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# Structural and Functional Neuroplasticity in Relation to Traumatic Stress

**Iris-Tatjana Kolassa and Thomas Elbert**

*University of Konstanz, Konstanz, Germany*

**ABSTRACT**—***The body's stress response is an essential adaptive and protective mechanism to cope with threatening situations. However, chronic or traumatic stress leads to structural and functional alterations in the traumatized brain. We argue for a building-block effect: Exposure to different types of traumatic events increases the probability of developing posttraumatic stress disorder (PTSD), via incremental enlargement of a fear network. We summarize evidence of brain changes in PTSD, including recent results from research on animal models of stress-related neuroplastic remodeling, with an emphasis on structural and functional changes in the hippocampus, the amygdala, and the medial prefrontal cortex.***

**KEYWORDS**—*amygdala; hippocampus; neuroplasticity; posttraumatic stress disorder; stress*

The human brain and body are capable of dealing with stressors such as danger or violent experiences in a flexible and adaptive way. Chronic or repeated traumatic stress, however, can damage organs, including the brain, and may weaken regulatory functional systems such as the hypothalamic-pituitary-adrenal (HPA) axis. The hippocampus and the HPA axis are involved in the feedback regulation of the stress hormone cortisol and thus in the body's reaction to danger. Regulatory dysfunctions in these systems in the aftermath of highly stressful life events may result in mental illness. Whereas stressful life events like bereavement or role changes can lead to depressive disorders, exposure to extreme (traumatic) stress may lead to posttraumatic stress disorder (PTSD).

PTSD is characterized by ongoing, intrusive (i.e., uncontrollable) memories, including nightmares; a constant state of alarm (hyperarousal); and avoidance symptoms, including emotional numbing. Sleep disturbances, substance abuse, depression, and enhanced risk for suicide are common consequences, as are poor self-reported well-being, poor physical health, and increased health-care utilization.

Traumatic stress refers to potentially harmful experiences eliciting feelings of helplessness, intense fear, or horror, with an associated alarm response (cf. Elbert, Rockstroh, Kolassa, Schauer, & Neuner, 2006)—that is, the acute release of stress hormones. Each such experience is appropriately referred to as a trauma (Greek for "wound"); traumas render a person more vulnerable to develop PTSD in a cumulative manner.

## BUILDING BLOCKS: DIFFERENT TRAUMATIC STRESSORS ADD UP TO PRODUCE PTSD

Investigating more than 3,000 war refugees with varying degrees of traumatic stress exposure, Neuner et al. (2004) found that the greater the number of various types of traumatic events experienced by an individual (e.g., torture, fighting, shelling, abduction, abuse/rape, forcible female circumcision), the more likely the individual was to have PTSD, with more pronounced symptoms. PTSD prevalence rates reached 100% for individuals having experienced 28 or more different traumatic-event types (Fig. 1)—a "building block" effect. Neuner et al. interpreted this to mean that nearly anyone would develop PTSD if they were exposed to a sufficiently high number of different traumatic stressors.

This building-block effect may be a direct result of the development of a neural fear network, which is strengthened and extended in response to each new traumatic event (cf. Elbert et al., 2006). During a traumatic event, perceptual and emotional features of the situation are stored in memory—autobiographical context information (dates, external circumstances) as neutral or "cold" memories and sensory-perceptual information (fear, helplessness, high pulse) as emotionally charged or "hot"

Address correspondence to Iris-Tatjana Kolassa, Department of Psychology, Clinical & Neuropsychology, University of Konstanz, 78457 Konstanz, Germany; e-mail: iris.kolassa@uni-konstanz.de.

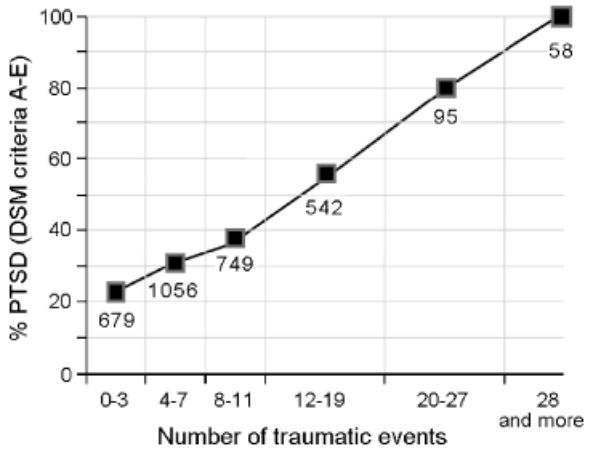


**Fig. 1.** Point prevalence of posttraumatic stress disorder (PTSD; i.e. the proportion of people in the population who fulfilled criteria of PTSD at the time of measurement) as a function of number of lifetime traumatic events. Number of individuals in each group is also given. The near linear rise of PTSD probability with traumatic-event load has been demonstrated in several large-scale studies. Figure adapted from Neuner et al. (2004).

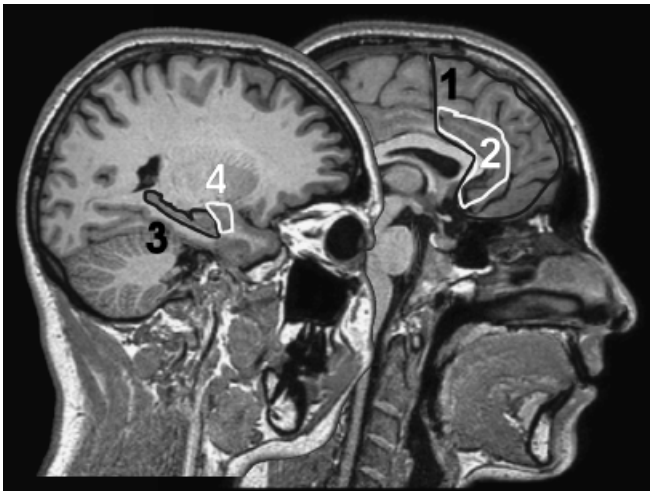


**Fig. 2.** The major brain regions associated with posttraumatic stress disorder: medial prefrontal cortex (1); including the anterior cingulate cortex (2), hippocampus (3), and amygdala (4).

memories (Metcalve & Jacobs, 1996), forming the nucleus of a network associated with the traumatic event. Subsequent traumatic events are associated with similar hot memories, leading to the integration of additional hot and cold memories into the existing fear network. Network connections are strengthened through synchronous activation via long-term potentiation: Neural assemblies firing repeatedly in synch will tend to become associated, so that activity in one facilitates activity in the other. When the fear network is fully formed, the activation of a single memory item (e.g., seeing a man in a uniform or feeling one's heartbeat) will cause the whole network to be activated in a cascade. Thus, memories of specific traumatic events will merge into an indistinct whole, and a fragmentation of autobiographic context memory results: it becomes harder and harder to associate specific cold memories with each traumatic experience (e.g., specific times, dates, locations and situation-specific information; cf. Elbert & Schauer, 2002). Consequently, traumatized persons often have difficulties in reconstructing dates and sequences of events associated with traumatic experiences (Foa & Riggs, 1993; cf. also McNally, 2006).

## BRAIN REGIONS IMPLICATED IN PTSD

Neuropsychological research suggests that exposure to traumatic events and the consequent alterations in stress hormones cause alterations in the structure and functioning of the brain, affecting brain systems involved in learning, memory, and affective regulation. The amygdala, the hippocampus, and the medial prefrontal cortex (mPFC), which includes the anterior cingulate cortex (ACC), appear to be particularly involved in trauma-related neurocircuitry (cf. Shin, Rauch, & Pitman, 2006; Fig. 2).

The amygdala is involved in the assessment of threat-related stimuli (cf. Shin et al., 2006). It has been suggested to be at the centre of a defence system involved in the acquisition and expression of conditioned fear. It receives information from all sensory modalities and projects to various subcortical structures involved in mediating specific signs of fear and anxiety, such as facial expression of fear, stress-hormone release, galvanic skin response, blood-pressure elevation, hypoalgesia (a decreased sensitivity to painful stimuli), and freezing. The amygdala thus plays a pivotal role in mediating stress-related effects on behavior and modulating hippocampal function.

The hippocampus is vital to memory formation and emotional regulation by putting specific events into their proper context, binding together multiple events that co-occur during an experience, and converting short-term into long-term memories. Thus, it plays a central role in the encoding of context during fear conditioning.

The mPFC inhibits activation of the amygdala and is involved in the extinction of conditioned fear. The mPFC includes the anterior cingulate cortex (ACC), which is implicated in evaluating the emotional significance of stimuli and in attentional function (Cardinal, Parkinson, Hall & Everitt, 2002).

## EVIDENCE FOR STRUCTURAL BRAIN CHANGES IN PTSD

### Studies on Animals

Animal studies, in particular research on tree shrews (*tupaia belangeri*), have revealed alterations in the ability of the hippocampus to change in response to various stressors, including less long-term potentiation, decreased formation of new nerve cells in the dentate gyrus (a subregion of the hippocampus), decreased hippocampal cell survival, and increased programmed

cell death (a regulated process that leads to the death of a cell in an organism; cf. Duman, 2005).

In the medial prefrontal cortex (mPFC), chronic stress results in atrophy of dendrites, whereas dendritic hypertrophy (overgrowth) is found in the amygdala. Thus, stress can lead to different changes in brain plasticity in different regions. Evidence exists that stress-induced atrophy is reversible in the hippocampus and mPFC once stress has ceased. However, amygdala hypertrophy appears less readily reversible. This might be one reason why PTSD symptoms often diminish very slowly and sometimes not at all (Miller & McEwen, 2006).

### Studies on Humans

A series of cross-sectional studies examined structural abnormalities of the hippocampus and other brain regions in subjects having experienced various traumas. A meta-analysis by Karl et al. (2006) found that individuals with traumatic experiences but without PTSD showed significantly smaller left hippocampal volume compared to nonexposed controls. A subset of studies even revealed bilaterally reduced hippocampal volume in such individuals. In addition, Karl et al. reported smaller hippocampal volumes in PTSD patients compared to trauma-exposed and non-exposed controls. Among PTSD patients, higher severity of PTSD was associated with medium-to-large bilateral hippocampal volume reduction, while moderate PTSD was associated with small effects, which may be a neurological correlate of the building-block effect of traumatic events posited above.

Abnormalities in the size of various brain structures in PTSD are not restricted to the hippocampus, although the effect sizes in other brain structures are smaller than in the hippocampus (Karl et al., 2006). Individuals with PTSD show smaller left amygdala volumes than trauma-exposed and nonexposed controls do. In addition, PTSD patients show smaller ACCs compared to trauma-exposed controls. It has been suggested that the ACC responds to the emotional significance of stimuli and uses this information to differentiate between similar conditioned stimuli: It thus helps in keeping conditioned reactions specific to the stimulus that was conditioned (Cardinal et al., 2002). In line with the fear-network model introduced above, various stimuli—and sometimes ones with only a peripheral association with the trauma—can trigger flashbacks and intrusions in people with PTSD. Thus, the functioning of the ACC may be disturbed in PTSD patients.

### Chicken or Egg?

It has been proposed that a smaller hippocampus may not only be a consequence of PTSD but may also reflect a genetic or at least a constitutional vulnerability for developing PTSD in the aftermath of traumatic events (McNally, 2006)—which could lead to selection effects in hippocampus studies. Gilbertson et al. (2002) studied monozygotic twins in which one member of each pair experienced combat in Vietnam while the other stayed at home. Combat veterans who developed PTSD had smaller hippocampi than combat veterans without PTSD. Crucially, the stay-at-home siblings of PTSD combat veterans also had smaller hippocampi, and the hippocampal volumes of the stay-at-home siblings were even negatively correlated with the severity of the combat siblings' PTSD. Thus, a smaller hippocampus may well be a predisposing factor to develop PTSD after a traumatic event. However, one could argue that both siblings with small hippocampi had been exposed to childhood traumas that may have led to smaller hippocampal volume. Indeed, both combat-exposed and combat-unexposed twins in pairs where the combat twin developed PTSD reported higher lifetime stress than pairs without PTSD did. However, the effect was insignificant, which may be due to the small number of participants.

Nevertheless, Gilbertson et al.'s (2002) study supports the building-block effect of repeated traumatic events as posited above: Combat veterans with PTSD reported more lifetime traumatic events than either their stay-at-home siblings or combat veterans without PTSD. Thus, a smaller hippocampus may be a predisposing factor for developing PTSD in the context of a dose-response relationship—the "critical dose" of different traumatic-event types needed to develop PTSD may decrease with decreasing hippocampal volume.

One problem in the field is that most studies investigating hippocampal atrophy in the aftermath of trauma have been cross-sectional. A longitudinal study by Bonne et al. (2001) investigated recent trauma survivors 1 week and 6 months after trauma and compared those who developed PTSD to those who did not develop PTSD. There was no significant difference in hippocampal volumes between the two groups at either time point, nor a reduction of hippocampal volume within participants. However, we do not know how long neuroplastic and degenerative changes take to influence hippocampal volume. Effects may appear after a longer interval after the traumatic event, as a consequence of more chronic and complicated PTSD, or after experiencing a higher traumatic load. Bonne et al. did not analyze the number of different traumatic-event types experienced by each individual.

In support of an effect of trauma on hippocampal volume, Carrion, Weems, and Reiss (2007) found that PTSD symptoms and prebedtime cortisol predicted hippocampal reduction in traumatized children over an ensuing 12- to 18-month interval. Thus, there is evidence for trauma-related reduction in hippocampal volume when one investigates a longer time frame.

## EVIDENCE FOR FUNCTIONAL CHANGES IN PTSD

In functional neuroimaging research, individuals with PTSD are typically presented with reminders of their trauma, to compare brain activations in response to trauma-related vs. neutral stimuli or to compare their activations to a matched non-PTSD control group. The major brain structures under investigation

have been the hippocampus, the amygdala, the mPFC, and Broca's area.

A few studies have investigated hippocampal function in PTSD. Findings are mixed, ranging from no or lower activation of the hippocampus during cognitive tasks to increased hippocampal activation at rest or across tasks (cf. Shin et al., 2006).

Amygdala sensitivity is enhanced in PTSD patients, even in response to non-trauma-related arousing stimuli. In addition, positive correlations between the severity of PTSD symptoms and blood flow in the amygdala during exposure to trauma-related stimuli have been found (cf. Shin et al., 2006). Consequently, emotional or sensory triggers may more easily elicit vivid memories of traumatic events or even induce flashbacks.

Patients with PTSD show decreased activity in the mPFC (Bremner et al., 1999) and ACC (Shin et al., 2006). The decreased activation of the ACC may be associated with the inability of people with PTSD to extinguish fear (Hull, 2002). Intrusive memories of the trauma accompanied by hyperarousal—both common in PTSD—are consistent with either a more responsive amygdala, a less active mPFC, or both (Shin et al., 2006).

Various studies reported a deactivation of Broca's area during paradigms designed to provoke PTSD symptoms (cf. Hull, 2002). Broca's area is the anterior language area located in the left frontal cortex of right-handed people. It is a common experience in clinical practice that PTSD patients have extreme difficulties verbalizing their traumatic experiences because the quality of emotional memories while re-experiencing is more emotional and sensory in nature.

However, while functional changes have been found in PTSD patients, it is unclear how these results are to be interpreted. Are neurons damaged, leading to less firing? Or has the number of neurons decreased? Or is functional connectivity between neurons changed in PTSD?

## GENETIC PREDISPOSITIONS

Recently, genetic variations that influence stress sensitivity and the building of emotional memories have come under scrutiny. For example, de Quervain et al. (2007) studied a Swiss population and found that individuals with a specific variant (deletion variant) of the gene coding for the alpha(2B)-adrenoceptor, a synaptic-membrane receptor targeted by stress hormones, show enhanced memory for emotionally arousing pictures (positive and negative, compared to neutral photographs taken from the international affective picture system, IAPS; Lang et al., 2005). Correspondingly, in survivors of the Rwandan genocide suffering from PTSD, the deletion variant was related to increased traumatic memory as measured by the intrusion-symptom score (Fig. 3).

This suggests that the price to pay for the deletion-related enhancement in emotional memory is increased traumatic memory, one of the core features of PTSD. Thus, genetics may influence stress sensitivity and vulnerability to adverse consequences after traumatic events, while any connection to neurological changes is so far unknown.

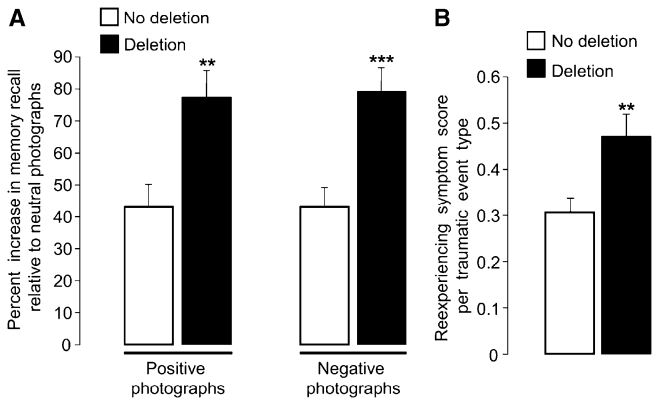


**Fig. 3.** Percent increase in memory recall of positive and negative photographs relative to neutral photographs for individuals with (deletion group) and without (no-deletion group) the specific genetic variation of the alpha(2b)-adrenergic receptor (A); and reexperiencing-symptom score per traumatic-event type (i.e., number of different traumatic events experienced by one person, such as being beaten, threatened with weapons, seeing mutilated bodies, etc.) for persons with (deletion group) and without (no-deletion group) the genetic variation (B). (Depicted are means and standard errors. Significance values: $^{**}p < .01$; $^{***}p < .001$. From "A Deletion Variant of the α2b-Adrenoceptor Is Related to Emotional Memory in Europeans and Africans," by D.J.-F. de Quervain, I.-T. Kolassa, V. Ertl, L.P. Onyut, F. Neuner, T. Elbert, & A. Papassotiropoulos, 2007, *Nature Neuroscience*, *10*, p. 1138. Reproduced with permission.

## CONCLUSIONS AND FUTURE DIRECTIONS

Animal research suggests a coherent picture of stress-induced atrophy in the hippocampus and the mPFC and of hypertrophy in the amygdala. Studies in PTSD patients indicate volumetric as well as functional changes in the hippocampus, amygdala, and mPFC, while the cause–effect relationship is unclear. In addition, functional alterations in Broca's area have been reported.

One key problem is that most existing studies on the neurological underpinnings of PTSD are cross-sectional. Changes in brain structure and function in response to traumatic events, PTSD development, or even PTSD therapy could better be understood from longitudinal studies. Unfortunately, ethical studies are hard to design in this field.

Future studies on PTSD need to take into account that hippocampal atrophy may be both a consequence of traumatic stress and a marker for increased vulnerability for PTSD, via a building-block effect. Thus, future research on the effects of traumatic stress on humans should focus on individuals who experienced traumatic events but did not develop PTSD, as well as analyze the number of different lifetime traumatic events, in order to better understand the building-block effect and the development of the fear network.

One implication of the neurological correlates of traumatic stress is that it may become possible to validate treatment

approaches to PTSD on a biological level. Indeed, the first evidence of functional changes due to exposure treatment have been found—for example, exposure therapy has been found to lead to reduced amygdala activation and increased ACC activation during fear processing (Felmingham et al., 2007)—which implies that structural and functional neuronal changes in PTSD may be reversible.

**Recommended Reading**

Kim, J.J., & Diamond, D.M. (2002). Distressed hippocampus, synaptic plasticity and lost memories. *Nature Reviews Neuroscience*, *3*, 453–462. A detailed overview of the neurobiology of stress–memory interactions.

Gillepsie, C.F., & Nemeroff, C.B. (2007). Corticotropin-releasing factor and the psychobiology of early-life stress. *Current Directions in Psychological Science*, *16*, 85–89. A clearly written overview for readers who wish to expand their knowledge on the neuroendocrine and psychiatric consequences of stress and trauma during childhood.

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