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## REM sleep in acutely traumatized individuals and interventions for the secondary prevention of post-traumatic stress disorder

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### ABSTRACT

Increasing evidence supports a close link between REM sleep and the consolidation of emotionally toned memories such as traumatic experiences. In order to investigate the role of sleep for the development of symptoms related to traumatic experiences, beyond experimental models in the laboratory, sleep of acutely traumatised individuals may be examined on the first night after trauma. This might allow us to identify EEG variables predicting the development of posttraumatic stress disorder (PTSD) symptoms, and guide the way to novel sleep interventions to prevent PTSD. Based on our experience, patients' acceptance of polysomnography in the first hours after treatment in an emergency room poses obstacles to such a strategy. Wearable, self-applicable sleep recorders might be an option for the investigation of sleep in the aftermath of trauma. They would considerably decrease the perceived burden for patients and thus increase the likelihood of successful patient recruitment. As one potential sleep intervention, sleep deprivation directly after trauma has been suggested to reduce the consolidation of traumatic memories and hence act as a secondary preventive measure. However, experimental data from sleep deprivation studies in healthy volunteers with the trauma film paradigm have been inconclusive regarding the beneficial or detrimental effects of sleep on traumatic memory processing. Depending on further insights into the role of sleep in traumatic memory consolidation through observational and experimental studies, several options for therapeutic sleep interventions are conceivable: besides behavioural sleep deprivation, selective REM sleep suppression or enhancement by a pharmacological intervention into the serotonergic, noradrenergic or cholinergic systems might provide novel therapeutic options. While REM-modulating drugs have been used with some success for the prevention of PTSD after trauma, they have never been tried before the first night of sleep. In conclusion, more experimental and observational research is needed before sleep interventions are performed in actual trauma victims.

### Sueño rem en individuos traumatizados de forma aguda e intervenciones para la prevención secundaria del trastorno de estrés postraumático

La evidencia creciente respalda un vínculo cercano entre el sueño REM y la consolidación de recuerdos emocionalmente teñidos tales como las experiencias traumáticas. Con el fin de investigar el papel del sueño REM para el desarrollo de síntomas clínicos relacionados con experiencias traumáticas, más allá de los modelos experimentales en el laboratorio, se examinó el sueño de individuos traumatizados de forma aguda la primera noche después del evento traumático. Esto nos permitiría identificar las variables de EEG que predicen el desarrollo de los síntomas del trastorno de estrés postraumático (TEPT) y guiar el camino hacia nuevas intervenciones del sueño para prevenir el TEPT. Basado en nuestra experiencia, la aceptación de los pacientes de la polisomnografía completa en las primeras horas después de su tratamiento en una sala de emergencias plantea obstáculos para dicha estrategia. Sistemas de registro de sueño que sean portables y autoinstalables podrían ser una opción para la investigación del sueño en las secuelas del trauma. Disminuirían considerablemente la carga percibida para los pacientes y, por lo tanto, aumentarían la probabilidad de un reclutamiento exitoso de pacientes. Como una posible intervención del sueño, se ha sugerido que la privación total del sueño posterior al trauma reduce la consolidación de los recuerdos traumáticos y, por lo tanto, actúa como una medida preventiva secundaria.

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### PALABRAS CLAVE

trastorno de estrés agudo; trastorno de estrés postraumático; prevención secundaria; polisomnografía; la privación del sueño; sueño REM; supresión del sueño REM

### 关键词

急性应激障碍; 创伤后应激障碍; 二级预防; 多导睡眠检测; 睡眠剥夺; REM睡眠; REM睡眠抑制

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Sin embargo, los datos experimentales de estudios de privación del sueño en voluntarios sanos con el 'trauma film paradigm' no han sido concluyentes con respecto a los efectos beneficiosos o perjudiciales del sueño en el procesamiento de la memoria traumática.

Dado que la privación del sueño en la primera noche después de la traumatización podría no ser aceptable para muchas personas traumatizadas, la supresión selectiva del sueño REM, por ejemplo, mediante una intervención farmacológica, podría ser una alternativa dado el papel del sueño REM en la consolidación de la memoria emocional. Si bien los antidepresivos supresores de REM ya se han utilizado con cierto éxito para la prevención del TEPT, hasta ahora no se han probado antes de la primera noche de sueño después de un trauma. En conclusión, se necesita más investigación experimental y observacional antes de que se realicen intervenciones de sueño en víctimas de trauma reales.

### 急性创伤者的REM睡眠和创伤后应激障碍二级预防的干预措施

越来越多的证据支持REM睡眠与创伤经历之类的情绪化记忆巩固之间的紧密联系。为了探究REM睡眠在创伤经历相关临床症状发展中的作用,除实验室中的实验模型之外,还可以考查急性创伤者在创伤事件发生后第一晚的睡眠。这可能帮助我们识别出预测创伤后应激障碍(PTSD)症状发展的EEG变量,并为预防PTSD的新型睡眠干预提供指导。根据我们的经验,患者在急诊室治疗前几个小时接受的全面多导睡眠监测,对此策略有所妨碍。可自用穿戴式睡眠记录仪可能是创伤后睡眠研究的一种选择。它们将大大减轻患者负担,从而增加成功招募患者的可能性。作为一种潜在睡眠干预措施的完全睡眠剥夺,已被建议在创伤后立即进行,以减少创伤记忆的巩固,从而作为二级预防措施。然而,就睡眠对创伤记忆加工的影响是利是弊,在对健康志愿者采用创伤电影范式进行的睡眠剥夺研究的实验数据中尚无定论。鉴于创伤后第一晚的睡眠剥夺可能无法被许多创伤者所接受,并考虑到REM睡眠在情绪记忆巩固中的作用,选择性REM睡眠抑制(例如药物干预)可能是一种替代方法。尽管抑制REM的抗抑郁药已经成功用于创伤后PTSD的预防,但从未尝试在第一晚睡眠中应用。总之,在对真实的创伤受害者进行睡眠干预之前,需要更多的实验和观察性研究。

## 1. Background

Emotions are one of the strongest memory enhancers – remembering events that elicit strong emotions, such as fear, provide an advantage from an evolutionary perspective. It is thus not surprising that traumatic events build strong memories. While the majority of the individuals that are exposed to trauma experience symptoms of posttraumatic stress in the immediate aftermath of the event, prospective studies indicate that these reactions typically extinguish over time (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992). However, some individuals develop further psychopathology that leads to the diagnosis of posttraumatic stress disorder (PTSD).

Modulation of fearful memories has been studied with several lines of research (Phelps & Hofmann, 2019). Many interventions are however unsafe for use in humans, while others have produced inconsistent results (Monfils & Holmes, 2018). For the prevention of PTSD, one would need to intervene in the memory consolidation phase e.g. within hours after the event. Traditionally used, stress management interventions such as psychological debriefing have been abandoned since studies have shown that debriefing might have negative effects (Rose, Bisson, Churchill, & Wessely, 2002), presumably by facilitating consolidation of the traumatic event. Cognitive behavioural therapy interventions are promising (Roberts, Kitchiner, Kenardy, & Bisson, 2010), especially if they are exposure-based (Rothbaum et al., 2012). There have also been studies examining the effects of a number of drugs administered directly after the traumatic event, however, the results have not been

conclusive (Amos, Stein, & Ipser, 2014; Shalev, Liberzon, & Marmar, 2017). Due to the lack of effective preventive measures, there is a need for alternatives and sleep-based interventions might be a feasible option for secondary prevention.

It might be argued that regular sleep is just a general biological prerequisite to ensure cognitive functioning and therefore sleep trivially facilitates memory consolidation in comparison to sleep deprivation. But, experimental paradigms without sleep deprivation likewise demonstrate a role of sleep in memory consolidation (e.g. Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Increasing evidence supports a close link between REM sleep and the consolidation of emotionally toned memories (Genzel, Spoomaker, Konrad, & Dresler, 2015). While at first sight REM sleep may seem to unequivocally strengthen emotional memories, some studies suggest a more complicated picture of simultaneously reducing the affective tone of these memories (Pace-Schott et al., 2011). Referring to the fact that emotional experiences are remembered better than neutral ones, whereas their emotional tone during retrieval decreases with time, Walker and van der Helm (2009) proposed that REM sleep serves an emotional decoupling function; we sleep to remember emotionally tagged information, yet sleep to forget the associated emotional tone. For the development of PTSD, the attenuation of the emotional tone is of particular interest, and several studies in both healthy and sleep-disordered individuals have demonstrated that REM sleep disturbances increase emotional reactivity (Lipinska & Thomas, 2019; van der Helm et al., 2011; Wassing et al., 2019). Changes in sleep, and particularly

REM sleep, are symptoms of psychiatric disorders and especially PTSD (Germain, 2013; Mellman, Kobayashi, Lavela, Wilson, & Hall Brown, 2014; Ross, Ball, Sullivan, & Caroff, 1989). A meta-analysis of polysomnographic studies with PTSD patients found decreased total sleep time, slow wave sleep and sleep efficiency, and increased wake time after sleep onset in PTSD patients compared with healthy controls (Zhang et al., 2019). REM sleep percentage was significantly decreased in PTSD patients compared with controls in studies including participants with mean age below 30 years, but not in studies with greater mean ages, a result that the authors see as indirect support for the role of disturbed REM sleep in the aetiology of posttraumatic stress disorder since differences across age cohorts could reflect time since the precipitating trauma.

Based on the general association between sleep and emotional memory consolidation, it has been suggested that sleep deprivation in the first night after trauma could serve as a preventive measure against the development of PTSD (Wagner, Hallschmid, Rasch, & Born, 2006). This has never been tested, but the effects of sleep deprivation on traumatic memories have been modelled with the trauma film paradigm. In this well-established experimental analogue of witnessing a traumatic event, healthy volunteers view aversive film clips of traumatic events, such as interpersonal violence and severe accidents. Such film footage induces, temporarily, intrusive memories of the stimuli. Sleep deprivation of one night after exposure to a trauma film reduced the emotional effect of the film and the frequency of intrusive memories in the first two days after watching the film (Porcheret, Holmes, Goodwin, Foster, & Wulff, 2015). A follow-up study was not able to replicate the initial finding, showing no difference between sleep and sleep deprivation (Porcheret et al., 2019). In another study, Kleim, Wysokowsky, Schmid, Seifritz, and Rasch (2016) did not observe a protective effect of sleep deprivation in the first two post-intervention days, but found fewer and less distressing intrusive memories in the sleep compared to the wake condition towards the end of the week after experimental trauma. In a follow-up nap study, the same authors did not find differences between sleep and wake conditions in intrusions frequency and level of distress, however, participants with periods of REM sleep experienced fewer and less distressing intrusions than those without REM sleep and those who stayed awake (Kleim & Wilhelm, 2019). This is in line with a study examining the effects of partial sleep deprivation in the second half of the night (in which REM sleep dominates) on memory of traumatic picture stories: both stronger explicit trauma memory and fewer intrusions after sleep than following partial sleep deprivation were observed (Sopp, Brueckner, Schafer, Lass-Hennemann, & Michael,

2019). Our own group is performing a laboratory-based, sleep deprivation study with the trauma film paradigm with the largest cohort of participants so far. Nevertheless, trauma film studies are still a proxy and hence more research on the sleep of acutely traumatised individuals is necessary before we are warranted to give recommendations for sleep or sleep deprivation to individuals presenting themselves directly after trauma.

## 2. Challenges in current research

The logical step forward is to examine the relationship between sleep and consolidation of actual traumatic memories as well as PTSD development. This should start with the characterization of sleep of individuals directly after they were confronted with a traumatic event in their daily life. Full polysomnography (PSG) of the first night after trauma would provide insights into the relationship between specific sleep characteristics, such as total amount of REM and ratio of REM to other sleep stages, and the development of PTSD symptoms. Based on early research showing a role of REM sleep in emotional memory consolidation, we hypothesise that REM sleep correlates with the development of psychopathology. In case a straightforward positive association between REM sleep and psychopathology could be established, a further step would be to deprive sleep totally or REM sleep selectively directly after trauma in order to prevent PTSD. In contrast, if the association between REM sleep and psychopathology turns out to be negative, interventions to enhance sleep in general or REM sleep in particular would be advisable.

Our group has tried to collect first data on these research questions in a study that was performed under a protocol approved by the independent Ethics Committee of the German Psychological Society (SK062016\_rev) and conducted according to the codes of ethics on human experimentation established by the Declaration of Helsinki and its amendments. Potential participants were individuals who arrived in the hospital emergency room (ER) of a university medical centre in Berlin, Germany after a traumatic event. This was defined as exposure to actual or threatened death, serious injury or sexual violence as conceptualized in the trauma criterion of PTSD in DSM-5 (American Psychiatric Association, 2013). ER records were screened and potential participants were approached before being discharged from the ER. If the trauma criterion was fulfilled and the patient was emotionally and physically in the position to provide informed consent and to comply with the protocol, a participation in the study would have been offered. After inclusion, setting up of the PSG device would have followed and

the participant would have been discharged at home without any recommendation whether to sleep or not. The participant would have been asked to fill in the evening and the next morning the Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988), wear an actigraphy device and keep a standardized diary of bed times and intrusions for one week. If data from the first phase of the study confirmed our initial hypothesis of a positive association between REM sleep and PTSD, in a second phase of the study, the trial would have been extended to include an intervention with participants being randomized in two groups: one that would be encouraged to sleep as usual and one that would be asked to stay awake for 24 hours after the event.

In a pilot phase of the study, the ER reports of patients were screened and a convenient sample of potential participants was also screened in person. All patients had experienced or witnessed a non-traumatic motor vehicle accident and did not fulfil the trauma criterion as defined for this study. Hence, none of them could be included in the study. Since, per protocol, data were only collected after inclusion, no data on this sample can be provided. After this test phase, the study was deemed not feasible and was terminated prematurely. Beside the expected low number of potential participants and more recently emerging experimental evidence rendering benefits of sleep deprivation more ambiguous, a major reason for the early termination was the feedback we received from patients. ER patients were highly reluctant in accepting the application of the PSG device. After being informed about the study featuring a sleep deprivation intervention, all patients stated that they would have declined being randomised in a sleep deprivation condition.

### 3. Discussion and ideas for further research

In this paper, we have proposed the analysis of sleep of acutely traumatised individuals in the first night after a traumatic event by using home-based PSG in order to find sleep-based factors predictive of the development of PTSD. One of the major challenges of such a study is the recruitment of individuals on the day of traumatization, a known limitation in the study of interventions in this patient population (Rothbaum et al., 2012). However, based on our own experience we found that the small sample of potentially eligible participants would have been further limited by the rejection of PSG. ER patients that were given information about the study felt that the PSG device would have been a great burden for them. The main reason was the wish to leave the ER as soon as possible, which would not have allowed ample time for applying the PSG device. Besides, they articulated worries that the PSG device would disturb their sleep. In two previous studies that applied full PSG in (injured)

patients after trauma, Mellman et al. were only able to obtain PSG recordings after on average 17.1 (Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002) and 20 days (Mellman, Pigeon, Nowell, & Nolan, 2007) respectively, whereas the recruitment rate was also rather low. Moreover, for the approached patients sleep deprivation in the first night after a traumatic event did not seem to be an acceptable intervention either. This probably reflects a notion of laypersons that sleep, with its regenerative properties, would have healing qualities after traumatization – which is partly backed up by more recent studies on the association between experimental trauma and sleep. A previous attempt to perform a study that discourages sleep following trauma has been identified in a registry for clinical trials, but the registration has not been updated since 2012 nor have the results been published (ClinicalTrials.gov: NCT01684085).

A night of sleep deprivation is most likely rather challenging after traumatization, at least based on the feedback that we received from a non-representative sample of patients treated in an ER after a minor motor vehicle accident. Maybe this cannot be generalized to individuals that are more psychologically burdened since they might be more interested in preventive measures and less dismissive of the idea of sleep deprivation, especially since sleep would seem difficult due to hyperarousal anyway. If we were to believe that sleep deprivation is feasible and beneficial, we would, however, also had to bear in mind that the behaviour of the traumatised individual during this wake period would also influence the effect of the intervention (i.e. the sleep deprivation). In an experimental study with traumatic films it was shown that sleep deprivation potentiated the negative emotional reaction (as measured by the autonomic response) that was induced by active suppression of the memory (Kuriyama, Honma, Yoshiike, & Kim, 2013). In addition, Hørlyck, Bisby, King, and Burgess (2019) have shown that after watching traumatic films, wakeful rest (but not a simple vigilance (0-back) task) led to fewer intrusions. Therefore, if sleep deprivation were to be suggested for actually traumatised individuals, it should be combined with psychological support that encourages rest and discourages suppression of the traumatic memory. Since this is difficult to expect from a, most likely hyperaroused, traumatised individual, the need for adequate professional support in the direct aftermath of trauma becomes paramount. This is in line with already existing preliminary evidence for the positive effects of psychotherapy and in particular exposure-based therapy in the first hours after trauma (Rothbaum et al., 2012). This way the modified, therapy-informed memory would be the first (and only one) to be consolidated. This should be coupled with sleep hygiene interventions in order to avoid the development of sleep disturbances, a risk factor for the development of PTSD, and support through healthy sleep the consolidation of both therapeutically induced and naturally learned extinction

(Pace-Schott, Germain, & Milad, 2015). There are, however, practical limitations on the widespread implementation of such an intervention.

Pharmacological options to disrupt the over-consolidation of traumatic memories directly after trauma should also be considered. Given the importance of REM sleep for emotional memory consolidation, future research should examine the effects of pharmacological agents that specifically affect neurotransmitter systems involved in REM sleep regulation. For the noradrenergic system, administration of the  $\beta$ -blocker propranolol has shown ambiguous but mostly null results in trials with patients (Argolo, Cavalcanti-Ribeiro, Netto, & Quarantini, 2015) and recent experimental studies have also questioned its feasibility and effectiveness as a preventive intervention (Else, Bekker, De Bree, & Kindt, 2019).  $A_1$ -adrenergic receptor antagonists such as the REM-enhancing prazosin (Taylor et al., 2008) have been used with some success in the treatment of PTSD-related nightmares (although newer research has questioned this practice s. Raskind et al., 2018). There is no study that has used an  $\alpha_1$ -adrenergic receptor antagonists for the prevention of PTSD nor a study that had explored their effects with the trauma film paradigm. However, clonidine, a drug that also inhibits noradrenergic activity, did not lead to less intrusions after an analogue trauma (Rombold et al., 2016). Another pharmacological option to acutely enhance REM sleep would be acetylcholinesterase inhibitors such as galantamine (Biard, Douglass, Robillard, & De Koninck, 2016). Galantamine has not been proven effective in PTSD patients (McAllister et al., 2016), nor has been given directly after trauma. On the contrary, several antidepressants acting on the serotonergic system significantly suppress REM sleep (Wichniak, Wierzbicka, & Jernajczyk, 2012; Wilson & Argyropoulos, 2005), and thus could represent possible secondary prevention interventions for the possibility of a positive association between REM sleep and PTSD. In fact, many antidepressants suppress REM sleep even after one single dose making such an intervention feasible in the first night after trauma. After cessation of the medication a REM sleep rebound occurs, which would be important for the consolidation of extinction memory (Pace-Schott et al., 2015). It is therefore an open question whether a treatment for only one night (i.e. the critical consolidation phase) is more advisable than a longer treatment period, as it is common with antidepressants. There are some studies that have tested the latter, in particular the use of escitalopram after trauma for the prevention of PTSD: in a study that tested escitalopram starting within one month after trauma, no effect was shown (Shalev et al., 2012). However, a refusal rate of over 40% led to small sample sizes and could not refute a potential protective effect. In a subsequent study, escitalopram when administered within a month after trauma again did not lead to a prevention of PTSD (Zohar et al., 2018).

Nevertheless, in this study a significant protective effect was shown for a subset of patients who experienced an intentional, man-made trauma. Interestingly, in the analysis of the whole group there was a significant impact of the antidepressant on sleep quality. Since this outcome was measured after medication discontinuation, this effect reflects an alteration in the disorder development and not a direct pharmacological effect. We can only speculate whether the effects would have been more prominent if the treatment started before the first night's sleep. This should be the topic of a future project since treatment with a widely used medication could be more acceptable than sleep deprivation in the aftermath of a traumatic event.

Several aspects should be addressed in future protocols. To begin with, recruitment would be facilitated by screening ER admissions in several hospitals leading to a higher number of potential participants. Additional ways of recruitment should also be considered such as recruiting in the field or approaching first responders. Capturing all relevant EEG variables by applying full PSG seems to be unrealistic in this patient population. Though the gold standard, it appears to be not the right instrument for acutely traumatized individuals, since it cannot be applied fast enough and requires a lot of compliance from the patient. Beyond simple sleep time estimation with actigraphy, more recent developments in wearable, easily self-applicable sleep EEG headbands (Depner et al., 2019) might provide novel options for the investigation of sleep in the aftermath of trauma. Such investigation into the details of the association between sleep and traumatic memory consolidation is necessary before testing sleep deprivation as a secondary prevention measure as has been argued elsewhere earlier (Wagner et al., 2006). At the moment, a growing number of studies emphasizes a role of sleep in the consolidation of emotional and in particular traumatic memory traces, however the temporal dynamics and the specific contribution of different sleep stages still remains to be clarified. Before sleep interventions are applied in trauma victims, more observational and experimental research is needed to design sleep-based therapeutic approaches to prevent PTSD.

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