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EDITORIAL

Sleep, circadian system and traumatic stress

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ABSTRACT

The human circadian system creates and maintains cellular and systemic rhythmicity essential for the temporal organization of physiological processes promoting homeostasis and environmental adaptation. Sleep disruption and loss of circadian rhythmicity fundamentally affects master homeostasic regulating systems at the crossroads of peripheral and central susceptibility pathways, similar to acute or chronic stress and, thus, may play a central role in the development of stress-related disorders. Direct and indirect human and animal PTSD research accordingly suggests circadian-system-linked sleep, neuroendocrine, immune, metabolic and autonomic dysregulation, linking circadian misalignment to PTSD pathophysiology. Additionally, there is evidence that sleep and circadian disruption may represent a vital pre-existing risk factor in the prediction of PTSD development, while sleep-related symptoms are among the most prominent in trauma-associated disorders. These facts may represent a need for a shift towards a more chronobiological understanding of traumatic sequel and could support better prevention, evaluation and treatment of sleep and circadian disruption as first steps in PTSD management. In this special issue, we highlight and review recent advances from human sleep and chronobiological research that enhances our understanding of the development and maintenance of trauma-related disorders.

Sueño, sistema circadiano y estres traumatico

El sistema circadiano humano crea y mantiene la ritmicidad celular y sistémica esencial para la organización temporal de los procesos fisiológicos que promueven la homeostasis y la adaptación ambiental. La alteración del sueño y la pérdida del ritmo circadiano afectan fundamentalmente a los sistemas de regulación homeostáticos maestros en la encrucijada de las vías de susceptibilidad periféricas y centrales, similar al estrés agudo o crónico y, por lo tanto, pueden desempeñar un papel central en el desarrollo de trastornos relacionados con el estrés. Investigación directa e indirecta en TEPT en humanos y animales respectivamente, sugiere que el sueño ligado al sistema circadiano, la desregulación neuroendocrina, inmune, metabólica y autónoma vincula la desalineación circadiana con la fisiopatología del TEPT. Además, existe evidencia que el sueño y la alteración circadiana pueden representar un factor de riesgo vital preexistente en predicción del desarrollo de TEPT, mientras que los síntomas relacionados con el sueño se encuentran entre los mas importantes en los trastornos asociados a trauma. Estos hechos pueden representar la necesidad de un cambio hacia una comprensión más cronobiológica de la secuela traumática y podría apoyar una mejor prevención, evaluación y tratamiento del sueño y la alteración circadiana como primeros pasos en el manejo del TEPT. En este número especial, destacamos y revisamos los avances recientes del sueño en el ser humano y la investigación cronobiológica que pueda mejorar nuestra comprensión del desarrollo y mantenimiento de los trastornos relacionados con el trauma.

睡眠、昼夜节律系统和创伤性应激

人类昼夜节律系统创造并维持细胞和全身节律FF0C这对于促进内稳态和环境适应生理过程的时间组织至关重要。类似于急性或慢性应激FF0C睡眠中断和昼夜节律的丧失从根本上影响外周和中枢易感性通路交叉的主要内稳态调节系统FF0C因此可能在应激相关疾病的发展中发挥核心作用。直接和间接的人类和动物 PTSD 研究表明FF0C昼夜节律系统相关的睡眠、神经内分泌、免疫、代谢和自主神经失调FF0C将昼夜节律失调与 PTSD 病理生理学联系起来。此外FF0C有证据表明FF0C睡眠和昼夜节律紊乱可能是预测 PTSD 发展的重要先存风险因素FF0C而睡眠相关症状在创伤相关疾病中最为突出。这些事实可能代表需要转向对创伤后遗症的更多时间生物学理解FF0C并且可以支持对睡眠和昼夜节律紊乱更好的预防、评估和治疗作为 PTSD 管理的第一步。在本期特刊中FF0C我们重点介绍并回顾了增强我们对创伤相关疾病发展和维持理解的人类睡眠和时间生物学研究的最新进展。

KEYWORDS
Circadian system; stress; trauma; posttraumatic stress disorder (PTSD); hpa axis; autonomic nervous system; cortisol; glucocorticoids; sleep; insomnia; nightmares

PALABRAS CLAVE
Sistema circadiano; estrés; trauma; trastorno de estrés postraumático (TEPT); eje HHA; sistema nervioso autónomo; cortisol; glucocorticoides; sueño; insomnio; pesadillas

关键词
心理韧性; 应激; 恢复速度; 日常韧性; 心理健康

HIGHLIGHTS

- Sleep and circadian disruption may be crucially involved in the development and maintenance of traumatic-stress-related disorders.
- There is a need for a chronobiological shift towards better evaluation, understanding and treatment of traumatic stress sequel.

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1. Introduction

The human stress system is closely and bidirectionally interconnected to the human circadian system, as both systems regulate each other's activity across 24 hours. For example, stress system activity and sensitivity to stressors greatly varies by circadian timing. On the other hand, stress can majorly affect circadian rhythmicity and potentially lead to acute/reversible or sustained circadian dysregulation (i.e. chronodisruption) (Agorastos et al., 2019). Stress-related effects on biological rhythms and sleep have, thus, been increasingly in the focus of related research, suggesting that stress-related sleep and circadian dysregulation may be heavily implicated in the pathophysiology of stress- and specifically trauma-related disorders (Agorastos, Kellner, Baker, & Otte, 2014; Germain, Buysse, & Nofzinger, 2008; Lavie, 2001; Mellman & Hipolito, 2006). Traumatic-stress-related chronodisruption can acutely affect traumatic memory consolidation (Henckens, Hermans, Pu, Joels, & Fernandez, 2009) and enhance long-term maladaptive neuroendocrine and autonomic stress regulation (Agorastos, Pervanidou, Chrousos, & Kolaitis, 2018; Mellman, Knorr, Pigeon, Leiter, & Akay, 2004; Spoormaker & Montgomery, 2008), representing a core pathway mediating the long-term neurobiological effects of trauma and related comorbidities (Agorastos, 2017; Pervanidou, Agorastos, Kolaitis, & Chrousos, 2017). For example, a recent study investigating whether abnormalities in sleep continuity mediate the effects of maltreatment on brain morphometry showed that maltreatment-associated sleep disruption is the sole factor mediating the effects of maltreatment on hippocampal volume (Teicher et al., 2017).

This close and probably causal association between traumatic stress and circadian/sleep dysregulation becomes more apparent in post-traumatic stress disorder (PTSD), the model disorder following a potentially traumatic event (American Psychiatric Association, 2013). Sleep disruption (e.g. insomnia, nightmares, delayed sleep latency, etc.) represent hallmark clinical symptoms of the disorder with very high prevalence (American Psychiatric Association, 2013; Germain, 2013; Germain et al., 2008; Spoormaker & Montgomery, 2008) and chronicity (Kajeepeta, Gelaye, Jackson, & Williams, 2015), possibly interfering with fear extinction and compromising recovery and often closely related to the overall PTSD symptom severity (Clum, Nishith, & Resick, 2001; Nishith, Resick, & Mueser, 2001).

Neurobiological evidence of chronodisruption in PTSD originates from findings on altered rest-activity rhythmicity patterns (Sandahl, Baandrup, Vindbjerg, Jennum, & Carlsson, 2021) and blunted neuroendocrine, autonomic and immune rhythmicity, similar to human sleep deprivation studies, suggesting that neurobiological alterations in PTSD may be significantly mediated by sleep and circadian disruption (Agorastos et al., 2014; Germain et al., 2008; Meerlo, Sgoifo, & Suchecki, 2008; Otte et al., 2005). Sleep disruption in PTSD is mainly associated with arousal regulation (Mellman, 1997) and include insomnia, nightmares, hyperarousal states, night terrors, body-movement and breathing-related sleep symptoms (Harvey, Jones, & Schmidt, 2003; Maher, Rego, & Asnis, 2006; Mellman & Hipolito, 2006; Pillar, Malhotra, & Lavie, 2000; Spoormaker & Montgomery, 2008; Westermeyer et al., 2010), with heightened sympathovagal tone during rapid-eye-movement (REM) sleep, fragmented REM sleep patterns, reduced REM theta activity (Germain, 2013; Germain et al., 2008; Kobayashi, Boarts, & Delahanty, 2007; Lamarche & De Koninck, 2007; Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002; Mellman & Hipolito, 2006) and pronounced changes in EEG spectral topologies during both NREM and REM sleep (de Boer et al., 2020). In addition, candidate-gene and genome-wide association studies have recently involved two core clock genes PACAP (adenylate cyclase-activating polypeptide, involved in phase resetting in response to light) and RORA-α (retinoid-related orphan receptor alpha, regulating circadian gene activity) as candidate risk genes for PTSD, although these findings have not been replicated yet (Amstadter et al., 2013; Dias & Ressler, 2013; Logue et al., 2013; Ressler et al., 2011). Similarly, another GWAS study, showed a shared genetic aetiology between specific sleep phenotypes and PTSD (Lind et al., 2020).

Interestingly, sleep disruption immediately after (Koren, Arnon, Lavie, & Klein, 2002; Luik, Iyadurai, Gebhardt, & Holmes, 2019; Meewisse et al., 2005; Mellman et al., 2002; Mellman & Hipolito, 2006; Thormar et al., 2014), as well as prior to trauma exposure could both increase the risk of PTSD development (Acheson et al., 2019; Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2010; DeViva, McCarthy, Southwick, Tsai, & Pietrzak, 2021; Koffel, Polusny, Arbisi, & Erbes, 2013), suggesting a perpetual circle with pre-existing sleep disturbances increasing the risk for PTSD and vice versa (van Liempt, 2012).

2. In this issue

In this issue, we received a range of extremely interesting papers ranging from experimental neuroscience to epidemiological, longitudinal and clinical practice papers as well as review papers on chronobiological and sleep-related aspects of traumatic stress and PTSD.

First, in a large-scale, longitudinal cohort study of over 2,400 deployed Marines, Acheson et al. (2019) examined the long-term relationship between pre-deployment sleep disturbance and post-deployment

PTSD symptomatology through several multifactorial pathway models, suggesting that sleep disturbances at pre-deployment remained the most important independent risk factor for the development of PTSD symptoms after deployment. In another prospective study, Yeh et al. (2021) investigated subjective and objective (polysomnographic) sleep quality at baseline and after one year of treatment in young women with and without sexual-assault-related PTSD, suggesting large subjective but only moderate objective differences in sleep quality between the two groups. Thereby, higher PTSD symptomology was associated with larger sleep impairment. Interestingly, this study also verified previous findings on the independent predictive role of better sleep quality on later PTSD improvement. In another longitudinal, follow-up study, Lies, Drummond, and Jobson (2020) investigated associations between mental health (PTSD, anxiety, depression), sleep symptoms (insomnia severity, pre-sleep arousal), and factors predicting mental health, over a 12-month period in a population of Syrian refugees. Interestingly, only pre-sleep arousal at baseline was the only predictor of mental health 12 months later and a significant mediator between change in post-migration stress and change in mental health symptoms.

Although the stress-related disruption of nocturnal memory consolidation is known to play a crucial role in the development of PTSD, there is conflicting evidence on a potential protective role of sleep or rather sleep deprivation directly after trauma experience. In a very interesting study, Sopp, Brueckner, Schäfer, Lass-Hennemann, and Michael (2019) examined how normal sleep – as opposed to partial sleep deprivation – modulates explicit and implicit trauma memory and intrusive thoughts of potential trauma reminders. The results of this study revealed higher explicit memory for potential trauma reminders and fewer intrusions after sleep as compared to partial sleep deprivation, supporting a protective role of sleep in trauma memory processing. As further evidence supports a particular close relationship between REM sleep stage and memory consolidation of traumatic experiences, Repantis et al. (2020) propose a potentially important role of objective (polysomnographic) sleep-stage monitoring for acutely traumatised individuals in the first night after trauma. The identification of objective sleep-related biosignatures of trauma through easy-applicable EEG-devices might enhance the ability to correctly predict potential PTSD development and guide the way to novel sleep interventions to prevent PTSD. In addition, the authors suggest a potential role of modulatory REM sleep interventions in the prevention of PTSD, such as behavioural sleep deprivation and selective pharmacological (e.g. serotonergic, noradrenergic, cholinergic) REM sleep suppression or enhancement.

Although there is evidence for circadian disruption leading to higher nocturnal autonomic activity and higher pre-sleep arousal leading to impaired pre-sleep cognitive activity and subsequent insomnia, pre-sleep thoughts and their association with sleep quality have not been yet investigated in PTSD in detail. Woodward, Sachschal, Beierl, and Ehlers (2019) have therefore developed and validated in different clinical groups a new, brief self-report measure of the content of trauma-related pre-sleep thoughts: the Trauma Thoughts before Sleep Inventory (TTSI). In this article, the authors report on the validation procedure, reliability and validity of the questionnaire and its discriminating ability to identify individuals with PTSD from individuals with only depression and insomnia, based on pre-sleep thoughts and arousal. As sleep disturbances have been also associated with dissociative symptoms, Dimitrova et al. (2020) investigated the relationship between dissociative symptoms, cognition, fantasy proneness and sleep after controlling for childhood and adult traumatic experiences. The authors concluded that, although patients with dissociative identity disorder and PTSD both report higher levels of sleep disturbances, this association is strictly moderated by traumatic experiences, suggesting no evidence between sleep and dissociative symptoms when traumatizing events were controlled for. In another cross-sectional study, Kleim et al. (submitted) examined the effects of circadian timing on intrusive re-experiencing over a whole week in trauma survivors. The authors report a curvilinear pattern of intrusive memories with a peak at about 2 p.m. Interestingly, PTSD patients showed a constantly higher level of intrusions in the evening hours, while non-PTSD controls showed a descending slope in the evening hours, pointing at circadian differences between groups and the need for time-adjusted interventions.

In a study assessing the prevalence of sleep problems and the concurrence with distress in parents of children treated for cancer, Rensen et al. (2019) reported a relatively high risk of reporting sleep problems in parents of children with cancer, while these mainly co-occurred with higher levels of distress and only rarely alone. Parents reporting both sleep disturbances and clinical distress, were also more likely to report parenting problems, chronic illness, insufficient social support, pre-existent sleep problems and be of female gender. However, although sleep disturbance has been described as a 'hallmark' symptom of PTSD, and several meta-analytic reviews have offered evidence for subjective sleep disturbances in PTSD and objective sleep EEG alterations, evidence of objective sleep disturbances measured by actigraphy is sparse. In this issue, Lewis et al. (2020) have conducted a systematic review and meta-analysis of actigraphic case-control studies in PTSD. Interestingly, the authors did not find any statistically significant difference between PTSD patients and controls in any of the investigated measures. As only six studies of moderate quality were included, further high-quality research is required to properly assess this issue.

Finally, we (Agorastos & Olff, 2020) offer a detailed overview article on the neurobiology linking traumatic stress to the circadian system and its dysregulation, as well as the respective timing parameters that play a significant role. In this article, we present the functional components of the stress and circadian system and their multilevel interactions and discuss how traumatic stress can affect the harmonious interplay between the two systems. We additionally propose the new scientific term 'posttraumatic chronodisruption' in order to describe the core mechanism mediating enduring neurobiological correlates of traumatic stress through a loss of the temporal order at different organizational levels. Given that many traumatic events occur in the late evening or night hours, we also describe how the time of day of trauma exposure can differentially affect the stress system and its sensitivity and, finally, discuss potential chronotherapeutic interventions.

3. Future perspectives

Post-traumatic sleep and circadian disruption fundamentally affect the neuroendocrine, immune and autonomic system, leading to a breakdown of biobehavioral adaptive mechanisms with increased stress sensitivity and vulnerability, and may thus play a causal role in the development of stress-related disorders and PTSD in particular. Sleep and circadian disruption after trauma represent core features of PTSD and may be both a precipitating and perpetuating factor of the disorder (Ticlea, Bajor, & Osser, 2013; van Liempt, 2012). Assessment of sleep quality and circadian patterns should, thus, be a priority in the routine clinical assessment of trauma-exposed individuals.

In addition, interventions aimed at normalizing sleep and circadian function may be important as therapeutic strategies in PTSD. Specific pharmacological treatments for PTSD-related sleep disruption have emerged through the years (i.e. adrenoreceptor modulatory agents prazosin, clonidine and trazodone, allosteric $GABA_A$ modulator eszopiclone), which have been shown not only positively influence sleep problems, but also overall PTSD symptom severity. However, there is a need for the introduction and clinical investigation of novel chronobiological interventions, capable of effectively restoring post-traumatic chronodisruption by influencing the interplay between stress and circadian system (Comai & Gobbi, 2014; Marshall & Garakani, 2002; Mendlewicz, 2009; Pilorz et al., 2014). Newest findings implicate serotonergic, melatonergic, opioidergic, GABA-ergic, cannabinoidergic and glucocorticoid signalling, as well as MDMA as potential new treatment strategies (Agorastos & Olff, 2020). In addition, non-pharmacological sleep and circadian approaches should not be forgotten. Cognitive-behavioural sleep management and social rhythm group therapy constitute an acceptable and effective treatment option in PTSD (Epstein, Babcock-Parziale, Haynes, & Herb, 2012; Haynes et al., 2016; Margolies, Rybarczyk, Vrana, Leszczyszyn, & Lynch, 2013; Schoenfeld, Deviva, & Manber, 2012; Talbot et al., 2014). Interestingly, two recent studies also support the efficacy of morning bright light treatment in reducing overall PTSD symptoms (Youngstedt et al., 2021; Zalta, Bravo, Valdespino-Hayden, Pollack, & Burgess, 2019), supporting the importance of circadian synchronization in the treatment of the disorder. Finally, there are first findings for an additional prevention potential of chronobiological measures (e.g. sleep deprivation, glucocorticoids) in the immediate aftermath of the trauma (Cohen, Kaplan, Zohar, & Cohen, 2017; Cohen et al., 2012), that might alleviate the impact of trauma on biological systems. Here, it is important to note, that specific agents immediately after trauma and in the first post-traumatic phase are not indicated and should be avoided (e.g. benzodiazepines) (Guina, Rossetter, Derhodes, Nahhas, & Welton, 2015).

Understanding the temporal relationship between stressors and stress responses and the pathways susceptible to chronodisruption following traumatic stress could deliver new insights into stress pathophysiology, provide better psychochronobiological treatment alternatives and enhance preventive strategies in stress-exposed populations (Agorastos & Chrousos, 2021). Novel state-of-the-art methods of sleep and circadian assessment and chronobiological treatment are needed to bridge the gap between clinical significance and limited understanding of the relationship between traumatic stress, sleep and circadian system.

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