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Biological Studies of Posttraumatic Stress Disorder

Roger K. Pitman[a,b], **Ann M. Rasmusson**[c], **Karestan C. Koenen**[d], **Lisa M. Shin**[a,e], **Scott P. Orr**[a,b], **Mark W. Gilbertson**[b,f,g], **Mohammed R. Milad**[a,b], and **Israel Liberzon**[h]

[a]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, 02114

[b]Department of Psychiatry, Harvard Medical School, Boston, MA, 02115

[c]VA Boston Healthcare System and National Center for PTSD, Women's Health Science Division, Boston, MA 02130; Department of Psychiatry, Boston University School of Medicine, Boston, MA, 02118

[d]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY

[e]Department of Psychology, Tufts University, Boston, MA, 02155

[f]Research Service, VA Medical Center, Manchester, NH, 03104

[g]Department of Psychiatry, Brigham and Women's Hospital, Boston, MA, 02115

[h]Psychiatry Service, VA Medical Center, Ann Arbor, MI and Department of Psychiatry, University of Michigan, Ann Arbor, MI 48103

Preface

Posttraumatic stress disorder (PTSD) is the only major mental disorder for which a cause is considered to be known, viz., an event that involves threat to the physical integrity of oneself or others and induces a response of intense fear, helplessness, or horror. Although PTSD is still largely regarded as a psychological phenomenon, over the past three decades the growth of the biological PTSD literature has been explosive, and thousands of references now exist. Ultimately, the impact of an environmental event, such as a psychological trauma, must be understood at organic, cellular, and molecular levels. The present review attempts to present the current state of this understanding, based upon psychophysiological, structural and functional neuroimaging, endocrinological, genetic, and molecular biological studies in humans and in animal models.

Introduction

A day scarcely passes that one does not see a mention of PTSD in the media. However, this has not always been the case. In American history, posttraumatic psychopathology has been recognized under various names following wars: soldier's heart from the Civil War, shell

Correspondence to R.K.P., roger_pitman@hms.harvard.edu.

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shock from WW I, combat fatigue from WW II, delayed stress from the Vietnam War. However, between these wars, the condition was all but forgotten. Finally, spearheaded by Vietnam veterans and their advocates, PTSD made its way into the American psychiatric nomenclature as a formal diagnostic entity in 1980.[1] Because of the political impetus behind its introduction, and the fact that PTSD is largely diagnosed on the basis of patients' reports (which may be influenced by secondary motives), the new disorder was initially met with suspicion. Discoveries of biological markers for PTSD, however, have gone a long way to counteracting this skepticism and bolstering the now widespread acceptance of the disorder.

As currently understood, the PTSD syndrome is a blend of intrusive memories of the traumatic event, avoidance of reminders of it, emotional numbing, and hyperarousal.[2] Initially, PTSD was conceptualized nearly entirely in psychological terms, and the PTSD biological literature consisted only of sparse psychophysiological observations.[3] Although purely psychological research into PTSD is important, it is enhanced by an understanding of the neurobiological mechanisms underlying the disorder. The purpose of this article is to review the current state of biological research into PTSD. Such a review is timely and important if the popular understanding of PTSD is not to outstrip its scientific basis, and if PTSD is to be grounded in the field of medicine. This article will also review animal models, which have stimulated hypotheses about PTSD in humans and which point the way to future developments in the field. The ultimate goals of biological research are to identify risk factors, elucidate the mechanisms involved in the development of PTSD, establish biomarkers, and generate novel preventive and therapeutic interventions aimed at alleviating the substantial suffering and dysfunction this disorder imposes.

It is tempting to assume that because PTSD by definition is caused by a psychologically traumatic environmental event, any biological abnormality found to accompany PTSD must also have been traumatically induced. However, it is also possible that an abnormality pre-dated the traumatic event and came to be associated with PTSD because it increased the risk of this disorder's developing upon the traumatic exposure — a psychiatric epitome of gene x environment interaction. Readers should keep this in mind as they digest the rich material that follows.

Psychophysiological Studies

Measures of heart rate, skin conductance, facial electromyogram (EMG), and cortical electroencephalographic event-related potentials (ERPs) have been extensively applied to the study of PTSD for more than 25 years.[4, 5] A robust literature addresses the heightened emotional reactivity to trauma-related cues, exaggerated startle, impaired extinction, and increased sensitivity to stimulation observed in people with PTSD, as well as their use in predicting PTSD risk and assessing treatment outcome. A meta-analysis of studies comparing resting psychophysiological levels, trauma-related cue reactivity, and exaggerated startle responses between groups of individuals diagnosed with vs. individuals without PTSD attests to the maturation of this field.[6]

Psychophysiological markers for PTSD

The majority of psychophysiological research on PTSD has been performed in cross-sectional studies that compared individuals with PTSD to trauma-exposed or -unexposed individuals without the disorder. One of the earliest and most replicated PTSD findings is that of heightened autonomic (heart rate, skin conductance) and facial EMG reactivity to external, trauma-related stimuli such as combat sounds and film clips [7], as well as to internal, mental imagery of the traumatic event [8]. Reactivity to trauma-related cues correlates with severity of the disorder.[9, 10] In addition to research focused on reactions to trauma reminders, a substantial body of work has examined exaggerated startle, as measured by eyeblink EMG, to sudden loud sounds.[4, 6] Although there is compelling evidence for increased startle in PTSD, it is unclear whether this represents a pre-existing trait, increased sensitivity to contextual threat, or sensitization of the nervous system. Patients with PTSD also show heightened heart rate responses to startling stimuli, which appear to be acquired.[11, 12] Reduced P3b ERPs to infrequent target stimuli, and larger skin conductance responses to novel stimuli[4] could reflect the PTSD symptoms of difficulty concentrating and hypervigilance respectively.

Psychophysiological assessments of treatment outcome provide more objective information than a patient's report and may be a more sensitive measure of progress. For example, heart rate, skin conductance and facial EMG reactivity during personal traumatic imagery was lower in a group that had received post-trauma propranolol, a β-adrenergic antagonist that has been found in animal and human studies to attenuate the consolidation of stressful memories, compared to placebo, even though groups did not differ in subjective PTSD symptom severity.[13] A recent study that examined psychophysiological responses before and after cognitive-behavioral therapy for PTSD found that treatment responders showed a significant reduction in eye-blink EMG, heart rate, and skin conductance responses to loud tones, whereas treatment non-responders did not.[14] Understanding discordances between psychophysiological and subjective measures of treatment outcome will require further research. Pre-treatment psychophysiological assessments might be examined for their usefulness in guiding treatment selection. For example, individuals who show heightened psychophysiological reactivity to trauma-related cues might benefit from exposure-based therapies that aim to desensitize the emotional arousal associated with traumatic memories.

Conditioning and sensitization

Symptoms related to re-experiencing of the traumatic event are a defining feature of PTSD and may be conceptualized within a fear-conditioning framework. In contrast, anxiety and hyperarousal in the absence of trauma-related cues may reflect a general sensitization of the nervous system. Alterations in fear conditioning, extinction learning, extinction retention, and sensitization are likely involved in the development and/or maintenance of PTSD.[15] Recent findings suggest that PTSD is associated with deficits in the ability to extinguish or maintain extinction learning of an acquired fear response, as measured by skin conductance[16] and/or fear-potentiated startle.[17] In addition, PTSD has been found to be associated with extinction failure of a second-order conditioned skin conductance response, after this response was established by pairing a neutral stimulus with a trauma-specific stimulus.[18] A recent study in identical twins discordant for combat exposure (i.e., one

member of each pair was a Vietnam combat veteran and the other had no combat exposure) found that PTSD twins showed poorer extinction retention of a conditioned skin conductance response; this appeared to be an acquired, rather than pre-existing, PTSD feature, because it was not shared by the PTSD veterans' twins.[19] Impaired extinction or extinction retention would likely interfere with recovery from PTSD symptoms that are based upon conditioned fear.

Evidence for increased nervous system sensitization comes from findings of larger heart rate responses to loud-tone stimuli and larger skin conductance orienting responses,[4] as well as increased intensity dependence of the P2 ERP response.[20] In a study that involved both startle and conditioned fear assessments, individuals with PTSD were found to show increased eyeblink EMG startle responses during testing that followed a previous session involving aversive fear conditioning.[21] A possible explanation for this finding is that administration of the shock unconditioned stimulus several days earlier sensitized individuals with PTSD such that they showed a subsequent increase in baseline startle reactivity. Findings from identical twin[11, 20] and longitudinal[12, 22] studies strongly suggest that the heightened heart rate reactivity to loud tones observed in individuals with PTSD is an acquired feature of the disorder; however, it may not be specific to PTSD.[23]

Psychophysiological risk factors for PTSD

The possibility that some measures of psychophysiological reactivity represent pre-existing vulnerability traits has stimulated research examining potential predictors of risk for developing PTSD. A prospective study of firefighter trainees found that increased skin conductance and eyeblink EMG responses to a series of loud tones[24] and slower extinction of fear-conditioned corrugator EMG responses[25] predicted severity of posttraumatic stress symptoms following subsequent exposure to a traumatic event. Another prospective study also implicated slower extinction of fear-conditioned corrugator EMG responses in predicting posttraumatic stress symptoms.[26] Increased physiological reactivity to trauma-related cues soon after exposure to a traumatic event is predictive of subsequent severity and/or persistence of PTSD symptoms.[9, 27, 28] For example, women who showed an increased heart rate response while engaging in personal traumatic imagery two weeks after trauma exposure had higher symptom severity and were more likely than female nonresponders and men to develop PTSD six months later.[10] Whether resting heart rate obtained immediately post-trauma predicts the subsequent development of PTSD is currently unclear.[27, 29]

Sleep

Although sleep disturbance is a PTSD diagnostic criterion, support for it in the polysomnography laboratory has not been as straightforward as might have been expected. However, more Stage 1 sleep and less slow wave sleep, indicative of shallower sleeping, as well as greater rapid-eye-movement density, have been demonstrated in PTSD subjects.[30]

Structural Neuroimaging Studies

Because of findings in experimental animals suggesting that chronic stress damages the hippocampus,[31] this brain structure was a logical starting place for structural magnetic resonance imaging (sMRI) studies in PTSD patients. In fact, the most replicated structural abnormality found in PTSD is lower volume of the hippocampus. Lower volume of ventromedial prefrontal cortex (vmPFC), another structure damaged by chronic stress in animals, has also been reported. However, just because these structures can be damaged by chronic stress in animals does not necessarily mean that this is the origin of their diminutions in PTSD; they may also represent premorbid risk factors. To the extent that diminished volume may underlie diminished function, these findings whatever their origin are consistent with a model of PTSD that posits a reduced cortical capacity to inhibit fear and other negative emotional responses. In this view, hippocampus may fail to utilize contextual cues in the environment to signal safety, and vmPFC may fail to adaptively maintain extinction of conditioned emotional responses once traumatic learning is no longer relevant.

Hippocampus

Pioneering sMRI studies found significantly smaller hippocampi in subjects with PTSD compared to trauma- and non-trauma-exposed subjects without PTSD.[32–34] Since then, a large literature has emerged, the majority of which, along with meta-analyses,[35] has provided empirical support for lower hippocampal volume in PTSD. A recent study that utilized high-resolution sMRI found the most substantial hippocampal volumetric diminution in the CA3 and dentate gyrus subfields.[36] Recent meta-analyses have concluded that smaller hippocampal volume in PTSD is bilateral,[37, 38] and they have not provided strong evidence for a gender effect.[39] The severity of PTSD symptoms may be an important factor in determining effect sizes of PTSD-related hippocampal differences;[38, 40] studies of adults with PTSD that failed to replicate the finding of smaller hippocampal volumes generally employed subjects with less severe or less chronic illness.[41, 42] Studies conducted in children with PTSD have often also failed to reveal smaller hippocampi, suggesting a role for neuromaturational factors in the development of hippocampal diminution.[43] Numerous investigations have attempted to control for the impact of confounding comorbid conditions; most have concluded that hippocampal volume differences in PTSD are not accounted for by histories of alcohol abuse or depression.[40, 44, 45] Moreover, studies using magnetic resonance spectroscopic imaging (MRSI), which quantifies N-acetylaspartate (NAA) as a marker of neuronal density, have also consistently found neuronal reduction in the hippocampus of patients with PTSD.[46, 47]

Controversy exists as to whether smaller hippocampal size in PTSD is a result of trauma exposure or rather represents a risk factor for PTSD that is of genetic and/or shared environmental origin. A study of identical twins discordant for combat exposure in Vietnam (Figure 1) found that the (high-risk) combat-unexposed, non-PTSD co-twins of combat veterans with PTSD had hippocampal volumes that were comparable that of their PTSD twins but lower than the hippocampal volume of combat veterans without PTSD and their (low-risk) unexposed co-twins.[40] This finding suggests that hippocampal volume serves as a

pre-trauma risk factor for PTSD. Cavum septum pellucidum (so-called “fifth ventricle”), a neurodevelopmental abnormality in part related to hippocampal maldevelopment, is found more frequently in persons with PTSD.[48] Not all neuroimaging evidence is consistent with a risk factor interpretation of hippocampal diminution.[49] Pharmacological treatment of PTSD with the selective serotonin reuptake inhibitor (SSRI) paroxetine has been reported to increase hippocampal volume,[50] suggesting that it could be an acquired, reversible abnormality; however, even pre-existing risk factors may be malleable. In addition, although PTSD subjects were found to show diminished hippocampal volume relative to trauma-exposed subjects without PTSD, this difference was smaller than that observed in the comparison between PTSD subjects and non-trauma-exposed control subjects.[37, 38] Similarly, a recent meta-analysis revealed that non-PTSD, trauma-exposed subjects have smaller hippocampi than non-PTSD, non-trauma-exposed subjects.[51] These findings suggest that trauma may reduce hippocampal volume regardless of the development of subsequent PTSD, or that reduced hippocampal volume may also represent a risk factor for trauma exposure. However, trauma-exposed subjects who are not categorically classified as having PTSD may still have some PTSD symptoms, and this could also account for their lower hippocampal volume. In short, the debate between risk-factor vs. acquired origin of hippocampal diminution in PTSD has not been resolved; it is quite possible that both play a role.

Prefrontal cortex

The PTSD neuroimaging literature also documents volume reductions in prefrontal brain regions. Structural MRI studies have found reduced volume in individuals with PTSD in both the rostral (or pregenual) vmPFC[52] and in the dorsal anterior cingulate cortex (dACC).[53] Youth with more PTSD symptoms (but not full-blown PTSD) were found to have less total brain tissue and lower total cerebral gray matter volumes, with specific diminution in left ventral inferior prefrontal regions.[54] In contrast to the findings in hippocampus, a sMRI study of combat-discordant twins that employed voxel-based morphometry suggested that reduction in ACC volume represents an acquired feature of PTSD rather than a pre-existing vulnerability.[52] MRSI studies have also reported diminished neuronal density in the ACC of PTSD patients.[46, 47] Furthermore, studies employing diffusion tensor imaging, which provides a measure of the integrity of white matter tracts, have shown aberrant white matter integrity in the cingulum bundle, a major neuronal tract that connects the ACC with the amygdala,[55] which may be a basis for impaired inhibitory interaction between these two regions, as further discussed below.

A recent study capitalized on a sample of subject who had undergone sMRI prior to an earthquake; 42 subjects returned for re-scanning afterwards. Although none of these developed full-blown PTSD, higher gray matter volume in the right ventral ACC before the earthquake were negatively associated with PTSD symptoms, i.e., conferred resilience. Subjects with more PTSD symptoms showed a greater decrease in gray matter volume in the left orbitofrontal cortex from before to after the earthquake, suggestive of acquired diminution in this brain region.[56]

Functional Neuroimaging Studies

Functional neuroimaging studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) have shown altered activity in individuals with PTSD in the amygdala, vmPFC and dACC, as well as in the hippocampus and insular cortex (Figure 2.) During the last two decades, rodent studies have outlined the neural networks involved in fear learning and its extinction. These have shown that the amygdala is a key structure for both the recognition of dangerous stimuli and the coordination of the fear response. Its activity is modulated by higher cortical influences — in rodents mainly by the infralimbic (IL) and prelimbic (PL) cortices. Evidence from pharmacological, electrophysiological, stimulation, and molecular approaches in animals points to PL as a brain region facilitating the expression of conditioned fear, whereas IL is critical for the consolidation and expression of fear extinction memory (i.e. extinction retention), resulting in lowered fear.[57–59] Fear conditioning and extinction paradigms in humans have identified functionally homologous brain regions in the human brain, with the dACC and vmPFC being putative human homologues of PL and IL, respectively. [59]

Amygdala

The amygdala plays a crucial role in the detection of threat, fear learning, fear expression, and heightening memory for emotional events. Functional neuroimaging studies have reported exaggerated amygdala activation in response to trauma-related stimuli (e.g., narratives, photographs, odors, sounds)[60] as well as generic stimuli (e.g., fearful facial expressions, emotional photographs, tones) in patients with PTSD compared to control subjects.[61] PTSD patients show greater amygdala activation during the acquisition of conditioned fear.[62]

Ventral medial prefrontal cortex

Areas in the vmPFC (including the rostral ACC), subcallosal cortex, and medial frontal gyri show decreased activation in PTSD subjects during tasks that employ either trauma-related[63] or trauma-unrelated[64, 65] stimuli. Ventromedial PFC activation during the recollection of personal traumatic events negatively correlates with PTSD symptom severity.[66] Furthermore, degree of symptomatic improvement after cognitive behavioral therapy has been positively correlated with increase in rostral ACC activation.[67] In PTSD subjects, failure to recall extinction learning is accompanied by lower vmPFC activation[68] (Figure 3). PTSD subjects also show deficient vmPFC activation during emotional cognitive interference tasks.[69]

Dorsal anterior cingulate cortex

The dACC subserves response selection, error detection, pain perception, and fear learning and expression. Activation in the dACC is increased in PTSD vs. control groups during fear conditioning,[72] reduced recall of extinction learning[68] (Figure 3), and auditory oddball tasks[73, 74] (which measure responses to infrequent or novel stimuli). Such functional abnormalities are positively associated with PTSD symptom severity.[75] Individuals with PTSD as well as their identical (high-risk) co-twins showed greater resting dACC glucose metabolism in a PET study,[76] and greater dACC activation during a non-emotional cognitive

interference task in an fMRI study,[77] compared to trauma-exposed individuals without PTSD and their identical (low-risk) co-twins. These latter findings suggest that elevated dACC activity is a biomarker reflecting familial risk for developing PTSD after trauma.

Hippocampus

The hippocampus is involved in the encoding and recognition of episodic memories and environmental cues (e.g., contexts), including those that are present during fear learning and extinction. Functional neuroimaging findings in the hippocampus in patients with PTSD have been mixed, with some studies reporting less[78] and others reporting more[79] activation than in comparison groups. These different findings could be due to differences in the types of paradigms and/or analyses conducted across studies. In PTSD subjects, failure to recall extinction learning is associated with lower hippocampal activation.[68] Whether potential functional abnormalities in the hippocampus in PTSD are linked to smaller hippocampal volume has yet to be determined.

Insular cortex

The insular cortex is involved in monitoring internal bodily states. Individuals with PTSD exhibit greater insular cortex activation, possibly reflecting heightened detection of bodily arousal, during the anticipation of aversive images and in response to fearful facial expressions, painful stimuli, and traumatic memories.[80–82] Insular cortex activation appears to be positively correlated with PTSD symptom severity. [80] Elevated insular cortex activation has also been observed in other anxiety disorders[61] and therefore is not specific to PTSD.

Neurocircuitry of PTSD

A recent meta-analysis of 79 functional PTSD neuroimaging studies found that mid- and dorsal anterior cingulate cortex and bilateral amygdala were the most hyperactivated regions, whereas vmPFC and inferior frontal gyrus were the most hypoactivated regions. Decreased vmPFC activity was associated with increased amygdala activity.[83] Neurocircuitry models of PTSD[84, 85] posit that vmPFC fails to inhibit the amygdala, leading to attentional bias toward threat, increased fear responses, impaired extinction of traumatic memories and its retention, and deficits in emotion regulation. The later neurodevelopment of prefrontal cortex relative to amygdala may help to explain the increased risk for PTSD associated with younger age in combat veterans.[86] In contrast to vmPFC, dACC appears to promote fear expression. Hippocampal dysfunction may be associated with memory impairments for neutral material and deficits in recognizing safe contexts. A hyperactive insular cortex, which may reflect heightened interoceptive awareness, may confer proneness to anxiety.

Receptor imaging

A functional imaging technique that has been less utilized in PTSD is the use of selective, exogenously administered radioligands to assess the binding and distribution of various neurotransmitter receptors in the brain via PET. One such study found a reduction in $GABA_A$ binding throughout the cortex, hippocampus, and thalamus in veterans with compared to without PTSD,[87] suggestive of globally diminished inhibitory brain function.

The fact that the changes were so widespread prohibits relating this finding to any specific PTSD neurocircuitry. Another study of non-combat-related PTSD found decreased serotonin (also known as 5-hydroxytryptamine or 5-HT) transporter binding in the amygdala,[88] which the authors suggested is consistent with findings of amygdala hyperactivity upon exposure to trauma- or fear-related stimuli in PTSD reviewed above. However, the absence of a trauma-exposed, non-PTSD control group limited inferences regarding the specificity of this finding to PTSD. Indeed, in two other exogenous ligand studies — one that found reductions in μ-opioid receptor binding potential in various limbic and paralimbic brain regions,[89] and another that found reduced serotonin-1B receptor expression in caudate, amygdala, and ACC[90] — abnormalities occurred both in PTSD subjects and in trauma-exposed, non-PTSD subjects, raising the possibility that they reflect the effect of trauma exposure on the brain rather than specific aspects of PTSD pathophysiology. Finally, interpretation of results of exogenous ligand studies is often obscured by incomplete knowledge of the underlying microanatomy (e.g., neuron is an excitatory projection neuron vs. an inhibitory interneuron; receptor is a post-synaptic receptor vs. an autoreceptor vs. a heteroceptor) and physiology (e.g., binding is lower because receptor number/affinity is reduced vs. binding is lower because receptor is already occupied with endogenous ligand; down (or up) -regulation is primary vs. compensatory). Variations in these details can have different, or even opposite, implications.

Neuroendocrinological Studies

Abnormalities in catecholamines and cortisol were among the first findings in individuals with PTSD. Subsequent studies have revealed changes in many other hormonal and neuroregulatory factors among populations of patients with PTSD as well.

Catecholamines

Numerous studies have provided compelling evidence for the presence of sympathetic system hyperreactivity in PTSD.[91] It has been suggested that an excessively strong adrenergic response to the traumatic event may mediate the formation of the durable traumatic memories that in part characterize the disorder.[92] Factors that may contribute to the increased release of norepinephrine (NE, also known as nordrenaline) in response to sympathetic system activation in PTSD include genetic or stress-induced decrements in neuropeptide Y (NPY),[93] which inhibits norepinephrine release, as well as a lower number[94] or affinity[95] of alpha-2-adrenergic autoreceptors. Noradrenergic hyperreactivity in patients with PTSD is associated with hyperarousal and re-experiencing symptoms, including trauma-related nightmares, flashbacks, intrusive memories, and emotional and physiological reactions to traumatic cues.[96–99] In addition, sympathetic system activation induced by administration of yohimbine (an alpha-2-adrenergic autoreceptor antagonist) decreased orbitofrontal and prefrontal cortical metabolic activity in subjects with PTSD, whereas it increased metabolic activity in these regions in control subjects.[100] Studies demonstrating the efficacy of prazosin, a post-synaptic alpha-1-noradrenergic receptor inhibitor, for the treatment of nightmares or daytime hyperarousal and re-experiencing symptoms of PTSD[101, 102] are consistent with these findings. Results of early studies suggested that

propranolol, a beta-adrenergic antagonist, had value in the acute prevention of PTSD,[13, 103] but these results have not been consistently replicated.[104, 105]

Indoleamines

The serotonin system also appears to be implicated in both the acute mediation of PTSD symptoms and the modulation of PTSD risk, as neuropharmacological, treatment, and genetic epidemiological studies have indicated. Administration of meta-chlorophenylpiperazine (mCPP), which acts as a 5-HT agonist, resulted in acute anxiety, panic attacks, and PTSD symptoms (including flashbacks) in a subgroup of male combat veterans with PTSD.[106] Interaction of mCPP with the 5-HT transporter[107] and multiple 5-HT receptor subtypes results in increased extracellular 5HT, as well as behavioral, psychological, and cognitive effects reminiscent of PTSD that are reversible by administration of mixed 5HT1c/5HT2 antagonists.[108] This suggests that a phasic increase in serotonin acting at post-synaptic 5HT1c/5HT2 receptors may induce PTSD symptom expression, which is supported by findings in the rodent single prolonged stress model of PTSD (see below). It also accords with the potential clinical benefits of chronic use of selective serotonin reuptake inhibitor (SSRI) drugs, which appear to result in 5HT2c receptor desensitization.[109] Further evidence for a role of the serotonin system in PTSD is provided by studies of the serotonin transporter gene (see below).

Neuropeptide Y

Research has demonstrated that NPY has protective effects during stress, likely mediated by the modulation of sympathetic responses[93] and antagonism of the anxiogenic effects of corticotropin-releasing hormone (CRH, also known as corticotropin releasing factor, or CRF).[110] Humans possessing NPY gene variants associated with increased gene expression showed lower levels of trait anxiety and less amygdala reactivity to emotionally provocative stimuli.[111] Similarly, male military personnel who exhibited higher plasma NPY levels during intense training stress showed less distress and dissociation and superior performance.[112] In contrast, lower cerebrospinal fluid (CSF) and resting plasma NPY levels and/or a blunted NPY response to sympathetic activation have been associated with more PTSD symptoms.[93, 113] In addition, a retrospective study in male veterans showed that lower plasma NPY levels were associated with less improvement in PTSD symptoms over time.[114] Efforts to develop pharmacological agents with clinically relevant, circumscribed NPY receptor-mediated effects have so far been unsuccessful. Manipulating the NPY system epigenetically may have greater promise as a strategy for the development of NPY-based therapeutics.

Corticotropin-releasing hormone

Corticotropin-releasing hormone has anxiogenic physiological and behavioral effects.[115] Increased CRH levels have been found in the CSF and/or blood of several different cohorts of patients with PTSD.[116, 117] However, a recent study found that CSF CRH levels decreased among PTSD patients watching a trauma-related video,[118] indicating that much is yet to be learned about the dynamics of CRH in the CNS during stress. Although recent clinical treatment trials of newly developed CRH antagonists have had to be aborted due to

hepatic toxicity, interest in pharmacological treatments for PTSD directed at the CRH system continues.

Cortisol

Early research produced the paradoxical finding of abnormally low cortisol levels in PTSD,[119] although this finding has not been consistently replicated in large studies. Nevertheless, sufficient evidence has accumulated to conclude that PTSD is not characterized by elevated tonic cortisol levels,[120] as might be expected in a state of chronic stress. In contrast, greater suppression of plasma cortisol after a low dose of dexamethasone, reported in some studies of PTSD,[121] is consistent with excessive shutting down of the hypothalamic-pituitary-adrenal cortical (HPA) axis due to enhanced sensitivity to negative feedback. Research has supported a higher number of glucocorticoid receptors (GRs) in lymphocytes of such PTSD subjects.[122] The foregoing findings are thought to represent, at least in part, a pre-trauma risk factor for the disorder.[123] A gene of current high interest related to PTSD risk, viz., *FKBP5,* is a co-chaperone of the glucocorticoid receptor, and polymorphisms in this gene have been related to GR supersensitivity and risk for PTSD.[124] An exception to the absence of elevated cortisol in PTSD patients may presented by persons, mainly women, with comorbid major depressive disorder.[108, 125, 126] Premenopausal women with PTSD also exhibited elevated phasic cortisol responses to CRH and adrenocorticotropin.[127]

The proposition that a cortisol deficit may play a role in the pathogenesis of PTSD has been supported by findings that administration of supplemental doses of cortisol to acutely ill medical patients reduces the PTSD outcome.[128] A recent preliminary study found that high-dose cortisol administration within hours of a traumatic event reduced the subsequent development of PTSD;[129] these encouraging therapeutic results call for testing in larger samples. Another study found beneficial effects of cortisol administered to patients who already had PTSD, which was attributed to the well-recognized inhibitory effect of cortisol on memory retrieval (in this case traumatic memory retrieval).[130] However, the possibility that cortisol could worsen PTSD in some cases, e.g., in patients without a deficit, should not be dismissed.

Despite the above, there still exists preclinical evidence suggesting the possibility that increased responses of this stress hormone could play a role in PTSD pathogenesis. Cortisol, like epinephrine, potentiates memory consolidation;[131] an acute cortisol response to the traumatic event could contribute to formation of a durable traumatic memory. Whether this possibility is relevant to PTSD remains to be directly tested. Baseline levels, phasic responses to stress, dosage (physiological vs. pharmacological), target of action, and the possibility of an inverted U-shaped, dose-response curve may all be important parameters to address in resolving the mixed cortisol findings in PTSD. Indeed, both too high and too low a level of glucocorticoids can interfere with frontal lobe-mediated working memory and long-term potentiation (LTP) in the hippocampus, in part through dose- and time-dependent effects on glutamatergic neurotransmission during learning.[132] On the other hand, glucocorticoids are critical to stress adaptation, and many genes with relevance to resilience,

including those encoding enzymes involved in the synthesis of allopregnanolone (see below) and NPY, contain glucocorticoid response elements.[133]

In future clinical research, it will be important to evaluate cortisol (and CRH) levels in relation to other neuroendocrinological factors that it regulates (e.g., allopregnanolone and NPY), or that confer protection from its potentially deleterious effects (e.g., dehydroepiandrosterone, or DHEA). It will also be important to take into account specific psychiatric comorbidities such as depression and nicotine[134] and other substance dependence; gender, reproductive and menstrual phase; and genetic polymorphism known to affect HPA axis regulation. (These considerations may apply to other endocrinological variables as well.) It also will be important to study central as well as peripheral cortisol regulation in relation to PTSD symptoms. Results of one study suggest that cortisol regulation in the CNS may differ from that in the periphery. Plasma cortisol levels were comparable between male veterans with PTSD and healthy comparison subjects, whereas CSF cortisol levels (arguably a better reflection of the level of brain exposure to cortisol) were higher in the veterans with PTSD and were correlated with CSF CRH levels[116] Recent work has also highlighted the possible importance of performing cortisol measurements by gas chromatography with mass spectrometry (GC-MS) because standard cortisol measurement by radioimmunoassay (RIA) does not discriminate between cortisol and its inactive metabolites. For example, a relationship between low total glucocorticoid species (measured simply as “cortisol” by RIA) and resistance to prolonged exposure therapy for PTSD was attributable to low levels of an inactive cortisol metabolite synthesized by 5-alpha reductase rather than to low levels of cortisol per se.[135]

Dehydroepiandrosterone

Adrenally derived dehydroepiandosterone (DHEA), the immediate precursor of the androgens, is secreted synchronously with cortisol and is also thought to be the source of its active sulfated metabolite, DHEAS.[136] In the brain, DHEA and DHEAS both antagonize $GABA_A$ receptors and facilitate NMDA receptor function, which in the amygdala is essential to both fear conditioning and fear extinction. In the hippocampus, DHEA reverses cortisol-induced impairments in LTP, protects against excitatory amino acid- and oxidative stress-induced neuronal damage, regulates programmed cell death, and promotes neurogenesis.[136] Such regional neuroprotective effects may be conferred by the anti-glucocorticoid properties of DHEA.[137, 138] Although clinical studies have demonstrated increases in adrenal DHEA release and increased plasma DHEA(S) levels in individuals with PTSD, they paradoxically have also shown negative relationships between these indices and general severity of PTSD and comorbid negative mood symptoms.[139–142] In addition, there are studies showing a positive relationship between DHEA(S) levels, or the ratio of DHEA to cortisol, and stress resilience in active duty military personnel[143, 144] and long-term recovery from PTSD in male veterans.[145] These findings could suggest that stress-associated increases in DHEA confer resilience, but such an interpretation may need qualification. For example, sleep disturbance in the context of PTSD has been associated with high DHEA responses to adrenal activation[141] and with high baseline blood DHEAS levels.[140] It may be that the balance between levels of this neuroprotective, excitatory neuroactive steroid and other neuroendocrine factors such as cortisol or the inhibitory

GABAergic neurosteroids such as allopregnanolone[146] (see below) is relevant. In humans, administration of DHEA reduces blood levels of cortisol and increases levels of allopregnanolone, testosterone and estrogen, effects that may be variously beneficial in PTSD.[147] Chronic DHEA administration has also been found to have antidepressant effects in multiple clinical trials,[148] but to date, no trials have assessed its therapeutic effects in PTSD.

Allopregnanolone and pregnanolone

CSF levels of the adrenal- and brain-derived neuroactive steroids allopregnanolone and its equipotent enantiomer pregnanolone (together termed ALLO) relate strongly and negatively to PTSD re-experiencing and depressive symptoms.[146] The ratio of allopregnanolone level to the level of its progesterone precursors is also low in the CSF and serum of patients with PTSD, suggesting that ALLO synthesis is deficient. ALLO is the most potent and selective positive endogenous modulator of GABA action at brain $GABA_A$ receptors. At extrasynaptic $GABA_A$ receptors, ALLO maintains a tonic inhibitory conductance that moderates gain in neuronal output during periods of increased excitation, such as occurs during stress.[149] Functionally, ALLO provides long-loop negative feedback at the HPA axis and confers anxiolytic, sedative, anesthetic, neuroprotective, and regenerative effects. Results of an animal study suggest that the effects of SSRIs (the current drug treatment of choice for PTSD) may be due to ALLO increases rather than to serotonin reuptake blockade.[150] It is possible that a deficiency in ALLO synthesis accounts for the substantial rate of SSRI treatment resistance in PTSD, but this remains to be determined.

Putative brain-state shift in PTSD

The development of PTSD may involve a shift in brain state from high-level processing of multimodal contextual and mnemonic stimuli (dependent on hippocampus and PFC-mediated working memory) (Figure 4A) — to more primitive amygdala-mediated formation of time-locked sensory associations and expression of the species-specific defense response (Figure 4B). Individual constitutional and personality (e.g., intelligence, neuroticism) differences may influence the stimulus threshold at which this shift occurs and thereby impact vulnerability. A number of neuroregulatory and neuroendocrinological factors discussed above may influence this ‘brain state shift;’ these factors vary across individuals due to genetic and epigenetic influences, as well as within individuals over time due to environmental influences such as intervening stressful events. These neuroendocrine factors probably interact in both counter-regulatory and synergistic manners that are likely to influence PTSD risk, symptom profiles, and severity, as well as capacity for recovery, thus providing potentially exploitable pharmacological and epigenetic targets for the development of new PTSD treatments.

Genetic Studies

Genetic influences account for 30%[159, 160] to 72%[161] of vulnerability to PTSD. These estimates take into account genetic factors that may contribute to exposure to traumatic events such as combat or interpersonal violence. [160,162, 163] Genetic influences on exposure to trauma are thought to function largely through heritable personality traits. Genetic risk

factors that are common to major depression, generalized anxiety disorder, and panic disorder also account for the majority of genetic variation in PTSD identified to date. Thus, genes that affect risk for PTSD also influence risk for other psychiatric disorders and *vice versa*. As with other mental disorders,[163–166] influences on PTSD are likely polygenic; at least 17 gene variants have been associated with PTSD in at least one published study (Supplementary Table 1). These include genes involved in dopaminergic and serotonergic systems, HPA axis regulation, the locus coeruleus/noradrenergic system, and neurotrophins.

Recent studies have attempted to identify the mechanisms by which gene variants influence PTSD risk. For example, a single nucleotide polymorphism (SNP) in a putative estrogen response element within the gene encoding adenylate cyclase activating polypeptide 1 (pituitary) receptor type I (*ADCYAP1R1*, also known as *PACAPR1*) predicted PTSD diagnosis and symptoms in females only.[167] This SNP was associated with brain ADCYAP1R1 mRNA expression and fear discrimination. However, the genetic association reported in this paper was not replicated in two large independent samples.[168] Similar to other psychiatric disorders, the candidate gene approach has not yet been successful in leading to the identification of robust genetic variants that confer vulnerability to (or resilience against) PTSD.

Gene expression

A growing literature has provided evidence for gene expression patterns that distinguish between individuals with and without PTSD. An early microarray study of RNA derived from peripheral blood cells identified 656 transcripts involving immune and hormonal systems that were differentially expressed in acutely traumatized persons who went on to develop PTSD.[169] Another study found 19 differentially expressed transcripts involving immune functions or reactive oxygen species, 5 of which were upregulated and 14 downregulated in people with PTSD compared to individuals without PTSD who had been exposed to the same traumatic event almost 20 years earlier.[170] More recently, 16 distinct genes involved in signal transduction, neuronal signaling and survival, and immune cell function, and HPA axis activity were found to be differentially expressed in individual with PTSD vs. individuals without PTSD who had been exposed to the 9/11 World Trade Center attack.[171] The gene encoding mannosidase, alpha, class 2C, member 1 (*MAN2C1*) showed the largest expression difference and had not previously been linked to PTSD. Another recent study found methylation differences in this gene in blood cells of patients with PTSD.[172]

Epigenetic mechanisms

The lack of consistency of associations between specific genetic variants and PTSD may be explained by epistatic effects (modification of genetic effects by other genes) and/or by environmental factors not accounted for across studies. For example, some studies have found significant effects for specific genetic variants only under conditions of extreme traumatic stress[173] or a history thereof.[174] The environment modifies genetic effects through epigenetic mechanisms such as DNA methylation. PTSD has been distinguished by methylation profiles suggesting upregulation in immune system-related genes and downregulation in genes involved in neurogenesis and the startle response.[175, 176]

Methylation of *ADCYAP1R1* in peripheral blood was associated with PTSD.[167] *ADCYAP1R1* appears to be an important gene in fear learning.[167]

A joint consideration of genotype and methylation patterns may clarify inconsistencies in the PTSD genetics literature. *SLC6A4* (also called *SERT*, *HTT, 5HTT, 5-HTTLPR*), which regulates synaptic serotonin reuptake and thereby influences emotional behavior, has been the most studied gene in relation to PTSD. Published findings for this locus have been contradictory, with most studies implicating the short (S) allele, which is associated with decreased gene expression, but others implicating the long (L) allele, associated with increased expression. Several studies have found significant genotype by environment interactions.[164] Childhood adversity appears to be a particularly potent modifier of genetic risk for PTSD.[174, 177, 178] Social context also appears to modify PTSD risk, e.g., the S allele was associated with decreased PTSD risk in environments with low crime and unemployment rates, but with increased PTSD risk in opposite environments.[179] Emerging evidence suggests that methylation at downstream CpG sites modifies *SLC6A4* expression.[180] A recent study showed that *SLC6A4* methylation modified the effect of the number of traumatic events on PTSD after controlling for *SLC6A4* genotype.[181] Specifically, persons who had a greater number of experienced traumatic events were at greater risk for PTSD only if *SLC6A4* methylation levels were low. By contrast, high *SLC6A4* methylation levels seemed to protect people who had experienced a greater number of traumatic events from developing PTSD. These findings suggest that both genotype and gene-specific methylation patterns contribute to either PTSD vulnerability or resilience. Histone deacetylation is another molecular epigenetic mechanism that may be involved in PTSD pathogenesis.[182]

Collectively, the above studies suggest that genotype, methylation/histone deacetylation, and gene expression differences influence or accompany the development of PTSD. However, we are unaware of any study that has incorporated all three forms of genetic information into one study. Nor are there definitive findings for any one gene or gene system in the etiology of PTSD. Importantly, epigenetic changes and gene expression in living humans presently can only be assessed in peripheral blood cells, which severely limits the interpretation of the findings. For example, the frequent finding of genetic immune system alterations in PTSD could be an artifact of the tissue used in these analyses, viz., white blood cells, a chief function of which is to regulate the immune response. The most important tissue, viz., that from brain regions reviewed in this article, in which variations in molecular epigenesis and gene transcription are most likely to be relevant to PTSD, is currently off limits (except in post-mortem tissue, which is not without problems[183]). Technological developments that could make live human brain tissue accessible for methylation/histone deacetyation and gene transcript research could lead to breakthroughs, but such developments may be a long way off. Meanwhile, this points to the need for animal models.

Animal Models of PTSD

A full explanation of the mechanisms involved in the development of PTSD requires prospective studies. Experimentally inducing stressors of the magnitude capable of causing PTSD is ethically impermissible in humans, so researchers have relied on animal models.

Such studies have identified candidate brain circuits and cellular/molecular processes involved in PTSD pathophysiology and tested molecular therapeutic targets and specific interventions.

Early animal models of PTSD were based largely on face validity. Some utilized experimental manipulations that seemed as if they would be “traumatic” to the animals, and some were non-specific stress models such as inescapable shock. Although these approaches were useful, they provided limited PTSD-specific information. Similarly, exposure to fear conditioning alone, being a normative animal and human phenomenon, is insufficient to produce the PTSD phenotype.[184] Newer models have incorporated construct validity by capitalizing on the increasing understanding of the pathophysiology of PTSD. These models have employed one or more “PTSD-specific” end-points, such as abnormal fear learning, exaggerated acoustic startle response, enhanced glucocorticoid negative feedback, and exaggerated catecholamine release. Here we review only studies that have utilized models with both satisfactory face and construct validity. These models include predator exposure, exposure to single prolonged stress, and exposure to foot shock with additional stressors.

Predator exposure (PredEx) models expose animals (e.g., rats) to a natural predator (e.g., cat, ferret) or to predator scents (e.g., cat litter, fox urine) in an environment from which the animal cannot escape. Exposed animals develop enhanced acoustic startle and show increased behavioral manifestations of anxiety.[185, 186] Some studies have added “cut-off behavioral criteria” that capitalize on individual variability in stress reactivity in order to identify animals that exhibit extreme responses thought to be analogous to PTSD.[187] In some instances, a subsequent psychosocial stress is added to the predator exposure.[188]

Single prolonged stress (SPS) paradigms involve serial exposure to multiple stressors, e.g., restraint, cold swim or ether anesthesia, that independently activate the HPA axis, followed by a one-week ‘no-touch’ sensitization period. The sensitization period is necessary for the development of the enhanced glucocorticoid negative feedback[189] and increased acoustic startle response[190] reported in PTSD (See Figure 5). Time-dependent sensitization and stress–restress can be seen as variants of the SPS model, with stress–restress adding another stressful exposure (or electric shock) at the end of the sensitization period.

Foot shock with additional stress (here called foot shock plus, or FS+) models use a single session of exposure to an electric shock (sometimes paired with a conditioned stimulus, in which case it is a fear conditioning paradigm) followed by additional shocks[191] or contextual reminders.[192] A variant of this model pre-exposes animals to repeated stress prior to fear conditioning. Using post-conditioning reminders leads to enhancement of acoustic startle,[191, 192] whereas using pre-conditioning stress leads to enhanced fear conditioning and sensitization.[193]

These animal models have been important in identifying the PTSD-specific neurocircuitry described in the sections above. Animal learning studies lead to hypotheses regarding fear conditioning and/or extinction abnormalities in PTSD, and sensitization studies lead to hypotheses regarding abnormal unconditioned response in PTSD such as startle. Results of animal models have also implicated cellular processes such as protein synthesis and

apoptosis[194] in brain regions within this circuitry, suggesting novel interventions targeting these processes. However, the major contribution of animal models to date has been the identification of molecular biological processes that may be involved in PTSD pathophysiology, which too may be targets for interventions. These include alterations in neuroendocrine (HPA), neurotransmitter (glutamatergic, serotonergic, catecholaminergic), and cellular, brain-derived neurotrophic factor (BDNF)/TrkB receptor systems.

HPA axis

Elevated hippocampal glucocorticoid receptor (GR) levels have been found in SPS[189] and PredEx (using cut-off behavioral criteria)[195] models, as has an increased hippocampal GR/MR ratio in SPS.[189, 196] Pretreatment with a GR antagonist (RU40555) prevented SPS-induced changes in fear conditioning and LTP in the hippocampal CA1 region.[190] Similarly, GR antagonism (in combination with a beta-noradrenergic blocker),[197] CRF1 antagonism,[198] and early treatment with high-dose corticosterone[199] prevented the development of a PTSD-like phenotype in a PredEx model. Together, the foregoing findings implicate hippocampal glucocorticoid receptors in the development of posttraumatic psychopathology, a role that is supported by recent evidence that high-dose glucocorticoid administration shifts appropriate contextual conditioned responding to generalized, context-inappropriate responding. Moreover, this shift was accompanied by c-fos expression changes in the dorsal CA1and ventral dentate gyrus regions of hippocampus.[200] These animal data are consistent with GR hypersensitivity found in PTSD patients and support further exploration of GR-targeted interventions as potential PTSD prevention and/or treatment approaches.

Glutamate and NMDA

Abnormal vmPFC glutamate levels and hippocampal NMDA receptor levels have been found in SPS[201] and stress-restress[202] models, respectively. In addition, SPS models showed alterations in the level of the NMDA receptor modulator glycine and glycine transporter mRNA in the hippocampus.[203] Because glutamatergic projections from the vmPFC and the hippocampus are critical in the modulation of fear extinction and contextual fear conditioning, decreased glutamatergic signaling could contribute to impaired extinction recall or enhanced contextual fear. Indeed, the NMDA receptor modulator D-cycloserine prevented SPS-induced changes in fear extinction and NMDA receptor mRNA expression,[204] and the NMDA antagonist CPP blocked the effects of predator stress on pCREB-like immunoreactivity in brain areas implicated in fear behavior.[205] These findings offer specific molecular targets for therapeutic strategies aimed at addressing fear memories and intrusive recollection in PTSD patients, in addition to shedding light on pathophysiology

Serotonin

The serotonin system plays a key role in regulating mood, anxiety, and stress responses. Serotonin transporter knockout mice show an enhanced vulnerability to predator stress.[206] Changes in hippocampal serotonin levels have been implicated in SPS/stress–restress models,[207] and a serotonin reuptake inhibitor reversed behavioral changes in a PredEx model.[208] Increases in 5-HT1A receptor levels in the dorsal raphe nucleus[209] and hippocampus[210] have been reported in SPS and time-dependent sensitization models,

respectively, and 5-HT1A receptor antagonist (WAY-100635) inhibited SPS-induced increases in GR and CRF expression in hippocampus and hypothalamus.[211] In an SPS model, amygdala 5HT2c receptor gene expression was increased, and administration of a 5HT2c receptor antagonist decreased SPS-induced contextual fear-related freezing.[212] Although the exact role of serotonin systems in trauma-related psychopathology awaits further clarification, the animal data suggest that targeting potential upregulation of 5-HT1A and 5HT2c receptors might prove a useful strategy in expanding PTSD treatment/prevention arsenal.

Catecholamines

Noradrenergic transmission plays a key role in arousal regulation and, together with glucocorticoids, in memory processes. Abnormal hippocampal NE levels have been implicated in SPS.[207] Animals exposed to PredEx and chronic stress show an abnormal behavioral and endocrine response to the α_2-adrenergic autoreceptor antagonist yohimbine.[186] Noradrenergic abnormalities have also been reported in a modified FS +reminders model.[213] Beta-adrenergic blockers prevent the anxiogenic effects of PredEx,[197] and blockade of postsynaptic alpha-1-adrenoreceptors normalizes the behavioral abnormalities in a modified FS+reminders model.[213] Together with human data, these findings suggest that noradrenergic signaling might be a useful target for the development of treatment strategies aimed at decreasing arousal and stress reactivity.

BDNF–TrkB

BDNF–TrkB signaling is critical for hippocampal-dependent memory, so associated abnormalities could contribute to PTSD symptomatology. Changes in BDNF levels (mRNA and protein) and levels of the BDNF receptor TrkB have been reported in SPS and PredEx models. Interestingly, hippocampal TrkB levels were increased in both models, whereas BDNF levels were increased in SPS[214] but down-regulated in PredEx.[215] *BDNF* DNA methylation may be differentially regulated in hippocampal subfields,[216] which might explain this discrepancy. These findings are particularly interesting because there have been no identified effective neurotrophic-factor-based treatment strategies to date. As these novel approaches become available, their applicability to PTSD will need to be examined.

Data from the above animal models suggest that multiple molecular pathways may be involved in PTSD pathophysiology. This is hardly surprising considering the fact that on the one hand PTSD symptomatology is heterogeneous, and on the other hand, three of the five systems identified (glucocorticoid, catecholamine and serotonin systems) interact and often regulate or modulate each other's activity. These models also have identified intriguing changes in glutamatergic and *BDNF–TrkB* systems that warrant further exploration as potential novel targets for prevention and intervention. Further research is needed to narrow these foci and translate potential targets into effective therapeutic strategies.

General Conclusions

The research findings reviewed in this article suggest that PTSD has become one of the better understood psychiatric disorders from the biological standpoint, although much work

remains. A substantial achievement has been the identification of core biological abnormalities that cut across a wide variety of traumatic events, ranging from child abuse to military combat. Part of the reason for the impressive progress in biological PTSD research has been the fact that, unlike in many psychiatric conditions, the causal environmental event and hence the onset of the pathophysiological process are considered to be known. This has provided a jump-start for investigating in both human patients and animal models the organic, cellular, and molecular pathophysiological processes set in motion by the traumatic event.

PTSD biomarkers

As reviewed above, a number of biological abnormalities have been found statistically to discriminate PTSD from non-PTSD control groups in various studies; on this basis, they may loosely be regarded as biomarkers. However, none of them possesses the specificity and sensitivity that is necessary to be used as a stand-alone diagnostic test for PTSD. The current "gold standard" for PTSD is the DSM-IV-TR diagnostic criteria, which rely heavily on patients' subjective reports. The reliability of subjectively reported symptoms directly impacts the sensitivity and specificity of PTSD biomarkers, because the latter can be no more reliable or accurate than the diagnostic standard. Someday a biomarker (or combination of biomarkers) may be the gold standard for PTSD, against which the accuracy of subjective measures will be judged.

From an applied standpoint, biomarkers that are likely to represent pre-existing risk factors might be used to identify individuals who are at especially high risk for PTSD for preventive intervention. However, no putative biomarker has yet progressed to the point of practical utility. Acquired biomarkers (that is, biomarkers of the disorder itself rather than of vulnerability for the disorder) offer promise as targets of therapeutic intervention. Importantly, however, blood, CSF, and/or brain neuroimaging markers that are collected during a resting state may turn out to be inadequate to fully characterize PTSD, given that a central feature of the PTSD diagnosis is an abnormal reactivity to both trauma-related and -unrelated stimuli. Measures acquired under conditions of symptom provocation, e.g., responses to traumatic reminders, may offer more promise as PTSD diagnostic biomarkers.[217]

Translational PTSD research

It is scarcely possible to read a grant proposal nowadays without encountering the buzz word "translational." If translational is taken to mean the cross-fertilization that can be achieved when results from animal research are used to inform human studies and *vice versa*, then PTSD research has been highly fruitful in this regard. However, if translational is taken to mean the conversion of research results into novel and effective treatments, the story is different. The currently most effective treatment for PTSD, viz., cognitive behavioral therapy, was conceived entirely on psychological grounds. Trials of the most effective drugs for PTSD, viz., SSRIs, were based upon these drugs' observed anti-depressant effect; the recognition that the 5-HT system in is involved in the biology of PTSD did not come until afterwards. Indeed, despite the abundance of biological insights into PTSD that have been achieved, it is difficult to think of examples of any of these having improved treatment.

A recent example of translational research that could potentially lead to a clinical application is the preliminary finding, described above, that a high dose of cortisol given shortly after the traumatic event reduced the probability of developing PTSD.[129] This study was inspired by observations that the natural cortisol response to a traumatic event may be lower in persons who go on to develop PTSD.[218, 219] If the results of this preliminary study are replicated, high-dose cortisol may become part of psychiatrists' and emergency room physicians' armamentarium for preventing this disorder.

An example of a *potential* translational treatment for PTSD is blockade of traumatic memory reconsolidation.[220, 221] This approach is based upon animal findings that a fear memory may not necessarily last forever but rather may be susceptible to pharmacological intervention after it has been activated. However, insufficient human studies exist to conclude that this intervention is efficacious in PTSD. Non-pharmacological memory updating procedures based upon reconsolidation may also offer promise, but these have only been studied pre-clinically.[222] To date, the development of PTSD treatments has not been different from the history of much of medicine: effective agents are discovered by serendipity, and their biological mechanisms of actions clarified later.

Future directions

A conspicuous limitation in PTSD research to date has been reliance on cross-sectional, i.e., correlational, designs in the overwhelming majority of studies in PTSD patients. There is presently a dearth of pre-trauma prospective studies, which are required to establish causation. That such studies are expensive and difficult to perform is the likely reason they are few in number, but they will be required if biological PTSD research is to advance above the plateau posed by cross-sectional designs. Especially useful will be prospective treatment studies attempting to identify biomarkers that inform prognosis and aid in treatment selection, about which little guidance currently exists. Novel molecular targets implicated by validated animal models, e.g., neurotrophic factors, should be examined as potential biomarkers, as well as used to further dissect molecular processes involved. It will be necessary to continue to move from serendipitous discovery to testing translational hypotheses derived from preclinical animal and human work, as guided for example by the National Institute of Mental Health's recent emphasis on "research domain criteria." Progress may be also expected from capitalizing on technological advances, e.g., utilization of mass spectography in place of radioimmunoassay to better characterize critical molecules, the development of radioligands with greater receptor specificity, improved neuroimaging resolution capable, for example, of measuring activity in functionally different amygdala substructures, finding a way to perform DNA analyses on live brain tissue, and the application of new fusion algorithms derived from bioengineering to complex, multivariable data.

Glossary

Allele
one or more alternate forms of a genetic locus or a gene

Brain-derived neurotrophic factor (BDNF)

A protein, often released from a neuron, that is involved in growth and the differentiation of new neurons and synapses

CA3 subfield
A sector of the cornu ammonis subfield of the hippocampus and a major target of glucocorticoids

Conditioned fear response
A fear response that is elicited by a conditioned stimulus, or cue, following fear conditioning. Typical measures include freezing in rodents, skin conductance in humans, and potentiated startle in both.

Construct validity
The degree to which a model or a term corresponds to or reflects an underlying theory

Corrugator EMG
A measure of electromyographic activity associated with contraction of the corrugator supercilii muscle, which draws the inner brow inward and downward during negatively valenced emotion

DNA methylation
The modification of a strand of DNA in which a methyl group is added to a cytosine molecule that stands directly before a guanine molecule in the same chain. It has the effect of reducing gene expression.

Dentate gyrus
A subfield of the hippocampus, which contains adult neural stem cells and is an important site of neurogenesis

Diffusion tensor imaging (DTI)
A structural magnetic resonance imaging-based technique that tracks the diffusion of water molecules within a closed space, usually a tube such as a neural axon. It is useful in revealing white matter fiber structure and providing information regarding regional brain connectivity.

Dorsal anterior cingulate cortex (dACC)
A cortical area that roughly corresponds to Brodmann area (BA) 24. May also be called anterior mid cingulate cortex (aMCC)

Epigenesis
One or more mechanisms that regulate gene function without altering underlying DNA sequence

Extinction
A procedure by which a conditioned stimulus is repeatedly presented in the absence of the unconditioned stimulus, resulting in diminution of the conditioned response.

Extinction recall (or retention)

Memory that a conditioned stimulus has been previously been extinguished, expressed as a continuing reduction of the conditioned response.

Extrasynaptic receptor
A neuronal receptor located outside the synapse. Extrasynaptic receptors can be accessed by neuromodulatory factors derived from the periphery and circulating in the cerebrospinal fluid.

Face validity
The degree to which a model or a term appears to measure what it is supposed to measure.

Fear conditioning
An experimental paradigm that teaches an animal or human to associate a previously neutral conditioned stimulus (CS, e.g., a light or a tone) with an aversive unconditioned stimulus (US, e.g., an electric shock), the latter of which produces an aversive unconditioned response (UR). Eventually because of the association the CS alone comes to elicit a fear response.

Fear-potentiated startle
Increased electromyographic responsiveness to a startling stimulus that occurs when an animal or human is afraid.

Functional magnetic resonance imaging (fMRI)
A functional neuroimaging technique that uses a magnetic field and radio waves to measure blood oxygenation level dependent (BOLD) signal, which serves as an index of regional brain activation.

Glucocorticoid negative feedback
A negative feedback phenomenon by which cortisol reduces its own release through inhibition of the hypothalamic-pituitary-adrenal cortical (HPA) axis.

Heritable
Capable of being passed from one generation to the next via DNA.

Magnetic resonance spectroscopic imaging (MRSI)
A non-invasive research and diagnostic technique that is similar to magnetic resonance imaging but uses a stronger field to detect regional body chemistry at the cellular level. Also called 1H-nuclear magnetic resonance spectroscopic imaging and proton magnetic resonance spectroscopic imaging.

N-acetylaspartate (NAA)
A putative marker of neuronal integrity thought to be present predominantly in neuronal cell bodies. It emits the largest signal in magnetic resonance spectroscopic imaging of the human brain.

Neuromodulation
An alteration in the response of a neuron induced by a substance that would not, by itself, affect neuronal firing rate

P2
An electroencephalographic event-related potential response that is positive and reaches its maximum deflection approximately 200 miliseconds after a stimulus is presented. It is thought to reflect “tuning” of a mechanism that regulates the amount of sensory input to the cortex.

P3b
An electroencephalographic event-related potential response that is positive and reaches its maximum deflection approximately 300 miliseconds after a stimulus is presented. It is thought to reflect the amount of attentional resources allocated to a particular stimulus.

Phasic
Designating intermittent signaling, usually in response to a stimulus

Positron emission tomography (PET)
A functional neuroimaging technique that uses radioactive isotopes to quantify regional cerebral blood flow, glucose metabolism, or receptor occupancy.

Single nucleotide polymorphism (SNP)
A variation in a DNA sequence in which a single nucleotide (A, C, G, or T) at a specific locus differs between members of the same biological species or between paired chromosomes of an individual

Skin conductance
A measure of sweat activity recorded from two adjacent fingers and/or the thenar and hpothenar eminences of the palm of the hand. It is thought to be primarily under sympathetic nervous system influence.

Structural magnetic resonance imaging (sMRI)
A non-invasive diagnostic and research procedure that utilizes a magnetic field and radio waves to create detailed sectional images of the internal structure of the body, including the brain

Tonic
Designating continuous, steady, or baseline signaling

TrkB
A membranous tyrosine kinase receptor that binds BDNF and other neurotrophic factors, or neurotrophins

Ventromedial prefrontal cortex (vmPFC)
A region within the medial wall of prefrontal cortex that roughly corresponds to Brodmann area (BA) 10. Some studies treat portions of adjacent Brodmann areas as part of vmPFC

Voxel-based morphometry (VBM)
An automated neuroimaging analytic technique that allows the investigation of focal differences in brain anatomy using the statistical approaches of statistical parametric mapping and smoothing applied to structural images

Biographies

Roger K. Pitman, M.D. is Professor of Psychiatry at Harvard Medical School and Psychiatrist at Massachusetts General Hospital. He is a recipient of the International Society for Traumatic Stress Studies (ISTSS) Award for Outstanding Scientific Achievement in the Field of PTSD and the ISTSS Lifetime Achievement Award. He is a Distinguished Life Fellow of the American Psychiatric Association and a Fellow of the American College of Neuropsychopharmacology (ACNP). His PTSD research has included psychophysiological, neuroimaging, and other biological approaches to PTSD and has also employed identical twins discordant for combat exposure in Vietnam.

Ann M. Rasmusson, M.D. is Associate Professor of Psychiatry at Boston University School of Medicine, Psychiatry Liaison for PTSD Research and Education at the VA Boston Healthcare System, and an affiliate of the National Center for PTSD Women's Health Science Division. Her research focuses on the neuroendocrinology of PTSD and PTSD-comorbid medical and other psychiatric disorders, as well as the development of new PTSD therapeutics.

Karestan Chase Koenen, M.A., Ph.D., is Associate Professor of Epidemiology at Columbia University's Mailman School of Public Health. She is a recipient of the ISTSS Young Professional Award and the American Psychopathological Association Young Investigator Award. Dr. Koenen is currently President-Elect of the ISTSS. Her research interests include the interplay of genetic and environmental factors in the etiology of stress-related mental disorders such as PTSD and depression.

Lisa M. Shin, Ph.D. is Professor of Psychology at Tufts University and Associate Researcher in the Department of Psychiatry at the Massachusetts General Hospital. She is a recipient of the Anxiety Disorders Association of America Young Investigator 's Research Award and the ISTSS Young Professional Award. Her research involves using functional neuroimaging to study brain abnormalities in PTSD and whether these are acquired characteristics of the disorder or familial vulnerability factors, as well as determining how such abnormalities predict treatment response.

Scott P. Orr, Ph.D. is Associate Professor of Psychology in the Department of Psychiatry at Harvard Medical School and Massachusetts General Hospital. He is a recipient of the ISTSS Award for Outstanding Scientific Achievement in the Field of Traumatic Stress. His major research interest is the psychophysiology of PTSD, including the identification or risk factors and predictors of treatment response.

Mark W. Gilbertson, Ph.D. is Instructor in the Department of Psychiatry at Harvard Medical School and Brigham & Women's Hospital. He is Research & Development Coordinator for the Manchester, NH VA Medical Center. Dr. Gilbertson's published work has centered on structural neuroimaging and neurocognitive function. His current interests include the role of hippocampus in contextual processing as it relates to the development and maintenance of chronic PTSD.

Mohammed R. Milad, Ph.D. is Associate Professor of Psychiatry at Harvard Medical School and Director of the Behavioral Neuroscience Lab at Massachusetts General Hospital. He is the recipient of the Positive Neuroscience Award from the Templeton Foundation and was an invited Kavli Frontier of Science Speaker in 2009. His research involves the use of neuropharmacological and molecular tools in rodents, and structural and functional neuroimaging and psychophysiological tools in humans, to examine the function of the fear extinction network across mental disorders. He also studies the influence of sex hormones on fear extinction.

Israel Liberzon, M.D. is Professor of Psychiatry, Psychology and Neuroscience at the University of Michigan and Associate Chair for Academic Development at the Department of Psychiatry. He is an ACNP Fellow and a Past President of the Psychiatric Research Society. His research focus is on the neurobiology and the neuroanatomy of stress, negative emotions, and cognitive-emotional interactions in PTSD patients and healthy individuals. His research program encompasses both basic science (genetic, molecular biology and animal models) and clinical/translational projects (fMRI, neuroendocrinology, and treatment outcome studies).

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At-a-Glance Summary

- Perhaps the best replicated biological finding in PTSD is higher autonomic (heart rate, skin conductance) and facial EMG responding during internal, mental imagery of the traumatic event, and upon exposure to external, trauma-related cues.
- Higher heart rate responding to sudden loud tones in PTSD likely reflects an acquired sensitization of the nervous system.
- Diminished volumes of hippocampus and anterior cingulate cortex represent the most frequently replicated neuroanatomic findings in patients with PTSD. These do not appear to be fully explained by co-morbid conditions such as substance abuse and depression.
- Some evidence exists to support both pre-existing vulnerability and neurotoxicity and as origins of brain volume reductions in PTSD. Based upon present data, it is going too far to say that stress damages the brain, but there is no doubt that it changes it.
- Functional neuroimaging studies suggest that amygdala and dorsal anterior cingulate cortex are *hyper*(re)active, whereas ventral medial prefrontal cortex is *hypo*(re)active, in PTSD. These abnormalities likely underlie the attentional bias toward threat, impaired emotion regulation, and persistence of fear memories in this disorder.
- The classic model of stress based upon chronic hyperactivity of the hypothalamic-pituitary-adrenal cortical axis does not characterize PTSD.
- A number of neurotransmitters and neuroendocrinological factors interact to influence PTSD risk, symptom profiles, and severity. These factors vary across individuals due to genetic and epigenetic factors, as well as within individuals over time in response to environmental influences including exposure to psychological trauma.
- As with other mental disorders, genetic vulnerability to PTSD likely involves the sum of contributions from multiple alleles each with small effects.
- The full range of molecular genetic factors, which include genotype, methylation/histone deacetylation, and gene expression, likely influence or accompany the development of PTSD. However, at this time there are no definitive findings for any one gene or gene system in the disorder's etiology.
- Animal models have identified important molecular pathways that likely contribute to PTSD's pathophysiology and may constitute promising therapeutic targets.

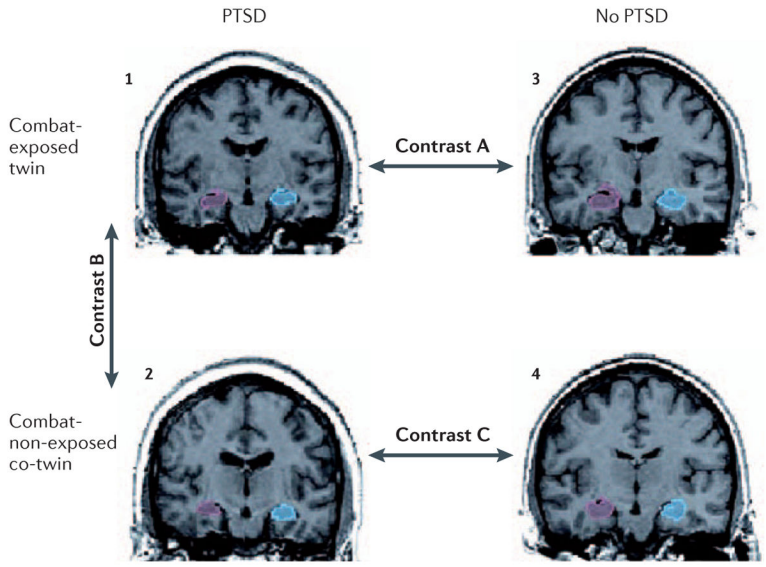

Figure 1. Assessing structural abnormalities in PTSD using a combat-discordant identical-twin design

Sample coronal structural magnetic resonance images of right (red) and left (blue) hippocampi in a twin pair consisting of a combat veteran with PTSD (1) and his combat-unexposed co-twin (2), who has no PTSD but is considered “high risk” because his identical twin developed PTSD when exposed to trauma; as well as a control twin pair consisting of a combat-exposed veteran without PTSD (3) and his “low-risk” combat-unexposed co-twin (4), who also has no PTSD. *Contrast A* provides a replication test of studies demonstrating smaller hippocampal volume in combat veterans with vs. without PTSD. Two additional contrasts can shed light on whether this abnormality is a result of combat exposure or of having PTSD, or whether it represents a pre-existing vulnerability factor. *Contrast B* compares hippocampal volumes in combat-exposed PTSD veterans with their own high-risk co-twins. If the twin with PTSD (1) has smaller hippocampal volume than his co-twin (2), the trait has likely been acquired. *Contrast C* compares hippocampal volumes in high vs. low-risk co-twins. If the trauma unexposed, non-PTSD twin of the veteran with PTSD (2) has smaller hippocampal volume than the unexposed, non-PTSD twin of the veteran without PTSD (4), it is likely that the trait represents a pre-existing vulnerability factor. This type of design can also be used to assess the origin of other abnormalities observed in patients with PTSD.

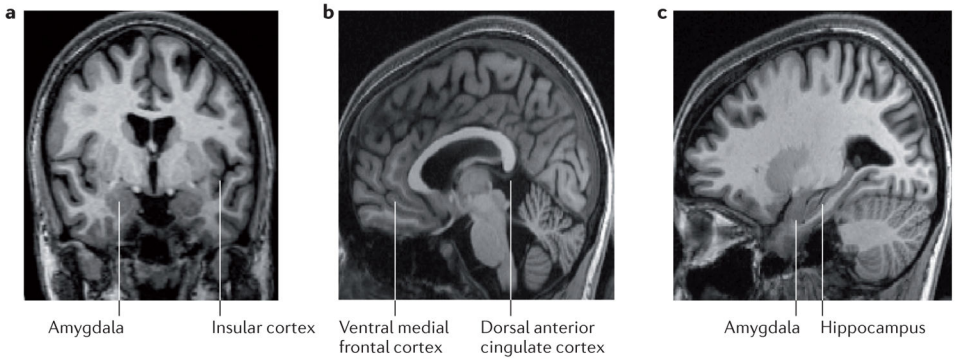

Figure 2. Brain regions implicated in PTSD functional neuroimaging studies

The amygdala (shown in Panels A and C) is involved in recognizing both conditioned and unconditioned stimuli signaling danger, as well as in expressing the fear response. Amygdala reactivity is exaggerated in individuals with PTSD and is positively correlated with symptom severity. The insular cortex (Panel A) and dorsal anterior cingulate cortex (Panel B) are also hyperreactive in PTSD; these structures may modulate (in these cases enhance) the amygdala's expression of fear. In contrast, activation in the ventral medial prefrontal cortex (Panel B), which also modulates (in this case reduces) the amygdala's expression of the fear response, is diminished in PTSD; vmPFC activity is also negatively correlated with symptom severity. Functional neuroimaging findings in the hippocampus (Panel C), which is involved in recognizing both safe and dangerous contexts, have been mixed in PTSD, with both hypo- and hyperreactivity observed.

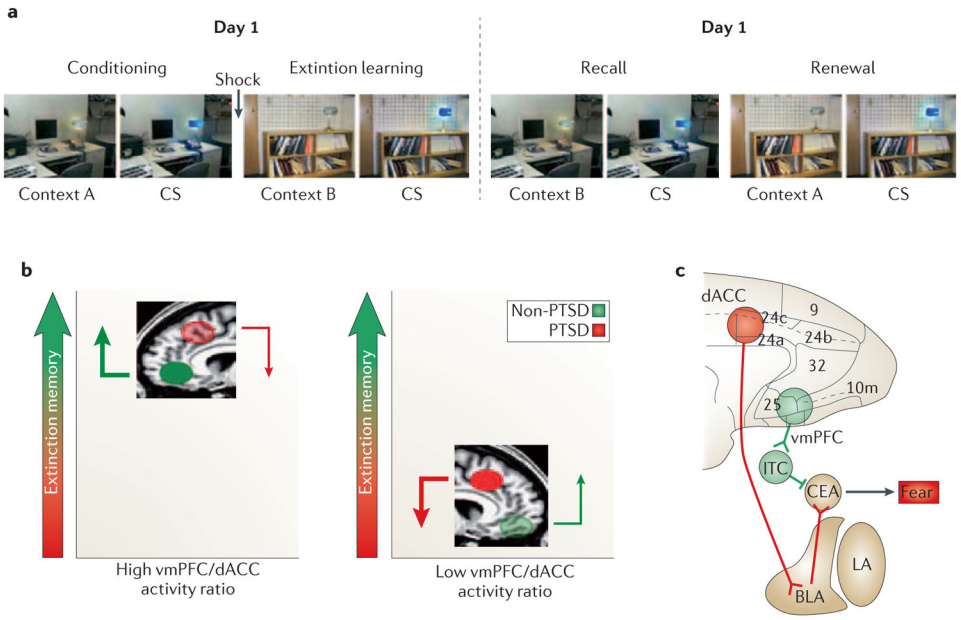

Figure 3. Contribution of prefrontal regions to fear regulation and expression

A. Activation in the human brain during fear conditioning and extinction can be investigated in a Pavlovian fear conditioning and extinction paradigm. During conditioning, a conditioned stimulus (a colored light) is paired with a mild electric shock to the fingers in a particular context (context A). The acquisition of conditioned fear in this paradigm can be measured by the skin conductance response to the light. During extinction learning, the light is subsequently repeatedly presented without the shock in a different context (context B). This leads to extinction of the conditioned response. The next day, the light is again presented in the absence of the shock in Context B (extinction recall), and then again in Context A (fear renewal). Greater retention of extinction learning is associated with a lower fear response during extinction recall. Extinction retention is context-dependent: the hippocampus is thought to recognize whether a context is safe (B) or dangerous (A) and to communicate this information to other structures in the fear network.

B. fMRI studies have shown that activation of ventromedial prefrontal cortex (vmPFC, shown in green) during extinction recall is positively correlated with extinction retention,[70] whereas activation of dorsal anterior cingulate cortex (dACC, shown in red) is negatively correlated with extinction retention.[71] Ventromedial PFC sends excitatory glutamatergic projections to gamma-aminobutyric acid (GABA) -ergic intercalated cells (ITC) in amygdala, which in turn inhibit the expression of the fear response by the amygdala's central nucleus (Ce). In contrast, dACC sends excitatory glutamatergic projections to amygdala's basolateral nucleus, which in turns activates the expression of the fear response by Ce. LA=lateral amygdala nucleus.

C. Non-PTSD subjects (left) have a relatively high vmPFC/dACC activation ratio during extinction recall, which tips the balance toward better extinction retention and less fear expression. By contrast, PTSD subjects (right) have a lower vmPFC/dACC activation ratio, which tips the balance toward less extinction retention and more fear expression.[68]

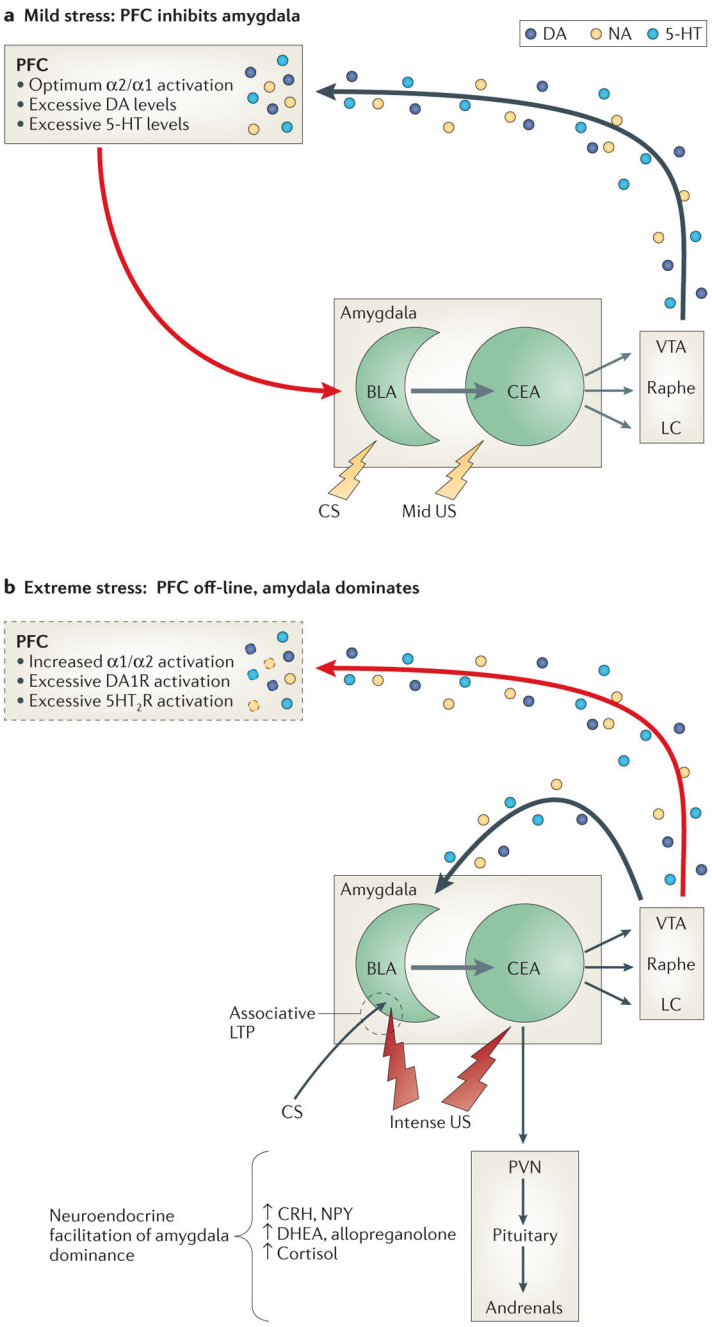

Figure 4. Putative brain-state relevant to PTSD

Panel A (resilience): The response of either a) previously nontraumatized individuals exposed to mild or moderately arousing *unconditioned* threat stimuli, b) resilient individuals who are resistant to the arousing effects of more extreme *unconditioned* threat, or c) individuals with PTSD after undergoing extinction and recovery so that *conditioned* threat stimuli are no longer highly arousing. **Panel B (risk):** The response of a) previously nontraumatized individuals exposed to *unconditioned* threat that is highly arousing, b)

individuals with PTSD who are re-exposed to trauma-related cues (*conditioned* threat) prior to extinction and recovery, or c) individuals with PTSD who are resistant to recovery.

A. Neuromodulation contributing to relative prefrontal cortical dominance (resilience). *Mild to moderately arousing* sensory stimuli activate the central nucleus (CE) of the amygdala, which projects both directly and indirectly to brainstem monoaminergic cell body regions to activate mesocorticolimbic dopamine (DA) pathways emanating from the ventral tegmental area (VTA), as well as more widely disseminating NE and serotonergic (5-HT) pathways emanating from the locus coeruleus (LC) and median/dorsal raphe nuclei, respectively.[151] In the prefrontal cortex (PFC), the resulting mild to moderate increases in synaptic levels of these monoamines engage high-affinity (e.g., noradrenergic alpha-2) receptors to enhance working memory[152] and activate glutamatergic pyramidal output neurons that project back to the amygdala. There, glutamatergic activation of GABAergic interneurons in the basolateral (BLA) and/or intercalated nuclei suppresses associative learning and *inhibits* excitatory BLA pyramidal cell projections to the CE and the expression of the species-specific defense response (see below).[153]

B. Neuromodulation contributing to relative amygdala dominance (risk). *Strongly arousing unconditioned* threat stimuli (due to objective threat characteristics or an individual's increased sensitivity to objective threat) or *conditioned* threat stimuli in persons with PTSD activate the amygdala to a greater degree, which in turn excites brainstem mesocorticolimbic monoaminergic neurons more vigorously[57, 151]—a process likely facilitated by reductions in GABAergic neurotransmission within the amygdala.[154, 155] In the PFC, higher synaptic levels of these monoamines engage low-affinity noradrenergic alpha-1, as well as DA1 and 5HT2 receptors, resulting in working memory impairment and a reduction in PFC inhibition of amygdala.[152] Consequent lifting of the PFC "brake" reduces GABAergic tone within the BLA and intercalated nuclei of the amygdala to enable associative pairing of unconditioned threat stimuli (US) and convergent contextual stimuli (CS) or later reconsolidation of conditioned stimuli, as well as activation of the species-specific defense response (SSDR(, which includes increases in blood pressure and heart rate, HPA axis activation, engagement in reflexive defensive behaviors (fight, flight, freezing), and restriction of high-level information processing to enable efficient focus on survival-relevant phenomena. Direct catecholamine effects in the amygdala also facilitate defensive responding: activation of D1 receptors on PFC projection neuron terminals inhibits glutamate activation of GABAergic interneurons, whereas activation of post-synaptic D2 receptors on BLA to CE pyramidal projection neurons increases their excitation by convergent US-CS inputs, as well as adventitious sensory stimuli. This likely facilitates or maintains associative fear conditioning and may contribute to generalization of fear.[156] In contrast, neuronal activity in the BLA is generally suppressed by NE alpha-2 and alpha-1 receptor stimulation, though the latter effect, mediated by enhanced terminal release of GABA, is reduced by chronic stress.[157] In contrast NE beta-receptor activation is excitatory and enhances US-CS pairing.[158]

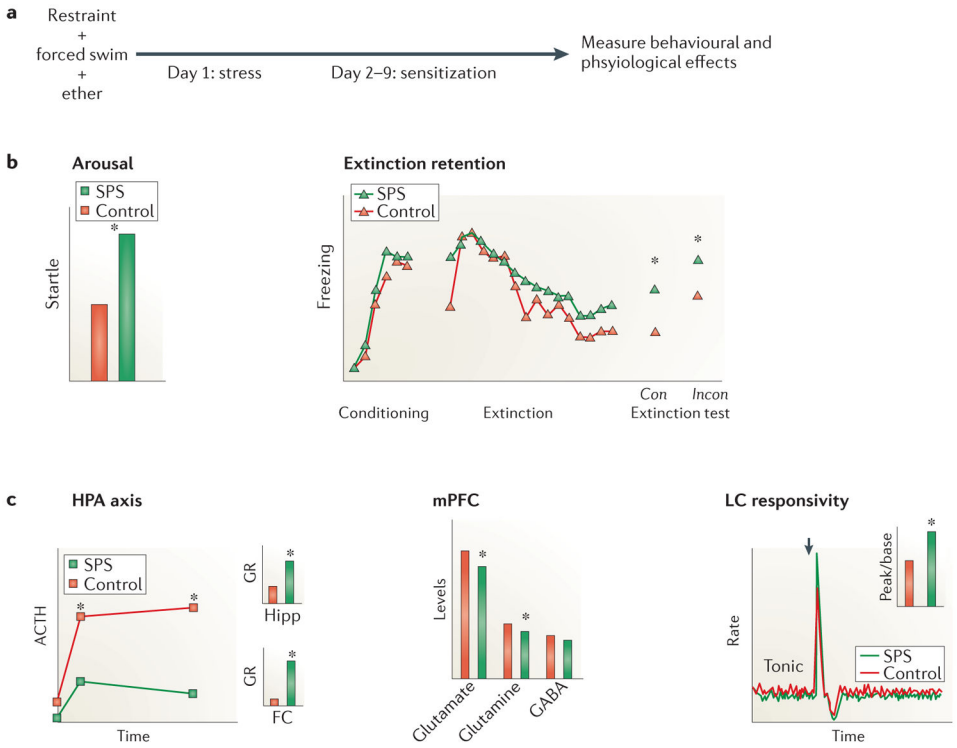

Figure 5. Behavioral and physiological changes in a PTSD animal model

A. A prototypic rodent model of PTSD: (single prolonged stress (SPS). B. Behavioral effects of exposure to SPS include increased arousal as reflected in startle response (left) and decreased extinction retention in contexts that are either consistent (con) or inconsistent (incon) with the extinction context (right). C. Physiological effects of exposure to SPS include enhanced glucocorticoid receptor (GR) expression in the hippocampus (Hipp) and frontal cortex (FC) and negative feedback in the HPA axis (left), decreased excitatory tone in the medial prefrontal cortex (mPFC) (middle), and decreases in tonic as well as increases in phasic responses to stimulation (arrow) of locus coeruleus (LC) neurons (right). Note: data are illustrative.

Table 1

Summary of Candidate Genes Studied in Relation to Posttraumatic Stress Disorder*

Gene	Common name(s)	Location	Total Number of Published Reports	Significant Findings	Null Findings
RD2 (D2R, D2DR)	Dopamine receptor DR	11q23	6	4	2
DRD4 (D4DR)	Dopamine receptor D4	11p15.5	1	1	0
SLC6A3 (DAT1)	Dopamine transporter	5p15.3	4	3	1
DBH	Dopamine beta-hydroxylase	9q34	1	0	1
SLC6A4 (HTT, 5HTT, SERT, 5-HTTLPR)	Serotonin transporter	17q11	16	12	4
HTR2 (5-HT2A)	5-hydroxytryptamine (serotonin) receptor 2A	13q14-q21	1	1	0
FKBP5	FK506 binding protein 5	6p21	4	4	0
GCCR (NR3C1)	Glucocorticoid receptor	5q31.3	1	0	1
CRHR1	Corticotropin-releasing hormone receptor 1	17q12-22	1	1	0
RGS2	Regulator of G-protein signaling 2	1q31	1	1	0
CNR1 (CB1, CNR)	Cannabinoid receptor 1 (brain)	6q14-q15	1	0	1
APOE	Apolopoprotein E	19q13	1	1	0
BDNF	Brain-derived neurotrophic factor	11p13	3	0	3
NPY	Neuropeptide Y	7p15.1	1	0	1
GABRA2	$GABA_A$	4p12	1	1	0
COMT	Catechol-O-methyltransferase	22q11	2	2	0
ADCYAP1R1	Receptor for adenylate cyclase-activating polypeptide 1	7p14	2	1	1
DTNBP1	Dystrobrevin-binding protein 1	6p22	1	1	0
CRNA5	Cholinergic receptor, neuronal nicotinic, alpha polypeptide 5	15q25.1	2	1	1
PRKCA	Protein kinase C alpha	17q22-q23.2	1	1	0
TPH1	Tryptophan hydroxylase 1	11p15.3-p14	1	1	0
TPH2	Tryptophan hydroxylase 2	12q21.1	1	1	0

*A referenced version of this Table appears as Table 1S in Supplemental Material.