Post-traumatic stress disorder

Rachel Yehuda[1,2], Charles W. Hoge[3], Alexander C. McFarlane[4], Eric Vermetten[5–7], Ruth A. Lanius[8], Caroline M. Nievergelt[9,10], Stevan E. Hobfoll[11], Karestan C. Koenen[12,13], Thomas C. Neylan[14,15] and Steven E. Hyman[13,16]

Abstract | Post-traumatic stress disorder (PTSD) occurs in 5–10% of the population and is twice as common in women as in men. Although trauma exposure is the precipitating event for PTSD to develop, biological and psychosocial risk factors are increasingly viewed as predictors of symptom onset, severity and chronicity. PTSD affects multiple biological systems, such as brain circuitry and neurochemistry, and cellular, immune, endocrine and metabolic function. Treatment approaches involve a combination of medications and psychotherapy, with psychotherapy overall showing greatest efficacy. Studies of PTSD pathophysiology initially focused on the psychophysiology and neurobiology of stress responses, and the acquisition and the extinction of fear memories. However, increasing emphasis is being placed on identifying factors that explain individual differences in responses to trauma and promotion of resilience, such as genetic and social factors, brain developmental processes, cumulative biological and psychological effects of early childhood and other stressful lifetime events. The field of PTSD is currently challenged by fluctuations in diagnostic criteria, which have implications for epidemiological, biological, genetic and treatment studies. However, the advent of new biological methodologies offers the possibility of large-scale approaches to heterogeneous and genetically complex brain disorders, and provides optimism that individualized approaches to diagnosis and treatment will be discovered.

Post-traumatic stress disorder (PTSD) is a condition that can develop following exposure to extremely traumatic events such as interpersonal violence, combat, life-threatening accidents or natural disasters. Symptoms of PTSD include distressing and intrusive memories and nightmares of the trauma, irritability, hypervigilance (enhanced state of threat sensitivity or preoccupation with the potential for danger), difficulty sleeping, poor concentration and emotional withdrawal. Individuals with PTSD frequently avoid places, activities or things that could remind them of the trauma[1]. PTSD severity is worsened by co-occurring conditions that also arise concomitantly with PTSD, as a result of the trauma exposure, of shared causal determinants or of PTSD itself, and disproportionally affect disadvantaged populations[1] (BOX 1). Co-occurring conditions can include substance abuse, mood and anxiety disorders, impulsive or dangerous behaviour or self-harm[2]. PTSD is also associated with considerable medical comorbidities, including chronic pain and inflammation, cardiometabolic disorders and heightened risk of dementia[3–5]. Thus, the total disease burden (disability plus premature mortality) that is attributable to PTSD is extremely high[6].

TABLE 1 describes current diagnostic criteria for PTSD according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) and highlights areas of change from DSM-IV. These include several criteria and symptoms that must be fulfilled. Alongside these changes in diagnostic criteria, there has been a major shift in scientific research in PTSD. Initial studies aimed to examine processes associated with stress responses and fear memories, with the idea that trauma exposure was the proximal cause of PTSD[7–9]. The study of PTSD has a distinct scientific advantage compared with many other psychiatric disorders in that amygdala-based fear circuitry and hypothalamically regulated endocrine responses to stress are fairly conserved across species, which makes inferences from basic animal research translationally useful. However, traditional animal models lack neural areas that approximate a human prefrontal cortex and, accordingly, lack the ability to model human cognitive control of stress and conditioned fear. Limitations of exposure-based animal models also became apparent as epidemiological studies highlighted that the majority of trauma survivors do not develop PTSD. These considerations prompted an increased emphasis on individual differences in humans that contribute to symptom onset, progression and resilience following trauma exposure[7]. In this Primer, we discuss advances in understanding pathophysiology and treatment of PTSD.

Correspondence to R.Y.
e-mail: rachel.yehuda@va.gov
James J. Peters Veterans Affairs Medical Center, 130 West Kingsbridge Road, New York, New York 10468, USA.

Article number: 15057
doi:10.1038/nrdp.2015.57
Published online
8 October 2015

Author addresses

[1]James J. Peters Veterans Affairs Medical Center, 130 West Kingsbridge Road, New York, New York 10468, USA.
[2]Icahn School of Medicine at Mount Sinai, New York, New York, USA.
[3]Walter Reed Army Institute of Research, Silver Spring, Maryland, USA.
[4]Centre for Traumatic Stress Studies, The University of Adelaide, Adelaide, South Australia, Australia.
[5]Military Mental Health Research Center, Ministry of Defense, Utrecht, The Netherlands.
[6]Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands.
[7]Arq Psychotrauma Expert Group, Diemen, The Netherlands.
[8]Department of Psychiatry, Western University of Canada, London, Ontario, Canada.
[9]Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, California, USA.
[10]VA Center of Excellence for Stress and Mental Health (CESAMH), VA San Diego Healthcare System, La Jolla, California, USA.
[11]Department of Behavioral Sciences, Rush University Medical Center, Chicago, Illinois, USA.
[12]Department of Epidemiology, Harvard T.H. Chan School of Public Health and Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA.
[13]The Stanley Center, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA.
[14]Department of Psychiatry, University of California San Francisco, San Francisco, California, USA.
[15]Mental Health Service, San Francisco Veterans Affairs Medical Center, San Francisco, California, USA.
[16]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, Massachusetts, USA.

Epidemiology

Military

One of the first large epidemiological studies of PTSD was carried out soon after the establishment of the DSM-III diagnosis to ascertain the scope of the problem in a nationally representative sample of Vietnam War veterans in the United States[10]. Initial estimates suggested a lifetime PTSD prevalence of 30%, with 15% of veterans still experiencing symptoms of PTSD more than 10 years after the conclusion of the war. A reanalysis of these data to determine the proportion of PTSD directly attributable to war-zone trauma (verified with military records and adjusted for functional impairment) showed that 19% of veterans developed war-related PTSD during their lifetime and 9% continued to have PTSD at the time of the original assessment[11]. 10 years after the conclusion of the Vietnam War, the rates of current PTSD were as high as 28% in veterans who had experienced combat exposure. A recent follow-up study of the original cohort showed that, 40 years after the end of the war, 11% of Vietnam veterans are currently experiencing PTSD symptoms that impair functioning[12].

More recent studies of war fighters from various countries who have served in Iraq or Afghanistan over the past 13 years show high variation in PTSD rates. However, analyses of combined data sets, as well as meta-analyses, have shown that differences in estimates are directly related to the level of combat exposure, with an overall average prevalence of 6% in population samples from all services and countries (including support personnel) and 13% in combat-exposed infantry units[13,14]. One study that merged data sets from UK and US military personnel who had served in Iraq showed that apparent national differences in PTSD prevalence were mostly owing to the differences in the level of exposure to combat[14]. Interestingly, the 'dose–response' curve associating PTSD with severity of combat trauma (measured as the number of direct and indirect combat events) tended to reach a plateau at approximately 25–30% developing the condition, which suggests that once a certain threshold of severe exposure was reached, the risk did not continue to increase. This may be an epidemiological indicator of resiliency[11,15]. Prospective longitudinal studies of military service members have greatly added to our knowledge by showing that the clinical course of combat-related PTSD is often chronic, but also includes spontaneous recovery, as well as late-onset or delayed PTSD[16].

Civilian

Epidemiological studies in the general population have evaluated the prevalence of both trauma exposure and PTSD[17,18]. An initially surprising observation was the high frequency of exposure to traumatic events in populations given that PTSD was first defined in the DSM-III as a response to events "outside the range of normal human experience" (REF. 19). Studies revealed that approximately 70% of adult women in the United States had been exposed to a serious trauma[18], and the majority of the population regardless of sex experienced exposure to at least one traumatic event in their lifetime[17]. Studies from multiple countries have reported similarly high estimates of trauma exposure[20–22].

As in military samples, studies in the general population have consistently shown that the majority of trauma-exposed individuals do not develop PTSD[17] (FIG. 1a). In 2014, the only large-scale study so far was reported, examining PTSD prevalence across representative international population samples using identical methodology. The study showed that current PTSD prevalence (that is, in the past 12 months) averaged 1.1% (with a range of 0.2–3.8%)[23] (FIG. 1b). However, the lifetime burden is substantially higher; for example, for South Africa, the 12-month prevalence is 0.4% whereas the lifetime prevalence is 2.3%. PTSD prevalence, early age of PTSD onset and level of social or occupational impairment strongly correlated with the number of lifetime traumatic events: that is, the more exposures the more likely PTSD

Box 1 | **PTSD in the global context**

Post-traumatic stress disorder (PTSD) is a condition that recognizes tragedy and human suffering, whether they are products of nature, human cruelty, or their combination. Reflected in this reality is that adversity disproportionally affects the most vulnerable members of society, including but not limited to ethnic minority populations, socioeconomically disadvantaged populations and people in zones of conflict[233]. These populations often have the fewest personal, social or material resources available to offset the direct effect of loss that is associated with PTSD and to prevent the cascade into loss cycles that prolong the effects of the disorder[234]. Under-resourced and ethnic minority individuals are disproportionally exposed to violence and sexual violence[235,236]. Within conflict zones, whole ethnic populations are often attacked, subjected to torture and forced to flee, which results in high rates of PTSD in these communities[237].
Even when there is no human intent to harm, vast numbers of socioeconomically disadvantaged people are disproportionally affected by tsunamis, earthquakes, drought and famine, and they are less likely to have access to post-trauma care. Hence, our strategies to address trauma, PTSD and the other psychological and medical sequalae that occur in these instances must be on the global, political and policy levels and will be advanced by insights that emphasize social factors, culture and public health solutions.

Table 1 | **DSM-5 criteria for PTSD**

Criterion*	Description	Specific examples	Requirements	Compared with DSM-IV
Criterion A	Exposure to stressor	• Direct exposure • Witnessing trauma • Learning of a trauma • Repeat or extreme indirect exposure to aversive details	DSM-5 recognizes that exposure to trauma can occur either by direct or indirect confrontation with extreme trauma	Specific definition of details of the stressor needed, including repeated experience or extreme exposure to details of events
Criterion B	Intrusion symptoms	• Recurrent memories • Traumatic nightmares • Dissociative reactions (flashbacks) • Psychological distress at traumatic reminders • Marked physiological reactivity to reminders	At least one of these five examples is required	No change, but further clarification of the dissociative quality of flashbacks needed
Criterion C	Persistent avoidance	• Trauma-related thoughts or feelings • Trauma-related external reminders such as people, places or activities	At least one of these two examples is required	DSM-IV did not separate the avoidance criterion
Criterion D	Negative alterations in cognitions and mood	• Dissociative amnesia • Persistent negative beliefs and expectations • Persistent distorted blame of self or others for causing trauma • Negative trauma-related emotions: fear, horror, guilt, shame and anger • Diminished interest in activities • Detachment or estrangement from others • Inability to experience positive emotions	At least two of these seven examples are required	DSM-IV noted social estrangement and restricted the range of affect; numbing redefined to positive rather than all affects
Criterion E	Alterations in arousal and reactivity	• Irritable and aggressive behaviour • Self-destructive and reckless behaviour • Hypervigilance • Exaggerated startle • Problems concentrating • Sleep disturbance	At least two of these six examples are required	Self-destructive and risk-taking behaviours were not defined in DSM-IV
Criterion F	Duration	Must experience criteria B, C, D and F for >1 month	Acute stress disorder is diagnosed for symptoms occurring for <1 month post trauma	No change
Criterion G	Functional significance	Impairment in social, occupational or other domains	Disability in at least one of these domains is required	No change
Criterion H	Exclusion	Not attributable to medication, substance use or other illness	Symptoms must not be secondary to other causes	Not stated in DSM -IV
Subtypes	• Dissociative subtype: used when depersonalization and derealization occur in tandem with other symptoms described above. • Delayed subtype: used to describe the emergence of symptoms following a period post trauma in which symptoms were not present or were present at a subthreshold level.			

DSM, Diagnostic and Statistical Manual of Mental Disorders; PTSD, post-traumatic stress disorder. *Criteria according to DSM-5 (REF. 1).

is to manifest early, persist and be severe. PTSD prevalence has also been shown to be directly related to the severity of traumatic events, with certain events, such as rape or direct combat trauma, conferring very high risk (≥25–50%).

Across different populations and countries, differences in PTSD prevalence can be to attributed to geographically specific distributions of trauma type and severity, or to other factors such as the resultant loss of personal, social and material resources, which are crucial predictors of the development and the persistence of PTSD[17,18,24,25]. However, cross-national differences might also be attributable to cultural differences in reporting or experiencing of PTSD symptoms. Similarly, the greater PTSD prevalence in women could result from greater exposure to experiences that are associated with the highest prevalence of PTSD[17,18], but it might also associate with sex-specific risk factors[26] (BOX 2). Multiple studies have shown a strong association of PTSD with comorbid conditions, particularly depression and substance use disorders, and general physical health effects spanning all disease categories in both military personnel and civilians[3–5,27,28]. A range of brain, molecular, neuroendocrine and autonomic nervous system disturbances associated with PTSD are likely to influence these comorbid conditions and to provide challenges for treatment.

Mechanisms/pathophysiology

Molecular and neurochemical factors

Early studies in patients with PTSD showed autonomic reactivity, indicated by increased heart rate and skin conductance in response to trauma-related cues, and exaggerated startle responses. These findings recapitulated symptoms of general hyperarousal and distress following traumatic reminders in PTSD[29,30]. Indeed, several pharmacological challenge studies with yohimbine (an α2-adrenergic receptor antagonist) showed exaggerated neurochemical and behavioural responses consistent with central noradrenergic hyper-reactivity in PTSD[9,30,31].

The hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system constitute the body's fundamental stress response; however, contrary to initial predictions of elevated stress hormones in PTSD, an unusual pattern of low basal (unstimulated) cortisol levels and raised catecholamine levels is evident and has been widely replicated in trauma survivors with PTSD[31,32]. Epigenetic, molecular and endocrine studies of glucocorticoid signalling and glucocorticoid receptor sensitivity later confirmed a distinct set of HPA axis alterations that reflect exaggerated negative feedback sensitivity in PTSD (FIG. 2), with some evidence for the role of genetic variants in HPA axis-related genes, including nuclear receptor subfamily 3 group C member 1 (*NR3C1*; encoding the glucocorticoid receptor) and *FKBP5* (encoding FK506-binding protein 5)[33,34]. The glucocorticoid receptor functions as a transcription factor that binds to glucocorticoid response elements in the promoters of glucocorticoid-responsive genes and activates their transcription; the receptor also regulates other transcription factors. FKBP5 has a role in immunoregulation but also has important functions in regulating the amount of glucocorticoids that are available to the glucocorticoid receptor. Prospective longitudinal studies have shown that markers, such as increased startle reactivity, were not observed in those at risk for PTSD but were observed weeks following exposure in those with PTSD[30]. By contrast, reduced glucocorticoid signalling was observed before, and shortly after, trauma exposure in those who developed PTSD[35,36], which confirms an early hypothesis that insufficient glucocorticoid signalling at the time of trauma results in unopposed sympathetic nervous system activation that enhances the consolidation (BOX 3) of the traumatic memory[32]. Converging data support the idea that frequent voluntary or involuntary retrieval of traumatic memories promotes a traumatic memory that is highly distressing and, therefore, difficult to extinguish[37,38]. The formation of strong emotional memories is adaptive because remembering danger when appropriately signalled might enhance survival. However, in the absence of sufficient glucocorticoid signalling, the distress that occurs once reminded, and the generalization of triggers, could result in a cascade of maladaptive symptoms. Psychophysiological data from multiple centres also showed deficits in fear conditioning and extinction learning (BOX 3) in PTSD[30,39], which have been supplemented by neuroimaging and genetic data in animal models and patients with PTSD[40].

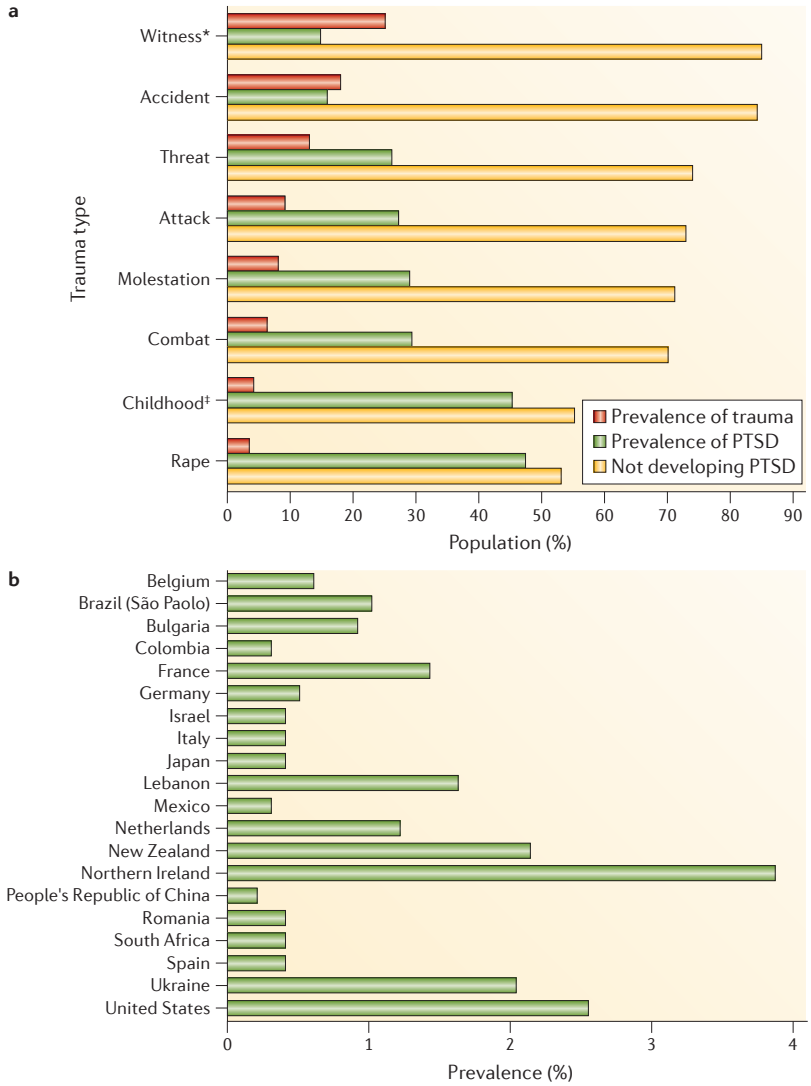


Figure 1 | **The prevalence of PTSD. a** | Most individuals exposed to trauma do not develop post-traumatic stress disorder (PTSD)[17]. Such low rates of PTSD after trauma suggest that PTSD is only one of many responses to trauma. Many individuals do not develop mental health symptoms following trauma exposure. **b** | The mean 12-month prevalence of PTSD in various countries around the world is shown[23]. *Witnessing a trauma can be deemed a trauma in and of itself. ‡Childhood traumas are any traumatic exposures that occur in childhood and can include (but are not exclusively) child abuse.

Pro-inflammatory cytokines, endocannabinoids and neurosteroids are of interest as mediators of the stress response[9,41–43], particularly in the setting of low glucocorticoid signalling in PTSD[44,45]. Multiple studies have shown immune activation in PTSD that is consistent with inflammation[43–47]. Immune-related genes and pathways have also been identified in genome-wide gene expression and methylation studies in peripheral blood[46,48]. In addition, endocannabinoids are functionally associated with glucocorticoid regulation and are involved in both the initiation and the termination of the acute stress response[49]. Glucocorticoid action to facilitate the consolidation of aversive memories is mediated by cannabinoid type 1 (CB1) receptors. Altered blood levels of 2-arachidonoylglycerol and anandamide in patients with PTSD have been shown in three studies of civilian trauma[41,50,51]. Neurosteroids such as allopregnanolone have been investigated in several studies because of their inhibitory effects on glucocorticoid and noradrenaline signalling[30,31]. Finally, sleep physiology studies from multiple centres have indicated rapid eye movement sleep fragmentation and decreased slow wave sleep in those with PTSD[52]; alterations in circadian rhythmicity of cortisol and other HPA axis changes have been linked with sleep disturbances in PTSD[53,54].

Interest in the neurobiology of resilience and in endogenous substances that might promote resilience

Box 2 | **PTSD in women**

Current research offers competing explanations for the observation that the lifetime risk for post-traumatic stress disorder (PTSD) in women is twice that in men[17]. One theory explains the greater prevalence in women as a function of greater exposure to events that are highly causally linked with PTSD, such as sexual abuse and rape[238]. Indeed, the female sex effect on PTSD symptoms became nonsignificant after accounting for patient sexual victimization history[239]. Women are also more likely to be revictimized or exposed to multiple forms of violence in their lifetime than men, which can be difficult to capture in prevalence studies. Of note, a meta-analysis of sex differences in PTSD prevalence did not report a difference in lifetime risk of PTSD among survivors of rape, childhood sexual abuse or nonsexual child abuse or neglect[240].

By contrast, some epidemiological surveys involving a broad range of traumatic exposures have shown that the twofold greater risk for PTSD in women cannot be accounted for by greater exposure to trauma, even when accounting for prior history of victimization or abuse. This finding suggests that women are more vulnerable to PTSD than men[241,242]. The sex difference seems to be consistent across many trauma types[240]. Genetic studies have suggested higher heritability risk in women[77], and molecular genetic studies confirmed allelic variation in the adenylate cyclase activating polypeptide 1 (pituitary) receptor type I (*ADCYAP1R1*) gene in relation to PTSD risk in women[26].

In reality, the greater prevalence of PTSD in women might reflect a combination of greater exposure and vulnerability. A prospective epidemiological study of PTSD risk in abused and neglected children showed that the higher level of revictimization in female victims than in male victims explained a substantial proportion (39%) of the sex differences in PTSD risk. However, a significant sex difference remained after adjusting for greater exposure in women. More research is clearly needed.

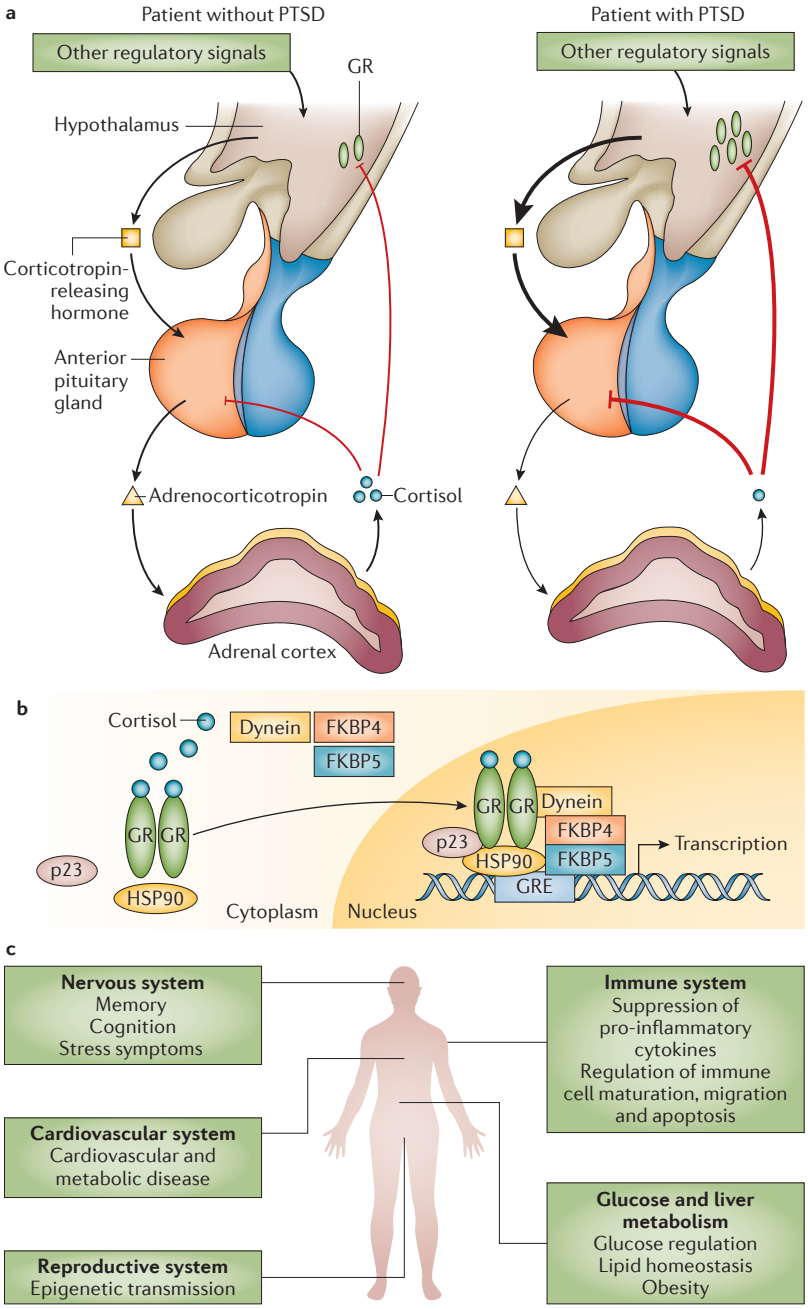
such as neuropeptide Y (NPY), dehydroepiandrosterone (DHEA) and brain-derived neurotrophic factor (BDNF)[9,31] has grown. Indeed, many of these factors have been considered as potential treatment targets[55,56]. However, more research is needed to replicate preliminary findings in adequately powered studies and to determine whether the markers that are thought to be important to PTSD pathophysiology can be identified in large longitudinal genome-wide epigenetic or transcriptomic studies[57]. Any mechanistic relevance that these 'resilience' factors have remains to be determined.

Longitudinal studies have highlighted the importance of cumulative traumatic exposures and the progressive dysregulation of biological systems in the development of PTSD[36,58,59]. Thus, it is important to identify biological alterations associated with pre-traumatic and peri-traumatic risk factors for PTSD and to determine how these 'set the stage' for processes that sustain symptoms[60]. For example, although glucocorticoid signalling alterations have been associated with both PTSD risk and early peri-traumatic responses, some evidence suggests that these alterations change in association with symptom severity[61–67]. That is, a patient can experience a worsening of symptoms related to the acquisition of other alterations to these pathways. Similarly, inflammatory processes can be predictors of PTSD but have been shown (in one prospective study) to change over time and to be linked with the development of comorbid medical illness[68]. Emergent studies are highlighting that ameliorative experiences, such as successful psychotherapy, can reverse some markers associated with PTSD[64,69–71], and such studies will greatly supplement knowledge about the biological mechanisms associated with recovery.

Genetic factors

As has been amply shown across many fields of medicine, discovery of risk-associated alleles can provide initial clues to pathogenesis, which might lead to novel therapeutics or tools for stratifying patients for basic and clinical research. The rationale for examining genetic factors in PTSD has come from twin studies that suggest that PTSD risk is moderately heritable[72]. However, the genetic contribution to PTSD is complex, as genetic factors can also influence exposure to potentially traumatic events such as combat or assaultive violence[73,74]. Even after accounting for genetic effects on risk of exposure, a substantial proportion of vulnerability to PTSD is heritable[73,75–77]. Twin studies might highlight the importance of heritable temperamental factors, such as novelty-seeking behaviour and neuroticism in PTSD, or they might identify biological markers that associate with PTSD risk[78]. For some, trauma exposure functions as a catalyst to augment the effect of hereditary and other environmental contributions to PTSD, such that individuals with the greatest exposure to combat trauma were at increased risk for PTSD as a function of both genetic and environmental factors[79]. Furthermore, a specific functional polymorphism of *FKBP5* has been shown to be associated with increased risk of developing PTSD and other stress-related disorders in response to childhood trauma[80]. Specifically, DNA demethylation occurs in the functional glucocorticoid response elements of *FKBP5* and regulates its function, providing an initial observation of a molecular mechanism of genotype-directed epigenetic change in response to environmental stressors[81]. Interestingly, a large proportion of the genetic liability for PTSD is shared with other psychiatric disorders that can be comorbid with PTSD, such as anxiety and panic disorder, major depression and substance use; genes that confer risk for PTSD might also influence risk for other psychiatric disorders and vice versa[82].

As the data from large-scale genetic studies emerge, it will be important to re-evaluate conclusions drawn from twin studies. Indeed, to the same extent that parental PTSD is a risk factor on the basis of non-genetic mechanisms of transmission, a twin could have shared genetic risk factors as well as shared developmental experiences. For example, maternal PTSD is a risk factor for PTSD[83] and could contribute risk through epigenetic changes[61] independent of allelic variation[81]. For this reason, it is important to carry out large-scale genome-wide association studies (GWAS), perform adequately powered large epigenomic studies[46,84] and replicate findings in independent studies[85]. Unlike in GWAS, considerable conceptual and technical problems must be resolved to address epigenetic influences on PTSD risk[86]. In particular, our knowledge about the epigenome is still fairly limited, making it difficult to interpret epigenetic variations as relating to stable disease processes. Furthermore, in PTSD, studies of epigenetic regulation have had to focus on peripheral cells such as leukocytes. Such cells inhabit different regulatory environments from critical brain circuits and, therefore, these studies have limitations. Studies of gene expression in critical neural circuits are similarly limited. Nonetheless, studies examining genetic, epigenetic and gene expression



◀ Figure 2 | **The function of the HPA axis in PTSD and controls. a** | Network-level differences in hypothalamic–pituitary–adrenal (HPA) responses to stress are evident in post-traumatic stress disorder (PTSD). The increased secretion of corticotropin-releasing hormone from the hypothalamus in PTSD is represented by a thick black line. The decreased adrenal release of cortisol in PTSD is represented by the thin black line. The increased negative feedback inhibition of the HPA axis by cortisol in PTSD is represented by thick red lines. **b** | Key molecular factors affecting genomic sensitivity to glucocorticoid signalling are shown. Cortisol binds to the glucocorticoid receptor (GR) in the cytoplasm, which is coded by nuclear receptor subfamily 3 group C member 1 (*NR3C1*). The glucocorticoid–GR complex is further bound by chaperone proteins that include FK506-binding protein 5 (FKBP5). Genetic variation of *NR3C1* and *FKBP5* are implicated in functional differences in glucocorticoid signalling in PTSD. The chaperone-bound glucocorticoid–GR complex is translocated into the nucleus and binds to glucocorticoid response elements (GRE), which ultimately affects transcription of a large number of genes. **c** | Several systems are affected by differential glucocorticoid signalling, including the brain, cardiometabolic sites, reproductive organs and the immune system. HSP90, heat shock protein 90. Part **a** adapted with permission from REF. 32, Massachusetts Medical Society.

markers from blood can be compared with neuroendocrine information from blood, providing some validation of functional relevance[87,88]. The fact that neuroendocrine biomarkers change over time in association with symptom severity provides additional validation[87,89]. As these methodologies are embraced, methods that provide durable insights will be required. For example, validation of candidate markers through unbiased genome-wide sampling will be required; this has been achieved with respect to the identification of variation in levels of glucocorticoid receptor co-chaperones in those with PTSD, such as *FKBP5* (REFS 84,88). Furthermore, as methylation is only one of several mechanisms for gene regulation, other mechanisms of epigenetic regulation must be examined[90,91].

Only five GWAS in patients with PTSD have so far been published. These encompass diverse settings including all-male or all-female cohorts, subjects of European or African ancestry (that is, African Americans) in the United States and exposure to military, civilian and childhood trauma. The hypothesis-free GWAS approach has already identified several novel potential PTSD-associated loci, including those containing the gene encoding nuclear receptor RORα (*RORA*)[92], the gene encoding Tolloid-like protein 1 (*TLL1*)[93], a novel RNA gene long intergenic non-coding RNA (lincRNA) AC068718.1 (REF. 94), the gene encoding phosphoribosyl transferase domain-containing protein 1 (*PRTFDC1*)[95] and the single-nucleotide polymorphism rs717947 at chromosome 4p15 (REF. 85). Although promising, these first studies were fairly small and underpowered[96], and most did not meet the conventional criteria of genome-wide significance (set at $P < 5 \times 10^{-8}$), did not replicate the same single-nucleotide polymorphisms or have an effect in the same direction in an independent sample.

Pending progress in GWAS, genetic variants confidently associated with PTSD have yet to be identified. However, some genes have been identified in small candidate gene association studies[97,98], including those related to the HPA axis, the noradrenergic system and the limbic amygdala frontal pathway that mediates fear processing. In one study, polymorphisms in *FKBP5* were shown to have a significant association with severity of child abuse in the prediction of adult PTSD symptoms[80], and the gene was subsequently shown to be demethylated in another intron after trauma[81]. These findings require follow-up because the expression of *FKBP5* has been identified as altered in a genome-wide gene expression study of PTSD[88] and was found to associate with the disorder in cross-sectional and longitudinal studies as described above.

Finally, a current effort is underway to evaluate data obtained from very large sample sizes (>10,000 participants)[98]. The Psychiatric Genomics Consortium (PGC) has a PTSD working group that aims to carry out field-wide meta-analyses of genetic data obtained from patients with PTSD to identify new samples on which to perform additional GWAS[98]. Thus, there is every reason to believe that the identification and validation of relevant PTSD risk genes are imminent.

Cognitive factors and neurocircuitry

The earliest neuroimaging and neurochemistry studies in PTSD focused on hippocampal dysregulation because deficits in memory performance and information processing were observed in patients with PTSD. Hippocampal functioning in PTSD was also of interest because of the role of the hippocampus in fear extinction and facilitation of the neuroendocrine response to stress, and because stress exposure and concomitant increases in brain glucocorticoid activity were found to damage hippocampal neurons in animal models and studies of human ageing[99]. Great interest was generated by an initial report of smaller hippocampal volume in those with PTSD[100]. However, a subsequent study of identical twins suggested that smaller hippocampal volumes reflected risk for PTSD rather than stress-induced glucocorticoid toxicity, which has not been shown in PTSD[78]. Smaller hippocampal volume has been shown to be a vulnerability factor in the persistence of PTSD[101].

Subsequent research expanded the focus from the hippocampus and identified circuits associated with the amygdala, medial prefrontal cortex, cingulate gyrus and insula as abnormal in patients with PTSD[102]. These studies were influenced by animal and human studies of fear conditioning and extinction[7]. A large number of studies showed decreased ventromedial prefrontal cortex and rostral anterior cingulate activation in response to both trauma-related and non-trauma-related stimuli in individuals with PTSD[30,103–106]. Consistent with diminished prefrontal inhibition of fear circuitry, increased amygdala activation in those with the disorder was also shown in response to both trauma and non-trauma-related emotional stimuli in some[30,106–109] but not all studies. Meta-analyses of functional neuroimaging studies in PTSD suggested the amygdala can show hyperactivity and hypoactivity within the ventral anterior and dorsal posterior regions, respectively, which is consistent with the functional specificity of amygdala sub-nuclei[106]. Patients with PTSD who show symptoms of emotional detachment (such as depersonalization, derealization and emotional numbing) have increased activation of medial prefrontal cortex and rostral anterior cingulate regions[110], which is consistent with inhibition of limbic regions[111]. These findings suggest that there are distinct patterns of amygdala activity and connectivity in different PTSD phenotypes and indicate the importance of considering the heterogeneous nature of this disorder when designing PTSD studies.

Indeed, PTSD can be characterized by two extremes of emotional dysregulation[112] (FIG. 3). Emotional undermodulation involves diminished prefrontal inhibition of circuits involved in emotion processing and increased autonomic responsivity as shown during re-experiencing, fear, anger, guilt and shame. However, there is also evidence that patients experience emotional overmodulation, which reflects an exaggerated dampening of emotional expression and related emotional detachment, such as states of depersonalization and derealization, numbing and diminished somatic sensations. Such overmodulation is reflected by a heightened inhibition of limbic regions[112]. These contrasting states associate with distinct patterns of fronto-limbic activity and recapitulate the fundamental dynamic of PTSD as a condition in which individuals struggle to modulate

Box 3 | **Key terms in PTSD**

- Cognitive behavioural therapy (CBT): therapy that focuses on challenging negative thoughts and perceptions one has about the world and oneself to bring about desired changes in mood, feelings and behaviours.
- Cognitive processing therapy: a type of CBT that focuses on understanding why recovery from traumatic events has been difficult and developing a narrative that helps to change the way survivors feel about what has occurred and why it happened.
- Consolidation: the process of 'stabilizing' a memory after initial acquisition and transferring it to long-term memory storage.
- Depersonalization: a state of consciousness in which a person feels unreal and detached from himself or herself and the world.
- Derealization: a state of consciousness in which the person perceives the world as unreal.
- Desensitization: diminished emotional responsiveness in response to a repeated negative exposure.
- Extinction learning: the gradual decrease in a fear response that occurs when the (neutral) stimulus is no longer paired with an adverse consequence.
- Eye movement desensitization processing: a therapy aiming to process distressing memories by having the patient recall distressing images while receiving one of several types of bilateral sensory input, including side-to-side eye movements.
- Fear conditioning: a behavioural paradigm in which humans or animals learn to fear objects or situations by linking adverse stimuli, such as shock, to neutral stimuli, such as lights or tones.
- Habituation: in response to a repeated stimulus, habituation is the process in which the response is diminished.
- Interpersonal therapy: a type of psychotherapy that views faulty communication or interaction as the causes of maladaptive behaviour and seeks to help the patient to regain control of mood and functioning through better communication skills.
- Non-directive counselling: a process whereby the therapist encourages the patient to express thoughts freely and refrains from giving advice or interpretation to enable the patient to identify conflicts and feelings on the basis of hearing his or her thoughts out loud.
- Present-centred therapy: a therapy based on the idea that the patient has the internal resources to improve. The therapist's role is to listen to and then reflect and restate what the patient has said without judgement; the goal is personal growth.
- Prolonged exposure therapy: a form of CBT characterized by re-experiencing the traumatic event through remembering it and engaging with (rather than avoiding) the reminders of the trauma (also known as triggers).
- Retrieval: remembering an event; in post-traumatic stress disorder (PTSD), retrieving a memory can be equivalent to re-experiencing it first-hand.
- Supportive therapy: a therapy designed to reinforce a person's ability to cope by reinforcing well-being and self-reliance rather than attempting direct changes to the person's character structure or behaviour.
- Wait-list conditions: in a treatment study, participants can be randomly assigned to wait for a specified period before beginning treatment. Symptom improvement during this time of no treatment is usually compared with an active treatment.

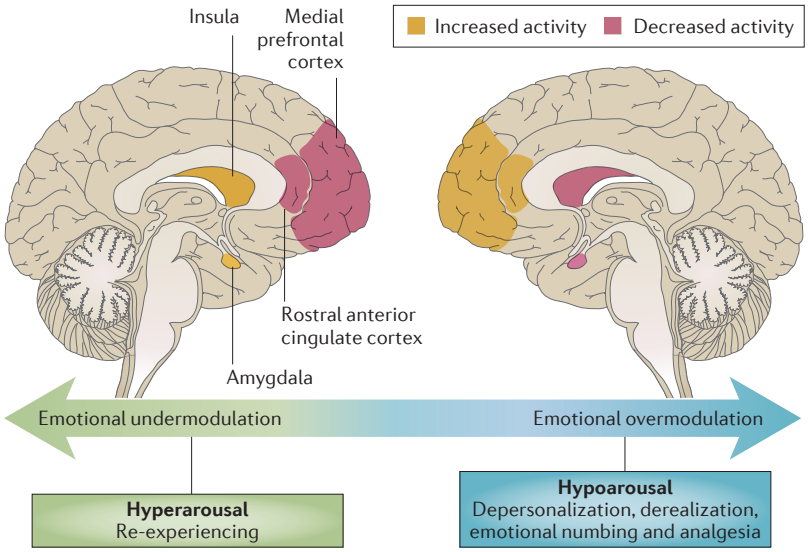


Figure 3 | **Emotional undermodulation and overmodulation in PTSD.** Emotional undermodulation refers to diminished control or heightened emotional and autonomic responding as shown during re-experiencing, fear, anger, guilt and shame responses. Emotional overmodulation encompasses increased control of emotional states and related emotional detachment, such as states of depersonalization and derealization, emotional numbing and analgesia. These contrasting forms of emotion dysregulation suggest that post-traumatic stress disorder (PTSD) is a dynamic disorder that involves fluctuations between states of heightened emotional and autonomic experience and states of diminished emotional experience and autonomic blunting. This symptom complexity also seems to be represented in the neural circuitry that underlies PTSD. Consistent with diminished prefrontal inhibition of limbic regions during emotional undermodulation, studies have indicated decreased ventromedial prefrontal cortex and rostral anterior cingulate activation and increased amygdala activation in response to trauma and non-trauma-related emotional stimuli in those with PTSD[30,104–107,109]. By contrast, patients who have emotional overmodulation have shown increased activation of medial prefrontal cortex and rostral anterior cingulate regions, which have been suggested to lead to decreased amygdala activation[112]. Figure adapted with permission from REF. 243, Wiley.

distress associated with extreme arousal with avoidance and disengagement.

A more-comprehensive model of PTSD neurocircuitry has been suggested to acknowledge the interaction of three systems other than the fronto-limbic circuits. These systems are the default mode network, the salience network and the central executive network[113–115] (FIG. 4). Fluctuations in the activity of these circuits can explain how a patient with PTSD shifts into dramatically different states in an attempt to regulate their extreme emotional responses to cues or trains of thought[116,117].

An important area of neuroimaging research has involved delineating brain neurochemistry using PET imaging. However, such studies have been limited by the lack of relevant PET tracers, for example, for glucocorticoid receptors or receptors for neuropeptides (such as corticotropin-releasing hormone and NPY). A single-photon emission computed tomography study has revealed lower GABA-A (γ-aminobutyric acid A) receptor binding in combat veterans with PTSD than in those without PTSD[118]. Other promising findings include differences in endocannabinoid receptor sensitivity, assessed using a selective cannabinoid-type receptor radioligand, between those with and those without the disorder[51]. Receptor number in tandem with blood anandamide (an endocannabinoid neurotransmitter) and cortisol concentrations could correctly classify 85% of patients with PTSD[51]. In another study, the distribution of selective dynorphin (an opioid peptide) and κ-type opioid receptor in the amygdala–anterior cingulate cortex–ventral striatal circuit was associated with the trauma of loss, a relationship that was influenced by glucocorticoid levels[41]. Reduced binding to the serotonin transporter in the amygdala has also been noted[119], as have regionally specific, differential responses in glucose use following glucocorticoid injection in those with PTSD compared with unaffected individuals[120].

It will be crucial to examine brain networks and neurochemistry in a longitudinal manner. In addition, the effects of pre-trauma risk factors, exposure to stressors, protective factors and the age of trauma onset on the development of PTSD will require focused investigation. It has yet to be established whether fear or chronic repeated re-experiencing of the traumatic event leads to sensitization and augmentation of emotional reactivity to promote the emergence and maintenance of brain changes or whether these changes result from genetic or early childhood factors that alter the circuitry, making recovery difficult.

Diagnosis, screening and prevention

Classification

The original PTSD conceptualization emphasized the re-experiencing of phenomena, such as intrusive traumatic memories, nightmares and dissociation by patients as hallmark symptoms[121]. PTSD was first introduced into DSM-III in 1980 (REF. 19) partly owing to emerging concerns about long-term stress responses in Vietnam War veterans. Psychiatry had previously recognized that long-standing traumatic neuroses could occur following combat exposure, but it was becoming apparent that similar symptoms were present in those who experienced interpersonal violence such as rape or assault, survived ethnic cleansing or genocide, or experienced serious accidents or natural disasters[122]. Given that the prevailing theory at that time was that stress effects would remit with removal of the stressor, the PTSD diagnosis was revolutionary in asserting long-term and transformative effects of trauma. When first conceptualized, no epidemiological studies of trauma exposure and its aftermath had been carried out that could inform the diagnosis[122]. Instead, PTSD was thought to be a reflection of a natural response to an unnatural circumstance. However, subsequent studies documented that, although trauma exposure was common, PTSD occurred in only a minority of survivors.

The DSM-III definition included 12 symptoms and highlighted the importance of re-experiencing the trauma. Numbing and constricted affect was a second symptom cluster. A variety of symptoms — such as hyperarousal, sleep disturbance, guilt, memory impairment and avoidance of traumatic triggers — were described in a third nonspecific cluster. The revised DSM-III (DSM-IIIR (1988)) and the DSM-IV (1994) definitions both included 17 symptoms and were based on observations that avoidance, numbing and interpersonal estrangement

represented a dynamic adaptation that was thought to lessen the distress of traumatic memories; other symptoms were thought to represent physiological expressions of arousal or hyperviligence[123].

The first major revision to the definition since 1988 occurred in 2013 in DSM-5. Among the changes in diagnostic criteria for PTSD in DSM-5 (REF. 1), which now includes 20 symptoms, was a modification of the avoidance and the interpersonal estrangement criterion C. The DSM-IV criteria are now separated into two subcategories: avoidance, and negative cognitions and mood symptoms, partly on the basis of factor analytical studies[124]. These changes have led to considerable diagnostic discordance between DSM-IV and DSM-5 PTSD in up to 30% of patients, which raises questions about the clinical use and implications of the recent changes[125,126]. Both diagnostic formulations are currently in use clinically and in the research setting. As negative cognitions are the focus of cognitive behavioural therapy (CBT) for PTSD, including them as a separate cluster could inadvertently increase the proportion of patients who respond to treatments designed to affect cognitions compared with treatments that preferentially target other PTSD symptoms or related dysfunctions. Moreover, negative cognitions might reflect second-order characteristics that are not directly tied to the underlying neurobiology of PTSD[126]. These controversies about DSM-5 and the need for continuity in the literature have meant that DSM-5 criteria have not been automatically embraced in international academic, clinical or legal circles.

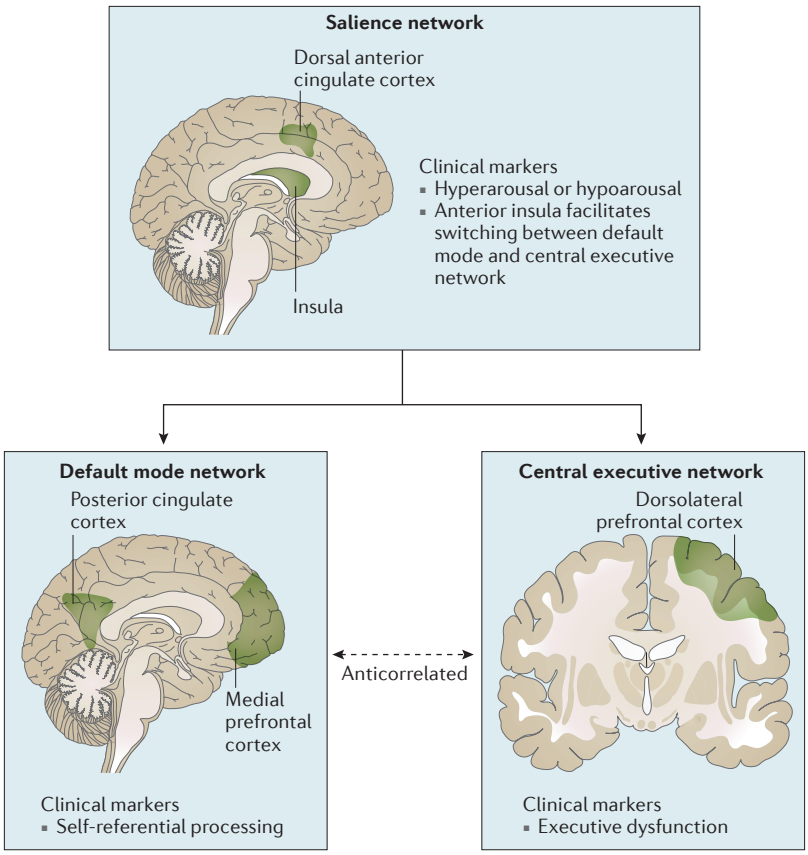


Figure 4 | **The default mode, salience and central executive networks in PTSD.** Three intrinsic connectivity networks in the human brain have been identified as central to the understanding of higher cognitive function[113]: the central executive, salience and default mode networks. The responses of these networks generally increase and decrease proportionally and antagonistically during cognitive tasks. The central executive network is a frontoparietal network that is crucial to working memory and cognitive control of thought, emotion and behaviour. The salience network consists of the dorsal anterior cingulate cortex and the frontoinsular cortex and is involved in the detection of personally salient internal and external stimuli to direct behaviour with the goal of maintaining homeostasis. The default mode network, which consists of cortical midline structures and lateral parietal lobes, plays an important part in self-related processes, emotion regulation, social cognition, autobiographical memory and future-oriented thinking. Crucially, the anterior insula is thought to mediate the dynamic interface between externally oriented attention and internal self-reflective functioning, mediating switching between engagement of the central executive network and disengagement of the default mode network and facilitating engagement of brain areas mediating attention, working memory and higher-order cognitive processes. These three intrinsic networks might be associated with specific clinical symptoms observed in post-traumatic stress disorder (PTSD), including cognitive dysfunction (in the case of the central executive network), altered arousal and interoception (in the case of the salience network) and altered self-referential processing (in the case of the default mode network). Figure adapted from REF. 188.

An examination of data from the World Mental Health Survey comparing the DSM-IV, DSM-5, International System of Classification (ICD-10) and proposed ICD-11 criteria showed that only one-third of patients met PTSD criteria across all four diagnostic schemes[127]. Accordingly, adopting the DSM-5 classification to epidemiological, biological and treatment research will probably yield results different from those that have previously been obtained. Furthermore, definitions of what constitutes a traumatic event in the DSM and ICD classification systems are different (TABLE 2). If studies are to remain comparable over time, evaluation of biological markers and treatment response on the basis of specific, well-described symptom clusters, rather than relying on DSM-5 criteria alone, will be of importance. However, against this background, an important development in DSM-5 has been the inclusion of a more developmentally sensitive phenotypic characterization of the disorder in young children.

A major advance in understanding PTSD signs and symptoms has come from longitudinal studies. These studies have confirmed that PTSD can emerge many years after the traumatic exposure. In the initial years after the diagnosis was first codified in 1980, the concept of delayed PTSD was controversial because it challenged the idea that PTSD is caused by the acute stress response or by its failure to resolve[16,128]. Indeed, symptomatic distress can increase with the passage of time rather than reflect delayed presentation for treatment[129]. This temporal increase can be partly attributed to further stresses in the aftermath of the initiating traumatic exposure or the erosion of previously effective self-regulation or extinction learning[128]. Increased distress may also be explained by biological phenomena such as kindling and sensitization[130]. Kindling refers to the process through which patterns of negative information processing become easier to activate even with increasingly minimal cues[131]. Sensitization refers to the progressively greater responses that develop over time in those who are repeatedly exposed to environmental risk factors that magnify the intensity of the response to a single new perturbation[132]. Delayed-onset PTSD is often preceded

by subsyndromal symptoms, which impart morbidity in their own right, as well being predictors of 'full' PTSD[130].

Another classification issue has concerned the definition of trauma exposure, including which events should be used in the stressor criterion[1]. This matter has relevance for establishing causation in litigation, disability assessment and compensation. For example, the effect of bullying, the sudden death of one's child as a result of illness, or situations involving interpersonal stress stemming from electronic or social media would not be considered to meet the definition under DSM-5 unless an assault is threatened or occurs, the trauma was accidental or violent, or if the patient is repeatedly exposed to images of traumatic events (for example, as in the case of emergency first responders)[1]. DSM-5 also recognizes that subjective responses such as fear, helplessness or horror might not be immediate responses to trauma. Indeed, military and emergency service personnel learn to override their avoidance and fear reactivity to carry out their duties and do not regularly report these reactions[133].

Finally, DSM-5 also removed PTSD from the anxiety disorder section and created a new category of trauma-related disorder[1]. However, other diagnoses, including depression and panic disorder, frequently emerge following trauma exposure in the absence of PTSD[128]. Accordingly, the question arises as to whether the traumatic stress response contributing to these disorders differentiates them from the same diagnoses emerging in the absence of a traumatic stressor. The issue of shared causal mechanisms[106] is also relevant to the investigation of comorbid disorders that are also present in the majority of patients with PTSD[134–136].

Diagnosis

In principle, it is straightforward to diagnose PTSD in circumstances in which the clinician knows or suspects the patient has been exposed to an extremely traumatic event or critical incident. A series of questions can be asked to determine the presence, frequency and intensity of the symptoms of PTSD. However, diagnosing PTSD when symptoms are present but when the patient does not volunteer information is difficult, particularly if the clinician does not ask (or does not know to ask) about potential exposures.

Furthermore, cross-cultural validity of the diagnosis is an important consideration because of the relevance of the disorder in refugee populations and in global humanitarian and disaster settings. Specifically, studies have confirmed the symptom clusters across cultures but practitioners in these settings should have an awareness of specific culture-bound trauma constructs[137]. The diagnosis is also difficult to make when the patient does not wish to be identified as someone who has PTSD, such as military personnel or emergency first responders. Moreover, many of the symptoms of PTSD are not apparent and rely on disclosures of traumatic nightmares, numbing, avoidance or impaired concentration, of which patients might have limited awareness. In addition, patients might believe that disclosing these symptoms will result in occupational or other restrictions. Alternatively, some might wish to exaggerate their symptoms for secondary gain.

Even among those who do not have a specific reason to conceal or to amplify symptoms, the diagnosis of PTSD can be difficult to make because of the propensity to colloquially normalize distress after traumatic

Table 2 | **Definition of a traumatic event in DSM and ICD classification systems**

Classification	Definition of traumatic event	Refs
DSM-III	"a stressor that would be markedly distressing to almost anyone … and is outside the range of usual human experience"	19
DSM-IIIR	"The most common traumata involve either a serious threat to one's life or physical integrity; a serious threat or harm to one's children, spouse, or other close relatives and friends; sudden destruction of one's home or community; or seeing another person who has recently been, or is being, seriously injured or killed as the result of an accident or physical violence."	244
ICD-10 (World Health Organization 1992)	"[PTSD] arises from a delayed and/or protracted response to a stressful event or situation (either short-lived or long-lasting) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone (for example, natural or man-made disaster, combat, serious accident, witnessing the violent death of others, or being the victim of torture, terrorism, rape or other crime)."	245
DSM-IV	"The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others. The person's response involved intense fear, helplessness, or horror."	123
DSM-5	"The person was exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence as follows: (one required) 1. Direct exposure. 2. Witnessing, in person. 3. Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental. 4. Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (for example, first responders, those collecting body parts or professionals repeatedly exposed to details of child abuse). This does not include indirect non-professional exposure through electronic media, television, movies or pictures."	1

DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International System of Classification.

events[138], compounded with a tendency to avoid speaking of distressing memories. Often, patients with PTSD focus on their co-occurring somatic complaints such as musculoskeletal pain or gastrointestinal or neurocognitive symptoms[28,139]. As a consequence, PTSD can present a diagnostic challenge in non-mental health settings. A study in a primary care setting identified that only 11% of patients with PTSD detected by structured interview were listed as such in clinical files[140]. To complicate matters, somatic symptoms, which can relate to neuroendocrine and autonomic dysregulation in PTSD, might also be attributed to illness caused by toxic environmental exposures, especially in combat environments, and have led to controversies about the existence of distinct illnesses, such as Gulf War Syndrome[141]. Thus, self-reporting instruments and structured diagnostic interviews are recommended in clinical practice to improve the reliability of diagnosis.

No objective laboratory tests can so far confirm the presence of trauma exposure or PTSD, although there is great interest in the development of these tools. Indeed, biological assessments might identify a range of physiological and neurobiological signs and symptoms that might facilitate diagnostic assessment and the prediction of treatment response[30,142].

Screening

The prevalence and the burden of diseases associated with PTSD highlight the importance of screening in clinical settings, including primary care, and in populations at risk for trauma exposure. Any health professional involved in the follow-up care of those with physical injuries of accidents or assault should be able to detect PTSD symptoms[32]. Many screening measures are available that can detect cumulative exposure to trauma and resultant symptoms[143–145]. A positive finding should be followed up by a comprehensive mental health evaluation. Ideally, screening will also assess other comorbid disorders.

In populations at risk of delayed-onset PTSD, continued assessment is recommended[128]. In some settings, such as primary care, annual screening is a reasonable minimum recommended standard but should be implemented more frequently in settings in which trauma exposures are common[146]. For military populations, there is greater acceptance of the benefits of screening at post-deployment than at pre-deployment[146]. The challenges of screening for PTSD include the inability to determine the cause of symptoms, the high false-positive rate and low predictive value in settings in which prevalence is expected to be fairly low[145]. Screening in primary care settings and screening that is combined with care coordination seem to be more effective than population screening[147], particularly in high-risk populations.

Prevention

Opportunities for PTSD prevention are considerable for military personnel, emergency first responders and, increasingly, journalistic war correspondents. Prevention programmes aim to promote good psychological health and adaptive methods for coping in the face of adversity[146]. Several approaches — such as resilience training, prevention interventions and reintegration interventions — have been implemented on the basis of theoretical frameworks in military settings[148]. Although data are lacking regarding the success of such programmes, rehearsal and preparation for trauma are thought to remove some of the elements of shock and to permit adaptive responding during a threat. In civilians, preparedness for trauma might also enhance resilience[149].

Preventing PTSD is difficult among persons already exposed to mass communal violence and major disasters. However, relevant information about what to do in the aftermath of trauma is scant, and concerns have been raised that scientific research or programme evaluation in emergency settings might interfere with the provision of care. The sense of urgency to help after major events such as disasters makes research very difficult to carry out in these circumstances and is often perceived as showing intellectual indifference rather than a desire to assist[150]. Furthermore, experience with critical incident stress debriefing — which aims to enhance individuals' natural resilience and coping capacity following adversity — highlights that not all attempts guarantee effectiveness; no benefit was shown in intervention trials[146]. In addition, reviews of clinical trials do not support this approach in civilians[151]; however, such interventions might have a role in occupational groups, such as emergency first responders, though data are lacking. The current standard is to offer psychological 'first aid', but little systematic evidence is available to support this approach[146].

Another area of great interest is the development of PTSD prophylaxis through the administration of medication in the emergency room or in intensive care units[152,153]. These studies are based on evidence that reactivated memory traces are vulnerable to disruption in the peri-traumatic phase, offering a potential 'time window' to enhance cognition by affecting reconsolidation of trauma memories[154,155]. Naturalistic studies have shown that people who take large doses of opiates during or immediately after trauma exposure are less likely to develop PTSD than those who do not take such medications[156,157]; propranolol was the first of these treatments to be proposed for this use as it has the potential to interfere with the role of noradrenaline in the consolidation of traumatic memories[158]. However, the results so far in clinical trials have shown no benefit[159]. The role of cortisol in preventing PTSD has also been considered given that low levels of cortisol in the immediate aftermath of traumatic events has been found to predict later PTSD diagnosis[160,161]. In this example, naturalistic studies have shown that, in patients with septic shock, prednisone administration was associated with the development of fewer traumatic memories than placebo treatment[162]. In the case of cortisol prophylaxis, several early studies have yielded promising results, particularly when a high dose is administered once during the 'golden hours' following trauma exposure[159,163]. Given that a prevailing model of PTSD development involves a failure to mount neural defensive responses to sympathetic nervous system activation (leading to the development of a stronger and a more emotional memory), cortisol treatment during a critical post-traumatic window might facilitate such

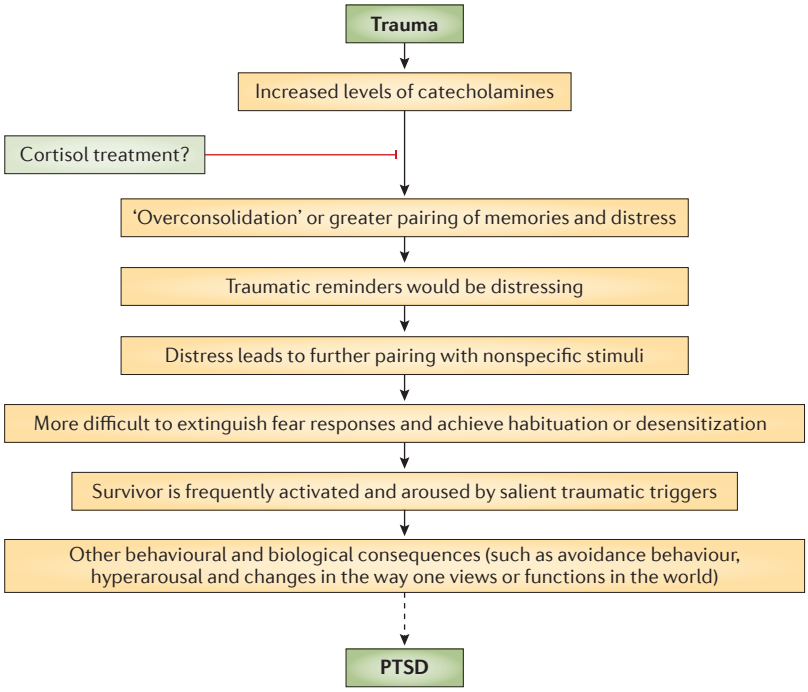


Figure 5 | **Consequences of reduced cortisol signalling in acute aftermath of trauma.** In response to trauma, catecholamines (such as adrenaline (epinephrine) and noradrenaline (norepinephrine)) are produced, which mediate the sympathetic nervous system response to stress and have a role in memory formation. In patients who develop post-traumatic stress disorder (PTSD), the role of cortisol to counteract these stress hormones is thought to be reduced. Some evidence suggests that administration of cortisol in the aftermath of trauma might prevent the eventual development of PTSD.

responses[163] (FIG. 5). Cortisol not only reduces sympathetic nervous system activation but also facilitates fear extinction. One small randomized trial found that hydrocortisone administration within 12 hours of trauma also decreased the risk of PTSD[164]. Two studies showed that the dose of narcotic analgesic administered during admission to hospital after traumatic injury decreased the risk of PTSD independently of the severity of injury; however, the role of narcotic analgesics in preventing PTSD has not been tested in a clinical trial[157,165].

Management

Psychotherapy

Despite the emerging understanding of PTSD as a disorder involving substantial brain, molecular and neurochemical change, pharmacotherapy treatments have not conclusively shown efficacy that is equivalent to psychotherapy, which is generally recommended as a first-line treatment (TABLE 3). A range of trauma-focused as well as non-trauma-focused psychotherapies, including CBT, supportive therapy, non-directive counselling, present-centred therapy and interpersonal therapy (BOX 3) have shown clinical benefits in the treatment of PTSD[166,167]. Some treatment approaches favour targeting specific trauma-related symptoms, behaviours, thoughts or perceptions, whereas others have a wider focus on meaning making or addressing current life stressors and goals. Both trauma-focused CBT and non-trauma-focused therapy have consistently been shown to be superior to wait-list conditions (BOX 3) in reducing PTSD symptoms; trauma-focused treatments are generally accepted as the most efficacious. Of course, comparison of no treatment to active treatment can fail to account for nonspecific effects of therapy and can lead to overstated conclusions about the superiority of an identified treatment[168].

A typical psychotherapeutic treatment for PTSD is delivered through weekly sessions, generally over 6–16 weeks as the global standard. However, patients might require several more sessions over months or years. The discrepancy between treatment recommendations in the literature and those used in clinical practice has not been sufficiently addressed. Indeed, although these treatments are often provided in healthcare systems such as the Veterans Administration in the United States, most patients with PTSD remain with a considerable symptom burden over prolonged periods of time.

Trauma-focused CBTs, such as prolonged exposure therapy and cognitive processing therapy, for symptoms of PTSD have been the most thoroughly studied and have shown equivalent effectiveness in head-to-head comparisons[169]. These therapies are based on the idea that promoting emotion regulation and extinction learning will neutralize the distress of trauma-related thoughts and images and obviate the need for avoidance behaviours[170,171]. Prolonged exposure therapy facilitates habituation using principles of extinction learning, habituation and desensitization through progressive exposure to the trauma narrative and triggering settings (FIG. 6). Cognitive processing therapy addresses shame, guilt or feelings of mistrust. More recently, narrative exposure therapy has been described, which focuses on life histories through narration and has been successfully used in complex forms of PTSD. This therapy is particularly helpful with refugees and asylum seekers and has been successfully provided by lay counsellors who have no formal clinical education[172].

Eye movement desensitization and reprocessing (EMDR) is another trauma-focused therapy for which efficacy has been shown. Though its mechanism of action is a subject of debate, EMDR also incorporates elements of exposure, cognitive restructuring and relaxation. In EMDR, the therapist uses different forms of bilateral stimulation (most commonly lateral eye movements) to encourage a dual awareness while the patient recollects the trauma[173,174]. Once accessed, the memory is amenable to modification and positive cognitions can be introduced in the place of negative ones. In direct comparison studies, EMDR has been shown to be as efficacious as other trauma-focused CBTs[175,168].

Treatments that do not involve direct confrontation with traumatic material, such as present-centred or interpersonal therapy approaches, have been shown to be almost comparable to trauma-focused approaches in some studies, with the potential benefit of lower drop-out rates[176–178]. However, almost all clinical guidelines and expert reviews have assigned higher evidence statements to trauma-focused approaches[179–184], probably because of how well studied these therapies have been in large-scale efficacy and effectiveness trials. Furthermore, trauma-focused therapies aim to target fear-based emotional

reactions that are thought to underpin PTSD pathology, as described above.

Patients with a history of interpersonal violence, early-life trauma or those with a complex presentation of PTSD that includes emotional detachment might be better treated with phase-oriented approaches[185]. Phase-oriented therapies involve skills training, mood regulation and grounding, identifying attachment schemas and developing competence in social interactions. Once these skills have been developed, the patient can then participate in modified exposure-based therapy focusing on emotional stability and negative personal schemas[186,187]. Other therapies of interest include self-regulation therapies (for example, biofeedback and neurofeedback) and behaviour-based self-regulation therapies (for example, yoga and mindfulness training). These treatments permit brain, central nervous system and behavioural regulation of stress, arousal and interoceptive awareness[188,189].

Pharmacological treatment

Only two medications, which are both selective serotonin reuptake inhibitors (sertraline and paroxetine), have received an indication from the FDA for use in PTSD, but many medications are used off label on the basis of existent and emerging studies of PTSD biology (TABLE 3). Several national societies have adopted recommendations from international consensus guidelines (TABLE 4), which have varied widely in the past 10 years,

Table 3 | **Overview of interventions for PTSD**

Intervention or system	Biological target	Candidate example(s)	Status
Psychotherapies			
Trauma-focused psychotherapies	Extinction of conditioned fear responses and emotional regulation; (pre)frontal cortex (inhibition); stress regulation; trauma-related thoughts and cognitions; behaviours and perceptions (frontal and parietal cortex and limbic system)	Cognitive behavioural therapies; prolonged exposure therapy; eye movement desensitization and reprocessing; and narrative exposure therapy	Currently used
Non-trauma-focused psychotherapy	Emotion regulation; stress regulation (self-referential processing, coping, meaning making, acceptance and acknowledgement); frontal and cingulate cortex; and limbic system	Supportive therapy; non-directive counselling; mindfulness and present-centred therapy; and interpersonal therapy	Currently used
Pharmacotherapies			
Corticotropin-releasing hormone system	Corticotropin-releasing hormone and noradrenaline modulation	Antalarmin	Preclinical
Hypothalamus–pituitary–adrenal axis	Glucocorticoid receptor and glucocorticoid production and downregulation of glucocorticoid receptor	Mifepristone and hydrocortisone	Clinical trials ongoing
Dopaminergic system	Dopamine turnover and/or uptake	Risperidone, olanzapine and quetiapine	Currently used
Serotonergic function	Serotonergic dysregulation*	Paroxetine, sertraline, phenelzine, imipramine, desipramine, amitriptyline, fluoxetine, brofaromine, bupropion and mirtazapine	Currently used
Endocannabinoid system	CB1 receptor and memory consolidation	Endocannabinoids	Clinical trials ongoing
Excitatory and inhibitory amino acids	GABA and glutamate and kindling of limbic structures‡	Valproate, carbamazepine, phenytoin, dilantin, phenobarbital, lamotrigine, topiramate and tiagabine	Currently used
	NMDA receptors	NMDA facilitators and ketamine	Clinical trials ongoing
Neuropeptides	Neuropeptide Y receptors	Neuropeptide Y antagonists	Clinical trials ongoing
	Cholecystokinin	Cholecystokinin antagonists	Preclinical
	(Endogenous) opioids	Nalmefene	Clinical trials ongoing
	Substance P	Substance P antagonists	Preclinical
Neuroimmunological system and pro-inflammatory cytokines	Cyclooygenase enzymes	Aspirin and ibuprofen	Clinical trials ongoing
Hippocampal structure and neural plasticity	Neurogenesis and alteration of glutamate receptor activity (AMPA receptors and NMDA receptors) and release of BDNF	Phenytoin and tianeptine	Clinical trials ongoing
Noradrenergic regulation	α1- and α2-adrenergic receptors and β-adrenergic receptors	Prazosin, guanfacine, alfuzosin, doxazosin, propranolol and clonidine	Currently used
Glycine	Glycine receptor	D-Cycloserine	Clinical trials ongoing

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CB1, cannabinoid type 1; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; PTSD, post-traumatic stress disorder. *Suspected only on the basis of the mechanism of action of the drug. ‡Typical drugs used are anti-epileptics (also known as anticonvulsants).

and tailored these to their current systems of care. The initial interest in using selective serotonin reuptake inhibitors in PTSD was based on the high comorbidity of PTSD with mood and anxiety disorders for which antidepressants are effective. This rationale also prompted extensive studies of tricyclic antidepressants and monoamine oxidase inhibitors, but these drugs were associated with considerable adverse effects and higher drop-out rates than selective serotonin reuptake inhibitors[190,191]. As shown in TABLE 4, considerable variation is evident in the recommendations that have been made over the past decade. There are good grounds for caution against the widespread use of atypical antipsychotic medications given the risks that were initially not well appreciated, especially cardiovascular and metabolic risks[192]. Current evidence favours selective serotonin reuptake inhibitors as the class with the most evidence supporting their use as first-line psychopharmacological treatment options for patients requiring medications[190,191,193]. There is also much attention on addressing specific symptoms, such as sleep disturbance or nightmares.

It has been tempting to make inferences about PTSD neurobiology on the basis of the presumed mechanisms of drugs used to treat PTSD and, conversely, to use evidence obtained in animal and human studies of PTSD to explain why antidepressants are effective. However, such research suffers from post hoc fallacy: even in trials in which selective serotonin reuptake inhibitors show efficacy in PTSD, this does not necessarily indicate that the condition has anything to do with dysregulation or deficiency in serotonin systems.

Conversely, attempts to identify pharmacological agents for PTSD on the basis of PTSD pathophysiology have also presented some challenges. These efforts have been constrained by the lack of both appropriate tools for the study of structure and function of the living human brain and data from unbiased large-scale molecular and genomic studies. In the absence of these, the PTSD field has developed and tested pharmacological strategies on the basis of emergent findings of biological alterations in PTSD, with limited success. For example, following observations of hippocampal abnormalities in PTSD, there was interest in phenytoin and tianeptine[194] for their potential to reverse stress-induced hippocampal atrophy. Later studies, including the above-mentioned twin studies[69] called into question that glucococorticoid-induced apoptosis was the cause of the neuroimaging findings of smaller hippocampal volumes in patients with PTSD[195–197].

Similarly, anti-adrenergic drugs (such as α2-adrenergic agonists or β-adrenergic antagonists) have received attention on the basis of evidence for noradrenergic dysregulation in PTSD. However, experiences with clonidine or propranolol in PTSD were disappointing. There has been interest in the α1-adrenergic blocker prazosin for the treatment of PTSD-related nightmares[198], but results from a large multicentre Veterans Affairs trial in the United States seemed to show limited or no efficacy compared with placebo (preliminary results)[199]. The development of glucocorticoid-based treatments for PTSD has also been an important emerging area of research given the substantial evidence for HPA axis alteration in PTSD[200]. A small trial with the glucocorticoid receptor antagonist mifepristone yielded modest results[201], and several small trials using cortisol treatment have reported significant efficacy[202,203]. However, these data await confirmation from larger trials, which are currently ongoing.

Some definitive conclusions can be drawn regarding the use of medications in PTSD treatment. What is clear from meta-analyses of randomized clinical trials is that certain drug treatments, particularly selective serotonin reuptake inhibitors, are superior to placebo in reducing PTSD severity[204]. Effect sizes in medication studies are also lower than those observed in psychotherapy trials, and medication effects are less enduring than those of psychotherapy. The lower effect sizes might partly result from higher but considerable placebo effects in medication trials that are more difficult to control for than in psychotherapy trials (which compare active treatment to wait-listed controls), and this might be a source of confounding variables. It is also clear that some medications, such as the benzodiazepines, should not be used in the treatment of PTSD[205]. Benzodiazepines are problematic because of the development of dependence and the possibility of withdrawal symptoms, which can exacerbate PTSD symptoms[190,191]. Similar caution is warranted for hypnotics even though they are highly prescribed in clinical practice. An important area requiring clarification is whether medications should be used in addition to, or instead of, psychotherapeutic approaches. In the absence of studies that directly compare these two modalities, most published guidelines include separate recommendations for medications and psychotherapy.

New developments

Some promising pharmacological treatments for PTSD are being developed on the basis of emerging information about PTSD pathophysiology. In addition to the

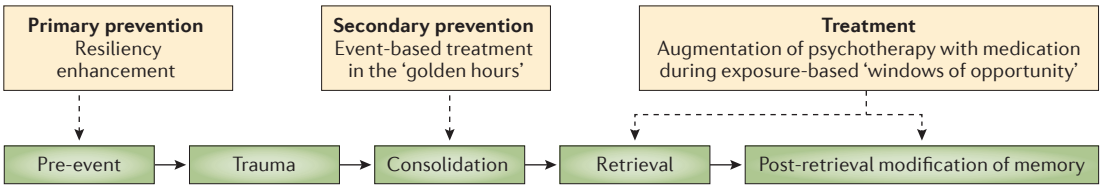


Figure 6 | **The timing of treatment of PTSD.** Psychotherapies aim to promote emotion regulation and extinction learning to neutralize the distress of trauma-related thoughts. Administration of drugs that have the capacity to manipulate the process of memory formation, consolidation, retrieval, reconsolidation or extinction can be used to prevent the onset of post-traumatic stress disorder (PTSD) or to treat the condition once it is apparent.

Table 4 | **Key recommendations from several clinical practice guidelines for PTSD**

Guideline	Year	Recommendations	Refs
UK National Institute for Health and Care Excellence	2005	Trauma-focused cognitive behavioural therapy or EMDR recommended as first-line treatment. Drug treatments should not be used as a routine first-line treatment.	246
Canadian Psychiatric Association	2006	Fluoxetine, paroxetine, sertraline or venlafaxine extended release recommended as first-line treatments. Mirtazapine, fluvoxamine, phenelzine, moclobemide, with or without adjuctive olanzapine or risperidone recommended as second-line treatments.	247
International Psychopharmacology Algorithm Project	2005–2011	Prazosin and trazodone are emphasized at initial step; if considerable PTSD symptoms remain, an antidepressant (SSRI, SNRI or TCA) may be tried. With partial improvement and residual symptomatology, augmentation may be tried; the best options are antipsychotics, clonidine, topiramate and lamotrigine.	248
International Society for Traumatic Stress Studies	2005–2009	Cognitive behavioural therapy that comprises exposure therapy, cognitive therapy, stress inoculation training or a combination of these; or EMDR; or SSRIs; or SNRIs are all recommended first-line treatments. There is good evidence for augmentation with atypical antipsychotics. Adjunctive treatments with prazosin and mirtazapine have proved promising.	249,250
American Psychiatric Association	2004 and 2009	Cognitive behavioural therapy, SSRIs or EMDR are all considered to have strong evidence of efficacy. Various other medications may be useful.	251,252
US Veterans Affairs and Department of Defense	2010	Trauma-focused psychotherapy that includes components of exposure and/or cognitive restructuring; or stress inoculation training; or SSRIs; or SNRIs are all recommended first-line treatments. Other medications may be useful.	253
Australian Centre Posttraumatic Mental Health	2013	Trauma-focused cognitive behavioural interventions or EMDR with *in vivo* exposure are recommended as first-line treatments. Drug treatments should not be used as routine first-line treatments. When medication is considered, SSRIs are the first choice.	254

EMDR, eye movement desensitization and reprocessing; PTSD, post-traumatic stress disorder; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

glucocorticoid-based therapies described above, other novel compounds that require further research include corticotropin-releasing hormone antagonists[206] and drugs that affect the endocannabinoid system. CB1 receptor-mediated endocannabinoid signalling has also been implicated in the extinction of adverse memories in animal studies. Augmenting levels of anandamide (an endogenous cannabinoid) in the amygdala modulates short-term fear extinction[207,208]. Elevated CB1 receptor availability in those with PTSD was shown using a selective PET ligand, with correspondingly lower circulating levels of anandamide in blood. These findings might also have implications for the use of cannabinoids, including tetrahydrocannabinol, in PTSD treatment.

Another compound of interest is ketamine. Ketamine is a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors that affects learning and memory. A rapid reduction in PTSD symptoms has been shown following the intravenous administration of ketamine[209]. Drugs such as 3,4-methylenedioxy-methamphetamine (MDMA), which blocks dopamine reuptake and has been linked with NMDA receptor action, has also garnered interest. Given that these compounds have the potential for abuse, determining whether their use in PTSD treatment outweighs the potential risks is important[210,211]. Finally, drugs that might enhance resilience — such as NPY agonists — are also an important development for the field of PTSD treatment[55]. The use of transcranial magnetic stimulation, deep brain stimulation and new neurofeedback techniques is another potential frontier in PTSD[212,213].

The use of pharmacotherapy as adjunctive treatment with established trauma-focused psychological therapies is another intense focus of research[214]. The most well studied of these has been the use of D-cycloserine in conjunction with prolonged exposure psychotherapy to accelerate extinction of fear conditioning[215]. D-Cycloserine is a glycine receptor agonist with demonstrated effects on extinction learning in animals[215]. This treatment has not yet proven to be successful in augmenting or accelerating efficacy of exposure-based therapy, but several trials are currently underway with the anticipation that a subgroup of patients showing fear-based symptoms may benefit. An initial trial with hydrocortisone augmentation suggested that this adjunctive treatment might prevent drop-outs[216]. This study was also noteworthy in suggesting that specific subgroups with glucocorticoid dysregulation may be more responsive to this augmentation strategy.

Quality of life

PTSD by definition can only be diagnosed if it appreciably affects occupational, interpersonal or social quality of life domains[1,217]. More severe PTSD symptoms are associated with poorer quality of life[218], an association that has been shown across cultures[219]. FIGURE 7 outlines the timing of quality of life issues in association with PTSD.

Symptoms such as poor sleep quality as a result of nightmares or hyperarousal can lead to poor concentration and irritability, affecting work performance and professional relationships. For deployment-related PTSD, interaction with authority figures can be a reminder of the environment in which the exposure occurred, leading the survivor to avoid the workplace or result in altercations with workplace superiors[220]. Victims of interpersonal assault might overgeneralize contact with individuals reminiscent of their attacker and the survivor might feel uncomfortable in close physical

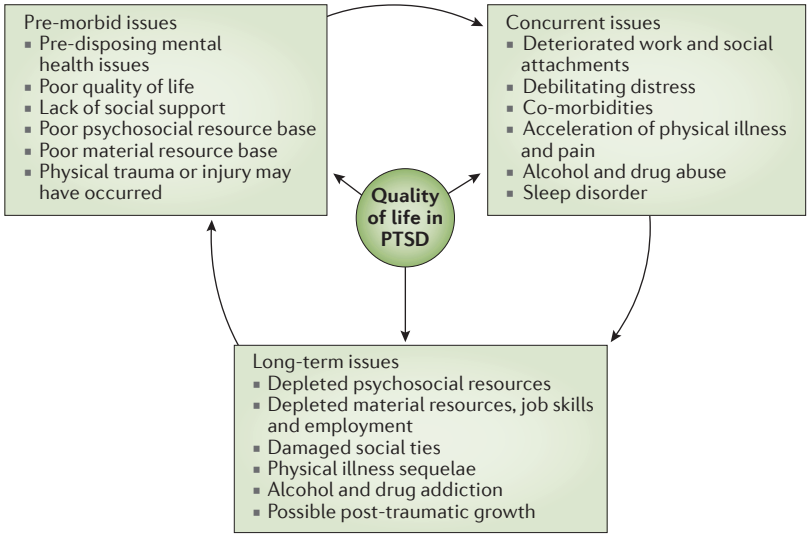


Figure 7 | **Timing of quality of life issues with PTSD.** Several domains of quality of life are affected in patients with post-traumatic stress disorder (PTSD) at different times.

proximity to co-workers. Sexual assault victims can also experience chronic pelvic pain and other somatic complaints[221]. These problems can also occur in social settings. Avoidance symptoms and phobic behaviours are common, extending to reluctance or refusal to take public transportation to and from work or other activities, which further exacerbates social isolation.

Individuals who have poor social support are less likely to recover from the effects of PTSD[222]. However, having PTSD directly undermines social support networks, placing a substantial burden on personal and familial relationships. Many individuals with PTSD have difficulties with intimacy at all levels, ranging from physical contact to engaging in personal dialogue requiring empathy and an implicit assumption of safety[223]. The generalized emotional numbing makes it difficult for patients to receive and to give affection and increases isolation. Indeed, PTSD is associated with disruption of familial ties and poor parenting behaviour, leading to separation, divorce and disruption of the family, even further undermining the most salient social supports that can promote resilience[220,224].

Quality of life is also affected by lack of resources[222,225]. When trauma exposure results in devastating loss of home and material possessions, such as in response to natural disaster or displacement, or when trauma occurs in an impoverished environment, the considerable life disruption further decreases quality of life. Finally, PTSD itself often results in the loss of personal, social and material resources, leading to a pattern of declining quality of life over time[222,226]. Psychotherapy can be successful in improving PTSD and quality of life[227,228]. However, the longer the duration of PTSD illness, the more these secondary losses in quality of life will remain even if symptoms themselves improve with treatment[229].

Outlook

Biological studies have largely supported the idea that PTSD is a multisystem disorder that affects stress-activated central and peripheral processes. These studies have also highlighted the heterogeneity of PTSD among individuals. This heterogeneity probably represents the complexity of genetic, developmental and cognitive risk factors, psychiatric comorbidity, the age at which trauma exposure occurs, and the trauma 'dose' and repetition. The course of the disorder is dynamic and fluctuates in its presentation over time. Similarly to most psychiatric disorders, it is not yet clear whether PTSD can be distinguished into categorical subtypes or whether the diversity of presentations will be better captured dimensionally.

Appropriate stratification of patients by genetic risk factors, when possible, will permit a clearer understanding of the specific vulnerabilities to biological or psychosocial factors. Although PTSD is clearly precipitated by circumstances, stratification by genetics offers the potential for advancement in this field. Such stratification might 'liberate' investigators from reliance on putative subtypes on the basis of signs and symptoms and might help in the interpretation of developmental risk factors. Furthermore, current efforts to identify risk-associated alleles for PTSD through large-scale GWAS are prompting alignment of phenotypic assessments (including symptoms, trauma exposure measures and intermediate phenotypes), which should facilitate our ability to evaluate and to synthesize information from smaller studies.

Given human genetic and cultural diversity and the complexity of social and other environmental risk factors, approaches must be developed that extend collection of samples from patients with diverse ancestral backgrounds. Indeed, from a scientific point of view and from a global health equity perspective, it is important to determine the degree to which treatment response depends on individual genetics, local environmental factors and sociocultural factors. It will also be important to use genetic information to better understand the neurobiology of PTSD. Parallel efforts in understanding genome-wide epigenetics and differential expression of genes might yield advance development of novel treatment and prevention strategies (FIG. 8).

Indeed, although genes contribute to risk of PTSD, twin studies show that nongenetic factors also considerably contribute to the risk of developing PTSD following trauma. The major candidate mechanisms by which developmental experience is thought to modulate PTSD risk include epigenetic regulation of gene expression and both implicit and explicit forms of long-term memory. These mechanisms probably come into play both during development and following trauma. The epigenetic contributions to risk are of interest, not only in PTSD but also in many mental disorders. Regulation of gene expression, including epigenetic regulation, is exquisitely cell type-specific and is indeed central to the definition of cell types. Gene regulation in response to environmental stimuli — whether normal sensory or physiological stimuli or extreme stimuli (such as trauma) — depend on the specific receptors, signal transduction machinery and enzymes that modify transcription factors, histones or DNA in the cell. As a result, as described in earlier

sections, barriers to epigenetic research in mental illness stem from the difficulty in obtaining relevant brain tissue from patients and in obtaining adequate samples post mortem. In post-mortem tissue, the effects of traumatic events might prove difficult to disentangle from other causes of epigenetic regulation that might represent responses to other experiential stimuli, physiological changes, drugs or illness. While studies of epigenetic regulation in peripheral tissues may not reflect neural underpinnings of PTSD, they may be relevant since PTSD is a multisystem disease involving peripheral neural and hormonal responses. Another concern in the interpretation of epigenetic studies is the independent effect size of regulating any particular gene. The combination of inherited allelic variants and the regulation of many genes in relevant cells and circuits probably contribute to PTSD. Future research has the opportunity to pursue correlative studies of central and peripheral components of gene regulation in translational models.

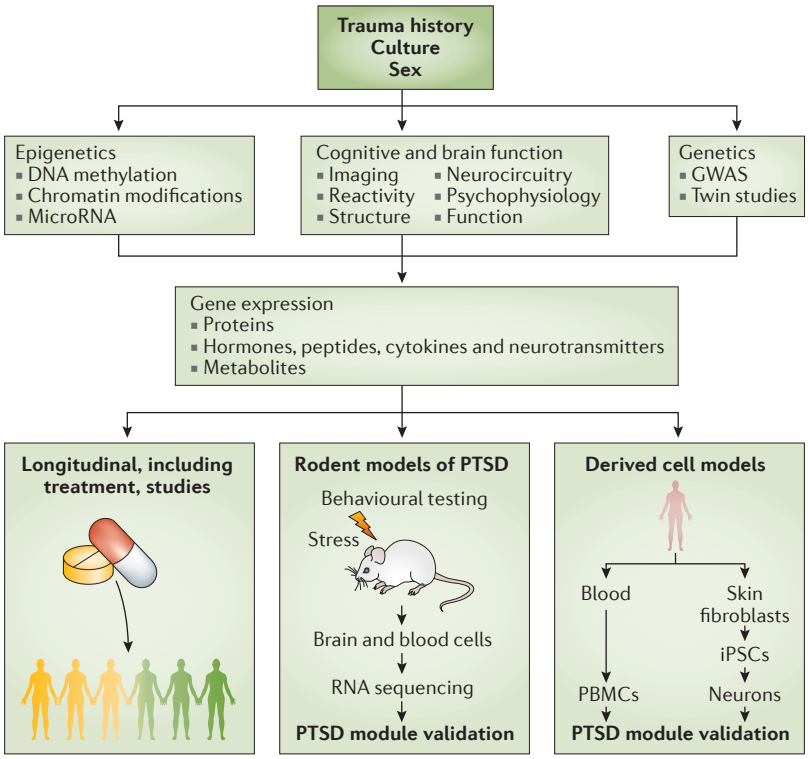


Figure 8 | **Systems biology approach to biomarker discovery and validation.** Bioinformatic techniques applied to multidimensional data — including developmental events, culture, gender, genetic variants, epigenetic modifications, brain structural and functional measures, gene transcripts, proteins and metabolites — are used to detect molecular networks and signalling pathways that are key drivers in biologically valid subtypes of post-traumatic stress disorder (PTSD). Validation of identified networks requires multiple approaches that include large-scale longitudinal cohort studies in humans and relevant animal models of specific relevant behaviours. The animal models enable validation of measurement of identified networks in brain regions with proxy markers in peripheral tissues, such as circulating mononuclear cells. The identification of key driver molecular networks linked to PTSD can be interrogated *in vitro* with neurons derived from reprogrammed skin fibroblasts. These *in vitro*-derived cells can be used for a variety of discovery purposes, including the study of cell–cell signalling and high-throughput screening to test if existing and novel drugs target the key driver molecular networks identified in PTSD. GWAS, genome-wide association studies; iPSCs, induced pluripotent stem cells; PBMCs, peripheral blood mononuclear cells.

Human studies of PTSD should similarly examine correlations among blood, cerebrospinal fluid, fresh human brain tissue when available and post-mortem brain samples to validate informative methodologies.

Animal studies can also continue to provide important information regarding the relationship between blood and brain pathways, provided that the question of evolutionary conservation from the chosen animal model to the human is kept in mind. An example of this integrative approach recently showed that glucocorticoid receptor signalling was the only convergent pathway identified by gene expression analysis from blood, the hippocampus and the amygdala in both male and female rats that showed vulnerability to prior exposure to predator-scent stress[230]. This approach provides a basis for comparative gene network analyses from stress-exposed vulnerable and resilient animals and trauma-exposed people who do or do not have PTSD. Such data will facilitate further developments in molecular studies of PTSD in blood.

The field of PTSD has begun to consider multiomic technology and the promise of systems biology, which have showed value in other medical areas such as cancer[231,232]. This approach remains aspirational for understanding PTSD pathophysiology but could ultimately yield clinically useful diagnostic biomarkers and molecular targets for drug discovery. With the increasing ability to obtain high-dimensional data — including genome-scale genetic and epigenetic data, as well as transcriptomic, proteomic and metabolomic data — there will be opportunities to develop and to test computational strategies for identifying molecular networks that are relevant to PTSD in peripheral tissues and probably in post-mortem brain and in patient-derived cells that have been reprogrammed into neurons. Indeed, the value of high-dimensional data will be greatly increased as the field of PTSD explores the application of new technologies including reprogramming of isogenic stem cell lines and patient fibroblasts or lymphocytes into neurons and brain organoids, which can be compared with post-mortem brain samples from patients. Such technologies, although still in their early stages, are exciting because they provide access to human cells to study the effects of molecular risk factors for a human condition. Integration of information about the cellular effects of genetic risk, and of transcriptomic and proteomic data sets from isogenic and patient-derived cells reprogrammed into neurons, with data sets derived from studies of patients with PTSD should lead to a deeper understanding of the molecules and the pathways underlying PTSD risk and resilience.

The path is long but the identification of genetic and other contributors to risk and the study of their functions in appropriate cell types should facilitate the identification of new drug targets. Such advances should make cell-based screens of chemical libraries and existing drugs possible, with a view to using existing drugs for a different purpose, as has been the practice in cancer, autoimmunity and many other fields of medicine. With a great deal of hard work, drug discovery for PTSD can move from the limited number of hypotheses available today to a vast number of new possibilities.

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: (DSM-5)* (American Psychiatric Association, 2013).
2. Kessler, R. C. & Wang, P. S. The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annu. Rev. Publ. Health* **29**, 115–129 (2008).
3. Michopoulos, V. *et al.* Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *Am. J. Psychiatry* **172**, 353–362 (2015).
4. Lohr, J. B. *et al.* Is post-traumatic stress disorder associated with premature senescence? A review of the literature. *Am. J. Geriatr. Psychiatry* **23**, 709–725 (2015).
5. Rosenbaum, S. *et al.* The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: a systematic review and meta-analysis. *Metabolism* **64**, 926–933 (2015).
6. Kessler, R. C. Posttraumatic stress disorder: the burden to the individual and to society. *J. Clin. Psychiatry* **61,** S4–S12; discussion S13–S14 (2000).
7. Yehuda, R. & LeDoux, J. Response variation following trauma: a translational neuroscience approach to understanding PTSD. *Neuron* **56**, 19–32 (2007).
8. Charney, D. S., Deutch, A. Y., Krystal, J. H., Southwick, S. M. & Davis, M. Psychobiologic mechanisms of posttraumatic stress disorder. *Arch. General Psychiatry* **50**, 295–305 (1993).
9. Charney, D. S. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am. J. Psychiatry* **161**, 195–216 (2004).
10. Kulka, R. A. *Contractual Report of Findings From the National Vietnam Veterans Readjustment Study* (Research Triangle Institute, 1988).
11. Dohrenwend, B. P. *et al.* The psychological risks of Vietnam for US veterans: a revisit with new data and methods. *Science* **313**, 979–982 (2006).
12. Marmar, C. R. *et al.* Course of posttraumatic stress disorder 40 years after the Vietnam War: findings from the National Vietnam Veterans Longitudinal Study. *JAMA Psychiatry* **72**, 875–881 (2015).
This is the most important longitudinal study of the Vietnam War generation.
13. Kok, B. C., Herrell, R. K., Thomas, J. L. & Hoge, C. W. Posttraumatic stress disorder associated with combat service in Iraq or Afghanistan: reconciling prevalence differences between studies. *J. Nerv. Mental Dis.* **200**, 444–450 (2012).
14. Sundin, J. *et al.* Mental health outcomes in US and UK military personnel returning from Iraq. *Br. J. Psychiatry* **204**, 200–207 (2014).
15. Hoge, C. W. *et al.* Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N. Engl. J. Med.* **351**, 13–22 (2004).
This is the initial paper that showed the effect of the recent war in Iraq and highlighted the importance of stigma and barriers to help-seeking.
16. Smid, G. E., Mooren, T. T., van der Mast, R. C., Gersons, B. P. & Kleber, R. J. Delayed posttraumatic stress disorder: systematic review, meta-analysis, and meta-regression analysis of prospective studies. *J. Clin. Psychiatry* **70**, 1572–1582 (2009).
17. Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M. & Nelson, C. B. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch. General Psychiatry* **52**, 1048–1060 (1995).
Results from this study indicate that trauma exposure is common but only a minority of exposed individuals develop PTSD. Findings also showed that conditional PTSD varied by trauma type and that the disorder is highly comorbid with other psychiatric conditions.
18. Resnick, H. S., Kilpatrick, D. G., Dansky, B. S., Saunders, B. E. & Best, C. L. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J. Consult. Clin. Psychol.* **61**, 984 (1993).
19. American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (American Psychiatric Association, 1985).
20. Mills, K. L. *et al.* Assessing the prevalence of trauma exposure in epidemiological surveys. *Austral. N. Z. J. Psychiatry* **45**, 407–415 (2011).
21. De Jong, J. T. *et al.* Lifetime events and posttraumatic stress disorder in 4 postconflict settings. *JAMA* **286**, 555–562 (2001).
22. Atwoli, L. *et al.* Trauma and posttraumatic stress disorder in South Africa: analysis from the South African Stress and Health Study. *BMC Psychiatry* **13**, 182 (2013).
23. Karam, E. G. *et al.* Cumulative traumas and risk thresholds: 12-month PTSD in the World Mental Health (WMH) surveys. *Depress. Anxiety* **31**, 130–142 (2014).
24. Hobfoll, S. E. *et al.* Five essential elements of immediate and mid-term mass trauma intervention: empirical evidence. *Psychiatry* **70**, 283–315; discussion 316–369 (2007).
25. Lowe, S. R., Galea, S., Uddin, M. & Koenen, K. C. Trajectories of posttraumatic stress among urban residents. *Am. J. Commun. Psychol.* **53**, 159–172 (2014).
26. Ressler, K. J. *et al.* Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature* **470**, 492–497 (2011).
27. Kessler, R. C., Chiu, W. T., Demler, O. & Walters, E. E. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. General Psychiatry* **62**, 617–627 (2005).
28. Hoge, C. W., Terhakopian, A., Castro, C. A., Messer, S. C. & Engel, C. C. Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans. *Am. J. Psychiatry* **164**, 150–153 (2007).
29. Pole, N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. *Psychol. Bull.* **133**, 725–746 (2007).
30. Pitman, R. K. *et al.* Biological studies of post-traumatic stress disorder. *Nat. Rev. Neurosci.* **13**, 769–787 (2012).
31. Zoladz, P. R. & Diamond, D. M. Current status on behavioral and biological markers of PTSD: a search for clarity in a conflicting literature. *Neurosci. Biobehav. Rev.* **37**, 860–895 (2013).
32. Yehuda, R. Post-traumatic stress disorder. *N. Engl. J. Med.* **346**, 108–114 (2002).
33. Zannas, A. S., Provencal, N. & Binder, E. B. Epigenetics of posttraumatic stress disorder: current evidence, challenges, and future directions. *Biol. Psychiatry* **78**, 327–335 (2015).
34. Daskalakis, N. P., Lehrner, A. & Yehuda, R. Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. *Endocrinol. Metab. Clin. North Am.* **42**, 503–513 (2013).
35. Galatzer-Levy, I. R. *et al.* Cortisol response to an experimental stress paradigm prospectively predicts long-term distress and resilience trajectories in response to active police service. *J. Psychiatr. Res.* **56**, 36–42 (2014).
36. van Zuiden, M. *et al.* Pre-existing high glucocorticoid receptor number predicting development of posttraumatic stress symptoms after military deployment. *Am. J. Psychiatry* **168**, 89–96 (2011).
This is the first biological prospective study in PTSD that showed that combat veterans who developed PTSD post-deployment had a higher number of glucocorticoid receptors at pre-deployment.
37. de Quervain, D. J., Aerni, A., Schelling, G. & Roozendaal, B. Glucocorticoids and the regulation of memory in health and disease. *Front. Neuroendocrinol.* **30**, 358–370 (2009).
38. Parsons, R. G. & Ressler, K. J. Implications of memory modulation for post-traumatic stress and fear disorders. *Nat. Neurosci.* **16**, 146–153 (2013).
39. Duits, P. *et al.* Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depress. Anxiety* **32**, 239–253 (2015).
40. Jovanovic, T. & Ressler, K. J. How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *Am. J. Psychiatry* **167**, 648–662 (2010).
41. Pietrzak, R. H. *et al.* Association of *in vivo* κ-opioid receptor availability and the transdiagnostic dimensional expression of trauma-related psychopathology. *JAMA Psychiatry* **71**, 1262–1270 (2014).
42. Neumeister, A., Seidel, J., Ragen, B. J. & Pietrzak, R. H. Translational evidence for a role of endocannabinoids in the etiology and treatment of posttraumatic stress disorder. *Psychoneuroendocrinology* **51**, 577–584 (2015).
43. O'Donovan, A., Slavich, G. M., Epel, E. S. & Neylan, T. C. Exaggerated neurobiological sensitivity to threat as a mechanism linking anxiety with increased risk for diseases of aging. *Neurosci. Biobehav Rev.* **37**, 96–108 (2013).
This is a comprehensive review of the relationship of threat sensitivity and inflammation to increased risk for diseases of ageing in PTSD.
44. Baker, D. G. *et al.* Plasma and cerebrospinal fluid interleukin-6 concentrations in posttraumatic stress disorder. *Neuroimmunomodulation* **9**, 209–217 (2001).
45. Bonne, O. *et al.* Corticotropin-releasing factor, interleukin-6, brain-derived neurotrophic factor, insulin-like growth factor-1, and substance P in the cerebrospinal fluid of civilians with posttraumatic stress disorder before and after treatment with paroxetine. *J. Clin. Psychiatry* **72**, 1124–1128 (2011).
46. Uddin, M. *et al.* Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proc. Natl Acad. Sci. USA* **107**, 9470–9475 (2010).
47. Gill, J. M., Saligan, L., Woods, S. & Page, G. PTSD is associated with an excess of inflammatory immune activities. *Perspect. Psychiatr. Care* **45**, 262–277 (2009).
48. O'Donovan, A. *et al.* Transcriptional control of monocyte gene expression in post-traumatic stress disorder. *Dis. Markers* **30**, 123–132 (2011).
49. Hill, M. N. & McEwen, B. S. Endocannabinoids: the silent partner of glucocorticoids in the synapse. *Proc. Natl Acad. Sci. USA* **106**, 4579–4580 (2009).
50. Hill, M. N. *et al.* Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks. *Psychoneuroendocrinology* **38**, 2952–2961 (2013).
51. Neumeister, A. *et al.* Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study. *Mol. Psychiatry* **18**, 1034–1040 (2013).
52. Neylan, T. C., Otte, C., Yehuda, R. & Marmar, C. R. Neuroendocrine regulation of sleep disturbances in PTSD. *Ann. NY Acad. Sci.* **1071**, 203–215 (2006).
53. Agorastos, A., Kellner, M., Baker, D. G. & Otte, C. When time stands still: an integrative review on the role of chronodisruption in posttraumatic stress disorder. *Curr. Opin. Psychiatry* **27**, 385–392 (2014).
54. Yehuda, R., Teicher, M. H., Trestman, R. L., Levengood, R. A. & Siever, L. J. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. *Biol. Psychiatry* **40**, 79–88 (1996).
55. Cohen, H. *et al.* The neuropeptide Y (NPY)-ergic system is associated with behavioral resilience to stress exposure in an animal model of post-traumatic stress disorder. *Neuropsychopharmacology* **37**, 350–363 (2012).
56. Serova, L. I. *et al.* Single intranasal neuropeptide Y infusion attenuates development of PTSD-like symptoms to traumatic stress in rats. *Neuroscience* **236**, 298–312 (2013).
57. Yehuda, R., Flory, J. D., Southwick, S. & Charney, D. S. Developing an agenda for translational studies of resilience and vulnerability following trauma exposure. *Ann. NY Acad. Sci.* **1071**, 379–396 (2006).
58. Vermetten, E., Baker, D. & Yehuda, R. New findings from prospective studies. *Psychoneuroendocrinology* **51**, 441–443 (2015).
59. Delahanty, D. L. & Nugent, N. R. Predicting PTSD prospectively based on prior trauma history and immediate biological responses. *Ann. NY Acad. Sci.* **1071**, 27–40 (2006).
60. Bonne, O. *et al.* Prospective evaluation of plasma cortisol in recent trauma survivors with posttraumatic stress disorder. *Psychiatry Res.* **119**, 171–175 (2003).
61. Yehuda, R. *et al.* Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. *Am. J. Psychiatry* **171**, 872–880 (2014).
62. Yehuda, R., McFarlane, A. C. & Shalev, A. Y. Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biol. Psychiatry* **44**, 1305–1313 (1998).
63. Yehuda, R., Morris, A., Labinsky, E., Zemelman, S. & Schmeidler, J. Ten-year follow-up study of cortisol levels in aging holocaust survivors with and without PTSD. *J. Trauma Stress* **20**, 757–761 (2007).
64. Olff, M., de Vries, G. J., Guzelcan, Y., Assies, J. & Gersons, B. P. Changes in cortisol and DHEA plasma levels after psychotherapy for PTSD. *Psychoneuroendocrinology* **32**, 619–626 (2007).
65. Walsh, K. *et al.* Cortisol at the emergency room rape visit as a predictor of PTSD and depression symptoms over time. *Psychoneuroendocrinology* **38**, 2520–2528 (2013).
66. Delahanty, D. L., Raimonde, A. J. & Spoonster, E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biol. Psychiatry* **48**, 940–947 (2000).

67. van Zuiden, M. *et al.* Glucocorticoid receptor pathway components predict posttraumatic stress disorder symptom development: a prospective study. *Biol. Psychiatry* **71**, 309–316 (2012).
68. Eraly, S. A. *et al.* Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. *JAMA Psychiatry* **71**, 423–431 (2014).
69. Yehuda, R. *et al.* Glucocorticoid-related predictors and correlates of post-traumatic stress disorder treatment response in combat veterans. *Interface Focus* **4**, 20140048 (2014).
70. Rauch, S. A. *et al.* Biological and symptom changes in posttraumatic stress disorder treatment: a randomized clinical trial. *Depress. Anxiety* **32**, 204–212 (2015).
71. Levy-Gigi, E., Szabo, C., Kelemen, O. & Keri, S. Association among clinical response, hippocampal volume, and *FKBP5* gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy. *Biol. Psychiatry* **74**, 793–800 (2013).
72. Afifi, T. O., Asmundson, G. J., Taylor, S. & Jang, K. L. The role of genes and environment on trauma exposure and posttraumatic stress disorder symptoms: a review of twin studies. *Clin. Psychol. Rev.* **30**, 101–112 (2010).
73. Stein, M. B., Jang, K. J., Taylor, S., Vernon, P. A. & Livesley, W. J. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder: a twin study. *Am. J. Psychiatry* **159**, 1675–1681 (2002).
74. Koenen, K. C., Duncan, L. E., Liberzon, I. & Ressler, K. J. From candidate genes to genome-wide association: the challenges and promise of posttraumatic stress disorder genetic studies. *Biol. Psychiatry* **74**, 634–636 (2013).
75. True, W. J. *et al.* A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. *Arch. General Psychiatry* **50**, 257–264 (1993).
76. Sartor, C. E. *et al.* Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. *Arch. General Psychiatry* **69**, 293–299 (2012).
77. Sartor, C. E. *et al.* Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychol. Med.* **41**, 1497–1505 (2011).
78. Gilbertson, M. W. *et al.* Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat. Neurosci.* **5**, 1242–1247 (2002).
79. Wolf, E. J., Mitchell, K. S., Koenen, K. C. & Miller, M. W. Combat exposure severity as a moderator of genetic and environmental liability to post-traumatic stress disorder. *Psychol. Med.* **44**, 1499–1509 (2013).
80. Binder, E. B. *et al.* Association of *FKBP5* polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA* **299**, 1291–1305 (2008).
This paper describes that genetic variants of a chaperone protein involved in glucocorticoid signalling, together with exposure to child trauma, predict adult PTSD.
81. Klengel, T. *et al.* Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions. *Nat. Neurosci.* **16**, 33–41 (2013).
82. Nugent, N. R., Amstadter, A. B. & Koenen, K. C. Genetics of post-traumatic stress disorder: informing clinical conceptualizations and promoting future research. *Am. J. Med. Genet. C Semin. Med. Genet.* **148**, 127–132 (2008).
83. Yehuda, R., Bell, A., Bierer, L. M. & Schmeidler, J. Maternal, not paternal, PTSD is related to increased risk for PTSD in offspring of Holocaust survivors. *J. Psychiatr. Res.* **42**, 1104–1111 (2008).
84. Mehta, D. *et al.* Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proc. Natl Acad. Sci. USA* **110**, 8302–8307 (2013).
85. Almli, L. M. *et al.* A genome-wide identified risk variant for PTSD is a methylation quantitative trait locus and confers decreased cortical activation to fearful faces. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **168**, 327–336 (2015).
86. Heijmans, B. T. & Mill, J. Commentary: the seven plagues of epigenetic epidemiology. *Int. J. Epidemiol.* **41**, 74–78 (2012).
87. Yehuda, R. *et al.* Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Front. Psychiatry* **4**, 118 (2013).
88. Yehuda, R. *et al.* Gene expression patterns associated with posttraumatic stress disorder following exposure to the World Trade Center attacks. *Biol. Psychiatry* **66**, 708–711 (2009).
This is the first genome-wide gene expression study in PTSD that identified genes associated with glucocorticoid receptor functioning, such as *FKBP5*.
89. Sipahi, L. *et al.* Longitudinal epigenetic variation of DNA methyltransferase genes is associated with vulnerability to post-traumatic stress disorder. *Psychol. Med.* **44**, 3165–3179 (2014).
90. Schmidt, U., Keck, M. E. & Buell, D. R. miRNAs and other non-coding RNAs in posttraumatic stress disorder: a systematic review of clinical and animal studies. *J. Psychiatr. Res.* **65**, 1–8 (2015).
91. Zhou, J. *et al.* Dysregulation in microRNA expression is associated with alterations in immune functions in combat veterans with post-traumatic stress disorder. *PLoS ONE* **9**, e94075 (2014).
92. Logue, M. W. *et al.* A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor-α (*RORA*) gene as a significant risk locus. *Mol. Psychiatry* **18**, 937–942 (2013).
93. Xie, P. *et al.* Genome-wide association study identifies new susceptibility loci for posttraumatic stress disorder. *Biol. Psychiatry* **74**, 656–663 (2013).
94. Guffanti, G. *et al.* Genome-wide association study implicates a novel RNA gene, the lincRNA AC068718.1, as a risk factor for post-traumatic stress disorder in women. *Psychoneuroendocrinology* **38**, 3029–3038 (2013).
95. Nievergelt, C. M. *et al.* Genomic predictors of combat stress vulnerability and resilience in U. S. Marines: a genome-wide association study across multiple ancestries implicates *PRTFDC1* as a potential PTSD gene. *Psychoneuroendocrinology* **51**, 459–471 (2015).
96. Button, K. S. *et al.* Power failure: why small sample size undermines the reliability of neuroscience. *Nat. Rev. Neurosci.* **14**, 365–376 (2013).
97. Almli, L. M., Fani, N., Smith, A. K. & Ressler, K. J. Genetic approaches to understanding post-traumatic stress disorder. *Int. J. Neuropsychopharmacol.* **17**, 355–370 (2014).
98. Logue, M. W. *et al.* The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup: posttraumatic stress disorder enters the age of large-scale genomic collaboration. *Neuropsychopharmacology* **40**, 2287–2297 (2015).
This paper describes the formation of a large-scale GWAS consortium dedicated to the study of PTSD genetics that will lead the search for replicable genetic associations.
99. Bremner, J. D. Does stress damage the brain? *Biol. Psychiatry* **45**, 797–805 (1999).
100. Bremner, J. D. *et al.* Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse — a preliminary report. *Biol. Psychiatry* **41**, 23–32 (1997).
101. van Rooij, S. J. *et al.* Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. *Psychol. Med.* **45**, 2737–2746 (2015).
102. Shin, L. M. & Liberzon, I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology* **35**, 169–191 (2010).
103. Shin, L. M. *et al.* Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. *Am. J. Psychiatry* **156**, 575–584 (1999).
104. Gold, A. L. *et al.* Decreased regional cerebral blood flow in medial prefrontal cortex during trauma-unrelated stressful imagery in Vietnam veterans with post-traumatic stress disorder. *Psychol. Med.* **41**, 2563–2572 (2011).
105. Lanius, R. A. *et al.* Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. *Biol. Psychiatry* **53**, 204–210 (2003).
106. Etkin, A. & Wager, T. D. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am. J. Psychiatry* **164**, 1476–1488 (2007).
107. Sartory, G. *et al.* In search of the trauma memory: a meta-analysis of functional neuroimaging studies of symptom provocation in posttraumatic stress disorder (PTSD). *PLoS ONE* **8**, e58150 (2013).
108. Taber, K. H., Rauch, S. L., Lanius, R. A. & Hurley, R. A. Functional magnetic resonance imaging: application to posttraumatic stress disorder. *J. Neuropsychiatry Clin. Neurosci.* **15**, 125–129 (2003).
109. Hayes, J. P., Hayes, S. M. & Mikedis, A. M. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biol. Mood Anxiety Disord.* **2**, 9 (2012).
110. Lanius, R. A., Bluhm, R., Lanius, U. & Pain, C. A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. *J. Psychiatr. Res.* **40**, 709–729 (2006).
111. Nicholson, A. A. *et al.* The dissociative subtype of posttraumatic stress disorder: unique resting-state functional connectivity of basolateral and centromedial amygdala complexes. *Neuropsychopharmacology* **40**, 2317–2326 (2015).
112. Lanius, R. *et al.* Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. *Am. J. Psychiatry* **167**, 640–647 (2010).
This article focuses on the neural manifestations of the dissociative subtype in PTSD and compares them to those underlying the re-experiencing and hyperaroused subtype. These findings have important implications for the treatment of PTSD, including the need to assess patients with PTSD for dissociative symptoms and to incorporate the treatment of dissociative symptoms into stage-oriented trauma treatment.
113. Menon, V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn. Sci.* **15**, 483–506 (2011).
114. Patel, R., Spreng, R. N., Shin, L. M. & Girard, T. A. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci. Biobehav. Rev.* **36**, 2130–2142 (2012).
115. Sripada, R. K. *et al.* Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. *Psychosomat. Med.* **74**, 904–911 (2012).
116. Rabellino, D. *et al.* Intrinsic connectivity networks in post-traumatic stress disorder during sub- and supraliminal processing of threat-related stimuli. *Acta Psychiatr. Scand.* **35**, 258–266 (2015).
117. Daniels, J. K. *et al.* Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity. *J. Psychiatry Neurosci.* **35**, 258–266 (2010).
118. Geuze, E. *et al.* Reduced $GABA_A$ benzodiazepine receptor binding in veterans with post-traumatic stress disorder. *Mol. Psychiatry* **13**, 74–83, 3 (2008).
119. Murrough, J. W. *et al.* Reduced amygdala serotonin transporter binding in posttraumatic stress disorder. *Biol. Psychiatry* **70**, 1033–1038 (2011).
120. Yehuda, R. *et al.* Changes in relative glucose metabolic rate following cortisol administration in aging veterans with posttraumatic stress disorder: an FDG-PET neuroimaging study. *J. Neuropsychiatry Clin. Neurosci.* **21**, 132–143 (2009).
121. Brewin, C. R. Episodic memory, perceptual memory, and their interaction: foundations for a theory of posttraumatic stress disorder. *Psychol. Bull.* **140**, 69–97 (2014).
122. Yehuda, R. & McFarlane, A. C. Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. *Am. J. Psychiatry* **152**, 1705–1713 (1995).
This is a seminal review showing that biological measures from PTSD do not conform to predictions from known acute stress biology.
123. American Psychiatric Association. *DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 1994).
124. Friedman, M. J., Resick, P. A., Bryant, R. A. & Brewin, C. R. Considering PTSD for DSM-5. *Depress. Anxiety* **28**, 750–769 (2011).
125. Hoge, C. W., Riviere, L. A., Wilk, J. E., Herrell, R. K. & Weathers, F. W. The prevalence of post-traumatic stress disorder (PTSD) in US combat soldiers: a head-to-head comparison of DSM-5 versus DSM-IV-TR symptom criteria with the PTSD checklist. *Lancet Psychiatry* **1**, 269–277 (2014).
126. McFarlane, A. C. PTSD and DSM-5: unintended consequences of change. *Lancet Psychiatry* **1**, 246–247 (2014).
127. Stein, D. J. *et al.* DSM-5 and ICD-11 definitions of posttraumatic stress disorder: investigating 'narrow' and 'broad' approaches. *Depress. Anxiety* **31**, 494–505 (2014).
This paper highlights the conceptual questions of validity with the existence of different sets of diagnostic criteria and the need to consider the challenge of the lack of overlap of DSM and ICD systems.

128. Bryant, R. A., O'Donnell, M. L., Creamer, M., McFarlane, A. C. & Silove, D. A multisite analysis of the fluctuating course of posttraumatic stress disorder. *JAMA Psychiatry* **70**, 839–846 (2013).
129. Bunting, B. P., Murphy, S. D., O'Neill, S. M. & Ferry, F. R. Lifetime prevalence of mental health disorders and delay in treatment following initial onset: evidence from the Northern Ireland Study of Health and Stress. *Psychol. Med.* **42**, 1727–1739 (2012).
130. McFarlane, A. C. The long-term costs of traumatic stress: intertwined physical and psychological consequences. *World Psychiatry* **9**, 3–10 (2010).
This paper shows that the prevalence of delayed-onset PTSD and the associated physical comorbidities highlight the need for the long-term effect of traumatic stress exposure to be a clear focus in clinical settings.
131. Kendler, K. S., Thornton, L. M. & Gardner, C. O. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the 'kindling' hypothesis. *Am. J. Psychiatry* **157**, 1243–1251 (2000).
132. Collip, D., Myin-Germeys, I. & Van Os, J. Does the concept of 'sensitization' provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophr. Bull.* **34**, 220–225 (2008).
133. Adler, A. B., Wright, K. M., Bliese, P. D., Eckford, R. & Hoge, C. W. A2 diagnostic criterion for combat-related posttraumatic stress disorder. *J. Trauma. Stress* **21**, 301–308 (2008).
134. Brady, K. T., Killeen, T. K., Brewerton, T. & Lucerini, S. Comorbidity of psychiatric disorders and posttraumatic stress disorder. *J. Clin. Psychiatry* **61** S22–S32 (2000).
135. Debell, F. *et al.* A systematic review of the comorbidity between PTSD and alcohol misuse. *Soc. Psychiatry Psychiatr. Epidemiol.* **49**, 1401–1425 (2014).
136. Rytwinski, N. K., Scur, M. D., Feeny, N. C. & Youngstrom, E. A. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J. Trauma. Stress* **26**, 299–309 (2013).
137. Rasmussen, A., Keatley, E. & Joscelyne, A. Posttraumatic stress in emergency settings outside North America and Europe: a review of the emic literature. *Soc. Sci. Med.* **109**, 44–54 (2014).
138. Brewin, C. R. *et al.* Promoting mental health following the London bombings: a screen and treat approach. *J. Trauma. Stress* **21**, 3–8 (2008).
This paper shows the underestimation of the clinical significance of distress and symptoms by general practitioners when diagnosing PTSD, despite patients seeking help and benefiting from treatment when identified in a population-based screening and treatment intervention.
139. Gupta, M. A. Review of somatic symptoms in post-traumatic stress disorder. *Int. Rev. Psychiatry* **25**, 86–99 (2013).
140. Liebschutz, J. *et al.* PTSD in urban primary care: high prevalence and low physician recognition. *J. Gen. Intern. Med.* **22**, 719–726 (2007).
141. Battaglia, S. *et al.* Elevated NCOR1 disrupts PPARα/γ signaling in prostate cancer and forms a targetable epigenetic lesion. *Carcinogenesis* **31**, 1650–1660 (2010).
142. Lehrner, A. & Yehuda, R. Biomarkers of PTSD: military applications and considerations. *Eur. J. Psychotraumatol.* **5**, 23797 (2014).
143. Searle, A. K. *et al.* The validity of military screening for mental health problems: diagnostic accuracy of the PCL, K10 and AUDIT scales in an entire military population. *Int. J. Methods Psychiatr. Res.* **24**, 32–45 (2015).
144. Lee, D. J., Warner, C. H. & Hoge, C. W. Advances and controversies in military posttraumatic stress disorder screening. *Curr. Psychiatry Rep.* **16**, 467 (2014).
145. Terhakopian, A., Sinaii, N., Engel, C. C., Schnurr, P. P. & Hoge, C. W. Estimating population prevalence of posttraumatic stress disorder: an example using the PTSD checklist. *J. Trauma Stress* **21**, 290–300 (2008).
146. Australian Centre for Posttraumatic Mental Health. *Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder* (ACPMH, 2013).
147. Warner, C. H., Appenzeller, G. N., Parker, J. R., Warner, C. M. & Hoge, C. W. Effectiveness of mental health screening and coordination of in-theater care prior to deployment to Iraq: a cohort study. *Am. J. Psychiatry* **168**, 378–385 (2011).
148. Institute of Medicine. *Preventing Psychological Disorders in Service Members and Their Families: An Assessment of Programs* (The National Academies Press, 2014).
149. McCabe, O. L. *et al.* Building a national model of public mental health preparedness and community resilience: validation of a dual-intervention, systems-based approach. *Disaster Med. Publ. Health Prep.* **8**, 511–526 (2014).
150. Yehuda, R. Learning from September 11, 2001. *CNS Spectr.* **7**, 566–567 (2002).
151. Roberts, N. P., Kitchiner, N. J., Kenardy, J. & Bisson, J. Multiple session early psychological interventions for the prevention of post-traumatic stress disorder. *Cochrane Database Syst. Rev.* **3**, CD006869 (2009).
152. Vermetten, E., Zhohar, J. & Krugers, H. J. Pharmacotherapy in the aftermath of trauma; opportunities in the 'golden hours'. *Curr. Psychiatry Rep.* **16**, 455 (2014).
153. Sijbrandij, M., Kleiboer, A., Bisson, J. I., Barbui, C. & Cuijpers, P. Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. *Lancet Psychiatry* **2**, 413–421 (2015).
This is the first systematic review to examine the effects of pharmacotherapies (for example, β-blockers, hydrocortisone and selective serotonin reuptake inhibitors) given within the first month after a traumatic or aversive event to prevent PTSD or acute stress disorder compared with no pharmacotherapy or a placebo control.
154. Marin, M. F., Lonak, S. F. & Milad, M. R. Augmentation of evidence-based psychotherapy for PTSD with cognitive enhancers. *Curr. Psychiatry Rep.* **17**, 39 (2015).
155. Merlo, E., Milton, A. L. & Everitt, B. J. Enhancing cognition by affecting memory reconsolidation. *Curr. Opin. Behav. Sci.* **4**, 41–47 (2015).
156. Saxe, G. *et al.* Relationship between acute morphine and the course of PTSD in children with burns. *J. Am. Acad. Child Adolesc. Psychiatry* **40**, 915–921 (2001).
157. Bryant, R. A., Creamer, M., O'Donnell, M., Silove, D. & McFarlane, A. C. A study of the protective function of acute morphine administration on subsequent posttraumatic stress disorder. *Biol. Psychiatry* **65**, 438–440 (2009).
158. Pitman, R. K. *et al.* Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol. Psychiatry* **51**, 189–192 (2002).
159. Amos, T., Stein, D. J. & Ipser, J. C. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). *Cochrane Database Syst. Rev.* **7**, CD006239 (2014).
This Cochrane Database Systematic Review focuses on the effects of pharmacological interventions for the prevention of adult PTSD. Evidence suggests that hydrocortisone might be moderately effective for the prevention of PTSD. There was no evidence to support the use of propranolol, temazapam, gabapentin and escitalopram in the prevention of PTSD onset.
160. McFarlane, A. C., Barton, C. A., Yehuda, R. & Wittert, G. Cortisol response to acute trauma and risk of posttraumatic stress disorder. *Psychoneuroendocrinology* **36**, 720–727 (2011).
161. Mouthaan, J. *et al.* The role of acute cortisol and DHEAS in predicting acute and chronic PTSD symptoms. *Psychoneuroendocrinology* **45**, 179–186 (2014).
162. Schelling, G. *et al.* The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. *Biol. Psychiatry* **50**, 978–985 (2001).
163. Zohar, J. *et al.* High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: interplay between clinical and animal studies. *Eur. Neuropsychopharmacol.* **21**, 796–809 (2011).
164. Delahanty, D. L. *et al.* The efficacy of initial hydrocortisone administration at preventing posttraumatic distress in adult trauma patients: a randomized trial. *CNS Spectr.* **18**, 103–111 (2013).
165. Holbrook, T. L., Galarneau, M. R., Dye, J. L., Quinn, K. & Dougherty, A. L. Morphine use after combat injury in Iraq and post-traumatic stress disorder. *N. Engl. J. Med.* **362**, 110–117 (2010).
166. Markowitz, J. C. *et al.* Is exposure necessary? A randomized clinical trial of interpersonal psychotherapy for PTSD. *Am. J. Psychiatry* **172**, 430–440 (2015).
167. Bisson, J. & Andrew, M. Psychological treatment of post-traumatic stress disorder (PTSD). *Cochrane Database Syst. Rev.* **3**, CD003388 (2007).
This Cochrane Database Systematic Review reports the effects of randomized controlled trials of individual trauma-focused treatments for adult PTSD. Results indicate that individual trauma-focused CBT and EMDR were superior to wait-list and usual care in reducing clinician-assessed PTSD symptoms.
168. Bisson, J. I., Roberts, N. P., Andrew, M., Cooper, R. & Lewis, C. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst. Rev.* **12**, CD003388 (2013).
169. Mello, P. G., Silva, G. R., Donat, J. C. & Kristensen, C. H. An update on the efficacy of cognitive-behavioral therapy, cognitive therapy, and exposure therapy for posttraumatic stress disorder. *Int. J. Psychiatry Med.* **46**, 339–357 (2013).
170. Rauch, S. A., Eftekhari, A. & Ruzek, J. I. Review of exposure therapy: a gold standard for PTSD treatment. *J. Rehabil. Res. Dev.* **49**, 679–687 (2012).
171. McLean, C. P. & Foa, E. B. Prolonged exposure therapy for post-traumatic stress disorder: a review of evidence and dissemination. *Expert Rev. Neurother.* **11**, 1151–1163 (2011).
172. Morkved, N. *et al.* A comparison of narrative exposure therapy and prolonged exposure therapy for PTSD. *Clin. Psychol. Rev.* **34**, 453–467 (2014).
173. Leer, A., Engelhard, I. M., Altink, A. & van den Hout, M. A. Eye movements during recall of aversive memory decreases conditioned fear. *Behav. Res. Ther.* **51**, 633–640 (2013).
174. Engelhard, I. M. *et al.* Reducing vividness and emotional intensity of recurrent 'flashforwards' by taxing working memory: an analogue study. *J. Anxiety Disord.* **25**, 599–603 (2011).
175. Seidler, G. H. & Wagner, F. E. Comparing the efficacy of EMDR and trauma-focused cognitive-behavioral therapy in the treatment of PTSD: a meta-analytic study. *Psychol. Med.* **36**, 1515–1522 (2006).
176. Schottenbauer, M. A., Glass, C. R., Arnkoff, D. B. & Gray, S. H. Contributions of psychodynamic approaches to treatment of PTSD and trauma: a review of the empirical treatment and psychopathology literature. *Psychiatry* **71**, 13–34 (2008).
177. Ehlers, A. *et al.* Predicting response to exposure treatment in PTSD: the role of mental defeat and alienation. *J. Trauma Stress* **11**, 457–471 (1998).
178. Schnurr, P. P. *et al.* Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *JAMA* **297**, 820–830 (2007).
179. Stein, D. J., Ipser, J. & McAnda, N. Pharmacotherapy of posttraumatic stress disorder: a review of meta-analyses and treatment guidelines. *CNS Spectr.* **14**, 25–31 (2009).
180. Eisenman, D. *et al.* The ISTSS/Rand guidelines on mental health training of primary healthcare providers for trauma-exposed populations in conflict-affected countries. *J. Trauma Stress* **19**, 5–17 (2006).
181. Weine, S. *et al.* Guidelines for international training in mental health and psychosocial interventions for trauma exposed populations in clinical and community settings. *Psychiatry* **65**, 156–164 (2002).
182. Cloitre, M. *et al.* Treatment of complex PTSD: results of the ISTSS expert clinician survey on best practices. *J. Trauma Stress* **24**, 615–627 (2011).
183. Rosen, C. S. *et al.* VA practice patterns and practice guidelines for treating posttraumatic stress disorder. *J. Trauma Stress* **17**, 213–222 (2004).
184. Susskind, O., Ruzek, J. I. & Friedman, M. J. The VA/DOD clinical practice guideline for management of post-traumatic stress (update 2010): development and methodology. *J. Rehabil. Res. Dev.* **4**, xvii–xxviii (2012).
185. Wolf, E. J., Lunney, C. A. & Schnurr, P. P. The influence of the dissociative subtype of posttraumatic stress disorder on treatment efficacy in female veterans and active duty service members. *J. Consult Clin. Psychol.* http//dx.doi.org/10.1037/ccp0000036 (2015).
186. Cloitre, M. *et al.* Treatment for PTSD related to childhood abuse: a randomized controlled trial. *Am. J. Psychiatry* **167**, 915–924 (2010).
187. Cloitre, M., Petkova, E., Wang, J. & Lu Lassell, F. An examination of the influence of a sequential treatment on the course and impact of dissociation among women with PTSD related to childhood abuse. *Depress. Anxiety* **29**, 709–717 (2012).

188. Lanius, R. A., Frewen, P. A., Tursich, M., Jetly, R. & McKinnon, M. C. Restoring large-scale brain networks in PTSD and related disorders: a proposal for neuroscientifically-informed treatment interventions. *Eur. J. Psychotraumatol.* **6**, 27313 (2015).
189. Dorahy, M. J. *et al.* Dissociation, shame, complex PTSD, child maltreatment and intimate relationship self-concept in dissociative disorder, chronic PTSD and mixed psychiatric groups. *J. Affect. Disord.* **172**, 195–203 (2014).
190. Albucher, R. C. & Liberzon, I. Psychopharmacological treatment in PTSD: a critical review. *J. Psychiatr. Res.* **36**, 355–367 (2002).
191. Schoenfeld, F. B., Marmar, C. R. & Neylan, T. C. Current concepts in pharmacotherapy for posttraumatic stress disorder. *Psychiatr. Serv.* **55**, 519–531 (2004).
192. Drici, M. D. & Priori, S. Cardiovascular risks of atypical antipsychotic drug treatment. *Pharmacoepidemiol. Drug Saf.* **16**, 882–890 (2007).
193. Hageman, I., Andersen, H. S. & Jorgensen, M. B. Post-traumatic stress disorder: a review of psychobiology and pharmacotherapy. *Acta Psychiatr. Scand.* **104**, 411–422 (2001).
194. Watanabe, Y., Sakai, R. R., McEwen, B. S. & Mendelson, S. Stress and antidepressant effects on hippocampal and cortical 5-HT_{1A} and 5-HT_2 receptors and transport sites for serotonin. *Brain Res.* **615**, 87–94 (1993).
195. Yehuda, R. *et al.* Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: relation to risk and resilience factors. *J. Psychiatr. Res.* **41**, 435–445 (2007).
196. Neylan, T. C. *et al.* Insomnia severity is associated with a decreased volume of the CA3/dentate gyrus hippocampal subfield. *Biol. Psychiatry* **68**, 494–496 (2010).
197. Karl, A. *et al.* A meta-analysis of structural brain abnormalities in PTSD. *Neurosci. Biobehav. Rev.* **30**, 1004–1031 (2006).
198. Raskind, M. A. *et al.* A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am. J. Psychiatry* **170**, 1003–1010 (2013).
199. Department of Veterans Affairs; VA Puget Sound Health Care System. Prazosin and combat trauma PTSD (PACT). *ClinicalTrials.gov* [online], https://clinicaltrials.gov/ct2/show/results/NCT00532493?sect=X70156NLM Identifier:NCT00532493 (2014).
200. de Quervain, D. J. Glucocorticoid-induced reduction of traumatic memories: implications for the treatment of PTSD. *Prog. Brain Res.* **167**, 239–247 (2008).
201. Golier, J. A., Caramanica, K., Demaria, R. & Yehuda, R. A pilot study of mifepristone in combat-related PTSD. *Depress Res. Treat.* **2012**, 393251 (2012).
202. Aerni, A. *et al.* Low-dose cortisol for symptoms of posttraumatic stress disorder. *Am. J. Psychiatry* **161**, 1488–1490 (2004).
203. Suris, A., North, C., Adinoff, B., Powell, C. M. & Greene, R. Effects of exogenous glucocorticoid on combat-related PTSD symptoms. *Ann. Clin. Psychiatry* **22**, 274–279 (2010).
204. Ipser, J. C. & Stein, D. J. Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). *Int. J. Neuropsychopharmacol.* **15**, 825–840 (2012).
205. Management of Post-Traumatic Stress Working Group. VA/DoD clinical practice guideline for the management of post-traumatic stress. *U.S. Department of Veteran Affairs* [online], http://www.healthquality.va.gov/ptsd/Mgmt_of_PTSD_final_92111.pdf (2010).
206. Dunlop, B. W. *et al.* Evaluation of a corticotropin releasing hormone type 1 receptor antagonist in women with posttraumatic stress disorder: study protocol for a randomized controlled trial. *Trials* **15**, 240 (2014).
207. Cameron, C., Watson, D. & Robinson, J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. *J. Clin. Psychopharmacol.* **34**, 559–564 (2014).
208. Jetly, R., Heber, A., Fraser, G. & Boisvert, D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology* **51**, 585–588 (2015).
209. Feder, A. *et al.* Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry* **71**, 681–688 (2014).
210. de Kleine, R. A., Rothbaum, B. O. & van Minnen, A. Pharmacological enhancement of exposure-based treatment in PTSD: a qualitative review. *Eur. J. Psychotraumatol.* **4**, 21626 (2013).
211. Kupferschmidt, K. Can ecstasy treat the agony of PTSD? *Science* **345**, 22–23 (2014).
212. Novakovic, V. *et al.* Brain stimulation in posttraumatic stress disorder. *Eur. J. Psychotraumatol.* **2**, 5609 (2011).
213. Karsen, E. F., Watts, B. V. & Holtzheimer, P. E. Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. *Brain Stimul.* **7**, 151–157 (2014).
214. Steckler, T. & Risbrough, V. Pharmacological treatment of PTSD — established and new approaches. *Neuropharmacology* **62**, 617–627 (2012).
215. Rothbaum, B. O. *et al.* A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. *Am. J. Psychiatry* **171**, 640–648 (2014).
216. Yehuda, R. *et al.* Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: randomized trial showing improved treatment retention and outcome. *Psychoneuroendocrinology* **51**, 589–597 (2015).
217. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (American Psychiatric Association, 2000).
218. Pietrzak, R. H. *et al.* Functional significance of a novel 7-factor model of DSM-5 PTSD symptoms: results from the National Health and Resilience in Veterans Study. *J. Affect. Disord.* **174**, 522–526 (2015).
219. Rapaport, M. H., Clary, C., Fayyad, R. & Endicott, J. Quality-of-life impairment in depressive and anxiety disorders. *Am. J. Psychiatry* **162**, 1171–1178 (2005).
220. Harvey, S. B. *et al.* The long-term consequences of military deployment: a 5-year cohort study of United Kingdom reservists deployed to Iraq in 2003. *Am. J. Epidemiol.* **176**, 1177–1184 (2012).
221. Bosco, M. A., Gallinati, J. L. & Clark, M. E. Conceptualizing and treating comorbid chronic pain and PTSD. *Pain Res. Treatment* **2013**, 1–10 (2013).
222. Kaniasty, K. & Norris, F. H. Longitudinal linkages between perceived social support and posttraumatic stress symptoms: sequential roles of social causation and social selection. *J. Traumat. Stress* **21**, 274–281 (2008).
Examining a large sample of natural disaster victims in Mexico, the authors of this study find that initially lower social support leads to greater rates of PTSD. However, over time, PTSD erodes social support, making individuals increasingly vulnerable to downstream challenges.
223. Yehuda, R., Lehrner, A. & Rosenbaum, T. Y. PTSD and sexual dysfunction in men and women. *J. Sex. Med.* **12**, 1107–1119 (2015).
224. Hobfoll, S. E. Traumatic stress: a theory based on rapid loss of resources. *Anxiety Res.* **4**, 187–197 (1991).
The theory presented in this paper proposes that individuals experiencing traumatic stress often experience the concordant loss of personal, social and material resources, and this process occurs rapidly.
225. Hobfoll, S. E. *Stress, Culture, and Community: the Psychology and Philosophy of Stress* (Plenum, 1998).
226. Hall, B. J., Bonanno, G. A., Bolton, P. A. & Bass, J. K. A longitudinal investigation of changes to social resources associated with psychological distress among Kurdish torture survivors living in Northern Iraq. *J. Trauma. Stress* **27**, 446–453 (2014).
227. Goodson, J. T., Lefkowitz, C. M., Helstrom, A. W. & Gawrysiak, M. J. Outcomes of prolonged exposure therapy for veterans with posttraumatic stress disorder. *J. Trauma. Stress* **26**, 419–425 (2013).
228. Giacco, D., Matanov, A. & Priebe, S. Symptoms and subjective quality of life in post-traumatic stress disorder: a longitudinal study. *PLoS ONE* **8**, e60991 (2013).
229. Lamarche, L. J. & De Koninck, J. Sleep disturbance in adults with posttraumatic stress disorder: a review. *J. Clin. Psychiatry* **68**, 1257–1270 (2007).
230. Daskalakis, N. P., Cohen, H., Cai, G., Buxbaum, J. D. & Yehuda, R. Expression profiling associates blood and brain glucocorticoid receptor signaling with trauma-related individual differences in both sexes. *Proc. Natl Acad. Sci. USA* **111**, 13529–13534 (2014).
This paper is important because it uses an unbiased approach to look at convergent pathways in the blood and the brain. Furthermore, this animal model separates biological differences resulting from stress exposure and individual differences in pathological behaviour.
231. Neylan, T. C., Schadt, E. E. & Yehuda, R. Biomarkers for combat-related PTSD: focus on molecular networks from high-dimensional data. *Eur. J. Psychotraumatol.* **5**, 23938 (2014).
This paper explains how big data and novel computational methods from converging data sets will help to identify molecular networks in PTSD. Furthermore, this paper shows how animal and human data can be used together to advance the field.
232. Thakur, G. S. *et al.* Systems biology approach to understanding post-traumatic stress disorder. *Mol. Biosyst.* **11**, 980–993 (2015).
233. De Jong, J. in *Broken Spirits: The Treatment of Asylum Seekers and Refugees with PTSD* (eds Wilson, J. P. & Drodzek, B.) 159–179 (Brunner/Routledge Press, 2005).
234. Hobfoll, S. E. Resource caravans and resource caravan passageways: a new paradigm for trauma responding. *Intervention* **12**, 21–32 (2014).
235. Jewkes, R., Fulu, E., Roselli, T. & Garcia-Moreno, C. Prevalence of and factors associated with non-partner rape perpetration: findings from the UN Multi-country Cross-sectional Study on Men and Violence in Asia and the Pacific. *Lancet Glob. Health* **1**, e208–e218 (2013).
236. Alegria, M. *et al.* Prevalence, risk, and correlates of posttraumatic stress disorder across ethnic and racial minority groups in the United States. *Med. Care* **51**, 1114–1123 (2013).
237. Moisander, P. A. & Edston, E. Torture and its sequel — a comparison between victims from six countries. *Forens. Sci. Int.* **137**, 133–140 (2003).
238. Wolfe, J. & Kimerling, R. in *Assessing Psychological Trauma and PTSD* (eds Wilson, J. P. & Keane, T. M.) 192–238 (Guilford, 1997).
239. Cortina, L. M. & Kubiak, S. P. Gender and posttraumatic stress: sexual violence as an explanation for women's increased risk. *J. Abnorm. Psychol.* **115**, 753–759 (2006).
240. Tolin, D. F. & Foa, E. B. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. *Psychol. Bull.* **132**, 959–992 (2006).
241. Breslau, N., Chilcoat, H. D., Kessler, R. C., Peterson, E. L. & Lucia, V. C. Vulnerability to assaultive violence: further specification of the sex difference in post-traumatic stress disorder. *Psychol. Med.* **29**, 813–821 (1999).
242. Breslau, N. & Anthony, J. C. Gender differences in the sensitivity to posttraumatic stress disorder: an epidemiological study of urban young adults. *J. Abnormal Psychol.* **116**, 607–611 (2007).
243. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (American Psychiatric Association, 1987).
244. Hopper, J. W., Frewen, P. A., van der Kolk, B. A. & Lanius, R. A. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: Symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. *J. Trauma. Stress* **20**, 713–725 (2007).
245. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research* (Geneva, 1992).
246. NICE. Post-traumatic stress disorder: the management of PTSD in adults and children in primary and secondary care. *NICE* [online], https://www.nice.org.uk/guidance/cg26 (2005).
247. Canadian Psychiatric Association. Clinical practice guidelines: management of anxiety disorders. *Canadian J. Psychiatry* **51** (Suppl. 2), 9S–91S (2006).
248. Bajor, L. A., Ticlea, A. N. & Osser, D. N. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: an update on posttraumatic stress disorder. *Harvard Rev. Psychiatry* **19**, 240–258 (2011).

249. Forbes, D. *et al.* A guide to guidelines for the treatment of PTSD and related conditions. *J. Trauma. Stress* **23**, 537–552 (2010).
250. Foa, E. B., Keane, T. M., Friedman, M. J. & Cohen, J. A. *Effective treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies* (Guilford Press, 2008).
251. Ursano, R. J. *et al.* Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *Am. J. Psychiatry* **161**, 3–31 (2004).
252. Benedek, D. M., Friedman, M. J., Zatzick, D. & Ursano, R. J. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *Psychiatry Online* [online], http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/acutestressdisorderptsd.pdf (2009).
253. Bernardy, N. C. & Friedman, M. J. 2010 VA/DOD Clinical Practice Guideline for Management of Post-Traumatic Stress: how busy clinicians can best adopt updated recommendations. *J. Rehabil. Res. Dev.* **49**, vii–viii (2012).
254. Forbes, D. *et al.* Australian guidelines for the treatment of adults with acute stress disorder and post-traumatic stress disorder. *Aust. N. Z. J. Psychiatry* **41**, 637–648 (2007).

Acknowledgements
R.Y. is supported by grants from the US Department of Defense (DOD W81XWH-10-2-0072 and DOD W81XWH-13-1-0071) and a grant from the Lightfighter Trust Foundation (LFT2009-02-1). A.C.M. is supported in part by National Health and Medical Research Council Program Grant number 568970. C.M.N. is supported in part by US National Institutes of Health (NIH) grant R01MH093500. S.E. Hobfoll is partly supported by a grant from the National Institute of Mental Health (RO1MH073687) and the Rush Center for Urban Health Equity (NIH-NHLBI 1P50HL105189). K.C.K. is supported by grants NIH MH078928 and MH093612. T.C.N. is supported in part by a research grant that was awarded and administered by the U.S. Army Medical Research & Materiel Command (USAMRMC; TCN: W81XWH-11-2-0189) and the Mental Illness Research and Education Clinical Center of the US Veterans Health Administration. The authors would like to thank L. M. Bierer for her careful final review of the manuscript, M. E. Bowers for assistance with the development of the graphics and review of references, and H. Bader for administrative coordination and integration of multiple versions of the document.

Author contributions
Introduction (R.Y.); Epidemiology (K.C.K. and C.W.H.); Mechanisms/pathophysiology (T.C.N., R.Y., C.M.N. and R.A.L.); Diagnosis, screening and prevention (A.C.M.); Management (E.V.); Quality of life (S. E. Hobfoll); Outlook (S. E. Hyman and R.Y.); overview of Primer (R.Y.). All authors contributed to the review and to the editing of the final manuscript.

Competing interests
R.Y. has a patent entitled Genes Associated with Posttraumatic Stress Disorder (2012/0039,812). A.C.M. receives research funding from the Australian Department of Defense and the Australian Department of Veterans Affairs. He is a Group Captain in the RAAF specialist reserves and is an advisor to the Department of Veterans Affairs. K.C.K. has consulted for Synchroneuron Inc. and Accellient Partners. T.C.N. has consulted for Genentech and has received study medication from Actelion for a study funded by the US Department of Defense, and from Glaxo-Smith-Kline for a study funded by the US Department of Veterans Affairs. S. E. Hyman has consulted on early stage drug discovery for Novartis and Sunovion. C.W.H., E.V., R.A.L., C.M.N. and S. E. Hobfoll declare no competing interests.

Disclaimer
The views expressed in this article are those of the authors and do not represent an official position of the US Army, US Department of Defense or any of the affiliated institutions listed.