Traumatic Stress, Brain Changes, and Memory Deficits
A Critical Note

Marko Jelicic, PhD, and Harald Merckelbach, PhD*†*

Abstract: Memory deficits are frequently observed in posttraumatic stress disorder. According to some authors, these memory impairments are a result of hippocampal damage caused by traumatic stress. This article contains a critical review of studies on changes in hippocampal volume and memory performance in posttraumatic stress disorder. We conclude that most studies in this area suffer from methodological weaknesses and therefore do no allow for firm conclusions about the causal linkage among traumatic stress, hippocampal functioning, and memory. Suggestions for future research, circumventing methodological flaws, are given.

Key Words: Traumatic stress, PTSD, hippocampus, memory.

(*J Nerv Ment Dis* 2004;192: 548–553)

Poor performance on standard memory tests is frequently observed in patients with posttraumatic stress disorder (PTSD). Bremner et al. (1993) studied memory performance in Vietnam veterans with PTSD and matched controls. They found no differences between the two groups with regard to general cognitive functioning, but patients with PTSD were outperformed by controls on several memory tests. These findings have been replicated in other samples of Vietnam veterans (Uddo et al., 1993), in rape victims (Jenkins et al., 1998), and in other traumatized people (Moradi et al., 1999). Some studies, however, failed to document memory impairments in patients with PTSD (Gil et al., 1990; Stein et al., 1999). Furthermore, cognitive deficits in patients with PTSD are not limited to memory performance; patients with this disorder often perform poorly on attentional tasks as well (Sachinvala et al., 2000; Vasterling et al., 1998).

To account for memory deficits in PTSD, Sapolsky (1996) and Bremner (1999, 2002) proposed the following hypothesis: Prolonged exposure to excessive blood levels of cortisol, a glucocorticoid hormone secreted by the human adrenal cortex during stressful episodes, would lead to atrophy of the hippocampus. Because this structure in the medial temporal lobe plays a vital role in learning new information (*cf*. Squire, 1992), patients with PTSD would often exhibit memory impairments. Note that in his recent book, *Does Stress Damage the Brain?,* Bremner (2002) argued that PTSD is basically a neurological disorder. Referring to the hippocampus and adjacent brain areas, he stated that "stress results in long-term changes in the brain structures and systems that lead to symptoms of stress-related psychiatric disorders, including PTSD and dissociative disorders" (p. 222).

The stress-induced glucocorticoid toxicity hypothesis put forward by Sapolsky (1996) and Bremner (1999) is consistent with several observations. For instance, elevated blood levels of cortisol may cause memory deficits. Hypersecretion of cortisol is one of the features of Cushing syndrome (Tirell et al., 1994). A number of studies have shown that patients with this syndrome perform worse on memory tests than matched controls (Mauri et al., 1993; Starkman and Schteingart, 1981). Moreover, the degree of memory impairment in Cushing syndrome seems to be related to hippocampal volume as measured with magnetic resonance imaging (MRI). That is, a smaller hippocampus has been found to be associated with poorer memory performance (Starkman et al., 1992). In a similar vein, Lupien et al. (1998) noted that an increase in cortisol levels over a 4-year period in normal elderly subjects was accompanied by a decline in memory performance and loss of hippocampal volume, determined with MRI. Note that cortisol levels are often lowered in patients with PTSD (Golier and Yehuda, 1998; Yehuda, 2001). According to Bremner (1999, 2002), such lowered cortisol levels in PTSD do not necessarily pose a problem for the glucocorticoid toxicity hypothesis. This author argued that exposure to high levels of cortisol—brought about by chronic traumatic stress—eventually may lead to dysregula-

*Department of Experimental Psychology, University of Maastricht, Maastricht, The Netherlands; and †Faculty of Law, University of Maastricht, The Netherlands.

Supported by a grant from the Dutch Organisation for Scientific Research NWO (grant # 452-02-006-A).

Send requests for reprints to Marko Jelicic, Department of Experimental Psychology, University of Maastricht, P. O. Box 616, 6200 MD Maastricht, The Netherlands.

ISSN: 0022-3018/04/19208-0548
DOI: 10.1097/01.nmd.0000135494.20416.59

tion of the cortisol system (the hypothalamus-pituitary-adrenal cortex system) in PTSD. As a result, levels of cortisol would sometimes be lowered in patients with PTSD. Although this argument seems to possess some prima facie plausibility, it is difficult to reconcile with the observation that in laboratory animals, chronic stress is associated with permanently elevated cortisol levels. No drop in cortisol has been observed in animals after chronic stress (McEwen and Sapolsky, 1995). Even if one accepts the idea that high cortisol levels during stress may eventually cause lowered levels of this stress hormone, low cortisol in PTSD does hurt the glucocorticoid toxicity hypothesis. It has recently been found that a reduction in cortisol level in patients treated for Cushing syndrome was related to an improvement in memory performance and an increase in hippocampal volume, measured with MRI (Starkman et al., 2003).

In a number of studies, MRI techniques have been used to measure hippocampal volume in patients with PTSD and matched control participants. In most of these investigations, participants were also administered memory tests. MRI studies that found hippocampal abnormalities in PTSD are interpreted by Sapolsky (1996), Bremner (1999, 2002), and other authors (Brown et al., 1998) as providing strong evidence for the glucocorticoid toxicity hypothesis. Some authors have even gone as far as to view this hypothesis as a validated part of neuroscientific evidence. A case in point is Joseph (1999), who summarizes the state of art in this research domain as follows: "Depending on individual differences and the degree of repetitive nature of the trauma, memory loss may range from minimal to a profound dissociative amnesia; a consequence of the secretion and buildup of a variety of stress-related neurochemicals including glucocosteroids which can injure and induce hippocampal atrophy" (p. 722). Similarly, Elzinga and Bremner (2002) recently stated that "imaging studies in PTSD are consistent with the hypothesis that stress affects the hippocampus" (p. 11). Unfortunately, methodological limitations of the MRI evidence for the glucocorticoid toxicity hypothesis are often ignored (see for exceptions Jelicic and Bonke, 2001; McNally, 2003; Pitman, 2001; Yehuda, 2001). In addition, advocates of the glucocorticoid toxicity hypothesis address the issue of causality only superficially. Does traumatic stress cause brain abnormalities? Or do brain abnormalities predispose to PTSD? The aim of this critical note is to evaluate the status of the hypothesis that traumatic stress may lead to structural brain changes and memory deficits. Although Hull (2002) also reviewed the literature in this area, his article did not focus on methodological issues. Our note consists of the following sections. First, we review studies measuring hippocampal volume and memory performance in patients with PTSD and controls. Special attention is given to methodological aspects of these studies. Next, our focus is on the causal linkage among hippocampal abnormalities, memory deficits, and PTSD. Finally, we discuss the current status of the glucocorticoid toxicity hypothesis. Suggestions for future research in this area are also given.

REVIEW OF THE MAGNETIC RESONANCE IMAGING EVIDENCE

Both the Medline and the PsycInfo databases were searched using combinations of key words such as *MRI*, *hippocampus*, *posttraumatic stress disorder*, and *traumatic stress*. Nine empirical studies, eight with a cross-sectional and one with a longitudinal design, were identified. Three studies focused on combat veterans with PTSD. Bremner et al. (1995) studied 26 Vietnam combat veterans with PTSD and 22 control participants matched for age, demographic characteristics, and alcohol abuse. Hippocampal volume was measured with MRI, and memory performance was assessed with the Wechsler Memory Scale (WMS). Patients with PTSD had a 8% smaller right hippocampal volume relative to that of the controls. Although patients performed worse on verbal memory measures than controls, there were no differences between the two groups with regard to nonverbal memory performance. In the patients subsample, verbal memory deficits were correlated with right hippocampal volume—that is, poor performance on memory tests was associated with a smaller hippocampus. Note that the two groups were not matched for drug abuse and that almost all patients with PTSD suffered from comorbid psychiatric disorders, most notably depression. Myslobodsky et al. (1995) relied on MRI techniques to detect brain abnormalities in 10 combat veterans with PTSD and 10 without a psychiatric disorder. Patients and controls were matched for age, socioeconomic background, and military experience. In half of the PTSD patients, a small cleft was observed in the colossal-septal interface. No other neuroanatomic abnormalities were found in the patients. Given the small sample size, it is possible that this study lacked statistical power to detect hippocampal atrophy in the patients with PTSD. In a study by Gurvits et al. (1996), seven Vietnam combat veterans with PTSD were compared with seven combat veterans without PTSD. Hippocampal volume was measured with MRI, and cognitive functions were assessed with a battery of neuropsychological tests (including the WMS). After controlling for age and alcohol abuse, patients with PTSD patients had a smaller left hippocampus than the controls. There were no differences between the two groups on any of the seven memory measures, but this might have been a result of the small sample size. Hippocampal volume in patients with PTSD was correlated with only one memory test. Again, it is noteworthy that the PTSD group had more comorbid psychiatric disorders than the control group.

In four studies, the focus was on survivors of childhood abuse with PTSD. Bremner et al. (1997) studied adult 17 survivors of physical or sexual childhood abuse or both with

PTSD and 17 control participants matched for age, demographic characteristics, and alcohol abuse. MRI was used to measure hippocampal volume, and parts of the WMS were used to assess verbal memory performance. The patients with PTSD had a 12% smaller left hippocampal volume than controls. Patients performed worse than controls on several verbal memory measures, but none of the memory tests was correlated with hippocampal volume. Most of the patients with PTSD had from comorbid psychiatric disorders, mainly depression. In a study by Stein et al. (1997), 21 adult survivors of severe childhood sexual abuse were compared with 21 control participants matched for age and demographic variables. People currently suffering from a major psychiatric disorder and those with a history of head injury were excluded from the study. Hippocampal volume was measured with MRI, and participants were also administered some cognitive tests, including the California Verbal Learning Test. Survivors of childhood abuse had a 5% smaller left hippocampus than controls. There were no differences between the two groups with regard to cognitive performance. No correlations between hippocampal volume and memory measures were found. Although none of the survivors of childhood abuse currently suffered from a major psychiatric disorder, they did report more depressive symptoms than controls. In addition, they reported more alcohol and drug use relative to the controls. Bremner et al. (2003) studied hippocampal volume with MRI in 22 adult survivors of childhood abuse with ($N = 10$) or without PTSD ($N = 12$) and 11 control participants. The three groups were matched for age and demographic variables. None of the participants was currently abusing substances or alcohol. It was found that the patients with PTSD had a 16% smaller volume of the hippocampus than the participants with a history of abuse and without PTSD. The patients with PTSD had a 19% smaller hippocampus relative to the normal controls. Note that 80% of the patients with PTSD (and 25% of the participants with abuse and without PTSD) fulfilled the criteria for a lifetime history of major depression. Instead of studying adult survivors of childhood abuse, De Bellis et al. (1999) investigated brain abnormalities in maltreated children and adolescents with PTSD. MRI was used to measure the volume of different brain structures in 44 patients with PTSD and 61 matched controls. It was found that several brain structures were smaller in patients with PTSD than in control participants. However, no reduction of hippocampal volume was observed in the children and adolescents with PTSD.

One longitudinal study has been published on hippocampal abnormalities in PTSD. Using MRI, Bonne et al. (2001) measured hippocampal volume in 37 survivors of traumatic events within a week of the event and 6 months later. Ten survivors had developed PTSD at follow-up. These survivors did not differ from those without PTSD in hippocampal volume at 1 week or 6 months. Moreover, in survivors with PTSD, there was no reduction in hippocampal volume between the first and second measurement. Note, however, that the survivors had been exposed to a single traumatic event.

Finally, in a recent study by Driessen et al. (2000), 21 female patients with borderline personality disorder (BPD) and a healthy control group were compared with respect to MRI volumes of the hippocampus and the amygdala, self-reported traumatization, depression, and neuropsychological functioning. As expected, patients with BPD had higher depression levels and reported more childhood traumas than controls. In addition, volumetric findings indicated that patients had smaller (bilateral) volumes of the hippocampus (16%) and the amygdala (8%) than controls. Interestingly, performance on neuropsychological tests, including memory tasks, was related to depression rather than hippocampal volumes. Although patients with BPD differ from those with PTSD in many respects, we decided to include this study in the current article because childhood trauma is thought to be related to BPD (see Goodman and Yehuda, 2002, for a discussion).

METHODOLOGICAL ISSUES

At first sight, most studies cited above seem to yield evidence for the hypothesis that traumatic stress may lead to hippocampal damage and memory deficits (Bremner, 1999, 2002; Sapolsky, 1996). Only Myslobodsky et al. (1995), DeBellis et al. (1999), and Bonne et al. (2001) failed to find evidence for reduced hippocampal volume in patients with PTSD. However, studies that reported differences between patients with PTSD or BPD and controls are equivocal with respect to hippocampal laterality. Sometimes a smaller right hippocampus is observed (Bremner et al., 1995), whereas in other cases, a smaller left hippocampus is found (Bremner et al., 1997; Gurvits et al., 1996; Stein et al., 1997), and in two studies, the volumetric reduction is bilateral (Bremner et al., 2003; Driessen et al., 2000).

Can traumatic stress be held responsible for reduced hippocampal volume in patients with PTSD or BPD? Most studies cited above suffer from one or more methodological drawbacks that make it impossible to answer this question. There are five methodological issues that deserve some comment. First, Kopelman (2002) argued that some of the first studies in this area—for instance, the study by Bremner et al. (1995)—have used rather crude MRI measurements. Second, selection of control participants may have been a source of confounding variables in at least some of the cross-sectional studies. Bremner et al. (1995) compared combat veterans with PTSD with controls who had no military experience. Likewise, in the studies by Bremner et al. (1997) and Stein et al. (1997), survivors of childhood abuse with PTSD were compared with participants who had not been traumatized during childhood. Much the same is true for the study by

Driessen et al. (2000), who compared patients with BPD with healthy controls. Possibly, people with prolonged combat experience or with a history of childhood abuse may have sustained hippocampal damage caused by head injury (Warden et al., 1996). In virtually all cross-sectional studies, patients with PTSD also had more comorbid psychiatric disorders than control subjects. The majority of participants with PTSD were suffering from depression. Of course it would have been possible to control statistically for the effect of depressive symptomatology on hippocampal volume (*e.g.*, by using analysis of covariance), but most authors failed to apply such a statistical correction. Note that there is growing evidence that depression is accompanied by hippocampal abnormalities (Mervaala et al., 2000; von Gunten et al., 2000). The question then arises: are reductions in hippocampal volume observed in patients with PTSD caused by exposure to traumatic stress or depressive symptoms?

Most studies cited above use a cross-sectional design. It is intuitively tempting to take neuroanatomic abnormalities (*i.e.*, reduced hippocampal volumes) as antecedents and memory performance as consequences. However, the literature on ventricular enlargement in schizophrenia reminds us of the fact that one should be cautious in making such causal inferences (Harrop et al., 1996). Thus, it is conceivable that patients with PTSD had relatively small hippocampi before developing any symptoms. Soldiers with learning disabilities caused by hippocampal abnormalities may have been sent to the battlefront earlier than soldiers without cognitive impairments (Warden et al., 1996). In addition, people with a relatively small hippocampus may be more vulnerable to develop a psychiatric disorder in the face of psychological trauma. The finding that people with relatively low IQs are at a higher risk to develop PTSD is in line with this possibility (Macklin et al., 1998). The idea that smaller hippocampi might be a risk factor for PTSD is supported by two other studies. Bremner et al. (2003) reported that survivors of childhood abuse who developed PTSD had less hippocampal volume than survivors of such abuse who did not develop PTSD. In a somewhat related vein, Gilbertson et al. (2002) found that patients with PTSD and their identical twins had smaller hippocampi than controls. This latter finding indeed suggests that a small hippocampus is a risk factor for PTSD and not a consequence of psychological trauma.

To circumvent problems with causality, Bonne et al. (2001) used a prospective design to study the relationship between traumatic stress and the development of hippocampal abnormalities. These authors failed to find evidence for a reduction in hippocampal volume in victims who had developed PTSD. On the other hand, participants in their study were survivors of a single traumatic event. As a consequence, their cortisol levels may have been elevated for a relatively short period—not long enough to cause hippocampal damage.

A fourth point that needs to be emphasized has to do with memory performance measures. In contrast with a range of previous studies (Bremner et al., 1993; Jenkins et al., 1998; Moradi et al., 1999; Sachinvaala et al., 2000; Uddo et al., 1993; Vasterling et al., 1998), patients with PTSD were not ubiquitously outperformed by controls in the studies reviewed above. Bremner et al. (1997) found that patients with PTSD performed worse than controls on a series of memory tests. A few years earlier, Bremner et al. (1995) reported that controls performed better on verbal memory tests than patients with PTSD but not on nonverbal memory measures. To complicate matters even more, Gurvits et al. (1996) and Stein et al. (1997) were unable to find differences in memory performance between the two groups. Although these null effects may reflect insufficient statistical power, it might also be that memory impairments in PTSD are generally quite mild (Vasterling et al., 1998). On a related note, in the studies reviewed above, the relationship between hippocampal abnormalities and memory deficits in PTSD is not a very robust one. Bremner et al. (1995) reported a straightforward correlation ($r = 0.64$) between hippocampal volume and memory performance in patients with PTSD. Other studies, however, did not yield clear evidence for an association between volume of the hippocampus and impairments of memory (Bremner et al., 1997; Gurvits et al., 1996; Stein et al., 1997). Thus, although hippocampal abnormalities can be observed in patients with PTSD, they are not invariably associated with memory deficits. A fifth and final point concerns the issues of self-reports. To some extent, information about severity of PTSD symptoms and previous traumatization critically depends on self-reports of patients. There are good reasons to consider the possibility that at least some patients with PTSD (*e.g.*, combat veterans) have a tendency to overreport symptoms (Frueh et al., 2000) and to give inflated accounts of previous trauma (Roemer et al., 1998). Such biased self-reports may spuriously increase or decrease correlations among hippocampus volumes, PTSD symptoms, and memory performance.

DISCUSSION

What is the empirical support for the idea that traumatic stress may cause memory impairments through hippocampal damage (Bremner, 1999, 2002; Sapolsky, 1996)? Given that most studies in this area have methodological limitations, it would be an overstatement to claim that this idea has a firm empirical basis. Because causal relationships cannot be determined, cross-sectional designs may not be very well suited to study hippocampal damage in patients with PTSD. Hence, we promote longitudinal research into the relationship between traumatic stress and hippocampal volume. In contrast with the study by Bonne et al. (2001), it would be preferable to study people who are frequently exposed to well-documented traumatic events, such as ambulance drivers or rescue

workers (Aardal-Erikson et al., 1999). Hippocampal volume may then be measured at baseline, right after having started the job, and some time later, when some people have developed the symptoms of PTSD. To find out whether changes in hippocampal volume are caused by elevated levels of cortisol as suggested by Sapolsky (1996) and Bremner (1999, 2002), cortisol levels—at both baseline and follow-up—might also be determined. Although memory performance does not seem to be reliably correlated with hippocampal volume in PTSD, subjects should also be administered some memory tests at both occasions.

In contrast with the hypothesis put forward by Sapolsky (1996) and Bremner (1999, 2002), cortisol levels are often lowered in PTSD (Golier and Yehuda, 1998; Yehuda, 2001). Hence, it could be that memory deficits in PTSD are caused by factors other than hippocampal abnormalities. Vasterling et al. (1998), for instance, pointed out that patients with PTSD do not exhibit global memory deficits, but rather seem to perform poorly on memory tests because of commission and intrusion errors. According to these authors, arousal dysregulation may be held responsible for the pattern of selective memory impairments and poor attentional performance in PTSD. Elevated levels of arousal might lead to mild deficits in acquisition of information, and somewhat greater deficits in retrieval from memory. Retrieval of recently learned information would be especially problematic because hyperarousal reduces the ability of inhibiting inaccurate responses and filtering irrelevant information. Recently, positron emission tomography and functional MRI have been used to study active brain processes in patients with PTSD and control participants (Lanius et al., 2001; Shin et al., 1999). While their brains were scanned, participants were presented with a trauma-related story. Less activation was found in the thalamus and prefrontal cortex in patients with PTSD relative to controls. Because both the thalamus and the prefrontal cortex are involved in arousal modulation (Stuss and Benson, 1986), this finding would support the notion of arousal dysregulation in PTSD. Evidence for the memory-undermining effects of stressful intrusions comes also from research on the phenomenon of overgeneralized memories. Several studies have found that patients suffering from PTSD find it difficult to react with specific autobiographical memories to cue words (Harvey et al., 1998; McNally et al., 1995). Because of its close links to autobiography and problem-solving abilities, the phenomenon of overgeneral recall is highly relevant to both clinicians and researchers in the area of psychopathology. Indeed, it would be interesting for future studies to examine whether overgeneral recall is related to hippocampal volumes in patients with PTSD.

Summing up, the glucocorticoid toxicity hypothesis is an intriguing notion that has inspired a series of recent studies. Although these studies have yielded interesting findings, they have also reported conflicting results. Moreover, most studies in this area have methodological drawbacks. As it stands, the glucocorticoid toxicity hypothesis is just what it is: an interesting hypothesis that is in need of further empirical testing. Currently, it cannot be considered a validated part of clinical neuroscience.

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