We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Sleep Disturbances in PTSD

Laurie L. Wellman, Richard J. Ross and
Larry D. Sanford

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64189>

Abstract

Stress-induced alterations in sleep have been linked to the development of post-traumatic stress disorder (PTSD) and sleep complaints and disturbances in arousal are continuing symptoms in patients. PTSD-related changes in sleep have not been fully characterized but involve persistent disturbances in both rapid eye movement sleep (REMS) and non-rapid eye movement sleep (NREMS). PTSD is considered a disorder of the fear circuitry, which includes the amygdala, dorsal anterior cingulate, hippocampus, and ventromedial prefrontal cortex. Currently, several animal models are used to examine the underlying neurobiology of PTSD; however, sleep has been characterized in only a limited number of models. Intense conditioned fear training, which may best model PTSD in rodents, can produce reductions in REMS as well as alterations in NREMS that may vary with mouse and rat strains. The amygdala, a central region in current concepts of PTSD, plays significant roles in regulating the stress response and changes in stress-induced alterations in arousal and sleep. This chapter reviews sleep-related findings in patients with PTSD and in animal experimental paradigms currently utilized to model the disorder, as well as the neurobiology that has been linked to disturbed sleep in PTSD. It will also discuss the impact of PTSD treatments on sleep disturbances.

Keywords: amygdala, animal models, conditioned fear, rapid eye movement sleep, stress

1. Introduction

Post-traumatic stress disorder (PTSD) is a neuropsychiatric disorder which develops in a significant subset of the population following psychological trauma. It is estimated that 70% of individuals will experience a traumatic event sometime in their lifetime; however, only an

estimated 20% of those who experience significant trauma will go on to develop PTSD. Sleep complaints and disturbances in arousal are continuing and distressing symptoms in PTSD and stress-induced alterations in sleep have been linked to the development of PTSD. However, the exact role sleep plays in PTSD is unknown. This chapter will describe our current understanding of disturbed sleep in PTSD patients, how sleep is altered in animal models employed to study PTSD, linkages between the neurobiology of PTSD and sleep regulation, and current therapies for treating sleep disturbances in PTSD. Our review will discuss the complex effects of stress on sleep, stress parameters that appear to be important in determining post-stress sleep, and the neuroanatomical substrates important in regulating the relationship between stress and sleep. Lastly, we will discuss some of the limitations that need to be addressed in order to advance our understanding of the role that sleep may play in PTSD.

2. Sleep in PTSD patients

PTSD is unique among mental disorders in that a disturbance of sleep is included twice among the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]—as recurrent nightmares, a re-experiencing symptom, and also as insomnia, a symptom of hyperarousal. By self-report, 52–96% of individuals with PTSD have endorsed experiencing frequent nightmares [2, 3] while insomnia is reported by up to 70% of individuals with PTSD [4]. Unmentioned in the DSM-5, but well recognized by clinicians and PTSD patients alike, is excessive, disruptive movement during sleep [5].

In recent years, much has been learned about the clinical phenomenology and pathophysiology of PTSD, including the sleep disturbances. However, there have been remarkably few studies of the optimal approaches to treating the recurrent nightmares and insomnia that are so prevalent in the disorder and represent two of its major morbidities. We proceed to provide a description of the sleep disturbances experienced by individuals with PTSD, the brain mechanisms implicated by clinical studies, and the treatments, both psychotherapeutic and pharmacological, that have been proposed.

Largely because nightmares occur during rapid eye movement sleep (REMS) and are a distinguishing symptom of only PTSD, among all mental disorders, we (RJR; [5]) originally proposed that REMS mechanisms are essential to the pathophysiology of disturbed sleep in PTSD. At the same time dreams, albeit less vivid and more thought-like than nightmares, also emerge from non-REMS (NREMS) and as such a role of NREMS mechanisms must also be considered. The extant polysomnographic (PSG) literature provides no firm consensus regarding defining sleep abnormalities in PTSD. Enhanced, fragmented, and preserved REMS all have been reported [6–9]. Mellman et al. [10] have emphasized the likely importance of the duration of time following the trauma as an explanation of the diverse PSG findings in PTSD. In a non-clinical community sample of young adults assessed retrospectively by patient interview, both REMS percentage (amount of time spent in REMS/total sleep time) and average REMS segment duration were positively correlated with PTSD chronicity [10]. In addition, REMS latency (time from sleep onset to the start of the first REMS episode of the sleep period)

was negatively correlated [10]. These findings point to a view of PTSD pathogenesis in which REMS plays a prominent role, as a biomarker or perhaps as a central etiologic element.

Mellman et al. [10] suggested that increases in REMS percentage and continuity that occur over time post-trauma could indicate a role of REMS in promoting adaptation to, and recovery from, trauma. While acknowledging that this hypothesis fits well with independent evidence that REMS processes help in the processing of emotional memories, we (RJR; [11]) have suggested that the reconstituted REMS observed long after traumatization may be pathological and, in fact, a sign of poor adaptation to a severe stressor. In a psychoanalytic framework, the repeating traumatic dream would be an indication of the failure of the normal dream mechanism.

An increase in REMS continuity with the passage of time following trauma warrants consideration in the context of the extant PTSD treatment literature. The alpha-adrenoceptor antagonist prazosin is arguably the most effective pharmacotherapy for recurrent post-traumatic nightmares. Although PSG has not been carried out in most prazosin trials, Taylor et al. [12] reported that the drug increased total REMS time and average REMS episode duration in a civilian group with PTSD. This suggests that prazosin's therapeutic effect may depend on a normalization of REMS continuity. Pharmacotherapy for PTSD will be reviewed at greater length below.

Understanding the dynamics of REMS changes after exposure to a traumatic stressor must account for phasic as well as tonic REMS processes. REM density (number of rapid eye movements/REMS time) is the phasic REMS measure most often reported in clinical investigations. In a meta-analysis of 20 PSG studies of PTSD, an increased REM density was the strongest finding [13]. An emphasis on heightened REM density in PTSD is consistent with the early observation of a direct relation between rapid eye movement activity and the intensity of dream mentation in healthy subjects [14].

A greater frequency of phasic leg muscle twitches (calculated as the percentage of REMS epochs with at least one prolonged tibialis anterior twitch; REMS phasic leg activity (RPLA) index) also has been described in PTSD [15]. Although no clear association between RPLA and rapid eye movement activity was seen overall, a single recorded nightmare occurred out of a REMS episode with a particularly high REM density. This observation led to the hypothesis that, as a nightmare unfolds, diverse REMS phasic processes, which can otherwise be uncoupled, may be recruited en masse [15].

Largely because investigations in animals have implicated REMS phasic activity in the processing of fearful stimuli [16, 17], it is important to consider the possibility that severe psychological stress initiates processes in REMS phasic event generators that promote adaptation to trauma, or, alternatively, maladaptation in the form of PTSD. Studying fear conditioning in rats, DaSilva et al. [18] proposed that failure to mount a strong phasic REMS response in the early aftermath of a stressful experience could predispose individuals to the increase in REMS phasic activity that has been observed in humans with chronic PTSD.

PTSD is very often comorbid with other mental disorders, most commonly depression [19]. In addition, new to the criteria for diagnosing PTSD is a set of symptoms, including low self-worth and anhedonia, classed as "negative alterations in cognition and mood" [1]. This raises

the question whether REMS abnormalities that have been described in PTSD are in fact a function of depression, for which heightened “REMS pressure” (analogous to increased REMS continuity in evolving PTSD), is the best characterized PSG finding [20].

In order to clarify the distinct roles of PTSD and depression in the REMS changes observed after psychological traumatization, Ross et al. [9] analyzed PSG data by thirds of the night and found increases in REMS percentage and REM density throughout the sleep period in a group of military veterans with chronic combat-related PTSD. These distributions were distinguished from shifts in REMS amount and REM number to earlier in the night, which characterize major depressive disorder [20]. Supporting the importance of brain mechanisms fundamental to PTSD in mediating REMS changes following traumatization, Mellman et al. [10] found that a positive correlation between REMS percentage and time elapsed following traumatization remained significant after excluding subjects with comorbid major depression. Nonetheless, the current emphasis by the National Institutes of Health on Research Domain Criteria (RDoC) in neurobehavioral research provides an alternative perspective, in which both PTSD and depression can be conceptualized as disorders of “dysphoric hyperarousal,” sharing in elements of a common REMS pathophysiology.

3. Stress, sleep, and PTSD animal models

By definition, stress is a significant component of putative animal models of PTSD. However, experiments in animals have shown that virtually any stressful experience can significantly impact subsequent sleep [21]. Exposure to many experimental stressors induces a period of arousal [22] followed by subsequent rebound sleep (increases in REMS and/or NREMS) that occur at various latencies after the stressor is removed. REMS appears to be particularly susceptible to the effects of stress and can either be decreased or increased depending on stressor characteristics, for example, controllability [23, 24] or possibly individual resilience or vulnerability to stress [25].

Sleep disturbances, both before [26] and after [27, 28] a traumatic event, may be predictive of future development of emotional and physical disorders. This suggests that stress-induced sleep alterations in animal models may be critical for assessing their value for examining underlying neural mechanisms that produce long-term pathological alterations in behavior as well as for understanding the linkage between stress and continuing sleep disturbances in PTSD. Unfortunately, current efforts are hampered by a lack of full understanding of alterations in sleep associated with traumatic events that lead to PTSD. There also is relatively limited work examining sleep in animal stress models as well as an incomplete understanding of what those stress-induced alterations indicate with respect to successful or unsuccessful coping with stressful events. That is, although stress can have a significant, long-lasting negative impact on health, stressors are commonly encountered in daily life without producing permanent or pathological changes, and the majority of individuals cope with traumatic life events with only transitory effects. Many of the stress models that have been explored produce differences in subsequent sleep, as illustrated in the models discussed below; however, their actual relevance to PTSD, for the most part, is not known.

3.1. Fear conditioning stress

PTSD is viewed as a disorder of the brain's fear system [29]. As such, experimental fear conditioning is a leading experimental model of processes thought to be related to PTSD as it allows exploration of learned fear and anxiety in animals [30–35]. Fear conditioning occurs when a neutral stimulus or context becomes associated with the occurrence of a significant aversive emotional event; subsequently, those previously neutral stimuli and contexts alone can elicit behavioral and physiological fear responses similar to those induced by the aversive event itself. During training, animals are exposed to an aversive stimulus (unconditioned stimulus; US (usually footshock)) in experimental paradigms that utilize various numbers of trials, shock intensities, and durations. For cued fear conditioning a tone or light is utilized (conditioned stimulus; CS) to alert the animals to the shock. Contextual fear conditioning does not alert the animal to the shock and as such the animal simply associates the context (also a CS) with the shock. After training, the cued or contextual CS elicits physiological and behavioral response (conditioned response; CR) similar to those produced by the US. The animal can be tested for fear memory by presenting the CS and measuring the CR.

Fear conditioning models are particularly relevant for PTSD as they can engage fear memory processes without requiring a full re-experiencing of the stressful event. These paradigms are also valuable because they allow stressor parameters (e.g., duration, intensity, controllability) to be manipulated and allow fear memory processes to be assessed and manipulated. They have been highly used for explorations of the relationship between fear memory and sleep. However, it is important to note that conditioned fear also can underlie adaptive behavior that typically is extinguished when the fear-inducing situation is removed. Fear “extinction” learning creates a new memory that inhibits subsequent fear without erasing the original memory for fear conditioning [36]. It is the failure of extinction that has been linked to persisting symptoms of PTSD [37]. The effects on sleep of stress, conditioned responses, and extinction in paradigms related to fear conditioning are discussed below.

3.1.1. Footshock stress

Footshock has been utilized as a stressor in models relevant to anxiety and depression, as well as specifically to PTSD. Like some other stress models, the effects on sleep vary with stressor parameters as well as the putative resilience and vulnerability of the animal receiving the stressful experience.

A variety of studies have demonstrated enhanced REMS in rats [38–42] and mice [43] (and rats also denser ponto-geniculo-occipital (PGO) waves, a signature characteristic of REMS [38]) at various latencies after shock avoidance training in a shuttle box. In the avoidance paradigm, animals are signaled of imminent shock and can learn to jump to safety without shock ever being delivered. The increases in REMS have typically been viewed in the context of learning and interpreted as indicating a role for REMS in memory consolidation, but there is potential significant stress as the learning is motivated by footshock.

By comparison, Adrien et al. [44] in an early study using an extensive inescapable shock (IS) paradigm (60 footshocks of relatively high intensity (0.8 mA) and duration (15 s)) found greater

REMS latency, reduced REMS and increased light NREMS compared to the control group and their own baseline sleep. Afterwards, REMS returned to control amounts, but no REMS rebound was observed in recordings that night or the following day. We have also conducted studies utilizing extensive shock training in mice and failed to observe a REMS rebound over ten days of post-training recording [45]. This lack of recovery REMS is different than most other forms of stress (including water maze, exposure to novel objects, open field, ether exposure, cage change, and some types of social stress), which cause an initial REMS decrease followed by an increase (rebound) later during the recording period (reviewed in [21, 125]).

One of the significant differences between typical IS training used for fear conditioning and avoidance training is that animals can learn to totally avoid receiving shock. We have utilized a yoked footshock paradigm in which animals receive identical amounts of footshock, but one of a pair can learn an escape response (simply moving to the safe side of a shuttle box) whereas the yoked animal cannot. Escapable footshock (ES) can produce significant increases in REMS whereas IS can produce significant decreases in REMS (with variable changes on NREMS) [23, 24, 46]. Changing the paradigm (e.g., signaling the footshock) can modify subsequent sleep after ES [47].

Together, these studies indicate that the type of environmental information available to the animal, and the associated learning, are important factors in the effects of footshock stress on REMS. They also suggest that these factors can be manipulated to produce either increases or decreases in REMS, and potentially enable assessment of the role that REMS may have in mediating the effects of stress.

3.1.2. Fearful reminders

It is believed that PTSD patients have impaired contextualization, the inability to appropriately contextualize the traumatic events in autobiographic memory. That is, PTSD patients are unable to process traumatic experiences as time and context limited events. Therefore, it is beneficial to use a model which not only has a physical trauma (e.g., shock) but also enables probing memories of stressful events. Critically, evoking memories of shock training can produce alterations in sleep similar to those produced by the shock experience itself. That is, cues or contextual reminders of footshock training experiences that decrease REMS also decrease REMS (in mice [45, 48, 49] and rats [50–54]) whereas reminders of footshock training experiences that increase REMS also can increase REMS [23, 24, 46]. These directionally different alterations in sleep can occur even though behavioral freezing (the gold standard CR for measuring fear in this paradigm) is virtually identical for both reminders that decrease REMS and those that increase REMS. Pawlyk et al. [54] also showed that cue exposure at day 14 following IS training produced greater freezing than cue exposure on day 1 suggesting that the fear memory can strengthen over time.

3.1.3. Extinction

PTSD patients are generally deficient at learning that stimuli previously associated with adverse outcomes no longer produce a threat. As such prolonged exposure (PE) therapy is

utilized to help change the processing of the fearful memory trace (for full description see Section 5.1 in this chapter). In the laboratory, the extinction paradigm is utilized to assess changes in behavior and sleep related to creating a new stronger memory to the previously fearful cue or context. As such, the animals are exposed to the US until they no longer show the CR (typically freezing). We have shown that extinction training is followed by increased REMS (beyond baseline levels) [55]. Furthermore, if the extinction training is unsuccessful, the negative effects on sleep and overt behavior will continue. Work in other laboratories has also found positive correlations between extinction and sleep [16].

3.2. Single prolonged stress (SPS)

SPS has been argued to be an appropriate model for simulating the chronic stress conditions potentially experienced by military personnel. In the SPS model, the animal experiences 2 h of restraint immediately followed by 20 m of forced swim and, after an additional 15 m, exposure to ether until unconsciousness. The SPS model does produce, in animals, increased fast negative feedback of the hypohypothalamic–pituitary–adrenal (HPA) axis [56] and enhanced contextual fear [57] similar to patients with PTSD. Furthermore, following SPS, rats show increased percentage of REMS, increased transitions to REMS, and increased wakefulness during the dark period [58].

Upon subsequent exposure to mild cued fear conditioning, the SPS animals showed impairment to extinction recall compared to the control animals [58, 59]. Unfortunately, sleep alterations associated with fear conditioning and extinction were not recorded, so it is unknown what effect prior SPS and fear conditioning together have on subsequent sleep.

3.3. Immobilization stress

Immobilization stress has been utilized to study processes thought involved in PTSD. Conceptually, immobilization is argued to generate PTSD-like anxiety as it involves the animal (mouse or rat) being restrained for an *unknown* period of time. It can produce both behavioral anxiety and increased negative HPA feedback which are seen in patients with PTSD [60]. Additionally, the timing can be altered from relatively mild (1 h) to extensive (20 h) and acute (1 time) to chronic (across several days) exposure. With a short period of acute immobilization (1–2 h) during the light period, NREMS is increased while REMS may be initially decreased but ultimately increased over the dark period [61–63]. A much more extensive immobilization lasting 20 h a day for 4 days in rats decreased both NREMS and REMS [64]. When the immobilization was conducted for 1 h at the start of the dark period, NREMS and REMS were increased during various phases of the dark period in rats [65–67]. Using rats, Marinesco et al. [68] compared 1, 2, and 4 h immobilization at the beginning of the dark period and found different effects for each duration including no change in sleep following 4 h of restraint. Other authors have also found differences in the effects on sleep depending on when immobilization was experienced [47]. Thus, the duration of immobilization, the acute or chronic nature of the stressor, and the time of the circadian cycle are important for its effects on subsequent sleep. It is not clear which, if any, of the changes in sleep model those occurring in PTSD. Immobili-

zation also does not simulate the situational reminders that often produce symptoms in patients with PTSD.

3.4. Limitation of models

One of the critical problems in studying the effects of stress on sleep in animals with respect to modeling the development of PTSD is the lack of a clear understanding of the nature of the alterations in sleep that are associated with the development of PTSD as opposed to those associated with a normal, and therefore non-pathological, stress response. As noted above, virtually all stressors produce alterations in sleep and it is highly unlikely that all reflect pathological processes. It is also not known whether the initial stress-induced alterations in sleep are the same as those that occur in later stages of PTSD or how they may be modified over time by subsequent life experiences. In addition, work in animals has generally focused on acute stress manipulations and their immediate or near-term effects on sleep. Potential longer-term changes in sleep and their relationship to behaviors indicative of PTSD have received much less attention.

Genetic differences are an important factor in the development of stress-related pathology as approximately 20–30% of individuals who experience traumatic events may develop PTSD [69, 70]. A few attempts to develop animal models that better represent individual differences in clinical populations have included selecting low and high responders to stressors in outbred rat strains [69–71]. However, the potential role of individual differences in resilience and vulnerability has been minimally explored, particularly in studies that involve sleep. The potential differences in sleep among those who develop PTSD and those that adequately cope with significant stress are not known. We have demonstrated that mouse strains that exhibit greater anxiety-like behaviors in response to challenges in wakefulness also show greater and longer duration alterations in sleep after training with inescapable shock and after fearful cues [48] and contexts [72]. Recently, we have also found significant individual differences in stress and conditioned changes in sleep within outbred Wistar strain rats [25].

Thus, significant limitations in animal models of sleep disturbances in PTSD arise from an imperfect understanding of which stressful experiences can lead to persisting psychopathology, how those may interact with individual differences in resilience and vulnerability, and of the role that sleep may play in adaptive coping with stress. These factors suggest that refinement is needed in the way that stress and sleep are studied if truly successful models are to be developed.

4. Neurobiology linking fear and sleep

In order to identify and compare circuitry in normal versus pathological fear responses in humans, cued fear conditioning paradigms are utilized in conjunction with brain imaging. As such, activity within the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), and dorsal anterior cingulate cortex (dACC) have been identified as key structures for fear conditioning as well as being central to current concepts of PTSD neurobiology.

4.1. Normal fear circuitry

Amygdala activity is especially important for fear expression and extinction [73–78]. During reversal training, different subnuclei of the amygdala have been implicated related to associational and attentional processes [79]. The hippocampus has been linked to the contextual features associated with fear conditioning and expression and hippocampal activity has been observed during fear behavior in several imaging studies [78, 80–82]. The hippocampus is also implicated in extinction training and recall of extinction [82, 83]. Activity in the vmPFC has been shown to be decreased during acquisition and expression of fear and increased during extinction of fear behavior and recall of extinction [77]. Conversely, dACC is increased during fear acquisition and expression [75, 77, 82]. The amygdala, hippocampus, vmPFC, and dACC are functionally connected during fear expression, whereas just the amygdala, hippocampus, and vmPFC are functionally connected during fear extinction.

It is important to note here that two of the regions involved in the circuitry of normal fear, the amygdala and mPFC, are also involved in modulation of sleep. Neuronal activity of amygdala varies across the sleep-wake states, with increased activity during REMS and less activity during NREMS compared to wakefulness [84, 85]. It is also interconnected with wakefulness promoting and sleep promoting areas throughout the brain. Regions of mPFC also have interconnections with sleep-promoting regions and may be involved in modulation of sleep following fear conditioning. In fact, a recent study found vmPFC activity during fear conditioning was positively correlated with subsequent REMS [86].

4.2. Fear circuitry alterations in patients with PTSD

Imaging studies have found structural abnormalities in fear neurocircuitry, specifically in the dACC, amygdala, and hippocampus in patients with PTSD [87, 88]. Furthermore, this neurocircuitry appears to be activated inappropriately in patients with PTSD. In one study, when asked to recollect traumatic events, PTSD patients had decreased activity in the vmPFC and increased activity in the amygdala compared to controls (reviewed in [89]). This finding was replicated using a task that had presentation of fearful faces [89, 90]. In another experiment, patients with PTSD showed normal extinction learning, but exhibited impaired extinction retention accompanied by increased activation of dACC and decreased activation of hippocampus and vmPFC [83]. It has been suggested that persistent fear in PTSD patients is due to hyperactivation of amygdala and dACC and hypoactivation of vmPFC and hippocampus [83, 91, 92]. This hyperresponsivity of the amygdala to threat-related stimuli may be combined with inadequate top-down governance by the vmPFC leads to hyperarousal and deficits in extinction learning/recall [89].

4.3. Insight from animal models

The amygdala, mPFC, and hippocampus have established roles in fear conditioning and fear extinction (e.g., [37, 93]) as well as being central to current concepts of PTSD (e.g., [94]). Of these regions, the amygdala has a recognized role in regulating fear- and stress-induced alterations in sleep, especially REMS [53, 95, 50] as well as in the acquisition and

consolidation of fear conditioning (e.g., [96–102]). In addition to its roles in mediating fear memory and fear responses, the amygdala is important in the regulation of behavioral, physiological, and neuroendocrine responses to stress [103–105] and it appears to be a vital interface between stressful events, stressful memories, and their impact on sleep and arousal.

The amygdala has a strong influence on REMS (e.g., [106–110]), which can be significantly altered by stress [48, 111, 72]. However, there is also evidence that the amygdala can influence all sleep-wakefulness states [107, 109, 110, 112]. This influence most likely involves amygdalar projections to thalamic, hypothalamic, and brainstem target regions [113] that are involved in the control of sleep and arousal. These include direct projections via the central nucleus of the amygdala (CNA; e.g., [114–118]) and the lateral division of the bed nucleus of the stria terminalis (reviewed in [113, 119]), the sources of the major descending outputs of the amygdala to brainstem regions linked to the regulation of REMS.

The functional role of the amygdala in mediating the effects of stress on sleep has been demonstrated. For example, blocking inactivation of the CNA with microinjections of gamma-aminobutyric acid (GABA_A) antagonist, bicuculline, immediately following IS can eliminate the reduction in REMS commonly seen following IS [95]. Moreover, blocking inactivation of CNA can alter brain activation, as indicated by c-Fos (a marker of neuronal activity) in a manner consistent with the reduced effect on REMS. That is, there was a reduction in c-Fos activity in the locus coeruleus (LC), an area implicated in the regulation of REMS [120], consistent with enhanced REMS. By comparison, inactivation CNA with microinjections of the GABA_A agonist, muscimol, did not significantly alter the reduction of REMS or c-Fos activation in LC that can be produced by IS.

In addition to its role in the acquisition and consolidation of fear conditioning (e.g., [96–102]), the basolateral nucleus of the amygdala (BLA) also appears to be critical for determining how and whether fear memories impact sleep. For example, the corticotropin-releasing factor antagonist, antalarmin, administered into BLA of rats prior to IS training blocked both IS-induced reductions in REMS and the formation of memories that alter sleep without blocking fear memory as indicated by contextual freezing [53]. By comparison, global inactivation of BLA with microinjections of muscimol prior to IS blocked the post-training reduction in REMS seen in vehicle-treated rats and attenuated contextual freezing and subsequent reductions in REMS [121]. Together, these data indicate that BLA plays a significant role in regulating the initial effects of stress and fear on sleep and in mediating the subsequent effects of fearful memories.

Stressor controllability is an important determinant of the effects of stress and stress-related memories on sleep. The mPFC is a critical region in the perception of control and in mediating the consequences of stress [122–124]. For example, blocking activation of the vmPFC with muscimol in rats presented with escapable shock produced failure in escape learning and greater fear conditioning [124]. By comparison, activation of vmPFC with picrotoxin, a GABA_A antagonist, prior to IS promoted later escape learning in rats provided an opportunity to escape shock in a shuttle box [124].

Unfortunately, the role of the mPFC in mediating the effects of stressor controllability on sleep has not been examined. However, part of the influence of mPFC [124] is enacted through its effects brainstem regions that play roles in modulating REMS [120] as well as in the stress response (reviewed in [125]), thereby providing a potential substrate for regulating the effects of stress on REMS. There also are projections to the BLA and CNA and projections to GABAergic neurons in the intercalated nuclei, which have inhibitory control over CNA output [126]. Thus, projections from the mPFC to brainstem regulatory regions and the amygdala provide a substrate by which stressor controllability could influence REMS.

5. Clinical treatment

Studies of the first-line treatments of PTSD, both psychotherapeutic and pharmacological, have rarely examined the effectiveness of these therapeutic modalities for PTSD-related sleep symptoms. This is especially concerning given the evidence for clinically significant residual sleep problems during and following PTSD treatment [127, 128]. In addition, persistent insomnia and recurrent nightmares can compromise treatment responses to empirically supported PTSD interventions.

5.1. Psychotherapy

The most widely accepted psychotherapies for PTSD are cognitive behavioral treatments (CBTs) and include PE and cognitive processing therapy (CPT) [129]. Galovski and colleagues [130] found that both PE and CPT were effective in reducing global sleep disturbance in adult, female rape survivors; however, sleep impairment remained clinically significant in both groups despite an overall improvement in PTSD symptoms. Gutner and colleagues [128] examined the long-term effects of CPT and PE on sleep disturbance. Similar to previous studies [130, 131], they found significant improvements in waking PTSD symptoms but no remission of the sleep disturbance.

CBT for insomnia (CBT-I) is a brief intervention aimed at improving overall sleep quality [132, 133]. It includes instruction in stimulus control (in order to reduce negative associations with the bed and bedroom) and sleep restriction (in order to increase sleep drive by first limiting, and then gradually raising, the amount of time allowed in bed); cognitive restructuring (to identify and challenge inaccurate beliefs that interfere with sleep); education in sleep hygiene; and relaxation training (to minimize physical and mental tension around sleep onset) [132, 134].

CBT-I may be beneficial for insomnia in PTSD. In a randomized clinical trial (RCT) of CBT-I compared to a waitlist control in a community sample in treatment for PTSD, the CBT-I group had a superior response on measures of sleep amount and quality [135]. However, both groups reported reductions in PTSD symptom severity and post-traumatic nightmares, limiting any conclusions that can be drawn about the therapeutic elements of CBT-I specifically.

Imagery rehearsal (IR) [136–138] is a form of CBT that targets recurrent nightmares. There is evidence that it promotes increased mastery of nightmare content and experience [139]. IR protocols share the following basic steps: choosing a repetitive nightmare, rescripting it during waking, and imaginably rehearsing the new dream script at bedtime. Two recent meta-analyses of predominantly uncontrolled trials of IR reported large effect sizes for nightmare frequency and sleep quality as well as overall PTSD symptomatology [137, 140]. However, a RCT in Vietnam War veterans with chronic, severe PTSD suggested that IR may hold no advantage over a comparison treatment with elements of CBT-I [141]. In a meta-analysis of studies of CBT-I combined with IR, a large gain in sleep quality was reported, but there was no significant improvement in PTSD severity and the nightmare disturbance [140].

5.2. Pharmacotherapies

The selective serotonin reuptake inhibitors (SSRIs) have the strongest evidence base among pharmacotherapies for PTSD [142, 143]. The use of selective norepinephrine-serotonin reuptake inhibitors (SNRIs), in particular venlafaxine, is also supported by clinical guidelines [142]. However, there is little evidence that insomnia and recurrent nightmares in PTSD respond to either the SSRIs or the SNRIs.

The tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) have not been studied in large RCTs in PTSD [144]. There is only weak support for the usefulness of these classes of psychotropic medication in controlling recurrent nightmares [145]. Considering the prominent REMS suppressant effect of the MAOIs and the evidence that most nightmares emerge from REMS, a methodical investigation of the MAOIs is warranted [145].

The atypical antipsychotic drugs have been minimally studied as a treatment for PTSD. One small placebo-controlled trial of adjunctive olanzapine for combat-related PTSD non-responsive to an SSRI found a greater improvement in sleep, as measured by the Pittsburgh Sleep Quality Index [146]. However, a larger study in veterans showed no significant effect of adjunctive risperidone [147]. There have been no completed RCTs of other medications in this class.

Little is known about the treatment of insomnia in PTSD with benzodiazepines, commonly used to treat other forms of insomnia [148]. Clonazepam, the mainstay of pharmacological treatment for REMS behavior disorder, could have a role in managing excessive movement during sleep in PTSD, a topic for future research. One RCT of the non-benzodiazepine receptor agonist eszopiclone reported greater improvements in PTSD symptoms including sleep disturbance [149].

As noted above, there is strong support for the alpha-1 adrenoceptor antagonist prazosin as a treatment for the nightmare disturbance in PTSD. Four placebo-controlled trials of prazosin, two in veterans, one in active-duty US service members, and one in civilians, support its efficacy [12, 150–152]. Prazosin must be administered continuously to avoid the recurrence of

nightmares. It is not known whether there could be a lasting beneficial effect after drug discontinuation.

6. Conclusion

Disturbances of sleep and arousal are significant symptoms of PTSD. Sleep disturbances have also been implicated in the development of PTSD, although, at this time, there is no clear consensus on the role these disturbances may play. As a diagnosis of PTSD may not be determined for several months, there are little data concerning sleep architecture immediately following the precipitating trauma. Thus, the potential role that stress-induced alterations in sleep may play in the development of PTSD is poorly understood and the research questions that could provide answers are inadequately articulated. Problems arise in part because work in animal models, to date, has primarily been descriptive and hypotheses have been based on the effects on sleep arising from experimental stressors that produce diverse effects on subsequent sleep, and can be impacted by a variety of stressor parameters as well as differences in subject vulnerability and resilience. This has led to difficulties in developing hypotheses regarding the potential role of specific sleep states in mediating the outcomes of stress. Thus, improved models of PTSD and improved understanding of the role sleep plays in mediating stress-related psychopathology will be critical for developing more effective treatments for PTSD and sleep symptomatology.

Acknowledgements

Portions of this work were supported by NIH research Grant MH64827 (L.D.S).

Conflict of interest

The views expressed in this article do not represent those of the Department of Veterans Affairs or the US Government

Author details

Laurie L. Wellman¹, Richard J. Ross² and Larry D. Sanford^{1*}

*Address all correspondence to: sanforld@evms.edu

1 Sleep Research Laboratory, Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, USA

2 Department of Veterans Affairs Medical Center, Philadelphia, USA

References

- [1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.): American Psychiatric Publishing: Arlington, VA.; 2013.
- [2] Leskin G. A., Woodward S. H., Young H. E., Sheikh J. I. Effects of comorbid diagnoses on sleep disturbance in PTSD. *J Psychiatr Res.* 2002;36:449–52.
- [3] Neylan T. C., Marmar C. R., Metzler T. J., Weiss D. S., Zatzick D. F., Delucchi K. L., et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. *Am J Psychiatry.* 1998;155:929–33.
- [4] Ohayon M. M., Shapiro C. M. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Compr Psychiatry.* 2000;41:469–78.
- [5] Ross R. J., Ball W. A., Sullivan K. A., Caroff S. N. Sleep disturbance as the hallmark of posttraumatic stress disorder. *Am J Psychiatry.* 1989;146:697–707.
- [6] Breslau N., Roth T., Burduvali E., Kapke A., Schultz L., Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. *Arch Gen Psychiatry.* 2004;61:508–16.
- [7] Habukawa M., Uchimura N., Maeda M., Kotorii N., Maeda H. Sleep findings in young adult patients with posttraumatic stress disorder. *Biol Psychiatry.* 2007;62:1179–82.
- [8] Hurwitz T. D., Mahowald M. W., Kuskowski M., Engdahl B. E. Polysomnographic sleep is not clinically impaired in Vietnam combat veterans with chronic posttraumatic stress disorder. *Biol Psychiatry.* 1998;44:1066–73.
- [9] Ross R. J., Ball W. A., Dinges D. F., Kribbs N. B., Morrison A. R., Silver S. M., et al. Rapid eye movement sleep disturbance in posttraumatic stress disorder. *Biol Psychiatry.* 1994;35:195–202.
- [10] Mellman T. A., Kobayashi I., Lavela J., Wilson B., Hall Brown T. S. A relationship between REM sleep measures and the duration of posttraumatic stress disorder in a young adult urban minority population. *Sleep.* 2014;37:1321–6.
- [11] Ross R. J. The changing REM sleep signature of posttraumatic stress disorder. *Sleep.* 2014;37:1281–2.
- [12] Taylor F. B., Martin P., Thompson C., Williams J., Mellman T. A., Gross 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.
- [13] Kobayashi I., Boarts J. M., Delahanty D. L. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. *Psychophysiology.* 2007;44:660–9.

- [14] Rechtschaffen A. The psychophysiology of mental activity during sleep. In: McGuigan FJ, Schoonover RA, editors. *The Psychophysiology of Thinking*. New York: Academic; 1973.
- [15] Ross R. J., Ball W. A., Dinges D. F., Kribbs N. B., Morrison A. R., Silver S. M., et al. Motor dysfunction during sleep in posttraumatic stress disorder. *Sleep*. 1994;17:723–32.
- [16] Datta S., O'Malley M. W. Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. *J Neurosci*. 2013;33:4561–9.
- [17] Mavanji V., Datta S. Activation of the phasic pontine-wave generator enhances improvement of learning performance: a mechanism for sleep-dependent plasticity. *Eur J Neurosci*. 2003;17:359–70.
- [18] DaSilva J. K., Lei Y., Madan V., Mann G. L., Ross R. J., Tejani-Butt S., et al. Fear conditioning fragments REM sleep in stress-sensitive Wistar-Kyoto, but not Wistar, rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:67–73.
- [19] Magruder K. M., Frueh B. C., Knapp R. G., Davis L., Hamner M. B., Martin R. H., et al. Prevalence of posttraumatic stress disorder in Veterans Affairs primary care clinics. *Gen Hosp Psychiatry*. 2005;27:169–79.
- [20] Reynolds C.F., Gillin J.C., Kupfer D.J. Sleep and affective disorders. In: Meltzer HY, editor. *Psychopharmacology: the third generation of progress*. New York: Raven Press; 1987. pp. 647–54.
- [21] Pawlyk A. C., Morrison A. R., Ross R. J., Brennan F. X. Stress-induced changes in sleep in rodents: models and mechanisms. *Neurosci Biobehav Rev*. 2008;32:99–117.
- [22] Chrousos G. P. Stressors, stress, and neuroendocrine integration of the adaptive response. *Ann N Y Acad Sci*. 1998;851:311–35.
- [23] Sanford L. D., Yang L., Wellman L. L., Liu X., Tang X. Differential effects of controllable and uncontrollable footshock stress on sleep in mice. *Sleep*. 2010;33:621–30.
- [24] Yang L., Wellman L.L., Tang, X., Sanford LD. Effects of corticotropin releasing factor (CRF) on increased rapid eye movement sleep and body temperature following controllable footshock stress in mice. *Physiol Behav*. 2011;104:886–92.
- [25] Wellman L. L., Fitzpatrick M. E., Kuzmina O. Y., Sutton A. M., Williams B. L., Sanford L. D. Individual differences in animal stress models: considering resilience, vulnerability and the amygdala in mediating the effects of stress and conditioned fear on sleep. *SLEEP*. 2016, 39:1293–303.
- [26] Bryant R. A., Creamer M., O'Donnell M., Silove D., McFarlane A. C. Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder. *Sleep*. 2010;33:69–74.

- [27] Lavie P. Sleep disturbances in the wake of traumatic events. *N Engl J Med.* 2001;345:1825–32.
- [28] Klein E., Koren D., Arnon I., Lavie P. Sleep complaints are not corroborated by objective sleep measures in post-traumatic stress disorder: a 1-year prospective study in survivors of motor vehicle crashes. *J Sleep Res.* 2003;12:35–41.
- [29] Shvil E., Rusch H. L., Sullivan G. M., Neria Y. Neural, psychophysiological, and behavioral markers of fear processing in PTSD: a review of the literature. *Curr Psychiatry Rep.* 2013;15:358.
- [30] Davis M. Animal models of anxiety based on classical conditioning: the conditioned emotional response (CER) and the fear-potentiated startle effect. *Pharmacol Ther.* 1990;47:147–65.
- [31] Davis M. The role of the amygdala in fear and anxiety. *Ann Rev Neurosci.* 1992;15:353–75.
- [32] Davis M. The role of the amygdala in conditioned fear. In: Aggleton J, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction.* New York: Wiley-Liss, Inc.; 1992. pp. 255–305.
- [33] Foa E. B., Zinbarg R., Rothbaum B. O. Uncontrollability and unpredictability in post-traumatic stress disorder: an animal model. *Psychol Bull.* 1992;112:218–38.
- [34] Grillon C., Southwick S. M., Charney D. S. The psychobiological basis of posttraumatic stress disorder. *Mol Psychiatry.* 1996;1:278–97.
- [35] Shalev A. Y., Ragel-Fuchs Y., Pitman R. K. Conditioned fear and psychological trauma. *Biol Psychiatry.* 1992;31:863–5.
- [36] Bouton M. E. Context and behavioral processes in extinction. *Learn Mem.* 2004;11:485–94.
- [37] Myers K. M., Davis M. Mechanisms of fear extinction. *Mol Psychiatry.* 2007;12:120–50.
- [38] Datta S. Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. *J Neurosci.* 2000;20:8607–13.
- [39] Smith C., Lapp L. Prolonged increases in both PS and number of REMS following a shuttle avoidance task. *Physiol Behav.* 1986;36:1053–7.
- [40] Smith C., Young J., Young W. Prolonged increases in paradoxical sleep during and after avoidance-task acquisition. *Sleep.* 1980;3:67–81.
- [41] Smith C. Sleep states and learning: a review of the animal literature. *Neurosci Biobehav Rev.* 1985;9:157–68.
- [42] Smith C. Sleep states and memory processes. *Behav Brain Res.* 1995;69:137–45.

- [43] Smith C., Kitahama K., Valatx J. L., Jouvet M. Increased paradoxical sleep in mice during acquisition of a shock avoidance task. *Brain Res.* 1974;77:221–30.
- [44] Adrien J, Dugovic C, Martin P. Sleep-wakefulness patterns in the helpless rat. *Physiol Behav.* 1991;49:257–62.
- [45] Sanford L. D., Fang J., Tang X. Sleep after differing amounts of conditioned fear training in BALB/cJ mice. *Behav Brain Res.* 2003;147:193–202.
- [46] Yang L., Wellman L. L., Ambrozewicz M. A., Sanford L. D. Effects of stressor predictability and controllability on sleep, temperature, and fear behavior in mice. *Sleep.* 2011;34:759–71.
- [47] Machida M., Yang L., Wellman L. L., Sanford L. D. Effects of stressor predictability on escape learning and sleep in mice. *Sleep.* 2013;36:421–30.
- [48] Sanford L. D., Tang X., Ross R. J., Morrison A. R. Influence of shock training and explicit fear-conditioned cues on sleep architecture in mice: strain comparison. *Behav Genet.* 2003;33:43–58.
- [49] Yang L., Tang X., Wellman L. L., Liu X., Sanford L. D. Corticotropin releasing factor (CRF) modulates fear-induced alterations in sleep in mice. *Brain Res.* 2009;1276:112–22.
- [50] Liu X., Wellman L. L., Yang L., Ambrozewicz M. A., Tang X., Sanford L. D. Antagonizing corticotropin-releasing factor in the central nucleus of the amygdala attenuates fear-induced reductions in sleep but not freezing. *Sleep.* 2011;34:1539–49.
- [51] Tang X., Yang L., Sanford L. D. Rat strain differences in freezing and sleep alterations associated with contextual fear. *Sleep.* 2005;28:1235–44.
- [52] Wellman L. L., Fitzpatrick M. E., Machida M., Sanford L. D. The basolateral amygdala determines the effects of fear memory on sleep in an animal model of PTSD. *Exp Brain Res.* 2014;232:1555–65.
- [53] Wellman L. L., Yang L., Ambrozewicz M. A., Machida M., Sanford L. D. Basolateral amygdala and the regulation of fear-conditioned changes in sleep: role of corticotropin-releasing factor. *Sleep.* 2013;36:471–80.
- [54] Pawlyk A. C., Jha S. K., Brennan F. X., Morrison A. R., Ross R. J. A rodent model of sleep disturbances in posttraumatic stress disorder: the role of context after fear conditioning. *Biol Psychiatry.* 2005;57:268–77.
- [55] Wellman L. L., Yang L., Tang X., Sanford L. D. Contextual fear extinction ameliorates sleep disturbances found following fear conditioning in rats. *Sleep.* 2008;31:1035–42.
- [56] Liberzon I., Lopez J. F., Flagel S. B., Vazquez D. M., Young E. A. Differential regulation of hippocampal glucocorticoid receptors mRNA and fast feedback: relevance to post-traumatic stress disorder. *J Neuroendocrinol.* 1999;11:11–7.

- [57] Iwamoto Y., Morinobu S., Takahashi T., Yamawaki S. Single prolonged stress increases contextual freezing and the expression of glycine transporter 1 and vesicle-associated membrane protein 2 mRNA in the hippocampus of rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:642–51.
- [58] Vanderheyden W. M., George S. A., Urpa L., Kehoe M., Liberzon I., Poe G. R. Sleep alterations following exposure to stress predict fear-associated memory impairments in a rodent model of PTSD. *Exp Brain Res*. 2015;233:2335–46.
- [59] Knox D., Nault T., Henderson C., Liberzon I. Glucocorticoid receptors and extinction retention deficits in the single prolonged stress model. *Neuroscience*. 2012;223:163–73.
- [60] Neylan T. C., Otte C., Yehuda R., Marmar C. R. Neuroendocrine regulation of sleep disturbances in PTSD. *Ann NY Acad Sci*. 2006;1071:203–15.
- [61] Meerlo P., Easton A., Bergmann B. M., Turek F. W. Restraint increases prolactin and REM sleep in C57BL/6J mice but not in BALB/cJ mice. *Am J Physiol Regul Integr Comp Physiol*. 2001;281:R846–54.
- [62] Vazquez-Palacios G., Velazquez-Moctezuma J. Effect of electric foot shocks, immobilization, and corticosterone administration on the sleep-wake pattern in the rat. *Physiol Behav*. 2000;71:23–8.
- [63] Tiba P. A., Palma B. D., Tufik S., Suchecki D. Effects of early handling on basal and stress-induced sleep parameters in rats. *Brain Res*. 2003;975:158–66.
- [64] Papale L. A., Andersen M. L., Antunes I. B., Alvarenga T. A., Tufik S. Sleep pattern in rats under different stress modalities. *Brain Res*. 2005;1060:47–54.
- [65] Bonnet C., Lger L., Baubet V., Debilly G., Cespuglio R. Influence of a 1 h immobilization stress on sleep states and corticotropin-like intermediate lobe peptide (CLIP or ACTH18-39, Ph-ACTH18-39) brain contents in the rat. *Brain Res*. 1997;751:54–63.
- [66] Koehl M., Bouyer J. J., Darnaudery M., Le Moal M., Mayo W. The effect of restraint stress on paradoxical sleep is influenced by the circadian cycle. *Brain Res*. 2002;937:45–50.
- [67] Dewasmes G., Loos N., Delanaud S., Dewasmes D., Ramadan W. Pattern of rapid-eye movement sleep episode occurrence after an immobilization stress in the rat. *Neurosci Lett*. 2004;355:17–20.
- [68] Marinesco S., Bonnet C., Cespuglio R. Influence of stress duration on the sleep rebound induced by immobilization in the rat: a possible role for corticosterone. *Neuroscience*. 1999;92:921–33.
- [69] Cohen H., Zohar J., Matar M. The relevance of differential response to trauma in an animal model of posttraumatic stress disorder. *Biol Psychiatry*. 2003;53:463–73.

- [70] Kerns J. G., Cohen J. D., MacDonald A. W., 3rd, Cho R. Y., Stenger V. A., Carter C. S. Anterior cingulate conflict monitoring and adjustments in control. *Science*. 2004;303:1023–6.
- [71] Bush D. E., Sotres-Bayon F., LeDoux J. E. Individual differences in fear: isolating fear reactivity and fear recovery phenotypes. *J Trauma Stress*. 2007;20:413–22.
- [72] Sanford L. D., Yang L., Tang X. Influence of contextual fear on sleep in mice: a strain comparison. *Sleep*. 2003;26:527–40.
- [73] Buchel C., Dolan R. J. Classical fear conditioning in functional neuroimaging. *Curr Opin Neurobiol*. 2000;10:219–23.
- [74] LaBar K. S., Gatenby J. C., Gore J. C., LeDoux J. E., Phelps E. A. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron*. 1998;20:937–45.
- [75] Linnman C., Rougemont-Bucking A., Beucke J. C., Zeffiro T. A., Milad M. R. Unconditioned responses and functional fear networks in human classical conditioning. *Behav Brain Res*. 2011;221:237–45.
- [76] Milad M. R., Quirk G. J., Pitman R. K., Orr S. P., Fischl B., Rauch S. L. A role for the human dorsal anterior cingulate cortex in fear expression. *Biol Psychiatry*. 2007;62:1191–4.
- [77] Phelps E. A., Delgado M. R., Nearing K. I., LeDoux J. E. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron*. 2004;43:897–905.
- [78] Sehlmeier C., Schoning S., Zwitserlood P., Pfleiderer B., Kircher T., Arolt V., et al. Human fear conditioning and extinction in neuroimaging: a systematic review. *PLoS One*. 2009;4:e5865.
- [79] Boll S., Gamer M., Gluth S., Finsterbusch J., Buchel C. Separate amygdala subregions signal surprise and predictiveness during associative fear learning in humans. *Eur J Neurosci*. 2013;37:758–67.
- [80] Kalisch R., Wiech K., Critchley H. D., Dolan R. J. Levels of appraisal: a medial prefrontal role in high-level appraisal of emotional material. *Neuroimage*. 2006;30:1458–66.
- [81] Knight D. C., Waters N. S., Bandettini P. A. Neural substrates of explicit and implicit fear memory. *Neuroimage*. 2009;45:208–14.
- [82] Milad M. R., Wright C. I., Orr S. P., Pitman R. K., Quirk G. J., Rauch S. L. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry*. 2007;62:446–54.
- [83] Milad M. R., Pitman R. K., Ellis C. B., Gold A. L., Shin L. M., Lasko N. B., et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol Psychiatry*. 2009;66:1075–82.

- [84] Nofzinger E. A., Buysse D. J., Miewald J. M., Meltzer C. C., Price J. C., Sembrat R. C., et al. Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. *Brain*. 2002;125:1105–15.
- [85] Braun A. R., Balkin T. J., Wesenten N. J., Carson R. E., Varga M., Baldwin P., et al. Regional cerebral blood flow throughout the sleep-wake cycle. An H₂(15)O PET study. *Brain*. 1997;120(Pt 7):1173–97.
- [86] Spoormaker V. I., Gvozdanovic G. A., Samann P. G., Czeisler M. Ventromedial prefrontal cortex activity and rapid eye movement sleep are associated with subsequent fear expression in human subjects. *Exp Brain Res*. 2014;232:1547–54.
- [87] Shin L. M., Rauch S. L., Pitman R. K. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann NY Acad Sci*. 2006;1071:67–79.
- [88] Kitayama N., Quinn S., Bremner J. D. Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *J Affect Disord*. 2006;90(2–3):171–4.
- [89] Rauch S. L., Shin L. M., Phelps E. A. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biol Psychiatry*. 2006;60:376–82.
- [90] Shin L. M., Wright C. I., Cannistraro P. A., Wedig M. M., McMullin K., Martis B., et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiatry*. 2005;62:273–81.
- [91] Rauch S. L., Whalen P. J., Shin L. M., McInerney S. C., Macklin M. L., Lasko N. B., et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry*. 2000;47:769–76.
- [92] Milad M. R., Quirk G. J. Fear extinction as a model for translational neuroscience: ten years of progress. *Annu Rev Psychol*. 2012;63:129–51.
- [93] Maren S., Phan K. L., Liberzon I. The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nat Rev Neurosci*. 2013;14:417–28.
- [94] Bremner J. D., Vermetten E., Schmahl C., Vaccarino V., Vythilingam M., Afzal N., et al. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med*. 2005;35:791–806.
- [95] Liu X., Yang L., Wellman L. L., Tang X., Sanford L. D. GABAergic antagonism of the central nucleus of the amygdala attenuates reductions in rapid eye movement sleep after inescapable footshock stress. *Sleep*. 2009;32:888–96.
- [96] Cousens G., Otto T. Both pre- and posttraining excitotoxic lesions of the basolateral amygdala abolish the expression of olfactory and contextual fear conditioning. *Behav Neurosci*. 1998;112:1092–103.

- [97] Koo J. W., Han J. S., Kim J. J. Selective neurotoxic lesions of basolateral and central nuclei of the amygdala produce differential effects on fear conditioning. *J Neurosci.* 2004;24:7654–62.
- [98] Maren S. Overtraining does not mitigate contextual fear conditioning deficits produced by neurotoxic lesions of the basolateral amygdala. *J Neurosci.* 1998;18:3088–97.
- [99] Maren S., Aharonov G., Fanselow M. S. Retrograde abolition of conditional fear after excitotoxic lesions in the basolateral amygdala of rats: absence of a temporal gradient. *Behav Neurosci.* 1996;110:718–26.
- [100] Sacchetti B., Lorenzini C. A., Baldi E., Tassoni G., Bucherelli C. Auditory thalamus, dorsal hippocampus, basolateral amygdala, and perirhinal cortex role in the consolidation of conditioned freezing to context and to acoustic conditioned stimulus in the rat. *J Neurosci.* 1999;19:9570–8.
- [101] Helmstetter F. J., Bellgowan P. S. Effects of muscimol applied to the basolateral amygdala on acquisition and expression of contextual fear conditioning in rats. *Behav Neurosci.* 1994;108:1005–9.
- [102] Muller J., Corodimas K. P., Fridel Z., LeDoux J. E. Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit conditioned stimulus and to contextual stimuli. *Behav Neurosci.* 1997;111:683–91.
- [103] Bohus B., Koolhaas J. M., Luiten P. G. M., Korte S. M., Roozendaal B, Wiersma A. The neurobiology of the central nucleus of the amygdala in relation to neuroendocrine outflow. *Prog Brain Res.* 1996;107:447–60.
- [104] Roozendaal B, Koolhaus J. M., Bohus B. Attenuated cardiovascular, neuroendocrine, and behavioral responses after a single footshock in central amygdaloid lesioned male rats. *Physiol Behav.* 1991;50:771–5.
- [105] Roozendaal B, Koolhaus J. M., Bohus B. Central amygdala lesions affect behavioral and autonomic balance during stress in rats. *Physiol Behav.* 1991;50:777–81.
- [106] Sanford L. D., Parris B., Tang X. GABAergic regulation of the central nucleus of the amygdala: implications for sleep control. *Brain Res.* 2002;956:276–84.
- [107] Sanford L. D., Tejani-Butt S. M., Ross R. J., Morrison A. R. Amygdaloid control of alerting and behavioral arousal in rats: involvement of serotonergic mechanisms. *Arch Ital Biol.* 1995;134:81–99.
- [108] Calvo J. M., Simón-Arceo K., Fernández-Mas R. Prolonged enhancement of REM sleep produced by carbachol microinjection into the amygdala. *Neuro Rep.* 1996;7:577–80.
- [109] Sanford L. D., Nassar P., Ross R. J., Schulkin J., Morrison A. R. Prolactin microinjections into the amygdalar central nucleus lead to decreased NREM sleep. *Sleep Res Online.* 1998;1:109–13.

- [110] Zhu G. Q., Zhong M. K., Zhang J. X., Zhao L. Z., Ke D. P., Wang M., et al. [Role of basolateral amygdaloid nuclei in sleep and wakeful state regulation]. *Sheng Li Xue Bao.* 1998;50:688–92.
- [111] Jha S. K., Brennan F. X., Pawlyk A. C., Ross R. J., Morrison A. R. REM sleep: a sensitive index of fear conditioning in rats. *Eur J Neurosci.* 2005;21:1077–80.
- [112] Sanford L. D., Yang L., Liu X., Tang X. Effects of tetrodotoxin (TTX) inactivation of the central nucleus of the amygdala (CNA) on dark period sleep and activity. *Brain Res.* 2006;1084:80–8.
- [113] Amaral D. G., Price J. L., Pitkanen A., Carmichael S. T. Anatomical organization of the primate amygdaloid complex. In: Aggleton J, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction.* New York: Wiley-Liss, Inc.; 1992. p. 1–66.
- [114] Krettek J. E., Price J. L. Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. *J Comp Neurol.* 1978;178:225–54.
- [115] Peyron C., Petit J. M., Rampon C., Jouvet M., Luppi P. H. Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience.* 1998;82:443–68.
- [116] Price J. L., Russchen F. T., Amaral D. G. The limbic region. II: The amygdaloid complex. In: Swanson L, editor. *Handbook of chemical neuroanatomy Integrated systems of the CNA, Part I.* New York: Elsevier; 1987. p. 279–375.
- [117] Semba K., Fibiger H. C. Afferent connections of the laterodorsal and the pedunculo-pontine tegmental nuclei in the rat: a retro- and antero-grade transport and immuno-histochemical study. *J Comp Neurol.* 1992;323:387–410.
- [118] Inagaki S., Kawai Y., Matsuzaki T., Shiosaka S., Tohyama M. Precise terminal fields of the descending somatostatinergic neuron system from the amygdaloid complex of the rat. *J Hirnforsch.* 1983;24:345–56.
- [119] Davis M., Whalen P. J. The amygdala: vigilance and emotion. *Mol Psychiatry.* 2001;6:13–34.
- [120] Steriade M., McCarley R.W. *Brainstem Control of Wakefulness and Sleep.* New York: Plenum Press; 1990.
- [121] Falls W. A., Carlson S., Turner J. G., Willott J. F. Fear-potentiated startle in two strains of inbred mice. *Behav Neurosci.* 1997;111:855–61.
- [122] Smith S. M., Vale W. W. The role of the hypothalamic-pituitary-adrenal axis in neuro-endocrine responses to stress. *Dialogues Clin Neurosci.* 2006;8:383–95.
- [123] Irit Akirav and Mouna Maroun, “The Role of the Medial Prefrontal Cortex-Amygdala Circuit in Stress Effects on the Extinction of Fear,” *Neural Plasticity*, vol. 2007, Article ID 30873, 11 pages, 2007. doi:10.1155/2007/30873

- [124] Maier S. F., Amat J., Baratta M. V., Paul E., Watkins L. R. Behavioral control, the medial prefrontal cortex, and resilience. *Dialogues Clin Neurosci.* 2006;8:397–406.
- [125] Sanford L. D., Suchecki D., Meerlo P. Stress, arousal, and sleep. *Curr Top Behav Neurosci.* 2015;25:379–410.
- [126] Vertes R. P. Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse.* 2004;51:32–58.
- [127] Belleville G., Guay S., Marchand A. Persistence of sleep disturbances following cognitive-behavior therapy for posttraumatic stress disorder. *J Psychosom Res.* 2011;70:318–27.
- [128] Gutner C. A., Casement M. D., Stavitsky Gilbert K., Resick P. A. Change in sleep symptoms across cognitive processing therapy and prolonged exposure: a longitudinal perspective. *Behav Res Ther.* 2013;51:817–22.
- [129] Jonas D. E., Cusack K., Forneris C. A., Wilkins T. M., Sonis J., Middleton J. C., et al. Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD). Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Apr. Report No.: 13-EHC011-EF.2013.
- [130] Galovski T. E., Monson C., Bruce S. E., Resick P. A. Does cognitive-behavioral therapy for PTSD improve perceived health and sleep impairment? *J Trauma Stress.* 2009;22:197–204.
- [131] Zayfert C., DeViva J. C. Residual insomnia following cognitive behavioral therapy for PTSD. *J Traum Stress.* 2004;17:69–73.
- [132] Morin C.M., Espie C.A. *Insomnia: a clinical guide to assessment and treatment.* New York: Kluwer Academic/Plenum Publisher; 2003.
- [133] Morin C. M., Benca R. Chronic insomnia. *Lancet.* 2012;379:1129–41.
- [134] Siebern A. T., Manber R. New developments in cognitive behavioral therapy as the first-line treatment of insomnia. *Psychol Res Behav Manag.* 2011;4:21–8.
- [135] Talbot L. S., Maguen S., Metzler T. J., Schmitz M., McCaslin S. E., Richards A., et al. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. *Sleep.* 2014;37:327–41.
- [136] Cooper N. A., Clum G. A. Imaginal flooding as a supplementary treatment for PTSD in combat veterans: a controlled study. *Behav Ther.* 1989;20:381–91.
- [137] Hansen K., Hofling V., Kroner-Borowik T., Stangier U., Steil R. Efficacy of psychological interventions aiming to reduce chronic nightmares: a meta-analysis. *Clin Psychol Rev.* 2013;33:146–55.

- [138] Nappi C. M., Drummond S. P., Hall J. M. Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. *Neuropharmacology*. 2012;62:576–85.
- [139] Germain A., Krakow B., Faucher B., Zadra A., Nielsen T., Hollifield M., et al. Increased mastery elements associated with imagery rehearsal treatment for nightmares in sexual assault survivors with PTSD. *Dreaming*. 2004;14:195–206.
- [140] Casement M. D., Swanson L. M. A meta-analysis of imagery rehearsal for post-trauma nightmares: effects on nightmare frequency, sleep quality, and posttraumatic stress. *Clin Psychol Rev*. 2012;32:566–74.
- [141] Cook J. M., Harb G. C., Gehrman P. R., Cary M. S., Gamble G. M., Forbes D., et al. Imagery rehearsal for posttraumatic nightmares: a randomized controlled trial. *J Trauma Stress*. 2010;23:553–63.
- [142] Institute of Medicine. Treatment of posttraumatic stress disorder in military and veteran populations: final assessment. Washington, DC.: National Academies Press; 2014.
- [143] Watts B. V., Schnurr P. P., Mayo L., Young-Xu Y., Weeks W. B., Friedman M. J. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry*. 2013;74:e541–50.
- [144] Ravindran L. N., Stein M. B. Pharmacotherapy of PTSD: premises, principles, and priorities. *Brain Res*. 2009;1293:24–39.
- [145] Aurora R. N., Zak R. S., Auerbach S. H., Casey K. R., Chowdhuri S., Karippot A., et al. Best practice guide for the treatment of nightmare disorder in adults. *J Clin Sleep Med*. 2010;6:389–401.
- [146] Stein M. B., Kline N. A., Matloff J. L. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002;159:1777–9.
- [147] Han C., Pae C. U., Wang S. M., Lee S. J., Patkar A. A., Masand P. S., et al. The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder. *J Psychiatr Res*. 2014;56:72–81.
- [148] Schutte-Rodin S., Broch L., Buysse D., Dorsey C., Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4:487–504.
- [149] Pollack M. H., Hoge E. A., Worthington J. J., Moshier S. J., Wechsler R. S., Brandes M., et al. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2011;72:892–7.

- [150] Raskind M. A., Peterson K., Williams T., Hoff D. J., Hart K., Holmes H., et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry*. 2013;170:1003–10.
- [151] Raskind M. A., Peskind E. R., Kanter E. D., Petrie E. C., Radant A., Thompson C. E., 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.
- [152] Raskind M. A., Peskind E. R., Hoff D. J., Hart K. L., Holmes H. A., Warren D., 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.