CHAPTER 12

Structural and functional plasticity of the human brain in posttraumatic stress disorder

J. Douglas Bremner[1,*], Bernet Elzinga[2], Christian Schmahl[3] and Eric Vermetten[4]

[1]Departments of Psychiatry and Behavioral Sciences and Radiology, Emory University School of Medicine, Atlanta, GA, USA and the Atlanta VAMC, Atlanta, GA, USA
[2]University of Leiden, Section of Clinical and Health Psychology, Leiden, The Netherlands
[3]Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany
[4]Dutch Military Hospital and University of Utrecht, Utrecht, The Netherlands

Abstract: Posttraumatic stress disorder (PTSD) is associated with long-term changes in neurobiology. Brain areas involved in the stress response include the medial prefrontal cortex, hippocampus, and amygdala. Neurohormonal systems that act on the brain areas to modulate PTSD symptoms and memory include glucocorticoids and norepinephrine. Dysfunction of these brain areas is responsible for the symptoms of PTSD. Brain imaging studies show that PTSD patients have increased amygdala reactivity during fear acquisition. Other studies show smaller hippocampal volume. A failure of medial prefrontal/anterior cingulate activation with re-experiencing of the trauma is hypothesized to represent a neural correlate of the failure of extinction seen in PTSD. The brain has the capacity for plasticity in the aftermath of traumatic stress. Antidepressant treatments and changes in environment can reverse the effects of stress on hippocampal neurogenesis, and humans with PTSD showed increased hippocampal volume with both paroxetine and phenytoin.

Introduction

Childhood abuse is a pervasive problem that is often associated with lasting psychopathology. For instance, 16% of women have a history of childhood sexual abuse (rape or fondling) based on nationwide surveys (McCauley et al., 1997). Ten percent of women (13 million) suffer from posttraumatic stress disorder (PTSD) at some time in their lives (Kessler et al., 1995), and PTSD is twice as common in women as in men. Childhood sexual abuse is the most common cause of PTSD in women (Kessler et al., 1995). This paper reviews the long-term effects of childhood abuse on brain and neurobiology, as well as the functional plasticity of the brain in the aftermath of trauma. Findings are reviewed in PTSD and other mental disorders related to early abuse, including borderline personality disorder (BPD) and dissociative identity disorder (DID).

Psychological effects of trauma

Trauma results in a range of mental symptoms, including PTSD, BPD, DID, substance abuse,

*Corresponding author. Tel.: +1 (404) 712 9569; Fax: +1 (404) 712-8442; E-mail: jdbremn@emory.edu

anxiety, and depression. Most of the research has been done in PTSD patients, however these patients frequently have co-morbid symptoms with these other disorders, which led to the use of the term "trauma-spectrum disorders" (Bremner, 2002). Risk factors for PTSD include prior history of stress, low years of education, prior psychiatric history, young age, and lack of social support (Bremner et al., 1995c). In one study Vietnam combat veterans with a history of childhood abuse had fourfold increased relative risk of PTSD (Bremner et al., 1993b). Childhood abuse was the factor most strongly associated with risk for PTSD, even after controlling for level of combat exposure, months in Vietnam, and participation in atrocities. Twin studies also show that there is a genetic contribution to PTSD risk (Goldberg et al., 1990).

Effects of stress on memory and the hippocampus

Studies in animals show that stress impacts adversely on the brain, especially on the hippocampus. Stress, acting through increased excitatory amino acids, decreased brain-derived neurotrophic factor (BDNF), and/or increased glucocorticoids, is associated with a loss of branching of neurons in the hippocampus and an inhibition of hippocampal neurogenesis (Uno et al., 1989; Sapolsky et al., 1990; Nibuya et al., 1995; Smith et al., 1995; Sapolsky, 1996; Duman et al., 1997). These effects are reversed by a variety of antidepressant treatments (Malberg et al., 2000; Duman et al., 2001; Santarelli et al., 2003; Duman, 2004). In addition, an enriched environment has been shown to promote hippocampal neurogenesis (Kempermann et al., 1997, 1998).

Consistent with the effects of stress on brain structures that mediate memory, including the hippocampus, prefrontal cortex, and amygdala, PTSD is associated with a wide range of memory deficits (Bremner, 2003). Memory can be categorized as declarative (memory for facts or lists, mediated in part by the hippocampus) or nondeclarative (memory for things like riding a bike, or conditioned responses) (Schacter, 1996). PTSD patients show deficits in declarative memory,

enhanced responses to conditioning, and perseverative errors (possibly related to frontal lobe dysfunction) (Elzinga and Bremner, 2002).

Studies in PTSD showed deficits in hippocampal function as measured with neuropsychological tests of declarative memory function (Bremner et al., 1993a, 1995a, 2004b; Uddo et al., 1993; Yehuda et al., 1995; Vasterling et al., 2002, 2006; Vasterling and Bremner, 2006). One recent study showed a decline in verbal declarative memory function from before to after Iraq deployment, showing that combat exposure resulted in changes in cognitive function (Vasterling et al., 2006). Several studies have also shown smaller hippocampal volume and/or N-acetyl aspartate (NAA, a marker of neuronal integrity) measured with magnetic resonance imaging (MRI) in PTSD (Bremner et al., 1995b, 1997b, 2003c; Stein et al., 1997; Freeman et al., 1998; Schuff et al., 2001; Villarreal et al., 2002; Lindauer et al., 2004; Shin et al., 2004; Kitayama et al., 2005; Vythilingam et al., 2005; Jatzko et al., 2006). Two recent meta-analyses showed that this effect was seen for both left and right hippocampus, and was seen equally in men and women (Kitayama et al., 2005; Smith, 2005; Jatzko et al., 2006). However effects were only seen in adults (including those with early life stress) and not in children (De Bellis et al., 1999, 2001; Carrion et al., 2001). Findings from animal studies in fact show that early life stress may not have an immediate effect on the hippocampus, but may only manifest during the adult phase of development (Brunson et al., 2001).

Bremner has outlined a model of trauma-spectrum disorders (Bremner, 2002). These psychiatric disorders, ranging from depression to BPD, DID and PTSD, are all linked to stress and share (at least in part) common bases in the brain. Studies in these disorders in fact show that exposure to early childhood abuse is associated with smaller hippocampal volume, including depression (Vythilingam et al., 2002), PTSD (Bremner et al., 1997b, 2003c), BPD (Driessen et al., 2000; Schmahl et al., 2003), and DID (Vermetten et al., 2006a). In addition, these disorders are associated with increased cortisol response to symptom provoking stressors for PTSD (Bremner et al., 2003a; Elzinga et al., 2003) and BPD (Elzinga et al., unpublished data, 12/12/06).

BPD (Driessen et al., 2000; Schmahl et al., 2003) and DID (Vermetten et al., 2006a) (but not PTSD) are also associated with smaller amygdala volume.

Stress and neurohormonal systems

Alterations in the hypothalamic-pituitary-adrenal (HPA) axis have also been associated with stress-related psychiatric disorders. Corticotropin releasing factor (CRF) plays an important role in the stress response. Chronic stress exposure is associated with increases in CRF in animal studies (Arborelius et al., 1999). Central CRF administration is associated with fear-related behaviors (decreased exploration, increased startle, decreased grooming). Stress-induced lesions of the hippocampus result in a removal of inhibition of CRF release from the hypothalamus. Other findings from animal studies include a blunted adrenocorticotropin hormone (ACTH) response to CRF challenge, increased cortisol in the periphery, and resistance to negative feedback of dexamethasone (Arborelius et al., 1999). Two studies have shown increased concentrations of CRF in PTSD (Bremner et al., 1997a; Baker et al., 1999). Some studies (Yehuda et al., 1991b, 1994, 1996), but not others (Young and Breslau, 2004a, b) found decreased cortisol in 24 h urines or in diurnal salivary samples. Two studies using comprehensive measurement of plasma cortisol at multiple time points found lower cortisol concentrations in the afternoon (Yehuda et al., 1996; Bremner et al., 2007). Women with early childhood sexual abuse and PTSD were found to have lower afternoon cortisol and an increase in cortisol pulsatility compared to controls (Bremner et al., 2007). Other studies found increased lymphocyte glucocorticoid receptors (Yehuda et al., 1991a), super-suppression of cortisol with low-dose (0.5 mg) dexamethasone (Yehuda et al., 1993), blunted ACTH response to CRF, increased cortisol response to stressors (Bremner et al., 2003a) and to traumatic reminders of early trauma (Elzinga et al., 2003). Women with depression and early trauma also had increased cortisol response to public speaking (Heim et al., 2000).

There has been considerable interest in the relationship between stress, aging, and dehydroepiandosterone (DHEA). DHEA declines with aging (Orentreich et al., 1992; Barrett-Connor and Edelstein, 1994; Flynn, 1999; Johnson et al., 2002) and there has been considerable interest in the ability of DHEA supplements to block the normal effects of aging, although there is no convincing data that DHEA has such effects. DHEA also is important in the stress response. Chronic stress increases DHEA and DHEA-S (Fuller et al., 1984). DHEA also has antistress effects, blocking the effects of glucocorticoids on peripheral tissues as well as the hippocampus (Kimonides et al., 1998; Kaminska et al., 2000) and decreasing anxiety (Prasad et al., 1997). Studies of DHEA in patients with stress-related psychiatric disorders are contradictory, while studies in adult depressed patients showed both increases (Heuser et al., 1998) and decreases (Goodyer et al., 1996; Herbert et al., 1996) as well as no change (Michael et al., 2000; Young et al., 2002) in levels. Studies of DHEA in PTSD have been equally contradictory, with one study citing lower concentrations relative to controls (Kanter et al., 2001) while the other showed elevations (Spivak et al., 2000). We recently measured DHEA and DHEA-S at multiple time points over a 24 h period in women with early abuse and PTSD, and found elevations in both DHEA and DHEA-S (Bremner et al., 2007).

We performed a comprehensive assessment of memory, cortisol, DHEA, and the hippocampus in women with sexual abuse before 13, with and without PTSD, and healthy nonabused women. All subjects underwent assessment of hippocampal structure with MRI, assessment of hippocampal function with PET in conjunction with a paragraph encoding declarative memory task, assessment of HPA axis function at baseline and with a stressful challenge, and neuropsychological testing of declarative memory function. Early childhood sexual abuse before the age of 13 was defined as rape or molestation as assessed with the Early Trauma Inventory (Bremner et al., 2000). All subjects were free of psychotropic medication for 4 weeks before study.

Women with a history of early childhood sexual abuse and the diagnosis of PTSD ($N = 10$) were

compared to abused non-PTSD women ($N = 12$) for hippocampal function using PET. All subjects were scanned during encoding of a paragraph and control task in conjunction with injection of 0–15 water and PET imaging of the brain. MR images were obtained for measurement of hippocampal volume, with an additional group of nonabused normal women (total $N = 33$). Subjects ($N = 56$) were also admitted to the GCRC for a 24 h period, for measurement of plasma cortisol, DHEA, and estradiol measured at 15 min intervals for 24 h. Salivary cortisol was measured after reading of a traumatic script related to personalized childhood abuse experiences.

In addition, salivary cortisol was measured before and after a 20 min cognitive challenge (arithmetic, color-word naming, problem solving under time pressure, and negative feedback). Women with abuse and PTSD had smaller hippocampal volume (Bremner et al., 2003b), a failure of hippocampal activation with declarative memory tasks (Bremner et al., 2003b), lower plasma cortisol concentrations in the afternoon (Bremner et al., 2007), increased cortisol pulsatility (Bremner et al., 2007), increased plasma DHEA concentrations (Bremner et al., 2007), increased cortisol response to stress (Bremner et al., 2003a), increased cortisol response to traumatic reminders (Elzinga et al., 2003), and impaired declarative memory measured with neuropsychological testing (Bremner et al., 2004b).

Neurohormonal modulation of memory

Glucocorticoids affect learning and memory. Elevations of glucocorticoids within the physiological range result in reversible deficits in memory function in animals (Oitzl and de Kloet, 1992; Bodnoff et al., 1995) as well as human subjects (Newcomer et al., 1994, 1999; Kirschbaum et al., 1996; Lupien et al., 1997, 1999, 2002; de Quervain et al., 2000; Wolf et al., 2001). Glucocorticoids released during stress, possibly acting through the hippocampus, may explain in part the acutely reversible as well as chronic effects that stress has on declarative memory (Kirschbaum et al., 1996; Porter and Landfield, 1998; de Kloet et al., 1999; Wolf, 2003).

Greater deficits are seen in younger subjects in comparison to older subjects, hypothesized to be secondary to age-related decreases in glucocorticoid receptor density (Newcomer et al., 1995). Impairment of working memory by glucocorticoids may require noradrenergic stimulation to have its effect (Elzinga and Roelofs, 2005). We used a protocol of 1 mg of dexamethasone, followed by 2 mg one day later, and found an impairment in declarative memory function (percent retention of a paragraph after a delay) in healthy subjects, but not patients with depression (Bremner et al., 2004d) or PTSD (Bremner et al., 2005c). We hypothesized that this might be due to disease-related decreases in glucocorticoid receptor function. This is consistent with the idea of PTSD as an "accelerated aging" (Bremner and Narayan, 1998) related to common theories of progressive hippocampal atrophy and dysfunction in both processes. We have also shown that endogenous cortisol release stimulated by a cognitive stress challenge in healthy subjects impaired delayed recall of words and a spatial memory task at 24 h (Elzinga et al., 2005).

In women (with and without PTSD), with a history of early abuse, memory functioning was also affected after exposure to personalized scripts (Elzinga et al., 2003). For neutral paragraphs encoded after exposure to the trauma scripts there was an impairment in delayed recall relative to paragraphs encoded in a no-stress condition (Fig. 1). Recall 24 h later of an emotional paragraph presented immediately after the trauma scripts was positively correlated with cortisol response to the stressful challenge, meaning that cortisol enhanced consolidation of emotional memories. Another study in male healthy subjects has shown that endogenous cortisol levels in healthy subjects who became upset during a social speech task were positively correlated with enhanced delayed memory recall of pictures, which was especially prominent for recall of unpleasant pictures (Abercrombie et al., 2005). Taken together, these findings are consistent with animal models suggesting that glucocorticoid effects on learning require emotional arousal (Roozendaal, 2000).

Catecholamines released during stress also modulate the encoding and retrieval of memory (McGaugh, 2000). Administration of epinephrine

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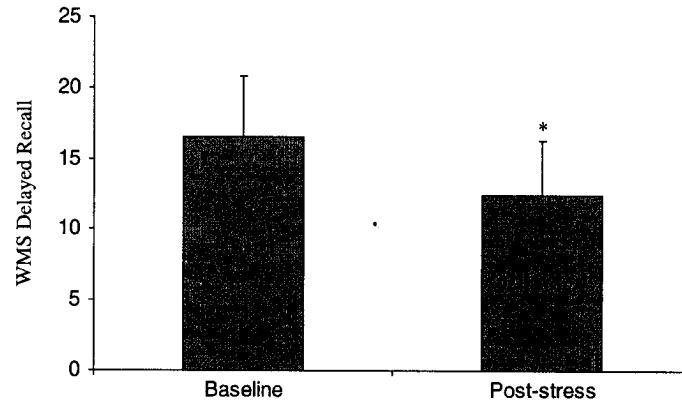ether,
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Fig. 1. Effects of a traumatic script on memory recall. There was a significant difference in delayed paragraph recall for paragraphs encoded after exposure to traumatic scripts compared to paragraphs encoded at a pre-stress baseline ($t(22) = -3.39$, $p<0.01$). This showed that stress impaired the ability to consolidate declarative memory.

(which is released from the adrenal) affects memory consolidation with an inverted U-shaped curve. Memory improves up to a point and decreases with high doses (Gold and van Buskirk, 1975; Liang et al., 1986). Lower doses of norepinephrine injected into the amygdala promote memory for an inhibitory avoidance task while higher doses inhibit memory (Liang et al., 1990). In humans, noradrenergic beta-blocker medications blocked the formation of emotional memories (Cahill et al., 1994), while enhanced norepinephrine release was associated with enhanced encoding of emotional memories (Southwick et al., 2002). Vasopressin and oxytocin have been shown to modulate memory formation in both animals (McGaugh, 2000) and human subjects (including those with PTSD) (Pitman et al., 1993).

Fear conditioning and extinction

One of the most classic laboratory paradigms that has been used as a model for PTSD is conditioned fear. In animal models, the pairing of light and shock leads to fear responses to the light alone. With exposure to light alone there is a gradual decrease in fear responding (called "extinction to fear") (Davis, 1992). Re-exposure to the light-shock at a later time point results in a rapid return of fear responding (Quirk, 2002). Medial

prefrontal cortical inhibition of the amygdala (which plays a critical role in fear responses) is felt to represent the neural mechanism of extinction to fear responding (Quirk et al., 2006). This brain area is known to mediate emotion, as represented by the famous case of Phineas Gage (Damasio et al., 1994). Phineas Gage was a 19th century railroad worker who was injured by a spike that entered through his eye socket and lesioned his medial prefrontal cortex (mPFC). Areas involved included the orbitofrontal, anterior cingulate (25/24/32), and mesofrontal cortex (9). Speech and cognition remained intact. He had marked deficits in his ability to judge social contexts, behave appropriately in social contexts, and assess emotional nonverbal signals from others. Based on these findings and others, the mPFC has been judged to play a critical role in the emotion and social function.

This medial prefrontal area also plays an important role in the modulation of the neurohormonal response to stress. This area mediates peripheral cortisol and sympathetic responses to stress (Diorio et al., 1993). Dysfunction of this area could explain altered neurohormonal responses to stress in PTSD patients.

Studies in PTSD have shown dysfunction in the medial prefrontal cortical response to stress and traumatic reminders. We previously found decreased medial prefrontal function in combat veterans with PTSD exposed to combat-related PTSD

(Bremner et al., 1999b). In a second study we showed that women with PTSD related to early childhood sexual abuse had a decrease in medial prefrontal function in response to scripts of early childhood sexual abuse (Bremner et al., 1999a). A second study of exposure to emotional word pairs (e.g., rape-mutilate) showed decreased medial prefrontal and hippocampal function in abused women with PTSD (Bremner et al., 2003d). Another study used "Stroop" words (say the color of a color word, e.g., green, which leads to slowing of response time, due to inhibition of response) with an emotional Stroop component (name the color of a word like "rape"). The Stroop paradigm is associated with activation of anterior cingulate. Studies of the emotional Stroop (e.g., say the color of the word rape) has been associated with a slower response time in abuse-related (Foa et al., 1991) or combat-related PTSD (McNally et al., 1990). We studied neural correlates of the emotional Stroop in women with a history of early abuse with and without PTSD. We found that performance of the emotional Stroop was associated with decreased function in the mPFC in the PTSD patients (Bremner et al., 2004c).

We also have assessed neural correlates of conditioned fear in PTSD. Pairing of light and shock leads to increased fear responding and increased startle to light alone (conditioned fear). Conditioned fear and startle response are mediated by the central nucleus of the amygdala. Failure of extinction occurs with lesions of the mPFC (which inhibits the amygdala).

We studied fear conditioning with PET in women with a history of early abuse and PTSD and healthy nonabused women (Bremner et al., 2005b). Subjects were exposed to repeated and intermittent exposure to a blue square on a screen in the absence of shock (habituation), exposure to a blue square with a shock (fear acquisition), and then exposure to the blue square in the absence of shock (extinction). On a separate control day, they received random shocks instead of paired exposures; otherwise the protocol was the same. PTSD subjects experienced increased anxiety with fear acquisition and extinction. PTSD subjects also had increased amygdala blood flow during fear acquisition and decreased medial prefrontal blood flow

during extinction. Increased amygdala blood flow during fear acquisition in the PTSD patients was correlated with increased PTSD symptoms, anxiety, and dissociation during fear acquisition. Increased amygdala blood flow during fear acquisition was correlated with decreased medial prefrontal blood flow during fear extinction in all of the subjects. There was a highly significant negative correlation between increased anxiety and decreased medial prefrontal blood flow during extinction in the PTSD patients ($r = -0.90$; $p = 0.006$).

Effects of treatment on the brain in PTSD

We have also assessed the effects of the selective serotonin reuptake inhibitor paroxetine on brain and cognition in PTSD. Previous multisite randomized placebo-controlled trials have shown efficacy for paroxetine over placebo in PTSD (Marshall et al., 2001; Tucker et al., 2001). Antidepressants have also been shown to promote neurogenesis in the hippocampus, a brain area involved in learning and memory (Duman et al., 1997). In an open-label study we showed a 5% increase in hippocampal volume after 9 months of treatment with paroxetine, as well as a 30% improvement in verbal declarative memory function measured with neuropsychological testing (Vermetten et al., 2003). Paroxetine treatment was also associated with a decreased cortisol and heart rate response to a stressful task (Vermetten et al., 2006b).

Glutamate, dissociation, and PTSD

Alterations in glutamatergic function has also been implicated in PTSD as well as dissociation (Krystal et al., 1996; Chambers et al., 1999). Symptoms of dissociation are an important part of the psychopathological response to stress. Symptoms of dissociation measured with the Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998) are:

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Do things seem to be unreal to you, as if you are in a dream?

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Do you feel as if you are watching the situation as an observer or spectator?
Do you feel disconnected from your own body?
Do you see things as if you were in a tunnel, or looking through a wide-angle photographic lens?
Does this experience seem to take much longer than you would have expected?

Increased dissociative symptoms at the time of trauma predict long-term PTSD (Bremner et al., 1992; Marmar et al., 1994). Although symptoms of dissociation are not part of the DSM criteria for PTSD, they are part of the criteria for acute stress disorder, and symptoms of dissociation are frequently seen in PTSD patients. PTSD patients are observed clinically to have an increased dissociative response to the original trauma, and then have chronic increased susceptibility to dissociative responses to minor stressors and traumatic reminders.

Although the neurobiology of dissociation has been studied less than PTSD, alterations in stress hormones likely play a role in these symptoms. One particular neurotransmitter system that has been hypothesized to play a role in dissociative symptoms is the excitatory amino acid glutamate (Krystal et al., 1994, 1996; Chambers et al., 1999). Glutamate is released during stress (Moghaddam et al., 1997), and high levels of glutamate are associated with toxicity to the hippocampus. Glutamate acts at the N-methyl-D-aspartic acid (NMDA) receptor, and is highly concentrated in the hippocampus. Glutamate is involved in memory at the molecular level. Excessive levels of glutamate can cause cytotoxicity as seen in patients with epilepsy. Stress inhibits glucose utilization, and thereby impairs reuptake of glutamate in glia with associated cytotoxicity.

Several lines of evidence support alterations of glutamatergic function in dissociation. The NMDA antagonist, Ketamine, when administered to normal subjects, results in an increased dissociative symptoms as measured with the CADSS (Krystal et al., 1994). In addition, increased
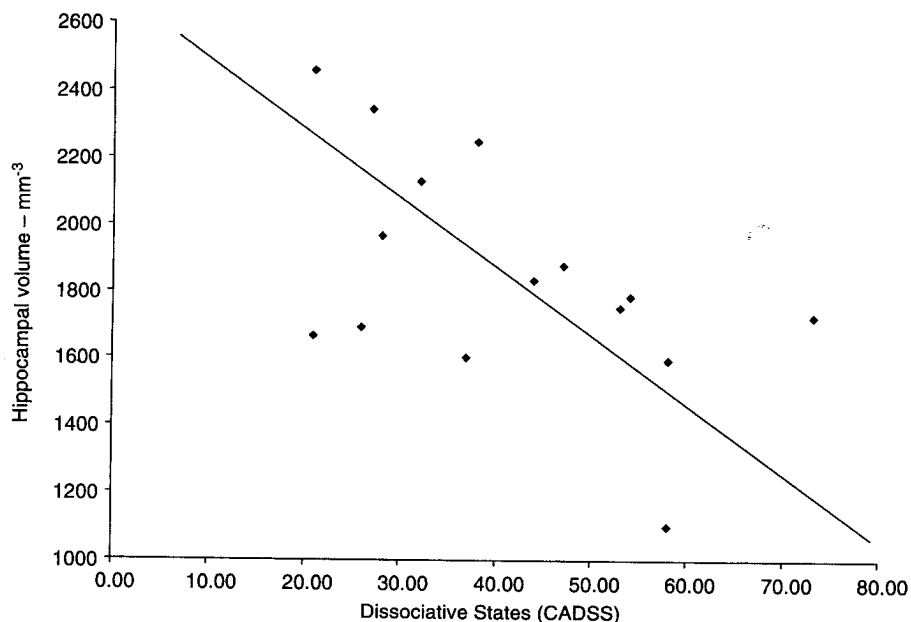

Fig. 2. Relationship between hippocampal volume measured with MRI and dissociative states measured with the CADSS in women with early abuse and the diagnosis of dissociative identity disorder. There was a significant negative correlation between hippocampal volume and dissociative states ($r = -0.54$; df $= 14$; $p < 0.05$), suggesting that increased levels of dissociation were related to smaller hippocampal volume. This correlation was not shown for amygdala volume. In addition there was not an association between level of PTSD symptoms and hippocampal volume in these patients.

dissociative states correlate with smaller volume of the hippocampus (which as noted above has a high concentration of NMDA receptors) in women with early abuse and PTSD (Stein et al., 1997; Bremner et al., 2003b). A correlation between dissociative states as measured with the CADSS and smaller hippocampal volume was seen in women with early abuse and DID (Fig. 2). Phenytoin (dilantin) is an antiepileptic drug that is efficacious in the treatment of epilepsy. Phenytoin modulates glutamatergic function and blocks the effects of stress on the hippocampus in animal studies (Watanabe et al., 1992). We conducted a pilot project in nine PTSD subjects of the effect of phenytoin on symptoms of PTSD and the brain. Phenytoin resulted in a decrease in PTSD symptoms (Bremner et al., 2004a) as well as a 5% increase in right hippocampal and right cerebral volume (Bremner et al., 2005a).

Conclusions

We have presented evidence for long-term alterations in brain and neurobiology in PTSD. Brain areas involved in the stress response include the mPFC, hippocampus, and amygdala. Neurohormonal systems that act on the brain areas to modulate PTSD symptoms and memory include glucocorticoids and norepinephrine. Dysfunction of these brain areas is responsible for symptoms of PTSD.

The related symptom area of dissociation is felt to be related to alterations in glutamatergic function; however, more research is needed in this area.

Brain imaging studies show that PTSD patients have increased amygdala reactivity during fear acquisition. Other studies show smaller hippocampal volume. A failure of medial prefrontal/anterior cingulate activation with re-experiencing of the trauma is hypothesized to represent a neural correlate of the failure of extinction seen in PTSD.

The brain has the capacity for plasticity in the aftermath of traumatic stress. Antidepressant treatments and changes in environment can reverse the effects of stress on hippocampal neurogenesis. In humans with PTSD, paroxetine increases hippocampal volume and improves

memory function in conjunction with improving PTSD symptoms. Phenytoin, which blocks the effects of stress on the hippocampus in animal studies, also increases hippocampal volume in PTSD patients.

Future studies should use brain imaging and neurobiology to assess plasticity in PTSD. These can include both functional neuroimaging and neuroreceptor imaging to track the course of change during treatment, or to predict which traumatized individuals will develop chronic PTSD. The information from such studies will provide valuable information that will guide the development of new treatments.

Abbreviations

ACTH	adrenocorticotropin
BDNF	brain-derived neurotrophic factor
BPD	borderline personality disorder
CRF	corticotropin releasing factor
DHEA	dehydroepiandosterone
DID	dissociative identity disorder
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
NAA	N-acetyl aspartic acid
NMDA	N-methyl-D-aspartic acid
PET	positron emission tomography
PTSD	posttraumatic stress disorder

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