The expression of trace conditioning during non-REM sleep and its relation to subjective experience

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ABSTRACT

Research in animals has demonstrated that patterns of neural activity first seen during waking experience are later "replayed" during sleep, in hippocampal and cortical networks. The characteristics of memory reactivation during human sleep, however, have not yet been fully described. Meanwhile, the possible relationship of dreaming to this "replay" of memories in the sleeping brain is entirely unknown. In the present study, we induced hippocampus-dependent memory retrieval during human sleep using a "trace conditioning" procedure. Prior to sleep, subjects underwent either trace (hippocampus-dependent) or delay (hippocampus-independent) auditory fear conditioning. Conditioned stimuli were then presented to subjects during non-REM sleep. Both delay-conditioned and trace-conditioned subjects exhibited conditioned EEG responses during post-training sleep. However, selectively in trace-conditioned subjects, fear-conditioned cues also affected the valence of dreamed emotions. These findings suggest that hippocampus-dependent learning is accessible during non-REM sleep, and that hippocampus-mediated memory reactivation may be expressed, not only through neural activity in the sleeping brain, but also within concomitant subjective experience.

1. Dreaming of the hippocampus: The expression of trace fear conditioning during non-REM sleep

Consolidation of hippocampus-dependent memory is thought to be facilitated by non-rapid eye movement sleep (NREM), as the hippocampus mediates "reactivation" of neural ensembles involved in recent experience (Buzsaki, 1996; Gais & Born, 2004; Maquet, 2001; Peigneux et al., 2004; Wilson & McNaughton, 1994). Behavioral studies in humans support this model, showing that periods of NREM sleep facilitate performance on declarative memory tasks (Plihal & Born, 1997; Tucker et al., 2006). Meanwhile, in rodents, patterns of neural activity first seen during waking experience are later re-expressed during sleep, in the hippocampus and cortex (Ji & Wilson, 2007; Lee & Wilson, 2002; Wilson & McNaughton, 1994). This evidence that memories are "replayed" in sleep has prompted speculation that reactivation of experience on the neural level might be evident within reports of sleep mentation (i.e., "dreaming") (Maquet, 2001; Paller & Voss, 2004; Payne & Nadel, 2004). No direct experimental evidence has yet addressed this critical question. Indeed, with little data to connect neural-level memory reactivation seen in rodents to sleep-

dependent performance benefits in humans, the relationship between sleep and declarative memory as a whole still remains a controversial topic (Vertes & Siegel, 2005). Here, we used a conditioning paradigm to further describe the functioning of declarative memory systems during human sleep, and to test the hypothesis that retrieval of hippocampus-dependent learning is expressed within subjective reports of sleep mentation.

A handful of prior studies provide tentative evidence for a connection between recent learning and mentation recalled from post-training sleep. Smith and Hanke (2004), for example, found that subjects reported REM mentation related to a mirror-tracing task, particularly when cued during sleep using a sound heard at learning. Fiss, Kremer, and Lichtman (1977) have meanwhile reported that dreaming of stories learned prior to sleep is associated with enhanced recall of that verbal material in the morning. Conversely, mental content from REM awakenings is better remembered in the morning if it is related to a pre-sleep learning task (Cipolli, Fagioli, Mazzetti, & Tuozzi, 2004). Finally, Stickgold and colleagues have shown that pre-sleep training on engaging visuomotor videogames consistently results in sleep onset mentation unambiguously related to these intensive learning tasks (Stickgold, Malia, Maguire, Roddenberry, & O'Connor, 2000; Wamsley, Emberger, Djonlagic, Babkes, & Stickgold, in preparation). Taken together, these findings suggest that dreaming is influenced by the retrieval of recent memories in the sleeping brain. Yet the neural basis for incorporation of recent events into dream content remains entirely obscure.

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In particular, the involvement of the hippocampus in this process is unknown. Early work suggested that as a result of temporally graded retrograde amnesia, patients with hippocampal damage reported stereotyped dreams of remote memory but were unable to dream of recent experiences (Torda, 1969a, b). In contrast, Stickgold, Malia, Maguire, Roddenberry, and O'Connor (2000) found that during the first few minutes after sleep onset, amnesiacs reported imagery related to an experimental learning task at rates similar to control subjects. A specific goal of the present study was therefore to clarify the role of the hippocampus in generating sleep mentation related to recent memories.

In the present study, we used a "trace conditioning" protocol to induce expression of hippocampus-dependent memory during human NREM sleep, while observing the effect of this cued memory retrieval on reports of dreaming. Trace conditioning has recently emerged as a well-characterized, simple model of hippocampus-dependent memory (Clark, Manns, & Squire, 2002). In contrast, classical "delay" fear conditioning relies primarily on amygdala and brainstem circuitry (Maren, 2001), without requiring hippocampal contributions (Gabrieli et al., 1995; Kotani, Kawahara, & Kirino, 2002; McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; McEchron, Tseng, & Disterhoft, 2000). In a standard delay fear conditioning protocol, an initially neutral "conditioned stimulus" (the CS) predicts the immediately subsequent occurrence of an aversive "unconditioned stimulus" (the UCS). Repeated pairings of the CS and UCS eventually lead an organism to exhibit fear even when the CS is presented alone, without the aversive UCS. Trace conditioning is unique in that a temporal gap between the offset of the CS and onset of the UCS (the "trace interval", see Fig. 1) renders the hippocampal complex necessary for both learning and retrieval of trace associations. Lesion studies in animals unequivocally demonstrate that an intact hippocampus is critical for the both the *acquisition* (Burman, Starr, & Gewirtz, 2006; Chowdhury, Quinn, & Fanselow, 2005; Fendt, Fanselow, & Koch, 2005) *and the retrieval* (Burman et al., 2006; Trivedi & Coover, 2006) of trace fear conditioning. Although the acquisition and retrieval of delay conditioning may also be accompanied by increases in hippocampal activation (Cheng, Disterhoft, Power, Ellis, & Desmond, 2008), the important distinction for the purposes of this study is that only trace conditioning *requires* hippocampal contributions for acquisition and retrieval. Supporting this work, human studies show that amnesiacs with bilateral hippocampal damage are impaired in acquiring trace, but not delay conditioning (McGlinchey-Berroth, Carrillo, Gabrieli, Brawn, & Disterhoft, 1997), and that hippocampal activity consistently occurs during trace fear conditioning imaging protocols (Buchel, Dolan, Armony, & Friston, 1999; Knight, Cheng, Smith, Stein, & Helmstetter, 2004). Taken

together, this literature strongly suggests that expression of trace-conditioned, but not delay-conditioned, responses critically relies on recruitment of the hippocampal complex – while both forms of conditioning can be incidentally *accompanied by* hippocampal activity, only trace conditioning *requires* the contribution of the hippocampal memory system. Recent animal studies suggest that hippocampal dependence in fear conditioning is maximal when longer trace intervals (i.e., of at least 5 s) are employed (Chowdhury et al., 2005; Misane et al., 2005).

Several prior experiments have demonstrated that delay-conditioned responses can be expressed when a CS cue is presented during sleep (Beh & Barratt, 1965; Conduit & Coleman, 1998; Hennevin & Maho, 2005; Ikeda & Morotomi, 1997). In the present study, we examined the retrieval of trace conditioning during NREM sleep, and its effects on sleep mentation. Subjects were trained prior to sleep on either a *trace-conditioning* (hippocampus-dependent) or *delay conditioning* (hippocampus-independent) protocol. Fear-conditioned cues were later administered to sleeping subjects during stage 2 NREM. As previously observed, participants successfully exhibited delay-conditioned responses in sleep. Our data demonstrate that trace-conditioned responses were also successfully induced during NREM sleep, providing behavioral evidence that the hippocampal memory system is functional during this sleep stage. Furthermore, cued retrieval of hippocampus-dependent fear memory affected the emotional valence of concomitant subjective experience, suggesting that hippocampal activity contributes to the construction of mentation during human sleep.

2. Methods

Participants (*n* = 43, 17 male and 26 female) were healthy undergraduate students from The City College of New York, recruited from psychology courses. By self-report, all subjects were free of mental disorders, sleep disorders, and sleep-altering medication. Participants underwent discriminatory auditory fear conditioning prior to sleep, under either a delay conditioning or a trace conditioning protocol (Fig. 1). Expression of conditioned responses under these paradigms was then assessed by presenting auditory conditioned stimuli during stage 2 NREM sleep. This was a 2(Conditioning Type: trace vs. delay) × 2(Cue Type: Conditioned Stimulus/CS+ vs. Control Cue/CS−) mixed factorial design. Six participants were excluded from final analyses due to technical difficulties, including failure to maintain a sufficient amount of sleep, technical problems with the conditioning procedure, or the emergence of REM sleep during stimulus presentation. The final sample for analysis consisted of *n* = 18 trace-conditioned participants and *n* = 19 delay-conditioned participants.
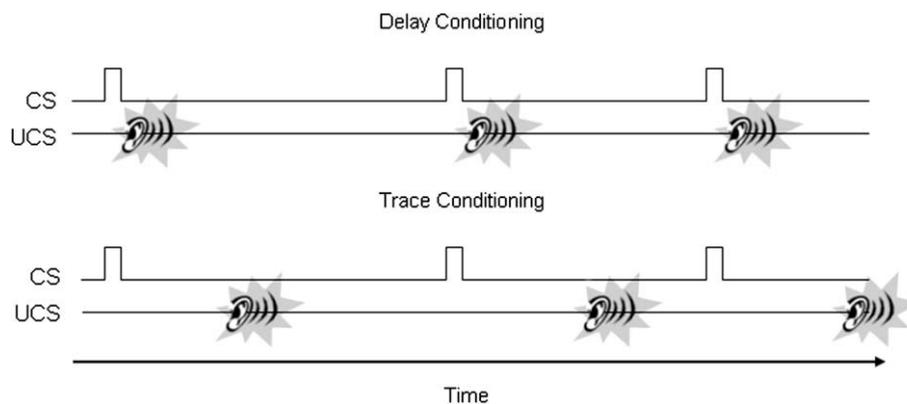

Fig. 1. In delay conditioning (top) the UCS is initiated immediately at the offset of the CS. In trace conditioning (bottom), a trace interval is present between the offset of the CS and the onset of the UCS. In the present study, a 15 s "trace interval" between CS offset and UCS onset was employed.

2.1. Pre-sleep procedures

Upon arriving at the laboratory at 9:30 pm, participants were familiarized with the facilities and signed informed consent. Polysomnographic variables were measured using a standard EEG (C3-A2, C4-A1), EOG, EMG, and EKG montage. Signals were acquired using Grass Model 7 amplifiers and digitally converted using Grass-Telefactor's *Gamma* software. Thirty minutes prior to an experimental bedtime of 12:00 am, participants were trained using either:

1. A *trace conditioning* paradigm in which a neutral auditory stimulus predicted the subsequent occurrence of a startling sound, following a 15 s interval of silence.
2. A *delay conditioning* paradigm in which a neutral auditory stimulus predicted the subsequent occurrence of a startling sound that initiated exactly at the offset of the CS.

During conditioning, subjects lay in a sound-attenuated bedroom. The unconditioned stimulus (UCS) was the sound of a car horn (100 dB, duration = 1 s), which always followed presentation of the conditioned stimulus (CS+). Participants were also intermittently exposed to a control stimulus (CS−), which was equal in intensity and duration to the CS+, but which was never paired with the UCS. The CS+ and CS− were 200 Hz pulsed and 1200 Hz pure tones, each 1 s in duration, with tone assignment as the CS+ or CS− counterbalanced across subjects. Prior to conditioning, each stimulus (UCS, CS+, and CS−) was played twice in an unpaired fashion, in order to habituate participants to the sounds. Subjects were then asked to lie without moving and attend to the sounds, being instructed that they would be hearing two "*quieter sounds*" and one "*loud sound*" and should notice that the loud sound "*will always follow one of the quieter sounds, and will never come after the other quieter sound*". All participants were therefore explicitly informed that stimulus contingencies would be present, and all participants were given identical instructions, regardless of experimental condition. These explicit instructions were given in order to ensure that all subjects were equivalent in their awareness of stimulus contingencies at learning, a factor which may substantially impact the acquisition of trace conditioning tasks (Clark et al., 2002). It is possible that these instructions could have strengthened a declarative component of learning in both subject groups. But presumably, the acquisition of both forms of conditioning necessarily engages declarative memory systems, regardless of instructions, inasmuch as any experience results in the formation of an episodic memory.

A total of 10 CS+ and 10 CS− presentations were administered (see Supplementary material for further detail). For delay-conditioned participants, the UCS was always administered immediately at the offset of CS+ tones. For trace-conditioned participants, the UCS always initiated exactly 15 s after termination of CS+ tones. As described above, a substantial body of research supports the critical presumption that trace-conditioned (but not delay-conditioned) responses *require* hippocampal processes for retrieval. A relatively long trace interval of 15 s was employed in light of evidence that hippocampal dependence in trace fear conditioning may not emerge until longer intervals are used, relative to the short intervals often studied in trace eye blink conditioning (Chowdhury et al., 2005; Misane et al., 2005). In addition, hippocampal activation at retrieval decreases as subjects are exposed to larger numbers of trials, which tempered the decision in the present study to limit pre-sleep training to 10 pairings of the CS+ and UCS (Buchel et al., 1999). Following acquisition, a single probe trial was administered in which one presentation of the CS+ and one presentation of the CS− occurred without subsequent exposure to the UCS. Heart rate and EEG data were acquired throughout conditioning.

Table 1
Time since sleep onset by cue type and conditioning type.

	Time of stimulus delivery (min. since sleep onset)	p-value
Cue type		
CS − trials	209 ± 14	>.8
CS + trials	214 ± 14	
Conditioning type		
Delay participants	203 ± 14	>.9
Trace participants	219 ± 14	

Note: Minutes since sleep onset ±SEM.

2.2. Procedures during sleep

Subjects were put to bed 30 min following conditioning. During the night, CS+ and CS− tones were played over a speaker mounted above the bed in participants' rooms. Two CS+ and two CS− trials were conducted for each subject (a total of four stimulus presentations during the night), with order of cue type presentation counterbalanced across subjects. Mean time since sleep onset for CS+ and CS− trials was nearly equivalent (Table 1). Nocturnal stimulus delivery always began after at least 10 continuous minutes of stage 2 NREM sleep, at least 15 min from the last epoch of REM or wakefulness, and at least 20 min following initial sleep onset. In order to control for known individual differences and time of night effects on arousal and response thresholds, for each trial up to seven increasing stimulus intensity levels were administered. At each data collection point, tones were presented every 25 s, beginning at sub-threshold intensities, and increasing in 5 dB increments until a stimulus elicited >5 s of waking-frequency EEG (alpha or beta), at which point stimulus presentation was terminated. Thus, on each individual trial (CS+ or CS−), a *maximum* of seven tone intensities were presented. This ramping procedure was critical in order to control for variable response thresholds. It was not possible to determine a set stimulus intensity for each individual prior to the experimental night, because response and arousal thresholds also vary dramatically across the night, on a trial-by-trial basis. Heart rate and EEG responses were recorded throughout this procedure.

Following the presentation of the final stimulus, subjects were contacted by calling their name over a speaker once per second until they responded. Participants were then asked to verbally respond to two pre-recorded questions:

1. "Please tell me everything that was going through your mind just before I called."
2. "Do you recall hearing any sounds just before I called you? If so, please describe those sounds."

In cases where a participant was unable to recall any mentation in response to *question 1*, they were further asked, "*do you believe that you were having thoughts and/or imagery which you cannot remember?*" In agreement with prior research on NREM dream recall (Nielsen, 2000), participants provided verbal reports of sleep mentation on 44% of trials in response to *question 1*, and were unable to recall mentation during the remaining 56% of trials. In 100% of cases where recall was vague or inaccessible, participants responded in the affirmative that they believed there had been thoughts or imagery running through their mind which they were unable to access.

Participants also completed a visual analog scale (VAS) on which they rated their subjective emotional valence just prior to awakening. Poles of the VAS ranged from *intensely negative* emotion to *intensely positive* emotion, with the center of the scale indicating that emotion was neutral or absent. By placing an "x" at the

appropriate point on the line, subjects indicated how they felt *"just before I was awakened and asked to give my report"*.

2.3. Data analyses

2.3.1. EEG responses

EEG responses were scored by two experienced polysomnographic technicians, blind to experimental condition and to the specific hypotheses of the study. Each sleep record was scored for the presence of K-complexes and brief arousals evoked in response to experimental stimuli (CS+ and CS− cues). A "brief arousal" was defined as the intrusion of ⩽5 s of waking-frequency EEG (alpha or beta) into the sleep record, followed by an immediate return to theta-frequency EEG. The "awakening threshold" was defined as the stimulus intensity level (1–7) first inducing >5 s of waking EEG. Stimulus-induced K-complexes were evaluated at the stimulus intensity level *just prior to that which induced the first signs of EEG arousal*. Evoked arousals and K-complexes were scored only if they began within 2 s of stimulus onset. Subjects were classified as having awakened in response to a stimulus if >5 s of waking-frequency EEG appeared in the record following stimulus presentation, regardless of whether the subject returned to sleep immediately thereafter (which was often the case). Inter-rater reliability for determining the stimulus level inducing awakening was .95. Percentage agreement for determining the presence of *brief arousals* and *sub-arousal K-complexes* was 77.5% and 86.9%, respec-

tively. The presence of a given EEG event was scored only in cases where both raters were in agreement.

2.3.2. Heart rate responses

Evoked HR responses to the greatest stimulus intensity level prior to that which (a) caused awakening and (b) caused the first arousal were derived by calculating the *R-R* interval for each individual beat of the first 20 post-stimulus beats, on each trial. Heart rate responses are plotted (Fig. 2) on a beat-by-beat basis as change in beats per minute (BPM) from baseline (defined as mean BPM of the last 5 pre-stimulus beats). Based on previous research, conditioned responses were expected occur within the timeframe of the acceleratory auditory evoked HR component, peaking approximately during post-stimulus beats 4–6 (Maschke et al., 2002).

2.3.3. Mentation reports

Verbal reports of sleep mentation were transcribed prior to being scored by two blind raters. Amount of content reported was assessed using word information count (WIC), a modified word count measure which ignores non-words, repetitions, and all other words not providing new information about the sleep mentation (Antrobus, 1983; Wamsley, Hirota, Tucker, Smith, & Antrobus, 2007). Inter-rater reliability for WIC was .97. For each report, raters also assessed the presence of content related to the experimental procedures in each of the following categories (raters
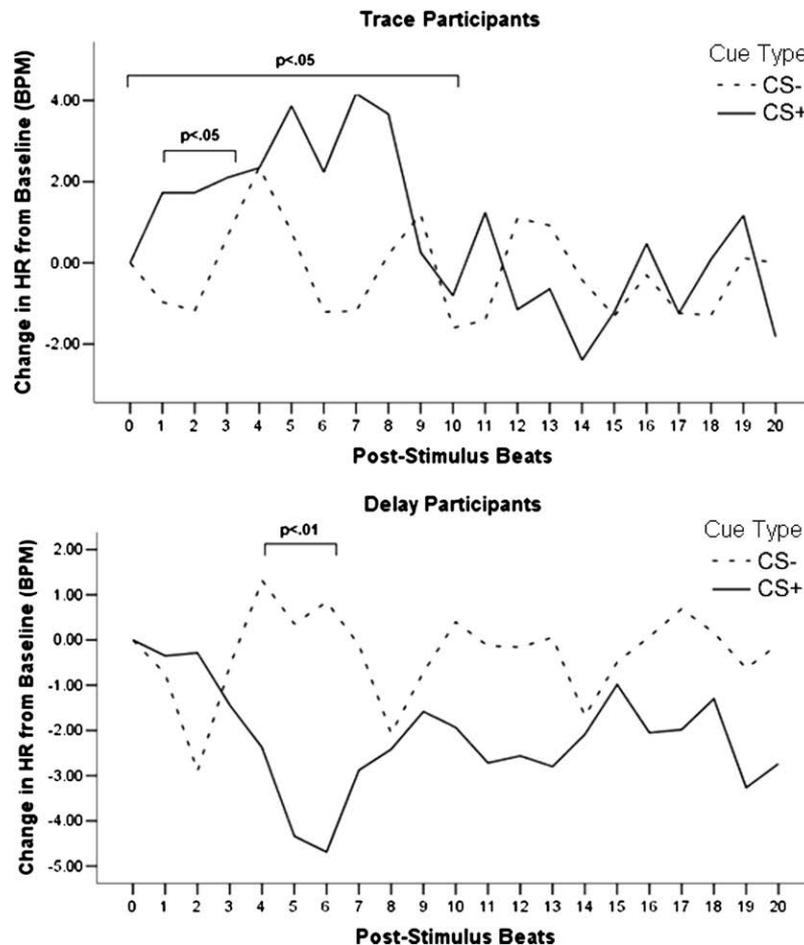

Fig. 2. Heart rate responses to the CS+ and CS− during the waking probe trial. HR is plotted as change in BPM from baseline values across the first 20 post-stimulus beats. In trace-conditioned participants (top) the conditioned HR response consisted of an extended acceleration from beats 1 to 10 ($t_{18} = 2.14$, $p < .05$), whereas delay-conditioned participants exhibited a conditioned deceleration maximal during beats 4–6 ($t_{18} = 2.99$, $p < .01$).

agreed on these determinations in 97.3% of cases, see Supplementary material for details):

(a) content directly related to the laboratory setting;
(b) specific mention of hearing a sound in the dream;
(c) specific mention of a car.

2.3.4. Statistical analyses

Primary tests of significance were conducted in the context of a 2(cue type: CS+ vs. CS−) × 2 (conditioning type: trace vs. delay) mixed ANOVA model, followed by planned pairwise comparisons. Where appropriate, t-tests and Pearson's correlations were also applied.

3. Results

3.1. Conditioned responses during pre-sleep wakefulness

Both delay-conditioned and trace-conditioned participants demonstrated fear-conditioned responses prior to sleep. Consistent with previous research (Maschke et al., 2002), in delay-conditioned subjects the CR consisted of a heart rate (HR) deceleration, maximal during post-stimulus beats 4–6 (Fig. 2). Deceleration in response to the CS+ was significantly greater than to the CS− control cue during this timeframe ($t_{18} = 2.99$, $p < .01$ for post-stimulus beats 4–6; Fig. 2). In trace-conditioned subjects the conditioned HR response consisted of an immediate and long-lasting acceleration evoked by the CS+, persisting throughout the first 10 post-stimulus beats ($t_{18} = 2.14$, $p < .05$ for post-stimulus beats 1–10; Fig. 2).

3.2. Conditioned responses during sleep

3.2.1. EEG responses

Both delay-conditioned and trace-conditioned participants exhibited conditioned EEG responses during stage 2 sleep. Overall, subjects were more likely to exhibit brief arousals in response to the CS+, as opposed to the control cue (main effect of cue type: $F_{1,35} = 6.21$, $p = .02$, $\eta_p^2 = .15$; Fig. 3). There was no interaction between cue type (CS+ vs. CS−) and type of conditioning ($p > .3$), and no main effect of conditioning type ($p > .7$). Post-hoc paired comparisons (Fisher's LSD) indicated that the CS+ vs. CS− comparison was significant for brief arousals in the delay-conditioned group ($p = .03$), but fell short of statistical significance in trace-conditioned subjects ($p = .2$). In contrast, trace ($t_{17} = 2.13$, $p = .05$), but not delay ($t_{18} = 1.07$, $p = .30$) participants were more likely to exhibit K-complexes in response to the CS+ vs. the CS- cue, at stimulus intensities prior to the appearance of any EEG arousal (cue type x conditioning type interaction for K-complexes: $F_{1,35} = 4.11$, $p < .05$, $\eta_p^2 = .15$; Fig. 4). There was also a near-significant trend for evoked K-complex responses to be generally more common in delay-conditioned subjects, independent of cue type (main effect of cue type: $F_{1,35} = 3.49$, $p = .07$; Fig. 4).

3.2.2. Heart rate responses

Though evoked HR responses were observed during sleep, conditioned responses were not clearly evident in this measure. Delay-conditioned participants did show a near-significant conditioned HR acceleration at the stimulus level just below that which induced awakening, during the early declaratory component of the evoked HR response (post-stimulus beats 1–3; $t_{18} = 1.78$, $p = .09$). This observation, in which CRs during sleep were acceleratory, contrasting with a deceleratory CR in prior wakefulness, is consistent with prior research (Ikeda & Morotomi, 1997). However, no other effects of cue type (CS+ vs. CS−) on HR components approached significance in either conditioning group ($p > .1$ for all t-tests).
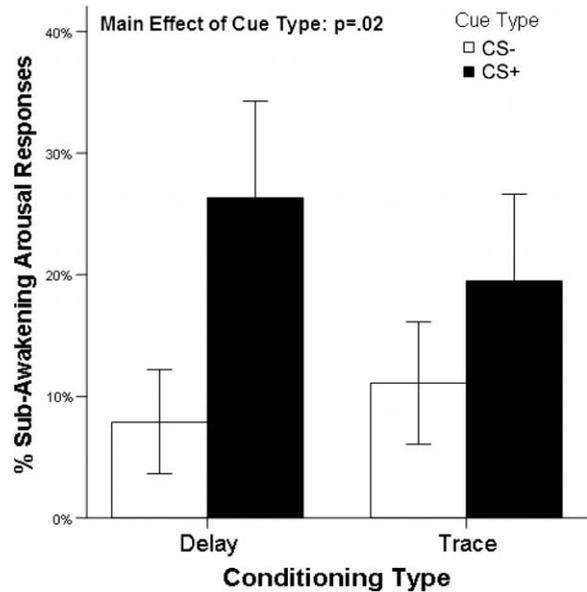

Fig. 3. Sub-awakening arousals occurred more often in response to the CS+ than to the CS− in both trace-conditioned and delay-conditioned participants (main effect of cue type: $F_{1,35} = 6.21$, $p = .02$, $\eta_p^2 = .15$). Error bars represent ±SEM.
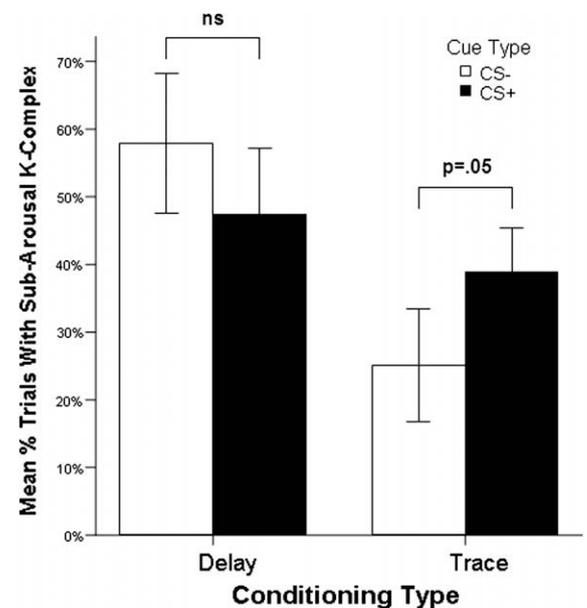

Fig. 4. In the trace-conditioned group only, K-complexes were more likely to occur in response to the CS+ than to the control cue, prior to any sign of EEG arousal ($t_{17} = 2.13$, $p = .05$). Error bars represent ±SEM.

Large variability in sleep HR responses may have obscured the ability of the present study to detect conditioned responses for this measure.

3.2.3. Awakening thresholds

The stimulus intensity which first induced awakening was similar for CS+ and CS− cues ($p > .2$ for main effect of cue in a 2(cue type) × 2 (conditioning type) mixed ANOVA), and similar for trace-conditioned and delay-conditioned participants ($p > .5$ for main effect of condition, no cue × conditioning type interaction). As anticipated, awakening thresholds varied substantially according to time of night, with thresholds for later trials being signifi-

cantly lower than for initial trials (threshold for 1st pair of trials = 5.33 ± 1.71SD, for 2nd pair of trials = 4.17, ±1.78SD; t_{54} = 2.13, $p < .001$). Awakening thresholds were negatively correlated with minutes since sleep onset on a per-trial basis ($r_{128} = -.27$, $p < .01$).

3.3. Conditioned cognitive responses in sleep

3.3.1. Emotional valence

Fear-conditioned cues affected the emotional characteristics of sleep mentation. Subjects rated their dreamed emotions as generally positive overall, but emotions were more negative on CS+ trials, relative to control trials (main effect of cue type: $F_{1,35}$ = 4.64, $p < .05$, $\eta_p^2 = .12$). Here, there was no effect of conditioning type, and no cue type × conditioning type interaction.

Further analyses revealed that the effect of the CS+ cue on dreamed emotion was expressed selectively in trace-conditioned subjects, and primarily during the first pair of trials, conducted earlier in the night. Overall, emotional valence ratings became more positive across the night, as a function of time since sleep onset ($r = .18$, $p < .05$). On the first set of trials during the night, cued retrieval of conditioning impacted dream emotions selectively in the trace-conditioned group (conditioning type x cue type interaction: $F_{1,34}$ = 4.25, $p < .05$, $\eta_p^2 = .11$; Fig. 5). The CS+ elicited relatively more negative emotion than the CS−, for trace participants (t_{17} = 2.67, $p < .05$; Fig. 5), but not for delay participants ($p > .7$; Fig. 5). On early trials, the CS+ also elicited relatively more negatively toned emotion ratings than the control cue overall (main effect of cue type: $F_{1,34}$ = 5.90, $p < .05$, $\eta_p^2 = .15$; Fig. 5). Later in the night, when the 2nd pair of trials was conducted, conditioned stimulus cues did not affect emotion in either trace-conditioned or delay-conditioned subjects ($p \geqslant .4$ for effects of cue type,

Table 2
Recall of experimental stimuli by conditioning type and cue type.

	% Sound recall
Delay conditioning	
CS−	34.2
CS+	31.6
Trace conditioning	
CS−	36.1
CS+	41.7

Note: Mean % of trials on which subjects recalled the experimental stimuli.

conditioning type, and interaction; Fig. 5). The other conditioned responses described above (i.e., K-complexes, arousals) did not vary as a function of time of night.

3.3.2. Word information count (WIC)

Mean WIC across all verbal reports was 18.6 (±11.9SD). There was no effect of cue type or conditioning type on WIC, as well as no cue × conditioning type interaction. There was also no effect of either cue or conditioning type on whether any mentation at all was reported for a particular trial. Neither WIC nor the frequency of mentation recall varied significantly as a function of time of night.

3.3.3. Recall of experimental stimuli

Though stimulus delivery frequently resulted in brief EEG arousal, subjects were largely unaware that any sounds had been presented, reporting hearing tones on only 37.7% of trials. Neither cue type nor conditioning type influenced the proportion of trials on which subjects recalled hearing tones ($p > .5$ for cue and conditioning type ANOVA main effects, and interaction; Table 2). Whether or not subjects reported hearing the stimulus on a particular trial did not influence emotion ratings (t_{125} = 1.31, $p = .2$) or whether mentation was recalled on that trial (χ_1 = 1.11, $p = .3$), arguing against the influence of demand characteristics. Furthermore, the same pattern of results as described above for emotional valence ratings is observed when the 37% of trials on which tones were heard are removed from analysis.

3.3.4. Relation of sleep mentation to experimental procedures

As expected (see Section 4), reports only infrequently incorporated content potentially related to the experimental procedures. Overall, only 5% of 130 mentation reports explicitly mentioned sounds, 3% explicitly mentioned cars, and 2% included direct mention of the laboratory context (Table 3). The low instance of these content elements precludes drawing meaningful conclusions regarding their distribution across condition, as expected cell counts are too low to support a valid approximation of the Chi-Square statistic. There were no apparent differences (in emotional valence ratings, EEG responses, or HR responses) between participants who did and participants who did not report this potentially task-related mentation. However, note that the small number of

Fig. 5. Emotional valence in trace-conditioned and delay-conditioned participants during the 1st and 2nd trials of the night. Emotional Valence was significantly more negative in response to the CS+ as compared to the CS− only in trace-conditioned participants, and only early in the night (t_{17} = 2.67, $p < .05$). Error bars represent ±SEM.

Table 3
Content potentially related to the experimental procedures.

	Sound	Laboratory context	Car
Delay conditioning			
CS−	2	0	1
CS+	2	1	1
Trace conditioning			
CS−	2	0	1
CS+	1	2	1

Note: Raw number of reports containing content in each of three predefined categories according to conditioning type (trace vs. delay) and cue type (CS− vs. CS+).
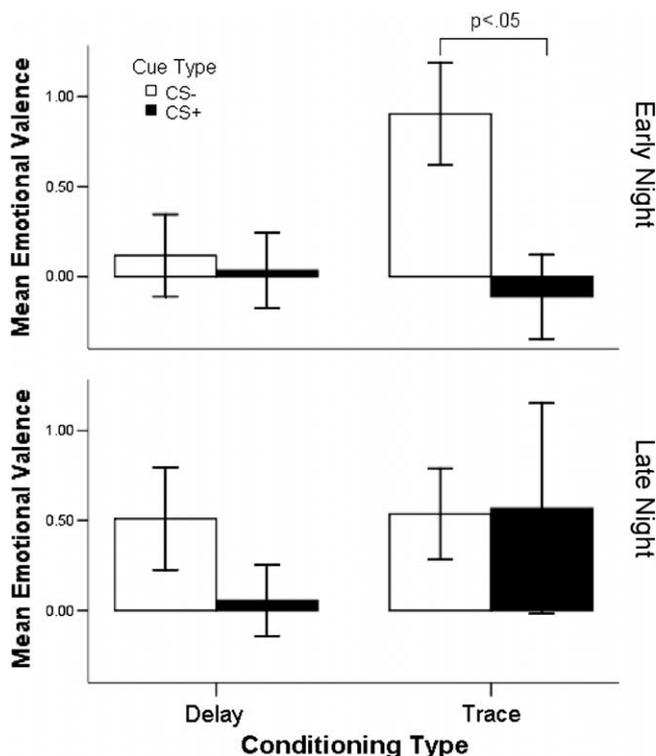
subjects with such reports prohibits a well-powered test of these hypotheses.

4. Discussion

The present study adds to a growing body of literature in support of the hypothesis that hippocampus-dependent learning can be reactivated and expressed during human sleep (Peigneux et al., 2004; Rasch, Buchel, Gais, & Born, 2007). Here, hippocampus-dependent learning was expressed in the form of trace-conditioned responses to auditory cues in NREM sleep. As hypothesized, the retrieval of hippocampus-dependent conditioning also affected the emotional quality of sleep mentation. These observations, though preliminary, suggest that the hippocampal memory system is functional during NREM sleep, and that the hippocampus participates in constructing dream experiences during this sleep stage.

Confirming the findings of several previous studies (Beh & Barratt, 1965; Conduit & Coleman, 1998; Hennevin & Maho, 2005), delay-conditioned responses established during wakefulness were again expressed during sleep. This was most clearly observed in a tendency for subjects to exhibit more brief (<5 s) arousals in response to the conditioned stimulus, as compared to the control cue. Although a delay-conditioned HR response during sleep fell short of significance, the observed response pattern, in which the CR during wakefulness consisted of an HR deceleration, while CRs in sleep were conversely acceleratory, is consistent with the results of a single previous study examining delay-conditioned HR responses in sleep (Ikeda & Morotomi, 1997).

We also report the novel observation that *trace-conditioned subjects* exhibited conditioned responses in NREM sleep. As discussed above, while delay-conditioned cues could have also induced hippocampal activation, only the expression of trace conditioning is known to *require* hippocampal contributions. The observation of trace-conditioned responses in NREM sleep therefore provides evidence that hippocampus-*dependent* learning is accessible during this sleep stage. For trace conditioning, physiological CRs were most clearly expressed through a tendency to exhibit more K-complexes in response to the CS+, as compared to the control cue. Trace-conditioned participants also exhibited a trend towards expressing more brief arousals following the CS+, as compared to the control cue. K-complex responses were obtained at stimulus intensities prior to the emergence of any EEG arousal, mitigating concerns that this physiological expression of trace conditioning might be contaminated by the presence of brief wakefulness. To our knowledge, there is only one prior study which may have demonstrated conditioned responses during NREM sleep following training with a trace interval (McDonald, Schicht, Frazier, Shallenberger, & Edwards, 1975). However, due to the use of a short trace interval and a large number of conditioning trials, relative to the present study (see Section 2), it cannot be said with confidence that the responses observed by McDonald et al.(1975) were hippocampus-dependent. In contrast, the training parameters employed here were specifically designed to ensure hippocampal dependence of trace-conditioned responses (see Section 2).

That only trace-conditioned participants exhibited conditioned K-complex responses is likely a result the increased involvement of hippocampal and cortical structures in trace, as compared to delay conditioning. Like trace conditioning, evoked K-complexes have also been associated with higher-level declarative memory processing, occurring preferentially in response to personally meaningful semantic information (Perrin, Garcia-Larrea, Mauguiere, & Bastuji, 1999).

The expression of trace fear conditioning during NREM sleep was also observed in the emotional valence of subjects' sleep mentation, early in the night. Again, this conditioning-dependent effect on sleep mentation within the trace group almost certainly relied

on hippocampus-mediated memory retrieval, suggesting that hippocampal output plays a role in constructing at least some features of dreaming during NREM sleep. Conversely, in delay-conditioned subjects, where the cortex and hippocampus were not necessary for retrieval, fear-conditioned cues apparently had no effect on the emotional quality of dreaming. Note that, based on prior research, we hypothesized *a priori* that these conditioning effects would be more clearly evident within emotional valence ratings, rather than within the "content" of dreams per se. Reports of subjective experience recalled from sleep are notoriously subject to rapid forgetting, and experimental awakenings likely yield description of only a fraction of the mentation occurring within a sleep interval of interest. Verbal dream reports therefore provide an insensitive measure of sleep mentation (albeit the best measure available). Historically, it has been difficult to experimentally manipulate the content of dreams using stimuli presented prior to sleep (Arkin & Antrobus, 1991). In those cases where methodologically sound research has manipulated dreaming, this has almost always taken the form of effects on *qualitative dream features,* such as affect or vividness, rather than on the specific content of dreams (Corsi-Cabrera et al., 1986; De Koninck & Brunette, 1991; Foulkes & Rechtschaffen, 1964; Hartmann, 2003).

Interestingly, the observed emotional valence effect could be interpreted as the result of an increased *positive* response to the control cue (CS−) in trace-conditioned subjects, rather than increased *negative* affect following the CS+ (Fig. 5). The present design is unable to distinguish between these two alternatives, thus prohibiting definitive conclusions about the potential role of *negative emotion*, in particular, in memory retrieval and/or dreaming processes. Though a matter of speculation, it is possible that this pattern of results was induced by a conditioned positive association with the "safe" CS− control cue in trace group. However, the critical observation remains that trace-conditioned participants exhibited a *different* emotional response following the CS+, which *relative to the control cue*, was more negative. Again, as the characteristics of CS+ and CS− trials were otherwise exactly matched, this cue type effect on emotional valence must be attributed to the expression of trace conditioning within the content of subjective experience.

Conditioned responses during sleep were thus observed both within sleep-specific electrophysiological responses and within the affect of dream experiences. Unfortunately, because HR conditioned responses did not reach significance during sleep for either the delay-conditioned or trace-conditioned groups, these CRs cannot be directly compared with those observed during pre-sleep conditioning. It therefore cannot be determined whether the expression of conditioned responses during NREM sleep might differ from the expression of CRs during acquisition.

In the present study, fear conditioning may have been particularly effective at manipulating dreamed emotion, not only because of the engagement of the hippocampal complex in trace-conditioned subjects, but also due to the role of the amygdala in processing emotionally salient stimulus relations. It has long been proposed that emotionally charged stimuli have a particularly strong effect on sleep mentation (Carpenter, 1988; Cartwright, Bernick, Borowitz, & Kling, 1969; De Koninck & Brunette, 1991; Goodenough, Witkin, Koulack, & Cohen, 1975; Witkin & Lewis, 1967). Meanwhile, more recent data suggest that emotional (as opposed to neutral) memories are preferentially processed during post-learning sleep (Hu, Stylos-Allan, & Walker, 2006; Payne, Stickgold, Swanberg, & Kensinger, 2008; Wagner, Gais, & Born, 2001). The amygdala and medial prefrontal cortices may play a role in "selecting" information with strong motivational and emotional relevance for processing during sleep, resulting in the emotionally charged content characteristic of vivid dream experiences. However, as the expression of delay conditioning also relies on amyg-

dala circuits, activation of this emotion-related structure was clearly not adequate to influence the experience of emotion during sleep in the present study. The selective impact of *trace* conditioning on dream reports suggests the possibility that the hippocampal complex is a necessary component of the neural network supporting subjective experience during sleep.

Conditioned responses expressed in the emotional valence of mentation reports were dependent on time of night (Fig. 5). A number of physiological variables likely differed between the first and second set of trials, including core body temperature (Czeisler et al., 1990; Wright, Hull, & Czeisler, 2002), cortisol levels (Uchiyama et al., 1998), slow wave activity (Borbely, Baumann, Brandeis, Strauch, & Lehmann, 1981), REM sleep propensity (Czeisler, Zimmerman, Ronda, Moore-Ede, & Weitzman, 1980; Wurts & Edgar, 2000), and the organization of recently acquired memory traces, as consolidation of memory is presumed to be proceeding across the night (Maquet, 2001; Plihal & Born, 1997; Walker & Stickgold, 2004). Changes in one or more of these variables across the night may have attenuated expression of conditioned responses within this cognitive variable. In addition, habituation of heart rate responses and extinction of various conditioned responses can occur during NREM sleep, though these processes might require a larger number of stimulus presentations than the present study employed (Coenen & Drinkenburg, 2002; McDonald & Carpenter, 1975). Other literature suggests that sleep and/or dreaming might directly facilitate the processing of emotional memories across the course of a night (Cartwright, Luten, Young, Mercer, & Bears, 1998; Wagner et al., 2001) – in the present study it is conceivable that intervening sleep could have altered conditioning-dependent memory traces in a way which lessened emotional reactivity to the trace-conditioned CS+ cue later in the night.

Here, we exclusively focused on memory retrieval during NREM sleep. Given the established role of NREM in processing recent declarative memories (Plihal & Born, 1997; Tucker et al., 2006), combined with the relatively well-defined physiological models of how consolidation might take place during NREM (Buzsaki, 1996; Eschenko, Molle, Born, & Sara, 2006; Eschenko, Ramadan, Molle, Born, & Sara, 2008; Hasselmo, 1999), it seemed that hippocampus-dependent memory processing would most likely be expressed in NREM, rather than REM sleep. Additionally, hippocampal output to the cortex could be attenuated during REM as a result of elevated acetylcholine levels (Hasselmo, 1999), which might prohibit the expression of trace conditioning in this sleep stage. Future studies using trace conditioning may be able to clarify the functionality of hippocampal memory systems during REM sleep. Furthermore, here we did not address the question of whether cued retrieval of trace and/or delay conditioning might also influence the magnitude of conditioned responses on the following day – this may also be a fruitful avenue for future research.

In summary, we examined the expression of hippocampus-dependent trace conditioning during stage 2 NREM sleep. Sleeping subjects expressed trace-conditioned responses, confirming that the hippocampal memory system is functional during NREM sleep. Furthermore, trace fear-conditioned cues affected dreamed emotions, suggesting that the hippocampus contributes to subjective experience during sleep. These data suggest the possibility that spontaneous reactivation of memory networks during sleep, a process thought to support the consolidation of declarative memory (Buzsaki, 1996; McClelland, McNaughton, & O'Reilly, 1995), may also be expressed within NREM mentation. Reports of subjective experience during sleep may provide a valuable methodology for observing sleep-dependent memory reactivation on the cognitive level, helping to elucidate the algorithms determining *which* memories are reactivated and consolidated in the sleeping brain, and how recent experiences are slowly integrated into existing neocortical memory networks.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.nlm.2009.02.012.

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