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The influence of sleep on fear extinction in trauma-related disorders

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ABSTRACT

In Posttraumatic Stress Disorder (PTSD), fear and anxiety become dysregulated following psychologically traumatic events. Regulation of fear and anxiety involves both high-level cognitive processes such as cognitive reattribution and low-level, partially automatic memory processes such as fear extinction, safety learning and habituation. These latter processes are believed to be deficient in PTSD. While insomnia and nightmares are characteristic symptoms of existing PTSD, abundant recent evidence suggests that sleep disruption prior to and acute sleep disturbance following traumatic events both can predispose an individual to develop PTSD. Sleep promotes consolidation in multiple memory systems and is believed to also do so for low-level emotion-regulatory memory processes. Consequently sleep disruption may contribute to the etiology of PTSD by interfering with consolidation in low-level emotion-regulatory memory systems. During the first weeks following a traumatic event, when in the course of everyday life resilient individuals begin to acquire and consolidate these low-level emotion-regulatory memories, those who will develop PTSD symptoms may fail to do so. This deficit may, in part, result from alterations of sleep that interfere with their consolidation, such as REM fragmentation, that have also been found to presage later PTSD symptoms. Here, sleep disruption in PTSD as well as fear extinction, safety learning and habituation and their known alterations in PTSD are first briefly reviewed. Then neural processes that occur during the early post-trauma period that might impede low-level emotion regulatory processes through alterations of sleep quality and physiology will be considered. Lastly, recent neuroimaging evidence from a fear conditioning and extinction paradigm in patient groups and their controls will be considered along with one possible neural process that may contribute to a vulnerability to PTSD following trauma.

1. Introduction

In the majority of individuals, there are adaptive processes leading to resilience and recovery following a traumatic event. Many, however, show varying degrees of acute sequela, some meeting DSM-5 criteria for Acute Stress Disorder (ASD) while a much smaller number develop a more enduring Posttraumatic Stress Disorder (PTSD). Illustrating that only a minority develop PTSD, approximately 50%–70% of adults worldwide experience at least one traumatic event during their lifetime, nonetheless lifetime prevalence of PTSD is only in the range of 3–15% (Atwoli et al., 2015; Benjet et al., 2016; Koenen et al., 2017). The US lifetime prevalence of PTSD falls in this range at 6.8%–8.7% (Kessler et al., 2005). Moreover, although elevated relative to the general population, only approximately 25% of combat-exposed veterans develop PTSD (Fulton et al., 2015; Kok et al., 2012). Insomnia is a ubiquitous sequel of trauma and may occur even in the absence of full ASD criteria (Sinha, 2016). Whereas in the general population world-wide approximately 30% of individuals experience insomnia symptoms and roughly 10% meet criteria for Insomnia Disorder (ID) (APA, 2022; Roth et al., 2007). insomnia symptoms have been estimated present in 63–90% of individuals with PTSD or post-traumatic stress symptoms (PTSS) worldwide (Ahmadi et al., 2022; Koffel et al., 2016). Factors leading from acute trauma reactivity to enduring PTSD might include the failure of adaptive processes supporting resilience and/or emergence of new maladaptive processes that prolong and worsen symptoms. How does disturbed sleep interact with peri-traumatic and acute stress reactions in such a way as to tip the balance toward PTSS or full PTSD criteria and not resilience? This review will explore effects of sleep disruption on

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low-level processes of emotion regulation– fear extinction, habituation and safety learning– that may play a role in the emergence of PTSS following a psychological trauma. Like idiopathic ID, posttraumatic insomnia is believed to reflect physiological hyperarousal that, following trauma, may become acutely elevated (Bryant et al., 2000; Shalev et al., 1998). We hypothesize that, in those who progress to PTSD following trauma, posttraumatic hyperarousal, by disrupting sleep, may impede consolidation of the extinction, habituation and safety memories that promote natural recovery in the resilient majority. REM sleep, in particular, has been implicated in offline consolidation of extinction and safety learning (Colvonen et al., 2019; Pace-Schott et al., 2015a,b), and REM abnormalities reported in the early aftermath of trauma have been hypothesized to play a significant role in the development of PTSD (Colvonen et al., 2019; Mellman et al., 2002; Mellman et al., 2007; Pace-Schott et al., 2015b; Straus et al., 2018a,b). Thus, after reviewing sleep and fear extinction in PTSD and healthy subjects, we will speculate on possible effects of acute posttraumatic physiology on sleep-dependent consolidation of low-level memory and, in turn, on the early development of PTSD. Lastly, we will summarize our recent neuroimaging studies of fear extinction in trauma-exposed individuals with and without PTSD and ID and suggest what these findings might add to our understanding of vulnerabilities to PTSD (Pace-Schott et al., 2015b).

2. Fear conditioning, fear extinction, habituation and safety learning

Fear conditioning occurs when an emotionally neutral stimulus is repeatedly paired with an inherently aversive unconditioned stimulus (US). The neutral stimulus thereby becomes a conditioned stimulus (CS) with the capability, on its own, to evoke a fearful response. This acquired response to a previously neutral stimulus is termed a conditioned response (CR). When this CS is subsequently presented repeatedly without the US, extinction (reduction) of the CR occurs. However, rather than erasing the CS-US association, extinction represents formation of a new inhibitory memory, viz. CS-no US, that competitively inhibits the memory of the CS-US contingency and its associated CR when the CS is again encountered (Bouton et al., 2006; Herry et al., 2010; Ji and Maren, 2007; Konorski, 1967; Maren, 2011; Milad and Quirk, 2012; Myers and Davis, 2002; Pavlov, 1927; Quirk and Mueller, 2008). In human fear conditioning and extinction studies, a US such as a mild electric shock or aversive sound is used to reinforce a CR (skin conductance or eye-blink startle responses) to one or more CS that are designated CS+. Typically, another CS is never reinforced, is designated a CS- and its CR serves as a comparator to demonstrate differential conditioning based on fear learning for the CS+ associated with the US. This type of paradigm allows for the measurement of fear memory (i.e., reactivity to the CS+ following a post-conditioning delay), safety signal memory (i.e., reactivity to the CS- following a post-conditioning delay Jovanovic et al., 2012; Straus et al., 2018a) and extinction memory (i.e., maintained lowered reactivity to the CS+ following a post-extinction-learning delay). Persons diagnosed with PTSD have repeatedly been found to have deficient recall of previously learned extinction (Milad et al., 2008; Milad et al., 2009; Pace-Schott et al., 2015b; VanElzakker et al., 2014; Zuj et al., 2016a,b) as well as deficient safety learning (Duits et al., 2015; Jovanovic et al., 2012; Straus et al., 2018a). Although a myriad of other biopsychosocial factors positively or negatively influence natural resilience following trauma (Pace-Schott et al., 2015b; Pitman et al., 2012; Shalev et al., 2017), it might be that extinction (e.g., of responses to trauma cues), habituation (e.g., to trauma memories) and safety learning (e.g., from resumption of routines) in the course of everyday life are robust in resilient persons and weaker in those who develop ASD, PTSS or PTSD.

Two important caveats should be noted. First, the term "fear conditioning" is imprecise with regard to the actual biological and psychological processes evoked in human paradigms and would more accurately be termed "threat conditioning" (LeDoux, 2014; LeDoux and Pine, 2016). Nonetheless "fear conditioning" is used here as it is the historical term for such paradigms. Second, there is a great deal of variation in the literature among techniques by which fear conditioning, extinction learning and extinction recall are measured as well as variation in how response variables and indices of these forms of learning and memory are calculated. In the case of the former, skin conductance response and fear potentiated startle (electromyography of blink startle response of the orbicularis oculi muscle) are the main physiological measures and shock expectancy or stimulus valence ratings serve as self-report measures (most often but not always accompanied by a physiological measure). Response variables, can be measured either as responses to the CS+ alone or as a differential measure that isolates learning of threat from nonspecific reactivity by subtracting responses to the CS- from those to the temporally corresponding CS+. Finally, with regard to indices of mnemonic processes, there have been multiple measures used, especially for extinction recall, a situation that has generated significant controversy with clear demonstration of non-equivalence among different extinction recall indices (Lonsdorf et al., 2022) and strong calls for standardization (Lonsdorf and Merz, 2017; Lonsdorf et al., 2019). Although beyond the scope of this review, detailed discussions can be found in (Kobayashi et al., in press; Lonsdorf et al., 2017).

3. Sleep and consolidation of fear, extinction and safety memory in healthy controls and PTSD

3.1. Healthy individuals

3.1.1. Overview

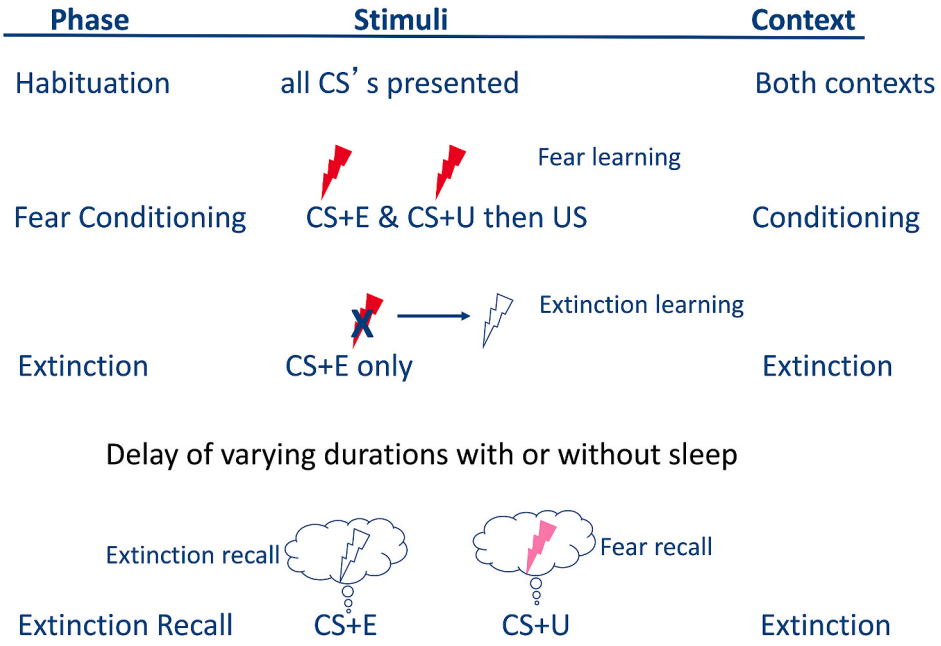
Sleep supports the consolidation and generalization of fear and extinction memories in laboratory studies with healthy adults, and sleep is widely hypothesized to also do so following analog (experimental) trauma as well as actual trauma and its treatment with exposure-based therapies (Chellappa and Aeschbach, 2022; Colvonen et al., 2019; Davidson and Pace-Schott, 2020, 2021; Pace-Schott et al., 2015a,b). Whereas findings remain mixed, both rapid eye-movement (REM) sleep and slow wave sleep (SWS) have been linked to processing these types of emotional experiences (Colvonen et al., 2019; Davidson and Pace-Schott, 2020; Pace-Schott et al., 2015a,b; Schenker et al., 2021). Retention delays vary across studies and include overnight sleep between each learning and recall phase (e.g., Marshall et al., 2014; Straus et al., 2017), extinction immediately following conditioning then a 12–24 h delay with overnight sleep (e.g., Bottary et al., 2020a,b; Pace-Schott et al., 2013; Seo et al., 2020), a many-day delay before extinction recall (Vanuk et al., 2022), or a daytime nap opportunity or wakefulness between learning and recall phases (e.g., Ai et al., 2015; Hauner et al., 2013; He et al., 2014; Spoormaker et al., 2010) and selective sleep stage deprivation paradigms (Spoormaker et al., 2012) (for a review see Kobayashi et al., in press, and for one example see Box 1). Varying when sleep occurs provides an opportunity to understand how sleep macro- and micro-architecture may influence encoding and consolidation processes (Davidson et al., 2021; Rasch and Born, 2013). Findings to date have direct translational relevance for understanding and treating anxiety and traumatic stress disorders, conditions in which sleep disturbances are extremely common (Pace-Schott et al., 2015b). Since fear extinction is believed to be an inhibitory memory that competes with fear memory (Bouton et al., 2006; Herry et al., 2010; Ji and Maren, 2007; Konorski, 1967; Maren, 2011; Milad and Quirk, 2012; Myers and Davis, 2002; Pavlov, 1927; Quirk and Mueller, 2008), it is important to compare the effects of sleep on both fear and its extinction in healthy individuals and those with PTSD.

3.1.2. Sleep and fear conditioning

Sleep, and REM sleep in particular, prior to and following fear conditioning, appear critical for fear learning as well as for fear memory consolidation and generalization. For example, participants deprived of

Box 1

One validated 2-day/2-session fear conditioning and extinction protocol, that can be adapted for use with or without fMRI imaging, is the widely employed Milad paradigm (Milad et al., 2007) illustrated below. In this protocol, during Session 1, following habituation to all stimuli that will be viewed, fear conditioning is established (via 63% partial reinforcement), using a mild electric shock, to 2 differently colored lamps (CS+), but not a third color (CS-), in a virtual "conditioning" context. Extinction learning immediately follows during which one CS+ (CS+E) but not the other (CS+U) is extinguished by un-reinforced presentations in an "extinction context". A delay follows during which the quality, duration or timing of sleep and wakefulness can be experimentally varied. Following a delay, in Session 2, responses to all 3 stimuli (CS+E, CS+U, CS-) are tested in the extinction context. Fear conditioning and its extinction are measured using skin conductance responses (SCR) and shock expectancy reports, both of which are easily obtained in the MR environment.



Box 1 Figure. The Milad two-day fear conditioning and extinction paradigm.

sleep on the night prior to fear conditioning report heightened subjective fear ratings (Feng et al., 2018a,b) and exhibit greater psychophysiological responding (Feng et al., 2018a, 2018b; Peters et al., 2014) during fear conditioning compared to those who slept. With respect to fear memory consolidation, participants who slept after fear conditioning, compared to participants deprived of sleep, exhibited greater fear recall in self-reported shock expectancy ratings, amygdala reactivity, and SCR responses, the last of which was positively associated with the amount of time spent in REM during the post-conditioning sleep period (Menz et al., 2013). Using a split-night design, Menz et al. (2016) further showed that fear recall was greater in participants who slept during a period rich in REM sleep compared to those who remained awake during an equivalent delay. Finally, Marshall et al. (2014) found that increased REM from the pre-fear-conditioning to post-fear-conditioning nights predicted greater fear recall. However, at least one study reported that sleep may, in fact, be beneficial for inhibiting fear recall, showing that participants exhibiting greater REM sleep duration on the night following fear conditioning exhibited lower fear recall as measured by reduced skin conductance response (SCR) reactivity and increased activation to the CS+ in the ventromedial prefrontal cortex (vmPFC) (Spoormaker et al., 2014), a region that exerts top-down inhibitory control on emotional brain regions such as the amygdala (Delgado et al., 2016; Kredlow et al., 2021; Milad and Quirk, 2012). With respect to fear generalization, at least one study (Davidson et al., 2018) has also reported that, compared to those who remained awake, participants who slept after fear conditioning better generalized learned fear from the CS+ to the CS-, as evidenced by significantly increased SCR responses to the CS- following sleep. However, other studies have reported either no benefit of sleep over continued wakefulness for fear memory generalization (Davidson et al., 2016), or even increased fear memory generalization following continued wakefulness (Zenses et al., 2020).

3.1.3. Sleep and extinction learning and recall

Like fear memories, sleep has been shown to benefit the encoding and consolidation of extinction memories in healthy adults (Pace-Schott et al., 2015a). For example, baseline sleep quality (Pace-Schott et al., 2015c) and sleep timing regularity (Bottary et al., 2020a,b) have both been shown to predict better extinction recall. In nap (Spoormaker et al., 2010), split-night (Menz et al., 2016), and overnight sleep (Bottary et al., 2020a,b; Straus et al., 2017) studies, greater amounts of post-extinction REM sleep have been shown to support extinction recall expressed behaviorally and in fear network activity in the brain (Menz et al., 2016; Spoormaker et al., 2010). Post-extinction sleep has also been shown to promote the generalization of extinction memories (Pace-Schott et al., 2009). On the other hand, sleep deprivation prior to extinction learning impairs engagement of fear-regulating and extinction-promoting brain regions during extinction learning (Seo et al., 2020) and impairs extinction recall (Straus et al., 2017). Further, REM-selective sleep deprivation following extinction learning impairs extinction recall

(Spoormaker et al., 2012).

3.1.4. Paradoxical effects of sleep on both fear and extinction memory

The apparently paradoxical advantage of the sleep state in the consolidation or generalization of both fear and its extinction may arise from a general enhancement of emotional memory processing during sleep (Pace-Schott et al., 2015a). Common mechanisms for emotional memory consolidation across valence are suggested by several observations. First, d-cycloserine, a memory-promoting partial NMDA agonist can enhance extinction memory following exposure therapy (Inslicht et al., 2022) but can also enhance fear memory in humans (Kalisch et al., 2009). Second, depending upon dose timing, glucocorticoids can enhance learning of either fear or fear extinction (de Quervain et al., 2017). Third, experimental studies using "analog trauma", as well as a few post-emergency room naturalistic studies, have shown mixed results with regard to the effect of sleep on subsequent intrusive memories (reviewed in Davidson and Pace-Schott, 2021). Assuming that emotional memory irrespective of valence may benefit from sleep (albeit likely no more so than other memory systems, Davidson et al., 2021), whether sleep benefits fear or fear extinction in PTSD may depend on relative temporal proximity of sleep to traumatic experiences, their fear-inducing recall or their therapeutic or naturalistic extinction. Moreover, individual differences in PTSD symptoms (e.g., trauma-related nightmares), continued traumatizing experiences, past trauma history, personality factors or comorbidities may also influence whether sleep serves to consolidate, extinguish or have no influence on traumatic memories. It is likely, however, that in the majority of individuals who do not develop PTSD following a traumatic experience, naturally occurring extinction learning (viz., of safety despite trauma reminders) is consolidated, as are other memories, during sleep.

3.1.5. Circadian effects on extinction learning and memory

In addition to sleep's effects on extinction, a number of experimental and clinical studies suggest that circadian rhythms affect extinction learning and recall. For example, in Pace-Schott et al. (2013), 6 groups completed the Milad protocol (Box 1) in either the morning or following 3 different delay durations. Fear conditioning did not differ between morning and evening, however, extinction was better learned in the morning. Collapsing across CS+E and CS+U stimuli, there was a smaller differential SCR at extinction recall in the morning. Morning extinction recall also showed better generalization from the CS+E to CS+U, i.e., the response to the CS+U, compared to the CS+E remained larger only in the evening. Thus, extinction was learned faster and its memory was better generalized in the morning than in the evening. In clinical settings, exposure-based therapy for panic disorder (PD) (Meuret et al., 2016) and spider phobia (Lass-Hennemann and Michael, 2014) showed greater efficacy when provided in the morning. The well-documented morning peak (acrophase) of endogenous cortisol (Lass-Hennemann and Michael, 2014; Meuret et al., 2015, 2016; Pace-Schott et al., 2013) is a potential mechanism producing this morning advantage (see Section 4.4.2 below).

3.1.6. Sleep and safety signal learning and recall

Unlike conditioned threat cues, which signal the potential for an aversive outcome, safety signals are cues that indicate the nonoccurrence of an aversive outcome (Christianson et al., 2012). Safety signals are differentiated from threat cues through a process of safety learning (Colvonen et al., 2019). Safety learning differs from extinction learning in that safety signals are either cues never associated with an aversive outcome (e.g., CS- in a differential fear conditioning paradigm), or cues that, when presented in combination with another cue previously signaling threat, are able to inhibit fear response (conditional discrimination paradigm) (Christianson et al., 2012; Jovanovic et al., 2012; Straus et al., 2018a). Extinction learning, on the other hand, involves creating a new memory associated with a once threatening cue that competes with the original threat memory for responding to that same cue. In traditional Pavolvian conditioning paradigms, CS- stimuli represent safety signals, as they are never paired with an aversive outcome, such as a finger shock, and are thus learned to signal the nonoccurrence of an aversive outcome. On the other hand, a CS+ stimulus, that is a stimulus that at one point was paired with an aversive outcome, may change in perceived valence contingent upon extinction learning during which its repeated presentations without the aversive outcome encode an inhibitory extinction memory. Sleep prior to and following safety learning has been shown to predict safety signal learning and retention. A recent meta-analysis suggested that greater pre-fear extinction learning percent SWS was associated with lower reactivity to safety signals (better safety signal learning) during extinction (Schenker et al., 2021). In an earlier study, REM sleep following safety signal learning was critical for safety signal consolidation (Marshall et al., 2014).

3.1.7. Sleep and non-associative memory

Neural changes underlying habituation, or its converse sensitization, are non-associative memories that, like fear conditioning and extinction, must consolidate in order to continue to influence behavior (Craske et al., 2008; McSweeney and Swindell, 2002). Habituation refers to the reduction in a behavior (e.g., fear response and avoidance in PTSD) with repeated exposure to stimuli (Rankin et al., 2009) including those that were once reinforced (i.e., accompanied trauma) (McSweeney and Murphy, 2009). Although habituation and extinction are dissociable features of learning and memory processes (McSweeney and Swindell, 2002), both habituation and extinction are likely to be taking place at encoding ("within session") and consolidation ("between session") stages (Cooper et al., 2017). Therefore, following experimental extinction (e.g., Kleim et al., 2014; Pace-Schott et al., 2012), naturalistic exposure, or exposure-based psychotherapy, sleep is likely to involve consolidation of between-session habituation as well as of extinction memory (Cooper et al., 2017; McSweeney and Swindell, 2002; Pace--Schott et al., 2015a). Sensitization, a non-associative mnemonic process opposite to between-session habituation, has been shown to exacerbate anxiety symptoms following trauma (Smid et al., 2012). Therefore it should be noted that sleep also appears to prevent between-session sensitization (Pace-Schott et al., 2011, 2012, 2014).

3.2. Sleep and extinction learning and memory in PTSD

3.2.1. Sleep abnormalities in PTSD

Degradation of subjective and objective sleep quality is commonly reported in studies of individuals diagnosed with PTSD (Babson and Feldner, 2010; Germain, 2013; Kobayashi et al., 2007; Mellman, 2008a; Pace-Schott et al., 2015b; Ross et al., 1989; Spoormaker and Montgomery, 2008; Zhang et al., 2019). Complete consideration of abnormalities of sleep quality, architecture and microstructure in PTSD is beyond the scope of this article. These topics have been thoroughly reviewed in recent meta-analyses (Kobayashi et al., 2007; Zhang et al., 2019) and reviews (Chellappa and Aeschbach, 2022; Richards et al., 2020). It should be noted that, in addition to sleep disorders directly linked with PTSD such as posttraumatic insomnia and nightmare disorder, certain intrinsic sleep disorders such as obstructive sleep apnea (OSA) have a much higher prevalence in individuals with PTSD (Colvonen et al., 2015; Krakow et al., 2015; Zhang et al., 2017), an elevated prevalence also seen among individuals with mood, anxiety, and psychotic disorders (Sharafkhaneh et al., 2005).

3.2.2. Sleep and abnormalities of extinction and safety learning and memory in PTSD

To translate basic fear and extinction memory findings from healthy participants to individuals with relevant psychological disorders, a small body of recent work has implemented the above-mentioned protocols in a variety of patient groups for which fear conditioning and extinction are critical. For example, trauma-exposed participants with and without

PTSD who obtained more REM sleep during a post-fear conditioning nap exhibited more rapid extinction learning (Richards et al., 2022). In a separate study, REM sleep following fear conditioning promoted extinction memory retention in healthy participants, but was detrimental for extinction memory retention in those with insomnia disorder, a common comorbidity of PTSD (Bottary et al., 2020). Because fear conditioning and extinction learning occurred on the same day in this study, we hypothesized that REM sleep-related emotional memory processing for those with insomnia disorder may have been biased toward the fear over the extinction memory trace (Bottary et al., 2020). While this is an intriguing possibility given that REM sleep abnormalities have been observed in both insomnia (Riemann et al., 2012) and PTSD (Colvonen et al., 2019), this hypothesis remains speculative. Lastly, Straus et al. (2018b) found that REM sleep percentage following fear conditioning was positively associated with safety signal recall in veterans with PTSD.

3.2.3. *Sleep's role in processing simulated and real-life trauma*

Several recent attempts have been made to study sleep's role in the processing of simulated and real-life traumas. One approach has been to expose participants to upsetting "analog trauma" films, and then monitor intrusive memories of the films across several subsequent days (Holmes and Bourne, 2008). Participants obtaining sleep, compared to those who remained awake or were deprived of sleep after trauma film viewing reported fewer and less intense trauma-film-related intrusive thoughts (Kleim et al., 2016; Sopp et al., 2019; Woud et al., 2018; Zeng et al., 2021), though see opposing results (Kuriyama et al., 2010; Porcheret et al., 2015) and for a review see (Davidson and Pace-Schott, 2021). REM sleep amount and theta power on the night after trauma film viewing has been linked to reduced analog PTSD symptoms, such as re-experiencing (Sopp et al., 2019), though a higher density of rapid eye-movements during REM sleep has been shown to increase trauma-film-related intrusive thoughts (Kleim et al., 2016).

3.2.4. *Uses for sleep in enhancing therapeutic extinction*

A small, but growing number of translational studies have been conducted in an attempt to use sleep as a means of enhancing therapeutic extinction learning (see Azza et al., 2020 for a review). For example, sleep versus wakefulness following a simulation of exposure therapy for spider phobia that involved repeatedly viewing videos of behaving spiders, promoted consolidation and generalization of acquired extinction (Pace-Schott et al., 2012). Similarly, a 90-min nap following virtual reality exposure reduced fearful thoughts when participants were exposed to real spiders (Kleim et al., 2014). In a separate study, Pace-Schott et al. (2018) demonstrated that brief naps following exposure-based psychotherapy for social anxiety disorder may enhance the physiological expression of extinction learning during a social challenge, albeit not influencing self-report clinical assessments.

4. Sleep, extinction and the early development of PTSD

4.1. *Overview*

Previous reviews have identified a number of ways in which abnormalities in low-level processes such as fear conditioning, extinction learning and memory, safety learning and habituation may predispose individuals to PTSD (Jovanovic et al., 2012; Jovanovic and Norrholm, 2011; Jovanovic et al., 2010; Milad and Quirk, 2012; Pitman et al., 2012; Straus et al., 2018a; Zuj et al., 2016b) as well as how sleep or sleep disruption may play a role in each of these processes (Colvonen et al., 2019; Germain et al., 2008; Pace-Schott et al., 2015a,b). There have, however, been fewer investigations of how sleep may influence the ways in which early responses to trauma can transform into the enduring and often worsening symptoms of PTSD. Following a traumatic event, sleep effects on low-level learning processes might constitute predisposing, precipitating, perpetuating factors as advanced in Spielman's influential 3-P model of insomnia (Spielman et al., 1987) as applied to other disease conditions (e.g., Wright et al., 2019). The influence of sleep quality and physiology on the memory systems that encode and consolidate fear and extinction may influence which individuals will develop ASD, PTSS or PTSD following a traumatic experience as well as inform strategies for early intervention. Most trauma-exposed individuals who progress to PTSD/PTSS show some acute symptoms (whether or not meeting criteria for ASD) and only a minority show a symptom-free delay before PTSD onset rather than a worsening of existing symptoms (Andrews et al., 2007; Bryant et al., 2012; Galatzer-Levy et al., 2018; Porcheret et al., 2020). Nonetheless, effects of acute stress on sleep and its associated emotional memory processing may influence emergence or worsening of symptoms during the initial weeks post-trauma. We will first review findings showing that features of pre-trauma or acute post-trauma sleep predict progression to PTSS/PTSD. We will then examine post-trauma factors that may influence the ability of sleep to consolidate threat or threat-inhibitory memory. Such factors include activation of central and peripheral stress mechanisms, generalized hyperarousal and post-traumatic insomnia, and alterations of REM sleep. There is, of course, much variability in these interactions. For example, sleep and memory interactions that follow isolated traumatic events undoubtedly differ from those resulting from sustained or repetitive stressors. Moreover, the effects of prolonged stress on sleep and memory are likely to differ in situations of sustained helplessness compared with situations in which individuals are able to employ strategies to suppress fear in order to preserve survival or functioning.

4.2. *Sleep symptoms as predictive/predisposing of PTSD*

PTSD has been described as a disorder of deficient fear regulation (Kredlow et al., 2021; Pitman et al., 2012; Shalev et al., 2017). As normal sleep helps regulate emotion (Goldstein and Walker, 2014), it is unsurprising that poor sleep quality that precedes a traumatic event (e.g., sleep disorders) or acute sleep abnormalities that follow a traumatic experience (e.g., posttraumatic insomnia, nightmares) are associated with elevated risk for later development of PTSS and PTSD (reviewed in Azza et al., 2020; Babson and Feldner, 2010; Pace-Schott et al., 2015b; Wright et al., 2011). For example, motor vehicle accident (MVA) survivors who later developed PTSS showed more severe sleep disturbances immediately post MVA that failed to normalize over time as compared with survivors who showed milder sequela (Koren et al., 2002). Similarly, during the initial weeks following traumatic injury, Mellman and colleagues have shown that subjective insomnia, nightmare severity, REM fragmentation and higher sympathetic tone during REM predict later development of PTSS (Mellman et al., 2002, 2004, 2007). Sleep disorders preceding trauma exposure also elevate risk of PTSD following trauma exposure as has been strikingly illustrated by prospective studies that evaluated military service members pre- and post-deployment. Pre-deployment short sleep, insomnia symptoms and nightmares have been shown to significantly increase the risk of developing PTSD post-deployment (Gehrman et al., 2013; Koffel et al., 2013; Saguin et al., 2021; van Liempt, 2012; van Liempt et al., 2013; Wang et al., 2018; Wright et al., 2011). This finding in military PTSD has recently also been shown in civilians following MVAs (Neylan et al., 2021). This latter prospective study began in the ER where individuals' pre-MVA sleep quality, including ID symptoms, sleep reactivity (see Drake et al., 2004) and nightmares were determined by questionnaire. Each of these 3 pre-MVA sleep symptoms were found to predict PTSD at 8-week follow-up as mediated by 2-week PTSD symptoms (Neylan et al., 2021). Pre- or post-trauma sleep-quality related risk of PTSD might reflect inter-individual differences in reactivity of stress systems and vulnerability to developing a chronically elevated set-point of CNS arousal post-trauma. Preexisting high baseline levels of arousal, such as those believed to underlie ID (Bonnet and Arand, 2010; Nofzinger et al., 2004; Riemann et al., 2010), may increase vulnerability to a further increase following trauma. Thus sleep disturbances may play a key role

in the etiology of PTSD (Babson et al., 2012a; Babson et al., 2012b; Babson and Feldner, 2010; Germain, 2013; Germain et al., 2008; Mellman, 2008b; Pace-Schott et al., 2015b; Spoormaker and Montgomery, 2008; Wright et al., 2011) possibly by impeding the processing of emotional memories such as those for extinction, safety and habituation (Colvonen et al., 2019; Mellman and Hipolito, 2006; Pace-Schott et al., 2015b; Straus et al., 2017, 2018b). A small number of studies have explored the relationship between sleep in the early aftermath of actual traumas and its impact on subsequent trauma-related intrusive thoughts. For example, in the week following an actual trauma, participants reporting poorer sleep quality also reported a greater number of trauma-related intrusive thoughts (Luik et al., 2019). In another study (Porcheret et al., 2015), sleep on the night following an actual trauma predicted trauma-related intrusive thought frequency in a U-shaped distribution: sleeping less than ~2 h or more than ~11 h resulted in more intrusive thoughts over the subsequent week. These investigators note that it was the magnitude of change from pre-trauma sleep duration, rather than sleep duration itself on the night following trauma, that best predicted number of intrusive memories. Such change in either direction may be related to the magnitude of the trauma's impact on excitatory/inhibitory balance in the CNS and reflect individual differences in response to extreme stress. Notably, hypersomnia is observed in some individuals with PTSD (Gupta, 2017). Although the contribution of primary sleep disorders preceding the occurrence of trauma requires knowledge of prior medical histories, clinical studies of such sleep disorders occurring co-morbidly with PTSD strongly suggest they increase vulnerability to PTSD. For example, OSA is associated with higher severity of PTSD symptoms (Mayer et al., 2021; Miles et al., 2022), worsened insomnia symptoms (Krakow et al., 2019) and poorer PTSD treatment outcome (Reist et al., 2017; Taylor et al., 2020) whereas treatment of OSA is associated with an improved PTSD therapeutic outcome (Hurwitz and Khawaja, 2010; Krakow et al., 2000, 2019). Similarly, pre-treatment insomnia is associated with lesser treatment gains (Sullan et al., 2021) and residual sleep symptoms have been shown to predict poorer response to prolonged exposure therapy (PE) (Brownlow et al., 2016; Lopez et al., 2017; Taylor et al., 2020). In addition to OSA and insomnia, primary sleep disorders such as periodic limb movement disorder (PLMD) are frequently observed in PTSD (Brown and Boudewyns, 1996; Koffel et al., 2016; Ross et al., 1994).

4.3. ASD and PTSS/PTSD

The immediate post-trauma period may or may not be characterized by diagnosable ASD– a constellation of symptoms closely resembling those of PTSD but occurring during the first month after the traumatic event (Bryant, 2017, 2018; Bryant et al., 2010, 2017). Notably, not all cases of ASD lead to PTSD and not all cases of PTSD are preceded by ASD (Bryant, 2017, 2018). Four major trajectories of posttraumatic symptoms following a traumatic event have been suggested by Galatzer-Levy et al. (2018). They include in order of frequency, resilience, recovery, chronicity and delayed onset with approximate frequencies of 65.7%, 20.8%, 10.6% and 8.9% respectively (Galatzer-Levy et al., 2018). Of these, delayed onset was rarest and was often associated with continued stressors. An earlier review concluded that if delayed onset PTSD (using DSM-IV-TR criteria) is defined as having no symptoms until at least 6 months had passed since trauma, it is rare to nonexistent, whereas "re-activation or exacerbation" of pre-existing symptoms occurs in around 15% of civilian cases and about a third of military cases (Andrews et al., 2007). Such cases are likely to correspond to the above late onset trajectory plus another less consistent trajectory, "worsening", both of which were hypothesized to be associated with continued stressors such as might be encountered by service members readjusting to civilian life (Galatzer-Levy et al., 2018). Symptom trajectories closely corresponding to those proposed by Galatzer-Levy et al. (2018) have been described by Bryant (2018) across multiple types of trauma. Contrasting resilience/recovery trajectories with those of chronic or worsening symptoms emphasizes that the weeks closely following a traumatic event may be crucial in determining the course of PTSD/PTSS. Moreover because the course of chronic PTSD involves widely fluctuating levels of symptoms over time (Bryant, 2018), factors that determined initial trajectory may continue to influence patterns of relapse and remission. We suggest that sleep quality during the first month following trauma, and in some cases during ASD, can affect low-level memory processes such as extinction, habituation and safety learning and, in turn, determine whether or not ASD will evolve into PTSD/PTSS. Indeed Bryant (2018) has suggested that, following trauma, both ASD and PTSD can be conceptualized as failure of extinction. Moreover, comparison of ASD and PTSD participants has shown that the inability to transfer safety learning from one context to another, thought to be a key cognitive characteristic of PTSD (Jovanovic et al., 2012), is present in ASD as well as PTSD (Jovanovic et al., 2013) and may represent another sleep-dependent capacity impacted by poor sleep following trauma (Straus et al., 2017, 2018a).

Deficits of fear inhibition in PTSD have been shown in fear-potentiated startle paradigms (Jovanovic et al., 2010, 2012). Although extinction recall has been reported impaired in those with PTSD, impaired extinction learning is usually not detected (Milad et al., 2008; Milad et al., 2009a; Pineles et al., 2020; Zuj et al., 2016a,b). There is weak evidence of a prospective relationship between extinction learning and PTSS (see Scheveneels et al., 2021 for a review). For example, Guthrie and Bryant (Guthrie and Bryant, 2006) found that an aversively conditioned corrugator EMG response, but not skin conductance response, during a standard fear acquisition and extinction learning protocol in cadet firefighters prior to active duty predicted Impact of Events (IES) scores two years later. Orr et al. (2012) also found that EMG response during extinction learning in police or fire cadets, when combined with several other factors to form a composite variable, predicted the level of PTSS following a subsequent index (foremost) trauma. Lommen et al. (2013) found that poorer extinction learning, measured as shock expectancy, in Dutch military before deployment to Afghanistan predicted higher Posttraumatic Symptom Scale scores upon return. Nonetheless, a recent attempt to replicate these findings of extinction learning as a predictor of vulnerability to PTSD in active firefighters was negative (Lommen and Boddez, 2022). Thus behavioral and peripheral physiological measures show small or absent deficits in extinction learning. Nonetheless, fMRI data suggests that activation of neural substrates of extinction learning may be delayed in sleep-compromised individuals (see Section 5.5).

4.4. Sleep and responses to stress in CNS and periphery

Trauma-related sleep disturbances have been linked with activation of central and peripheral stress systems including the sympathetic response, the hypothalamic-pituitary-adrenal (HPA) axis and the central extra-hypothalamic stress system (Pawlyk et al., 2008; Sanford et al., 2014), and abnormalities in each of these systems have been reported in PTSD (Awasthi et al., 2020; Pitman et al., 2012; Szeszko et al., 2018) (Fig. 1).

4.4.1. Sympathetic activation and central extra-hypothalamic stress systems

Secretion of norepinephrine (NE) by the locus coeruleus (LC) is responsible for the acute central stress response of the sympathetic nervous system (SNS) that triggers the rapid release of peripheral circulating catecholamines via the sympathetic–adrenal–medullary (SAM) axis. PTSD is associated with elevated levels of central (Geracioti et al., 2001; Southwick et al., 1999) and peripheral (Mellman et al., 1995) NE, an elevation that has also been observed during sleep (Mellman et al., 1995). Normal NREM sleep is associated with a marked decrease in SNS and increase in parasympathetic (PNS) drive (Brandenberger et al., 2001; Meerlo et al., 2008; Trinder et al., 2001). Heart rate variability (HRV) studies have shown that parasympathetic tone is

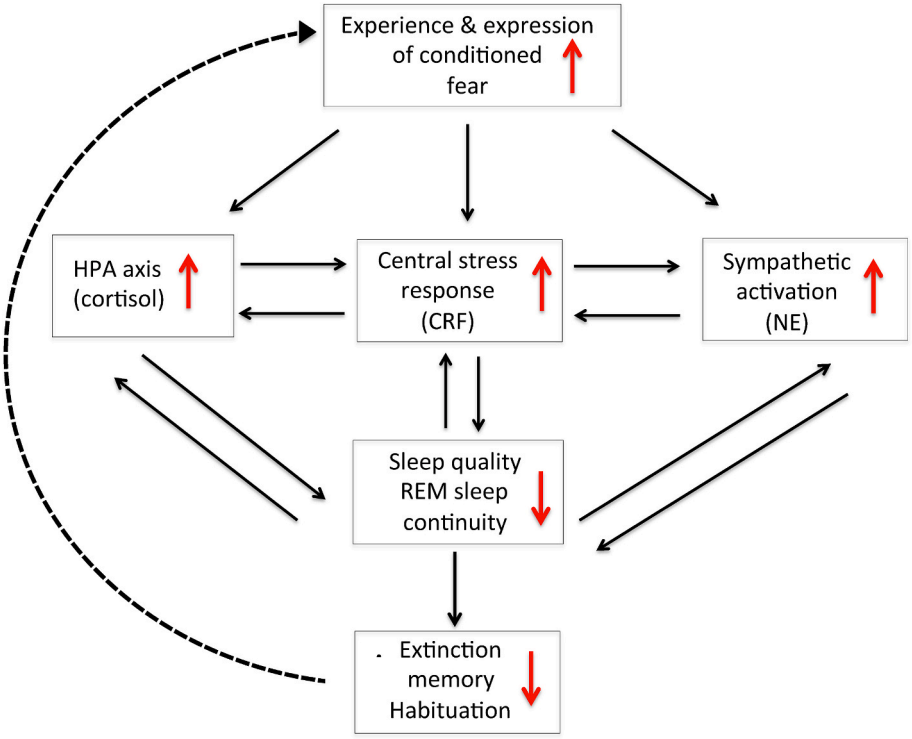


Fig. 1. Following trauma, stress systems are activated and sleep is disrupted. Positive feedback results in mutually exacerbating interactions between the different stress mechanisms and between each stress system and sleep quality, including the integrity of REM, that, in turn, impairs the consolidation of extinction memory. An additional positive feedback mechanism depicted by the dashed line illustrates how poor extinction memory might promote continued activation of neuroendocrine stress systems. HPA: hypothalamic-pituitary-adrenal, Central CRF: extra-hypothalamic actions in extended amygdala, CRF: corticotropin releasing factor, NE: norepinephrine. From Pace-Schott et al. (2015b).

decreased in persons with PTSD during wakefulness (Ge et al., 2020; Schneider and Schwerdtfeger, 2020), NREM (Ulmer et al., 2018) and REM sleep (Daffre et al., 2022; Mellman et al., 2004). Central NE declines with sleep onset and further declines as NREM deepens reaching its nadir in REM sleep (Pace-Schott and Hobson, 2002). Elevated nocturnal secretion of NE in PTSD (Geracioti et al., 2001; Mellman et al., 1995; Southwick et al., 1999) may underlie both fragmentation REM sleep during the early post-trauma period and trauma-related nightmares during chronic PTSD (Germain et al., 2008). The success of the alpha-adrenergic antagonist prazosin in treating posttraumatic nightmares (Kung et al., 2012; Raskind et al., 2013) is further evidence of elevated noradrenergic drive, although mixed findings suggest that its efficacy may be highest in subpopulations with noradrenergic dysregulation as evidenced by greater hyperarousal symptoms and hypertension (Hendrickson et al., 2021; Manhapra et al., 2019; Raskind et al., 2018; Yucel et al., 2020). In the extra-hypothalamic stress system, PTSD is associated with both elevated levels of central norepinephrine (Geracioti et al., 2001; Pan et al., 2018; Southwick et al., 1999) and corticotrophin-releasing factor (CRF) (Baker et al., 1999; Bremner et al., 1997; Sautter et al., 2003), the latter having been suggested to result from diminished feedback inhibition due to hypocortisolemia (see below) (Heim, 2020). In addition to its role in the HPA axis, CRF is a key neuromodulator activating the extra-hypothalamic stress system (Heinrichs and Koob, 2004; Koob, 1999) as is NE (Dunn et al., 2004; Flavin and Winder, 2013), the principal modulator of the acute sympathetic response (Itoi and Sugimoto, 2010; Lambert, 2001; Samuels and Szabadi, 2008a, 2008b). CRF-ergic activation promotes secretion of NE (Heim and Nemeroff, 2001; Krohg et al., 2008) and, in turn, increased NE can stimulate further CRF release (Dunn et al., 2004; Heim and Nemeroff, 2001). NE is a key regulator of arousal and of the REM/NREM cycle (see below). Exogenous (Sanford et al., 2008) and endogenous (Fadda and Fratta, 1997) CRF also show wake-promoting properties and, in rats, are responsible for stress-induced disruption of REM (Liu et al., 2011; Wellman et al., 2013; Yang et al., 2009). Hence posttraumatic activation of central stress mechanisms contributes to disturbance that in turn disrupts sleep quality and architecture and the processes they support.

4.4.2. *HPA axis and circadian rhythm of endogenous cortisol*

Unlike over activation of central stress systems with resulting elevated NE in PTSD (reviewed in Pace-Schott et al., 2015b), the final output of the HPA stress response, cortisol, is relatively suppressed in PTSD (Lehrner et al., 2016). Abnormally low levels of circulating cortisol are believed to reflect elevated glucocorticoid receptor sensitivity that results in greater negative feedback inhibition of CRH release by the hypothalamic paraventricular nucleus (PVN) and adrenocorticotropic hormone (ACTH) by the anterior pituitary (de Quervain et al., 2017; Szeszko et al., 2018). Higher levels of cortisol may be protective against PTSD at the time of trauma as well in its aftermath and during treatment (de Quervain et al., 2017). Individuals with lower levels of plasma cortisol at the time of trauma are more likely to develop PTSD (Jayan et al., 2022), high dose hydrocortisone given immediately after trauma can reduce symptoms of both ASD and PTSD (Zohar et al., 2011) and a meta-analysis of medications given within 3 months of trauma to prevent PTSD found that only hydrocortisone performed better than placebo (Astill Wright et al., 2019; Sijbrandij et al., 2015). Additionally, exogenous cortisol has been repeatedly shown to enhance exposure therapy for anxiety disorders (Bentz et al., 2010; de Quervain et al., 2011; Nakataki et al., 2017; Soravia et al., 2006, 2014, 2015) and PTSD (Aerni et al., 2004; de Quervain et al., 2017; de Quervain, 2008; de Quervain and Margraf, 2008; Suris et al., 2010; Yehuda et al., 2015; but see Raeder et al., 2019). Thus, activation of the HPA axis may be an adaptive response to acute trauma and may provide protection from PTSS by facilitating encoding of natural and treatment-related extinction. Conversely, lesser ability to mount an HPA-axis response in response to trauma may increase risk of developing PTSS. Cortisol may exert protective effects by enhancing the encoding and consolidation of fear extinction memory as well as by impeding retrieval of fear memory (de Quervain et al., 2009, 2017). Thus the prominent endogenous circadian rhythm of cortisol secretion may influence risk, perpetuation and treatment of PTSD. The morning acrophase of endogenous cortisol has been shown to be associated with enhanced fear extinction learning and generalization of fear extinction memory (Pace-Schott et al., 2013) as well as with enhanced exposure-based therapy for panic disorder (Meuret et al., 2016) and spider phobia (Lass-Hennemann and Michael,

2014). Endogenous cortisol levels at varying session times have also been shown to predict response to exposure therapy for PTSD (van Gelderen et al., 2020). Individuals who showed a higher cortisol awakening response (CAR) during the month following trauma were less likely to progress from ASD to PTSD (Marin et al., 2019) and respond better to treatment (Rapcencu et al., 2017). Thus the low levels of cortisol in PTSD can diminish the circadian output of the HPA axis with the potential to influence fear extinction and resilience.

4.4.3. *Post-traumatic sleep disturbance as manifestation of hyperarousal*

Considerable evidence exists that changes in sleep quality and physiology in persons with PTSD result from increased baseline arousal (Ebdlahad et al., 2013; Germain, 2013; Germain et al., 2008; Kobayashi et al., 2007; Woodward et al., 2000). In those who have developed PTSD, such hyperarousal may lighten sleep, reduce deeper, more restorative slow wave sleep (SWS) and alter the physiology of REM (Ebdlahad et al., 2013; Germain, 2013; Germain et al., 2008; Kobayashi et al., 2007). These changes following trauma may, in turn, oppose normal processing of emotional memories (Mellman and Hipolito, 2006), and impede the ability to consolidate memory for the extinction of fear associated with traumatic memories (Pace-Schott et al., 2015b). Individuals who experience hyperarousal during the period immediately following trauma are more likely to develop PTSD (Bryant et al., 2003; Felmingham et al., 2012; Marshall et al., 2006; Schell et al., 2004). For example, peri-traumatic hyperarousal, as indexed by elevated heart rate during post-trauma hospitalization or proximal to discharge, has been shown to predict individuals who will progress to PTSD (Bryant et al., 2000; Shalev et al., 1998). Since hyperarousal is strongly associated with insomnia (Bonnet and Arand, 2010; Kay and Buysse, 2017; Riemann et al., 2010), such individuals are likely to experience sleep disruption. Moreover, among individuals who underwent PSG on average one week post trauma, those who developed PTSD symptoms displayed higher sympathovagal balance during REM sleep (Mellman et al., 2004). Additionally, an indicator of sympathetic activation, skin conductance response to recounting a trauma in its early aftermath, predicts who will progress to PTSD (Hinrichs et al., 2019). Once PTSD is present, two meta-analyses (Kobayashi et al., 2007; Zhang et al., 2019) have reported that alterations of sleep in PTSD compared to control groups reflect elevated arousal during sleep. These alterations include: 1.) increased Stage 1 NREM sleep (the lightest stage of NREM), 2.) decreased SWS (the deepest stage of NREM) accompanied by decreased EEG spectral power in delta EEG frequencies (Neylan et al., 2003; Richards et al., 2013; Woodward et al., 2000), and 3.) increased rapid eye movement density (rapid eye movements per unit time in REM sleep) (Germain et al., 2004, 2013). In addition, autonomic balance during sleep in PTSD reflects reduced parasympathetic influence. For example, combat veterans with PTSD showed lower parasympathetic tone during NREM (Ulmer et al., 2018) and, among civilians within 2 years of a trauma, reduced parasympathetic tone during REM explained a significant amount of variance in the hyperarousal symptom cluster (Daffre et al., 2022). Particularly striking evidence of posttraumatic hyperarousal is a newly proposed parasomnia, Trauma-Associated Sleep Disorder (TSD) (Feemster et al., 2021; Mysliwiec et al., 2014, 2018). This severe syndrome is associated with having experienced severe trauma while in a sleep-deprived condition. It is most often seen in combat-related PTSD, involves disruptive nocturnal behaviors resembling REM Behavior Disorder as well as dream enactment and elevated sympathetic tone during nightmares (Feemster et al., 2021; Mysliwiec et al., 2014, 2018). Thus an underlying hyperarousal in PTSD may lighten sleep, decrease restorative SWS, alter the distinct physiology of REM sleep (see below) (Ebdlahad et al., 2013; Germain, 2013; Germain et al., 2008; Kobayashi et al., 2007) and thereby impede consolidation of extinction memory acquired in prior wakefulness.

4.4.4. *Posttraumatic insomnia and Acute Stress Disorder*

Posttraumatic insomnia is a ubiquitous manifestation of trauma-induced hyperarousal (Sinha, 2016) that is predictive of later PTSD (Babson and Feldner, 2010; Koren et al., 2002; Wright et al., 2011). Like PTSD, idiopathic insomnia disorder itself is widely believed to result from an underlying hyperarousal (Bonnet and Arand, 2010; Nofzinger et al., 2004; Riemann et al., 2010) in both peripheral (Bonnet and Arand, 2010) and central (Nofzinger et al., 2004) nervous systems. Acute insomnia follows a wide variety of stressors (Ellis et al., 2012) and risk of developing chronic insomnia is elevated in those showing strong sleep onset effects of acute stress of even a non-traumatic nature ("sleep reactivity") (Drake et al., 2011). In primary insomnia, ongoing stressors have been shown to additionally disrupt sleep, particularly delta frequencies in NREM (Hall et al., 2007). As noted above, trauma-induced insomnia can precede PTSD and hence the effects of sleep disturbance on fear generalization and extinction learning and memory may precede and contribute to development of the full complement of PTSD symptoms (Sinha, 2016). Neuroimaging studies of fear conditioning and extinction in primary insomnia, sleep deprivation in healthy controls, and in PTSD itself, detailed in section 5.5, suggest that disturbed sleep may delay engagement of the neural substrates of fear extinction (Seo et al., 2018, 2020, 2022). Notably, trauma-focused cognitive behavior therapy (CBT) with an exposure component has been shown to be the treatment most effective, in ASD, at reducing the incidence and severity of subsequent PTSD (Bryant, 2018). Efficacy of exposure is seen even if delivered in the emergency room during the initial hours post trauma (Rothbaum et al., 2012). Since exposure during CBT is an extinction-based strategy, posttraumatic sleep disruption may contribute to PTSD by impeding the naturalistic extinction learning and memory that occur in resilient individuals. Among individuals who develop ASD following a traumatic event, only approximately 30% develop PTSD (although some form of psychopathology emerges in 60%) (Bryant et al., 2012). Therefore, interference with the emotion regulatory function of sleep, including the consolidation of extinction memory, by posttraumatic insomnia and other sleep disturbances during the weeks immediately following trauma might be a crucial factor determining who progresses to PTSD.

4.4.5. *Alterations of specific sleep stages*

Sleep biomarkers that might predict development of PTSS or, conversely, predict resilience are of particular clinical interest. REM fragmentation has been frequently suggested to be a key acute post-traumatic symptom that predisposes individuals to PTSD/PTSS (Colvonen et al., 2019; Saguin et al., 2021). This abnormality may be an acute symptom transiently present in the weeks post-trauma that normalizes in chronic PTSD (Mellman et al., 2014). Thus the effects of REM disturbance on extinction learning and consolidation may occur specifically during the acute post-trauma period. Notably, there are animal models of stressor-related REM sleep effects. For example, fear conditioning with inescapable shock can produce sleep disruption and REM fragmentation (Greenwood et al., 2014; Liu et al., 2003; Mavanji et al., 2003; Sanford et al., 2003a; Sanford et al., 2014; Sanford et al., 2003b; Sanford et al., 2010; Vanderheyden et al., 2015) that can be ameliorated by extinction training (Wellman et al., 2008) and reinstated by cues associated with prior conditioning (Jha et al., 2005; Pawlyk et al., 2005; Pawlyk et al., 2008). Interestingly, REM fragmentation has also recently been suggested to contribute to subjective and objective symptoms of ID (Feige et al., 2008, 2013; Riemann et al., 2012), the most frequent sleep-related sequel of trauma (Sinha, 2016). REM sleep in the early aftermath of a trauma has specifically been linked to the development of post-traumatic symptomatology. Mellman and colleagues (Mellman et al., 2002) showed that individuals with fragmented REM sleep following a trauma were more likely to go on to develop PTSS (Mellman et al., 2002, 2007). This group also showed that while REM fragmentation is predictive of PTSS, trauma-exposed individuals who exhibited higher REM theta spectral power were more resilient to PTSD compared to those who developed PTSD (Cowdin et al., 2014). Higher beta spectral activity during REM also predicted reduced PTSD symptomatology,

including nightmare severity, at a two-month follow-up (Mellman et al., 2007). Similarly, in trauma-exposed persons who had experienced trauma in the previous 2 years, greater beta spectral power during NREM was associated with reduced PTSD symptomatology and nightmare frequency (Denis et al., 2021) as well as lower scores on the Depression, Anxiety and Stress Scale (Lovibond and Lovibond, 1995) and greater subjective ability to regulate emotions as measured by the Difficulties in Emotion Regulation Scale (Gratz and Roemer, 2004). This latter study also replicated a previous finding of higher oscillatory frequency of fast spindles during NREM in those with versus without PTSD (Wang et al., 2020). Thus, alterations of both macro- and micro-architecture of sleep in the days and weeks following a traumatic experience can contribute to neurocognitive functions favoring either PTSS or resilience.

5. Neuronal bases for sleep's effects on fear and extinction in PTSD

Full consideration of neuronal correlates of acute trauma and neural differences between PTSD and healthy adults, including their responses to experimental fear conditioning and extinction, are beyond the scope of this article but will here be briefly summarized. The reader is referred to relevant detailed reviews cited below. We will then describe our recent fMRI findings regarding the effects of sleep on fear conditioning and extinction and propose one potential mechanism leading to observed extinction deficits in PTSD.

5.1. Neuronal impacts of acute trauma

Abdallah and colleagues (Abdallah et al., 2019) have hypothesized two prominent synaptic effects of trauma and its aftermath. The first involves excitotoxicity resulting from an overabundance of extracellular glutamate that degrades synapses. In particular, synapses are reduced in the PFC and hippocampus, structures involved, respectively, in the inhibition of fear (extinction) and the ability to determine the appropriate contexts in which fear or extinction are advantageous. The PFC and hippocampus, both key elements of extinction and emotion regulatory networks, are hypothesized to be particularly vulnerable to such stress-related excitotoxicity (Kaplan et al., 2018). A second effect hypothesized, also serving to bias behavior in the direction of fearful responding, is monoamine-mediated synaptogenesis and possibly hypertrophy of the amygdala and other salience network regions (e.g., dACC, insula). These authors further suggest that one function of the salience network is to provide adaptive switching between activation of the exteroceptive central executive network and the interoceptive default mode network. They suggest that stress-related weakening of connectivity in the central executive reduces top-down control and disinhibits the salience network, thereby allowing excess excitability and poor control over the locus of attention.

Another mechanism by which traumatic stress may influence neuronal integrity and potentially contribute to ASD or PTSS/PTSD via a sleep-disturbance related mechanism involves chronic mild inflammation and associated elevation of pro-inflammatory cytokines such as CRP, IL1, IL6, IL1B and TNFα (Michopoulos et al., 2017). Acute psychological stress is known experimentally to elevate inflammatory cytokines (Marsland et al., 2017) and elevated inflammatory cytokines have been widely documented in those diagnosed with PTSD (Miller et al., 2018; Passos et al., 2015) as well as those exposed to psychological trauma with or without PTSD (Tursich et al., 2014). Elevation of inflammatory cytokines may be due, in part, to abnormally low levels of cortisol in PTSD with a consequent decrease in its anti-inflammatory effects (Daskalakis et al., 2016; Irwin, 2019; Rohleder et al., 2010). In those with PTSS, elevated inflammatory cytokines predict a more severe subsequent course of illness (Eswarappa et al., 2019). Although in the immediately peri-trauma period, the ability to mount an inflammatory response may, paradoxically, be protective against developing PTSD (Heim, 2020; Lalonde et al., 2021), the time course following trauma leading to chronic inflammation seen in PTSD is not known. Additionally, pre-trauma higher levels of CRP may increase susceptibility to PTSD following trauma (Olff and van Zuiden, 2017; Wang et al., 2017). Poor sleep quality (Besedovsky et al., 2019; Irwin et al., 2016) and insomnia (Irwin and Piber, 2018) also elevate pro-inflammatory cytokines especially when chronic insomnia is accompanied by objective short sleep (Fernandez-Mendoza et al., 2017; Lerman et al., 2022). Notably, as is the case for stress systems, inflammation can itself disrupt sleep (Besedovsky et al., 2019) and hence, in theory, create positive feedback conditions that exacerbate abnormalities in both. Sleep, especially SWS, has been shown to promote the consolidation of immunological memory (i.e., adaptive immunity) in a manner analogous to memory in the CNS though operating via different mechanisms (Besedovsky et al., 2019; Irwin, 2019). Moreover, mild inflammatory states of the acute phase response have repeatedly been shown to reduce REM but elevate NREM (Besedovsky et al., 2019; Irwin, 2019). If, as often hypothesized, REM physiology constitutes a specific sleep substrate for emotion regulation (Goldstein & Walker, 2014) and acute stress and PTSD both impact REM and its facilitation of extinction-memory consolidation (Colvonen et al., 2019; Pace-Schott et al., 2015a,b), then inflammation may also promote PTSS by this mechanism (Quinones et al., 2016). Inflammation itself may also specifically promote fear learning (Jones et al., 2015; Wang et al., 2017). Notably, whereas a rodent study reported impaired fear extinction learning and recall resulting from experimentally induced inflammation (Quinones et al., 2016), the first human study testing this effect in healthy adult males did not show differences in extinction recall between an experimentally induced inflammatory state and a control condition (Benson et al., 2020). However, as these latter authors point out, women and/or individuals with psychopathology might show such effects. Hence posttraumatic insomnia may exacerbate the effects of acute stress on inflammatory processes and both may impede low-level emotion regulation such as fear extinction.

5.2. Neural differences between PTSD and controls, a substrate of hyperarousal

Functional and structural brain abnormalities in PTSD suggest that hyperarousal symptoms involve increased activation of excitatory, fear-supportive regions and decreased activation of emotion-regulatory structures (Abdallah et al., 2019). Resting state fMRI studies of PTSD report amygdala hyperactivation (Chung et al., 2006; Semple et al., 2000) as do task-based experiments designed to elicit emotional responses (Bryant et al., 2008; Milad et al., 2009), and this may contribute to exaggerated fear response in this disorder (reviewed in Shvil et al., 2013). For example, during experimental fear conditioning and extinction, individuals with PTSD show greater salience-network activation (e.g., amygdala and dorsal anterior cingulate cortex (dACC)) suggesting heightened processing of threatening stimuli (Bremner et al., 2005; Linnman et al., 2011; Milad et al., 2008, 2009). Hypoactivation of emotion regulatory areas such as medial prefrontal cortex (mPFC), ventromedial prefrontal cortex (vmPFC), and rostral anterior cingulate cortex (rACC) is also observed in PTSD, suggesting lesser ability to exert top-down control over salience network structures such as the amygdala, insula, and dACC (Abdallah et al., 2019; Etkin and Wager, 2007; Shin and Liberzon, 2010). A similar pattern has been reported in Generalized Anxiety Disorder (GAD) and Panic Disorder (Etkin and Wager, 2007; Shin and Liberzon, 2010). Structural abnormalities of these regulatory areas have also been reported in PTSD (Kühn and Gallinat, 2013; Rauch et al., 2006; Shin and Liberzon, 2010). Generalization and context dependency of fear conditioning and extinction learning specifically engage the hippocampus (Lissek et al., 2013; Milad and Quirk, 2012). Both increases and decreases in hippocampal activity have been associated with severity of PTSD (reviewed in Shin and Liberzon, 2010 and Duval et al., 2015). Abnormal hippocampal function

may influence the tendency of PTSD patients to generalize their fear response to situations and contexts that differ from their index trauma. Supporting this hypothesis, decreased hippocampal and vmPFC volumes have been reported in patients with PTSD (Bremner et al., 1995; Bremner et al., 1997; Bremner et al., 2003; Kitayama et al., 2005; Kühn and Gallinat, 2013; Woon et al., 2010). Reduced hippocampal volume may also precede and be a risk factor for PTSD development. In a twin study of combat-exposed individuals, the twin-sibling of veterans with PTSD had smaller hippocampal volume than that of twins of veterans without PTSD, independently of trauma-exposure (Gilbertson et al., 2002) reviewed in (Pitman et al., 2012). Thus functional, structural and resting state neuroimaging studies comparing those with and without PTSD all suggest involvement of neural substrates of hyperarousal.

5.3. Neural correlates of fear and extinction in healthy adults

Activation of networks homologous to those established in animal models have been widely replicated when neuroimaging human fear conditioning and extinction (Graham and Milad, 2011; Milad and Quirk, 2012; Milad and Rauch, 2012). Milad and colleagues propose distinct, mutually opposed networks for the acquisition/expression and extinction of conditioned fear (Graham and Milad, 2011; Milad and Quirk, 2012). The amygdala and dACC activate during expression of conditioned fear whereas the vmPFC becomes activated during extinction learning and recall (Milad et al., 2007; Milad et al., 2007). Contextual factors determine if extinction recall recruits the hippocampus as well as the vmPFC (Kalisch et al., 2006; Milad et al., 2007). However, recent meta-analyses have shown that, in humans, much broader regions of the forebrain and brainstem are recruited in experimental models of both fear conditioning and extinction (Fullana et al., 2016, 2018). Areas activated in common during fear conditioning included medial cortices in both frontal and parietal areas, lateral frontal areas, insula and adjacent lateral frontal cortex, ventral striatum, thalamus, basal forebrain and brainstem regions (Fullana et al., 2016). Areas activated in common across studies of fear extinction learning included anterior cingulate cortex (ACC), pre-supplementary motor cortex (pre-SMA), mPFC, bilateral anterior insula and adjacent frontal cortex, ventral striatum, pallidum, thalamus and rostral brainstem (Fullana et al., 2018). At extinction recall, regions activated during the key comparison of a conditioned and extinguished stimulus (CS+E) to one that was only conditioned (CS+U) (Box 1) included previously reported areas such as vmPFC, subgenual cingulate cortex and hippocampus, but also additional areas including dorsolateral and orbitofrontal prefrontal cortices (Fullana et al., 2018). Thus, in humans, in addition to homologs of the well-established substrates of fear conditioning and extinction in rodents, much broader regions of the lateral and medial cortex as well as subcortex participate in these processes.

5.4. Neurocircuitry of fear conditioning and extinction in PTSD

A recent meta-analysis has summarized differences in activation between PTSD and TEC across 7 studies using protocols similar to the one described in Box 1 (Suarez-Jimenez et al., 2020). These authors reported contrasts from 7 fear conditioning, 5 extinction learning and 4 extinction recall phases. They report that, throughout all 3 phases, those with PTSD showed greater activation to CS+ vs. CS- contrasts in areas of the salience network including amygdala, insula and ACC (Suarez-Jimenez et al., 2020). During fear conditioning, these authors also report greater activation among those with PTSD in multiple regions of medial and lateral PFC as well as hippocampus. During extinction learning, along with continued activation of the amygdala and insula, those with PTSD showed lesser activation of medial PFC regions including vmPFC, and orbitofrontal cortex (OFC). During extinction recall, patients with PTSD showed greater amygdala, hippocampus, dACC, and vmPFC activation than trauma exposed individuals without PTSD (TEC). However, patients with PTSD showed an overall decreased activation in the thalamus during all phases. A recent dynamic functional connectivity study comparing a large pooled sample of PTSD and anxiety disorder patients with their respective controls using the fear conditioning and extinction protocol shown in Box 1, revealed an increased functional connectivity among large scale brain networks across extinction in controls that did not occur in patients (Wen et al., 2021, 2022). Recent meta-analyses (Fullana et al., 2018) and empirical studies pooling large samples (Wen et al., 2021, 2022) have shown that, in addition to core structures supporting extinction, large cortical networks participate in extinction learning and memory. Thus, effects of sleep symptoms on such networks may contribute to differences between those with PTSD and those showing resilience to trauma.

5.5. New neuroimaging findings on sleep and PTSD

Recent neuroimaging studies from our laboratory have begun to suggest how disrupted sleep might directly impact processes of fear conditioning and extinction (Seo et al., 2018, 2019, 2020, 2022). Using the protocol described in Box 1, we have noted a common pattern of differences in brain activation when experimental fear conditioning and extinction is contrasted between 3 diverse pairs of diagnostic categories: (1) individuals with Insomnia Disorder (ID) versus good-sleeping controls, (2) sleep-deprived versus fully rested healthy young adults, and (3) individuals recently exposed to trauma who developed PTSD versus TEC. (See Table 1 for characteristics of groups studied.) In each comparison, it appeared that in the less pathological and/or sleep-compromised group (i.e., healthy controls without ID, fully rested healthy individuals, or TEC) the neural substrates of both fear acquisition and extinction learning were engaged during the initial extinction learning that immediately followed fear conditioning in the first session. In contrast, in the more pathological and/or sleep-compromised individuals (i.e., those with ID, those who were sleep deprived, or those who had developed PTSD), engagement of these same neural regions was delayed until 12–24 h later at extinction recall when both conditioned and extinguished (CS+E) and conditioned only (CS+U) stimuli, along with the CS-, were presented. Because extinction does not erase fear memory but rather creates a new, inhibitory memory that competes with this memory, simultaneous activation of fear-expressive and fear-regulatory regions suggests engagement of this competition between the newly forming extinction memory and the previously acquired fear memory. Since sleep facilitates memory encoding and consolidation, we hypothesize that individuals with compromised sleep or excessive anxiety may be delayed in their ability to initiate the emotion-regulatory processes of fear extinction and thereby initiate the competitive encoding of safety. Alternatively, overlearning of extinction in the non-sleep compromised study groups during extinction learning may allow greater habituation to threat stimuli and/or automatization of fear inhibition processes in cortical areas, as has been described for overlearned cognitive or motor tasks (Puttemans et al., 2005).

In the first case (Seo et al., 2018) (Fig. 2), healthy, good-sleeping (GS) individuals and those with primary insomnia (i.e., ID without comorbidity) showed similar activation (CS+>CS- contrast) patterns of fear-related (salience network) structures (insula, dACC) during early and late fear conditioning. However, across extinction learning (late CS+>early CS+ contrast), GS activated both salience (dACC, insula) and extinction (regulatory) regions (rACC, OFC) whereas ID showed no activations. During extinction recall 24 h later, ID activated regulatory areas (vmPFC, OFC) to the CS+E > CS+U contrast and salience areas (insula, amygdala) to the CS+E > CS- contrast whereas GS showed no significant activations. This suggests that ID, relative to GS, had delayed the activation of the substrates of both fear and extinction until conditioned and extinguished stimuli were shown for a second time 24 h later.

In the second instance (Seo et al., 2020) (Fig. 3A), among healthy young adults, by the end of fear conditioning those who were fully rested (NS) activated regulatory structures (vmPFC, rACC, OFC), those entirely sleep deprived the previous night (SD) activated a much smaller subset

Table 1
Sample characteristics of cited neuroimaging studies (Section 5.5).

Study	Participants	Age (years)		Gender		Current comorbidities (number)	PSQI		ISI		CAPS-5		PCL-5	
		Mean	(SD)	Male	Female		Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Seo et al. (2018)	ID: $n = 23$	28.96	11.95	6	17	None	10.43	2.41	18.95	4.01				
	GS: $n = 23$	29.65	12.81	5	18	None	1.48	1.10	1.04	1.33				
Seo et al. 2020	NS: $n = 48$	23.80	3.65	21	27	None	1.60	1.05						
	SR: $n = 53$	24.23	3.32	24	29	None	2.09	1.18						
	SD: $n = 53$	23.59	3.26	26	27	None	1.79	1.03						
Seo et al. (2022)	PTSD: $n = 63$	24.79	5.55	13	50	MDD 4 GAD 6 SAD 5	8.27	3.18			32.13	8.33	40.73	12.18
	TEC: $n = 63$	23.54	4.56	27	36	GAD 3 SAD 1	5.77	269			11.31	6.38	19.35	10.79

CAPS-5 Clinician Administered PTSD Scale for DSM-5, GAD Generalized Anxiety Disorder, GS healthy good sleeper, ID Insomnia Disorder, ISI Insomnia Severity Index, MDD Major Depressive Disorder, NS healthy full night sleep, PCL-5 PTSD Checklist for DSM-5, PSQI Pittsburgh Sleep Quality Index, PTSD diagnosed Posttraumatic Stress Disorder, SAD Social Anxiety Disorder, SD healthy total sleep deprivation, SR healthy half-night's sleep, TEC trauma-exposed controls.

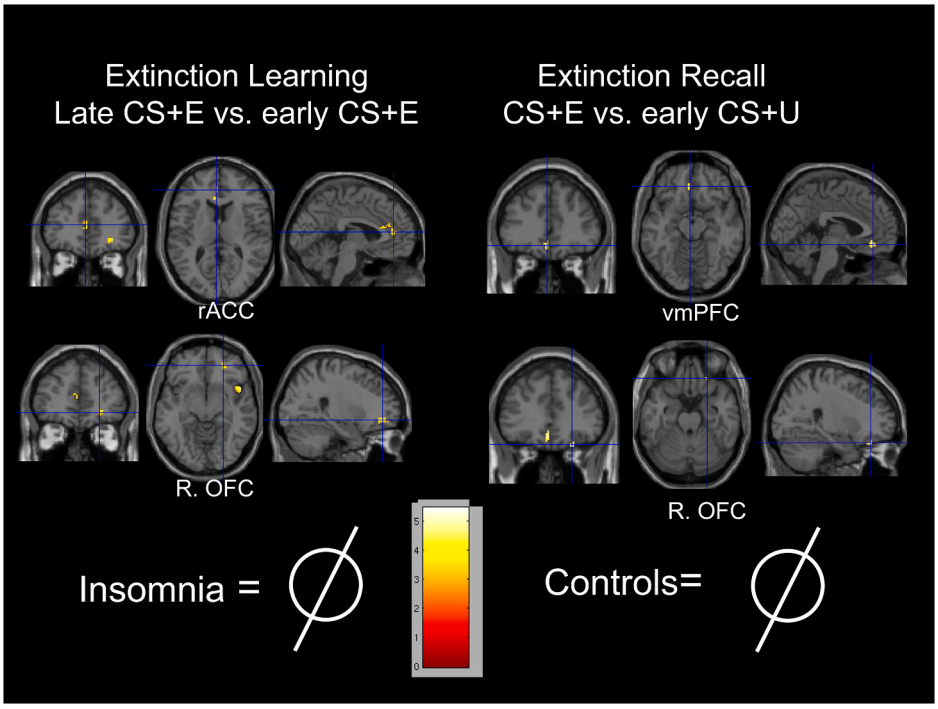


Fig. 2. Within-group comparison of brain activations in the anterior of prefrontal (emotion regulatory) regions across extinction learning and at early extinction recall in persons with primary insomnia (ID without comorbidity) and healthy, good sleeping controls. **A.** Brain activation evoked by the Late CS+E > Early CS+E contrast across extinction learning. **B.** Brain activation evoked by the CS+E > CS+U contrast during Early Extinction Recall. CS+E: CS reinforced at conditioning (CS+) and extinguished during extinction learning; CS+U: CS+ reinforced at conditioning but not extinguished during extinction learning; rACC: rostral anterior cingulate cortex, R.OCF: right orbitofrontal cortex; vmPFC: ventromedial prefrontal cortex.

of these areas, and those who were sleep restricted (SR) activated only salience regions. Across extinction learning (late CS+E > early CS+E contrast), NS activated both regulatory (OFC, inferior frontal cortex: IFC) and salience regions (insula, amygdala) whereas neither SD nor SR showed any activations. During extinction recall 12 h later, SD now activated both regulatory (right IFC) and salience (insula) regions to the CS+E > CS+U contrast, whereas NS showed no activations. One particularly interesting finding of this study was that those who were 50% sleep restricted (SR) did not engage regulatory regions at any point suggesting that short-term insufficient sleep may be even more pathogenic than short-term total sleep deprivation.

In the third instance (Seo et al., 2022) (Fig. 3B), among trauma-exposed individuals, when contrasting CS+>CS- at early conditioning, both PTSD and TEC activated large areas of both regulatory (mPFC) and salience (insula, dACC) networks. By the end of fear conditioning, however, areas activated to this same contrast had largely habituated in TEC but remained highly activated in PTSD. Subsequently, across extinction learning (late CS+E > early CS+E contrast), TEC activated large clusters in regulatory (dmPFC, superior prefrontal cortex (SFC)) regions whereas PTSD activated only a smaller area of SFC. Moreover, in region of interest (ROI) analyses, across extinction learning, TEC but not PTSD activated the hippocampus. At extinction recall, PTSD now activated regulatory regions (rACC) to the CS+E > CS+U contrast, whereas TEC showed no cortical activations but continued to show hippocampus activity whereas PTSD did not.

One commonality among these three studies is the temporal proximity (~5–10 min) for beginning extinction learning following the end of conditioning (Box 1). If engagement of regulatory brain regions is suppressed at this time in those who are sleep compromised or have sleep-disturbing psychopathology, such individuals may continue to process only fear following its acquisition rather than beginning to engage extinction mechanisms. The above noted increase in functional connectivity among large scale networks across extinction learning in healthy controls but not in PTSD and anxiety patients (Wen et al., 2022) may similarly reflect an inability to engage competitive encoding of safety immediately following fear acquisition. If an experimental protocol, such as in Box 1, models the immediate response to trauma, then one might speculate that those who cannot quickly engage automatic

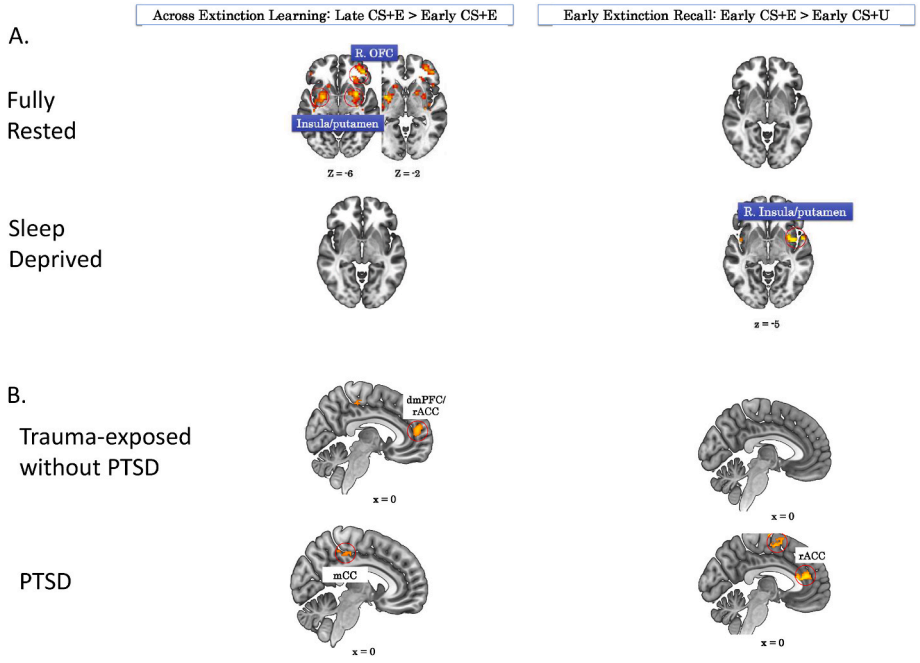


Fig. 3. Within-group comparison of brain activations in the anterior cerebrum across extinction learning and at early extinction recall between fully rested and sleep-deprived healthy adults (A) and between trauma-exposed individuals with and without PSTD (B). A. Activations across extinction learning (Late CS+E > Early CS+E) and at early extinction recall (CS+E > CS+U) in fully rested and sleep-deprived healthy adults. B. Same 2 contrasts in trauma-exposed individuals with and without PSTD. CS+E: CS reinforced at conditioning (CS+) and extinguished during extinction learning; CS+U: CS+ reinforced at conditioning but not extinguished during extinction learning; dlPFC: dorsolateral prefrontal cortex; mCC: middle cingulate cortex; rACC: rostral anterior cingulate cortex, R.OCF: right orbitofrontal cortex; vmPFC: ventromedial prefrontal cortex. Modified from Seo et al. (2020) and Seo et al. (2022).

emotion regulatory processes, such as fear extinction, may remain vulnerable to additional traumatization or to developing fearful attributions about the experience. However, this putative mechanism might not be seen in experimental paradigms in which a delay (typically 24 h) follows both fear conditioning and extinction learning phases [e.g., (Straus et al., 2017), see Kobayashi et al. (in press) for additional examples]. Nonetheless, temporally clustered and rapidly repeating traumatic experience is the rule, not exception, in many traumatic situations such as chronic domestic abuse or living in a war zone or as a refugee. With reference to the acute post-trauma period, the inability to immediately begin to counter a fear memory with extinction or safety learning may initiate a positive feedback relationship with poor sleep that causes anxiety symptoms to escalate (Pace-Schott, 2015b) (Fig. 1).

6. Conclusion

PTSD is widely hypothesized to involve failure to remember extinction of fear associated with reminders of a traumatic event (Colvonen et al., 2019; Kredlow et al., 2021; Pitman et al., 2012; Shalev et al., 2017) or to learn and remember post-trauma indications of safety (Straus et al., 2018a). Resilient individuals in the course their lives following trauma acquire these extinction and safety memories when encountering internal and external reminders of their traumatic experience that, presumably, are especially abundant in the days and weeks following this event. Sleep findings considered above (Seo et al., 2018, 2020, 2022) suggest that these first weeks post-trauma (when one could be diagnosed with ASD but not PTSD) might be times when individual traits and physiology can act to promote resilience versus psychopathology. Among the factors that could influence posttraumatic extinction or safety memories are features of sleep quality itself such as pre-existing sleep disorders (e.g., pre- or post-trauma insomnia, OSA) or sleep habits (e.g., occupational constraints). Others are aspects of pre- or post-trauma physiology that could directly or indirectly affect sleep. Among the latter considered here are: an individual's pre- and post-trauma set point of arousal, central and peripheral sympathetic activation, HPA-axis dysregulation and hypocortisolemia, post-trauma neuroinflammation or excitotoxicity, and individual circadian variability. In addition, pre- or post-trauma variability of neuroanatomical characteristics (e.g., hippocampal volume) or baseline capacity to extinguish fear (pre-trauma) or to activate the neural substrates of extinction (post-trauma) may contribute to clinical outcome following trauma. Of course, sleep is only one of numerous factors determining individual outcomes, and consolidation of extinction memory may be only one of sleep's important effects in promoting resilience. Moreover, personality traits (e.g., neuroticism), social constraints (e.g., shift work) and behavioral effects of psychopathology itself (e.g., substance use) strongly influence both sleep quality and its determinants. The complex network structure of mutual effects among all the above factors, including positive and negative feedback relations, is undoubtedly itself an important determinant of resilience. The relative importance of different biopsychosocial factors during the early post-trauma period in determining clinical outcomes awaits findings of large-scale prospective studies such as AURORA (Neylan et al., 2021; Stevens et al., 2021). Nonetheless, given the fact that sleep's effects pervade all of human physiology, it is certain that it plays some role in determining resilience and that its influence is of particular importance during initial recovery from psychological trauma.

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Credit authorship contribution statement

Edward F. Pace-Schott: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Jeehye Seo:** Data curation, Formal analysis, Visualization, (Section 5.5). **Ryan Bottary:** Writing – original draft, Writing – review & editing, (Sections 2 and 3).

Data availability

Pace-Schott Lab's data shared with NIMH Data Archive

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