Research Article

IMPAIRED FEAR EXTINCTION ASSOCIATED WITH PTSD INCREASES WITH HOURS-SINCE-WAKING

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Background: *Prior research has demonstrated that time-of-day may play an important role in the extinction of conditioned fear, with extinction better learned earlier in the day rather than later. Impaired fear extinction memory is widely considered a key mechanism of posttraumatic stress disorder (PTSD). The relationship between fear extinction and PTSD symptoms may be moderated by hours-since-waking.* **Method:** *In the present experiment, we examined whether hours-since-waking would moderate fear extinction learning ability in a clinical PTSD sample (n = 15), compared to trauma-exposed (n = 33) and nonexposed controls (n = 22). Participants completed a standardized differential fear conditioning and extinction paradigm, providing skin conductance response measures to quantify conditioned responding.* **Results:** *Mixed-model analysis of variance revealed a PTSD-specific impairment in extinction learning ability in the late extinction phase. A moderation analysis showed that hours-since-waking was a significant moderator of the relationship between impaired late extinction and PTSD symptoms. Specifically, we found that participants with higher PTSD symptoms demonstrated poorer fear extinction learning ability as they were awake for longer.* **Conclusions:** *The results of the current study add to a growing literature indicating deficits in fear extinction learning in PTSD samples, compared to trauma-exposed and nonexposed controls. These results support previous findings that fear extinction is impaired later in the day, and extends this to a clinical sample, suggesting that exposure-therapy may be optimized by scheduling sessions in the morning. Depression and Anxiety 33:203–210, 2016.*

Key words: *fear extinction; fear conditioning; psychophysiology; PTSD; time of waking; sleep*

INTRODUCTION

Posttraumatic stress disorder (PTSD) is characterized by distressing intrusive memories of a trauma and avoidance behaviors.[1] A prominent model posits that impaired fear extinction, the ability to extinguish a conditioned fear association, is an important mechanism underlying PTSD.[2] Extinction is the core principle of exposure therapy, the first-line treatment for PTSD,[3] and further investigation is needed to understand the processes that aid or impair extinction. Growing research implicates sleep in extinction learning and consolidation.[4] Pace-Schott et al.[5] revealed that sleep prior to extinction learning may enhance extinction, with homeostatic sleep demands increasing throughout the day, and reducing extinction potential. Therefore,

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hours-since-waking may be an important moderator of extinction learning.

Fear conditioning is central in explaining the development and persistence of PTSD symptoms.[6] Conditioning and extinction studies reveal PTSD-associated deficits in extinction learning[7–10] and extinction recall the following day.[11–13] Longitudinal studies assessing pretrauma extinction reveal impaired extinction learning predicts increased PTSD symptoms after trauma,[14,15] supporting the role of extinction learning in PTSD development.

Growing evidence suggests an important role of sleep in extinction consolidation.[4,16,17] The first study to examine such effects found that after extinction learning, a night of sleep led to the generalization of an extinguished CS+ to a previously unextinguished CS+, compared to a period of wakefulness.[18] Additionally, participants who achieved rapid eye movement (REM) sleep during a nap following extinction showed significantly smaller skin conductance response (SCR) to the extinguished CS+ after sleep, compared to participants who did not achieve REM sleep during the nap.[19] Evidence in patients with spider phobia found a reduction in spider fear following exposure therapy was significantly greater after a period of sleep than wakefulness,[20] confirming an earlier study of simulated exposure therapy for spider fear where sleep enhanced extinction retention and generalization compared to wakefulness.[21]

Sleep disturbances may contribute to issues in managing stressors, enhancing vulnerability for developing psychiatric disorders, including PTSD.[22] Indeed, prospective studies have found pre-, peri-, and posttrauma sleep disturbances significantly predict PTSD symptoms.[22–27] The sleep-wake cycle is regulated by the suprachiasmatic nucleus of the hypothalamus[28] and structures in the brainstem, hypothalamic, and basal forebrain arousal networks,[29] and hypothalamic and brainstem networks are also dysregulated in PTSD.[30] Further, amygdala and prefrontal activation impact sleep, and these networks are also dysregulated in PTSD,[31] suggesting a neurobiological relationship between these factors.

Time-of-day has a significant impact on extinction learning, with improved extinction and recall in the morning compared to the evening in healthy men.[4,5] Generalization of an extinguished stimulus to an unextinguished stimulus was also better 24 hours later if both learning and recall occurred in the morning when an individual is likely to be well-rested. Pace-Schott et al.[32] hypothesized that increased homeostatic sleep pressure may explain greater psychophysiological reactivity to conditioned stimuli in the evening, emphasizing the influence of the previous nights' sleep for extinction. During sleep deprivation, adenosine levels increase in the basal forebrain to promote sleep, and it is hypothesized that increasing adenosine levels may influence sleep homeostasis; that is, the increasing need for restorative sleep throughout the day.[33] Pace-Schott et al.[4] suggest strategically timed sleep may promote the consolidation of therapeutic extinction learning to maximize treatment benefit. These findings are limited to healthy men and yet to be examined in a clinically anxious population characterized by impaired fear extinction and impaired sleep, such as PTSD.

On the basis of accumulating evidence of PTSD-specific extinction impairments, we predicted participants with PTSD would have significantly impaired fear extinction learning compared to trauma-exposed and trauma-nonexposed controls. Furthermore, based on the recent finding of Pace-Schott et al.,[5] we hypothesized that hours-since-waking would be a significant moderator between fear extinction learning and PTSD symptoms, with increased periods of wakefulness predicting significantly poorer extinction learning in participants with greater PTSD symptom severity.

MATERIALS AND METHODS

PARTICIPANTS

Seventy participants aged 18–63 (M = 24.2 years, SD = 9.3 years; 25 males and 45 females) were tested between 12–6 PM, and comprised three groups: PTSD (n = 15), trauma-exposed (TC; n = 33), and trauma-nonexposed controls (NTC; n = 22). Participants were classified on the basis of exposure to a criterion A stressor that threatened physical integrity[34] using the Traumatic Events Questionnaire (TEQ;[35] war exposure n = 1; accident n = 13; natural disaster n = 18; witness n = 29; assaulted or molested n = 21; threatened or held captive n = 15; and tortured or terrorist victim n = 1). Mean years since trauma was 7.6 years (SD = 10.7). Individuals who reported never having experienced a traumatic event were classified as NTC. The PTSD Checklist-Civilian version (PCL-C)[36] was used to estimate PTSD "caseness" (score ≥ 40),[37] and participants who displayed minimal PTSD symptoms were classified as trauma-exposed controls. The study was conducted in accordance with the Declaration of Helsinki, the design was approved by the University of Tasmania Social Sciences Human Research Ethics Committee, and all participants gave full informed consent.

QUESTIONNAIRES

The PCL-C[36] was used for probable PTSD diagnosis according to DSM-IV criteria, and to provide a continuous measure of symptom severity. Participants also completed the Depression Anxiety Stress Scale 21-item version (DASS),[38] Pittsburgh Sleep Quality Index (PSQI),[39] and the Alcohol Use Disorder Identification Test (AUDIT).[40] Upon arrival to the lab, participants indicated their time-of-waking to derive the number of hours-since-waking.

STIMULI AND EXPERIMENTAL PROTOCOL

We adopted a differential fear conditioning and extinction paradigm used previously.[9] The unconditioned stimulus (UCS) was a 500 ms mild electric shock delivered by an electrode to the first interosseous muscle of the dominant hand, set at a level considered "highly annoying, but not painful."[9] Conditioned stimuli were red and blue circles presented individually for 12 s on a computer screen. The protocol included four experimental phases: *habituation*, *acquisition*, *early extinction*, and *late extinction*. During *habituation*, participants were exposed to four trials of each colored circle (eight trials in total). During *acquisition*, one of the colored circles was followed by the UCS (CS+) on all five trials (100% reinforcement schedule)[9] while the other colored circle was not reinforced on any of the five trials (CS–; 10 trials in total).

The *early extinction* phase consisted of five trials of the CS+ (with no reinforcement) and five trials of the CS– (10 trials in total) followed by the *late extinction* phase, which mirrored early extinction. Trial order was fixed-random, with no more than two consecutive CS+ or CS– trials.

SKIN CONDUCTANCE RESPONSE

Skin conductance level (SCL) was measured through a 22 mV_{rms}, 75 Hz constant-voltage coupler (FE116, ADInstruments) with bipolar electrodes placed on the intermediate phalange of the first and third finger of the nondominant hand, sampled at 512 Hz and stored at 64 Hz, and recorded in micro-Siemens (μS). Skin conductance response (SCR) to the CS+ and CS- was calculated by subtracting the mean SCL during the 2s prior to CS onset from the maximum SCR during the 12s CS duration. Scoring was conducted by a software macro blind to experimental conditions. SCR values were square-root transformed, and the absolute value of negative values was transformed and the negative sign replaced. Differential conditioned responding (DCR) was calculated by subtracting the SCR of the first CS– from the first CS+, and so on for all trials.[41] DCR scores were used to compute an extinction DCR change score for use in the moderation analysis, by subtracting the trial 5 DCR from the trial 1 DCR, with greater values indicating a greater decline in differential fear responding.

STATISTICAL ANALYSES

To assess fear conditioning and extinction, a 3 (group) × 2 (CS) × 5 (trial) mixed analysis of variance (ANOVA) was conducted on SCR data separately for each experimental phase (four trials for habituation and acquisition). The first CS+/– trials were removed from acquisition analyses as the UCS had not been encountered, and no learning had occurred. Successful fear conditioning was assessed with a significant CS main effect with greater SCR to the CS+ compared to the CS– during acquisition. Successful extinction learning was assessed with a significant CS × trial interaction, with SCRs decreasing over trials for early and late extinction, and with reduced discrimination between the CS+ and CS–. A moderation analysis was conducted using the PROCESS macro for SPSS (model 1)[42] with hours-since-waking as the moderator variable, extinction DCR change score as the predictor variable, and PCL total as the outcome variable.

An alpha level of $\alpha = .05$ was used for all tests of significance (two-tailed). Greenhouse–Geisser adjustments were made for within-subjects variables, with epsilon values and adjusted-df reported where necessary. Brown-Forsythe *F*-ratio corrections were made when homogeneity of variance was violated. For pairwise comparisons, Bonferroni corrections were made, with effect sizes reported as Cohen's *d*, following criteria of 0.2, 0.5, and 0.8 for small, moderate, and large effects, respectively.[43] For mixed model ANOVAs, effect sizes were reported as partial eta-squared (η_p^2).

RESULTS

CLINICAL AND DEMOGRAPHIC DATA

Table 1 displays descriptive and inferential statistics for clinical and demographic variables. A one-way ANOVA revealed a significant between-group effect of age, $F(2, 18.43) = 7.28$, $P = .005$. As seen in Table 1, participants in the PTSD group were, on average, significantly older than participants in the TC and NTC groups (*P*s < .05), who did not differ ($P = .375$). ANOVA revealed a significant between-group effect for total PCL score, $F(2, 18.30) = 76.44$, $P < .001$, with the PTSD group having a greater PCL total ($M = 50.60$, 95% CI [44.15, 57.05], $SD = 11.65$) than TCs ($M = 25.00$ [23.40, 26.60], $SD = 4.52$), and NTCs ($M = 19.91$ [18.73, 21.09], $SD = 2.65$), who also showed a significant difference ($P < .001$). Table 1 shows the PTSD group had significantly greater PCL scores for each symptom cluster. One-way ANOVA revealed participants in the PTSD group had significantly higher scores on the DASS subscales of depression, anxiety, and stress than TC and NTC participants, who did not significantly differ (*P*s > .05). Participants in the PTSD group had significantly poorer sleep quality compared to TC and NTC participants, who did not significantly differ ($P = .187$). There were no significant between-group differences in alcohol use ($P = .124$).

HOURS-SINCE-WAKING

Between-group differences in hours-since-waking showed no indication of group biases for hours-since-waking as a moderator: A one-way ANOVA revealed no significant between-group differences in hours-since-waking, $F(2, 67) = 1.24$, $P = .296$ (PTSD group = 7:02 hr, $SD = 2{:}30$; TC = 6:09, $SD = 2{:}26$; and NTC = 5:43, SD = 2:32). Further, a one-way ANOVA revealed no significant group differences for time-of-day when testing was conducted, $F(2, 67) = .34$, $P = .711$ (PTSD group = 14:43PM, $SD = 1{:}42$; TC = 15:04PM, $SD = 2{:}09$; and NTC = 14:40PM, $SD = 1{:}45$), indicating that circadian rhythm is unlikely to affect analyses involving hours-since-waking.

FEAR CONDITIONING AND EXTINCTION

Habituation. A 3 × 2 × 4 mixed-ANOVA showed no significant main effect of group or CS condition or interactions with these variables (*F*s < 1.07). There was a significant main effect of trial, $F(3, 201) = 5.52$, $P = .001$, $\eta_p^2 = .076$, with SCRs decreasing across trials (see Fig. 1A). There is likely a reduction in SCRs as participants become used to the task, reflecting an initial habituation of responses that is commonly observed.

Acquisition. The successful acquisition of a conditioned response to the CS+ is evidenced by a significant main effect of CS, $F(1, 67) = 69.29$, $P < .001$, $d = 0.84$. Mixed-model ANOVA revealed the CS+ elicited a significantly larger SCR ($M = 0.89$ [0.76, 1.02], $SD = 0.55$) than the CS– ($M = 0.37$ [0.25, 0.48], $SD = 0.49$). There was a significant main effect of trial, $F(2.68, 179.41) = 3.81$, $P = .014$, $\eta_p^2 = .054$, $\varepsilon = .893$. Additionally, ANOVA revealed a significant group main effect, $F(2, 67) = 4.09$, $P = .021$, $\eta_p^2 = .109$, with the TC group showing larger SCR ($M = 0.81$ [0.66, 0.96], $SD = 0.43$) compared to PTSD and NTC groups ($M = 0.59$ [0.37, 0.81], $SD = 0.43$; and $M = 0.49$ [0.31, 0.67], $SD = 0.43$, respectively). However, there were no significant group × CS, or group × trial interactions, indicating that responses to the CS+ and CS– did not differ between groups.

TABLE 1. Mean scores and SDs of demographic and clinical variables

Measures	PTSD ($n = 15$)	TC ($n = 33$)	NTC ($n = 22$)	Test statistic	P
Demographic data					
- Age (years)	32.87 (14.95)	22.52 (6.13)	20.82 (3.13)	$F_{(2, 18.43)} = 7.28$	$P = .005$
- Sex	8F, 7M	23F, 10M	14F, 8M	$\chi^2_{(2)} = 1.21$	$P = .546$
PCL-C					
- Intrusive	3.07 (1.16)	0.24 (0.61)	0.00 (0.00)	$F_{(2, 67)} = 109.54$	$P < .001$
- Avoidance	3.93 (2.15)	0.70 (0.85)	0.18 (0.50)	$F_{(2, 18.44)} = 34.12$	$P < .001$
- Hyperarousal	3.40 (0.99)	0.48 (0.87)	0.18 (0.50)	$F_{(2, 37.15)} = 82.25$	$P < .001$
DASS					
- Depression	7.80 (5.27)	1.91 (2.10)	1.14 (1.57)	$F_{(2, 19.50)} = 17.84$	$P < .001$
- Anxiety	7.63 (4.54)	2.18 (1.92)	1.23 (1.76)	$F_{(2, 21.57)} = 20.39$	$P < .001$
- Stress	12.23 (5.49)	4.33 (2.53)	2.43 (2.13)	$F_{(2, 22.32)} = 30.89$	$P < .001$
PSQI total	8.60 (4.52)	5.31 (2.16)	4.31 (1.91)	$F_{(2, 23.49)} = 8.25$	$P = .002$
AUDIT	7.87 (5.82)	5.13 (3.68)	5.23 (4.40)	$F_{(2, 65)} = 2.15$	$P = .124$

PCL-C, PTSD Checklist-Civilian version; DASS, Depression Anxiety Stress Scale; PSQI, Pittsburgh Sleep Quality Index; AUDIT, Alcohol Use Disorders Identification Test.

Early Extinction. Mixed ANOVA revealed a significant main effect of CS, with the CS+ eliciting a larger SCR ($M = 0.54$ [0.44, 0.65], $SD = 0.44$) than the CS– ($M = 0.42$ [0.33, 0.51], $SD = 0.39$), $F(1, 67) = 7.57$, $P = .008$, $d = 0.29$. There was no significant group × CS interaction ($P = .243$), indicating all groups were still displaying conditioned responding during the early extinction phase. ANOVA also revealed a significant main effect of trial, with a decline in SCR across the experimental phase, $F(3.29, 220.44) = 27.99$, $P < .001$, $\eta_p^2 = .295$, $\varepsilon = .823$, indicating an overall reduction in SCRs across trials (see Fig. 1C). Further, there was no significant CS × trial interaction, $F(3.78, 253.37) = 0.37$, $P = .819$, $\eta_p^2 = .006$, $\varepsilon = .945$, with no change in SCR to the CS+ and CS–, providing additional support that all groups were still displaying conditioned responses to the CS+ in early extinction (see Fig. 1C). No further main effects or interactions were significant (Fs < 1).

Late Extinction. There was a significant trial main effect, with SCRs decreasing across trials, $F(3.11, 208.53) = 16.82$, $P < .001$, $\eta_p^2 = .201$, $\varepsilon = .778$. There was no significant main effect of CS, $F(1, 67) = 1.16$, $P = .295$, $d = 0.08$, and a trend for a CS × trial interaction, $F(3.74, 250.75) = 2.43$, $P = .053$, $\eta_p^2 = .035$, $\varepsilon = .936$, suggesting a reduction in conditioned responding for all groups by the end of late extinction. Importantly, the mixed ANOVA revealed a significant group × CS × trial interaction, $F(7.49, 250.75) = 2.43$, $P = .018$, $\eta_p^2 = .068$, $\varepsilon = .936$. Tests of simple interaction effects revealed a significant CS × trial interaction for the PTSD group only, $F(2.44, 34.16) = 4.26$, $P = .017$, $\eta_p^2 = .233$, $\varepsilon = .610$. As seen in Fig. 2A, the PTSD group displayed a temporary increase in SCR to the CS+, followed by an increase in responding to the CS–. Notably, this interaction was only identified in the PTSD group, with no effects found for TCs and NTCs ($P = .184$ and $P = .585$, respectively), indicating a PTSD-specific impairment in extinguishing conditioned responses.

HOURS-SINCE-WAKING MODERATION

As a significant group effect was only found during late extinction, the DCR change score from this phase was calculated and entered into the moderation model as the predictor variable, with PCL total as the outcome variable, and hours-awake as the moderator (Table 2, Model 1). The model predicted a significant amount of variance in PCL scores, $R^2 = .18$, $F(3, 66) = 4.93$, $P = .004$. Table 2 shows late extinction DCR change was a significant predictor of PCL scores, with a trend for the role of hours-awake, and a significant hours-awake × late extinction DCR change interaction. Age, depression, anxiety, and stress were individually included in the model as covariates with little change to inferential statistics, and no change to the pattern of effects (see Supporting Information online).

As shown in Fig. 3, for participants with higher PTSD symptom severity, increased hours-awake was significantly associated with poorer extinction learning (as indexed by a smaller decline in DCR change over the late extinction phase), and this effect becomes stronger with increasing hours-awake. To ensure that increased responding to the CS- in trial 1 for the PTSD group did not drive this effect, a change score was calculated for the CS+ in late extinction (trial 5 SCR subtracted from trial 1 SCR) and included as the predictor variable. Table 2 (Model 2) shows a significant moderation interaction, with b-values revealing a consistent pattern with Model 1.

DISCUSSION

This study found hours-since-waking moderates the relationship between fear extinction and PTSD symptoms. Participants with higher PCL scores show significantly poorer extinction learning with increasing hours-awake. These findings support research identifying

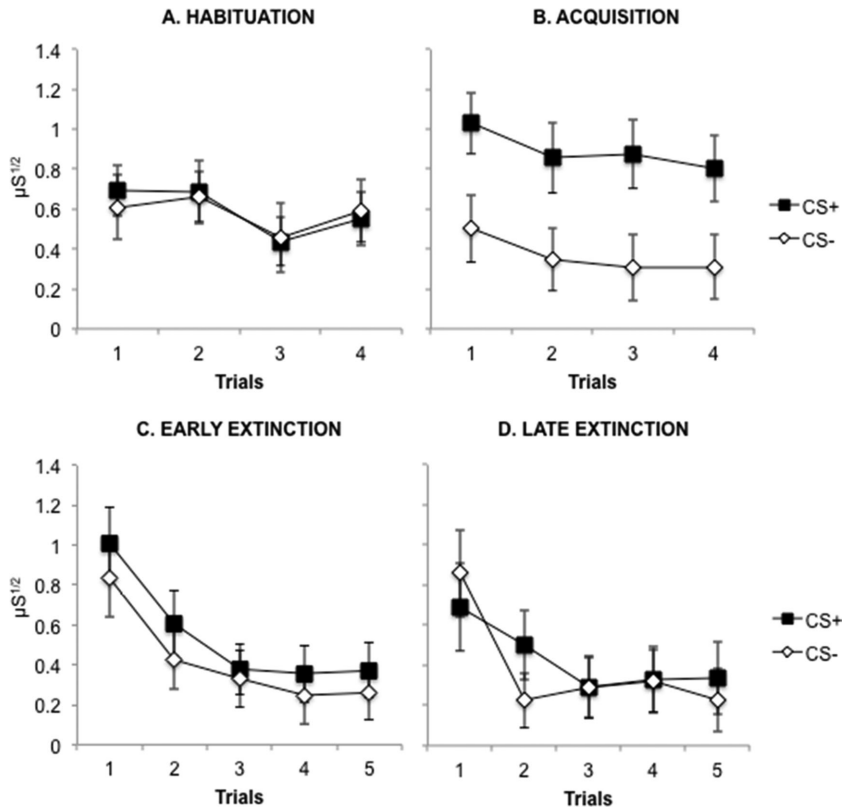

Figure 1. CS × Trial interactions for each experimental phase. Fear acquisition and extinction scores pooled across group for the CS+ and CS– across all trials. (A) During the acquisition phase, there was a statistically significant CS × trial interaction, with the difference in responses to the CS+ and CS– increasing across the acquisition phase, indicating greater CS+/– contingency awareness. (C) In early extinction, there was no significant CS × trial interaction, with means showing that the reduction of SCR from trial 1 to trial 5 did not differ between the CS+ and CS–. (D) During the late extinction phase, there was a trend for a CS × trial interaction, $F(3.74, 250.75) = 2.42$, $P = .053$, $\eta_p^2 = .035$, $\varepsilon = .936$, with a greater reduction in SCR from trial 1 to trial 2 for the CS– compared to the CS+. Error bars depict 95% confidence intervals of the mean. $\mu S^{1/2}$, SCR square-root transformed in micro-siemens.

poorer extinction learning in the evening in healthy controls,[5] and extends them to a clinical sample with PTSD compared to TC and NTC. Together, these results have important clinical implications for scheduling exposure therapy to optimize treatment benefit.

The findings of the present study are consistent with previous research that fear extinction learning is significantly impaired in PTSD compared with nonclinical controls.[7–10] The results highlight an interesting pattern, with extinction learning impairments limited to the

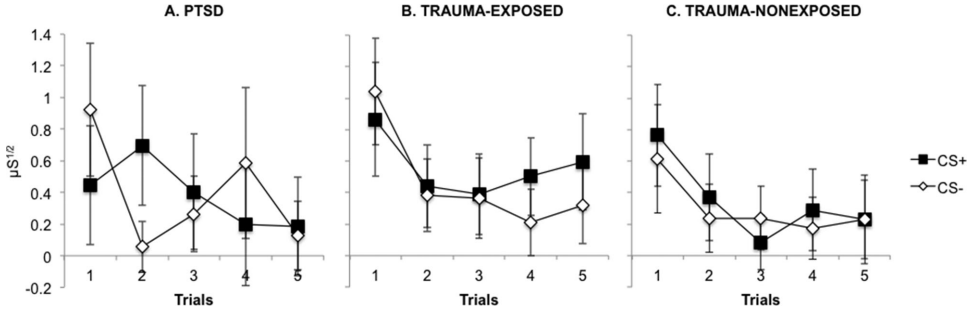

Figure 2. Group × CS × Trial interaction in late extinction. Late extinction SCR scores for the CS+ and CS– by trial for each: (A) PTSD; (B) TC; and (C) NTC groups. The PTSD group showed reduced extinction learning, with the CS+ eliciting a temporary increase in SCR, followed by an SCR increase to the CS–. CS × trial interactions for the TC and NTC groups were not significant ($P = .184$ and $P = .585$, respectively). Error bars depict 95% confidence intervals of the mean. $\mu S^{1/2}$, SCR square-root transformed in micro-siemens.

TABLE 2. Linear model of predictors of PCL total

	b	SE *b*	*t*	*P*
Model 1				
- Constant	28.88 [25.97, 31.80]	1.46	19.79	< .001
- Hours-awake	1.14 [–0.05, 2.32]	0.59	1.91	.060
- Late extinction DCR change	–2.37 [–4.68, –0.06]	1.16	–2.05	.045
- Hours-awake × late extinction	–1.18 [–2.07, –0.29]	0.45	–2.63	.011
Model 2				
- Constant	28.62 [25.67, 31.57]	1.48	19.38	< .001
- Hours-awake	1.22 [–0.11, 2.54]	0.66	1.84	.071
- CS+ SCR change	–2.47 [–5.63, 0.69]	1.58	–1.56	.124
- Hours-awake × CS+ change	–1.80 [–3.29, –0.30]	0.75	–2.40	.019

SE, Standard Error. Square brackets show 95% confidence intervals of *b*.

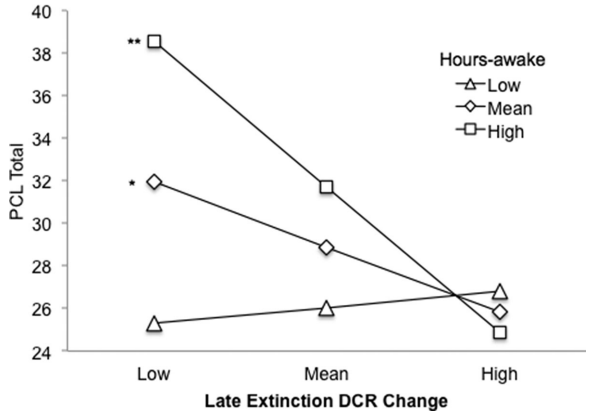

Figure 3. Hours-awake moderation. The relationship between hours-awake, late extinction DCR change and PCL total was significant at higher levels (+1 *SD*) of hours-awake (8.70 hours, $b = -5.31$ [–8.75, –1.87], $t = -3.08$, $P = .003$), and mean levels (6.21 hours, $b = -2.37$ [–4.68, –0.06], $t = -2.05$, $P = .045$), with no significant effects at lower levels (–1 *SD*) of hours-awake (3.71 hours, $b = 0.57$ [–2.39, 3.54], $t = 0.39$, $P = .700$). These findings indicate a linear relationship between late extinction DCR change and PCL total, at increasing levels of hours-since-waking, whereby participants with higher PCL scores demonstrate lower change in differential fear responding in the late extinction phase, and this relationship becomes stronger as participants are awake for longer. * $P < .05$, ** $P < .01$.

late extinction phase, with no between-group differences during early extinction. This pattern of findings is novel and may reflect early consolidation processes. Further investigations with varying extinction learning and recall periods (e.g., 2-day paradigms)[11–13] may provide some insight into the consolidation of extinction recall. Further, it should be noted that the PCL estimates probable PTSD diagnosis, and future research would benefit from using a Clinician Administered PTSD Scale.

Alternatively, participants in the PTSD group may develop increased state anxiety in anticipation of the UCS, despite clear learning of the CS+/– contingency during acquisition. During late extinction, participants in the PTSD group temporarily show larger SCR to the CS– compared to the CS+, suggesting fear generalization from the CS+ to the CS–. However, this effect dissipates quickly, which may be a result of the 100% reinforcement schedule during acquisition. The use of a partial reinforcement schedule (e.g., 60%)[44,45] may shed light on the mechanisms of fear generalization.

Pace-Schott et al.[5] found extinction learning was more effective in the morning compared to the evening in healthy males. The current results show higher PCL scores are negatively associated with extinction learning as participants are awake for longer, extending previous findings to a clinical sample of males and females. This supports the notion that extinction is better learned soon after sleep compared to later in the day, with greater physiological reactivity to stimuli partially attributed to increased sleep demands.[32] This idea is supported by research showing enhanced extinction learning and greater generalization of recall memories soon after sleep,[5,18,21,32] particularly REM sleep.[19,46]

In the current study, we found hours-since-waking moderates the relationship between fear extinction and PTSD symptoms. Previous research revealed elevated circadian levels of cortisol and testosterone in the morning, which may explain significantly enhanced extinction learning and recall in the morning.[5] PTSD is often characterized by hypocortisolism,[47] and increased cortisol levels enhance extinction learning.[48,49] Cortisol experiences circadian effects,[50] suggesting the cortisol acrophase in the morning may be one mechanism by which hours-awake impacts extinction in PTSD. Further, the PTSD group was, on average, significantly older than the TC and NTC groups. There was a weak negative correlation between age and late extinction DCR change, and including age as a covariate in the moderation analysis did not alter the findings (see Supporting Information online). This implies that age does not significantly influence the effects in the current study, however should be controlled in future research.

While the absence of physiological measures of sleep and waking are a limitation of the current study, our findings highlight the role that sleep plays in fear extinction ability. Self-report measures of sleep using the PSQI revealed the PTSD group reported significantly poorer

sleep quality compared to control groups. Poorer sleep quality in the PTSD group may reduce the restorative benefits of sleep, thereby increasing homeostatic sleep demands and producing a smaller window early in the day for maximum extinction potential. Further, recent evidence found extinction is learned faster and better generalized in the morning in participants who achieve sleep earlier and report higher-morningness,[51] suggesting chronotype may influence the present study's findings. Currently, the relationship between REM sleep and PTSD diagnosis is somewhat inconclusive,[16] however further polysomnographic sleep studies examining REM sleep as a moderator between fear extinction and PTSD symptoms may clarify this relationship.

CLINICAL IMPLICATIONS

Pace-Schott et al.[21] suggested the effectiveness of exposure therapy could be improved by scheduling treatment soon after sleep. The implications of the present study are in accordance with previous recommendations that a period of sleep shortly before or after exposure therapy may aid in therapeutic extinction learning.[20,21] This notion is supported by a wealth of research proposing that sleep aids in memory consolidation. e.g., [52,53]

CONCLUSION

The present study confirms impaired fear extinction learning associated with PTSD, and extends previous findings to reveal that this relationship is moderated by hours-since-waking, with PTSD-related extinction impairments increasing with time-awake. These findings suggest important implications for scheduling exposure-based treatments for PTSD, indicating that extinction learning potential, and thus benefit from exposure therapy, may decrease throughout the day. Future research would benefit from physiological measures of sleep to determine a role that REM sleep plays in enhancing this window of opportunity for optimized treatment benefit.

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