Bremner JD: Effects of traumatic stress on brain structure and function: Relevance to early responses to trauma. *J Trauma Dissociation* 2005; 6(2):51-68.

For: "Early Responses to Trauma"
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Abstract

The events of 9/11 and the widening impact of psychological trauma today have raised a higher level of awareness about the potentially deleterious effects of psychological trauma on the individual. One area of interest after 9/11 was the early trauma response and the most effective way to deal with window of time immediately after traumatization in order to prevent long term psychopathology. Understanding the neurobiology of the acute trauma response may be useful in designing prevention and treatment strategies. Studies in animals and humans have shown that biological stress response systems, including norepinephrine and cortisol, are affected in both the acute and chronic stages of the trauma response. Brain areas involved in memory, including the hippocampus, amygdala, and prefrontal cortex, may be areas of intervention in the early trauma response. Due to the difficulty of performing research in this time period, most research to date has been in patients with chronic disorders, such as chronic posttraumatic stress disorder (PTSD). Only a few treatment studies have been performed in the early trauma period, and more research in this area is needed.

Acute and Chronic Responses to Psychological Trauma

The psychological consequences of acute psychological trauma have long been recognized. In World War I syndromes of “traumatic neurosis” and “shell shock” were initially described. Soldiers were noted to forget their name or where they were on the battlefield, they also developed hyperarousal and extreme fear with reminders of the trauma (Saigh & Bremner, 1999a). Over the course of the 20th Century, diagnostic conceptualizations have changed, so that while in earlier versions of the Diagnostic and Statistical Manual (DSM) (the American Psychiatric Association’s guide for diagnostic criteria) Gross Stress Reaction was conceived as a temporary response, by the time of the inclusion of posttraumatic stress disorder (PTSD) in the DSM in 1980, the effects of stress were felt to be long-lasting in a subgroup of patients. Since the time when PTSD was first officially recognized, there has been increased awareness of the potentially debilitating effects of traumatic stress, that has recently culminated in the widespread recognition and awareness of the possible long-term effects of the attack on the World Trade Center on the U. S. society at large. In spite of the chilling images and heart-rending stories of the victims and the survivors of the WTC attack, little is currently known about the acute and chronic effects of these types of traumatic stressors. Studies performed in other populations, such as abuse survivors and combat veterans, may provide some insight into the potential long-term consequences of traumatic stress, and help to guide future research on the acute effects of trauma.

Posttraumatic stress disorder (PTSD) is characterized by specific symptoms that develop following exposure to a "threat to the life of oneself or others accompanied by intense fear, horror, or helplessness" (APA, 2000). Symptoms of PTSD include intrusions (intrusive memories, flashbacks, feeling worse with reminders of the trauma, nightmares), avoidance (avoidance of thinking about the event, avoidance of reminders, decreased concentration, amnesia, feeling cut off from others, sense of foreshortened future) and hyperarousal (increased startle, hyperarousal, hypervigilance, decreased sleep). Although earlier versions of DSM had acute and chronic PTSD, the last version of the DSM only included PTSD with a requirement of two months duration of symptoms. About 30% of e.g. Vietnam combat veterans will meet criteria for PTSD early after exposure to trauma, however this goes on to chronic PTSD in about half (15%) of those patients (Kulka et al., 1990). There is some evidence that early interventions can prevent the development of chronic PTSD. On a biological level, early modifications while memories are being consolidated are felt to be most useful, before the memories become strongly engraved and indelible to further intervention.

Other psychiatric disorders are associated with trauma exposure, including depression, anxiety, dissociative disorders, eating disorders, alcohol and substance abuse. Acute Stress Disorder captures the early aftermath (first month) after trauma exposure and includes symptoms of both PTSD and dissociation. There is considerable overlap or “comorbidity” in trauma patients with these diagnoses. Bremner (Bremner, 2002) has argued that these disorders should be considered as part of a *trauma spectrum* of psychiatric disorders, all sharing in common a stress-induced alteration in brain circuits and systems. This paper reviews alterations in brain structure and function following trauma in the context of understanding early responses to trauma. More comprehensive reviews of PTSD in general (Saigh & Bremner, 1999b) and the neurobiology of stress and PTSD have been more comprehensively reviewed elsewhere (Bremner, 2002; Bremner, Southwick, & Charney, 1999b).

Effects of Traumatic Stress on Physical Health

Stress appears to have lasting effects on physical health that may be compounded by the diagnosis of PTSD (Friedman, Charney, & Deutch, 1995). The stress hormones cortisol and adrenaline mediate many of the negative long term consequences of stress on the body. Although cortisol released during the time of the life-threatening danger is one of the most important factors that help us to survive, it may have long-term negative effects on several organ systems (Sapolsky, 1996). The parts of the body that are most sensitive to the "wear and tear" effects of stress over time are (logically enough) those areas that are mobilized during the stress response (McEwen & Stellar, 1993; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). Many of these effects are mediated by increased release of the body's hormonal systems—including cortisol—that act like fire alarms to mobilize the resources of the body in life-threatening situations. The hormones cortisol and adrenaline travel throughout the body and brain and have a number of actions that are critical for survival during life-threatening danger. Adrenaline has a number of actions in the body, including stimulation of the heart to beat more rapidly and squeeze harder with each contraction, whereas norepinephrine acting in the brain helps to sharpen focus and stimulate memory. Blood pressure increases to increase blood flow and delivery of oxygen and glucose (necessary energy stores for the cells of the body to cope with the increased demand). There is a shunting of blood flow away from the gut and toward the brain and the muscles. The spleen increases the release of red blood cells, that allows the body to send more oxygen to the muscles. The liver converts glycogen to glucose, the type of sugar that can be immediately used. Breathing becomes heavy, so that extra oxygen can get to the lungs, and the pupils dilate for better vision. Release of endogenous opiates acts on the brain to dull our sense of pain, so that the pain of a physical injury incurred during an attack does not impair our ability to escape from the situation. More delayed stress responses include release of cortisol, that dampens the immune system, and conversion of fat to glucose in the liver.

These stress hormones can have more insidious, detrimental long-term effects. For instance, excessive levels of cortisol result in a thinning of the lining of the stomach, that increases the risk for gastric ulcers. Cortisol also results in a thinning of the bones, that increases the risk of osteoporosis or bone fractures in older people, or impairment in reproduction. Other diseases that have been linked to stress include heart disease, diabetes, and asthma. Stress also impairs the immune system, which can lead to an increase in infections and possibly even increased rates of cancer. Chronic stress with decreased blood flow to the intestines can result in chronic ulcers.

There is also some preliminary evidence that stress and possibly PTSD and/or other stress-related disorders like depression are associated with an increased risk of heart disease. Cortisol released during stress acts to increase blood pressure, heart rate, and cholesterol, and raises blood levels of adrenaline (norepinephrine and epinephrine) (McEwen & Stellar, 1993). Increased sympathoadrenal function has been shown to affect cardiovascular function in several ways, including increasing heart rate and blood pressure, increasing endothelial injury, platelet aggregation, and vascular reactivity. Studies in animals in fact have found direct evidence for the damaging effects of stress on blood vessels in the heart and accelerated cardiovascular disease (Rozanski, Blumenthal, & Kaplan, 1999). Some studies have directly linked changes in platelet aggregation and vascular reactivity with depression (Musselman, Evans, & Nemeroff, 1998).

The effects of stress on physical health appear to be caused by a disruption of the balance between different organs of the body, or homeostasis. According to this model, stress results in long-term wear and tear that leads to poor health and an increased risk for

mortality. Some authors (McEwen & Stellar, 1993) have argued for such a multi-system approach to understanding the effects of stress on the individual, that incorporates neurological/cognitive, hormonal, cardiovascular, and metabolic parameters. This theoretical background has been used to construct a series of assessments of a variety of physical parameters related to endocrine, metabolic, neurological, cognitive, and cardiovascular parameters (Seeman et al., 1997). Using this data the authors constructed an index of 'allostatic load', which they hypothesized is related to the long-term effects of stress on physiology. They found that this index was associated with poorer long-term cognitive and physical function, as well as increased risk for cardiovascular disease, in a longitudinal study of an aging population (Seeman et al., 1997).

Neural Circuits and Structures in the Stress Response

Neuroimaging has provided powerful information about neural circuits involved in the stress response (Bremner, 2002). The first neuroimaging study in PTSD was performed using magnetic resonance imaging (MRI) to measure the volume of the hippocampus, a brain area that plays an important role in new learning and memory (Bremner et al., 1995). This research was based on animal studies showing that stress was associated with damage to the CA3 region of the hippocampus. Mechanisms proposed for the effects of stress on the hippocampus include elevated levels of the stress hormone cortisol or excitatory amino acids causing damage to the hippocampus (Sapolsky, 1996), stress induced reductions in brain-derived neurotrophic factor (BDNF) (Nibuya, Morinobu, & Duman, 1995) and stress-induced inhibition of neurogenesis (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998). Administration of the anti-epileptic medication, phenytoin (Dilantin), blocked the negative effects of stress on the hippocampus, probably acting through modulation of the excitatory amino acid system (Watanabe, Gould, Cameron, Daniels, & McEwen, 1992). Administration of selective serotonin reuptake inhibitors (SSRIs) also prevented the stress-induced inhibition of neurogenesis and promoted neurogenesis in the hippocampus (Duman, Heninger, & Nestler, 1997). An initial study in PTSD showed deficits in paragraph recall (Wechsler Memory Scale Delayed Recall) and new word learning, (Selective Reminding Test) in combat veterans that were correlated with decreased hippocampal volume (Bremner et al., 1993). Findings of deficits in hippocampal-based verbal declarative memory have been replicated in several studies of PTSD related to combat and abuse (Bremner, 2002). In order to assess hippocampal structure, we used MRI to quantitate hippocampal volume in patients with a history of traumatic stress and the diagnosis of PTSD related to Vietnam combat. This study showed an 8% decrease in MRI-based measurement of right hippocampal volume in patients with PTSD (N=26) in comparison to matched controls (N=22) ($p<0.05$). Decreases in right hippocampal volume in the PTSD patients were associated with deficits in short-term memory as measured by the WMS-Logical, percent retention subcomponent ($r=0.64$; $p<0.05$) (Bremner et al., 1995). Findings of smaller hippocampal volume have now been replicated several times in the published literature, with findings of a 26% reduction in bilateral hippocampal volume in combat-related PTSD (Gurvits et al., 1996), a 12% reduction in left hippocampal volume in abuse-related PTSD (Bremner et al., 1997b), and a 5% reduction in left hippocampal volume in women sexually abused as children, most of whom had PTSD (Stein, Koverola, Hanna, Torchia,

& McClarty, 1997). Other studies in combat veterans found reductions (Gilbertson et al., 2002; Villarreal et al., 2002) although not all studies consistently showed reductions (Schuff et al., 2001).

Several questions that arose from these early studies is how long it takes for hippocampal damage to develop, and whether the effects are reversible. Findings from animal studies suggest that the effects revert to normal; this suggests that for changes in hippocampal structure to be seen in human subjects, there is a need for chronic ongoing stressors. In fact, recent studies showing no hippocampal volume reduction in children with PTSD (Carrion et al., 2001; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; De Bellis et al., 1999) and new-onset PTSD (Bonne et al., 2001) suggest that hippocampal volume changes are primarily seen in chronic, severe PTSD. However, a process that leads to hippocampal volume changes with chronic PTSD likely begins with the initial acute trauma, and then other factors, such as the chronic stress of PTSD symptoms or increased vulnerability to re-traumatization that we know is part of the PTSD condition contribute to hippocampal volume changes, perhaps through an inhibition of neurogenesis or other factors. We do have some preliminary information on the potential for reversibility in human studies that is relevant to the acute trauma response. In an unpublished study, we treated 23 PTSD patients for one year with the SSRI paroxetine, and found a 5% increase in hippocampal volume and a 35% improvement in hippocampal based verbal declarative memory function (measured with the Wechsler Memory Scale). These findings raise the question of whether pre-treatment or early treatment with SSRIs may prevent the development of neurological deficits from acute trauma. Alternatively, other authors have argued that stress does not lead to hippocampal damage. Rather genetic predisposition to smaller hippocampal volume and lower memory function leads to a vulnerability to PTSD (Gilbertson et al., 2002).

Functional neuroimaging studies have also started to map a neural circuitry for PTSD. Yohimbine induced increases in noradrenergic release and PTSD symptoms resulted in decreased metabolism in hippocampus as well as other areas including medial prefrontal and orbitofrontal cortex (Bremner et al., 1997a). Several studies have used PET measurement of brain blood flow with radioactive water ($H_20[150]$) in conjunction with provocation of PTSD symptoms and traumatic remembrance using traumatic reminders such as combat slides and sounds and traumatic personalized scripts. One study that looked at PTSD patients with a range of traumas (N=8) (with no controls) exposed to trauma-related scripts found an increase in brain blood flow in limbic regions (right amygdala, insula, orbitofrontal cortex, and anterior cingulate), and decreased blood flow in middle temporal and left inferior frontal cortex (Rauch et al., 1996). In another study, 10 Vietnam veterans with PTSD and 10 Vietnam veterans without PTSD were exposed to combat-related slides and sounds in conjunction with PET imaging. Vietnam veterans with combat-related PTSD (but not non-PTSD) demonstrated a decrease in blood flow in the medial prefrontal cortex (Brodmann's area 25, or subcallosal gyrus) and middle temporal cortex (auditory cortex) during exposure to combat-related slides and sounds, with relative increases in activity in lingual gyrus (posterior parahippocampus), and posterior cingulate, as well as left inferior parietal and left motor cortex, and dorsal pons (Bremner et al., 1999c). Exposure to neutral and combat trauma related pictures (without sounds) and mental imagery in combat veterans with (N=7) and without (N=7) PTSD showed increased blood flow in anterior cingulate during combat versus neutral

imagery in PTSD. Blood flow was also increased in right amygdala during combat imagery versus exposure to combat-related pictures in PTSD, while controls (but not patients) had increased blood flow in orbitofrontal and medial prefrontal cortex during these conditions. Patients (but not controls) also had decreased blood flow in middle temporal and left inferior frontal cortex during exposure to traumatic mental imagery (Shin et al., 1997). Other studies showed decreased medial prefrontal function in combat-related PTSD during exposure to combat-related sounds (Liberzon et al., 1999).

Several studies have now examined neural correlates of childhood abuse-related PTSD. We measured brain blood flow with PET and $[^{15}O]H_2O$ during exposure to personalized scripts of childhood sexual abuse. Twenty two women with a history of childhood sexual abuse underwent injection of $H_2[^{15}O]$ followed by positron emission tomography (PET) imaging of the brain while listening to neutral and traumatic (personalized childhood sexual abuse events) scripts. Brain blood flow during exposure to traumatic versus neutral scripts was compared between sexually abused women with (N=10) and without PTSD (N=12). Memories of childhood sexual abuse were associated with greater increases in blood flow in portions of anterior prefrontal cortex (superior and middle frontal gyri-Areas 6 and 9), posterior cingulate (area 31), and motor cortex in sexually abused women with PTSD compared to sexually abused women without PTSD. Abuse memories were associated with alterations in blood flow in medial prefrontal cortex, with decreased blood flow in subcallosal gyrus-area 25, and a failure of activation in anterior cingulate-area 32. There was also decreased blood flow in right hippocampus, fusiform/inferior temporal gyrus, supra-marginal gyrus, and visual association cortex in PTSD relative to non-PTSD women (Bremner et al., 1999a). This study replicated findings of decreased function in medial prefrontal cortex and increased function in posterior cingulate in combat-related PTSD during exposure to combat-related slides and sounds. Another study looked at 8 women with childhood sexual abuse and PTSD and 8 women with abuse without PTSD using PET during exposure to script-driven imagery of childhood abuse. The authors found increases in orbitofrontal cortex and anterior temporal pole in both groups of subjects, with greater increases in these areas in the PTSD group. PTSD patients showed a relative failure of anterior cingulate activation compared to controls. The PTSD patients (but not controls) showed decreased blood flow in anteromedial portions of prefrontal cortex and left inferior frontal gyrus (Shin et al., 1999). Preliminary studies from our group found decreased hippocampal and medial prefrontal cortical function during remembrance of emotionally valenced words (e.g. “blood, stench”) in women with abuse-related PTSD (Bremner et al., 2003b).

In a second study, we utilized encoding of a paragraph as a probe of hippocampal function. This was based on the fact that we have consistently demonstrated deficits in paragraph recall in PTSD, the PET literature showing more consistent activation with encoding versus retrieval tasks, which we have reviewed elsewhere (Bremner et al., 2001), as well as our own pilot testing that showed greater activation with encoding than retrieval. PET imaging in conjunction with the performance of hippocampal-based verbal declarative memory tasks was performed in women with a history of early childhood sexual abuse with (N=10) and without (N=12) PTSD. Hippocampal volume was measured with magnetic resonance imaging (MRI) in three subject groups: women with early childhood sexual abuse and PTSD, women with early abuse without PTSD, and women without early abuse or PTSD. A failure of left hippocampal activation (F=14.94;

df=1,20; p<.001) and 16% smaller volume of the hippocampus was seen in women with abuse and PTSD compared to women with abuse without PTSD. Abused PTSD women also had a 19% smaller hippocampal volume relative to women without abuse or PTSD (Bremner et al., 2003a).

These studies did not find consistent activation of the amygdala, which is known to play a critical role in fear responses (Davis, 1992). Rauch et al did find increased amygdala activation in PTSD with exposure to masked fearful faces (Rauch et al., 2000). In subsequent studies from our group we have further mapped the neural correlates of PTSD using PET imaging in conjunction with the conditioned fear paradigm. In the conditioned fear paradigm, repeated pairing of an aversive unconditioned stimulus (e.g. electric shock; US) with a neutral conditioned stimulus (e.g. bright light; CS), results in a conditioned fear response to the light alone. Animal studies have shown that the amygdala plays a critical role in acquisition of conditioned fear responses, while the medial prefrontal cortex (including anterior cingulate), through inhibition of amygdala responsiveness, has been hypothesized to play a role in extinction of fear responses. In a study of PTSD we found that patients had increased left amygdala activation with fear acquisition, and decreased medial prefrontal (anterior cingulate) function during extinction, relative to controls. These findings implicate amygdala and medial prefrontal cortex (anterior cingulate) in the acquisition and extinction of fear responses, respectively, in PTSD. Another PET study with the Stroop paradigm showed a failure of anterior cingulate activation in PTSD.

Other studies have found deficits in anterior cingulate and medial prefrontal cortex in childhood trauma populations. One study used single voxel proton magnetic resonance spectroscopy (proton MRS) to measure relative concentration of N-acetylaspartate and creatinine (a marker of neuronal viability) in the anterior cingulate of 11 children with maltreatment-related PTSD and 11 controls. The authors found a reduction in the ratio of N-acetylaspartate to creatinine in PTSD relative to controls (De Bellis, Keshavan, Spencer, & Hall, 2000).

A number of PET studies have now implicated medial prefrontal cortex in both normal and pathological responses to stress and emotion. In the PET studies conducted by Bremner and colleagues there was a failure of activation of anterior cingulate and decreased blood flow in medial prefrontal cortex (subcallosal gyrus) during exposure to traumatic stimuli in PTSD. PET studies in normal subjects using a variety of paradigms to stimulate intense emotions have consistently demonstrated activation of the anterior cingulate (Area 32 and 24). Human subjects with lesions of medial prefrontal cortical areas (e.g. the famous case of Phineas Gage) have deficits in interpretation of emotional situations that are accompanied by impairments in social relatedness. Lesions of this area in animals result in impairments in mounting the peripheral glucocorticoid and sympathetic response to stress (Bremner, 2002).

Findings from imaging studies may also be relevant to the failure of extinction to fear responding that is characteristic of PTSD and other anxiety disorders. Recent evidence in fact suggests that extinction is mediated by cortical inhibition of amygdala responsiveness. Medial prefrontal cortex (area 25) or adjacent medial prefrontal regions (anterior cingulate, area 24 and 32, and orbitofrontal cortex) have inhibitory connections to the amygdala that play a role in extinction of fear responding, an important component of the symptom profile of PTSD. PET studies in PTSD during traumatic reminders

reviewed earlier showed decreased blood flow of the medial prefrontal cortex (area 25), with failure of activation of anterior cingulate and medial orbitofrontal cortex. Based on these findings we previously argued that anterior cingulate (area 32) activation represents a “normal” brain response to traumatic stimuli that serves to inhibit feelings of fearfulness when there is no true threat. Failure of activation in this area and/or decreased blood flow in adjacent medial prefrontal cortex (Area 25) in PTSD may lead to increased fearfulness that is not appropriate for the context, a behavioral response that is highly characteristic of patients with PTSD.

Plasticity in the hippocampus may also be relevant to the development of psychopathology following exposure to acute traumas. Preclinical studies show that there is a window during which modification of traumatic memories may affect long-term outcome. In animals who have encoded a traumatic memory, lesions of the hippocampus within the first month will cancel the traumatic memory, however after a month hippocampal lesions have no effect on the traumatic memory. These studies suggest that there is a critical window of memory consolidation during which memories are stored within the hippocampus and are susceptible to memory consolidation; after this time period memories are stored in the cerebral cortex and are indelible and no longer susceptible to modification (Bremner et al., 1999b). These findings suggest that early interventions are important to prevent the development of indelible memories that will maintain chronic PTSD, however as mentioned later we do not have enough evidence to support specific treatments for PTSD.

Acute and Chronic Neurobiological Responses to Trauma

Much of our knowledge related to the acute trauma response is based on anecdotal or clinically-based information. Military psychiatrists have long treated acutely traumatized soldiers with benzodiazepines or chlorpromazine on the battlefield and kept them close to the front lines. They knew from experience that if you removed a soldier from the front lines, it would be almost impossible to get them to go back. These military psychiatrists were in effect practicing a form of desensitization therapy. In other words, exposure to the front lines promoted extinction of fear responses to the traumatic stimulus, in this case reminders of combat.

Little is known about the acute neurobiological trauma response. Because the acute phase of the trauma response is generally felt to be limited to three months or less, it is difficult to obtain the necessary funding and investigational review board approval, and to plan and coordinate data collection, in the aftermath of large-scale disasters such as the WTC attack. For these reasons most studies have been conducted in individuals with chronic PTSD who are a year or more past their original trauma. Although these studies have their limitations in reference to understanding and treating the acute trauma response, they do represent an important starting point for this area.

Comparing the effects of treatment during the acute and chronic phases of the trauma response may provide insight into early responses to trauma (Mellman, Byers, & Augenstein, 1998). Robert et al compared imipramine to chloral hydrate for children who were acute burn victims; the authors found that imipramine treatment led to a significant improvement in psychiatric symptoms compared to chloral hydrate (Robert, Blakeney, Villarreal, Rosenberg, & Meyer, 1999). Gelpin et al found that treatment of

acute trauma survivors presenting to an emergency room with the benzodiazepine medication, alprazolam, when compared to placebo, actually made patients worse in terms of long-term development of PTSD (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996). Pitman et al showed that the noradrenergic beta receptor blocker, propanolol, administered in the emergency room to acute trauma victims, blocked the development of psychophysiological responses, although there was only a modest effect on PTSD symptoms .

Studies by Foa and others (Foa et al., 1999; Meadows & Foa, 1999) found cognitive behavioral therapies for rape victims to be more efficacious if they are delivered during the acute phase of the trauma response. Also reviewed in this issue are studies showing that other types of behavioral treatments such as psychological debriefing (PD) or critical incident stress debriefing (CISD) which are offered to acute trauma victims, have been found in several studies to actually worsen outcome relative to no treatment at all. Although there is a natural tendency to want to do something for the acute trauma victim, these studies should give us pause before we apply untested treatments to acute trauma victims.

These studies also suggest that there is a window of brain plasticity during the phase of the acute trauma response when there is a greater potential to affect the final outcome (for better or for worse) in terms of chronic PTSD. Preclinical studies provide a model for the mechanism of how this phenomenon may occur. For example, as noted earlier, lesions of the hippocampus in the first 30 days after an aversive learning event (i.e. the learning of a negative memory) will erase the memory. However after that time window, the memories are strongly engraved and more resistant to modification. This may be related to the transfer of memories to long-term storage in the cerebral cortex. Stress sensitization of neurochemical systems may also explain the change from acute to chronic trauma responses. After initial stress there is release of stress hormones and neurotransmitters including cortisol and norepinephrine. With chronic and repeated stress there is a potentiated release of, for example, norepinephrine following exposure to subsequent stressors. This process, called stress sensitization, may explain the transition from the acute to the chronic stress response. Another phenomenon that is relevant to understanding early responses to stress is extinction. We still do not understand the processes that are involved in turning off the fear response, which is a critical factor determining who will and will not develop chronic PTSD responses. However preliminary animal and human imaging data suggests that dysfunction in the medial prefrontal cortex with a failure to inhibit amygdala function may mediate in part this process. Repeated stress may also cause changes in brain areas such as the hippocampus, in a manner analogous to kindling, which is used as a model for understanding the development of epilepsy. Changes in the hippocampus may actually help to promote and maintain symptoms of the disorder.

Understanding the acute trauma response may be useful in the development of new treatments that can reverse early PTSD or even block the development of PTSD. Preclinical studies showing that stress-induced stimulation of noradrenergic function may modulate the laying down of traumatic memories have stimulated interest in the use of agents that may block noradrenergic function for the treatment of acute trauma. For example, animal studies have shown that pharmacological blockade of the beta receptor in the amygdala prevents the laying down of emotionally aversive memory. As

mentioned earlier, Pitman and colleagues treated patients in the emergency room with the noradrenergic beta blocker, propanolol, with hours of experiencing trauma, and continued treatment for several weeks later. The investigators found that propanolol did not lead to a significant reduction in PTSD symptoms compared to placebo; however there was a decrease in conditioned responses to traumatic reminders (Pitman et al., 2002). This study seemed to suggest that propanolol interfered with the acquisition of conditioned responses, but not the development of core PTSD symptoms per se. Theories of PTSD as related to kindling (mentioned earlier) underlie in part the application of medications used for epilepsy, like tegretol and valproic acid. These agents have effects on mood and have been shown to be efficacious in open-label trials in PTSD, while one 12 week placebo-controlled trial of lamotrigine showed improvement on both re-experiencing and avoidance/numbing symptoms (Hertzberg et al., 1999). Dilantin is particularly of interest, since it is efficacious in epilepsy and as reviewed earlier in this paper has been shown in animal studies to block the negative effects of stress on hippocampal morphology. Animal studies have also shown that treatment with corticotropin releasing factor (CRF) antagonists in the acute phase of the trauma response may prevent the long-term negative consequences of stress (Arborelius, Owens, Plotsky, & Nemeroff, 1999; Habib et al., 2000). This has prompted an interest in developing clinical trials for acute trauma victims.

There is also evidence from animal studies that stress is associated with alterations in the serotonin system. Pretreatment with serotonin reuptake inhibitors and tricyclics before stress exposure prevented the development of chronic behavioral disturbances. Also SSRIs prevent stress-induced inhibition of neurogenesis, or the growth of neurons, in the hippocampus. Hippocampal dysfunction may contribute to both cognitive dysfunction and emotional dysregulation in PTSD. There also may be window of opportunity in the acute aftermath of stress when these effects can be blocked or reversed. This leads us to the speculation that SSRIs given to acute trauma victims, or pre-administered to individuals at risk of stress, may prevent PTSD.

Summary and Conclusions

This paper has reviewed alterations in brain structure and function in PTSD in the context of early stress responses. Stress is associated with an acute physiological response, which includes release of stress hormones and neurotransmitters cortisol and norepinephrine. The physiological stress response also has negative long-term effects on physical health which is at least partially mediated by these hormones and neurotransmitters, conferring an increased risk for heart disease and other disorders. Acute stress responses following exposure to chronic stressors are associated with a potentiated release of norepinephrine. Difficulties in conducting biological research in acute trauma victims have resulted in a situation where most of our knowledge is based on studies in patients with chronic PTSD. These studies have implicated brain regions including the medial prefrontal cortex, hippocampus, and amygdala in the neural circuitry of PTSD. There may be a window of opportunity in the acute aftermath of stress where the detrimental effects of stress on these brain circuits and systems can be reversed or blocked, leading to the prevention of PTSD. Future studies are needed to assess the early response to trauma and longitudinal course of the development of PTSD, both in terms of

neurobiology and treatment.

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