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.
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.
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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
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(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 adrenocorticotropic 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, dihydroepiandrosterone, 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
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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 phenelzine 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 gabapentin 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.

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