# CHAPTER 1

# Posttraumatic stress disorder: from neurobiology to clinical presentation

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## 1.1 PTSD: prevalence, risk factors, and etiology

Posttraumatic stress disorder (PTSD) is a chronic, disabling, and prevalent anxiety disorder. It is triggered by exposure to a psychologically traumatic event, yet only a minority of those exposed actually develop the disorder. Trauma characteristics, as well as genetic, biological, and psychosocial risk factors, contribute to the occurrence of PTSD among survivors of traumatic events. PTSD, therefore is a prime example of gene-environment and psycho-biological interaction. There is a large amount of research in animals on the effects of stress on neurobiology. This has been translated into clinical neuroscience research in PTSD patients. The overarching goal is for our understanding of the neurobiology of the stress response and the long-term effects of stress on stress-responsive systems to inform treatment approaches to PTSD patients. The chapters in this volume, from researchers in all areas of the stress field, including basic scientists as well as research and clinical psychologists and psychiatrists, illustrate the advances in the field that have continued to move from neurobiology to treatment of PTSD. This chapter serves as an introduction to the volume and gives a broad overview of the field.

Posttraumatic stress disorder was first recognized as a distinct psychiatric disorder in the third edition of the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; APA, 1981). Subsequent studies have established – and slightly modified – the disorder's symptom structure, evaluated its natural course, and assessed the disorder's biological features. The DSM-IV-TR has been in use for many years, and PTSD symptoms based on that are shown in Box 1.1; however, recently the DSM-5 was released (APA, 2014), and the changes from DSM-IV-TR are described later in this chapter.

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**Box 1.1** *Diagnostic and statistical manual of mental disorders-IV-TR* criteria for posttraumatic stress disorder.

**A. The person has been exposed to a traumatic event in which both of the following were present:**

1. The person experienced, witnessed, or was confronted with an event that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
2. The person's response involved intense fear, helplessness, or horror. Note: In children this may be expressed, instead, by disorganized or agitated behavior.

**B. The traumatic event is persistently re-experienced in one (or more) of the following ways:**

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
2. Recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note: In young children, trauma-specific re-enactment may occur.
4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
5. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

**C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:**

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma.
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma.
3. Inability to recall an important aspect of the trauma.
4. Markedly diminished interest or participation in significant activities.
5. Feeling of detachment or estrangement from others.
6. Restricted range of affect (e.g., unable to have loving feelings).
7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

**D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:**

1. Difficulty falling or staying asleep.
2. Irritability or outbursts of anger.
3. Difficulty concentrating.

**4** Hypervigilance.
**5** Exaggerated startle response.

**E. Duration of the disturbance (symptoms in criteria B, C, and D) is more than 1 month.**

**F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.**

Specify if:
Acute – if duration of symptoms is less than 3 months.
Chronic – if duration of symptoms is 3 months or more.
With delayed onset – if onset of symptoms is at least 6 months after the stressor.

Posttraumatic stress disorder frequently follows a chronic course and can be associated with recurrences related to exposure to multiple traumas. In addition, PTSD is frequently comorbid with other psychiatric conditions, such as anxiety disorders, depression and substance abuse (Kessler et al., 1995).
Posttraumatic stress disorder is hypothesized to involve the brain's emotional-learning circuitry, and the various brain structures (e.g., prefrontal lobes) and neuroendocrine systems (e.g., the hypothalamic–pituitary–adrenal [HPA] axis) that modulate the acquisition, retention, and eventual extinction of fear conditioning (Bremner & Charney, 2010).

The purpose of this chapter is to bridge the gap between neurobiology and treatment of PTSD that is covered in more detail in the many chapters in this volume related to these topics. This chapter will address issues concerning the acquisition and course of PTSD, including physiological and neuroendocrine factors; recognition and impairment; recent studies of psychotherapy and pharmacotherapy and their effects on neurobiology as well as symptom response; and suggest some directions for research.

### 1.1.1 The syndrome

Formally, PTSD is defined by the co-occurrence of three clusters of symptoms (*re-experiencing*, *avoidance*, and *hyperarousal*) in an individual who had undergone a traumatic event (Box 1.1).

Symptoms of *re-experiencing* consist of intrusive, uncontrollable and involuntary instances of re-living the traumatic event, with feelings of fear and panic, and with corresponding physiological responses such as palpitation, sweating or muscular tension. Such "intrusive" experiences often occur upon exposure to cues that remind the person of the traumatic event, but they also occur spontaneously, such as during nightmares or periods of relaxed attention.

*Avoidance* in PTSD includes phobic avoidance (i.e., of cues and situations that resemble the traumatic event) along with extended avoidance and numbing, expressed as restricted range of affects, diminished interest in previously significant activities, feelings of detachment and estrangement from others and a sense of foreshortened future. The latter clearly resemble symptoms of depression, and may explain the frequent overlap between PTSD and depression.
Symptoms of *PTSD hyperarousal* include insomnia, anger, difficulties concentrating, hypervigilance and exaggerated startle. Importantly, these symptoms are unrelated to specific reminders of the traumatic event, and constitute an unrelenting and pervasive background of tension and irritability, affecting the patient's entire life.

In the recently released DSM-5, symptoms of PTSD have remained mostly the same, but the trauma definition no longer requires feelings of fear, helplessness, or horror in conjunction with the trauma (APA, 2014). In addition, new qualifying symptoms were added. As can be seen from Box 1.1, symptoms must be present for at least 1 month for a formal diagnosis of PTSD to be made. If symptoms are present for less than 3 months, the disorder is termed "acute," while symptoms enduring beyond 3 months are considered "chronic" PTSD.

The *symptom criteria* of PTSD have been rather consistent across successive revisions of the DSM. The few changes that were made concerned manifestations of guilt, which figured in DSM-III, and were omitted from subsequent editions, and the presence of bodily responses upon exposure to reminders of the traumatic event, a diagnostic criterion which has been moved from the "hyperarousal" cluster into the "re-experiencing" cluster. More recently, DSM-5 added a new criterion of negative alterations in cognition and mood, which comprises symptoms such as a persistent and distorted blame of self or others, and a persistent negative emotional state. A new symptom of reckless or destructive behavior was also added as part of the hyperarousal symptom cluster.

In contrast, the appraisal of the *traumatic event* has changed considerably. The original description of PTSD, in DSM-III, was clearly influenced by the consequences of the Vietnam war, and therefore defined the traumatic event as being out of the range of normal human experiences and capable of provoking distress among most subjects exposed. This perception has been eroded by studies that showed that PTSD could develop in the aftermath of frequently occurring traumata, such as road traffic accidents or physical assault (Shalev et al., 1988). Consequently, the current definition of a traumatic event is very permissive indeed and applies to a large array of situations and events. DSM-IV-TR required both *exposure* to a threatening event and *intense response* in the form of fear, horror, or helplessness in order for an event to formally qualify as "traumatic." The requirement of the latter was dropped in the most recent version, DSM-5. Overall the DSM-5 has loosened the criteria for PTSD, so that a much larger proportion

of the population is expected to meet criteria for PTSD under the new definition (APA, 2014).

The risk of developing PTSD varies according to the type of trauma. The disorder's lifetime prevalence rates among civilians has been estimated at 1.3–7.8% (Davidson et al., 1991; Kessler et al., 1995). A higher lifetime PTSD prevalence of around 30% has been reported for Vietnam veterans and female victims of rape in retrospective epidemiological studies (Kulka et al., 1990; Resnick et al., 1993). In common with many other psychiatric disorders, a higher prevalence of PTSD occurs in women than in men (Kessler et al., 1995).

### 1.1.2 Natural course, vulnerability and risk factors

Many trauma survivors develop transient and self-remitting forms of PTSD. Prospective studies have shown 66% recovery from fully expressed PTSD among survivors of motor vehicle accidents (Kessler et al., 1995), and 66% recovery within 1 year of a traumatic event of 236 survivors of miscellaneous civilian events who had PTSD 1 month after the traumatic event (Shalev et al., 1993b). However, the recovery curve of PTSD reaches a plateau after 72 months (Solomon et al., 1989), with most cases of recovery occurring during the first year that follows the traumatic event. Recovery from chronic PTSD is often incomplete (Pelcovitz et al., 1994; Shalev et al., 1993b), and those who recover remain vulnerable to subsequent stress.

Prospective studies have also shown that the symptoms of early and "recoverable" PTSD resemble those seen months and years later in people who remain ill (van der Kolk et al., 1996). Moreover, subjects who continue to suffer from PTSD seem to express the *same intensity* of symptoms that they have expressed shortly after the traumatic event. The phenotype, therefore, appears to remain over time, whereas the nature of the underlying mechanisms might change. This is in line with a general model of learning (Andreski et al., 1998), according to which neuronal mechanisms that mediate the *acquisition of new behavior* are not the same as those involved in its subsequent practice. Reversibility during the latter phase is obviously more difficult than during acquisition, and this may explain the prolonged and treatment-resistant nature of chronic PTSD.

In its chronic form, PTSD is often complicated by co-occurring depression. The nature of the association between PTSD and depression is unclear, with some studies suggesting that depression develops as a secondary consequence of PTSD (Solomon et al., 1989; Turnbull, 1998) and others suggesting that the two may be independent consequences of traumatic events, and develop simultaneously (Pelcovitz et al., 1997). In addition to depression, substance abuse is commonly reported in survivors of traumatic events with PTSD, physical health often declines, and social relationships can be adversely affected (Bremner et al., 1996c). Thus, chronic PTSD is very disabling, with symptoms affecting patients'

well-being, interpersonal relationships and vocational capacity. PTSD is associated with a significant loss of role functioning, as expressed by absence from work or unemployment (Shalev et al., 1996).

### 1.1.3 Understanding the occurrence of PTSD

There are two competing models for understanding the occurrence and the persistence of PTSD among some survivors. The first model assumes that PTSD is triggered by an abnormal *initial* response to traumatic stress, affecting memory consolidation and aversive learning (Chilcoat & Breslau, 1998; Fesler, 1991). This view is supported by findings of intense autonomic response during the traumatic event (Shalev et al., 1988, 1998). These initial "unconditioned" responses were thought to reinforce aversive learning via excessive adrenergic drive and through a failure to mount sufficient amounts of the protective stress hormone cortisol (Yehuda & Antelman, 1993). The model points to the need to address the very early bodily and emotional responses to a traumatic event in order to prevent PTSD.

The alternative model postulates that PTSD is significantly affected by factors that follow the traumatic event and is, therefore, a "disorder of recovery." In a recent meta-analysis of risk factors for PTSD, for example, deficient recovery environment and adversity following trauma were found to be the major risk factors for subsequent PTSD (Brewin et al., 2000). A prospective study has also shown that abnormal startle response – a typical symptom of PTSD – develops within the first few months after the traumatic event in individuals who continue to express PTSD symptoms (Shalev et al., 2000). These findings are in line with the *progressive sensitization* model of PTSD, according to which the occurrence and persistence of PTSD symptoms progressively alter the central nervous system (CNS). It suggests that preventive interventions be conducted during the acquisition phase of the disorder (i.e., the first few months following exposure).

Finally, the likelihood of developing PTSD is significantly affected by factors that precede the traumatic event. For example, a twin study of Vietnam veterans (Goldberg et al., 1990; True et al., 1993) showed a significant contribution of inherited vulnerability PTSD symptoms following combat. Inherited factors also affect the likelihood of being exposed to combat (Goldberg et al., 1990; True et al., 1993). Other vulnerability factors include lifetime occurrence of psychiatric disorders, cumulated exposure to traumatic events and adversities during childhood, lower education levels and adverse family environments.

Thus, PTSD should be seen as the compounded result of several risk factors, in the presence of which a traumatic event triggers a cascade of biological, mental and interpersonal processes leading to chronic PTSD.

Recent studies of the extinction of fear responses raise the previously discussed possibility that PTSD might be the result of a failure to extinguish an

initial fear response (Bremner & Charney, 2010). Functional brain imaging studies, reviewed later in this chapter, have explored the role of medial prefrontal structures in PTSD.

### 1.1.4 Delayed and chronic forms of PTSD

The onset of PTSD can be delayed for years. In a large study by Solomon et al. (1989) looking at individuals who presented for treatment within 6 years of the Lebanon war, 10% were considered delayed onset, 40% were delayed help-seeking, 33% were exacerbation of subclinical PTSD, 13% were reactivation of recovered PTSD, and the remaining 4% had other psychiatric disorders. This is confirmed in the study by Shalev et al. (1996), in which 5.1% of patients were truly delayed-onset PTSD and the rest were mainly PTSD patients who recovered and were then reactivated by another event.

Most cases of PTSD recover within 1 year, and after 6 years recovery without treatment is unlikely (Kessler et al., 1995). However, up to 40% of patients with acute PTSD end by having a chronic condition. Chronic PTSD is prolonged and may be unremitting, and subject to reactivation upon exposure to stressors. In addition, it can be disabling and associated with substantial comorbidity. The risk of developing secondary comorbid disorders is related to a number of factors, including the severity of the trauma, gender, family history, past history and the complexity of the PTSD reaction. Chronic PTSD is linked with abuse of alcohol, drugs and prescription medications (Kulka et al., 1990). It is also associated with an increase in suicidal behavior, although studies have not documented an increase in completed suicide (Krysinska & Lester, 2010). The percentages of individuals with PTSD who have at least one other lifetime disorder is 88.0% for men and 79.0% for women. The major comorbid disorder seen with PTSD is depression, occurring in 47.9% of men and 48.5% of women. Other comorbid disorders include dysthymia, simple phobia and generalized anxiety disorder.

### 1.1.5 Disability associated with PTSD

The chronic form of PTSD is often debilitating. The disability associated with PTSD includes work impairment, change in life trajectories, impaired social relations, marital instability and perpetuation of violence. This represents a burden not only to the individual but also to society.

In a study based on analysis of the National Comorbidity Survey (NCS) data, which examined the effects of mental disorders on work impairment, work loss (defined as missing a full day of work) and work cut-back (either missing part of a day or working less efficiently than usual) during the previous month were 0.8 and 2.8 days/month, respectively (Kessler & Frank, 1997). The amount of work impairment associated with PTSD was the same as that associated with major

depression but less than that associated with panic disorder (Kessler & Frank, 1997).

In term of disability to life events caused by PTSD in the NCS data, there is an increased risk of making suicide plans (odds ratio [OR] = 2.4; 95% confidence interval [CI] : 1.7–3.3) and an increased risk of attempting suicide (OR = 6; 95% CI : 3.4–10.7) for patients suffering from PTSD. In addition, marital instability, unemployment and increased use of outpatient care contribute greatly to the burden to society (Kessler, 2000). It remains unclear whether similar effects exist in other countries, although the NCS analyses showed that the most extreme adverse effects of traumatic events were associated with complex ongoing traumas that occur in childhood, such as parental violence, alcoholism or depression. Such experiences interfere with lifelong patterns of interpersonal relationships and the process of mastering basic educational skills.

In the study by Stein et al. (2000b), patients with PTSD reported significantly more functional impairment than patients without mental disorders. In addition, patients with PTSD made greater use of healthcare resources than non-mentally ill patients and encountered considerable functional impairment.

A study of the quality of life with PTSD reported greater impairment at baseline for subjects with PTSD relative to those with major depression and obsessive-compulsive disorder on several domains of the 36-item Short-Form Health Survey (Malik et al., 1999). Similarly, in a study of PTSD among civilians, significant impairment was associated with PTSD as seen on the Sheehan Disability Scale, which measures the total work, family and social/leisure disability, and the Vulnerability to the Effects of Stress Scale (Connor et al., 1999). Considerable improvement to this disability with PTSD was achieved through treatment in both these studies.

### 1.1.6 Comorbidity

Chronic PTSD is linked with abuse of alcohol, drugs and medication (Chilcoat & Breslau, 1998; Kessler, 2000). In common with many other anxiety disorders, PTSD is often complicated by secondary depression (60–80% of patients), particularly if the condition has not been treated. Patients will therefore present in either primary or secondary care with comorbid depression, which complicates the recognition of PTSD *per se*, and prevents the primary diagnosis from being made. Despite some of the symptoms of PTSD being shared with major depression, the clinician should be alerted by the presence of intrusive recollections and pervasive avoidance of a trauma. In addition, when PTSD is complicated by secondary depression, the symptom profile tends to differ from that of major depression, with less psychomotor retardation or agitation (Ballenger et al., 2000). In the study of PTSD in the primary care medical setting by Stein et al. (2000b), 11.8% of primary care attendees met diagnostic criteria for either full or partial PTSD.

Comorbidity with major depression (61% of cases of PTSD) and generalized anxiety disorder (39%) was common, but less so with social phobia (17%) and panic disorder (6%). Substance-use disorder comorbidity (22%) was also fairly common.

Patients who suffer from the effects of chronic interpersonal violence are more likely to have chronic PTSD, and the symptom profile is likely to be more complex and often involves severe forms of dissociation not found in more typical cases of PTSD. The profile is so distinct it has been argued for the creation of a separate diagnosis to characterize this response known as "complex PTSD" (Herman, 1992; Zlotnick et al., 1996) or "disorders of extreme stress not otherwise specified" (van der Kolk et al., 1996; Pelcovitz et al., 1997). Although this diagnosis is not included in the DSM-IV due to the fact that the vast majority of patients with this symptom cluster also meet criteria for PTSD, it is nonetheless clear that a complex PTSD subtype exists. This subtype is more chronic and disabling than other cases of PTSD, and it is particularly common among patients who were exposed at an early age to chronic traumatic interpersonal violence.

## 1.2 Neurobiology of PTSD

The neurobiology of the stress response involves mechanisms related to bodily survival and adaptation to change. Stress is associated with various types of learning, including the learning of conditioned fear responses and autobiographical memory formation. While these adaptations can have survival value, a failure of another type of learning – the turning off of the fear response (or extinction) when no longer needed – can lead to pathology, including symptoms of PTSD. The breadth of the topic can be appraised by examining the time frames of some of the typical responses. The latter extend from fragments of seconds (e.g., for defense reflexes such as auditory startle), to several seconds (for sympathetic activation), tens of minutes (for activation of the HPA axis), hours (for early gene expression), days (for memory consolidation) and months (for permanent changes in the CNS to occur) (Post, 1992).

Furthermore, at each stage, the biological responses to mental stressors are heavily modulated by appraisal (e.g., of the threat and of one's own resources; Lazarus & Folkman, 1984), controllability, and attribution of meaning, and by the relative success in coping with tasks related to survival and learning. Prior experiences and beliefs are also powerful modulators of the mental and therefore the biological response to adversities. Most adverse mental health consequences of traumatic events result from our immense ability to learn, remember, and reshape our behavior (and the underlying CNS functioning) on the basis of new – including catastrophic – experiences. The meaning conveyed to one's action (e.g., cowardice, heroism), as well as the meaningfulness of a group effort

(e.g., unnecessary war) can either soothe and down-regulate fear responses or maintain and reinforce them (Holloway & Ursano, 1984).

Stress results in acute and chronic changes in neurochemical systems and specific brain regions, which result in long-term changes in brain "circuits" involved in the stress response (Bremner, 2011; Vermetten & Bremner, 2002a,b). Brain regions that are felt to play an important role in PTSD include the hippocampus, the amygdala, and the medial prefrontal cortex. Cortisol and norepinephrine are two neurochemical systems that are critical in the stress response.

### 1.2.1 Cortisol and norepinephrine

The corticotropin-releasing factor (CRF)/HPA axis system plays an important role in the stress response (Chrousos & Gold, 1992) (see Chapter 11). CRF is released from the hypothalamus, with stimulation of adrenocorticotropin hormone (ACTH) release from the pituitary, resulting in glucocorticoid (cortisol in man) release from the adrenal, which in turn has a negative feedback effect on the axis at the level of the pituitary, as well as central brain sites including the hypothalamus and hippocampus. Cortisol has a number of effects that facilitate survival and triggers other neurochemical responses to stress, such as the noradrenergic system via the brainstem locus coeruleus (Melia & Duman, 1991). Other responses include an activation of brain areas related to perceiving and responding to the environment. Other players in the immediate response include nuclei controlling facial expression, breathing rhythm, startle response, and parasympathetic modulation of heart rate. This cluster of responses is controlled by the central nucleus of the amygdala – a powerful modulator of fear responses (Davis, 1992; LeDoux, 1993, 1996).

Stress also results in activation of the noradrenergic system, centered in the locus coeruleus. Noradrenergic neurons release transmitter throughout the brain which is associated with an increase in alerting and vigilance behaviors, critical for coping with acute threat (Abercrombie & Jacobs, 1987; Bremner et al., 1996a,b).

Studies in animals have shown that early stress has lasting effects on the HPA axis and norepinephrine (Plotsky & Meaney, 1993). These effects could be mediated by an increase in synthesis of CRH messenger RNA (mRNA) following stress (Makino et al., 1995). Exposure to chronic stress results in potentiation of noradrenergic responsiveness to subsequent stressors and increased release of norepinephrine in the hippocampus and other brain regions (Abercrombie & Jacobs, 1987). It has been theorized that a failure to mount appropriate levels of cortisol during traumatic events may lead to prolonged adrenergic activation and thereby increase the risk of developing PTSDs (Yehuda, 1998). Abnormally low cortisol levels following trauma were, in fact, reported in vulnerable rape victims and in road accident survivors who were at higher risk for developing PTSD (McFarlane et al., 1997; Resnick et al., 1995), but the causal link with PTSD has

not been established. A combination of adrenergic activation and low levels of cortisol has been shown to significantly increase emotional learning in animals (Bohus, 1984; Munck et al., 1984). Importantly, the hormonal stress response seems to "go wrong" in individuals whose prior life experience was particularly stressful (Resnick et al., 1995) – yet this also requires further confirmation. The intensity of biopsychological responses to traumatic events increases in circumstances that are uncontrollable and inescapable (Anisman et al., 1981; Breier, 1989; Seligman & Meier, 1967).

### 1.2.2 Biology of learning and adaptation in PTSD

Immediate alarm responses are followed, in the brain, by a cascade of metabolic and genomic (i.e., expression of new genes) events (Post, 1992). Importantly, the cascade of neuronal changes includes areas of the brain that are not directly involved in stress response. Particularly interesting is the activation of protein synthesis in brain areas related to learning and memory, such as the hippocampus and the amygdala (e.g., Davis, 1994) (see Chapter 6). Newly synthesized proteins in these areas constitute the biological basis of long-term memories of stressful events.

The distribution of these biological changes in the brain suggests that there are two types of memory traces of stressful events: explicit memories (i.e., verbal and retrievable) and implicit memories (e.g., changes in habits, conditioned responses). This is very important, because non-verbal, implicit memories of traumatic events may shape future behavior in the absence of conscious elaboration and verbal recall (e.g., by causing bodily alarm and emotional fear responses upon exposure to reminders of the traumatic event). Experimental work in animals has shown that a subtype of emotional memories, based on "quick and dirty" processing of sensory information, is acquired and stored in the lateral and basal nuclei of the amygdala (LeDoux, 1993, 1995). LeDoux has also shown that such "emotional" learning (indeed, fear conditioning) is relatively immune to change. Memory traces stored in the basal and lateral nuclei of the amygdala are subsequently used to interpret new sensory signals as to their aversive nature, such that when a stimulus is interpreted as immediately threatening, the central nucleus of the amygdala is activated (see earlier) and the fear response is put in motion.

Despite the persistence of emotional learning, the behavioral expression of fear conditioning can be inhibited by the activity of cortical areas of the brain (Morgan et al., 1993; Morgan & LeDoux, 1995). This is, in fact, what happens when aversive or conditioned responses subside; the information is not forgotten or erased, but rather put under inhibitory control (Quirk et al., 2006). Brain areas involved in such inhibitory control include sensory association areas, areas in the frontal lobe and the hippocampus. Memories of traumatic events, therefore, are not suppressed, but rather controlled and neglected, such that they have no

behavioral expression. Subsequent traumatization may activate such memories, yet the strategy of controlling the effect of aversive learning may also be stronger in individuals who recover from traumatic events. Exposure to stressful events, therefore, may either "sensitize" or "immunize" survivors (Solomon et al., 1987).

Further experimental work has shown that aversive memories, at the level of the amygdala, can be reinforced by elevated plasma levels of the stress hormone epinephrine (Cahill & McGaugh, 1998; McGaugh, 1985, 2000). An initial hypersecretion of the epinephrine could be involved in an exaggeration and a consolidation of fear-related memories of the traumatic event (Cahill et al., 1994; McGaugh et al., 1990). Moreover, the intensity of the adrenergic "stress" response can also foster emotional (and amygdala-mediated) learning at the expense of rational or declarative, hippocampus-mediated learning (Metcalfe & Jacobs, 1996). Supportive evidence for the link between an initial autonomic activation and subsequent PTSD has been found in a study of patients presenting to the emergency room after a trauma (Shalev et al., 1998). Heart rate levels upon admission were higher in subjects who subsequently developed PTSD. In another study of trauma survivors, the physiological response of heart rate, skin conductance and electromyography (*frontalis*) to mental imagery recorded a short time following the trauma was shown to differentiate between those who went on to develop PTSD and those who did not (Shalev et al., 1993a). Trauma survivors admitted to the emergency room, who subsequently went on to develop PTSD had higher heart rates at the emergency department and 1 week later, but not after 1 and 4 months (Shalev et al., 1988). PTSD patients can re-access their trauma memories as often as 100 times a day, and elicit these physiological reactions each time. PTSD patients possibly continue to reinforce the initial impact of the trauma by reactivating it in this way. PTSD patients have also been reported to differentiate from normal survivors by poor habituation of skin conductance to a repetition of loud startling noises (Shalev et al., 1992). This may represent a primary defect of the CNS that continues to identify and classify the loud tones as threatening in people with PTSD. PTSD patients, therefore, continue to react, rather than rejecting the noises as redundant information and stopping the reaction to them. In a prospective study of 239 trauma survivors (Shalev et al., 2000), the auditory startle response of all the trauma survivors is normal at 1 week. The response of those patients who go on to develop PTSD becomes abnormal between 1 and 4 months after the trauma, suggesting that this is the critical period during which the CNS adapts its response to ambiguous stimuli (such as loud noises) and determines whether PTSD develops.

There are two important questions for the clinician to address when trying to recognize the vulnerable patients who will develop PTSD: why does trauma lead to PTSD for them rather than some other psychiatric disorder or no disorder at all; and what are the risk factors for determining these patients? The acute stress response is universal and non-predictive of PTSD. Moreover, as mentioned,

patients who develop PTSD fail to show a remission of these acute symptoms and show abnormally increased heart rates several days after the trauma, as well as other abnormal physiological responses such as the increased startle response. It would therefore appear that PTSD might develop as a failure of the body to reverse the acute stress response.

Preclinical and clinical studies have shown alterations in memory function following traumatic stress as well as changes in a circuit of brain areas, including hippocampus, amygdala, and medial prefrontal cortex, that mediate alterations in memory (Bremner, 2003, 2010, 2011; Bremner & Charney, 2010; Garakani et al., 2011). The hippocampus, a brain area involved in verbal declarative memory, is very sensitive to the effects of stress (see Chapter 6). Stress in animals was associated with alterations in neuronal structure in the CA3 region of the hippocampus (which may be mediated by hypercortisolemia, decreased brain-derived neurotrophic factor, and/or elevated glutamate levels) and inhibition of neurogenesis (Magarinos & McEwen, 1995; Nibuya et al., 1995; Sapolsky et al., 1990). As reviewed in Chapter 6, high levels of glucocorticoids seen with stress were also associated with deficits in new learning (Diamond et al., 1996; Luine et al., 1994). Antidepressant treatments block the effects of stress and/or promote neurogenesis in the hippocampus (Nibuya et al., 1995; Santarelli et al., 2003), including phenytoin (Watanabe et al., 1992), tianeptine, dihydroepiandosterone, and fluoxetine (Czeh et al., 2001; D'Sa & Duman, 2002; Duman, 2004; Duman et al., 2001; Garcia, 2002; Lucassen et al., 2004; Malberg et al., 2000; McEwen & Chattarji, 2004), which may represent, at least in part, the mechanism of action of the behavioral effects of antidepressants (Santarelli et al., 2003; Watanabe et al., 1992; although see Henn & Vollmayr, 2004). Changes in the environment have also been shown to modulate neurogenesis in the dentate gyrus of the hippocampus, and slow the normal age-related decline in neurogenesis (Gould et al., 1999; Kempermann et al., 1998).

Chapter 11 of this volume reviews the long-term dysregulation of the HPA axis associated with PTSD. Findings include low or normal baseline levels of cortisol (Yehuda et al., 1991, 1995a) with two studies using multiple serial measurements in plasma showing a loss of normal diurnal rhythm and decreases at specific times of the day (Bremner et al., 1997; Yehuda et al., 1994), elevations in CRF (Baker et al., 1999; Bremner et al., 1997), increased negative feedback of the HPA axis after dexamethasone challenge (Stein et al., 1997; Yehuda et al., 1993) and increased cortisol response to stress, especially trauma-specific stressors (Elzinga et al., 2003).

### 1.2.3 Cognitive function and brain structure in PTSD

Studies in PTSD are consistent with changes in cognition and brain structure (see Chapter 12 in this volume for a review of brain imaging studies in PTSD). Multiple studies have demonstrated verbal declarative memory deficits in PTSD

(Brewin, 2001; Buckley et al., 2000; Elzinga & Bremner, 2002; Golier & Yehuda, 1998). Patients with PTSD secondary to combat (Bremner et al., 1993a; Golier et al., 1997; Uddo et al., 1993; Vasterling et al., 1998; Yehuda et al., 1995b), rape (Jenkins et al., 1998), the Holocaust (Golier et al., 2002; Yehuda et al., 1995b), and childhood abuse (Bremner et al., 1995a; Bremner et al., 2004; Moradi et al., 1999) were found to have deficits in verbal declarative memory function based on neuropsychological testing with a relative sparing of visual memory and IQ (Barrett et al., 1996; Bremner et al., 1993a, 1995a; Gil et al., 1990; Gilbertson et al., 2001; Golier et al., 1997, 2002; Jenkins et al., 1998; Moradi et al., 1999; Roca & Freeman, 2001; Sachinvala et al., 2000; Uddo et al., 1993; Vasterling et al., 1998, 2002; Yehuda et al., 1995b). Other types of memory disturbance studies in PTSD include gaps in memory for everyday events (dissociative amnesia; Bremner et al., 1993b), deficits in autobiographical memory (McNally et al., 1994), an attentional bias for trauma-related material (Beck et al., 2001; Bryant & Harvey, 1995; Cassiday et al., 1992; Foa et al., 1991; Golier et al., 2003; McNally et al., 1990, 1993; McNeil et al., 1999; Moradi et al., 2000; Thrasher et al., 1994) and frontal lobe-related impairments (Beckham et al., 1998). These studies show that PTSD is associated with deficits in verbal declarative memory (Elzinga & Bremner, 2002).

Studies have also shown a smaller volume of the hippocampus in PTSD (Bremner & Vermetten, 2012). Vietnam veterans with PTSD were originally shown to have 8% smaller right hippocampal volume based on magnetic resonance imaging (MRI) relative to controls matched for a variety of factors such as alcohol abuse and education (Bremner et al., 1995b). These studies, which are described in detail in Chapter 12 of this volume, were later extended to adults with PTSD from childhood abuse, but not children with PTSD. Other studies in PTSD have found smaller hippocampal volume and/or reductions in N-acetyl aspartate, a marker of neuronal integrity. Meta-analyses, in which data are pooled from all of the published studies, found smaller hippocampal volume for both the left and the right sides, equally in adult men and women with chronic PTSD, and no change in children (Kitayama et al., 2005; Smith, 2005; Woon et al., 2010). Several studies have shown that PTSD patients have deficits in hippocampal activation while performing a verbal declarative memory task (Astur et al., 2006; Bremner et al., 2003; Shin et al., 2004b).

In addition to the hippocampus, other brain structures have been implicated in a neural circuitry of stress, including the amygdala and prefrontal cortex. Animal studies also show that early stress is associated with a decrease in branching of neurons in the medial prefrontal cortex (Radley et al., 2004). Studies in PTSD found smaller volumes of the anterior cingulate based on MRI measurements (Kitayama et al., 2006; Rauch et al., 2003). Structural imaging studies in PTSD are reviewed in more detail in Chapter 12.

### 1.2.4 Neural circuits in PTSD

Brain imaging studies have shown alterations in a circuit, including medial prefrontal cortex (including anterior cingulate), hippocampus and amygdala, in PTSD (Bremner, 2011). Exposure to traumatic reminders in the form of traumatic slides and/or sounds or traumatic scripts was associated with an increase in PTSD symptoms and most consistently decreased blood flow and/or failure of activation in the medial prefrontal cortex/anterior cingulate, as well as decreased hippocampal function in some studies, as reviewed in more detail in Chapter 12. Exposure to specific fearful stimuli or fear conditioning resulted in increased amygdala function (Bremner et al., 1999, 2005; Rauch et al., 1996, 2000, 2006; Shin et al., 1997, 2004a) Studies have shown that treatment with medication, including the antidepressant paroxetine and phenytoin, and various psychotherapies and behavioral therapies, increase hippocampal volume in PTSD patients and reverse medial prefrontal cortical dysfunction.

In summary, dysfunction of a circuit involving the medial prefrontal cortex hippocampus and amygdala underlies symptoms of PTSD. Imaging studies are reviewed in more detail in Chapter 12.

## 1.3 Synthesis of findings: from neurobiology to treatment of PTSD

Traumatic stress has a broad range of effects on brain function and structure, as well as on neuropsychological components of memory. Brain areas implicated in the stress response include the amygdala, hippocampus, and prefrontal cortex. Neurochemical systems including cortisol and norepinephrine play a critical role in the stress response. These brain areas play an important role in the stress response. They also play a critical role in memory, highlighting the important interplay between memory and the traumatic stress response. Studies outlined in the chapters in this volume show that translation of basic science studies of the effects of stress on brain and behavior to clinically relevant aspects of approaches to PTSD treatment can potentially add to the treatment of PTSD.

Studies in patients with PTSD show alterations in brain areas implicated in animal studies, including the amygdala, hippocampus, and prefrontal cortex, as well as in neurochemical stress response systems, including cortisol and norepinephrine. Treatments that are efficacious for PTSD show a promotion of neurogenesis in animal studies, as well as a promotion of memory and increased hippocampal volume in PTSD. Studies also show an improvement with treatment in brain circuits underlying PTSD symptoms.

Intervening soon after the trauma is critical for long-term outcomes, because, with time, traumatic memories become indelible and resistant to treatment (Meadows & Foa, 1999). Early treatments are not necessarily effective. For

instance, studies have shown that critical incident stress debriefing (CISD) can be associated with a worsening of outcome relative to no treatment at all (Mayou et al., 2000). Pharmacological treatment of chronic PTSD has shown efficacy originally for imipramine, amitriptyline and phenalzine and later for brofaramine, paroxetine and sertraline (see Chapter 16). Selective serotonin reuptake inhibitors (SSRIs) are now recommended as first-line treatment for PTSD (Ballenger et al., 2004; Davidson, 2000, 2004; Davis et al., 2001; Foa et al., 1999; Stein et al., 2000a). The utility of early treatment is also demonstrated by animal studies showing that pretreatment before stress with antidepressants reduces chronic behavioral deficits related to stress (Petty et al., 1992; Sherman & Petty, 1982). Antidepressants, including both norepinephrine and SSRIs, as well as gabapentine and phenytoin, promote nerve growth (neurogenesis) in a part of the brain called the hippocampus, while stress inhibits neurogenesis (see Chapter 6). The chapters in this volume outline all aspects of research in PTSD, from epidemiology to the science of stress to evidence-based approaches to treatment. It is hoped that in future an integrated line of research will ultimately bear fruit in terms of successful new treatments for patients suffering from this crippling disorder and their families.

## References

Abercrombie ED, Jacobs BL (1987) Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and non-stressful stimuli. *J Neurosci* 7, 2837–2847.

American Psychiatric Association (APA) (1981) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn. American Psychiatric Association Press.

American Psychiatric Association (APA) (2014) *Diagnostic and Statistical Manual-5 (DSM-5)*. American Psychiatric Association Press.

Andreski P, Chilcoat H, Breslau N (1998) Post-traumatic stress disorder and somatization symptoms: a prospective study. *Psychiatry Res* 79, 131–138.

Anisman H, Ritch M, Sklar LS (1981) Noradrenergic and dopaminergic interactions in escape behavior: analysis of uncontrollable stress effects. *Psychopharmacology* 74, 263–268.

Astur RS, St Germain SA, Tolin D et al. (2006) Hippocampus function predicts severity of post-traumatic stress disorder. *Cyberpsychol Behav* 9, 234–240.

Baker DG, West SA, Nicholson WE et al. (1999) Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry* 156, 585–588.

Ballenger JC, Davidson JR, Lecrubier Y et al. (2000) Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. *Clin Psychiatry* 61, 60–66.

Ballenger JC, Davidson JR, Lecrubier Y et al. (2004) Consensus statement update on posttraumatic stress disorder from the international consensus group on depression and anxiety. *J Clin Psychiatry* 65 Suppl 1, 55–62.

Barrett DH, Green ML, Morris R et al. (1996) Cognitive functioning and posttraumatic stress disorder. *Am J Psychiatry* 153, 1492–1494.

Beck JG, Freeman JB, Shipherd JC et al. (2001) Specificity of Stroop interference in patients with pain and PTSD. *J Abnorm Psychology* 110, 536–543.

Beckham JC, Crawford AL, Feldman ME (1998) Trail making test performance in Vietnam combat veterans with and without posttraumatic stress disorder. *J Trauma Stress* 11, 811–819.

Bohus B (1984) Humoral modulation of learning and memory processes: physiological significance of brain and peripheral mechanisms. In: A Delacour (Ed.), The Memory System of the Brain. World Scientific, Singapore, pp. 337–364. In: Delacour A (ed.) *The Memory System of the Brain World Scientific, Singapore, pp* 337–364. World Scientific, Singapore, pp. 337–364.

Breier A (1989) Breier A (1989). Experimental approaches to human stress research: assessment of neurobiological mechanisms of stress in volunteers and psychiatric patients. *Biol Psychiatry* 26: 438–462.

Bremner JD (2003) Long-term effects of childhood abuse on brain and neurobiology. *Child Adolesc Psychiat Clin NA* 12, 271–292.

Bremner JD (2010) Imaging in CNS disease states: PTSD. In: Borsook D, Beccera L, Bullmore E et al. (eds) *Imaging in CNS Drug Discovery and Development: Implications for Disease and Therapy*. Springer, Basel, Switzerland, pp. 339–360.

Bremner JD (2011) Stress and human neuroimaging studies. In: Conrad CD (ed.) *The Handbook of Stress: Neuropsychological Effects on the Brain*. Wiley-Blackwell.

Bremner JD, Charney DS (2010) Neural circuits in fear and anxiety. In: Stein DJ, Hollander E, Rothbaum BO (eds) *Textbook of Anxiety Disorders*, 2nd edn. American Psychiatric Publishing, Arlington, VA, pp. 55–71.

Bremner JD, Krystal JH, Southwick SM et al. (1996a) Noradrenergic mechanisms in stress and anxiety: I. *Preclinical studies. Synapse* 23, 28–38.

Bremner JD, Krystal JH, Southwick SM et al. (1996b) Noradrenergic mechanisms in stress and anxiety: II. *Clinical studies. Synapse* 23, 39–51.

Bremner JD, Licinio J, Darnell A et al. (1997) Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry* 154, 624–629.

Bremner JD, Narayan M, Staib LH et al. (1999) Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Am J Psychiatry* 156, 1787–1795.

Bremner JD, Randall PR, Capelli S et al. (1995a) Deficits in short-term memory in adult survivors of childhood abuse. *Psychiatry Res* 59, 97–107.

Bremner JD, Randall PR, Scott TM et al. (1995b) MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 152, 973–981.

Bremner JD, Scott TM, Delaney RC et al. (1993a) Deficits in short-term memory in post-traumatic stress disorder. *Am J Psychiatry* 150, 1015–1019.

Bremner JD, Southwick SM, Darnell A et al. (1996c) Chronic PTSD in Vietnam combat veterans: Course of illness and substance abuse. *Am J Psychiatry* 153, 369–375.

Bremner JD, Steinberg M, Southwick SM et al. (1993b) Use of the Structured Clinical Interview for DSMIV-Dissociative Disorders for systematic assessment of dissociative symptoms in posttraumatic stress disorder. *Am J Psychiatry* 150, 1011–1014.

Bremner JD, Vermetten E (2012) The hippocampus and post-traumatic stress disorders. In: Bartsch T (ed.) *The Clinical Neurobiology of the Hippocampus: An integrative view*. Oxford University Press, USA, New York, NY, pp. 262–272.

Bremner JD, Vermetten E, Nafzal N et al. (2004) Deficits in verbal declarative memory function in women with childhood sexual abuse-related posttraumatic stress disorder (PTSD). *J Nerv Ment Dis* 192, 643–649.

Bremner JD, Vermetten E, Schmahl C et al. (2005) Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual abuse-related posttraumatic stress disorder. *Psychol Med* 35, 791–806.

Bremner JD, Vythilingam M, Vermetten E et al. (2003) MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* 160, 924–932.

Brewin CR (2001) A cognitive neuroscience account of post-traumatic stress disorder and its treatment. *Behav Res Ther* 39, 373–393.

Brewin CR, Andrews B, Valentine JD (2000) Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consulting Clin Psychol* 68, 748–766.

Bryant RA, Harvey AG (1995) Processing threatening information in posttraumatic stress disorder. *J Abnorm Psychology* 104, 537–541.

Buckley TC, Blanchard EB, Neill WT (2000) Information processing and PTSD: A review of the empirical literature. *Clin Psychol Rev* 28, 1041–1065.

Cahill L, McGaugh JL (1998) Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci* 21, 294–299.

Cahill L, Prins B, Weber M et al. (1994) Beta-adrenergic activation and memory for emotional events. *Nature* 371, 702–704.

Cassiday KL, McNally RJ, Zeitlin SB (1992) Cognitive processing of trauma cues in rape victims with posttraumatic stress disorder. *Cog Therap Res* 16, 283–295.

Chilcoat HD, Breslau N (1998) Posttraumatic stress disorder and drug disorders: testing causal pathways. *Arch Gen Psychiatry* 55, 913–917.

Chrousos GP, Gold PW (1992) The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. *JAMA* 267, 1244–1252.

Connor KM, Sutherland SM, Tupler LA et al. (1999) Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. *Br J Psychiatry* 175, 17–22.

Czeh B, Michaelis T, Watanabe T et al. (2001) Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proc Natl Acad Sci USA* 98, 12796–12801.

D'Sa C, Duman RS (2002) Antidepressants and neuroplasticity. *Bipolar Disorder* 4, 183–194.

Davidson JR (2000) Pharmacotherapy of posttraumatic stress disorder: treatment options, long-term follow-up, and predictors of outcome. *J Clin Psychiatry* 61, 52–56.

Davidson JR (2004) Long-term treatment and prevention of posttraumatic stress disorder. *J Clin Psychiatry* 65, 44–48.

Davidson JRT, Hughes D, Blazer DG (1991) Post-traumatic stress disorder in the community: an epidemiological study. *Psychol Med* 21, 713–721.

Davis LL, English BA, Ambrose SM et al. (2001) Pharmacotherapy for post-traumatic stress disorder: a comprehensive review. *Expert Opin Pharmacother* 2, 1583–1595.

Davis M (1992) The role of the amygdala in fear and anxiety. *Annu Rev Neurosci* 15, 353–375.

Diamond DM, Fleshner M, Ingersoll N et al. (1996) Psychological stress impairs spatial working memory: Relevance to electrophysiological studies of hippocampal function. *Behav Neurosci* 110, 661–672.

Duman RS (2004) Depression: a case of neuronal life and death? *Biol Psychiatry* 56, 140–145.

Duman RS, Malberg JE, Nakagawa S (2001) Regulation of adult neurogenesis by psychotropic drugs and stress. *J Pharmacol Exp Ther* 299, 401–407.

Elzinga BM, Bremner JD (2002) Are the neural substrates of memory the final common pathway in PTSD? *J Affect Disord* 70, 1–17.

Elzinga BM, Schmahl CS, Vermetten E et al. (2003) Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. *Neuropsychopharmacology* 28, 1656–1665.

Fesler FA (1991) Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 52, 361–364.

Foa EB, Davidson JRT, Frances A et al. (1999) The expert consensus guideline series: treatment of posttraumatic stress disorder. *J Clin Psychiatry* 60, 4–76.

Foa EB, Feske U, Murdock TB et al. (1991) Processing of threat related information in rape victims. *J Abnorm Psychology* 100, 156–162.

Garakani A, Murrough J, Mathew SJ et al. (2011) The neurobiology of anxiety disorders. In: Charney DS, Nestler EJ (eds) *Neurobiology of Mental Illness*.

Garcia R (2002) Stress, metaplasticity, and antidepressants. *Current Molecular Medicine* 2, 629–638.

Gil T, Calev A, Greenberg D et al. (1990) Cognitive functioning in posttraumatic stress disorder. *J Trauma Stress* 3, 29–45.

Gilbertson MW, Gurvits TV, Lasko NB et al. (2001) Multivariate assessment of explicit memory function in combat veterans with posttraumatic stress disorder. *J Trauma Stress* 14, 413–420.

Goldberg J, True WR, Eisen SA et al. (1990) A twin study of the effects of the Vietnam war on posttraumatic stress disorder. *JAMA* 263, 1227–1232.

Golier J, Yehuda R (1998) Neuroendocrine activity and memory-related impairments in posttraumatic stress disorder. *Dev Psychopathol* 10, 857–869.

Golier J, Yehuda R, Cornblatt B et al. (1997) Sustained attention in combat-related posttraumatic stress disorder. *Integr Physiol Behav Sci* 32, 52–61.

Golier JA, Yehuda R, Lupien SJ et al. (2003) Memory for trauma-related information in Holocaust survivors with PTSD. *Psychiatry Res* 121, 133–143.

Golier JA, Yehuda R, Lupien SJ et al. (2002) Memory performance in Holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry* 159, 1682–1688.

Henn FA, Vollmayr B (2004) Neurogenesis and depression: etiology or epiphenomenon? *Biol Psychiatry* 56, 146–150.

Herman JL (1992) Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. *J Trauma Stress* 5, 377–391.

Holloway HC, Ursano RJ (1984) The Vietnam veteran: memory, social context and metaphor. *Psychiatry* 47, 103–108.

Jenkins MA, Langlais PJ, Delis D et al. (1998) Learning and memory in rape victims with posttraumatic stress disorder. *Am J Psychiatry* 155, 278–279.

Kempermann, G., Kuhn, H. G., & Gage, F. H. (1998). Experience-induced neurogenesis in the senescent dentate gyrus. *Journal of Neuroscience* 18, 3206–3212.

Kessler RC (2000) Posttraumatic stress disorder: the burden to the individual and to society. *J Clin Psychiatry* 61, 4–12.

Kessler RC, Frank RG (1997) The impact of psychiatric disorders on work loss days. *Psychol Med* 27, 861–873.

Kessler RC, Sonnega A, Bromet E et al. (1995) Posttraumatic stress disorder in the national comorbidity survey. *Arch Gen Psychiatry* 52, 1048–1060.

Kitayama N, Quinn S, Bremner JD (2006) Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *J Affect Disord* 90, 171–174.

Kitayama N, Vaccarino V, Kutner M et al. (2005) Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: A meta-analysis. *J Affect Disord* 88, 79–86.

Krysinska K, Lester D (2010) Post-traumatic stress disorder and suicide risk: a systematic review. *Archives of Suicide Research* 14, 1–23.

Kulka RA, Schlenger WE, Fairbank JA et al. (1990) *Trauma and the Vietnam War Generation: Report of Findings from the National Vietnam Veterans Readjustment Study*. Brunner/Mazel, New York.

Lazarus RS, Folkman S (1984) *Stress, Appraisal and Coping*. Springer, New York.

LeDoux JE (1995) Setting stress into motion: brain mechanisms of stimulus evaluation. I In: Friedman JM, Charney DS, Deutch AY (eds) *Neurobiological and Clinical Consequences of Stress*. Lipincott-Raven, Philadelphia, pp. 125–134.

LeDoux JE (1996) *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. Simon & Schuster, New York, NY.

LeDoux JL (1993) In search of systems and synapses. *Ann NY Acad Sci* 702, 149–157.

Lucassen PJ, Fuchs E, Czeh B (2004) Antidepressant treatment with tianeptine reduces apoptosis in the hippocampal dentate gyrus and temporal cortex. *Eur J Neurosci* 14, 161–166.

Luine V, Villages M, Martinex C et al. (1994) Repeated stress causes reversible impairments of spatial memory performance. *Brain Res* 639, 167–170.

Magarinos AM, McEwen BS (1995) Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience* 1, 89–98.

Makino S, Smith MA, Gold PW (1995) Increased expression of corticotropin-releasing hormone and vasopressin messenger-ribonucleic acid (messenger RNA) in the hypothalamic paraventricular nucleus during repeated stress-association with reduction in glucocorticoid messenger-RNA levels. *Endocrinology* 136, 3299–3309.

Malberg JE, Eisch AJ, Nestler EJ et al. (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* 20, 9104–9110.

Malik ML, Connor KM, Sutherland SM et al. (1999) Quality of life and posttraumatic stress disorder: a pilot study assessing changes in SF-36 scores before and after treatment in a placebo-controlled trial of fluoxetine. *J Trauma Stress* 12, 387–393.

Mayou RA, Ehlers A, Hobbs M (2000) Psychological debriefing for road traffic accident victims. Three-year follow-up of a randomised controlled trial. *Br J Psychiatry* 176, 589–593.

McEwen BS, Chattarji S (2004) Molecular mechanisms of neuroplasticity and pharmacological implications: the example of tianeptine. *Eur Neuropsychopharmacol* 14 Suppl 5, S497–502.

McFarlane AC, Atchison M, Yehuda R (1997) The acute stress response following motor vehicle accidents and its relations to PTSD. *Ann NY Acad Sci* 821, 437–441.

McGaugh JL (1985) Peripheral and central adrenergic influences on brain systems involved in the modulation of memory storage. *Ann NY Acad Sci* 444, 150–161.

McGaugh JL (2000) Memory – A century of consolidation. *Science* 287, 248–251.

McGaugh JL, Introini-Collison IB, Nagahara AH et al. (1990) Involvement of the amygdaloid complex in neuromodulatory influences on memory storage. *Neurosci Biobehav Rev* 14, 425–431.

McNally RJ, English GE, Lipke HJ (1993) Assessment of intrusive cognition in PTSD: Use of the modified Stroop paradigm. *J Trauma Stress* 6, 33–41.

McNally RJ, Kaspi RJ, Riemann BC et al. (1990) Selective processing of threat cues in posttraumatic stress disorder. *J Abnorm Psychology* 99, 398–402.

McNally RJ, Litz BT, Prassas A et al. (1994) Emotional priming of autobiographical memory in posttraumatic stress disorder. *Cogn Emot* 8, 351–367.

McNeil DW, Tucker P, Miranda R et al. (1999) Response to depression and anxiety Stroop stimuli in posttraumatic stress disorder, obsessive-compulsive disorder and major depressive disorder. *J Nerv Ment Dis* 187, 512–516.

Meadows EA, Foa EB (1999) Cognitive-behavioral treatment of traumatized adults. In: Saigh PA, Bremner JD (eds) *Posttraumatic Stress Disorder: A Comprehensive Text*. Allyn & Bacon, Needham Heights, MA, pp. 376–390.

Melia KR, Duman RS (1991) Involvement of corticotropin-releasing factor in chronic stress regulation of the brain noradrenergic system. *Proc Natl Acad Sci USA* 88, 8382–8386.

Metcalfe J, Jacobs WJ (1996) A "hot-system/cool-system" view of memory under stress. *PTSD Research Quarterly* 7, 1–3.

Moradi AR, Doost HT, Taghavi MR et al. (1999) Everyday memory deficits in children and adolescents with PTSD: performance on the Rivermead Behavioural Memory Test. *J Child Psychol Psychiatr* 40, 357–361.

Moradi AR, Taghavi R, Neshat-Doost HT et al. (2000) Memory bias for emotional information in children and adolescents with posttraumatic stress disorder: A preliminary study. *J Anxiety Disord* 14, 521–534.

Morgan CA, LeDoux JE (1995) Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav Neurosci* 109, 681–688.

Morgan CA, Romanski LM, LeDoux JE (1993) Extinction of emotional learning: Contribution of medial prefrontal cortex. *Neurosci Lett* 163, 109–113.

Munck AP, Guyre PM, Holbrook NJ (1984) Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* 5, 25–44.

Nibuya M, Morinobu S, Duman RS (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* 15, 7539–7547.

Pelcovitz D, Kaplan S, Goldenberg B et al. (1994) Post-traumatic stress disorder in physically abused adolescents. *J Am Acad Child Adolesc Psychiatry* 33, 305–312.

Pelcovitz D, van der Kolk B, Roth S et al. (1997) Development of a criteria set and a Structured Interview for Disorders of Extreme Stress. *J Trauma Stress* 10, 3–16.

Petty F, Kramer G, Wilson L (1992) Prevention of learned helplessness: in vivo correlation with cortical serotonin. *Pharmacol Biochem Beh* 43, 361–367.

Plotsky PM, Meaney MJ (1993) Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Mol Brain Res* 18, 195–200.

Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 149, 999–1010.

Quirk GJ, Garcia R, Gonzalez-Lima F (2006) Prefrontal mechanisms in extinction of conditioned fear. *Biol Psychiatry* 60, 337–343.

Radley JJ, Sisti HM, Hao J et al. (2004) Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience* 125, 1–6.

Rauch SL, Shin LM, Phelps EA (2006) Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future. *Biol Psychiatry* 60, 376–382.

Rauch SL, Shin LM, Segal E et al. (2003) Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport* 14, 913–916.

Rauch SL, van der Kolk BA, Fisler RE et al. (1996) A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry* 53, 380–387.

Rauch SL, Whalen PJ, Shin LM et al. (2000) Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry* 47, 769–776.

Resnick HS, Kilpatrick DG, Dansky BS (1993) Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J Consult Clin Psychol* 61, 984–991.

Resnick HS, Yehuda R, Pitman RK et al. (1995) Effect of previous trauma on acute plasma cortisol level following rape. *Am J Psychiatry* 152, 1675–1677.

Roca V, Freeman TW (2001) Complaints of impaired memory in veterans with PTSD. *Am J Psychiatry* 158, 1738.

Sachinvala N, vonScotti H, McGuire M et al. (2000) Memory, attention, function, and mood among patients with chronic posttraumatic stress disorder. *J Nerv Ment Dis* 188, 818–823.

Santarelli L, Saxe M, Gross C et al. (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301, 805–809.

Sapolsky RM, Uno H, Rebert CS et al. (1990) Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 10, 2897–2902.

Seligman MEP, Meier SF (1967) Failure to escape traumatic shock. *J Exp Psychol* 74, 1–9.

Shalev AY, Freedman S, Peri T et al. (1988) Prospective study of post-traumatic stress disorder and depression following trauma. *Am J Psychiatry* 155, 630–637.

Shalev AY, Orr SP, Peri T et al. (1992) Physiologic responses to loud tones in Israeli patients with posttraumatic stress disorder. *Arch Gen Psychiatry* 49, 870–875.

Shalev AY, Orr SP, Pitman RK (1993a) Psychophysiologic assessment of traumatic imagery in Israeli civilian patients with posttraumatic stress disorder. *Am J Psychiatry* 150, 620–624.

Shalev AY, Peri T, Brandes D et al. (2000) Auditory startle response in trauma survivors with posttraumatic stress disorder: A prospective study. *Am J Psychiatry* 157, 255–261.

Shalev AY, Peri T, Canetti L et al. (1996) Predictors of PTSD in injured trauma survivors: A prospective study. *Am J Psychiatry* 153, 219–225.

Shalev AY, Sahar T, Freedman S et al. (1998) A prospective study of heart rate responses following trauma and the subsequent development of posttraumatic stress disorder. *Arch Gen Psychiatry* 55, 553–559.

Shalev AY, Schreiber S, Galai T (1993b) Early psychiatric responses to traumatic injury. *J Trauma Stress* 6, 441–450.

Sherman AD, Petty F (1982) Additivity of neurochemical changes in learned helplessness and imipramine. *Behav Neurol Biol* 35, 344–353.

Shin LM, Kosslyn SM, McNally RJ et al. (1997) Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Arch Gen Psychiatry* 54, 233–237.

Shin LM, Orr SP, Carson MA et al. (2004a) Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry* 61, 168–176.

Shin LM, Shin PS, Heckers S et al. (2004b) Hippocampal function in posttraumatic stress disorder. *Hippocampus* 14, 292–300.

Smith ME (2005) Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. *Hippocampus* 15, 798–807.

Solomon Z, Garb R, Bleich A et al. (1987) Reactivation of combat-related posttraumatic stress disorder. *Am J Psychiatry* 144, 51–55.

Solomon Z, Kotler M, Shalev A et al. (1989) Delayed post-traumatic stress disorders. *Psychiatry* 52, 428–436.

Stein DJ, Zungu-Dirwayi N, van der Linden GJ et al. (2000a) Pharmacotherapy for posttraumatic stress disorder. *Cochrane Database Systematic Review* 4, CD002795.

Stein MB, McQuaid JR, Pedrelli P et al. (2000b) Posttraumatic stress disorder in the primary care medical setting. *Gen Hosp Psychiatry* 22, 261–269.

Stein MB, Yehuda R, Koverola C et al. (1997) Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. *Biol Psychiatry* 42, 680–686.

Thrasher SM, Dalgleish T, Yule W (1994) Information processing in post-traumatic stress disorder. *Behav Res Ther* 32, 247–254.

True WR, Rice J, Eisen SA et al. (1993) A twin study of genetic and environmental contributions to liability for posttraumatic stress disorder symptoms. *Arch Gen Psychiatry* 50, 257–264.

Turnbull GJ (1998) A review of post-traumatic stress disorder. Part I: Historical development and classification. *Injury* 29, 87–91.

Uddo M, Vasterling JJ, Braily K et al. (1993) Memory and attention in posttraumatic stress disorder. *J Psychopathol Beh Assess* 15, 43–52.

van der Kolk BA, Pelcovitz D, Roth S et al. (1996) Dissociation, somatization, and affect dysregulation: the complexity of adaptation to trauma. *Am J Psychiatry* 153, 83–93.

Vasterling JJ, Brailey K, Constans JI et al. (1998) Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology* 12, 125–133.

Vasterling JJ, Duke LM, Brailey K et al. (2002) Attention, learning, and memory performance and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology* 16, 5–14.

Vermetten E, Bremner JD (2002a) Circuits and systems in stress. I. Preclinical studies. *Depress Anxiety* 15, 126–147.

Vermetten E, Bremner JD (2002b) Circuits and systems in stress. II. Applications to neurobiology and treatment of PTSD. *Depress Anxiety* 16, 14–38.

Watanabe YE, Gould H, Cameron D et al. (1992) Phenytoin prevents stress and corticosterone induced atrophy of CA3 pyramidal neurons. *Hippocampus* 2, 431–436.

Woon FL, Sood S, Hedges DW (2010) Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 34, 1181–1188.

Yehuda R (1998) Psychoneuroendocrinology of post-traumatic stress disorder. *Psychiatr Clin North Am* 21, 359–379.

Yehuda R, Antelman SM (1993) Criteria for rationally evaluating animal models of posttraumatic stress disorder. *Biol Psychiatry* 33, 479–486.

Yehuda R, Kahana B, Binder-Brynes K et al. (1995a) Low urinary cortisol excretion in holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry* 152, 982–986.

Yehuda R, Keefe RS, Harvey PD et al. (1995b) Learning and memory in combat veterans with posttraumatic stress disorder. *Am J Psychiatry* 152, 137–139.

Yehuda R, Southwick SM, Krystal JH et al. (1993) Enhanced suppression of cortisol with low dose dexamethasone in posttraumatic stress disorder. *Am J Psychiatry* 150, 83–86.

Yehuda R, Southwick SM, Nussbaum EL et al. (1991) Low urinary cortisol in PTSD. *J Nerv Ment Dis* 178, 366–369.

Yehuda R, Teicher MH, Levengood RA et al. (1994) Circadian regulation of basal cortisol levels in posttraumatic stress disorder. *Ann NY Acad Sci*, 378–380.

Zlotnick C, Zakriski AL, Shea MT et al. (1996) The long-term sequelae of sexual abuse: support for a complex posttraumatic stress disorder. *J Trauma Stress* 9, 195–205.