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Preclinical Perspectives on Posttraumatic Stress Disorder Criteria in DSM-5

Susannah Tye, PhD, **Elizabeth Van Voorhees, PhD**, **Chunling Hu, MD, PhD**, and **Timothy Lineberry, MD**

Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN (Drs. Tye, Hu, and Lineberry); Schools of Psychiatry and Medicine, Deakin University, Geelong, VIC, Australia (Dr. Tye); Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC (Dr. Van Voorhees); Mid-Atlantic Mental Illness Research, Education and Clinical Center, Durham, NC (Dr. Van Voorhees); Durham Veterans Affairs Medical Center, Durham, NC (Dr. Van Voorhees); Aurora Health Care, Green Bay, WI (Dr. Lineberry)

Abstract

Posttraumatic stress disorder (PTSD) now sits within the newly created “Trauma- and Stressor-Related Disorders” section of the Diagnostic and Statistical Manual of Mental Disorders (fifth edition; DSM-5). Through the refinement and expansion of diagnostic criteria, the DSM-5 version better clarifies the broad and pervasive effects of trauma on functioning, as well as the impact of development on trauma reactions. Aggressive and dissociative symptoms are more thoroughly characterized, reflecting increasing evidence that reactions to trauma often reach beyond the domains of fear and anxiety (these latter domains were emphasized in DSM-IV). These revised criteria are supported by decades of preclinical and clinical research quantifying traumatic stress–induced changes in neurobiological and behavioral function. Several features of the DSM-5 PTSD criteria are similarly and consistently represented in preclinical animal models and humans following exposure to extreme stress. In rodent models, for example, increases in anxiety-like, helplessness, or aggressive behavior, along with disruptions in circadian/neurovegetative function, are typically induced by severe, inescapable, and uncontrollable stress. These abnormalities are prominent features of PTSD and can help us in understanding the pathophysiology of this and other stress-associated psychiatric disorders. In this article we examine some of the changes to the diagnostic criteria of PTSD in the context of trauma-related neurobiological dysfunction, and discuss implications for how preclinical data can be useful in current and future clinical conceptualizations of trauma and trauma-related psychiatric disorders.

Keywords

animal models; DSM-5; plasticity; posttraumatic stress disorder; stress; trauma

Correspondence: Susannah Tye, PhD, Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN 55905. tye.susannah@mayo.edu.

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The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes important changes to the diagnostic criteria for posttraumatic stress disorder (PTSD). Although many of the symptoms remain consistent with DSM-IV-TR, the disorder has been moved to a new section entitled “Trauma- and Stressor-Related Disorders,” and the changes to the diagnostic criteria and their descriptions have expanded the section from just over one page to four pages. Much of the additional information is included under a subsection, “Posttraumatic Stress Disorder for Children 6 Years and Younger,” reflecting the greater attention to developmental differences in the manifestation of trauma symptomatology. Other key changes include: (1) removal of the requirement that the individual responded with fear, helplessness, or horror at the time of the trauma, (2) renaming the “re-experiencing” cluster symptoms as “intrusion” symptoms, (3) separating “avoidance” and “numbing” symptoms into two separate clusters, (4) subsuming “numbing” symptoms under a newly developed symptom cluster, “negative alterations in cognitions and mood,” (5) elaborating upon the “irritability or outbursts of anger” symptom to highlight the occurrence of verbal and physical aggression, (6) adding a specifier for a dissociative subtype.

These modifications represent at least two important changes in the conceptualization of how individuals respond to overwhelming trauma. First, the development of a separate category for trauma- and stressor-related disorders takes an important step toward acknowledging that trauma often has broad and pervasive effects on functioning beyond what can be adequately captured in a single diagnosis. Coupled with the greater emphasis on aggressive and dissociative symptoms within the diagnosis of PTSD, the presence of this new section reflects a deeper understanding that reactions to trauma can be pervasive and diverse, and that they often reach beyond our previous conceptualization of them as being limited to the domains of fear and anxiety, which DSM-IV emphasized.[1–16]

Second, the inclusion of reactive attachment disorder and disinhibited social engagement disorder in the trauma- and stressor-related disorders section, coupled with the elaboration of the description of trauma symptoms in children within the PTSD criteria, begins to integrate the decades of preclinical and clinical research demonstrating the profound impact that developmental timing of trauma exposure has on trauma reactions, both at the time of initial exposure and in response to stress and trauma experienced later in life.[17–31] In this article we examine changes to the diagnostic criteria of PTSD in the context of animal models of trauma-related neurobiological dysfunction, and discuss implications for how preclinical data can be useful in current and future clinical conceptualizations of trauma and trauma-related psychiatric disorders.

HOW CAN PRECLINICAL RESEARCH INFORM THE REFINEMENT OF DIAGNOSTIC CRITERIA FOR PTSD?

Preclinical models that complement clinical research can greatly enhance our understanding of the neurobiological underpinnings of neuropsychiatric traits. While animal studies are limited in their capacity to model human psychiatric phenomena, consideration of preclinical data of the demonstrated effects of stress on neurobiology and behavior can help us to better understand human responses to severe stress or trauma.[32] To confer this

complementary and evidence-based insight, animal models of complex disorders such as PTSD must demonstrate a satisfactory degree of reliability together with face, construct, and predictive validity. That is, behavioral responses must be observable and measurable, emulate clinical symptomatology, and be corrected with pharmacological treatments that alleviate similar indications in patients with the disorder.[33]

Preclinical models considered to phenotypically resemble clinical cases of PTSD in humans are characterized by long-lasting adaptations in stress and conditioned-fear responses, together with a generalized sensitization to stimuli following intense stress exposure.[34] In rodent models, simulation of a traumatic event can be induced via exposure to inescapable electric shocks, aggressive social confrontation, predator scent, or a short, varied sequence of stressors.[33,34] Animals exposed to such trauma typically demonstrate sensitized responses to novel stressful stimuli across neuroendocrine, cardiovascular, gastrointestinal, and immune systems for weeks to months after the exposure.[34] Increased sensitivity to pain, dysregulation of circadian biorhythms, greater depression-like behavior, and heightened fear and defensive reactivity are also observed.[35] Insights into the sensitizing effects of trauma exposure on systems involved in both physiological and affective stress regulation in animal models have provided the foundation for examining mechanisms of comorbidity of PTSD and a host of physical and psychiatric disorders, including cardiovascular and metabolic disease,[36,37] disrupted immune functioning,[38] chronic pain,[39–42] and depression.[31]

Cortisol and noradrenaline, adrenaline, and a host of other stress-mediated physiological sequelae work in concert to coordinate cellular responses in both the peripheral and central nervous systems, thereby facilitating an individual's behavioral response to an immediate threat.[43–52] These physiological cascades concurrently modulate synaptic plasticity and epigenetic mechanisms governing future cellular responses to stress.[53] These adaptations enable individuals to rapidly recall memories and biological responses, facilitating their avoidance of, or coping with, similar threats in the future. From this perspective, the psychophysiological symptoms of PTSD reflect augmentation of biologically engineered adaptations in behavioral coping (e.g., hyperarousal, aggressive defense, avoidance, and persistent negative alterations in cognitions and mood).[54]

Neurobiological adaptations—mediated by hyperactivation of both the hypothalamic-pituitary-adrenal axis and sympathetic nervous system during severe stress—attune neural systems, primed to facilitate cognitive and behavioral responses, to future threats.[55] These adaptations include augmenting memory consolidation at the cellular and systems level to prime an individual's future fight, flight, or freeze response when faced with similar threats. Rapid recall of memories, both psychologically and physiologically, are critical to this adaptive response. PTSD symptomatology is not per se a disruption of this system but is, instead, reflective of an inherently efficient and enduring memory storage and retrieval system. From an evolutionary perspective, therefore, symptoms of PTSD, including intrusive memories of the traumatic event, avoidance of reminders of it, emotional numbing or dysregulation, hyperarousal, and exaggerated active versus passive coping, can be considered natural adaptations to extreme stress that fail to subside once the threat is removed. The enduring nature of these stress-mediated neuroadaptations, which are thought to underlie symptom persistence in vulnerable individuals, has led to suggestions that PTSD

is a “forgetting” disorder, such that PTSD patients lose the ability to forget the trauma.[32] Consequently, when they encounter trauma-associated cues, vivid memories of the traumatic event are reexperienced together with associated emotional states and physiological stress responses.

Preclinical research suggests mechanisms mediating PTSD and other trauma- and stressor-related psychopathology are founded in a functionally adaptive stress response system evolved to rapidly and effectively store fear-related memories and facilitate the rapid recall of situationally relevant physiological and psychological reactions.[56–58] Once an individual previously exposed to trauma is in a safer environmental context, the situationally adaptive response is to attenuate recall of trauma-related memories and associated system-wide physiological reactions. In PTSD, however, the all-too-effective recall of memories formed during exposure to extreme stress, together with the rapid coordination of physiological and behavioral responses, can be disabling later, when the individual is no longer facing the impending threat. Building upon the understanding of mechanisms afforded by animal models, clinical studies have begun to demonstrate parallels between deficits in attention, learning, and memory observed in humans with PTSD and alterations in brain systems and structures identified in animals as underlying these processes.[10,34,59–61] Redefining PTSD as a “Trauma- and Stressor-Related Disorder” has helped to refine clinical criteria for diagnosis, better aligning the diagnosis with our understanding of the neurobiological mechanisms of stress reactivity and stress-mediated psychopathology.

REDEFINING PTSD AS A “TRAUMA- AND STRESSOR-RELATED DISORDER”

It has been argued for some time that the unique neurobiological adaptations to traumatic stress in PTSD validate its inclusion in a distinct diagnostic entity.[56,62,63] This perspective has been extended by the creation in the DSM-5 of a separate category for “Trauma- and Stressor-Related Disorders,” and the relocation of PTSD from “Anxiety Disorders” into this new section. These changes appear to reflect the growing appreciation that the characteristic symptom persistence of PTSD and other trauma- and stress-related disorders reflect allostatic overload to neurobiological stress-response systems[21,64,65] and the subsequent failure of re-adaptation to a safe environment at a neurophysiological level.[66] As discussed above, the cascading changes to neurobiological systems as a result of chronic or severe stress may manifest in changes to psychological and physiological functioning that reach far beyond symptoms of fear and anxiety. Indeed, behavioral neuroscience research across species suggests that when environmental stressors are too demanding and the individual is unable to effectively cope, poor health and psychopathology across multiple domains can result.[67]

The creation of a DSM-5 section specifically for disorders reflecting trauma- and stress-related psychopathology also may reflect an acknowledgment of the variability in the expression of post-traumatic reactions. That overwhelming stress can induce significant and enduring changes in cognitions, feelings, and behavior[56,68–72] remains the fundamental construct of PTSD and the other stress-related disorders in DSM-5. However, the greater consideration of stress-related adaptations in the specific diagnostic criteria for PTSD in

DSM-5 seems to reflect an increased awareness of the enduring impact of severe stress on mood and coping systems. The way in which an animal copes with stress is often colloquially referred to as the fight, flight, or freeze response, and reflects well-characterized confrontational and avoidant behavioral responses. In DSM-IV-TR, the role of the fear response in PTSD was acknowledged by its placement among the anxiety disorders. This emphasis on the role of fear and anxiety in PTSD has led to the development of effective therapies for PTSD that have built upon exposure and cognitive-behavior therapy for other anxiety disorders,[73,74] but it has also limited the development of therapies to address other trauma- and stress-related responses such as aggression or sleep disturbance.[75,76]

Nonconfrontational behavioral responses to stress, such as the flight response or freeze response, are a means through which an individual can withdraw and avoid the threat, thereby both conserving energy and avoiding aggressive conflicts.[77] Many of the symptoms of PTSD in both DSM-IV-TR and DSM-5 reflect such withdrawal from, or "depressive" responses to, stress, although this emphasis is more pronounced in the DSM-5 criteria. By contrast, confrontational responses to stress, though well represented by aggressive and territorial posturing (particularly in animals),[78] have been conspicuously absent from previous DSM formulations of PTSD. The elaboration of the DSM-IV symptom "irritability or outbursts of anger" to the DSM-5 symptom "irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects" takes an important step toward addressing this omission.[79,80] A more thorough consideration of such confrontational responses as they apply to anger and aggression in PTSD may facilitate the development of treatments that more effectively target the profound impact that these "externalizing" behaviors[81] have on interpersonal, occupational, and health-related outcomes.[2,5,7,75,79,80,82–85]

STRESS SENSITIZATION AND TRAUMA-RELATED PSYCHOPATHOLOGY

All of the coping behaviors described above are triggered and regulated by stress and are fundamental features of PTSD pathophysiology. Indeed, a wealth of neurobiological data demonstrates that exposure to stress (or stress hormones) serves to modify the expression of these behaviors through alteration of hypothalamic-pituitary-adrenal axis feedback and monoamine neurotransmission.[86,87] The enduring nature of stress-induced neurobiological adaptations in PTSD represents a critical feature of this disorder.[86] Behavioral coping is mediated, in part, through genetics and fine-tuned by exposure to stress, particularly in early life. Adaptations that occur within the neuroendocrine systems are also modified by prior stress exposure and serve to regulate neural systems mediating mood and coping.

Such adaptations may be influenced by the developmental timing, chronicity, and characteristic of the trauma(s). For example, long-term childhood maltreatment by primary caregivers may result in neural, endocrine, cognitive, and behavioral alterations that are distinct from those occurring in response to a single, prolonged stressor in adulthood, such as exposure to combat.[10,21,23–26,28,88,89] Preclinical models provide a valuable tool for elucidating the influence of gene × environment × development factors in the pathogenesis and symptomatic expression of PTSD.[90–93]

Animal models of PTSD have contributed significant insight into the neurobiological mechanisms mediating fear conditioning, extinction learning, retention of extinction learning, and behavioral and neuroendocrine sensitization involved in the development or maintenance of PTSD.[94,95] Such studies have demonstrated that exposure to stress, particularly early in life, can result in enduring changes in neuroendocrine regulation and also in neurobiological reorganization within the mesocorticolimbic system.[96] While important similarities can be identified across multiple stress-sensitive disorders, a core and unique feature of PTSD is to be unable to forget trauma memories, and to experience, and be unable to inhibit, exaggerated physiological stress responses to associated stimuli.[32] Classical associative fear conditioning, used extensively to model the traumatic memory features of PTSD in animals,[97] has shown that disruption of “for-getting” (extinction learning) is characterized by exaggerated amygdala responses together with deficits in frontal cortical and hippocampal function.[98] These functional and structural changes directly mediate memory recall and behavioral coping in the face of future stress and negatively affect the effectiveness of pharmacotherapies.[96]

Amygdala hyperactivity promotes acquisition of fear associations and responses (both freezing in reaction to similar stimuli and aggressive behaviors when socially challenged), whereas deficits in frontal and hippocampal function prevent both the suppression of attentional responses to trauma-related stimuli and the behavioral adaptation to safe contexts.[98] These anatomical regions are thought to be particularly sensitive to the impact of severe stress via the direct actions of glucocorticoids and their facilitation of glutamate-mediated, long-term synaptic plasticity.[99–101] Relevantly, functional and structural differences have been observed in both the amygdala and hippocampus in both children and adults with PTSD.[17,20,59,102–105] Preexisting risks for PTSD, including depression and early life stress, may prime these regional responses to stress, in part via differential methylation of glucocorticoid response genes.[53,106] Together with previously incurred structural and functional vulnerabilities, such insults may further serve to augment trauma-induced neuroadaptations. Although the relationship between genes, environment, and development in the etiology of PTSD is inherently complex, animal models provide a valuable means of elucidating pathophysiological mechanisms, identifying key biomarkers of vulnerability, and testing novel therapeutics.

PREVENTION AND TREATMENT IMPLICATIONS

Research into the neurobiology of susceptibility and resilience to development of PTSD in preclinical animal models provides novel avenues for treatment and prevention.[43,107–109] Psychotherapy is a critical first-line treatment for PTSD,[110] and the mechanistic understanding of the effects of stress and trauma on functioning (based upon animal models) has been fundamental to the development and testing of these nonpharmacological interventions. For example, animal research on the impact of trauma on learning and memory has been used to develop trauma-focused therapies for PTSD such as cognitive processing therapy and prolonged exposure therapy.[73,74,111] Likewise, animal research has illuminated the neurobiological substrates of PTSD, opening the door for research examining the effects of psychotherapy on relevant neurobiological systems.[59,112–114]

Moving forward, the more we understand the neurobiological mechanisms of stress and their implications for plasticity and treatment response, the broader our scope for treatment options becomes for both behavioral and somatic treatments. For example, pharmacotherapies that block the formation of trauma-related memories may help to prevent PTSD if given acutely and immediately post-trauma. Illustrating this point, morphine used acutely in early resuscitation and trauma care in US service members has been associated with a reduced risk of developing PTSD.[115] Conversely, drugs that functionally induce an adaptive state in otherwise resistant neural circuits affected by trauma will potentially facilitate recovery and efficacy of psychotherapeutic approaches, as demonstrated in treatment-resistant depression.[116]

To date, the selective serotonin reuptake inhibitor class of antidepressants has most commonly been used in managing PTSD.[117,118] Possible treatments that directly modulate mechanisms implicated in synaptic plasticity include D-cycloserine, a broad-spectrum antibiotic and partial N-methyl-D-aspartate receptor agonist;[119–122] dehydroepian-drosterone, a precursor to male and female sex hormones (androgens and estrogens);[123–125] and neuropeptides such as corticotropin-releasing hormone and neuropeptide-Y.[126] Each of these compounds serves to regulate neuroendocrine and behavioral responses to stress and, through direct actions on mechanisms mediating synaptic plasticity, has promise as a therapeutic intervention for PTSD.

CONCLUSIONS

Broadly, the changes to the conceptualization of PTSD reflected in DSM-5 mirror the field's ever deeper understanding of the long-term consequences of stress and trauma, and of the biological mechanisms underlying these changes, as derived from research using animal models over the past several decades. The critical role that trauma plays in cascading neurobiological changes underlying psychopathology, the importance of developmental timing in shaping posttraumatic outcomes, and the heterogeneity of emotional and behavioral dysfunction associated with exposure to severe trauma have all been elegantly interwoven into the new diagnostic criteria. Much work remains to be done, however, to integrate the knowledge we have gained from animal models into our diagnostic guidelines. Based on the above discussion, we conclude with some considerations for collaborative efforts between preclinical and clinical researchers. It is our hope that these collaborations will continue to lead us toward increasingly refined and nuanced formulations of the psychiatric effects of trauma in future versions of the DSM. The new DSM-5 structure separating out trauma- and stressor-related disorders potentially lays the groundwork for incorporating into the DSM framework both the impact of chronic trauma on personality development and the association of trauma with the onset of other psychiatric syndromes.

We recommend that in examining the implications of animal models for defining human responses to trauma, researchers and theorists continue to emphasize a developmental perspective on PTSD. Animal models demonstrate that early trauma exposure affects responsivity to later stressful events. Continuing to focus primarily on the effects of a single index event is, in light of the evidence, misguided. At the very least, this myopic view wastes valuable resources by discounting the vast literature suggesting that early experiences

shape neurobiological systems in ways that contribute formatively to the development of PTSD and other forms of psychopathology. More critically, however, such a narrow perspective inappropriately localizes the genesis of dysfunctional behavioral responses in PTSD to the individual without effectively acknowledging the influence of both genes and environment on neurodevelopmental processes that prime an individual to effectively store and recall trauma- and stress-related memories. This narrow perspective not only creates obstacles to the development of effective interventions but also risks exacerbating trauma-related alterations in cognition and mood by implicitly blaming the individual for problems having a strong biological basis, such as persistent negative emotional states and aggressive behavior.

With creation of the “Trauma- and Stressor-Related Disorders” section, we are now better placed to conceptualize PTSD as one clinical manifestation of an underlying neurobiological adaptation to stress. In addition to aiding our understanding of the basic neurobiology of PTSD, preclinical studies can help determine the influence of genetic, environmental, and developmental factors in mediating an individual’s vulnerability to develop PTSD. Preclinical studies can also help to identify the mechanisms through which these mediating factors can be therapeutically disrupted, thereby providing opportunities both to identify novel drug targets and therapeutic interventions and to enhance our capacity to personalize treatments based on the unique phenotypic expression of PTSD. Importantly, as we better appreciate the mechanisms through which an inherently efficient stress response facilitates the hard wiring of fear memories and behavioral coping responses at the core of PTSD pathophysiology, we take an important step toward destigmatizing this devastating illness.

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REFERENCES

1. Andrews B, Brewin CR, Rose S, Kirk M. Predicting PTSD symptoms in victims of violent crime: the role of shame, anger, and childhood abuse. J Abnorm Psychol. 2000; 109:69–73. [PubMed: 10740937]
2. Barazzone N, Davey GC. Anger potentiates the reporting of threatening interpretations: an experimental study. J Anxiety Disord. 2009; 23:489–95. [PubMed: 19070989]
3. Beckham JC, Vrana SR, Barefoot JC, Feldman ME, Fairbank J, Moore SD. Magnitude and duration of cardiovascular responses to anger in Vietnam veterans with and without posttraumatic stress disorder. J Consult Clin Psychol. 2002; 70:228–34. [PubMed: 11860049]
4. Chemtob CM, Novaco RW, Hamada RS, Gross DM, Smith G. Anger regulation deficits in combat-related posttraumatic stress disorder. J Trauma Stress. 1997; 10:17–36. [PubMed: 9018675]
5. Evans S, Giosan C, Patt I, Spielman L, Difede J. Anger and its association to distress and social/occupational functioning in symptomatic disaster relief workers responding to the September 11, 2001, World Trade Center disaster. J Trauma Stress. 2006; 19:147–52. [PubMed: 16568457]
6. Feeny NC, Zoellner LA, Foa EB. Anger, dissociation, and posttraumatic stress disorder among female assault victims. J Trauma Stress. 2000; 13:89–100. [PubMed: 10761176]
7. Hellmuth JC, Stappenbeck CA, Hoerster KD, Jakupcak M. Modeling PTSD symptom clusters, alcohol misuse, anger, and depression as they relate to aggression and suicidality in returning U.S. veterans. J Trauma Stress. 2012; 25:527–34. [PubMed: 23073972]

8. Jakupcak M, Conybeare D, Phelps L, et al. Anger, hostility, and aggression among Iraq and Afghanistan War veterans reporting PTSD and subthreshold PTSD. J Trauma Stress. 2007; 20:945–54. [PubMed: 18157891]
9. Kulkarni M, Porter KE, Rauch SA. Anger, dissociation, and PTSD among male veterans entering into PTSD treatment. J Anxiety Disord. 2012; 26:271–8. [PubMed: 22245698]
10. Lanius RA, Frewen PA, Vermetten E, Yehuda R. Fear conditioning and early life vulnerabilities: two distinct pathways of emotional dysregulation and brain dysfunction in PTSD. Eur J Psychotraumatol. 2010; 1
11. McHugh T, Forbes D, Bates G, Hopwood M, Creamer M. Anger in PTSD: is there a need for a concept of PTSD-related post-traumatic anger? Clin Psychol Rev. 2012; 32:93–104. [PubMed: 22236575]
12. Olatunji BO, Ciesielski BG, Tolin DF. Fear and loathing: a meta-analytic review of the specificity of anger in PTSD. Behav Ther. 2010; 41:93–105. [PubMed: 20171331]
13. Orth U, Wieland E. Anger, hostility, and posttraumatic stress disorder in trauma-exposed adults: a meta-analysis. J Consult Clin Psychol. 2006; 74:698–706. [PubMed: 16881777]
14. Power MJ, Fyvie C. The role of emotion in PTSD: two preliminary studies. Behav Cogn Psychother. 2013; 41:162–72. [PubMed: 22452905]
15. Taft C, Kaloupek D, Schumm J, et al. Posttraumatic stress disorder symptoms, physiological reactivity, alcohol problems, and aggression among military veterans. J Abnorm Psychol. 2007; 116:498–507. [PubMed: 17696706]
16. Teten AL, Miller LA, Stanford MS, et al. Characterizing aggression and its association to anger and hostility among male veterans with post-traumatic stress disorder. Mil Med. 2010; 175:405–10. [PubMed: 20572472]
17. Crozier, J.; Van Voorhees, E.; Hooper, S.; De Bellis, M. Effect of abuse and neglect on brain development. In: Jenny, C., editor. Child abuse and neglect: diagnosis, treatment and evidence. Elsevier Health Sciences; New York: 2010. p. 516-25.
18. De Bellis MD. Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. Psychoneuroendocrinology. 2002; 27:155–70. [PubMed: 11750776]
19. De Bellis MD, Baum AS, Birmaher B, et al. Developmental traumatology part I: biological stress systems. Biol Psychiatry. 1999; 45:1259–70. [PubMed: 10349032]
20. De Bellis MD, Keshavan MS, Clark DB, et al. Developmental traumatology part II: brain development. Biol Psychiatry. 1999; 45:1271–84. [PubMed: 10349033]
21. Doom JR, Gunnar MR. Stress physiology and developmental psychopathology: past, present, and future. Dev Psychopathol. 2013; 25:1359–73. [PubMed: 24342845]
22. Fergusson DM, McLeod GF, Horwood LJ. Childhood sexual abuse and adult developmental outcomes: findings from a 30-year longitudinal study in New Zealand. Child Abuse Negl. 2013; 37:664–74. [PubMed: 23623446]
23. Gunnar MR, Quevedo KM. Early care experiences and HPA axis regulation in children: a mechanism for later trauma vulnerability. Prog Brain Res. 2008; 167:137–49. [PubMed: 18037012]
24. Koenen KC. Developmental epidemiology of PTSD: self-regulation as a central mechanism. Ann N Y Acad Sci. 2006; 1071:255–66. [PubMed: 16891576]
25. Ogle CM, Rubin DC, Siegler IC. The impact of the developmental timing of trauma exposure on PTSD symptoms and psychosocial functioning among older adults. Dev Psychol. 2013; 49:2191–200. [PubMed: 23458662]
26. Pollak SD, Nelson CA, Schlaak MF, et al. Neurodevelopmental effects of early deprivation in postinstitutionalized children. Child Dev. 2010; 81:224–36. [PubMed: 20331664]
27. Taft C, Schumm JA, Marshall AD, Panuzio J, Holtzworth-Munroe A. Family-of-origin maltreatment, posttraumatic stress disorder symptoms, social information processing deficits, and relationship abuse perpetration. J Abnorm Psychol. 2008; 117:637–46. [PubMed: 18729615]
28. Van Voorhees E, Scarpa A. The effects of child maltreatment on the hypothalamic-pituitary-adrenal axis. Trauma Violence Abuse. 2004; 5:333–52. [PubMed: 15361587]

29. van Zuiden M, Geuze E, Willemen HL, et al. Glucocorticoid receptor pathway components predict posttraumatic stress disorder symptom development: a prospective study. Biol Psychiatry. 2012; 71:309–16. [PubMed: 22137507]
30. Yehuda R. Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. Ann N Y Acad Sci. 2006; 1071:137–66. [PubMed: 16891568]
31. Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biol Psychiatry. 1996; 40:79–88. [PubMed: 8793040]
32. Ursano RJ, Zhang L, Li H, et al. PTSD and traumatic stress from gene to community and bench to bedside. Brain Res. 2009; 1293:2–12. [PubMed: 19328776]
33. Cohen H, Kozlovsky N, Alona C, Matar MA, Joseph Z. Animal model for PTSD: from clinical concept to translational research. Neuropharmacology. 2012; 62:715–24. [PubMed: 21565209]
34. Stam R. PTSD and stress sensitisation: a tale of brain and body. Part 2: animal models. Neurosci Biobehav Rev. 2007; 31:558–84. [PubMed: 17350095]
35. Nijenhuis ER, Vanderlinden J, Spinhoven P. Animal defensive reactions as a model for trauma-induced dissociative reactions. J Trauma Stress. 1998; 11:243–60. [PubMed: 9565914]
36. Boscarino JA. Psychobiologic predictors of disease mortality after psychological trauma: implications for research and clinical surveillance. J Nerv Ment Dis. 2008; 196:100–7. [PubMed: 18277217]
37. Dedert EA, Calhoun PS, Watkins LL, Sherwood A, Beckham JC. Posttraumatic stress disorder, cardiovascular, and metabolic disease: a review of the evidence. Ann Behav Med. 2010; 39:61–78. [PubMed: 20174903]
38. Gill J, Vythilingam M, Page GG. Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. J Trauma Stress. 2008; 21:530–9. [PubMed: 19107725]
39. McLean SA, Clauw DJ, Abelson JL, Liberzon I. The development of persistent pain and psychological morbidity after motor vehicle collision: integrating the potential role of stress response systems into a biopsychosocial model. Psychosom Med. 2005; 67:783–90. [PubMed: 16204439]
40. Raphael KG, Janal MN, Nayak S. Comorbidity of fibromyalgia and posttraumatic stress disorder symptoms in a community sample of women. Pain Med. 2004; 5:33–41. [PubMed: 14996235]
41. Runnals, J.; Van Voorhees, E.; Calhoun, PS. Post-traumatic stress disorder and chronic pain. In: Coughlin, SS., editor. Post-traumatic stress disorder and chronic health conditions. American Public Health Association; Washington, DC: 2013. p. 113-46.
42. Wingenfeld K, Wagner D, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim C. The low-dose dexamethasone suppression test in fibromyalgia. J Psychosom Res. 2007; 62:85–91. [PubMed: 17188125]
43. Olson VG, Rockett HR, Reh RK, et al. The role of norepinephrine in differential response to stress in an animal model of posttraumatic stress disorder. Biol Psychiatry. 2011; 70:441–8. [PubMed: 21251647]
44. Southwick SM, Bremner JD, Rasmusson A, Morgan CA 3rd, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biol Pychiatry. 1999; 46:1192–204.
45. Geracioti TD Jr. Baker DG, Ekhator NN, et al. CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry. 2001; 158:1227–30. [PubMed: 11481155]
46. Bremner JD, Innis RB, Ng CK, et al. Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. Arch Gen Psychiatry. 1997; 54:246–54. [PubMed: 9075465]
47. Kinzie JD, Sack RL, Riley CM. The polysomnographic effects of clonidine on sleep disorders in posttraumatic stress disorder: a pilot study with Cambodian patients. J Nerv Ment Dis. 1994; 182:585–7. [PubMed: 7931208]
48. Kinzie JD, Leung P. Clonidine in Cambodian patients with post-traumatic stress disorder. J Nerv Ment Dis. 1989; 177:546–50. [PubMed: 2769247]
49. Boehnlein JK, Kinzie JD. Pharmacologic reduction of CNS noradrenergic activity in PTSD: the case for clonidine and prazosin. J Psychiatr Pract. 2007; 13:72–8. [PubMed: 17414682]

50. Taylor FB, Martin P, Thompson C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008; 63:629–32. [PubMed: 17868655]
51. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003; 160:371–3. [PubMed: 12562588]
52. Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007; 61:928–34. [PubMed: 17069768]
53. Heinzelmann M, Gill J. Epigenetic mechanisms shape the biological response to trauma and risk for PTSD: a critical review. Nurs Res Pract. 2013; 2013:417010. [PubMed: 23710355]
54. Adenauer H, Catani C, Keil J, Aichinger H, Neuner F. Is freezing an adaptive reaction to threat? Evidence from heart rate reactivity to emotional pictures in victims of war and torture. Psychophysiology. 2010; 47:315–22. [PubMed: 20030756]
55. Newport DJ, Nemeroff CB. Neurobiology of posttraumatic stress disorder. Curr Opin Neurobiol. 2000; 10:211–8. [PubMed: 10753802]
56. Friedman MJ, Resick PA, Bryant RA, Brewin CR. Considering PTSD for DSM-5. Depress Anxiety. 2011; 28:750–69. [PubMed: 21910184]
57. Brewin CR, Lanius RA, Novac A, Schnyder U, Galea S. Reformulating PTSD for DSM-V: life after criterion A. J Trauma Stress. 2009; 22:366–73. [PubMed: 19743480]
58. Shalev, AY. Psycho-biological perspectives on early reactions to traumatic events. In: Orner, R.; Schnyder, U., editors. Eur Soc Trauma Stress Stud. Oxford University Press; Oxford: 2003. p. 57-64.Reconstructing early intervention after trauma: innovations in the care of survivors
59. Brown VM, Labar KS, Haswell CC, et al. Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. Neuropsychopharmacology. 2014; 39:361–9.
60. Hayes JP, Vanelzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. Front Integr Neurosci. 2012; 6:89. [PubMed: 23087624]
61. Stam R. PTSD and stress sensitisation: a tale of brain and body. Part 1: human studies. Neurosci Biobehav Rev. 2007; 31:530–57. [PubMed: 17270271]
62. Yehuda R. Psychoneuroendocrinology of post-traumatic stress disorder. Psychiatr Clin North Am. 1998; 21:359–79. [PubMed: 9670231]
63. Kellner M, Yehuda R. Do panic disorder and posttraumatic stress disorder share a common psychoneuroendocrinology? Psychoneuroendocrinology. 1999; 24:485–504. [PubMed: 10378237]
64. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci. 2004; 1032:1–7. [PubMed: 15677391]
65. McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. Neuron. 2013; 79:16–29. [PubMed: 23849196]
66. Brewin CR, Gregory JD, Lipton M, Burgess N. Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. Psychol Rev. 2010; 117:210. [PubMed: 20063969]
67. Koolhaas JM, Korte SM, De Boer SF, et al. Coping styles in animals: current status in behavior and stress-physiology. Neurosci Biobehav Rev. 1999; 23:925–35. [PubMed: 10580307]
68. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995; 52:1048–60. [PubMed: 7492257]
69. Norris, FH.; Slone, LB. The epidemiology of trauma and PTSD. In: Friedman, MJ.; Keane, TM.; Resick, PA., editors. Handbook of PTSD: science and practice. Guilford; New York: 2007. p. 78-98.
70. Morgan L, Scourfield J, Williams D, Jasper A, Lewis G. The Aberfan disaster: 33-year follow-up of survivors. Br J Psychiatry. 2003; 182:532–6. [PubMed: 12777345]
71. Neria Y, Nandi A, Galea S. Post-traumatic stress disorder following disasters: a systematic review. Psychol Med. 2008; 38:467–80. [PubMed: 17803838]

72. Whalley MG, Brewin CR. Mental health following terrorist attacks. Br J Psychiatry. 2007; 190:94–6. [PubMed: 17267923]
73. Chard KM, Ricksecker EG, Healy ET, Karlin BE, Resick PA. Dissemination and experience with cognitive processing therapy. J Rehabil Res Dev. 2012; 49:667–78. [PubMed: 23015578]
74. Rauch SA, Eftekhari A, Ruzek JI. Review of exposure therapy: a gold standard for PTSD treatment. J Rehabil Res Dev. 2012; 49:679–87. [PubMed: 23015579]
75. Taft CT, Creech SK, Kachadourian L. Assessment and treatment of posttraumatic anger and aggression: a review. J Rehabil Res Dev. 2012; 49:777–88. [PubMed: 23015585]
76. Ulmer CS, Edinger JD, Calhoun PS. A multi-component cognitive-behavioral intervention for sleep disturbance in veterans with PTSD: a pilot study. J Clin Sleep Med. 2011; 7:57–68. [PubMed: 21344046]
77. Engel GL, Schmale AH. Conservation-withdrawal: a primary regulatory process for organismic homeostasis. Ciba Found Symp. 1972; 8:57–75. [PubMed: 4144967]
78. Cannon, WB. Bodily changes in pain, hunger, fear and rage: an account of recent researches into the function of emotional excitement. D. Appleton; New York; London: 1915.
79. Hartl TL, Rosen C, Drescher K, Lee TT, Gusman F. Predicting high-risk behaviors in veterans with posttraumatic stress disorder. J Nerv Ment Dis. 2005; 193:464–72. [PubMed: 15985841]
80. Strom TQ, Leskela J, James LM, et al. An exploratory examination of risk-taking behavior and PTSD symptom severity in a veteran sample. Mil Med. 2012; 177:390–6. [PubMed: 22594128]
81. Miller MW, Fogler JM, Wolf EJ, Kaloupek DG, Keane TM. The internalizing and externalizing structure of psychiatric comorbidity in combat veterans. J Trauma Stress. 2008; 21:58–65. [PubMed: 18302181]
82. Beckham JC, Calhoun PS, Glenn DM, Barefoot JC. Posttraumatic stress disorder, hostility, and health in women: a review of current research. Ann Behav Med. 2002; 24:219–28. [PubMed: 12173679]
83. Flood AM, Boyle SH, Calhoun PS, et al. Prospective study of externalizing and internalizing subtypes of posttraumatic stress disorder and their relationship to mortality among Vietnam veterans. Compr Psychiatry. 2010; 51:236–42. [PubMed: 20399332]
84. Taft C, Street AE, Marshall AD, Dowdall DJ, Riggs DS. Post-traumatic stress disorder, anger, and partner abuse among Vietnam combat veterans. J Fam Psychol. 2007; 21:270–7. [PubMed: 17605549]
85. Vrana SR, Hughes JW, Dennis MF, Calhoun PS, Beckham JC. Effects of posttraumatic stress disorder status and covert hostility on cardiovascular responses to relived anger in women with and without PTSD. Biol Psychol. 2009; 82:274–80. [PubMed: 19716397]
86. Ursano RJ, Li H, Zhang L, et al. Models of PTSD and traumatic stress: the importance of research “from bedside to bench to bedside. Prog Brain Res. 2008; 167:203–15. [PubMed: 18037016]
87. Walker AJ, Burnett SA, Hasebe K, et al. Chronic adrenocorticotrophic hormone treatment alters tricyclic antidepressant efficacy and prefrontal monoamine tissue levels. Behav Brain Res. 2013; 242:76–83. [PubMed: 23276607]
88. Van Voorhees EE, Dedert EA, Calhoun PS, Brancu M, Runnals J, Beckham JC. Childhood trauma exposure in Iraq and Afghanistan war era veterans: implications for posttraumatic stress disorder symptoms and adult functional social support. Child Abuse Negl. 2012; 36:423–32. [PubMed: 22633055]
89. Yehuda R, Flory JD, Pratchett LC, Buxbaum J, Ising M, Holsboer F. Putative biological mechanisms for the association between early life adversity and the subsequent development of PTSD. Psychopharmacology (Berl). 2010; 212:405–17. [PubMed: 20706708]
90. Grabe HJ, Spitzer C, Schwahn C, et al. Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder in the general population. Am J Psychiatry. 2009; 166:926–33. [PubMed: 19487392]
91. Koenen KC, Amstadter AB, Nugent NR. Gene-environment interaction in posttraumatic stress disorder: an update. J Trauma Stress. 2009; 22:416–26. [PubMed: 19743189]
92. Kolassa IT, Kolassa S, Ertl V, Papassotiropoulos A, De Quervain DJ. The risk of posttraumatic stress disorder after trauma depends on traumatic load and the catechol-O-methyltransferase Val(158)Met polymorphism. Biol Psychiatry. 2010; 67:304–8. [PubMed: 19944409]

93. Xie P, Kranzler HR, Poling J, et al. Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. Neuropsychopharmacology. 2010; 35:1684–92. [PubMed: 20393453]

94. Peri T, Ben-Shakhar G, Orr SP, Shalev AY. Psychophysiologic assessment of aversive conditioning in posttraumatic stress disorder. Biol Psychiatry. 2000; 47:512–9. [PubMed: 10715357]

95. Blechert J, Michael T, Vriends N, Margraf J, Wilhelm FH. Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experiential, and behavioural responses. Behav Res Ther. 2007; 45:2019–33. [PubMed: 17442266]

96. Marshall RD, Schneier FR, Fallon BA, et al. An open trial of paroxetine in patients with noncombat-related, chronic posttraumatic stress disorder. J Clin Psychopharmacol. 1998; 18:10–8. [PubMed: 9472837]

97. Yehuda R, LeDoux J. Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron. 2007; 56:19–32. [PubMed: 17920012]

98. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of post-traumatic stress disorder and extinction: human neuroimaging research—past, present, and future. Biol Psychiatry. 2006; 60:376–82. [PubMed: 16919525]

99. Diamond DM, Campbell AM, Park CR, Halonen J, Zoladz PR. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson law. Neural Plast. 2007; 2007:60803. [PubMed: 17641736]

100. Sigurdsson T, Doyere V, Cain CK, LeDoux JE. Long-term potentiation in the amygdala: a cellular mechanism of fear learning and memory. Neuropharmacology. 2007; 52:215–27. [PubMed: 16919687]

101. Sah P, Westbrook RF, Luthi A. Fear conditioning and long-term potentiation in the amygdala: what really is the connection? Ann N Y Acad Sci. 2008; 1129:88–95. [PubMed: 18591471]

102. Buckley TC, Blanchard EB, Neill WT. Information processing and PTSD: a review of the empirical literature. Clin Psychol Rev. 2000; 20:1041–65. [PubMed: 11098399]

103. Dickie EW, Brunet A, Akerib V, Armony JL. An fMRI investigation of memory encoding in PTSD: influence of symptom severity. Neuropsychologia. 2008; 46:1522–31. [PubMed: 18321537]

104. Francati V, Vermetten E, Bremner JD. Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. Depress Anxiety. 2007; 24:202–18. [PubMed: 16960853]

105. Jatzko A, Schmitt A, Demirakca T, Weimer E, Braus DF. Disturbance in the neural circuitry underlying positive emotional processing in post-traumatic stress disorder (PTSD). An fMRI study. Eur Arch Psychiatry Clin Neurosci. 2006; 256:112–4. [PubMed: 16143899]

106. Zovkic IB, Sweatt JD. Epigenetic mechanisms in learned fear: implications for PTSD. Neuropsychopharmacology. 2013; 38:77–93. [PubMed: 22692566]

107. Yehuda R, Flory JD, Southwick S, Charney DS. Developing an agenda for translational studies of resilience and vulnerability following trauma exposure. Ann N Y Acad Sci. 2006; 1071:379–96. [PubMed: 16891584]

108. Yehuda R. Risk and resilience in posttraumatic stress disorder. J Clin Psychiatry. 2004; 65(suppl 1):29–36. [PubMed: 14728094]

109. Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry. 2004; 161:195–216. [PubMed: 14754765]

110. Simon SL, Douglas P, Baltuch GH, Jaggi JL. Error analysis of MRI and leksell stereotactic frame target localization in deep brain stimulation surgery. Stereotact Funct Neurosurg. 2005; 83:1–5. [PubMed: 15695925]

111. Resick PA, Galovski TE, O'Brien Uhlmansiek M, Scher CD, Clum GA, Young-Xu Y. A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence. J Consult Clin Psychol. 2008; 76:243–58. [PubMed: 18377121]

112. Bryant RA, Felmingham K, Whitford TJ, et al. Rostral anterior cingulate volume predicts treatment response to cognitive-behavioural therapy for posttraumatic stress disorder. J Psychiatry Neurosci. 2008; 33:142–6. [PubMed: 18330460]
113. Olff M, de Vries GJ, Guzelcan Y, Assies J, Gersons BP. Changes in cortisol and DHEA plasma levels after psychotherapy for PTSD. Psychoneuroendocrinology. 2007; 32:619–26. [PubMed: 17570603]
114. Olff M, Langeland W, Gersons BP. Effects of appraisal and coping on the neuroendocrine response to extreme stress. Neurosci Biobehav Rev. 2005; 29:457–67. [PubMed: 15820550]
115. Holbrook TL, Galarneau MR, Dye JL, Quinn K, Dougherty AL. Morphine use after combat injury in Iraq and post-traumatic stress disorder. N Engl J Med. 2010; 362:110–7. [PubMed: 20071700]
116. Hyman SE, Nestler EJ. Initiation and adaptation: a paradigm for understanding psychotropic drug action. Am J Psychiatry. 1996; 153:151–62. [PubMed: 8561194]
117. Davidson JR. Pharmacotherapy of posttraumatic stress disorder: treatment options, long-term follow-up, and predictors of outcome. J Clin Psychiatry. 2000; 61(suppl 5):52–6. discussion 57–9. [PubMed: 10761679]
118. Davidson JR, Connor KM. Management of posttraumatic stress disorder: diagnostic and therapeutic issues. J Clin Psychiat. 1999; 60:33–8.
119. Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. Biol Psychiatry. 2006; 60:369–75. [PubMed: 16919524]
120. Davis M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. Am Psychol. 2006; 61:741–56. [PubMed: 17115806]
121. Ledgerwood L, Richardson R, Cranney J. D-cycloserine facilitates extinction of learned fear: effects on reacquisition and generalized extinction. Biol Psychiatry. 2005; 57:841–7. [PubMed: 15820704]
122. Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci. 2002; 22:2343–51. [PubMed: 11896173]
123. Naert G, Maurice T, Tapia-Arancibia L, Givalois L. Neuroactive steroids modulate HPA axis activity and cerebral brain-derived neurotrophic factor (BDNF) protein levels in adult male rats. Psychoneuroendocrinology. 2007; 32:1062–78. [PubMed: 17928160]
124. Diamond DM, Fleshner M, Rose GM. The enhancement of hippocampal primed burst potentiation by dehydroepiandrosterone sulfate (DHEAS) is blocked by psychological stress. Stress. 1999; 3:107–21. [PubMed: 10938573]
125. Alhaj HA, Massey AE, McAllister-Williams RH. Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: a double-blind, placebo-controlled study. Psychopharmacology. 2006; 188:541–51. [PubMed: 16231168]
126. Holmes A, Heilig M, Rupniak NM, Steckler T, Griebel G. Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. Trends Pharmacol Sci. 2003; 24:580–8. [PubMed: 14607081]