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Post-Traumatic Stress Disorder: Symptoms and its Relationship to Corticosteroid Dysregulation

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Abstract of the Thesis

Post-Traumatic Stress Disorder: symptoms and its relationship to Corticosteroid Dysregulation

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Stress is the subjective experience of encountering or being affected by psychological or physical threats. Depending on the situation and the individual's ability to adapt to the particular event will affect how the individual continues to function. Memory can be both adaptive and maladaptive to the individual recovering from the stress of the event. It is known that part of successful adaptation is remembering the important events of a trauma in order to better decide how to react in possible, similar future events. However, certain individuals can develop Post traumatic Stress disorder (PTSD) as a response to an event. PTSD develops after exposure to a traumatic event and sufferers experience symptoms such as flashbacks of the trauma, hyper-arousal, poor concentration, and difficulty recalling explicit memories of the traumatic event. The question becomes why do these individuals develop PTSD while others do not. To understand how the stress response of PTSD sufferers differed from the stress response of individuals who do not have the disorder I first researched the typical role of the hormones which are involved in the human stress response: the corticosteroids (both the mineralocorticoids and the glucocorticoids), and norepinephrine. Through my initial research I found a large body of literature devoted to experimental treatments of PTSD with corticosteroids. This led me to further study why corticosteroid treatments could be effective and how corticosteroid dysregulation could relate to PTSD. Additionally some research was done on current and experimental treatments for PTSD.

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List of Abbreviations

Post-Traumatic Stress Disorder - PTSD

Norepinephrine/Noradrenline - NE

Basolateral nucleus of the amygdala – BLA

Hypothalamic Pituitary Adrenal Axis – HPA

Mineralocorticoid receptor - MR

Glucocorticoid Receptor – GR

Prefrontal Cortex – PFC

miniature excitatory synaptic current - mEPSC

locus coeruleus – LC

Cortisol and Corticosterone - CORT

Emergency Room – ER

Sympathetic Nervous System - SNS

Clinical Administered PTSD Scale - CAPS

Cerebrospinal fluid - CSF

Medial Prefrontal Cotex – mPFC

Adrenocorticotropic Hormone - ACTH

Intra-cerebroventricuar - ICV

Inhibitory Avoidance (IA)

Noradrenaline transporter (NET)

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I Introduction

It is not currently understood why some individuals can experience a traumatic event and continue to adapt while others experience an event but develop PTSD. According to NIMH, the rate of PTSD among adults in America is 3.5%, which is about 10 million individuals with about 30% of these individuals having severe cases of the disorder. However, current treatments rarely exceed a 60% rate of success and fewer than 20-30% of patients achieve full remission (9). Since research has shown that administering corticosteroids to patients suffering from PTSD has some efficacy and may play a key role in treating the disorder. This paper will focus on the hormones noradrenaline and the corticosteroids (both mineralocorticoids and glucocorticoids) and their relationship to the symptoms of PTSD. My goal in this paper is to discuss the current symptoms seen in PTSD patients, the typical stress hormone response, how it differs in PTSD patients, and finally a discussion of treatments and current limitations in PTSD research.

II Normal Human Stress Response

Emotionally arousing experiences, such as traumatic events will induce the release of stress hormones such as epinephrine, norepinephrine and the corticosteroids. It is known that epinephrine does not directly affect brain activity as it does not pass the blood brain barrier, rather the effects are mediated by stimulation of B-adrenoreceptors located on the ascending vagus nerve that projects to the brain stem(2). Noradrenaline seems to be the primary hormone needed for remembering emotionally arousing events. Noradrenaline or norepinephrine is a catecholamine that is produced in the locus coeruleus (LC) and the brain stem. It is derived from dopamine and can be enzymatically converted to adrenaline (5). It acts through G-protein coupled membrane receptors that upon activation can rapidly change neuronal function(5). However activity is also rapidly terminated when noradrenaline levels drop (5). Interventional imaging studies blocking B-adrenoreceptors or enhancing noradrenaline activity pharmacologically have also confirmed that this emotional memory effect observed in the amygdala is controlled by noradrenergic activity and availability (5). The presence of noradrenaline is important for the facilitation of emotional memory in rodents; one study showed that noradrenaline positively correlated with retention latencies tested 24 hours after a test and that post-training infusions of B-adrenoceptor agonists into the Basolateral nucleus of the amygdala (BLA) produce a dose-dependent enhancement of memory consolidation (5). It is believed that noradrenaline primarily promotes the formation of stress related emotional memories via activation of basolateral amygdala while corticosteroids play a role as both facilitators and suppressors of noradrenaline mediated activation depending on timing (5).

Work by multiple scientists has shown that the BLA is essential for the formation of emotional memory and is associated with the release of noradrenaline and corticosteroids (5).

The normal fear response for an individual is characterized by a series of biological actions that allow the body to cope with stress. This involves activation of the sympathetic nervous system (SNS) and the hypothalamic pituitary adrenal axis (HPA) which working together, culminates in the release of the corticosteroids such as cortisol which helps contain the stress response once the threat or stressful stimulus is removed (15). So while noradrenaline may be the initial hormone which leads the body's response to a stressful response, the corticosteroids are there to modulate that stress response and eventually return the system to normal (1). The corticosteroid hormones are steroids that are produced in the cortex of the adrenal glands. Corticosteroids such as cortisol and the glucocorticoids are lipophilic and readily enter the brain when released or administered peripherally (2). They can then bind to the mineralocorticoid receptors (MR) and the glucocorticoid receptors (GR) (1). These corticosteroids will then bind the receptor and translocate to the nucleus where they bind either as dimers to recognition sites on DNA or use protein-protein interactions to influence other transcription factors to interact with DNA (5). These corticosteroids also have a faster, non-genomic way of changing neuronal cell function (5). Corticosteroids will normalize BLA neurons after they have been excited by noradrenaline (5).Elevated cortisol levels will exert a negative feedback loop which allows hormone levels to return to basal levels after they have been elevated, in the pituitary, hippocampus and amygdala which occurs because these structures contain glucocorticoid receptors (15).

III How the glucocorticoid and mineralocorticoid receptors relate to the stress

There are two corticosteroid receptors in the brain, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) (10). It is known that GR and MR differ in ligand affinity and distribution throughout the brain they are abundantly expressed and co-localized in neurons from several areas of the limbic system including the hippocampus, the amygdala and the PFC (10). Of the two MR has a 10 fold higher affinity for the corticosteroids compared to GR, but when corticosteroid levels rise, such as during stress, the GRs will be recruited and will bind the corticosteroids (10). GRs require stress levels of corticosteroids to translocate to the nucleus, so even though they are more widespread in the brain they are less frequently activated than MRs (5). Instead their actions exert complementary effects in coping with the stressor; the MR is important for the maintenance of neuronal integrity and stability in the face of the stress response as is shown after adrenalectomies wherein patients show increased apoptosis in the hippocampal dentate gyrus which can be restored

if exogenous corticosteroids are added in order to activate the MR (10). The GR prevents the initial stress reaction and facilitates recovery through promotion of energy metabolism (10). GR, in cooperation with amine and neuropeptide signals facilitate encoding of the experience while incoming information that is not relevant to the current situation is suppressed (10). Glucocorticoids work through Glucocorticoid receptors (GRs) which are activated when glucocorticoids bind to them; they are activated only during emotional arousal and can affect gene transcription directly by binding as homodimers to DNA (2). MR and GR act as ligand inducible transcription factors; they interact as dimers with the transcription machinery but do not modulate the same or similar events (10).

IV Hypotheses on the relationship of glucocorticoid and mineralocorticoid receptor dysregulation and disease state

The question of what makes some individuals more prone to stress than others has inevitably lead researches to consider possible genetic or epigenetic susceptibility to PTSD and stress in general. It is already understood that glucocorticoid hormones and receptors play an important role in the stress coping response (10). Current data shows that there may be epigenetic, genetic or other environmental influences which can cause glucocorticoid alterations that can then increase the likelihood of developing PTSD from a traumatic exposure (15).

It is not understood what causes this dysregulation in glucocorticoid actions which can cause them to change from helpful to harmful hormones. There are currently four hypotheses which are not mutually exclusive and that explain how problems with glucocorticoid and mineralocorticoid receptors can lead to a disease state. The first hypothesis is the the glucocorticoid cascade hypothesis. This states that the inability to cope with chronic stress cause a vicious cycle of excess glucocorticoids and down regulation of glucocorticoid receptors (GR) in the hippocampus (10). The second hypothesis is the balance hypothesis which states that the integral limbic MR:GR imbalance is causal to altered processing of information in circuits underlying fear (10). According to this hypothesis, a balance of MR:GR receptors leads to containment of initial stress reactions while an imbalance would make an individual more vulnerable to stress(10). Third is the maternal mediation hypothesis which states that the potent epigenetic stimulus of the maternal environment combines genes and environment lead to susceptibility to stress and anxiety disorders such as PTSD (10). Finally, the predictive adaptation hypothesis states that epigenetic effects due to early life stress can make an individual more resilient to adversity later in life.

Appreciation for the balance hypothesis requires knowledge of how MRs and GRs respond to stress hormones. The MR:GR balance operates in time through activation of the membrane MR by rising levels of CORT (cortisol and corticosterone) which act to amplify initial stress reaction in a feed-forward fashion (10).The containment of the initial stress reactions occur via membrane and genomic GR-mediated feedback while the processing and storage of the stressful event occurs (10). The MR:GR balance is thought to be altered by gene variants of these receptor complexes and experience related factors (10). If the control of the initial reaction as well as the management of the later adaptive phase becomes imbalanced, then critical neurotransmitters may change their patterns which in turn will enhance the individual's vulnerability to affective disorders such as PTSD (10). Gene variants of MR and GR have been identified and these variants have an impact on receptor function and stress response. Also, the GR is subject to enduring epigenetic changes in response to early life experiences (10). However, efforts to find a specific gene for PTSD have so far been unsuccessful; no association was found between two GR polymorphisms N363S and BclI and the diagnosis of PTSD, though PTSD patients with BclI GG genotype tended to be more responsive to a peripheral test of glucocorticoid sensitivity and displayed more severe PTSD symptoms (15). This knowledge of epigenetic changes is not only useful in explaining the balance hypothesis; it is also relevant to the Maternal mediation hypothesis. It is already accepted that early life adversities such as maternal distress, loss of a parent, exposure to maltreatment and violence are risk factors for multiple psychiatric diseases (10). Thus it seems rational that early life adversities may play a role in chronic stress levels and the adverse effects of high levels of stress and glucocorticoid imbalance. Animal models of enhanced maternal care have been shown to program for resilience while poor maternal care appears to program vulnerability to stress later in life (10). Studies done on newborn rodents showed that they were hyporesponsive to stress in the first two weeks of life; this is attributed to the presence of the mother rat (10). This was shown in one study by Oitzel et al (2009) in which rat pups were separated from their mother for 24h. In pups that were separated from their mother for more than 8h their hypo-responsive stress phase was disrupted and the pups became more responsive to mild stressors (10).

However, the last hypothesis, the predictive adaptation hypothesis, would suggest that the higher stress levels seen in maternally deprived mice was due to the mouse not "matching" the environment (10). In the predictive adaptation hypothesis the individual is believed to be least stressed when she is in an environment that she is used to and feels that she understands and is most stressed in a novel environment. Thus if an individual spends her early life in a very stressful

environment she will feel more normal if she continues to live in a stressful environment and would only become stressed when placed in an environment that has little or no stress. It is known that the inter-individual differences in coping with stress depend on the secretion and action of stress hormones which are largely shaped by the environment (10). Growing evidence shows that the epigenetic effects can be associated with resilience in individuals who were exposed to adversity in early life (10).

V Conflicting Findings in the Relationship of Norepinephrine and Cortisol levels, heart rate, and PTSD in a Clinical Setting

It was previously believed that PTSD was a very common disorder that could happen to anyone who experienced an extremely traumatic event. But as research continues to be done it is now more widely believed that the stressful events that can lead to PTSD are actually more common than previously believed. However only a minority of persons exposed to trauma failed to recover from initial fear reactions and move on to develop PTSD (15). The occurrence of PTSD has been equated with an abnormal acquisition or insufficient extinction of a conditioned fear response (11). Stress hormones modulate this acquisition and extinction process (11). Evidence of abnormal HPA axis functioning in PTSD comes from findings of lower resting levels of circulating cortisol and from constant evidence of heightened HPA response to challenge tests in chronic PTSD patients (11). In Shalev et al's (2008) study * adult survivors of traumatic events who were admitted to the emergency room (ER) had samples of plasma, saliva and urine taken for hormonal assays taken and underwent a CAPS test 5 months later to see if they had developed PTSD , individuals who already had PTSD were excluded from the study. Plasma levels and urinary excretion of Norepinephrine were measured in 155 survivors of traumatic events at 10days, 1 month and 5 months later (12). Though no difference was seen between PTSD and nonPTSD patients in plasma norepinephrine levels, the PTSD group had significantly lower levels of plasma Norepinephrine at 10 days, 1 month and 5 months (12). This observation is at odds with a previous study which described a positive correlation between initial urinary levels of norepinephrine, epinephrine and dopamine and acute PTSD symptoms in children (12). However, cortisol levels of individuals with and without PTSD did not show differences in plasma and salivary cortisol levels (11).

There was a weak correlation between the norepinephrine concentration in the Emergency Room (ER) and the concurrent heart rate of the patient; patients with an increased heart rate shortly after exposure to trauma developed PTSD (10). In this study, there was also a weak positive correlation between increased heart rate shortly after the exposure to the trauma and subsequent

PTSD development, but it did not appear to be significant (12). This is unusual as previous studies have shown a much stronger correlation between heart rate increase, possibly as a result of an increased adrenergic response, and PTSD development (12). Shalev et al (2008) argued that the unusual results of this study were possibly due to differences amongst civilian individuals; even the traumatic events were dissimilar, of the individuals who participated the traumatic events for this test were 125 traffic accident, 19 terror attacks and 11 listed as 'other' (12). Also, the scientists admitted that multiple hormones and processes were involved as PTSD is a complex disorder and the participants in the study were operating under conditions that were kept minimally stressful (12). Perhaps levels of cortisol and norepinephrine would have shown different results if patients had been under stressful conditions. Also, a previous study found elevated basement norepinephrine level in the cerebrospinal fluid (CSF) of combat veterans but no difference in plasma norepinephrine; since the plasma half life of norepinephrine is on is only a few minutes the study's results might not be an accurate reflection of the adrenergic response (12). Perhaps norepinephrine is already being localized in the brain by the time the patients arrived in the emergency room (12).

VI Relationship between Lower Cortisol Levels and Increased PTSD Symptom Severity

Since cortisol is necessary to return the body to homeostasis after the stressful event has ended it could be hypothesized that lower levels of cortisol which are present in PTSD patients simply do not rise to the level necessary to end the stress response. It is known that there is greater sympathetic nervous system (SNS) arousal as seen by catecholamine levels and increased heart rate in individuals with PTSD (15). If there is insufficient cortisol signaling then the catecholamine-induced arousal from the traumatic event might be prolonged and distress increased (15). That lower cortisol levels reflect PTSD risk is also supported by studies of Holocaust offspring wherein lower cortisol levels in the offspring were observed in association with parental PTSD (15). Also, urinary cortisol levels were negatively correlated with the severity of the parent's PTSD symptoms (15). Further evidence was found in salivary cortisol samples from offspring of mother's who had been exposed to the world trade center attacks on 9/11 wherein offspring of mothers who developed PTSD due to the event showed lower cortisol levels when compared to offspring of mothers who didn't develop PTSD (15). Further genetic evidence lies in the fact that trauma survivors show higher prevalence of PTSD if they had a twin who also had PTSD compared to those whose twin did not have PTSD. In addition, PTSD after trauma exposure is higher in monozygotic twins than dizygotic twins (15). Further evidence for the role of cortisol in PTSD was shown in one study in which patients who responded to psychotherapy showed increases in cortisol levels

compared to the cortisol levels pretreatment; non-responders to the treatment continued to show lower cortisol levels (15). This is particularly interesting because few treatment studies have bothered to incorporate glucocorticoid alterations before and after treatment (15). When administered as an intravenous bolus (17.5mg) hydrocortisone produced a greater decrease in corticotrophin (ACTH) in combat veterans with PTSD compared to combat veterans without PTSD, this finding suggests an exaggerated negative feedback of the GR (15). Of particular interest is the observation that the positive effects of glucocorticoids on PTSD symptoms was found when patients were given cortisone (a type of glucocorticoid) for the treatment of septic shock these patients were significantly less likely to develop PTSD (4). Further randomized testing was done to confirm this phenomenon and it was shown that glucocorticoids d reduce the likelihood of PTSD(15). These results suggest that it decreased the traumatizing effects of the memory of the event. Patients with PTSD tend to demonstrate a lower 24 hour urinary cortisol excretion level compared to healthy individuals, as well as individuals with different psychiatric disorders (15). Surprisingly, the profile of the PTSD patient, in which the plasma cortisol levels are low and the CRH levels are high compared to healthy individuals is that this profile also differs from the profile of individuals with chronic and acute stress and those with depression (15). However, the adrenal gland is still functional and able to produce cortisol in response to stress as seen from hormonal responses to naturalistic and laboratory provocations (15). Since PTSD may be due in part to low cortisol levels, it would be prudent to treat a PTSD patient with cortisol since this could offset the low endogenous quantities of cortisol so that the HPA axis could still function (15). It was shown in a rat study wherein the rats were exposed to a single prolonged stress that administration of a glucocorticoid antagonist prior to the stress exposure prevented the normally observed potentiation of fear conditioning in the amygdala and impaired long term potentiation in the hippocampus (15). Inactivating GRs in the amygdala post-retrieval similarly blocked processing the traumatic memory (15).

Some scientists hypothesize that the PTSD risk is related to enduring pre-traumatic changes that are not based on genetic polymorphisms but rather on differences in genes related to epigenetic alterations (15). There is now strong evidence that some features of glucocorticoid alterations in PTSD may be altered prior to trauma exposure, but the implications of this for understanding PTSD isn't clear (15). It is also hypothesized that PTSD may also be a dynamic disorder with symptom severity reaching high and low points depending on a wide range of factors generally associated with concurrent environmental stressors (15). Also, a recent longitudinal study of Holocaust survivors demonstrated that those whose PTSD symptoms were present and remained relatively

unchanged over a 10 year period had cortisol levels that were highly correlated at the Time 1 and Time 2 of the study; meanwhile, individuals who recovered from PTSD by Time 2 but had the disorder at Time 1 showed increased cortisol levels (15). The fact that individuals with PTSD at both time points had cortisol levels were relatively unchanged while individuals who recovered from PTSD by the second time point showed increases in cortisol levels clearly shows that cortisol levels are important in PTSD's etiology. Furthermore, since there were individuals who had the disease at Time 1 but not at Time 2 and some who did not have the disorder at Time 1 but developed it before Time 2; it seems that PTSD is not a stable disorder. If some people can recover while others take longer to succumb then there are clear implications that the disorder may be continually affected by different variables such as environmental stimuli.

VII Morphological Brain Abnormalities and their possible Role in PTSD

PTSD is a disorder that is diagnosed based on specific behavioral characteristics such as: hyperarousal, difficulty recalling explicit memories of the traumatic event, and flashbacks of the trauma, including nightmares. Based on current knowledge of neuro-circuitry it has been postulated that there should be abnormalities in the amygdala, the anterior cingulate, the medial prefrontal cortex (mPFC) and the hippocampus (3). Brain abnormalities are seen in various mental illnesses for instance, the amygdala becomes hyperactive in PTSD and depressive illness and hypertrophy of the amygdala nerve cells is reported after repeated stress in animal models; dendritic remodeling and suppression of neurogenesis also occurs in models of repeated stress in rodents (7). It is known that the hippocampus expresses adrenal steroid receptors and that it undergoes atrophy in several psychiatric disorders; this atrophy of the hippocampus is a common process that simply reflects an imbalance in the activity of the HPA axis (7). It is not known why an individual's body would not turn stress mediators off, one possible cause is elevation of amygdala activity which can occur with amygdala hypertrophy; since the amygdala is involved in fear processing its over-activation could be a first step in overwhelming the brain's physiologic attempts to cope with stress (7). Dysfunction of the hippocampus can then lead to elevated cortisol levels in the aftermath of the stress and an inability to associate context with stress so the individual has trouble discriminating between dangerous and safe situations (7). Damage to the brain can occur in stroke and seizures and is caused by excessive excitatory amino acids aided by glucocorticoids (7). But these glucocorticoids are not acting alone and their effects can be blocked by agents that interfere with glutamate and serotonin actions. The hippocampus is also known to play a role in shutting off the HPA stress

response and research shows that damage or atrophy of the hippocampus leads to a more prolonged HPA response to physiological stressors (8).

However, earlier imaging studies did not find evidence for accelerated hippocampal volume changes in PTSD over 6 months following the traumatic event (3). Cardenas et al (2011) attempted to determine whether chronic PTSD was associated with brain tissue loss by using deformation morphometry, a technique that is sensitive to detection of disease effects, on brain MRIs. In this study clinical psychologists first determined whether or not the subject met DSM-IV criteria, then MRIs were taken at baseline and again after at least 24 months (3). Individuals were tested again for PTSD at the time of the second MRI in order to categorize subjects into four categories: control, non-improvers (individuals whose symptoms remained unchanged or got worse), mild improvers (individuals whose symptoms were slightly less severe) and improvers (show much less severe PTSD symptoms)(1). The partitioning of subjects into three groups was due to the heterogeneous among patients such that classifying them all together would have yielded clinically insignificant results (3). The ongoing atrophy in patients with PTSD who had not improved was significantly greater than in the control group in many areas including the brain stem, the frontal WM, the subcortical structures and the anterior cingulated and faster rates of atrophy in the frontal lobe were associated with larger longitudinal increases in the CAPS scores (worsening symptoms) (3). For patients with PTSD who were improvers, their brain volume only differed from the controls brain volume in the supramarginal gyrus, a sensory association area implicated in visuo-spatial processing and response to threat (3). Cardenas et al (2011) did not see greater rates of atrophy in the hippocampus or the amygdala in subjects with PTSD versus those who did not and the question was raised as to whether hippocampus loss in PTSD patients might predate the traumatic exposure. Thus, a smaller hippocampus might be a sign of greater susceptibility to PTSD rather than a result of it. It would be interesting to see how the presence of a smaller hippocampus affects the amount of GRs and MRs. Since lowers amounts of these receptors may affect corticosteroid binding and therefore shutdown the stress response.

VIII Use of MRIs to measure changes in the Brain due to PTSD

It is known that different areas are activated when the brain is stimulated in patients with PTSD but findings have been inconsistent; the medial prefrontal cortex (mPFC) which is implicated in PTSD has been reported to show decreased, increased, and no activation in various studies(16). This may be due to the different cognitive demands of each study (16). The purpose of Yin et al's (2011) study was to measure the intrinsic functional baseline by using the ALFF (amplitude of low frequency

(0.01-0.08Hz) fluctuation) BOLD MRIs to see the spontaneous brain activity during the resting state in PTSD (16). The analysts studied 72 patients with PTSD and 86 traumatized volunteers without the disorder; all of the subjects had been exposed to the earthquake in Sichuan Province (16). Since it is not currently clear if the particular trauma that led to PTSD effects brain function or hormone balance, it is not clear if these results can be extrapolated to patients who developed PTSD from combat or vehicle accidents. PTSD patients showed decreased ALFF in the right insula, the visual cortex and the cerebellum and greater ALFF in the right medial frontal gyrus, right frontal lobe and middle frontal gyrus (16). The insula is thought to play a role in cognition and its activation has been correlated with encoding retrieval in episodic memory and complex verbal memory tasks in healthy subjects (16). Since memory deficits in PTSD patients have been noted in multiple studies and patients this result is not surprising. The mPFC has been implicated in processing of emotional arousal and anxiety and PTSD subjects were shown to exhibit increased cerebral blood flow in the mPFC compared to normal volunteers (16). Another study found heightened activity in the mPFC of combat veterans with PTSD compared to traumatized controls, particularly when visualizing traumatic events; the author of that paper argued that mPFC activation was associated with generating mental imagery of combat related pictures (16). Also, a correlation analysis linked ALFF values in mPFC to symptom severity of PTSD, such that higher ALFF values in the mPFC were found in the more severely symptomatic PTSD patients. In a previous study activation of mPFC was correlated with anxiety as seen when yohimbine was injected into healthy subjects; thus it is possible that activation of the mPFC is associated with subjective stress levels (16). Also interesting is that all altered ALFF values were localized to the right side in subjects with PTSD (16). Other studies reported that right side predominance may be associated with predominant nonverbal memory of traumatic event along with poor verbal performance in PTSD subjects (16).

IX Potential Treatment Therapies

PTSD causes alterations in glucocorticoid secretion and critically involves the limbic system, especially the amygdala (13). Symptoms of PTSD are thought to manifest themselves as classical conditioning of fear in animals and recurs each time trauma related cues remind a subject of the trauma (13). Using an animal model, Tronel et al (2007) showed that a traumatic memory is persistently disrupted if immediately after its retrieval glucocorticoid receptors are inactivated in the amygdala; this disruption of memory is long lasting and memory retention does not reemerge following strong reminders of conditioned fear. In this study, fear conditioning was induced by pairing a neutral stimuli (conditioned stimuli) with a fear inducing stimulus, foot-shock

(unconditioned stimulus)(13). These fear conditioned animals responded with fearful behavior and an abnormal glucocorticoid response; like these animals humans with PTSD also manifest abnormalities in their glucocorticoid systems and have increased startle response and enhanced autonomic nervous system response (13). In animals and humans the process of recalling a memory can transiently revert the stable state of memory into a labile one; so established memories can become sensitive to disruption (13). Previous studies have shown that pharmacological agents can disrupt fear memory reconsolidation if applied immediately after memory reactivation (13). For instance, a previous study used Intra-cerebroventricuar (ICV) infusions of a GR antagonist called RU38486 and administered the drug before or after training in a water maze and found that the was impairment of retention but not acquisition (13). In Tronel et al's (2007) study it was decided that if a rat hesitated to enter the shock chamber after having been exposed to a shock in that chamber 48 hours ago, this was a sign of fear acquisition (13). All the rats had canulla implants targeting which targeted the amygdala; these rodents received bilateral injection of RU38486 or just a vehicle solution (11). The result was dose dependent inhibition of fear in cases where the GR antagonist RU38486 was injected into the BLA following reactivation of the traumatic memory (13). RU38486 blocks reconsolidation and persistently disrupts memory which is not recovered even with subsequent reminders (an object or area that the rodent would otherwise associate with the trauma). The amnesia which results from the drug has long lasting and robust effects which are observed 1 week after treatment and animals remain insensitive to reminders that could otherwise reinstate extinguished fear in normal animals (13). Furthermore, RU38486 has been given to depressive patients and those with bipolar disorder and shown to be safe, though it is still unclear how effective this drug would be (13). The rats in this study had the drug infused straight into their brains but this seems to be a dangerous thing to do with human patients undergoing therapy for PTSD. Furthermore RU38486 has been shown to poorly cross the blood brain barrier so large quantities of the drug may need to be taken for an effect to be seen (13).

The cardinal symptom of PTSD is re-experiencing the traumatic event through intrusive memories and nightmares (14). These memories are thought to develop through classical fear conditioning. In rodents established memories, including fear conditioning, can be disrupted if interfering events or pharmacological treatments are presented or administered in a timely fashion following their retrieval (14). But to do so it is critical to know time course and dosage parameters to permit most powerful disruption or traumatic memory reconsolidation (14). For instance, pharmacologic treatment with RU38486, if applied in the absence of memory reactivation, produces

no effect on memory retention and does not disrupt the traumatic memories (14). Rather, previous studies have suggested that there is a time window of susceptibility to disruption is limited to only a few hours following reactivation; so drugs should be administered soon after re-experiencing session (12). Rats who were trained in inhibitory avoidance (IA) and 1 week later underwent 2 consecutive treatments with 30mg/kg RU38486 following memory reactivation separated by24 hours showed significant disruption of the traumatic memory but not other memories (14). It is known that in IA training RU 38486 disrupts reconsolidation of established memory only after the memory is reactivated; there is a significant difference between RU38486 injected in the absence of reactivation compared to ones who underwent reactivation (14). In Taubenfeld et al. (2009) study rats were trained in an inhibitory avoidance task wherein they were given foot shocks of either 0.9mA or 1.2mA. Rats trained in IA with 0.9mA and treated with RU38486 showed significant reduction in IA retention compared to vehicle injected controls though this was not observed in rats exposed to 1.2mA(14). It is not clear if the memory was too intense to be effected or if there was a ceiling effect which hid Ru38486's effect (14). For 0.9mA Taubenfeld et al. (2009) study it was seen that 1-2 treatments of RU38486 were sufficient to maximally disrupt a traumatic memory. It should be noted that RU38486 weakens the memory but does not cause amnesia (14).In rodents fear is defined operationally as a cessation of all bodily movements except those required for respiration (freezing), and increase in the amplitude of an acoustically elicited startle response (potentiated startle), an increase in blood pressure, changes in respiration, emission of distress calls, avoidance of place where shock occurred (14). However, these are not the symptoms that are used to define PTSD in humans which are flashbacks of the trauma, hyper-arousal, poor concentration, and difficulty recalling explicit memories of the traumatic event. Questions then arise about how effective it is to extrapolate data from rodent fear studies to human PTSD studies. As is the case with all animal studies it is worth noting that while the drug may remove obvious symptoms of the disorder from the animal, this does not mean it will remove symptoms from the human.

X Current Treatment options for PTSD sufferers and their Limitations

Certain medications such as selective serotonin re-uptake inhibitors are considered first line treatment for adult PTSD; but seratraline, the only FDA approved antidepressant to treat PTSD, has a remission rate of 25% (6). Furthermore, residual symptoms after treatment are more the rule than the exception; and to make matters worse, there is concern that chronicity leads to progressive treatment resistance (6). The longer a patient suffers from PTSD the harder it will be to effectively treat the disorder. There is evidence that noradrenaline activity in the cell bodies of the Locus

Coerulus and projections to the amygdala, hippocampus, and Prefrontal cortex are thought to be important in fear and stress responses and that abnormal regulation of brain NE exists in PTSD (6). Chronic depolarization of sympathetic neurons induces the NE transporter (NET) expression through increasing dopamine and NE (6). Antidepressant drugs that block NET have shown efficacy in stress associated mood and anxiety disorders (6). In the LC chronic stress leads to a reduction of NET availability which may result in exaggerated synaptic availability of NE in projection areas (6). There is tremendous genetic and phenotypic heterogeneity in PTSD and a lack of biological markers which makes it difficult to guide drug development (6).

XI Conclusions

The problems with studying PTSD are numerous and include the existence of a heterogenous population of individuals with the disorder. No "PTSD gene" has been found yet, suggesting that PTSD is not caused by a single genetic susceptibility but is more likely due to a wide array of genetic predispositions as well as environmental factors. Physiologic expressions of PTSD are also complicated and sometimes contradictory. Research is further complicated by the animal models used. PTSD is considered separate from a generalized anxiety disorder and while individuals with PTSD may exhibit avoidance behaviors of areas where trauma occurred there is some question of whether a mouse model can adequately capture the etiology of the disorder based on whether or not fear conditioning is successful. Questions quickly arise as to whether a complex psychiatric disorder can be mimicked in mice and whether it is valid to suggest that a drug which can cause extinction in a mouse's fear response will be effective in treating a human's PTSD symptoms. However, even though confounding variables are present there is clear evidence that cortisol levels indirectly correlate with PTSD symptom severity, where lower levels of cortisol being associated with more severe PTSD symptoms. The corticosteroids are clearly involved in PTSD symptomology and patients might benefit from more research into the efficacy of administering exogenous cortisol or one of the other corticosteroids.

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