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Extinction of conditioned fear is better learned and recalled in the morning than in the evening

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ABSTRACT

Sleep helps emotional memories consolidate and may promote generalization of fear extinction memory. We examined whether extinction learning and memory might differ in the morning and evening due, potentially, to circadian and/or sleep-homeostatic factors. Healthy men ($N = 109$) in 6 groups completed a 2-session protocol. In Session 1, fear conditioning was followed by extinction learning. Partial reinforcement with mild electric shock produced conditioned skin conductance responses (SCRs) to 2 differently colored lamps (CS+), but not a third color (CS−), within the computer image of a room (conditioning context). One CS+ (CS + E) but not the other (CS + U) was immediately extinguished by un-reinforced presentations in a different room (extinction context). Delay durations of 3 h (within AM or PM), 12 h (morning-to-evening or evening-to-morning) or 24 h (morning-to-morning or evening-to-evening) followed. In Session 2, extinction recall and contextual fear renewal were tested. We observed no significant effects of the delay interval on extinction memory but did observe an effect of time-of-day. Fear extinction was significantly better if learned in the morning ($p = .002$). Collapsing across CS + type, there was smaller morning differential SCR at both extinction recall ($p = .003$) and fear renewal ($p = .005$). Morning extinction recall showed better generalization from the CS + E to CS + U with the response to the CS + U significantly larger than to the CS + E only in the evening ($p = .028$). Thus, extinction is learned faster and its memory is better generalized in the morning. Cortisol and testosterone showed the expected greater salivary levels in the morning when higher testosterone/cortisol ratio also predicted better extinction learning. Circadian factors may promote morning extinction. Alternatively, evening homeostatic sleep pressure may impede extinction and favor recall of conditioned fear.

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1. Introduction

Current behavioral therapies for anxiety disorders employ controlled exposure to the feared object or situation, an experience leading to the formation of a therapeutic “extinction memory” that something that once signaling danger no longer does so (Craske et al., 2008; McNally, 2007). Of interest to clinicians treating anxiety disorders are ways to strengthen this therapeutic learning and prevent preexisting fear memories from provoking relapse (Craske et al., 2008). One potential moderator that has not been fully examined is whether the time-of-day during which a therapy session is delivered might influence treatment outcome. This is important because extinction is an emotional memory that might be augmented by sleep and/or hormones that exhibit circadian fluctuations (Diekelmann and Born, 2010; Walker and Stickgold, 2006).

Using a validated fear conditioning and extinction paradigm (Milad et al., 2007a), we have previously reported that overnight sleep, compared to over-day waking, promotes generalization of extinction learning (Pace-Schott et al., 2009). This finding could also be explained by a time-of-day effect, whereby extinction generalization is better expressed in the morning. Animal experiments demonstrate that the magnitude of both fear conditioning and extinction can show circadian rhythmicity (Chaudhury and Colwell, 2002). Nonetheless, an experimental model of exposure therapy that controlled for time-of-day effects showed sleep-dependent

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enhancement of extinction memory and generalization (Pace-Schott et al., 2012a). Moreover, inter-session habituation, a non-associative process related to extinction memory, was augmented by a nap vs. an equal duration of waking at the same time-of-day (Pace-Schott et al., 2011).

Because the aforementioned studies from our group have used very different procedures, the current study sought to determine whether time-of-day and/or duration of delay between extinction learning and recall would influence conditioned fear responses using the original paradigm (Milad et al., 2007a; Pace-Schott et al., 2009). All participants underwent differential fear conditioning and extinction training either in the morning or evening. Subsequently, participants in both groups underwent extinction recall and renewal tests 3, 12, or 24 h after extinction learning.

Salivary levels of cortisol and testosterone were obtained when fear conditioning and extinction were encoded and recalled. This was done because cortisol (Kalsbeek et al., 2012; Pannain and Van Cauter, 2007) and testosterone (Diver et al., 2003; Leymarie et al., 1974; Piro et al., 1973) both show a morning acrophase and evening nadir, and both modulate fear responses and emotional memory (Ackermann et al., 2012; de Quervain et al., 2009; Montoya et al., 2012). For example, high levels of glucocorticoids (cortisol in humans) enhance acquisition and consolidation of emotionally salient memories (Bentz, Michael, de Quervain, & Wilhelm, 2010; Blundell et al., 2011; de Quervain et al., 2009, 2011; Soravia et al., 2006) but block their retrieval (de Quervain, 2008; de Quervain et al., 2009). Similarly, exogenous testosterone can decrease fear (Hermans et al., 2007; van Honk et al., 2005) and modulate social emotions (Bos et al., 2012; van Honk et al., 1999).

Participants were restricted to males for 4 reasons. First, human extinction memory varies with levels of estradiol and phase of the menstrual cycle in females (Milad et al., 2006, 2010; Zeidan et al., 2011). Second, unlike estrogen, testosterone shows a clear circadian rhythm in males and hence might help explain time-of-day differences. Third, testosterone can be rapidly converted to estrogen in the brain (Cornil and Charlier, 2010) and endogenous estrogen has been shown to enhance extinction recall (Milad et al., 2009, 2010). And fourth, human sex differences have been reported for the effects of endogenous and exogenous cortisol on the acquisition of conditioned fear (Bentz et al., 2013; Jackson et al., 2006; Zorawski et al., 2005). Given such complex interactions, study of the simpler case in males was chosen as a first step.

Based upon preliminary findings (Pace-Schott et al., 2012b), we predicted that extinction learning and recall would both be better in the morning than in the evening. We also hypothesized that acquisition of extinction would vary positively with endogenous levels of cortisol and/or testosterone.

2. Methods

2.1. Participants

Healthy young adult males (n = 109) aged 18–27 yrs (mean 20.8, SD 2.6) were enrolled. Detailed inclusion and exclusion criteria are provided in Supplementary methods. This study was conducted in accordance with the principles of the declaration of Helsinki, procedures were approved by the University of Massachusetts, Amherst and the Partners Healthcare Institutional Review Boards and all participants provided written informed consent.

2.2. Pre-study week

During the week prior to the experiment, 97 participants were instructed to keep a regular sleep schedule consisting of a minimum of 7 h in bed each night, bedtime no later than 2:00 AM and no daytime napping. Compliance with these instructions was monitored with the Evening-Morning Sleep Questionnaire (EMSQ) diary and actigraphy (see Supplementary methods). Participants were also asked to abstain from alcohol, recreational drugs and, on study days, caffeine. The 12 remaining participants were only required to follow study restrictions on the 2 study days plus the prior day and night due to differing compensation (see Supplementary methods). All participants completed the Epworth Sleepiness Scale (ESS, Johns, 1991), the Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989) and the Morningness–Eveningness Questionnaire (MEQ, Horne and Ostberg, 1976). During one day of the pre-study week, participants provided 6 saliva samples at specified times for hormone assays.

2.3. Experimental schedule

The protocol included five experimental phases that took place over two Sessions (Sessions 1 and 2) with Habituation, Fear Conditioning, and Extinction Learning occurring in Session 1 and Extinction Recall and Fear Renewal in Session 2. There were two groups: a morning and an evening group. The morning group underwent Habituation, Fear Conditioning, and Extinction Learning between 7 and 10 AM. Subsequently, Extinction Recall and Fear Renewal were tested at either 3 ($n = 17$), 12 ($n = 17$), or 24 h ($n = 18$) following Extinction Learning. For the evening group, Habituation, Fear Conditioning and Extinction Learning occurred between 7 and 10 PM. Subsequently, Extinction Recall and Fear Renewal tests again took place 3 ($n = 19$), 12 ($n = 19$), or 24 h ($n = 19$) after Extinction Learning (Fig. 1).

2.4. Stimuli and experimental protocol

Stimuli were identical to those described previously (Linnman et al., 2011; Milad et al., 2009, 2007a,b; Pace-Schott et al., 2009; Zeidan et al., 2011). The unconditioned stimulus (US) was a mild electric shock, with a level selected by the subject to be “highly annoying but not painful” (Orr et al., 2000). Conditioned stimuli (CS) were digital photographs of 3 differently colored lamps (blue, red or yellow) displayed on a computer screen within the image of two different rooms, one of which served as the “conditioning context” and the other as the “extinction context”. During Habituation, participants viewed each possible combination of the three CS colors and two contexts. During Fear Conditioning, 2 of the 3 colors (CS+) were followed by the US after 5 of 8 presentations of each, with 16 un-reinforced presentations of the third color (CS−) pseudorandomly interspersed. During Extinction Learning, one CS+ color (CS + E) appeared 16 times in the extinction context unaccompanied by the US along with 16 interspersed CS−. The other CS+ color was not presented and hence remained unextinguished (CS + U). During Extinction Recall, the 8 CS + E and 8 CS + U were presented in the extinction context without any US presentations and with 16 interspersed CS−. During Fear Renewal, the 8 CS + E and 8 CS + U were similarly presented but in the conditioning context. (See Supplementary methods for details.) Thus, participants saw the conditioning context during Habituation, Conditioning and Fear Renewal phases whereas they saw the extinction context during the Habituation, Extinction Learning and Extinction Recall phases. The Stanford Sleepiness Scale (SSS, Hoddes et al., 1973) was administered at the beginning and end of each session.

2.5. Skin conductance response (SCR)

Skin conductance level was recorded using the MP150 system (BIOPAC Systems, Inc., Goleta, CA). A skin conductance response

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