that the prolonged release and subsequent higher basal levels of cortisol can result in altered functioning of the regulatory systems that modulate the HPA axis and play a substantial role in the development and maintenance of PTSD. To do so, brief reviews and integration of the literature will be provided for the three major regulatory systems that interact to facilitate functioning of the HPA axis: the hippocampus, the amygdala, and the prefrontal cortex. Furthermore, an overview of the impact of higher basal levels of, and prolonged exposure to, cortisol will be provided for each area.

Effects of Cortisol on the Hippocampus

The hippocampus is a brain region that is largely responsible for the formation, consolidation, and storage of memories—specifically declarative memory—and is indirectly implicated in emotion. Recent studies examining the effects of N-methyl-D-aspartate (NMDA) receptor subunit deletion (from the granule cells of the dentate gyrus) in genetically modified mice, suggest that the hippocampus may serve a functionally distinct role in anxiety. With NMDA receptor deletion in the ventral portion of the hippocampus, anxiety was reduced in addition to spatial memory impairment (Barkus et al., 2010). These dual roles make the hippocampus a prime structure in which to consider the implications of prolonged stress. Furthermore, the hippocampus has also been shown to negatively regulate the HPA axis by decreasing glucocorticoid secretion in rat and human brains following stimulation (Herman, Ostrander, Mueller, & Figueiredo, 2005). Following chronic stress conditions, glucocorticoid receptors in the hippocampus, which aid in dexamethasone-mediated negative feedback of the HPA, are down-regulated (Herman et al., 1989; Mizoguchi, Ishige, Aburada, & Tabira, 2003; Sapolsky, Krey, & McEwen, 1984). The down-regulation of glucocorticoid receptors disrupts the hippocampus' ability to provide inhibitory feedback under chronic stress conditions (Herman et al., 1989; Mizoguchi et al., 2003; Schloesser, Manji, & Martinowich, 2009).

Indeed, the hippocampus is one of the sites where a large number of Corticotropin-releasing hormone receptor 1 are found (Franklin et al., 2012). As a result, the structure is a primary target for glucocorticoids and exhibits a notable sensitivity to their binding, such that both marked neurochemical and electrophysiological changes are observed in their presence (Sapolsky, Uno, Rebert, & Finch, 1990). Furthermore, studies involving rodents have demonstrated that prolonged hippocampal exposure to cortisol can damage the structure and accelerate aging, create changes in electrical activity, and result in neuronal loss (Sapolsky et al., 1990). Sapolsky and colleagues (1990) sought to expand upon these findings by examining the impact of prolonged glucocorticoid exposure in four male vervet monkeys. The researchers surgically implanted pellets secreting either cortisol or cholesterol (control) into the hippocampus. After a year of exposure to these conditions, overall hippocampal size did not observably differ by group and the cholesterol group was essentially normal; however, in the cortisol group, damage was observed in the pyramidal neurons, which exhibited abnormal shrinkage or elongation of somas and abnormalities in dendritic stems and branches. The researchers concluded that the results were in agreement with literature suggesting that increased and prolonged exposure to cortisol accelerates hippocampal neuron loss. A more recent review by Sapolsky (2000) offers some insight as to why overall hippocampal size decreases were not observed, despite finding significant damage and neuron loss. Although overall hippocampal size did not differ, it is unclear to what extent this was examined in the study or whether examination was bilateral. Indeed, many studies that show decreased hippocampal size following stressors (usually traumatic events) do not demonstrate decreased size bilaterally (i.e., significantly smaller size in either right or left with a non-significant contralateral finding). Furthermore, Sapolsky et al. (1990) may not have found significant volume changes as a function of the magnitude of cortisol exposure (i.e., the amount

of cortisol may not have been sufficient to result in overall volume loss). Sapolsky's (2000) review found the common thread of trauma severity to be related to hippocampal volume loss. The more intense the trauma, the more likely we are to find a significant loss of volume in the hippocampus (Sapolsky, 2000). Perhaps the amount of cortisol exposure varies in a significant way as to result in differential hippocampal volume changes, or, more likely, it is the combined neurobiological and psychological effects following severe trauma that lead to these changes.

Such changes in the hippocampus, including volume loss and atrophy, create significant deficits in the hippocampus' ability to participate in the regulation of the HPA axis. Furthermore, the hippocampus' ability to regenerate these cells (neurogenesis) is impaired by exposure to stressors (Gould & Tanapat, 1999). Gould, McEwen, Tanapat, Galea, and Fuchs (1997) examined adult neurogenesis in the dentate gyrus of the hippocampus in tree shrews under stressful conditions. To examine whether granule cell production occurs under stress, the researchers injected bromodeoxyuridine (BrdU; a marker of DNA synthesis) into label cells in the dentate gyrus. Psychosocial stress was induced by removing an opaque partition that separated two adjacent cages, which resulted in competition and establishment of dominance between the shrews. The shrew that took the subordinate role was virtually immobile and showed characteristic signs of distress. After one hour, the partition was replaced and BrdU injections were given. Elevations in urinary cortisol levels were observed in the subordinate shrew compared to the dominant shrew and controls. Two hours after injection, the subordinate shrews were anesthetized, examined, and then compared to control shrews, which were not exposed to stress. The results indicated that a single exposure to psychosocial stress for one hour resulted in a significant decrease in BrdU-labeled cells in the dentate gyrus in comparison to controls and reflected a reliable change in the number of proliferating cells. Although these results may provide insight into the effects of stress on neurogenesis in the short-term, the long-term implications remain an empirical question. It would stand to reason that prolonged life stressors may exacerbate and perpetuate this effect, at least for some period of time; future studies are needed to examine both chronic stress conditions (e.g, trauma-exposure) and situational stress conditions (e.g., non-traumatic stress exposure) to explore differential effects of habituation.

In addition to changes in the structure and plasticity of cells in the hippocampus, inhibition of neurogenesis results in potentiated response from the HPA axis following stress. Schloesser et al. (2009) examined the impact of loss of neurogenesis in the hippocampus on the efficiency of the hippocampus to inhibit the HPA axis. Transgenic mice, genetically altered for complete suppression of the doublecortin-positive neuroblasts in the dentate gyrus, were used so that conditional suppression of adult neurogenesis was possible through viral kinase and promoter genes. Plasma concentrations of corticosterone (cortisol equivalent in mice) were measured in normal conditions (being in the home-cage environment) and under mild stress (being placed in a novel cage environment). A significant increase in corticosterone levels was observed in non-neurogenesis mice exposed to a mild stressor compared to non-neurogenesis mice that were not exposed to stress and controls. Their findings suggest that suppression of neurogenesis in the hippocampus results in an increased HPA axis response and that new neurons formed in the dentate gyrus are critical to the inhibitory regulation of the HPA axis by the hippocampus.

Given that prolonged and increased levels of cortisol are observed in the aftermath of psychologically traumatic events, and that the bioavailability of cortisol appears to be maintained over a longer term among those with PTSD, it is not difficult to begin to understand the vicious cycle that takes hold. The increased and chronic exposure to cortisol results in impairment of the hippocampus, which results in poorer anxiety coping and reduced inhibitory modulation of the HPA axis; this, in turn, leads to increased HPA activity under stress while leaving the individual with continuously increased anxiety response, as well as memory deficits resulting from hippocampal volume reduction (Bremner, 1999). Furthermore, the extinction of conditioned fear responses—the reduction and ultimate extinction of a conditioned fear response following repeated presentations of conditioned stimuli without the unconditioned, originally feared, stimuli—is contingent on the ability to efficiently form new

associative relationships. Fear responses to stimuli present during a traumatic event are often generalized to similar, innocuous stimuli. For example, the sound of gun fire is generalized to cars backfiring or a loud sound from a heavy falling object, thus resulting in an exaggerated startle or cover response. To this end, the hippocampus has been shown to be involved primarily in the acquisition of the fear response to stimuli (conditioned response) and may mediate the awareness of the conditioned stimulus to unconditioned stimulus relationship (Knight, Smith, Cheng, Stein, & Helmstetter, 2004). However, it is the amygdala that serves to aid in the processing of emotional content (Herbert et al., 2009), changes in environmental relationships among stimuli (Knight et al., 2004), and the principle site of convergence between the conditioned stimulus and unconditioned stimulus (Hashikawa et al., 2013; Knight et al., 2004). Not surprisingly, amygdalar functioning is also altered by increased exposure to cortisol (Ardayfio & Kim, 2006).

Effects of Cortisol on the Amygdala

Kluver and Bucy's (1939) lesion studies first implicated the amygdala as the structure mediating the emotional significance of stimuli. Specifically, the amygdala is primarily responsible for the automatic, non-conscious processing of threatening stimuli. The amygdala receives signals from sympathetically activated regions (e.g., brainstem, thalamus, and sensory) responsible for orienting attention toward a threat, which facilitates an individual's ability to target, identify, and assign emotional information to a stimuli in the interest of self-preservation. Thus, under stressful conditions, the amygdala aids in the ability to quickly discriminate between threatening and neutral stimuli, encode the emotionally salient information via projections to the hippocampus, and help prepare the body for action (Kensinger & Corkin, 2004).

As previously discussed, one of the amygdala's duties is to promote the stress response following stimulation from the locus coeruleus. However, with 13 distinct subnuclei, the amygdala is implicated in a number of emotional processing and stress modulating processes (Ressler, 2010). Among these is the process of fear extinction. Fear extinction appears to be dependent on intercalated amygdala cells within the central nuclei and, when disrupted, impairs extinction (National Institute of Health [NIH], 2010; Ressler, 2010). The central nuclei of the amygdala is responsible for the regulation of cortisol release via projections to the paraventricular nucleus of the hypothalamus (activating the HPA axis), as well as modulation of behavioral responses to fearful stimuli. Lesions in the central nuclei have been shown to result in elimination of conditioned fear responses in rodents (Ressler, 2010), as well as reduced ACTH and glucocorticoid release following stress (Herman et al., 2005).

Knight et al. (2004) utilized functional magnetic resonance imaging (fMRI) to examine brain activity during the acquisition and extinction of fear conditioning. During acquisition, human subjects were either exposed to a light paired with an electrical shock or a light without an electrical shock. During extinction, half of the subjects in the active group continued to receive the pairing while the remainder, as well as the control subjects, received the light without the shock. Results showed increased hippocampal activity during acquisition, whereas increased amygdalar activity was observed when experimental conditions changed, specifically in the absence of the shock following acquisition.

In addition to the amygdala's role in acquisition under uncertain stressful conditions or conditions that run counter to the learned expectation, the amygdala acts to moderate the consolidation of emotionally charged information (for a review see Paré, 2003). Buchanan and Lovallo (2001) examined the effects of cortisol versus placebo on human memory performance. Their findings demonstrated that exposure to cortisol during acquisition and encoding resulted in better long-term recall performance for emotionally charged stimuli compared to neutral stimuli. Therefore, under stressful conditions, memories are more efficiently consolidated when the stimuli are perceived as threatening or fear-congruent.

Another neuroimaging study conducted by van Stegeren et al. (2007) found that individuals with higher levels of cortisol showed significantly greater amygdalar activation when viewing emotional content compared to individuals with lower levels of cortisol. However, cortisol did not exert this effect in isolation. An interaction between the basal level of cortisol and levels of arousal-induced noradrenergic

activation in the basolateral complex of the amygdala appeared to highlight a synergistic relationship that may result in enhanced consolidation of emotional memories. This interactive relationship between increased cortisol and norepinephrine has been found in other studies, as well, and has been shown to result in an exaggerated amygdalar response equivalent to that found in individuals with PTSD (Gueze et al., 2012; Kukolja et al., 2008).

Kukolja and colleagues (2008) examined the role of the glucocorticoid-noradrenergic interaction in amygdalar activation using pharmacological interventions to artificially increase the levels of cortisol and norepinephrine. Sixty-two healthy human participants were assigned to one of four conditions: (a) placebo, (b) a selective norepinephrine reuptake inhibitor, (c) hydrocortisone, or (d) a combination of both drugs. Subjects were then placed in an fMRI scanner where amygdalar activation was measured during the presentation of emotional faces. Results indicated that a negative response bias was created under the combination condition, such that amygdalar activity was decreased in response to positive emotional content and increased in response to negative emotional content. This finding may provide insight into the restricted range of emotions (particularly positive) exhibited by individuals with PTSD.

These studies show that the amygdala is both responsible for the release of cortisol through its role in the HPA axis and, in the interaction with norepinephrine, affected by increased levels of cortisol. Studies examining the amygdala as a target for glucocorticoids have shown that the central and medial nuclei express both glucocorticoid and mineralocorticoid receptors, which make it reactive to basal levels of cortisol in addition to stress-related release (Herman, Ostrander, Mueller, & Figueiredo, 2005). Akana, Chu, Soriano, and Dallman (2001) examined the site-specific and state-dependent effects of glucocorticoids on the amygdala and the regulation of ACTH, insulin, and fat depots in rats. The adrenal glands were surgically removed from the rats and corticosterone was administered in low doses by the researchers. Half of the rats were kept in room-temperature environments, while the other half were subjected to cold (5° C) over five days before being restrained (as the stressor). Results indicated that implants of glucocorticoids in the central nucleus do not modulate the acute stress response; rather, they seem to be implicated in the alteration of neural output from the central nucleus to preganglionic sympathetic neurons while under chronic stress. Thus, in individuals with higher basal cortisol levels, the amygdala will likely continue to respond in the usual feed-forward fashion to potentiate the HPA axis while exerting, to some extent, an influence over the sympathetic branch of the autonomic nervous system. Though not explicitly stated in the literature reviewed, increased influence of the amygdala on autonomic function, as a result of exaggerated activity, may explain some of the pervasive hyper-arousal symptoms experienced by individuals with PTSD.

Effects of Cortisol on the Prefrontal Cortex

In addition to exaggerated amygdalar response, individuals with PTSD have been shown to exhibit inefficient functioning of the prefrontal cortex (Gueze et al., 2012). Indeed, a number of studies show support for prefrontal cortex influence on amygdalar function. For example, the ventro-medial prefrontal cortex is thought to play a role in the inhibition of the amygdala and may facilitate fear extinction (Delgado, Nearing, LeDoux, & Phelps, 2008).

The prefrontal cortex plays a role in higher order functions such as cognition, affect regulation, and social reasoning. Moreover, regions of the prefrontal cortex (particularly the anterior cingulate, medial, and ventromedial regions) have also been implicated in the stress response (Herman et al., 2005). Like the hippocampus, the prefrontal cortex plays a role in the inhibition of the HPA axis and takes on the added duty of inhibiting the amygdala. Furthermore, just as in both the hippocampus and the amygdala, the prefrontal cortex is home to a high density of glucocorticoid receptors, primarily in the medial region (Sanchez, Young, Plotsky, & Insel, 2000). Because of the role of the medial prefrontal cortex in higher order functions and its diverse ascending and descending projections, it is thought that this region is crucial to the overall function and regulation of the HPA axis (Kern et al., 2008). In rodent models, lesions to this area result in significant increases in adrenocorticotropic hormone and cortisol release under stress. It has been suggested that the ventral region of the medial

prefrontal cortex may exert an excitatory influence on the HPA axis, perhaps allowing the prefrontal cortex to play a larger role in the maintenance of HPA axis equilibrium.

Kern et al. (2008) sought to examine distinct patterns of prefrontal cortex involvement in neuroendocrine stress control. They hypothesized that both positive and negative associations between stress-induced glucose metabolic rate and saliva cortisol concentrations would be present depending on specific locations within the prefrontal cortex (positive associations in lateral regions, and negative associations in medial dorsal regions). The researchers assigned 14 human subjects to either a stress or control condition. Subjects attended three sessions and baseline positron emission tomography (PET) scans were established approximately 14 days after the first session (session one involved only informed consent and study procedure explanation) and another scan exactly one week later. Subjects in the stress condition were confronted with an established, structured psychosocial stress situation (a modified version of the Trier Social Stress Test; Kirschbaum, Pirke, & Hellhammer, 1993). The control condition followed a structured situation that was determined to be similar to the stress condition, without the stress component. Results implicated Brodmann areas 9 and 10 in the medial prefrontal cortex as part of the regulatory circuitry that modulates responses to stressful stimuli. Lateral regions were found to be associated with increased cortisol levels and appear to lend support to the relationship between this region and subjective discomfort experienced during stressful social interactions and the resultant withdrawal behavior. The authors conclude that their data lend support for Brodmann area 10 in voluntary regulation of negative emotion, particularly during socially threatening situations. Another finding with regard to Brodmann area 9 is its implication in voluntary down regulation of negative affect states, which is inactivated during perceived negative emotions. The authors conclude that Brodmann area 9 may function as an integration circuit, allowing the regulation of affective states while coordinating active coping behaviors under stress. Despite potential limitations due to small sample size, these results provide promising evidence that the prefrontal cortex provides substantial regulation of both neural circuits that modulate the HPA axis and the regulation of subjective affective content while under stress. However, as previously mentioned, the prefrontal cortex has a large number of glucocorticoid receptors. Just as other areas are vulnerable to alteration as a result of increased basal cortisol levels, detrimental effects on the functional efficiency of the prefrontal cortex have been observed.

Carrion, Weems, Richert, Hoffman, and Reiss (2010) examined the impact of increased cortisol on prefrontal cortex volume among adolescent humans with PTSD. Using magnetic resonance imaging (MRI) and salivary cortisol measurements, the authors found that higher levels of cortisol were related to significantly decreased prefrontal cortex tissue volume (particularly in the ventral and inferior regions) among subjects with PTSD symptoms. Although these findings are restricted to adolescents, the changes in structural volume found in this study are consistent with the effects of prolonged exposure to cortisol observed the amygdala and hippocampus. Thus, it may be prudent to consider, however cautiously, these findings in the context of impairments observed in adult PTSD. If these changes are taking place more generally, reduced volume in prefrontal cortical tissue may help to explain the overall restriction of positive emotions, social withdrawal and avoidance, irritability, and concentration difficulties experienced by individuals with PTSD. Furthermore, inefficiencies resulting from these changes in the prefrontal cortex may also explain the resistance of traumatic memories to the extinction process.

Livneh and Paz (2012) sought to examine the neural basis for the resistance to extinction of aversive memories. As with individuals suffering from PTSD, impaired fear extinction results in a maladaptive and persistent anxiety response despite the absence of actual threat. Whereas the amygdala has been shown to enhance the processing of emotional memories, the dorsal anterior cingulate cortex is thought to interact with the amygdala (via direct connections) and aid in the regulation of expressing learned fear responses. Furthermore, in terms of conditioned learning, the dorsal anterior cingulate cortex has been shown to play an important role in the processing of uncertainty (Huettel, Stowe, Gordon, Warner, & Platt, 2006; Krain, Wilson, Arbuckle,

Castellanous, & Milham, 2006) and functions differentially in the face of continuous and partial reinforcement (Dunsmoor, Bandettini, & Knight, 2007; Hartley, Fischl, & Phelps, 2011; Milad et al., 2007). Livneh and Paz (2012) hypothesized that the amygdala and this region of the prefrontal cortex would function differentially under different reinforcement schedules (continuous and partial). To test their theory, Livneh and Paz put two monkeys through a tone-odor conditioning task. A partial reinforcement schedule was used on randomly intermingled days with a continuous reinforcement schedule. Memory expression was measured by volume of breath intake (measured by a pressure-sensitive mask attached to the nose) that followed the tone prior to odor release, while activity in brain centers was measured by MRI-based electrodes. Results suggest that under continuous reinforcement schedules, activity in the amygdala precedes behavioral responses, whereas prefrontal cortex activity precedes behavioral responses under partial reinforcement. Furthermore, the persistence of the behavioral response, and ultimately the resistance to extinction, was observed in the prefrontal-mediated partial reinforcement condition but not the amygdalar-mediated continuous reinforcement condition. The authors conclude that this finding suggests that the tone-odor associations were acquired differentially, depending on reinforcement schedule. Thus, while the amygdala appears to function most efficiently when rapid, simple sensory associations must be made, more complex forms of conditional learning, like the probabilistic learning in the partial reinforcement trials, appear to recruit the dorsal anterior cingulate cortex, which results in resistance to extinction. Damage to the prefrontal cortex impairs these processes, thus it stands to reason that reduction in cortical volume in areas of the prefrontal cortex may lead to impaired, or at least inefficient, complex conditional learning.

Summary and Conclusion

The aim of the present review was to demonstrate that the prolonged release, and subsequent higher basal levels of cortisol, results in altered functioning of the regulatory systems that modulate the HPA axis. Furthermore, the aim was to show, to the extent possible, that these alterations in neural circuitry and neuroendocrines play a substantial role in the development and maintenance of PTSD. A review of the literature was conducted and summarized according to the three major regulatory systems that interact to facilitate functioning of the HPA axis: Hippocampus, amygdala, and prefrontal cortex.

Ultimately, while research regarding normal stress reactions has a long history of publication, much less has been done in respect to PTSD. Where possible, relevant research specific to PTSD was reviewed and research-informed speculation offered in its absence. Furthermore, where studies in humans are available they are often reliant on relatively young technologies (e.g., functional MRI), which reduce the confidence with which researchers can make definitive causal statements. Although support may be lent from animal studies, methodological differences between animal and human studies, as well as the usual translational problems, exist. However, despite these limitations, some consistent findings have been demonstrated across studies that may begin to paint a coherent picture of the interactions between the many processes involved in the stress response.

Overall, research has demonstrated that basal levels of cortisol may be increased in individuals who experience PTSD. Although some of the earlier literature appears to be mixed, some finding lower urinary levels of cortisol while others find higher levels, more recent studies utilizing more reliable measures of bioavailability (e.g., CSF) seem to be tending toward a model of higher basal cortisol levels following trauma. In the context of studies finding reduced efficiency in the metabolism of cortisol following traumatic stressors, it may help explain why studies find lower levels of cortisol in urinary samples, as it is not being processed and flushed by the kidneys due to enzymatic deficiencies.

This increase in the bioavailability of cortisol, which has broad reaching effects on the body and is free to cross the blood-brain barrier, may continuously bind to HPA regulatory structures and create a cycle of inefficient stress responses. Whereas normal function of the stress response utilizes cortisol to aid in the containment of stress responses, when cortisol is not maintained at appropriate levels, detrimental effects are observed in regulatory structures. Furthermore, prolonged exposure to high levels of cortisol has been

shown to result in significant alterations in the cells that comprise the structures. For example, chronic cortisol exposure was shown to significantly reduce hippocampal volume as a result of cellular atrophy, which ultimately disrupted neurogenesis. As a result of this disruption, the inhibitory regulation of the HPA axis by the hippocampus is prevented, which leads to an increased HPA response. Similarly, the central and medial nuclei of the amygdala express both glucocorticioid and mineralocorticoid receptors, which make it reactive to basal levels of cortisol in addition to stress-related release. For this reason, the amygdala will likely continue to promote and potentiate the HPA axis while also exerting influence over the sympathetic branch of the autonomic nervous system. Like the hippocampus, the prefrontal cortex exerts an inhibitory effect on the HPA axis, as well as on the amygdala, creating a down regulating effect. Thus, lesions to the prefrontal cortex not only reduce inhibitory effects on the HPA, but also free the amygdala to promote effects, thus increasing sympathetic activation. In all three cases, the ultimate response is some form of general failure to inhibit the HPA axis, which may ultimately contribute to the amount and circulation of cortisol that remains bioavailable.

With regard to the effects of these alterations on the development and maintenance of PTSD, each structure also appears to have a corresponding expression that is observable in PTSD. Though not always explicitly connected in the literature, fairly clear relationships appear to exist. As shown above, impairment of the hippocampal functioning results in poorer anxiety coping, leaving the individual with continuously increased anxiety response as well as memory deficits. Meanwhile, the amygdalar response bias toward negatively-charged emotional content following increased cortisol exposure map on to PTSD symptoms related to restricted range of emotions, irritability, and dysphoria. Furthermore, increased influence of the amygdala on autonomic function, as a result of exaggerated activity related to cortisol exposure, may also be related to hyperarousal symptoms experienced by individuals with PTSD. The amygdala is also related to the extinction of aversive reactions to traumatic and stressful memories. When this process is impaired there is disruption in the ability to extinguish conditional fear learning, which may relate to the frequency of recurrent, unwanted memories of traumatic events, as well as nightmares and other re-experiencing symptoms in PTSD. The prefrontal cortex has been shown to work closely with the amygdala and provide higher order functions that influence emotional content and mediate the appraisal of complex conditional learning paradigms. Together with the amygdala, reduced volume in prefrontal cortical tissue may aid in the overall restriction of positive emotions, social withdrawal and avoidance, irritability, and concentration difficulties experienced in PTSD, as well as difficulty extinguishing more complex, conditioned fear and anxiety following trauma.

One of the issues experienced during the present literature review was the need to interpret some results cautiously due to methodological flaws or limitations, or small sample sizes, which lack sufficient statistical power to establish reliable relationships between variables. Aside from quality issues and generalizability limitations, although a body of literature does exist, there is a surprisingly limited amount of translational research between psychology and neuroscience. Although the two fields have begun to cross-collaborate over the last decade, a great deal more work needs to be done with regard to examining the behavioral implications (like those expressed in PTSD) in the context of these complex neural systems. More collaborative research will not only advance the science and bridge the gaps between basic science and clinical practice, but also begin to provide reliable models of psychological reactions to specific alterations in neural systems.

While this may not happen in the immediate future, the clinical implications of such research might include more effective medications and better informed psychological interventions. Moreover, understanding the neural reactions to stressful events, both in the immediate aftermath and the long-term, would provide invaluable information regarding the development of preventative interventions that may allow us to minimize or eliminate the chances of developing a psychological disorder. In particular, given the findings reviewed herein, it is clear that an increased bioavailability of cortisol has a number of short and long-term deleterious

effects on the overall function of the stress response. Indeed, there is sufficient evidence to conclude that such prolonged exposure to cortisol serves to promote the development of PTSD. However, much more work is needed, particularly in human samples, and future research must consider not only cortisol, but the mechanisms involved in its regulation (e.g., enzymatic degradation to reduce the unchecked bioavailability of the hormone). Additionally, due to evidence that individuals with PTSD exhibit deficiencies that slow the body's ability to breakdown and pass cortisol, it is clear that examining urinary hormone levels will not yield reliable data. For this reason, researchers in this area will need to expand their training or collaborate with qualified individuals who can perform CSF sample extractions in order to glean more reliable comparisons. Such data may help to inform short-term interventions to improve prognosis. For example, if it is found that enzymatic deficiencies play a role in the chronicity of PTSD, perhaps pharmacological interventions (to improve cortisol degradation) may be developed to either reduce the chance of developing PTSD in the aftermath of trauma, or at least curb the impact prolonged cortisol exposure would have on the brain, thus making psychological interventions more effective.

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