Greater Sleep Disturbance and Longer Sleep Onset Latency Facilitate SCR-specific Fear Reinstatement in PTSD

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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.

Keywords: PTSD, Fear extinction, Reinstatement, Sleep

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, 2015a, 2015b), 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, 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., 2015a, 2015b). 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 hours 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; Pace-Schott et al., 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). 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 0-21 and seven equally weighted subscales with scores ranging from 0-3 (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 properties (Buysse et al., 1989; Mollayeva et al., 2016)**.**

2.3. Fear conditioning, extinction and reinstatement task

The present study used a standardized fear conditioning and extinction task described previously (Zuj, Palmer, Gray, et al., 2017; Zuj, Palmer, Hsu, et al., 2016; Zuj, Palmer, Malhi, et al., 2017). The unconditioned stimulus (US) was a 500ms mild electric shock set to a level considered "highly annoying, but not painful" by each participant prior to beginning the task, and delivered to the first interosseous muscle of the dominant hand. Conditioned stimuli (CS) were red and blue circles presented on a white computer screen for 12s, with an inter-trial interval ranging from 12-21s. CS presentation occurred in a pseudo-random order, with no more than two consecutive trials of each stimulus. CS presentation, frequency and timings were based off the standardized conditioning and extinction paradigm by Orr et al. (2000). Participants first completed a habituation phase, consisting of four presentations of each of the two CS types, with eight trials in total. During acquisition, participants received five presentations of each CS type, with one CS being reinforced by the US immediately following CS offset on all trials (CS+). That is, the current study used a 100% reinforcement schedule during the acquisition phase (Orr et al., 2000). Following acquisition, participants completed the early and late extinction phases, which were separated by a small break of no more than 1min (Milad, Orr, Pitman, & Rauch, 2005). Each fear extinction phase consisted of five CS+ presentations, and five CS- presentations, with no US-delivery on any trial. Reinstatement occurred immediately following extinction training, with two unsignalled presentations of the US (during passive viewing of the blank computer screen), followed by a return of fear test, with five presentations of each of the CS-types. All experimental phases

were conducted in a single context, and at the end of testing, participants were asked which coloured circle was associated with the mild electric shock, to which all participants reported accurate contingency awareness.

Skin conductance response. As with previous research from our lab, skin conductance level was measured through a 22 mV_{rms}, 75Hz constant-voltage coupler (FE116, ADI Instruments) with bipolar electrodes on the intermediate phalange of the first and third fingers of the non-dominant hand, sampled at 512Hz and stored at 64Hz, and recorded in micro-Siemens (μS). Participants were instructed to keep their hand as still as possible for the duration of the task, so as to reduce the potential for movement artefact. Skin conductance response (SCR) amplitude was calculated by subtracting the mean SCL in the 2s prior to CS onset from the maximum SCL during CS presentation (i.e., max SCL during CS – mean SCL in 2s prior to CS onset; Milad et al., 2013; Milad et al., 2008; Milad et al., 2005). Prior to statistical analyses, all SCR values were square-root transformed. The absolute value of negative SCR levels was transformed, and the negative sign replaced. For use in moderation analyses, a fear return index was calculated by subtracting the mean SCR amplitude of trials 4 and 5 of late extinction from the first trial of the return of fear phase. This index was calculated separately for each CS-type, with larger values indicating a greater return of fear.

US-expectancy ratings. During each presentation of the CS, participants were asked to provide a threat expectancy rating that the current CS would be followed by the aversive US. Ratings were made via a mouse-click on a scale from 0 (“certain no electrical stimulus”) to 100 (“certain electrical stimulus”), presented below the CS.

2.4. Statistical analyses

Demographic and clinical data were conducted using one-way analyses of variance (ANOVAs), and Welch adjusted *F*-ratios were reported where Levene's test of homogeneity of variance was violated. Follow-up comparisons were conducted using Bonferroni corrections, or Games-Howell analyses where appropriate. The habituation, acquisition, and extinction phases were analyzed with separate 2 (CS) × 5 (trial) × 3 (group) mixed ANOVAs (with 4 levels of trial for the habituation phase). The US-expectancy data from three participants was missing and thus were not included in US-expectancy analyses. Excluding these three participants from other analyses showed little difference to significance and effect sizes, and thus these participants were retained in all other analyses. Reinstatement effects were assessed using a 2 (time) × 2 (CS) × 3 (group) mixed ANOVA. Time was quantified as the SCR amplitude on the first trial of the return of fear phase subtracted from the average SCR amplitude on trials 4 and 5 of late extinction (Haaker et al., 2014; Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2010). Greenhouse-Geisser corrected degrees of freedom and epsilon values are reported for all repeated measures ANOVAs. Effect sizes are reported as partial eta-squared (η_p^2) for ANOVAs, and Cohen's *d* for pairwise comparisons, according to the criteria of 0.2, 0.5, and 0.8 as small, medium, and large effects, respectively (Cohen, 1988).

Moderation analyses were conducted using the PROCESS macro v3.0 for SPSS (Hayes, 2013). Moderation is a regression-based technique and all moderators and predictors were visually inspected for homoscedasticity of residuals. Moderation analyses were conducted individually for the PSQI total score and six subscales (the medications subscale was included as a covariate, alongside age), separately for the CS+ and CS-. Further, moderation analyses were repeated for reinstatement variables derived from SCR amplitude and US-expectancy ratings. To protect against the likelihood of Type I errors, a False Discovery Rate correction was applied to the subsequent 28 interaction terms at the value of

q = 0.05, according to the Benjamini-Hochberg correction method (Benjamini & Hochberg, 1995). All statistical analyses were conducted in SPSS version 24 for windows.

3. Results

3.1. Demographics

As shown in Table 1, one-way ANOVA revealed no significant between-group differences on age, $F(2, 41.56) = 2.56$, $p = .089$. As expected, there were significant between-group differences on the PCL-C total score, $F(2, 37.29) = 70.38$, $p < .001$, with the PTSD group displaying significantly greater symptom severity than the TC and NTC groups (ps < .001), who also significantly differed ($p = .001$). The ANOVA revealed a significant between-group difference on total scores for the PSQI, $F(2, 39.76) = 9.76$, $p < .001$, with the PTSD group reporting significantly poorer sleep quality than the TC and NTC groups (p = .010 and $p = .001$, respectively), who did not significantly differ ($p = .199$). See Table 1 for the descriptive and inferential statistics for the PSQI subscales. There were no significant between-group differences on the Alcohol Use Disorder Identification Test (AUDIT), $F(2, 71) = 1.15$, $p = .970$.

[INSERT TABLE 1 ABOUT HERE]

3.2. US-expectancy Ratings

Habituation. There was a significant main effect of trial during habituation, with US-expectancy ratings declining across the phase, irrespective of CS-type or group, $F(2.03, 137.68) = 6.79$, $p = .001$, $\eta_p^2 = .091$, $\varepsilon = .675$.

Acquisition. During acquisition there were significant main effects of CS-type, $F(1, 68) = 288.56$, $p < .001$, $d = 3.65$, and trial, $F(3.27, 222.18) = 5.23$, $p = .001$, $\eta_p^2 = .071$, $\varepsilon = .817$. These main effects were superseded by a significant CS × trial interaction, $F(3.37, 229.45) = 109.78$, $p < .001$, $\eta_p^2 = .618$, $\varepsilon = .844$. This interaction shows clear differential US-expectancy between the CS+ and CS- developing over the acquisition phase (see Fig. 1). There was no significant main effect of group ($p = .630$), or interaction involving group (ps > .098).

Early extinction. As with acquisition, the early extinction phase showed significant main effects of CS, $F(1, 68) = 55.00$, $p < .001$, $d = 1.09$, and trial, $F(2.50, 169.64) = 73.02$, $p < .001$, $\eta_p^2 = .518$, $\varepsilon = .624$. Similarly, there was also a significant CS × trial interaction, $F(3.40, 231.15) = 10.63$, $p < .001$, $\eta_p^2 = .091$, $\varepsilon = .850$, with differential expectancy ratings to the CS+/- reducing over early extinction (see Fig. 1), with no main effects or interactions involving group (ps > .200).

Late extinction. The late extinction phase also showed significant main effects of CS, $F(1, 68) = 20.70$, $p < .001$, $d = 0.44$, and trial, $F(2.19, 148.68) = 39.57$, $p < .001$, $\eta_p^2 = .368$, $\varepsilon = .547$. Again, these main effects were superseded by a significant CS × trial interaction, $F(4, 272) = 3.89$, $p = .004$, $\eta_p^2 = .054$. All groups showed further reductions in CS+/- discrimination across trials (see Fig. 1). There was also a significant group main effect, $F(2, 68) = 3.67$, $p = .031$, $\eta_p^2 = .097$, with the PTSD group reporting greater threat uncertainty ($M = 37.90$ [27.97, 47.82], $SD = 21.68$), relative to the TC and NTC groups ($M = 22.69$ [14.66, 30.72], $SD = 21.68$, and $M = 22.07$ [16.85, 27.30], $SD = 21.68$, respectively), who showed little difference. Threat uncertainty refers to scores closer to 50 – representing the middle-point of the US-expectancy scale – as opposed to greater reported confidence in the US being

absent or present, as indicated by expectancy ratings closer to 0 or 100, respectively. Between-group differences were no longer significant following a Bonferroni correction for multiple comparisons (*p*s > .053).

Reinstatement. ANOVA revealed a significant increase in US-expectancy ratings from the final two trials of late extinction (*M* = 29.71, 95% CI[20.54, 38.89], *SD* = 38.76) to the first trial post-reinstatement (*M* = 48.28 [42.95, 53.61], *SD* = 22.50), $F(1, 68) = 16.70$, $p < .001$, $d = 0.59$. There was also a significant main effect of CS-type, $F(1, 68) = 11.93$, $p = .001$, $d = 0.40$, with greater US-expectancy of the CS+ (*M* = 44.83 [37.44, 52.23], *SD* = 31.26) compared to the CS- (*M* = 33.16 [26.87, 39.45], *SD* = 26.54). There was, however, no significant time × CS interaction ($p = .631$) suggesting a generalized reinstatement of threat expectancy. ANOVA also revealed a significant main effect of group, $F(2, 68) = 4.38$, $p = .016$, $\eta_p^2 = .114$, with the PTSD group displaying significantly elevated threat expectancy (*M* = 52.04 [40.65, 63.43], *SD* = 24.87) compared to the TC group (*M* = 31.64 [22.42, 40.86], *SD* = 24.87; $p = .021$), and borderline significant threat expectancy compared to the NTC (*M* = 33.32 [22.97, 43.66], *SD* = 24.87; $p = .053$), averaged across time. The TC and NTC groups did not differ ($p = .993$). This effect indicates that – compared to the TC and NTC groups – the PTSD group displayed elevated uncertainty of the US over the end of the late extinction phase and beginning of the reinstatement (return of fear) phase, however there were no significant between-group increases from late extinction to return of fear test.

[INSERT FIGURE 1 ABOUT HERE]

3.3. SCR Amplitude

Habituation. ANOVA revealed a significant main effect of trial during the habituation phase, $F(2.77, 196.48) = 2.94$, $p = .038$, $\eta_p^2 = .040$, $\varepsilon = .922$, with SCR amplitude decreasing across trials, irrespective of group or CS-type. No further main effects or interactions were significant (all *p*s > .306).

Acquisition. During acquisition, SCR amplitude was significantly larger to the CS+ (*M* = 0.88 [0.76, 1.00], *SD* = 0.52) compared to the CS- (*M* = 0.42 [0.32, 0.53], *SD* = 0.46), $F(1, 71) = 82.03$, $p < .001$, $d = 0.94$. Further, there was a borderline significant group × CS interaction, $F(2, 71) = 2.73$, $p = .072$, $\eta_p^2 = .071$, which appears to be driven largely by a greater average differential conditioned response in the NTC group. ANOVA also showed a significant main effect of trial, with a significant overall reduction of SCR amplitude across the experimental phase (see Fig. 2), irrespective of group or CS-type, $F(3.54, 251.23) = 12.46$, $p < .001$, $\eta_p^2 = .149$, $\varepsilon = .885$. No further main effects or interactions were significant (all *p*s > .328).

Early extinction. Overall, participants were still displaying significantly larger SCR amplitude responses to the CS+ (*M* = 0.58 [0.49, 0.67], *SD* = 0.40), compared to the CS- (*M* = 0.42 [0.34, 0.50], *SD* = 0.34) during the early extinction phase, $F(1, 71) = 17.13$, $p < .001$, $d = 0.43$. Further, there was a significant main effect of trial, $F(3.49, 248.06) = 29.37$, $p < .001$, $\eta_p^2 = .293$, $\varepsilon = .873$, with SCR amplitude decreasing across the early extinction phase, irrespective of group or CS-type. No further main effects or interactions were significant (all *p*s > .174).

Late extinction. Irrespective of group, participants were still displaying significantly larger SCR amplitude responses to the CS+ (*M* = 0.47 [0.37, 0.58], *SD* = 0.46) than the CS-

(*M* = 0.39 [0.30, 0.47], *SD* = 0.37), *F*(1, 71) = 4.19, *p* = .044, *d* = 0.20. ANOVA also showed a significant main effect of trial, *F*(3.32, 235.50) = 16.70, *p* < .001, η_p^2 = .190, ε = .829, with SCR amplitudes further decreasing across trials, irrespective of group or CS-type. No further main effects or interactions were significant during late extinction (all *p*s > .276).

Reinstatement. As shown in Fig. 2, there was an increase in SCR amplitude from the end of late extinction, to immediately post-reinstatement, however there was no significant time × CS interaction, *F*(1, 71) = 2.54, *p* = .116, η_p^2 = .034, or effect involving group, indicating that all groups displayed a generalized reinstatement of fear to both the CS+ and CS-. There was a significant main effect of CS-type, with larger overall SCR amplitude to the CS+ (*M* = 0.60 [0.45, 0.76], *SD* = 0.67) than the CS- (*M* = 0.42 [0.29, 0.55], *SD* = 0.56), *F*(1, 71) = 6.70, *p* = .012, *d* = 0.30. No further main effects or interactions were significant (all *p*s > .116).

[INSERT FIGURE 2 ABOUT HERE]

3.4. Moderation

Moderation analyses were conducted using the PROCESS macro v3.0 for SPSS (Model 1; Hayes, 2013). PCL-C total was entered into the model as the outcome variable, and reinstatement of fear was calculated as the average response to trials 4 and 5 of late extinction, subtracted from the first trial of reinstatement. Analyses were conducted individually for the PSQI total score and six subscales (with the exception of the medications subscale). Analyses were further repeated for the CS+ and CS- and for the SCR and US-expectancy ratings.

Following a false discovery rate correction according to the Benjamini-Hochberg correction method for multiple comparisons (Benjamini & Hochberg, 1995), sleep disturbance was a significant moderator between fear return to the CS+ and PTSD symptom severity, such that there was a positive relationship between PTSD symptoms and fear reinstatement for high levels of sleep disturbance, but not for lower levels of sleep disturbance (see Fig. 3a**)**, $R^2 = .278$, $F(3, 70) = 8.96$, $p < .001$. For longer sleep onset latency, there was a positive relationship between PTSD symptoms and fear reinstatement. In contrast, for shorter sleep onset latency, there was a negative relationship between PTSD symptoms and fear reinstatement (see Fig. 3b), $R^2 = .210$, $F(3, 70) = 6.21$, $p < .001$. Analyses were repeated with age and PSQI medications subscale as covariates, resulting in the sleep onset latency moderation no longer found to be significant after a false discovery rate correction.

To further clarify the moderating role of sleep disturbance and sleep onset latency on PCL-C scores, we repeated analyses with each symptom cluster of the PCL-C for DSM-IV (i.e., intrusive memories, avoidance behaviours, and hyperarousal) as the outcome variable. Effects remained unchanged for each symptom cluster, suggesting a general effect of PTSD symptomatology (see Supplementary Materials).

[INSERT FIGURE 3 ABOUT HERE]

[INSERT TABLE 2 ABOUT HERE]

4. Discussion

We used a within-session differential *fear conditioning*, *extinction* and *reinstatement* paradigm to investigate sleep quality as a moderator of fear reinstatement in PTSD, compared

to trauma-exposed and non-exposed controls. Our findings show that increased fear expression to the CS+ after reinstatement was associated with greater PTSD symptom severity, and this relationship became stronger with greater – but not lower – levels of subjective sleep disturbance. A similar pattern was also found with increased sleep onset latency. Fear reinstatement was not associated with other subscales of the PSQI, and was not associated with PTSD symptoms independently, suggesting that sleep disturbance (and sleep onset latency) may be important boundary conditions of fear reinstatement. To our knowledge, this is the first investigation of the role of sleep in fear reinstatement, and also the first investigation of the PTSD-specific effects of fear reinstatement.

The boundary conditions of fear reinstatement are currently not well understood (with the exception of context; Haaker et al., 2014), and the findings of the current study suggest that sleep disturbance and sleep onset latency play an important role in PTSD-related fear reinstatement. Previous research has shown that sleep disturbances in PTSD are improved with exposure-based therapies (Gutner, Casement, Stavitsky Gilbert, & Resick, 2013; Long et al., 2011; although see Sexton et al., 2017), but also that imagery rehearsal therapy for nightmares lead to reductions in PTSD symptoms (Krakow et al., 2001). Exposure therapy is also strengthened in spider phobic patients if therapy is followed by a 90-minute nap, rather than wakefulness (Kleim et al., 2014). The results of the current study support these previous findings, suggesting that sleep quality plays an important mechanistic role in the consolidation of fear extinction memories.

The current study also found sleep onset latency to be a significant moderator between fear reinstatement and PTSD. It is important to note that after including age and sleep medication use as covariates, a false discovery rate correction resulted in this effect being deemed non-significant, and therefore the following explanations should be interpreted with caution. Previous research shows that adults with chronic PTSD report a number of

severe sleep disturbances, with longer sleep onset latency significantly associated with daily stressors (Gehrman, Harb, Cook, Barilla, & Ross, 2015). Further, increased sleep onset latency is significantly associated with anxiety sensitivity in anxious children (Weiner, Meredith Elkins, Pincus, & Comer, 2015) and adults (Babson, Trainor, Bunaciu, & Feldner, 2008). Previous research by Spoormaker et al. (2014) found that increased ventromedial prefrontal cortex (vmPFC) activity during fear conditioning is associated with greater sleep latency that night. Alternatively, vmPFC hypoactivity has been associated with poor consolidation of extinction memories over a 24-h period in PTSD (Milad et al., 2009). Nota and Coles (2018) recently demonstrated that longer sleep onset latency is associated with poor attentional disengagement from negative emotional stimuli in individuals who display repetitive negative thinking styles. Based on the aforementioned research, we speculate that longer sleep onset latency is associated with heightened physiological and emotional arousal immediately prior to sleep (Gehrman et al., 2015), which may reduce emotional capacity to accurately form extinction memories. As such, poorly consolidated extinction is likely to be particularly susceptible to fear reinstatement, with some involvement of vmPFC hypoactivity. As noted above, this explanation is speculative, but plausible, and further research is needed to investigate this explanation. Furthermore, we also found that shorter sleep latency showed a negative relationship between PTSD symptoms and reinstatement, such that greater return of fear was associated with lower PTSD symptoms. This effect was unexpected, and we are unsure of underlying mechanisms here.

The hippocampus also plays an important role in the above vmPFC-amygdala network in the consolidation of emotional fear memories. In particular, the hippocampus is involved in changes to contingency awareness (Lang et al., 2009; Milad et al., 2007), such as those brought on by contextual shifts or changes in the CS-US relationship. Reinstatement paradigms typically result in greater prediction error of the CS+ to accurately predict the US.

In addition, there is recent evidence that sleep deprivation prevents the inhibition of amygdala activity by the vmPFC during fear consolidation (Feng, Becker, Zheng, & Feng, 2018). With the amygdala-hippocampus-mPFC network showing greatest activation during REM sleep (Genzel, Spoormaker, Konrad, & Dresler, 2015), this cortical network could speculatively play an important role in fear reinstatement via cortical activity during REM sleep.

In the current study, sleep quality was measured retrospectively via the self-report Pittsburgh Sleep Quality Index (Buysse et al., 1989). While this scale is widely used and demonstrates strong psychometric properties (Mollayeva et al., 2016), the use of a sleep diary for a longitudinal assessment of sleep quality in the lead up to participation, and objective measures of sleep quality/behaviour (e.g., via actigraph or polysomnography) may shed light on the specific sleep mechanisms between fear reinstatement and PTSD symptoms. For example, recent research has shown important contributions of REM sleep amount in the extinction of fear (Spoormaker et al., 2014) and there is growing evidence for a role of slow-wave sleep architecture in emotional memory consolidation (Diekelmann & Born, 2010), with complementary processes between slow-wave and REM sleep (Cairney, Durrant, Power, & Lewis, 2015). Further, while participants reported abstinence from caffeine on the day of testing, future research would benefit from employing additional sleep hygiene steps in the days prior to testing.

Future research should also include a control group that does not receive the reinstatement stimuli, as this allows for stronger conclusions that return of fear effects are attributed to the unsignalled US presentations, rather than the passage of time from extinction learning to return of fear test (spontaneous recovery). Although this is unlikely to be an issue in the current study as reinstatement occurs immediately following extinction (Haaker et al., 2014). The use of a 100% US-reinforcement schedule during acquisition is known to result in

rapid extinction learning, and a partial reinforcement schedule may be more appropriate to increase the uncertainty and strength of conditioned responses. For example, Grady, Bowen, Hyde, Totsch, and Knight (2016) found that a partial reinforcement schedule during early acquisition, followed by 100% reinforcement for the remainder of the acquisition phase resulted in a stronger conditioning trace, and more persistent conditioned responses during extinction, relative to fully continuous or partial reinforcement schedules alone. Further, we had a mixed trauma sample, with single incident, cumulative incident, and multiple trauma types. Future research might benefit from control of trauma type, or examining the effect of trauma type or cumulative trauma on the propensity for fear reinstatement.

5. Conclusions

Here we show that sleep disturbance (and sleep onset latency) significantly moderate the relationship between reinstatement and PTSD symptoms. Specifically, the relationship between greater fear reinstatement and increased PTSD symptoms becomes stronger with greater sleep disturbances and longer sleep latency onset. Further, to our knowledge this is the first study examining fear reinstatement in a clinical sample with PTSD, and suggests that reinstatement effects do not present in isolation in PTSD, but rather interact with additional factors (such as sleep disturbance). As such, these findings imply that sleep disturbances and longer sleep onset latency may weaken fear extinction consolidation, resulting in a weaker extinction trace that is more prone to reinstatement.

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Conflict of Interest

The authors declare no conflicts of interest related to this publication.

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Table 1

Descriptive and between-group data for demographic and clinical measures

	PTSD (*n* = 20)	TC (*n* = 29)	NTC (*n* = 25)
	M [95% CI], *SD*	*M* [95% CI], *SD*	*M* [95% CI], *SD*
Demographic data			
Age (years)	33.3 [26.4, 40.1], 14.7	26.5 [22.7, 30.3], 9.9	24.5 [20.4, 28.6], 10.0
Sex	9M, 11F	15M, 14F	7M, 18F
PCL-C			
Total	51.1 [45.6, 56.5], 11.7	23.4 [21.9, 24.9], 3.9	20.0 [18.9, 21.0], 2.6
Intrusive	2.9 [2.3, 3.5], 1.3	0.2 [0.1, 0.4], 0.4	-
Avoidance	4.1 [3.2, 5.0], 1.9	0.4 [0.2, 0.7], 0.7	0.2 [0.0, 0.4], 0.5
Hyperarousal	3.3 [2.8, 3.8], 1.1	0.4 [0.2, 0.7], 0.7	0.2 [0.0, 0.4], 0.5
DASS			
Depression	8.8 [6.2, 11.4], 5.5	2.2 [1.3, 3.1], 2.5	1.3 [0.6, 2.1], 1.8
Anxiety	7.9 [5.8, 9.9], 4.4	2.0 [1.3, 2.8], 2.0	1.0 [0.4, 1.7], 1.6
Stress	12.8 [9.7, 15.8], 6.5	5.0 [3.8, 6.2], 3.2	2.4 [1.4, 3.3], 2.3
PSQI			
Total	8.0 [6.3, 9.7], 3.7	5.0 [4.1, 5.9], 2.4	4.1 [3.4, 4.8], 1.6
Disturbance	1.7 [1.4, 2.0], 0.6	1.4 [1.2, 1.6], 0.6	1.2 [1.0, 1.4], 0.4
Duration	0.6 [0.2, 0.9], 0.8	0.2 [0.1, 0.4], 0.4	0.1 [0.0, 0.2], 0.3
Day dysfunction	1.5 [1.1, 1.8], 0.7	0.9 [0.7, 1.1], 0.5	0.9 [0.6, 1.2], 0.7
Efficiency	0.8 [0.3, 1.3], 1.1	0.2 [0.0, 0.5], 0.5	0.2 [0.0, 0.3], 0.4
Latency	1.6 [1.0, 2.1], 1.2	1.3 [1.0, 1.7], 0.9	1.0 [0.7, 1.2], 0.7
Medications	0.6 [0.0, 1.1], 1.1	0.1 [-0.1, 0.2], 0.4	0.1 [0.0, 0.4], 0.7
Sleep quality	1.4 [1.1, 1.7], 0.7	1.0 [0.7, 1.3], 0.8	0.7 [0.5, 0.9], 0.5
AUDIT	6.2 [3.7, 8.7], 5.3	5.9 [4.5, 7.3], 3.8	6.1 [4.3, 7.8], 4.2

PTSD, Posttraumatic Stress Disorder; TC, Trauma-exposed controls; NTC, Non-trauma-exposed controls; PC
version; DASS, Depression Anxiety Stress Scale; PSQI, Pittsburgh Sleep Quality Index; AUDIT, Alcohol Us

[a]Welch adjusted *F*-ratio.

Table 2

Moderation analyses examining the relationship between reinstatement of fear to the CS+ and PCL-C total, moderated by PSQI subscales (sleep disturbances and sleep latency)

Analyses	*b*[95% CI]	SE*b*	*t*	*p*
PSQI sleep disturbance				
Constant	20.25 [11.13, 29.36]	4.57	4.43	< .001
ROF to the CS+	-15.48 [-26.65, -4.31]	5.60	-2.76	.007
PSQI disturbance	6.17 [-0.04, 12.39]	3.12	1.98	.052
ROF × disturbance	11.65 [4.35, 18.95]	3.66	3.18	.002[a]
PSQI sleep onset latency				
Constant	28.60 [22.95, 34.26]	2.84	10.09	< .001
ROF to the CS+	-9.26 [-16.08, -2.44]	3.42	-2.71	.009
PSQI latency	-0.84 [-5.18, 3.50]	2.18	-0.39	.701
ROF × latency	7.89 [3.59, 12.18]	2.15	3.66	< .001[b]

PSQI, Pittsburgh Sleep Quality Index; ROF, return of fear; SE, standard error.

[a]Significant following the inclusion of age and PSQI medications as covariates, and a further false discovery rate correction.

[b]Remains significant following the inclusion of age and PSQI medications as covariates, but is deemed non-significant by the subsequent false discovery rate correction.