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Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear

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ABSTRACT

Simulated exposure therapy for spider phobia served as a clinically naturalistic model to study effects of sleep on extinction. Spider-fearing, young adult women ($N = 66$), instrumented for skin conductance response (SCR), heart rate acceleration (HRA) and corrugator electromyography (EMG), viewed 14 identical 1-min videos of a behaving spider before a 12-hr delay containing a normal night's Sleep ($N = 20$) or continuous daytime Wake ($N = 23$), or a 2-hr delay of continuous wake in the Morning ($N = 11$) or Evening ($N = 12$). Following the delay, all groups viewed this same video 6 times followed by six 1-min videos of a novel spider. After each video, participants rated disgust, fearfulness and unpleasantness. In all 4 groups, all measures except corrugator EMG diminished across Session 1 (extinction learning) and, excepting SCR to a sudden noise, increased from the old to novel spider in Session 2. In Wake only, summed subjective ratings and SCR to the old spider significantly increased across the delay (extinction loss) and were greater for the novel vs. the old spider when it was equally novel at the beginning of Session 1 (sensitization). In Sleep only, SCR to a sudden noise decreased across the inter-session delay (extinction augmentation) and, along with HRA, was lower to the novel spider than initially to the old spider in Session 1 (extinction generalization). None of the above differentiated Morning and Evening groups suggesting that intervening sleep, rather than time-of-testing, produced differences between Sleep and Wake. Thus, sleep following exposure therapy may promote retention and generalization of extinction learning.

1. Introduction

Abnormal expression of fear, as occurs in anxiety disorders such as post-traumatic stress disorder (PTSD) and specific phobia, may result from abnormally strong fear conditioning (Armfield, 2006; Lissek et al., 2005; Mineka and Oehlberg, 2008; Orr et al., 2000), deficiency of inhibitory mechanisms that normally moderate fear expression (Craske et al., 2008; Hofmann, 2008; Milad et al., 2006), or both. Key among such inhibitory processes is extinction — learning that a once-feared object or event is no longer dangerous (Milad et al., 2006). Rather than erasing a fearful memory, extinction forms a new "safety memory" that competes with the fear memory when the once-feared object or event is re-encountered (Hermans et al., 2006; Quirk and Mueller, 2008).

Formation of such therapeutic extinction memories is the neurocognitive basis for the efficacy of exposure therapy, a first-line behavioral treatment for anxiety disorders (Craske et al., 2008; McNally, 2007). In order for exposure therapy to be successful, consolidation and retention of extinction learning acquired during therapy is essential (Craske et al., 2008). In addition, such learning must generalize in order to ensure that the reduction of fearful responding to specific cues in treatment will extend to stimuli encountered outside the therapist's office (Rowe and Craske, 1998; Vansteenwegen et al., 2007).

Using an experimental fear-conditioning paradigm (Milad et al., 2007), normal sleep has been shown to promote the generalization of extinction memories (Pace-Schott et al., 2009). However, unlike such experimentally induced *de-novo* fears, anxiety disorders are associated with long-standing fears that have complex, multifactorial origins and perpetuating factors (Armfield, 2006). Specific phobias, such as spider phobia, are highly prevalent, mild

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anxiety disorders (LeBeau et al., 2010; Lissek et al., 2007) in which treatment strategies, such as exposure therapy, can be studied in a non-clinical setting (e.g., Vansteenwegen et al., 2007).

Sleep enhances consolidation of emotional memory (reviewed in Walker, 2009). Here we characterize the effect of sleep on the retention and generalization of a specific emotional memory– the extinction of spider fear produced by simulated exposure therapy. We hypothesized that sleep following simulated exposure therapy in spider-phobic subjects would lead to greater retention of fear extinction for the spider to which they were repeatedly exposed. In addition, we predicted that sleep would enhance generalization of this extinction memory to a novel spider.

2. Methods and materials

2.1. Participants

Participants were 66 females (18–28 yrs, mean = 19.9) with significant fear of spiders operationally defined using thresholds of 80 on the Fear of Spiders Questionnaire [FSQ (Szymanski and O'Donohue, 1995)] and 15 on the Spider Phobia Questionnaire [SPQ (Klorman et al., 1974)]. Previous research has determined that these thresholds reflect significant fear of spiders (Muris and Merckelbach, 1996; Rodriguez et al., 1999; Guastella et al., 2007; Vansteenwegen et al., 2007). The FSQ was included in a large pre-screening for research participation by students at the University of Massachusetts, Amherst. Starting with the highest FSQ scores and working downward, such individuals were offered the opportunity to earn academic credit for participation if they confirmed eligibility via the SPQ.

Qualified respondents were pseudo-randomly assigned to Sleep ($N = 20$) and Wake ($N = 23$) experimental groups as well as Morning ($N = 11$) and Evening ($N = 12$) control groups. Invitations specified that participants must be non-smoking, without psychiatric, sleep, medical or neurological disorders and not using psychiatric or sleep-affecting drugs. A 23-item screening questionnaire administered at the first session queried these criteria. Only 12 individuals had one or more deviations from the invitation criteria (Table 1). However, because deviations were distributed between the groups and because co-morbidities are common in specific phobias (American Psychiatric Association, 2000), these individuals were included in analyses (see Supplementary methods for additional details). Physiological data could not be analyzed in 1 Wake, 2 Sleep and 1 Evening participants leaving $N = 18$ (Sleep), 22 (Wake), 11 (Morning) and 11 (Evening) for the physiological measures. This study was approved by the University of Massachusetts, Amherst, IRB and all participants provided written informed consent.

2.2. Procedure

Participants completed two sessions (Fig. 1) from approximately 8:00–9:00PM and 8:00–9:00AM the following morning (Sleep), 8:00–9:00AM and 8:00–9:00PM on a single day (Wake), 7:00–8:00 and 10:00–11:00AM (Morning) or 7:00–8:00 and 10:00–11:00PM (Evening). Procedures for the experimental groups (Sleep and Wake) and those for the control groups (Morning and Evening) were identical, except for the duration of the inter-session interval (12 h experimental vs. 2 h control). All participants were instructed to abstain from alcohol, recreational drugs and daytime napping from the day before Session 1 (S1) until completing Session 2 (S2). At S1 (Sleep and Wake) or immediately following S1 (Morning and Evening), participants completed a sleep diary that retrospectively queried sleep duration and quality on the 2 preceding nights. The Sleep group also completed this diary for the night between sessions. On the night before S1 (all groups) and between S1 and S2 (Sleep group), participants were instructed to allow themselves the opportunity for at least 7 h sleep and to have no caffeine after arising until the end of S2. Wake, Morning and Evening groups were specifically instructed to remain continuously awake between sessions. Between S1 and S2, all participants

Table 1
Demographic, self-reported habitual sleep, sleepiness and substance use, subjective sleep duration and psychological traits in the Sleep, Wake Morning and Evening groups.

Characteristic	Sleep (SD)	Wake (SD)	Morning (SD)	Evening (SD)	F(3,62)†
N	20	23	11	12	
Age	20.1 (1.5)	20.2 (2.1)	19.3 (1.4)	19.5 (1.1)	1.12
FSQ	101.4 (12.4)	107.1 (14.9)	110.8 (10.5)	110.3 (13.6)	1.72
SPQ	23.7 (3.3)	24.5 (4.3)	23.3 (2.4)	24.0 (3.2)	0.38
Habitual TST (hr)	7.6 (0.9)	7.4 (1.1)	7.7 (0.8)	7.7 (0.9)	0.38
Habitual SOL (min)	17.3 (10.9)	24.2 (23.7)	24.6 (15.3)	19.2 (13.5)	0.75
ESS	7.50 (3.29)	8.30 (4.42)	9.82 (4.36)	9.08 (3.80)	0.92
PSQI	4.80 (1.58)	5.09 (2.97)	5.67 (2.40)	4.92 (1.83)	0.30[a]
MEQ	39.50 (7.56)	44.83 (10.50)	43.00 (10.34)	39.13 (10.08)	1.52[b]
STAI-Trait	41.05 (8.41)	40.96 (10.11)	36.86 (11.49)	44.25 (10.11)	1.08
Disgust propensity	24.80 (5.14)	25.70 (5.87)	26.82 (4.75)	24.5 (3.09)	0.53
Disgust sensitivity	18.70 (4.51)	19.46 (7.88)	21.91 (5.84)	19.96 (3.48)	0.70
NEO-PI-R Neuroticism	103.63 (17.87)	101.52 (21.13)	95.64 (17.91)	101.67 (20.96)	0.75
NEO-PI-R Extraversion	118.40 (21.68)	128.28 (19.92)	138.45 (15.15)	123.92 (15.10)	2.79*
NEO-PI-R Openness	120.40 (14.54)	117.87 (18.71)	116.46 (21.09)	114.67 (15.61)	0.30
NEO-PI-R Agreeableness	120.75 (17.40)	116.30 (19.41)	110.09 (18.53)	116.25 (12.70)	0.87
NEO-PI-R Conscientiousness	111.20 (16.68)	116.74 (21.54)	120.55 (20.13)	108.83 (25.98)	0.86
Habitual daily caffeine (serv.)	1.5 (1.2)	1.5 (1.2)	1.1 (1.0)	1.0 (0.7)	0.44[c]
Habitual weekly EtOH (serv.)	3.3 (4.8)	2.4 (2.6)	3.6 (2.9)	3.8 (2.6)	0.50[d]
Diary sleep Day −1 (min)	489 (91)	458 (35)	455 (20)	555 (78)	6.87***[e]
Diary sleep Day −2 (min)	490 (68)	496 (98)	447 (109)	517 (116)	1.03[f]
Diary inter-session sleep	431 (25)				
(N) Criteria deviations	(3) Head injury, (1) Head injury & panic disorder & night terror, (1) "Sleep pill"	(3) Head injury, (2) Ritalin, (1) Head injury & Insomnia		(1) Head injury & Ritalin & Depression, (1) Fluoxetine	

*$p < .05$, Morning > Sleep ($p < .01$) and Evening ($p < .05$).
***$p < .001$, Evening > Morning ($p < .0001$), Wake ($p < .0001$) and Sleep ($p = .008$).
†Lower-case letters reflect smaller samples due to participant omission of data points: [a]$F(3,60)$ Morning $N = 9$; [b]$F(3,61)$ Morning $N = 10$; [c]$F(3,61)$ Wake $N = 22$; [d]$F(3,57)$ Wake $N = 21$, Morning $N = 10$, Evening $N = 10$; [e]$F(3,60)$ Sleep $N = 19$, Wake $N = 22$; [f]$F(3,59)$ Sleep $N = 19$, Wake $N = 22$, Morning $N = 10$.