Archival Report

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Sleep Deprivation Disrupts Recall of Conditioned Fear Extinction

Laura D. Straus, Dean T. Acheson, Victoria B. Risbrough, and Sean P.A. Drummond

ABSTRACT

BACKGROUND: Learned fear is crucial in the development and maintenance of posttraumatic stress disorder and other anxiety disorders, and extinction of learned fear is necessary for response to exposure-based treatments. In humans, research suggests that disrupted sleep impairs consolidation of extinction, though no studies have examined this experimentally using total sleep deprivation.

METHODS: Seventy-one healthy control subjects underwent a paradigm to acquire conditioned fear to a visual cue. Twenty-four hours after fear conditioning, participants underwent extinction learning. Twenty-four hours after extinction learning, participants underwent extinction recall. Participants were randomized to three groups: 1) well-rested throughout testing ("normal sleep"; $n = 21$); 2) 36 hours' total sleep deprivation before extinction learning ("pre-extinction deprivation"; $n = 25$); or 3) 36 hours' total sleep deprivation after extinction learning and before extinction recall ("post-extinction deprivation"; $n = 25$). The groups were compared on blink electromyography reactivity to the condition stimulus during extinction learning and recall.

RESULTS: There were no differences among the three groups during extinction learning. During extinction recall, the pre-extinction deprivation group demonstrated significantly less extinction recall than the normal sleep group did. There was no significant difference between the normal sleep and post-extinction deprivation group during extinction recall. Results indicated sleep deprivation before extinction training significantly disrupts extinction recall.

CONCLUSIONS: These findings suggest that 1) sleep deprivation in the immediate aftermath of trauma could be a potential contributor to posttraumatic stress disorder development and maintenance via interference with natural extinction processes and 2) management of sleep symptoms should be considered during extinction-based therapy.

Keywords: Extinction, Fear conditioning, Fear potentiated startle, PTSD, REM sleep, Sleep deprivation

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Fear processes play a critical role in the development and maintenance of posttraumatic stress disorder (PTSD) and other anxiety disorders. For example, patients with PTSD experience intense fear reactions to cues associated with a traumatic event, which provokes strong avoidance of these cues long after the trauma (1). During natural recovery from trauma, extinction learning reduces fear reactions to such cues (2). In behavioral interventions, repeated exposure to these cues in safe settings should lead to extinction, whereby the cues lose their predictive quality for danger (3,4). However, strong evidence suggests that patients with PTSD have impaired extinction learning and recall, as demonstrated in psychophysiology studies (5–7). To support better prevention and intervention strategies, it is critical to delineate potential mechanisms that interfere with extinction learning and recall. Such factors could support both the development and maintenance of PTSD and interfere with response to the gold standard treatment for PTSD, exposure-based therapy.

A growing body of research suggests that sleep disruption is one mechanism interfering with extinction processes [see (8) for a review]. In particular, animal studies report that sleep disruption may interfere with initial extinction learning (9) and consistently show that sleep disruption interferes with extinction recall, which is the subsequent ability to consolidate extinction learning and is the strongest predictor of long-term extinction (10–12). In the few studies that have translated this animal research to humans, all support the hypothesis that sleep, particularly rapid eye movement (REM) sleep, is important in extinction learning and recall. Pace-Schott *et al.* (13) showed that sleep in general promotes generalization of extinction, though they did not examine specific sleep stages. In another human study (14), safety learning was associated with subsequent REM consolidation, which in turn predicted fear and safety recall the following day. Spoormaker *et al.* (15) showed that REM sleep promotes extinction recall, with selective REM deprivation after extinction learning interfering with consolidation of that extinction learning (16). Although these studies suggest a role for sleep in extinction processes, no studies have examined sleep disruption before extinction learning to examine whether the results from animal studies extend to humans. Additionally, no studies have used experimental sleep deprivation to examine whether elimination of sleep altogether has the effects on extinction learning predicted by animal models. Such a study would have clinical implications. For example, sleep disruption is very common in PTSD (17,18). Demonstrating that sleep deprivation interferes

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with extinction learning or recall processes or both would suggest that sleep disruption may interfere both with an individual's ability to experience natural recovery immediately after a trauma and to benefit from exposure-based therapy once PTSD develops [see (19), for model].

Here, we examined the effect of 36 hours' total sleep deprivation on extinction learning and recall in healthy human subjects. All subjects (n = 71) underwent a laboratory paradigm to acquire conditioned fear to a visual cue. Twenty-four hours later, participants underwent an extinction learning session, and 24 hours after that, participants underwent extinction recall. Participants were randomized to three groups: 1) well-rested throughout testing; 2) 36 hours' total sleep deprivation before extinction learning; or 3) 36 hours' total sleep deprivation after extinction learning and before extinction recall. Consistent with the animal and human studies, we hypothesized total sleep deprivation would not interfere with extinction learning, but would interfere with recall of extinction memories.

METHODS AND MATERIALS

Participants

Seventy-three healthy young adults were enrolled. Following written informed consent, participants were screened for sleep disorders, drug use, psychiatric, and medical disorders via structured interview and laboratory tests. Inclusion criteria included 1) age 18 to 39 years old; 2) regular sleep-wake schedule that included 7 to 9 hours' time-in-bed with a bedtime of 10 PM to midnight and a wake time of 6 AM to 8 AM; 3) no current medical or psychiatric diagnoses; and 4) no personal history of any Axis I diagnosis or family history of mood or psychotic disorders. Female participants were studied in the early follicular phase of the menstrual cycle. Those not exhibiting consistent startle responding at screening (over 75% discernible responses to twelve 105-dB 40-ms startle pulses) were excluded. Of the 73 participants who completed the lab portion of the study, two participants had incomplete datasets and were therefore dropped from the final analyses. Overall, 71 participants were included in analyses. See Table 1 for demographic information.

Procedure

Participants maintained a regular sleep-wake schedule, matching their self-reported habitual schedule, at home for 7 days. Adherence was monitored via actigraphy, voicemail call-ins, and diaries. Participants then spent 4 consecutive days and nights in the laboratory (Figure 1), where they underwent a fear potentiated startle (FPS) protocol. The FPS consisted of three sessions: fear acquisition (day 1); extinction learning (day 2); and extinction recall (day 3). All testing took place in the evening, 10 to 12 hours following participants' habitual wake time. All testing took place in the same context to prevent context-dependent alterations in fear responding from influencing the results. Participants were randomized to one of three conditions: 1) well-rested throughout testing ("normal sleep"; n = 21); 2) 36 hours' total sleep deprivation before extinction learning ("pre-extinction deprivation"; n = 25); or 3) 36 hours' total sleep deprivation after extinction learning and before extinction recall ("post-extinction deprivation"; n = 25). Participants were not allowed to leave the laboratory during the study or engage in exercise more vigorous than walking short distances and were restricted from alcohol and caffeine or other stimulants beginning 48 hours before entering the laboratory. For each night of normal sleep, polysomnography, including eletroencephalography, electro-oculography, and chin electromyography, monitored sleep. To screen for unreported sleep apnea and periodic leg movements, additional monitors were added on the adaptation night. Placement of monitors and polysomnography scoring was per American Academy of Sleep Medicine recommendations (20).

Fear Conditioning and Extinction Procedure

The FPS apparatus and recording procedures have been described in detail elsewhere by our group and others (14,21,22) and are provided in the Supplement. Procedures and timeline for the three FPS sessions are illustrated in Figure 2. All sessions were designed similarly to those used in our previous work (14,21) as well as in the work of others (6). Each session began with six startle pulses presented in the absence of any other stimuli in order for the participants to acclimate or habituate startle responses to baseline level. The acquisition session (day 1) consisted of 1) eight 6-second presentations of a blue circle serving as a reinforced conditioned stimulus (CS+), followed by a 0.5-second electrical shock unconditioned stimulus (US) in 75% contingency coterminating with the CS+; 2) eight 6-second presentations of a red circle serving as the second CS+ followed by a 0.5-second electrical shock US in 75% contingency coterminating with the CS+; 3) 16 6-second presentations of a yellow circle serving as a nonreinforced conditioned stimulus (CS−) never followed by shock (i.e., safety signal); and 4) 16 presentations of the startle pulse in the absence of any stimuli (i.e., blank screen; "noise-alone trial" [NA]) serving as a measure of baseline startle reactivity across the session. The first half of the acquisition session consisted of presentation of only blue

Table 1. Subject Demographics

	Normal (n = 21)	Pre-Ext Dep (n = 25)	Post-Ext Dep (n = 25)
Age, Years	24.5 ± 5.5	23.6 ± 4.0	23.6 ± 4.4
Gender, Male/Female	61.9/38.1	60/40	56/44
Race, Caucasian/Asian/African American/Multiple	61.9/23.8/4.8/9.5	44/44/4/8	68/20/0/12
Ethnicity, Non-Hispanic/Hispanic	66.7/33.3	84/16	60/40
Education, Years	15.8 ± 2.0	15.4 ± 1.2	15.1 ± 2.4

Values are mean ± SD or percentages.
Dep, deprivation; Ext, extinction.