Behaviour Research and Therapy 110 (2018) 1–10

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

Greater sleep disturbance and longer sleep onset latency facilitate SCR-specific fear reinstatement in PTSD

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ARTICLE INFO

Keywords:
PTSD
Fear extinction
Reinstatement
Sleep

ABSTRACT

Fear reinstatement is one of several paradigms designed to measure fear return following extinction, as a laboratory model for the relapse of Posttraumatic Stress Disorder (PTSD) symptoms. Sleep is a key factor in emotional memory consolidation, and here we examined the relationship between sleep quality and fear reinstatement in PTSD, relative to trauma-exposed and non-exposed controls. The Pittsburgh Sleep Quality Index (PSQI) was used as a subjective measure of sleep quality, and skin conductance responses (SCR) and unconditioned stimulus (US)-expectancy ratings were used to index threat responses during a differential fear conditioning, extinction, and reinstatement paradigm. There were no significant between-group differences in the reinstatement of conditioned responding. Sleep disturbance and sleep onset latency were significant moderators between reinstatement of fear and PTSD symptom severity, such that there was a positive relationship between PTSD symptoms and fear reinstatement for higher levels – but not lower levels – of sleep disturbance and sleep onset latency. To our knowledge, this is the first study to investigate PTSD-specific reinstatement patterns and sleep as a boundary condition of reinstatement. Future research using polysomnographic measures of sleep-wave architecture may further clarify the relationship between fear reinstatement and sleep quality in clinical samples with PTSD relative to controls.

1. Introduction

A key biological model of Posttraumatic Stress Disorder (PTSD) is that fear-related symptoms are maintained, in part, due to impaired extinction of fear responses to benign stimuli that were conditioned with fear during the trauma (Mineka & Oehlberg, 2008; Pitman et al., 2012; Zuj, Palmer, Lommen, & Felmingham, 2016). Recently, the return of fear has been gaining attention as a laboratory model for the relapse of fear-related symptoms (Scheveneels, Boddez, Vervliet, & Hermans, 2016). Fear reinstatement refers to the return of fear following unsignalled encounters with an aversive stimulus (e.g., an electric shock; Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2004), and is considered an experimental analogue for the return of fearful symptoms after re-exposure to a trauma reminder or spontaneous panic attacks (Haaker, Golkar, Hermans, & Lonsdorf, 2014; Scheveneels et al., 2016). Currently, our understanding of the moderators of fear reinstatement is limited, and more research is needed to understand the boundary conditions by which fear returns following unsignalled encounters with the unconditioned stimulus (US; Haaker et al., 2014). Due to the strong influence of sleep on emotional memory consolidation (e.g., Stickgold, 2005) and fear extinction memory (Pace-Schott, Germain, & Milad, 2015b, 2015a), we hypothesized that the association between fear reinstatement and PTSD symptoms would vary depending on sleep quality.

Fear reinstatement refers to a series of unsignalled presentations of the US following successful extinction learning, resulting in a temporary return of fear. This event is argued to temporarily disrupt the memory for extinction, and 'reinstate' the dormant conditioned fear association (Hermans et al., 2005). These unsignalled US presentations typically result in a temporary return of fear to the previously reinforced conditioned stimulus (termed the CS+), as measured by US-expectancy ratings and fear ratings (Dirikx, Hermans, Vansteenwegen,

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https://doi.org/10.1016/j.brat.2018.08.005
Received 10 May 2018; Received in revised form 31 July 2018; Accepted 16 August 2018
Available online 18 August 2018
0005-7967/

Baeyens, & Eelen, 2007; Dirikx, Vansteenwegen, Eelen, & Hermans, 2009), skin conductance response (Kull, Muller, Blechert, Wilhelm, & Michael, 2012), and fear-potentiated startle (Norrholm et al., 2006). Further, fear reinstatement can also be non-differential, with a brief increase in fearful responding to the safety signal (i.e., the CS-) as well as the CS+ (Dirikx et al., 2009; Kull et al., 2012). Fear reinstatement has been studied extensively in rodents (for a review, see Haaker et al., 2014), and boundary conditions of the return of fear following reinstatement in humans are only recently being investigated. However to our knowledge reinstatement has not yet been investigated in individuals with PTSD.

Sleep disturbances are considered a hallmark feature of PTSD (Germain, 2013) and have been shown to contribute to the longitudinal development of PTSD symptoms (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2010; van Liempt, van Zuiden, Westenberg, Super, & Vermetten, 2013). Sleep quality is considered essential in the consolidation and accurate recall of emotional memories (Stickgold, 2005), including the consolidation and memory for fear extinction (Pace-Schott et al., 2015b, 2015a). Recent research has found that rapid eye movement (REM) sleep amount is negatively correlated with SCR amplitude during fear extinction, suggesting that increased REM sleep is associated with greater fear extinction (Spoormaker, Gvozdanovic, Samann, & Czisch, 2014). Further research has also shown that a full night of sleep can enhance the generalization of extinction memories to similar unextinguished stimuli, compared to 12 h of wakefulness throughout the day (Pace-Schott et al., 2009). Similarly, increased homeostatic sleep pressure, or the increased need for sleep throughout the day, can lead to poorer fear extinction learning in healthy men (Pace-Schott et al., 2013, 2014), and this relationship is stronger in PTSD (Zuj, Palmer, Hsu, et al., 2016). As far as we are aware, no research has looked at sleep quality as a possible moderator of the return of fear following reinstatement in healthy or clinical samples.

Sleep quality is a crucial factor in emotional memory consolidation (Diekelmann & Born, 2010; Stickgold, 2005), and we argue that sleep quality may act as a significant boundary condition of fear reinstatement. To our knowledge, the reinstatement of a conditioned fear has not yet been investigated in participants with PTSD, trauma-exposure without PTSD, and non-trauma-exposed healthy controls. For this reason, we did not hypothesize PTSD-specific reinstatement effects, but we did hypothesize that poor subjective sleep quality would be a significant moderator between the return of fear and PTSD symptoms. Specifically, we predicted that the association between fear return and PTSD symptoms would be stronger when subjective sleep quality is poor.

2. Method

2.1. Participants

Research participants were recruited to examine various moderators between processes of fear extinction learning and PTSD symptoms. As such, findings from this sample have been published previously examining hours-since-waking, cortisol reactivity, salivary α-amylase, and negative appraisals as potential moderators between fear extinction and PTSD symptoms (Zuj, Palmer, Gray, et al., 2017; Zuj, Palmer, Hsu, et al., 2016; Zuj, Palmer, Malhi, Bryant, & Felmingham, 2017, 2018). This paper makes a significant advance over previous published research from this sample, being the first to report on the findings of reinstatement and the relationship between reinstatement and sleep quality in PTSD. There were 74 participants aged 18–63 (31 males, 43 females). Participants completed the PTSD Checklist-Civilian version for DSM-IV (PCL-C, described below; Weathers, Litz, Huska, & Keane, 1994) to assess for the presence and severity of PTSD symptoms. The PCL-C for DSM-IV was used as diagnostic instruments for the DSM-5 were not available at the time of testing. Participants reported previous trauma exposure by self-report with the Traumatic Events Questionnaire (TEQ; Vrana & Lauterbach, 1994).

Responses on the PCL-C and TEQ determined allocation to one of three groups, high posttraumatic stress disorder symptoms (PTSD; $n = 20$), trauma-exposed controls (TC; $n = 29$), and non-trauma-exposed controls (NTC; $n = 25$). Participants were allocated to the PTSD group if they reported experiencing one or more Criterion A stressors on the TEQ, and displayed at least one intrusive memory symptom, three avoidance symptoms, and two hyperarousal symptoms, according to the diagnostic criteria for DSM-IV. Mean years since trauma was 10.7 years ($SD = 13$ years) for the PTSD group, and 8.1 years ($SD = 7.9$ years) for the TC group. All reported traumatic events included combat in a war (7%), a life-threatening accident (25.7%), fire, flood, or other life-threatening disaster (36.6%), witness injury or death (45.1%), seriously attacked, assaulted or molested (25.4%), threatened with a weapon, held captive or kidnapped (15.5%), tortured or the victim of terrorism (2.8%), experienced an extremely stressful or upsetting event (73.2%), and/or suffered a great shock because an event happened to somebody close (40.8%). Participants were allocated to the NTC group if they reported no experience of a Criterion A stressor.

Exclusion was based on the use of psychoactive medication to prevent confounds on sleep behaviour and psychophysiological arousal, and on neurological history, psychosis, and bipolar. This was done with the use of a self-report medical screening questionnaire rather than clinical interview, as the researchers were not clinicians. Participants were also requested to abstain from caffeinated beverages on the day of testing. Due to the frequent comorbidity between PTSD and depression, depression was applied as a covariate in relevant analyses, rather than as a basis for exclusion from participation. The University of Tasmania Social Sciences ethics committee approved the study protocol, and all participants provided full informed consent prior to involvement in the study.

2.2. Measures

PTSD-Checklist Civilian version (PCL-C). The PCL-C is a self-report questionnaire with 17 items that correspond with the diagnostic criteria of the DSM-IV (Weathers et al., 1994; National Center for Posttraumatic Stress Disorder, n.d.). Responses on the PCL-C are made on a five-point scale from 1 ("Not at all") to 5 ("Extremely"). Scores of 3 or higher are considered to be significant symptoms, contributing to the primary symptoms of intrusive memories, avoidance behaviors, and hyperarousal. All participants in the PTSD group had a PCL-C total score of at least 38. The minimum recommended cutoff for screening individuals in primary care settings is at least 30 (National Center for Posttraumatic Stress Disorder, n.d.). Participants were allocated to the TC group if they reported experience of one or more Criterion A stressors but did not meet the minimum recommended PCL-C cutoff of 30. Hence, the TC group showed a maximum PCL-C total score of 29. One participant in the TC group met potential criteria for sub-syndromal PTSD (as used by Shelby, Golden-Kreutz, & Andersen, 2008), with three hyperarousal symptoms. Omitting this participant had no effect on the statistical significance or direction of effects, and was retained in all analyses. The PCL-C for DSM-IV has excellent psychometric properties (Wilkins, Lang, & Norman, 2011).

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a 19 item questionnaire assessing subjective sleep quality over the past month (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Scores on the PSQI are used to calculate a global score ranging from 0 to 21 and seven equally weighted subscales with scores ranging from 0 to 3 (with higher scores indicating poorer sleep quality). The seven subscales are as follows: sleep disturbance, sleep duration, daytime dysfunction, habitual sleep efficiency, sleep latency, use of sleep medications, and subjective sleep quality. According to Buysse et al. (1989), global scores ≤ 5 indicate normal sleep, 6–10 indicate moderately impaired sleep, and scores ≥ 11 indicate severely impaired sleep. The PSQI is a widely used measure in clinical sleep research, and shows strong psychometric