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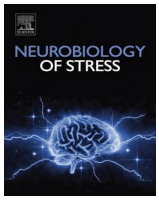

The importance of REM sleep fragmentation in the effects of stress on sleep: Perspectives from preclinical studies

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ABSTRACT

Psychological stress poses a risk for sleep disturbances. Importantly, trauma-exposed individuals who develop posttraumatic stress disorder (PTSD) frequently report insomnia and recurrent nightmares. Clinical studies have provided insight into the mechanisms of these sleep disturbances. We review polysomnographic findings in PTSD and identify analogous measures that have been made in animal models of PTSD. There is a rich empirical and theoretical literature on rapid eye movement sleep (REMS) substrates of insomnia and nightmares, with an emphasis on REMS fragmentation. For future investigations of stress-induced sleep changes, we recommend a focus on tonic, phasic and other microarchitectural REMS measures. Power spectral density analysis of the sleep EEG should also be utilized. Animal models with high construct validity can provide insight into gender and time following stressor exposure as moderating variables. Ultimately, preclinical studies with translational potential will lead to improved treatment for stress-related sleep disturbances.

1. Introduction to the effects of stress on sleep

Sleep disturbance is practically ubiquitous among mental disorders. Across diverse trauma-exposed clinical populations, sleep disturbances are frequently reported in both the acute aftermath of a traumatic event (Mellman et al., 2007) and chronically (Sharon et al., 2009). Of these disturbances, the most common sleep-related phenotypes observed in posttraumatic stress disorder (PTSD) are insomnia and recurrent nightmares, which we will discuss in detail below. Our discussions here add to the existing literature on stress, sleep and PTSD (Natraj and Murkar, 2023; Sanford et al., 2023; Murkar, 2018) by focusing on both acute and chronic stress experiences and on REMS fragmentation in PTSD which has received less attention than other characteristics of sleep architecture. For theoretical models of sleep disturbances underlying PTSD, please see (El-Solh et al., 2018; Krakow et al., 2015).

Among individuals with PTSD, 70–90% report insomnia (Maher et al., 2006), which also may be an independent risk factor for the development of PTSD (Wang et al., 2018; Gehrman et al., 2013). Polysomnographic (PSG) studies of insomnia have shown a disruption of sleep continuity, which may be most pronounced during REMS (Baglioni et al., 2014; Riemann et al., 2012; Feige et al., 2008; Wassing et al., 2016). Insomnia in PTSD has been quantified as long sleep onset latency (SOL; defined as time to transition to sleep from waking), reduced sleep efficiency (total sleep time/total recording time), and frequent awakenings after sleep onset (Neylan et al., 2003; Werner et al., 2016). A recent meta-analysis of PSG studies in PTSD patients compared to normal controls provides evidence for increased wake time after sleep onset (WASO) and reduced total sleep time and slow wave sleep (SWS) percentage (SWS time/total sleep time) (Zhang et al., 2019). Decreased sleep efficiency and SWS percentage were significantly associated with increased PTSD symptom severity (Zhang et al., 2019).

A hallmark of PTSD is re-experiencing the traumatic event as repetitive trauma-related nightmares (Ross et al., 1989; Mellman et al., 1995; Germain, 2013). These nightmares, which are reported by approximately 80% of PTSD patients, are long, frightening dreams that culminate in awakening (DSM-5, American Psychiatric Association, 2013; Kilpatrick et al., 1994). They may occur in non-REMS (NREMS) as well as REMS (Phelps et al., 2018; Mysliwiec et al., 2018), and they are associated with leg movements and increased heart rate on awakening (Phelps et al., 2018). REMS phasic activity typically is measured

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electrooculographically in clinical studies. Increased REM density (number of rapid eye movements/total REMS time), which has been related to the processing of fearful stimuli (Datta, 2000; Mavanji et al., 2003), and REMS fragmentation (a disruption of REMS continuity), which has been related to nightmare production, have been described in PTSD (Kobayashi et al., 2007; Habukawa et al., 2018; Ross et al., 1994). Younger individuals with PTSD, in particular, may show a decrease in REMS percentage (REMS time/total sleep time) (Zhang et al., 2019).

We view the relationship between REMS and traumatic stress as a critical area of study. Along with tonic REMS, phasic activity, power spectral densities (PSD), and other aspects of REMS microarchitecture should be explored. Such work also may provide insight into the mechanisms and management of insomnia, arguably a REMS disorder (Riemann et al., 2012; Feige et al., 2008). As noted above, NREMS mechanisms also have been implicated in sleep changes following traumatization and require further investigation; however, that is beyond the scope of this manuscript.

2. Overview of preclinical studies of effects of stress on sleep

Although there have been advances in the treatment of stress-related sleep disturbances (Raskind et al., 2002; Taylor and Pruiksma, 2014; Zhang et al., 2020), many patients remain symptomatic. It has been essential to utilize basic as well as human research to understand how emotional stress affects sleep and to translate these findings to advances in clinical care. Animal models can control for variables that have contributed to some divergence in PSG and other clinical findings (Kobayashi et al., 2007). For example, animal models are able to take a developmental perspective, accounting for time following stress presentation. Interestingly, clinical research has indicated that both REMS percentage and REMS segment length increase with time post-traumatization (Ross, 2014; Mellman et al., 2014). Animal models of the PTSD sleep disturbance have also begun to consider sex differences. This is of great importance because PTSD and acute stress disorder, with characteristic symptoms of PTSD persisting not longer than a month after trauma exposure, occur more commonly in women than men [Olff et al., 2007; Schenker et al., 2022; Richards et al., 2022]. Moreover, nightmares are reported more frequently by women [Richards et al., 2013].

Investigators have struggled to establish animal models of PTSD with high face validity. Most models do not include sleep measures and do not consider sex differences. The construct validity of an animal model depends on its parallels with human behavior. Although rodent sleep and human sleep have different sleep cycle durations and circadian timing, insomnia-like and nightmare-like features can be observed in rodents after stress exposure (McCarley, 2007; McKenna et al., 2007, 2008). We highlight paradigms that have assessed changes over time following stress presentation. These include repeated social defeat, repeated restraint stress, and fear conditioning (Papale et al., 2005; DaSilva et al., 2011b; Laitman et al., 2011; MacLean et al., 2012; Yu et al., 2015; Sharma et al., 2018; Grafe et al., 2020; Gargiulo et al., 2021). Repeated stress paradigms may be less likely to produce simple rebound changes in sleep compared to acute stress paradigms (Kant et al., 1995; Pawlyk et al., 2008) and therefore may be more translationally relevant. Despite the challenges in developing animal models due to variations in experimental methods, variations in trauma exposure factors (e.g., type and time since exposure) and in heterogeneity of samples, animal models offer an important opportunity to explore this variability and the developmental responses to trauma by controlling the conditions before, during, and after trauma exposure.

3. Insomnia-like features in animal models of relevance to PTSD

Insomnia-like features that can be quantified in animal models of stress include increased SOL, reduced sleep efficiency, increased WASO, and increased number of awakenings. The most robust effects of stress on SOL have been observed in animal models using predator or conspecific odor. Exposure to a cage soiled by a conspecific increased the latency to the onset of SWS in rats, and this effect was reversed by a dual orexin receptor antagonist (Gamble et al., 2021). Similarly, mice exposed to predator odor had persistent difficulty falling asleep (demonstrated by increased SWS and REMS latencies, which are the times to enter into these phases of sleep after initial sleep onset) and an increase in the frequency of waking bouts during the light period (Sharma et al., 2018).

Repeated stress has been found to reduce sleep efficiency. Daily immobilization stress (22h/day) significantly reduced sleep efficiency within two days, and the effect lasted at least four days (Papale et al., 2005). Compared to four days of foot shock (intermittent 2 mA shocks for 1h twice a day), swim stress (twice a day for 1h), and cold stress (1h at 4 °C per day), immobilization stress was more effective in reducing sleep efficiency, likely due to its longer duration (Papale et al., 2005). The decrease in sleep efficiency produced by fear conditioning (Pawlyk et al., 2005) could be reversed by social partnering (DaSilva et al., 2011a, 2017), a finding consistent with the observation that social interaction can increase sleep efficiency in humans (in a general civilian population and in soldiers returning from deployment; Cacioppo et al., 2002; Pietrzak et al., 2009).

Repeated social defeat and repeated restraint have been reported to increase WASO in rodents. Rats coping passively in response to defeat (characterized by rapid submission), compared to actively coping rats (characterized by resistance to defeat), showed an increase in WASO after seven days of social defeat, an effect that persisted two weeks after the end of social defeat (Grafe et al., 2020). Also, two exposures to social defeat increased the number of awakenings from sleep four days later. These findings demonstrate the importance of examining sleep several days or possibly weeks past the stressful experience (Kinn et al., 2008; Kinn Rød et al., 2014). Repeated restraint stress in rats increased the percent of time spent awake during the light period (Gargiulo et al., 2021). This increase was more pronounced in females and persisted during recovery days in females only. This finding aligns with a meta-regression analysis in humans that found that studies with a higher percentage of female patients showed increased WASO in PTSD patients compared to controls, which the authors hypothesized might be due to sex differences in the orexin system (Zhang et al., 2020).

4. Nightmare-like features in animal models of relevance to PTSD

As mentioned previously, nightmares in PTSD are associated with leg movements on awakening (Phelps et al., 2018). Thus, animal studies have aimed to capture motor activity occurring as an animal awakens from sleep via PSG recordings and behavioral observation, which may reflect one aspect of nightmare-like behavior. Repeated social defeat, repeated restraint, and foot shock stress all have been shown to produce robust motor activity during awakening. Rats using an active coping strategy in response to social defeat showed a less exaggerated motor response to waking from REMS than rats using a passive coping strategy (Grafe et al., 2020), suggesting that active coping may protect against the development of nightmare-like behavior. Repeated restraint stress has been shown to exaggerate motor responses to waking from REMS in female, but not male, rats, highlighting an important sex difference in the sleep response to stress (Gargiulo et al., 2021). Rats exposed to foot shock stress exhibited startled awakening (suddenly waking from undisturbed sleep with jumping behavior) (Yu et al., 2016). Interestingly, rats that observed another rat undergo foot shock stress reacted similarly, indicating that witnessing the stressor applied to a conspecific is sufficient to induce a nightmare-like response to stress (Yu et al., 2016). There is evidence that orexins, norepinephrine, and serotonin acting in brain regions important for fear memory retrieval during sleep are relevant neural substrates (Yu et al., 2015). In sum, various animal stress paradigms can influence motor activity during waking from sleep, with

both coping strategy and sex as modifiers. Examination of other possible nightmare-related measures, including heart and respiratory rates during waking, are likely to be informative as well (Stam, 2007)

5. REMS fragmentation in animal models of relevance to PTSD

REMS fragmentation has been described in PTSD (Mellman et al., 2002; Riemann et al., 2012). Some research suggests that such fragmentation in the early aftermath of trauma predicts the development of PTSD (Mellman et al., 2002; Breslau et al., 2004; Habukawa et al., 2007). Alternatively, REMS discontinuity may predate trauma exposure and increase susceptibility to PTSD (Lerner et al., 2017). In preclinical studies, REMS fragmentation has been analyzed by classifying single and sequential REMS episodes (Sin-REMS and Seq-REMS, respectively) (Amici et al., 1994). Sin-REMS is comprised of REMS episodes preceded and followed by $>$ 3-min intervals. Seq-REMS is comprised of REMS episodes separated by $\leq$ 3-min intervals and tending to occur in clusters. Fear conditioning was found to increase REMS fragmentation, here defined as a shift toward Seq-REMS, in stress-sensitive Wistar-Kyoto rats (DaSilva et al., 2011a, 2011b). The alpha adrenoceptor antagonist prazosin, which may effectively treat the nightmare disturbance in PTSD patients (Raskind et al., 2002), reduced this fragmentation (Laitman et al., 2011; Laitman et al., 2014), as did social partnering (DaSilva et al., 2011a). Repeated social defeat and repeated restraint have failed to produce long-lasting REMS fragmentation (Grafe et al., 2020; Gargiulo et al., 2021).

Wassing et al. (2016) posited a link between REMS fragmentation and heightened REMS phasic activity in humans. They defined "restless REMS" as REMS with a high number of phasic events and suggested that restless REMS interferes with the ability to manage emotional distress (Wassing et al., 2016). Work in animals that has implicated REMS phasic activity in the processing of fearful stimuli (Datta, 2000; Mavanji et al., 2003) is broadly consistent with this hypothesis. Studying fear conditioning in rats, DaSilva et al. (2011b) suggested that early failure to mount a strong phasic REMS response to a stressful experience (here measured as nuchal myoclonic twitch density) could contribute to the increase in REMS phasic activity that has been observed in humans with chronic PTSD (Kobayashi et al., 2007).

6. Power spectral density (PSD) signatures in animal models of relevance to PTSD

PSD describes the distribution of signal power over frequency (Dressler et al., 2004) and can inform how stress changes brain activity during wake and sleep states (Vyazovskiy and Delogu, 2014). Studies in humans have found an increase in beta band power and a decrease in alpha band power in psychologically stressful contexts (Hinrichs and Machleidt, 1992; Hayashida et al., 2010; Awang et al., 2011; Rajendran et al., 2021). The beta frequency band has been associated with an increase in mental workload and concentration under psychological stress (Palacios-García et al., 2021). In contrast, the alpha frequency band may indicate a relaxed state, with lower mental vigilance (MacLean et al., 2012; Kamzanova et al., 2014; Fernandez Rojas et al., 2020).

Zhang et al. (2019) conducted a meta-analysis of PSD in PTSD sleep. Compared to trauma-exposed controls, PTSD-diagnosed patients have exhibited reduced delta band power and increased power in higher frequency bands (de Boer et al., 2019; Wang et al., 2019). Decreased beta band power in REMS as well as NREMS also has been observed (Denis et al., 2021), and there are reports of changes in spindle range activity (de Boer et al., 2019; van der Heijden et al., 2022; Wang et al., 2020). In PTSD-diagnosed patients compared to trauma-exposed controls (de Boer et al., 2019; Denis et al., 2021), an increase in slow oscillation power during REMS, which was found together with power loss in high frequency bands, was strongly correlated with nightmare reports. Increased high frequency gamma band power also has been observed (Wang et al., 2019). It has been suggested that high frequency EEG activity during REMS is an index of fragmented REMS, which interferes with the resolution of emotional distress (Wassing et al., 2016; van der Helm et al., 2011).

In various animal models of repeated stress, increased beta power and lower delta power generally have been observed in both NREMS and REMS, indicating less deep and restful sleep (Fenzl et al., 2011; Nedelcovych et al., 2015). PSD analysis of the sleep EEG has helped to identify mechanisms of REMS fragmentation. Gamma oscillations in the EEG are synchronized throughout the brain in periods of focused attention during REMS as well as waking, which may indicate a temporal binding process (Bragin A et al., 1995; Jensen et al. (2007), Laitman et al. (2011) found that relative gamma power at REMS transitions was low in fear-conditioned, stress-sensitive Wistar-Kyoto compared to Wistar rats. Gamma oscillations during REMS have been associated with memory processing and dream formation (Cantero et al., 2004; Kahn et al., 1997). Thus, PSD data may be important for both detecting the memory processes occurring after trauma, as well as the quality of the subsequent sleep. The PSD during application of a stressor has not been studied systematically in animal models. Findings could identify brain biomarkers of the development of sleep disturbances in PTSD (Hinrichs and Machleidt, 1992; Hayashida et al., 2010; Awang et al., 2011; Rajendran et al., 2021). Further, there is not a good understanding of how acute stress compared to repeated stress may impact REMS and how long the impacts endure. This is an important issue for future consideration as PTSD may be related to a single traumatic event or repeated events and the mechanisms underlying changes in REMS may differ between acute and repeated stressful experiences.

7. Neurobiological substrates of REMS fragmentation

The neurobiological substrates of REMS fragmentation have not been well studied. Investigation of these will depend on knowledge of the biology of normal REMS. It is still not completely understood how REMS is induced and regulated. However, previous research suggests that REMS is partially regulated through the interplays between cholinergic and monoaminergic neurons in the brainstem (Wang et al., 2015). Specifically, a role for the locus coeruleus, which has norepinephrine-containing cells that are active during wake but cease firing during normal REMS (known as "REM off" neurons), is likely. Moreover, cholinergic neurons (known as "REM on" neurons) that project to the nucleus point oralis can induce REMS.

Beyond the interaction between norepinephrine and acetylcholine in REMS, wake-promoting hypothalamic orexin neurons are thought to play a key role in REMS regulation. Blocking orexin activity can reduce arousal during sleep and increase REMS percentage (Kaplan et al., 2022). A recent evaluation of the dual orexin receptor antagonist suvorexant compared to placebo in a sample of 37 patients with trauma-related insomnia found no group differences in improvement of insomnia and other PTSD symptoms (Mellman et al., 2022). Exploratory within-group analyses of the suvorexant group found increases in REMS percentage and segment duration, with the latter associated with improvement in PTSD symptom severity. Notably, no emergence of nightmare events was observed within the treatment group. Enhancing REMS continuity by targeting the orexin system may hold promise for treating trauma-associated insomnia and nightmares and should be a focus of future clinical and preclinical investigations.

As discussed by others (Pace-Schott et al., 2015; Bottary et al., 2023; Colvonen et al., 2019; Davidson and Pace-Schott, 2020), there is a strong link between fear learning processes and sleep in trauma. Mechanisms underlying fear learning including extinction and extinction retention involve the amygdala and hippocampus and other regions (for a discussion of these mechanisms, see Ressler et al., 2022). However, the mechanisms through which sleep impacts fear learning related to stress or trauma are not well described and deserve attention. Other preclinical data have begun to uncover another possible neural mechanism by which stress may induce REMS fragmentation. Specifically, social defeat

stress is thought to induce REMS fragmentation through a pathway from the prefrontal cortex (PFC) to the ventrolateral preoptic area (VLPO) (Chouvaeff et al., 2022). *In vivo* activation of PFC-VLPO projections interrupts ongoing REMS in favor of NREMS, leading to fragmented REM bouts. This exciting discovery could explain how top-down regulation is recruited in stressful situations to induce REMS fragmentation.

8. Conclusions

It is crucial that future work in animal models of PTSD includes insomnia-like and nightmare-like sleep measures. The former may have relevance to chronic insomnia disorder as well. Repeated stress models, in particular, may hold promise for identifying the neural mechanisms of sleep disruption in PTSD. Previous studies suggest the importance of REMS fragmentation, which can best be explored by incorporating phasic REMS measures, Sin-REMS/Seq-REMS analysis, and PSD into experimental designs. Sex differences in the response of sleep to stress require further investigation (Neylan et al., 2003; Otte et al., 2007; Schenker et al., 2021), especially as both PTSD and insomnia are more prevalent in women (DSM-5) and PTSD-diagnosed females have higher prevalences of insomnia and nightmares (Zhang and Wing, 2006; Habukawa et al., 2018, Richards et al., 2022; Schencker et al., 2022).

Overarching perspectives

- Perspective 1: Studies in animals of PTSD-like sleep disturbances should use stress models that allow for a developmental view of the response to trauma(s).
- Perspective 2: Studies in animals of PTSD-like sleep disturbances should examine sex differences because of the clear sex differences in the effects of stress and in clinical studies of PTSD.
- Perspective 3: Studies in animals of PTSD-like sleep disturbances should focus on REMS continuity using several measures of REMS microarchitecture.

CRediT authorship contribution statement

Laura Grafe: contributed to conceptualization, writing and editing of this manuscript. **Katherine E. Miller:** contributed to conceptualization, writing and editing of this manuscript. **Richard J. Ross:** contributed to conceptualization, writing and editing of this manuscript. **Seema Bhatnagar:** contributed to conceptualization, writing and editing of this manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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