

Sleep, stress and trauma

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SUMMARY

The potential impact of sleep and sleep disorders on stress responses has received increasing interest particularly in the context of Post-traumatic Stress Disorder (PTSD). This review aims at synthesizing current evidence concerning the link between trauma exposure, sleep, emotional regulation and stress. In the last decades, experimental investigations suggested a critical role of sleep on emotional memory formation and emotional reactivity; similarly, animal and human studies highlighted the relations between sleep and fear responses, supporting the notion that sleep disturbance plays an important role in PTSD-relevant processes such as fear learning and extinction. Although some crucial aspects of these interactions need further clarification, convincing evidence now suggests a complex physiological interaction of stress response and sleep. In the context of trauma-related disorders, sleep alterations have been suggested as core symptoms as well as risk and prognostic factors; importantly, sleep may also represent an important therapeutic target in mental health. However, evidence accumulated so far points to sleep disturbance as a marker not only of PTSD, but also of increased vulnerability to maladaptive stress responses. Novel models conceptualize sleep disturbance as a modifiable, transdiagnostic risk factor for mental disorders, with important theoretical and clinical implications.

Key words: sleep disturbances, trauma, emotional processing, post-traumatic stress disorder

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Conflict of interest

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Introduction

In the last years, the potential relation between sleep and trauma has received increasing interest, particularly in the context of trauma and stress-related disorders such as Post-traumatic Stress Disorder (PTSD). In the last two decades, experimental investigations have progressively highlighted the importance of sleep for cognitive as well as emotional functioning^{1,2}. A critical implication of sleep in emotional memory formation as well as emotional homeostasis is well documented, also leading to important implications for trauma-related disorders. Similarly, animal and human studies have probed the relationship between sleep, particularly Rapid Eye Movement (REM) sleep and fear responses, also providing strong support for the hypothesis that sleep disturbance plays an important role in trauma-related processes. Alterations of sleep pattern represent a typical behavioral consequence of acute stressful/traumatic exposure and a core symptom of PTSD. In this context, while sleep disorders could have a pathoplastic role in PTSD, the emotional hyper-reactivity associated with a traumatic experience itself may, in turn, affect subsequent sleep quality. A complex, bidirectional relation between sleep and stress/trauma emerges, whereby emotional processes can progressively affect and be affected by sleep disturbances. Overall, recent literature suggests that disturbed sleep can contribute to maladaptive stress and trauma responses and may constitute a modifiable, transdiagnostic vulnerability factor for poor psychiatric outcomes^{3,4}. Importantly, sleep disturbance is a modifiable vulnerability factor, and sleep restoration through effective

targeted sleep treatments may accelerate recovery from trauma exposure and PTSD. Further clarifying the neural substrate and the behavioral implications of the relation between sleep and trauma is a critical issue for the development of innovative strategies for risk management and treatment.

The aim of this review is to summarize relevant evidence on the relations between stress exposure and trauma, sleep and emotional regulation. Potential critical implications of sleep in the context of stress exposure, trauma-related disorders and interventions will be discussed. Further, critical issues for future research will be suggested.

Sleep disturbance in PTSD

Post-traumatic Stress Disorder is a psychiatric illness that can occur after the exposure to traumatic events. Lifetime prevalence of PTSD is estimated between 2.3%⁵ and 6.1%⁶ in civilians and 30% in veterans⁵. PTSD symptoms include four psychopathological dimensions, i.e. avoidance, negative affect, intrusions (including nightmares) and hyperarousal. In the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders⁷, sleep disorders are included among the criteria for PTSD as re-experiences of traumatic symptoms (nightmares, criteria B) as well as alterations in arousal and reactivity (sleep disturbance, criteria E). Difficulties in falling asleep, frequent awakenings, reduced sleep duration, restless sleep and fatigue represent typical complaints of PTSD patients. Particularly, nightmares and anxiety dreams, a Rapid-eye Movement (REM) sleep phenomenon, appear consistently associated with PTSD⁸, so that they are commonly considered a core symptom of PTSD⁹. Accordingly, disturbed sleep, particularly REM sleep disturbances and nightmares, have been considered as the hallmark of PTSD¹⁰. Although the presence of sleep disturbance is a diagnostic criterion for the disorder, a clear consensus regarding the link between sleep disorders and the development of PTSD is still lacking. Findings concerning objective sleep alterations in PTSD are contrasting. A meta-analytic review¹¹ showed more stage 1 sleep, less slow-wave sleep, and greater REM density in PTSD patients compared to controls. Conversely, REM sleep reduction or fragmentation has been observed both in the acute aftermath of trauma exposure and in subjects with PTSD several years after the onset of PTSD^{12,13}. Nevertheless, insomnia and REM sleep fragmentation following traumatic events are predictive of later development of PTSD¹⁴. Also, self-reported sleep disturbances have been showed to increase the likelihood of developing PTSD following a natural disaster¹⁵, thus also indicating a potential proactive role of sleep disturbance on the PTSD vulnerability.

Moreover, sleep-focused treatments can significantly improve both sleep and PTSD symptoms^{16,17}.

A recent general population survey conducted in 24 countries reported a lifetime prevalence of trauma exposure of approximately 70%¹⁸. An even higher lifetime rate of traumatic events has been estimated in clinical populations, with a lifetime prevalence of 90%¹⁹. Particularly, compared to the general population, the exposure to interpersonal traumatic events such as physical and sexual violence is higher in individuals with a severe mental illness²⁰, with a significant impact on personal and social functioning of patients with mental disorders^{21,22}. Although the exposure to traumatic events is common in both clinical samples and general population, only a minority of individuals will develop PTSD. In addition to trauma exposure, increasing evidence suggests alterations in emotional memory processing and emotional modulation as critical to PTSD and complex PTSD development and maintenance²³; in this context, evidence also exists in support of a causal role of sleep disturbance in such alterations.

Sleep and emotional processing: implications for trauma-related disorders

In the last two decades sleep research strongly supported a crucial relationship between sleep and learning/memory consolidation². Accumulating evidence suggests that sleep-related consolidation processes are essential for the long-term maintenance of emotional information¹. Behavioral investigations showed that post-learning sleep selectively favored the retention of negative emotional texts compared to neutral texts and this emotional memory enhancement may persist for several years^{24,25}. Similarly, napping may facilitate the consolidation and the post-sleep encoding of declarative emotional and neutral memories²⁶ or may promote preferential memory consolidation for negative emotional information²⁷. Furthermore, sleep deprivation literature converges at indicating that the sleeping brain provides ideal conditions for episodic memory consolidation, while sleep loss negatively affects emotional memory processing^{1,28-31}.

Importantly, accumulating evidence pointed to REM as the sleep stage specifically involved in emotional memory processing. Indeed, REM sleep stage is typically associated with reports of emotionally intense dreams³². REM sleep is accompanied by specific hyperactivity within brain areas implicated in memory functions during wake³³. A large literature now suggests that the link between the REM sleep neuroanatomophysiology and the emotional domain is not coincidental³⁴. During REM sleep, memories within

the neocortex are subjected to a plasticity-related cholinergic activity while remaining free from arousal-related noradrenergic interference, thus they potentially recombine each other and integrate into preexisting memory networks³⁵.

However, while a crucial implication of sleep in all stages of emotional memory formation is well documented^{30,31}, the specific impact of sleep on the next-day emotional reactivity is still controversial. According to Wagner and coworkers (2001) the REM sleep-mediated emotional memory consolidation is paralleled by the strengthening of the associated emotional charge. Consequently, REM sleep deprivation should prevent sleep-dependent neural reactivation assumed to be necessary for the consolidation of new memory traces, thus impairing the consolidation of a memory and of its associated emotional tone. In line with these assumptions, the use of sleep deprivation as a potential preventive therapeutic measure to hinder the long-term retention of traumatic events has been suggested^{24,25}.

In contrast to the previous hypothesis, the 'Sleep to remember, sleep to forget' model³⁴ posits that the inherent neurobiological state of REM sleep could support a de-potentialization of the emotional charge of a memory. Specifically, during REM sleep the activation of brain areas implicated in memory function, such as the amygdala and the hippocampus, would support the overnight reprocessing and long-term retention of emotional memories ('Sleep to remember')³⁶. Contextually, the suppressed adrenergic activity would gradually dissipate the autonomic charge associated with the emotional experiences ('Sleep to forget'). In this way, REM sleep could represent an 'overnight therapy' to adaptively preserve the salient aspects of a memory, dissipating at the same time the associated emotional tone, eventually promoting an accurate separation of the emotional charge from the declarative content of the mnemonic trace³⁶. Neuroimaging as well as behavioral studies offer support to this assumption. Indeed, after sleep loss, an amplified limbic activation in response to negative emotional stimuli has been observed, in association with a reduced functional connectivity between the amygdala and the ventro-medial prefrontal cortex (vmPFC). These alterations are suggestive of a dysfunction of the vmPFC-amygdala circuitry and a lack of top-down control by the prefrontal cortex (PFC) on the limbic system³⁷. Therefore, at the behavioral level, sleep loss may impose a more negative affective tone to memories³⁸. Within this framework, REM sleep has also been indicated as a preventive therapeutic measure for emotional brain homeostasis to preserve an effective functional PFC-limbic connectivity³⁶.

On the whole, investigations on the relationship between sleep and emotional reactivity produced contrasting

results, with evidence supporting both enhanced and diminished REM-related emotional reactivity, as well as no effect specifically associated with REM sleep¹. Although the specific direction of the sleep-dependent emotional modulation needs to be further clarified, these results support the importance of sleep for appropriate emotional memory processing and next-day emotional reactivity.

The complex relationship between sleep and trauma

Increasing evidence is providing important insight into the relationship between sleep and trauma. Such link is relevant in light of the robust relations between sleep disorders, adverse life events and mental disorders. While daytime affective symptoms can adversely affect sleep, there is growing evidence that sleep disturbances can reciprocally impact daytime symptoms³⁹.

In the last years, fear conditioning paradigms in mammals⁴⁰ confirmed that sleep plays a critical role in the encoding and long-term retention of fearful memories. Research in this field showed that an experimentally induced fear response can affect subsequent sleep, as well as sleep manipulation can influence subsequent fear conditioning/extinction processes. Fear conditioning investigations have linked post-learning sleep to the consolidation of both fear conditioning and fear extinction in humans¹. Although the specific direction of sleep-mediated modulation of fear remains unclear, sleep seems to promote the appropriate recognition of salient stimuli and the discrimination between fear and safety relevant stimuli, thus fostering the most appropriate response to the environment. This could be relevant since the dysfunctional persistence of fear conditioning and poor fear extinction has been implicated in the pathogenesis and maintenance of stress-related disorders and anxiety disorders. Indeed, dysfunctional fear expression in anxiety disorder may result from abnormally strong fear response or alterations of the inhibitory system modulating fear^{41,42}. In this respect, a dysfunctional activation of brain areas implicated in fear extinction has been shown to differentiate trauma-exposed individuals with and without PTSD; at the behavioral level, such alterations were associated with impaired recall of extinction memory⁴²⁻⁴⁴. Importantly, in clinical populations such as spider-fearing women, sleep after exposure therapy may promote the retention and generalization of extinction learning with the potential to enhance the efficacy of the treatment, possibly preventing sensitization to threat and fear generalization^{45,46}. Conversely, disturbed sleep may negatively influence the optimal processing of fear and extinction-related memory traces.

On the other hand, sleep disturbance represents a common behavioral consequence of acute and chronic

stress response⁴⁷. In the animal model, different types of inescapable experimental stress were associated with subsequent REM sleep fragmentation; furthermore, conditioned reminders have been shown to produce similar stress-induced alterations in sleep architecture that may persist long after the initial stressful experience, while extinction learning seems to reverse these alterations⁴⁸. Acute trauma-related hyperarousal itself could produce sleep disturbances that may lead, in turn, to a paradoxical hypervigilance response, thus perpetuating the stress response³⁹. Moreover, sleep disruption may further impair the sleep-dependent memory processing, hindering an adaptive emotional regulation. Accordingly, at the neuroendocrine level, a complex mutually interactive physiology of stress response and sleep has been suggested, whereby traumatic experience may prevent a subsequent appropriate sleep-dependent emotional homeostasis (i.e. reduction in catecholamine levels, sympathetic tone, hypothalamic pituitary adrenal (HPA) axis and central corticotropin releasing factor (CRF)-ergic activity) resulting in an abnormal daytime stress response³⁹. In the context of trauma-related disorders, these findings suggest that sleep alterations possess the potential to directly exacerbate initial symptoms and/or to impair the subsequent consolidation of appropriate extinction learning, thus contributing to the maintenance of maladaptive stress response.

Sleep disturbance: a transdiagnostic risk factor

The importance of understanding the link between sleep and emotional processing is evident in light of the robust evidence demonstrating associations between sleep alterations and mental disorders^{3,49}. Disturbed sleep represents both a core symptom and a potential pathophysiological factor of PTSD; however, in the DSM-5 sleep disturbance is a key symptom of many, if not all, psychiatric disorders. Accordingly, it has been suggested that sleep continuity disturbances imply a transdiagnostic imbalance in the arousal system that could represent a basic dimension of mental health³. As reported in epidemiological and prospective studies, pre-existing or peritraumatic sleep disturbance represents a risk factor not limited to PTSD, but also for mental disorders such as anxiety disorders, mood disorders and alcohol/substance use disorders^{50–54}. Similarly, insomnia is a risk factor for incident depression⁵⁵. In Major Depression, alterations in the sleep/wake cycle may emerge in a premorbid, symptoms-free age of life⁵⁶; similarly, differences in circadian profiles can be found in subjects with Depression and Panic Disorders even before the clinical onset of the disorders⁵⁷. The co-occurrence of sleep and psychiatric disorders tends to

attenuate treatment response; further, sleep alterations may increase the risk of relapse, thus suggesting an important prognostic significance of sleep disturbance in mental disorders^{58,59}.

In addition to their specific implication in PTSD, increasing evidence to date support the hypothesis that sleep disturbances may reflect a broad index of maladaptive stress responses to trauma exposure. The predictive relationship between sleep alterations and an increased risk for a broad range of subsequent disorders strongly suggests that sleep disturbances could be important indices of compromised resilience⁶⁰. In further support of this, the presence of consolidated sleep in trauma-exposed individuals⁶¹, as well as sleep improvements during treatment for affective disorders^{62,63}, are associated with better mental health outcomes. These findings therefore have important implication for the implementation of preventive and therapeutic strategies in mental health settings.

Conclusions and future directions

In the last years, increasingly evidence supported an intimate relationship between sleep and trauma. A large number of experimental investigations have demonstrated a crucial role of sleep on the processing of emotional memories. Similarly, fear conditioning studies have implicated sleep, particularly REM sleep, in the adaptive consolidation of both fear and extinction memories, a process that could be specifically impaired in PTSD. Literature also suggests that treating sleep disturbances immediately after the trauma exposure may reduce the development or severity of PTSD via consolidation and generalization of extinction memories. However, some crucial aspect of the sleep-mediated overnight emotional modulation should be further clarified, with important theoretical and clinical implications for trauma-related disorders. Specifically, the role of sleep in emotional processing should be further addressed in clinical PTSD samples, in order to better elucidate the specific direction of such relationship. In this respect, while restoring REM sleep may be related to appropriate extinction learning in PTSD, it could also promote the initial consolidation of fear memories, thus exerting an opposite effect on the emotional reactivity in the early aftermath of a trauma. This suggest the individuation of a precise, strategic time window for sleep interventions as a critical issue for future research on trauma-related disorders.

Future studies investigating the link between sleep and trauma should advance our understanding on the specific impact of potential vulnerability or protective factors. For example, differences in REM sleep propensity could moderate the effects of stress and trauma exposure on behavioral and physiological

outcomes⁶⁴. Sex-related differences in functional brain activity have been described in studies investigating emotional memory⁶⁵ and emotional reactivity^{66,67}; also, physiological estrogenic fluctuations may influence some aspects of the emotional processing⁶⁸. Moreover, a specific vulnerability of females to the detrimental effects of sleep loss⁶⁹ as well as to mood disorders⁷⁰ and sleep disturbances⁷¹ has been reported, suggesting the need to further investigate the specific contribution of sex-related differences in modulating the relation between sleep and emotions.

Moreover, future studies investigating the relations between sleep, stress and trauma should further clarify the potential role of neurobiological markers such as brain-derived neurotrophic factor (BDNF). In this respect, alterations in BDNF levels have been linked with post-traumatic stress spectrum symptoms⁷² and PTSD⁷³. Moreover, changes in BDNF levels are associated with chronotype⁷⁴, sleep loss and sleep quality⁷⁵, with evidence also pointing to sleep as a key mediator in the relation between stress and BDNF regulation⁷⁶, thus encouraging further research.

Future research should also be dedicated to a better understanding of the relations between sleep, trauma exposure and trauma-related disorders across different life stages. Retrospective studies suggested that

childhood trauma could be particularly associated with sleep disturbances later in life^{77,78}. Also, sleep problems in children or adolescents predict subsequent anxiety and depression disorders⁷⁹. Early adverse experiences may have long-lasting effects on REM sleep and brain development⁸⁰. These findings also raise the possibility that trauma exposure and altered sleep patterns during critical developmental stages may crucially interact in representing a significant transdiagnostic risk factor for subsequent mental illness.

Taken together, evidence accumulated so far supports the notion that sleep disturbance represents a sensitive index of heightened vulnerability to maladaptive stress responses and compromised resilience. In the context of trauma-related disorders, evidence-based sleep interventions have the potential to significantly advance clinical care. More generally, sleep disturbances should be conceptualized as a modifiable risk factor for poor psychiatric outcomes and therefore an important target for prevention and early intervention; novel models emphasize the transdiagnostic nature of sleep disturbance as a dimension for brain and mental health^{3,4,81}. Addressing sleep quality through accurate sleep assessment and interventions in populations at risk may represent an important preventive and therapeutic strategy in mental health.

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