THE COGNITIVE NEUROSCIENCE OF COGNITION IN SLEEP: CHRONOBIOLOGICAL FEATURES AND HIPPOCAMPAL MEMORY SOURCES

by

ERIN J. WAMSLEY

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy

The City University of New York

2007

UMI Number: 3245049

UMI Microform 3245049

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

This manuscript has been read and accepted for the
Graduate Faculty in Psychology in satisfaction of the
dissertation requirement for the degree of Doctor of Philosophy.

	John S. Antrobus
12/15/2006	
Date	Chair of Examining Committee
	Joseph Glick
12/15/2006	
Date	Executive Officer

Arthur Spielman

John J. Foxe

Robert Melara

Jessica Payne

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

THE COGNITIVE NEUROSCIENCE OF COGNITION IN SLEEP:
CHRONOBIOLOGICAL FEATURES AND HIPPOCAMPAL MEMORY SOURCES

by

Erin J. Wamsley

Adviser: Professor John S. Antrobus

Empirical work on the neural basis of mental activity in sleep has focused largely on describing and explaining differences between mentation reported from REM, as opposed to NREM sleep, an approach too often accompanied by the presumption that mechanisms specific to REM sleep constitute a complete model of the dreaming process. Yet such models have both failed to account for cognition outside of REM and to provide a detailed explanation of the mechanisms by which physiology in any sleep stage constructs the content of mentation.

In order to explore factors other than the REM/NREM cycle contributing to the production of mentation, we assessed the contribution of circadian and homeostatic factors to within-stage changes in sleep mentation across the diurnal cycle. *Study 1* examines dreaming across the night in both REM and NREM, finding that time of night modulates the reporting of mentation at least as strongly as the ultradian sleep cycle, though some dream features change across the night selectively in REM. A follow-up study examines the characteristics of NREM mentation during daytime naps, in order to address the possibility that homeostatic-based changes in propensity for slow wave activity, rather than exclusively endogenously-driven circadian factors, contributed to the

large time of night effect we report in *Study 1*. Overall, it is concluded that a purely circadian influence following the core body temperature cycle is inadequate to explain diurnal variations in mental activity during sleep. Two alternative neurobiological accounts are discussed.

The third study described here assesses the functioning of hippocampally-dependent declarative memory retrieval during NREM sleep and its role in generating sleep mentation. Evidence that neural "replay" of memories during NREM facilitates memory consolidation has naturally prompted speculation that NREM mentation may represent a cognitive component of sleep-dependent consolidation, but this assumption has thus far remained untested. *Study 3* examines the expression of hippocampally-dependent "trace" conditioning during NREM and its relation to dream content. These findings confirm that recent declarative learning can be accessed during NREM, and furthermore suggest that hippocampally-mediated reactivation of declarative-type memory directly influences qualitative characteristics of ongoing sleep mentation.

Acknowledgements

Special thanks to John Antrobus, Matthew Tucker, Yasutaka Hirota, and Mark Smith, who each played critical roles in the completion of the work described here. Also thanks to Sara Alger, Jason Birnbaum, Richard Flynn, Hiuyan Lau, Joshua Nelson and Gary Winkel for assistance in data collection, data scoring, and/or analysis.

Table of Contents

List of Tables

List of Figures

I.

Introduction: Cognition and Information Processing in NREM Sleep

Scientific interest in a neurobiological explanation of dreaming began with the discovery of REM (rapid eye movement) sleep (Aserinsky & Kleitman, 1953). The subsequent revelation that this sleep stage, characterized by waking-like desynchronized EEG activity, was strongly associated with reports of vivid dream experiences (Dement & Kleitman, 1957a) led to hopes that merely describing the neurophysiology of REM sleep would provide an eventual explanation of dreaming (Hobson & McCarley, 1977). This line of thinking, however, ultimately proved to be misguided, and resulted in an unfortunate lack of interest in exploring factors other than REM which might modulate the reporting of sleep mentation. Early studies of memory processing in sleep, as well, focused on the role of REM sleep in memory consolidation (McGrath & Cohen, 1978), often to the exclusion of giving NREM serious consideration as an important biological state during which active information processing might take place. Instead, if NREM were to have any beneficial effect for memory processing, it was presumed that this must be due to a general lack of interference operating during this supposedly quiescent state (Lovatt & Warr, 1968).

This lack of research attention to cognition and information processing during NREM was likely motivated by the fact that early measurements of neural activity in sleep were restricted to the use of EEG, which provides only a global picture of the averaged neural activity across a wide area of cortex. Relative to REM sleep and wakefulness, EEG during NREM sleep, and during slow wave sleep (SWS, stages 3&4) in particular, consists of high-amplitude, highly synchronized potentials. NREM has therefore

traditionally been conceptualized as a state characterized by a general lack of neural and cognitive activation. Indeed, the idea that NREM might support the kind of complex cognition seen in dreaming, or facilitate any type of information processing function, seemed highly counterintuitive during the early years of sleep research.

However, the synchronous scalp-recorded EEG seen during NREM sleep does not necessarily indicate a lack of cognitive processing. Alternative techniques of observing the sleeping brain provide a quite different picture of the nature of this sleep state. In recent years, the study of cognition in sleep has been revitalized by neuroimaging work (Braun et al., 1997; Maquet, 2000; Nofzinger et al., 2002) providing crucial information about changes in regional activation patterns from wakefulness across NREM and REM sleep. Though global cerebral blood flow measures are indeed decreased in NREM, relative to REM sleep and wakefulness, PET studies have demonstrated that certain regions remain at least as active, and perhaps more active, in NREM as in wakefulness. For example, though lateral prefrontal areas exhibit relative inactivity throughout sleep, medial prefrontal regions remain highly active in NREM as well as in REM sleep (Nofzinger et al., 2002). Meanwhile, rCBF (regional cerebral blood flow) to the hippocampus has been found to be actually greater in NREM than in either wakefulness or REM sleep (Nofzinger et al., 2002; Peigneux et al., 2004). ERP (event-related potential) studies compliment this work, demonstrating that a P300-like response to subject's own names is elicited during stage 2 NREM sleep, and that this response differs from ERP responses to other names, indicating that complex semantic processing persists at least during light NREM sleep (Atienza, Cantero, & Escera, 2001; Bastuji, Perrin, & Garcia-Larrea, 2002; Perrin, Garcia-Larrea, Mauguiere, & Bastuji, 1999).

Although the likelihood of experiencing vivid dreaming is greater during the desynchronized REM state than during NREM, mentation is nonetheless recalled from NREM sleep about 50% of the time (Nielsen, 2000). This substantial likelihood of recalling mentation from NREM is even higher during the late morning hours as subjects move towards wakefulness (Antrobus, Kondo, Reinsel, & Fein, 1995; Pivik & Foulkes, 1968; Wamsley et al., in press). Also contrary to traditional conceptualizations of SWS as a general state of inactivity, subjects recall an equal amount of NREM dreaming from the "deepest", most highly synchronized stages (3&4) as during lighter NREM sleep, i.e. stage 2, where EEG is much less synchronized (Nielsen, 2000; Tracy & Tracy, 1974).

Rapidly accumulating evidence from the study of memory consolidation in sleep points to synchronized, slow-wave-dominated sleep as actually presenting the *ideal* conditions for processing recent declarative memories and "consolidating" them into long-term storage in the cortex (Buzsaki, 1996, 1998; Gais & Born, 2004; Steriade & Timofeev, 2003). A number of studies in rodents utilizing single-cell recordings in the CA1 region of the hippocampus have demonstrated that patterns of correlated firing observed during waking exploration are re-expressed during post-learning NREM sleep (Kudrimoti, Barnes, & McNaughton, 1999; Lee & Wilson, 2002; Louie & Wilson, 2001; Nadasdy et al., 1999; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). Electrophysiological and imaging studies in humans have demonstrated similar reactivation of learning-related activity during post-training NREM sleep (Huber, Ghilardi, Massimini, & Tononi, 2004; Peigneux et al., 2004). This reactivation of memory traces is thought to be the result of transfer of recently-acquired declarative learning from a dependence on hippocampal to a dependence on neocortical networks for

retrieval. Observations of qualitative changes in memory representations mediated by post-training NREM sleep support this assumption (Ellenbogen et al., 2006; Orban et al., 2006; Takashima et al., 2006), and indeed, performance on declarative tasks is selectively facilitated by periods of NREM-dominated sleep (Plihal & Born, 1999; Tucker et al., 2006)

Within the hippocampus, neural replay of recent memories occurs preferentially during sharp wave-ripples (SPW-Rs), unique electrophysiological events that in sleep occur selectively during NREM (Nadasdy et al., 1999). SPW-Rs, initiated by pyramidal cells in CA3 of the hippocampus, are high amplitude population bursts in which 40,000-60,000 medial temporal lobe cells participate (Buzsaki, 1998). Very high frequency (140-200 Hz) "ripple" activity is superimposed on this relatively slow population burst (Behrens et al., 2005; Buzsaki, 1998). During SPW-R's, output layers of entorhinal cortex are selectively activated, suggesting that these events propagate activity out to the rest of the cortex (Chrobak & Buzsaki, 1994). SPW-R events are thought to induce LTP in participating cells, a hypothesis supported by in vitro studies (Behrens et al., 2005), and interestingly, they occur in temporal synchrony with NREM-specific cortical oscillations also hypothesized to induce plasticity in participating cells. Specifically, SPW-R events and sleep spindles are temporally synchronized (Siapas & Wilson, 1998; Sirota, Csicsvari, Buhl, & Buzsaki, 2003), and like SPW-R activity, spindles provide ideal conditions for synaptic modification within participating ensembles, via LTP mechanisms (Rosanova & Ulrich, 2005). SPW-R events are also synchronized with the up-state of the cortically-generated slow (<1Hz) oscillation (Battaglia, Sutherland, & McNaughton, 2004). In short, a variety of complex and interacting electrophysiological

events ideally suited for supporting sleep-dependent memory processing occur exclusively during NREM sleep.

Collectively, these observations call into question the over-simple assumption that increased EEG synchrony during NREM = less "brain activity" = a general lack of cognition and information processing. The three studies presented here examine cognition and information processing during stage 2 NREM sleep in an attempt to specify a) the neural basis of the generation of mentation in NREM and b) the potential influence of hippocampally-mediated memory reactivation on ongoing mentation in NREM.

Activation of the Neural Substrate for Dreaming Outside of REM Sleep

The first two studies discussed here address the neurobiological basis of mentation production within NREM sleep. Historically, research on the neural substrate for dreaming has largely consisted of examining the influence of the ultradian REM/NREM cycle on between-stage differences in dream reporting, while modulators of dreaming other than the REM cycle have received little attention. Although it has long been known that an increased amount of dreaming is reported later in the night (Pivik & Foulkes, 1968), the mechanisms underlying this effect remain unknown. *Study 1* presents evidence that circadian time influences dream reporting at least as strongly as the REM/NREM cycle, hitherto by far the strongest known predictor of dreaming. Importantly, circadian time modulated dream reporting similarly within both REM and NREM sleep. We attribute this large effect of circadian time to the fact that dream reports were collected with reference to an estimation of each subject's individual core body temperature cycle, whereas previous work demonstrating smaller time-of-night effects has typically examined dreaming as a linear effect of time since sleep onset (i.e.

Pivik & Foulkes, 1968; Stickgold et al., 2001b). A follow-up study addresses the possibility that this large time-of-night effect could have been influenced, not only by changes in circadian-driven activation, but also by homeostatic discharge of sleep need across the night, as evidenced in decreased slow wave propensity with increasing time since sleep onset. As an approach to this problem, *Study 2* assesses NREM mentation reports from daytime naps, during a period of presumably high circadian activation, but where report collection follows several hours of wakefulness during which sleep need has been allowed to accumulate.

It is concluded that a purely circadian influence on dreaming following the core body temperature cycle is inadequate to explain the observed diurnal variations in mentation reporting. Alternatively, dream production may follow a circadian time course with an acrophase of approximately 8am (Suzuki et al., 2004), or may be driven by the combined influence of circadian and homeostatic factors.

Hippocampally-Dependent Recent Declarative Memory and Mentation in NREM Sleep

Though both circadian and homeostatic processes may serve as sources of general activation supporting mentation in NREM, this says little about the specific neurobiological processes constructing and constraining the content of cognition during NREM sleep. Given the aforementioned evidence that declarative memories are consolidated during NREM, it has been speculated that NREM mentation is, at least in part, the result of hippocampally-mediated reactivation of recently learned material (Cartwright, 2004; Paller & Voss, 2004; Payne & Nadel, 2004; Steriade, 2006). *Study 3* tests this hypothesis by examining the expression of hippocampally dependent conditioning during NREM. It is concluded that, not only is hippocampally-dependent

recent learning accessible during NREM sleep, but the cued retrieval of hippocampally-dependent memories may affect the quality of ongoing mentation during this sleep stage. This constitutes the first experimental support for the hypothesis that dreaming in NREM sleep is influenced by processes involved in the consolidation of declarative memories.

II.

Circadian and Ultradian Influences on Dreaming: A Dual-Rhythm Model
(in press, *Brain Research Bulletin*)

This study evaluates the Dual Rhythm model of dreaming (Antrobus et al., 1995), which holds that, under high sensory thresholds, heightened cortical activation driven by both REM/NREM and circadian activation cycles produces the main characteristics of dreaming. The development of a neuroscientific explanation of dreaming has been handicapped for many years by strong claims that dreams occur exclusively in rapid eye movement (REM) sleep. Today, a central debate remains as to whether dreaming is generated only by mechanisms specific to REM sleep (Hobson & McCarley, 1977; Hobson, Pace-Schott, & Stickgold, 2000), or alternatively, whether dreaming might be dependent on overall levels of cortical activation, regardless of sleep stage (Antrobus, 1991; Cavallero et al., 1992; Wittmann, Palmy, & Schredl, 2004).

Although REM-sleep-related brainstem mechanisms are a major source of cortical activation in sleep, structures necessary for dream generation can also be activated in the absence of REM (Cicogna, Natale, Occhionero, & Bosinelli, 2000; Cicogna, Natale, Occhionero, & Bosinelli, 1998; Foulkes, 1967; Foulkes, 1962; Nielsen, 2000; Solms, 2000; Vogel, 1991). The Dual Rhythm model states that activation from the ultradian sleep cycle sums with circadian-driven activation to create an overall activation pattern which, coupled with attenuation of sensory input, produces dreaming. Simultaneously, some specific dream features, particularly emotionality, may be largely dependent on a regional activation pattern specific to REM sleep (McNamara et al., 2005; Smith et al., 2004).

Following Dement and Kleitman's (Dement & Kleitman, 1957b) discovery that REM is associated with a high rate of dream recall, researchers assumed that the physiological cause of dreaming had been found. It seemed likely that an examination of the precise brain mechanisms of REM sleep might pinpoint the origin of the dream process. Relying on this REM-focused strategy, Hobson & McCarley (Hobson & McCarley, 1977) proposed the influential "activation-synthesis" hypothesis, which described the brainstem generators of REM as the origin of dreaming. Throughout the last 50 years a vast amount of research has similarly attempted to understand dreaming through the study of REM-related subcortical brain mechanisms (Fosse, 2000; Nielsen, 2000; Pivik, 1991; Shapiro, Goodenough, Biederman, & Sleser, 1964; Wolpert, 1960).

However, evidence of dreaming in NREM sleep led some to question the extent to which REM-specific physiology constitutes an adequate explanation of dreaming (Antrobus, 1983; Cavallero et al., 1992; Domhoff, 2002; Foulkes & Schmidt, 1983; Solms, 2000). Despite clear and consistent evidence that dreaming occurs in NREM sleep (Cicogna et al., 2000; Cicogna et al., 1998; Foulkes, 1967; Foulkes, 1962; Nielsen, 2000; Vogel, 1991), researchers have continuously found ways to hold onto the REM=dreaming assumption. Although the early hypothesis that NREM dreams were really just a memory from a previous REM period has been discredited (Foulkes, 1962; Goodenough et al., 1965), the tenacious hold of the REM=dreaming connection lives on in the current theory that NREM dream reports are actually the result of "covert" REM sleep (Nielsen, 2000; Suzuki et al., 2004).

Circadian-driven changes in cortical activity are an excellent candidate for a source of activation to the dreaming process outside of REM sleep. Some evidence suggests that

dreams late in the sleep phase differ on various dimensions from early dreams (Antrobus et al., 1995; Casagrande et al., 1996; Cicogna et al., 1998; Fosse, Stickgold, & Hobson, 2004; Pivik & Foulkes, 1968; Stickgold et al., 2001b). Pivik & Foulkes (Pivik & Foulkes, 1968) were the first to report that dream length changed across the night, finding that NREM dreams became longer with each successive sleep cycle. Casagrande et al. (Casagrande et al., 1996) reported that dreams they collected from the second half of the night had greater length than dreams from the first half of the night. In a large longitudinal study of home-collected reports, Stickgold et al. (2001) reported a modest positive (r^2=.05) correlation between report length and time elapsed since sleep onset. Fosse et al. (Fosse et al., 2004) recently reported that instances of hallucinatory content increased in both REM and NREM sleep as the night progressed, although directed thought decreased across time in NREM. Antrobus et al. (Antrobus et al., 1995) assessed the relative influence of time of night vs. sleep stage on a number of dream variables and found that dream length and other cognitive and visual features increased in the late morning when subjects' sleep phase was delayed 3 hours (Antrobus et al., 1995). In this study, the circadian effect size was about one-third of that of the effect of sleep stage on dreaming (Antrobus et al., 1995).

These effects of time of night on mentation production may be explained by circadian-driven changes in cortical activation across the night (Antrobus et al., 1995). Antrobus et al. (1995) collected reports from periods separated by only about 2 hours, which could explain the small size of the diurnal effect relative to the REM/NREM effect. An effect of circadian activation on dream variables would be most clearly demonstrated by a design that compares reports collected from the low-point of the

circadian-driven cortical activation cycle with reports collected from the upswing of that cycle, as late in the morning as possible. A circadian-driven cycle of cortical activation would most likely reach its low point towards the middle of the night, when core body temperature (CBT) is at its minimum. The CBT rhythm is roughly correlated with both fluctuations in performance (Broughton, 1975; Carrier & Monk, 1999) and changes in the EEG (Czeisler & Khalsa, 2000; Deboer, 2002; Dijk et al., 1997). Specifically, circadian modulation of neural activity is manifested in the sleep EEG such that the peak of spectral power in the fast spindle range (~14 Hz), the nadir of alpha activity in REM, and propensity for REM sleep all coincide with rising CBT during the late morning hours (Benington, 2004; De Gennaro & Ferrara, 2003; Dijk et al., 1997). Therefore, we assume that the well-documented rhythm of body temperature may be used as a reasonably accurate, non-intrusive estimate of circadian-driven cortical activation, reaching its nadir near the middle of the night and rising in the late morning.

Although the core features of sleep mentation are produced by REM/NREM and circadian-driven *general* cortical activation, certain dream features, particularly emotion, are dependent on sleep-stage-specific *regional* neural activation patterns. In recent years, PET imaging studies have a) confirmed electrophysiological findings that general activation (here measured by global cerebral blood flow) is greater in REM than in NREM and b) provided us with preliminary information on how regional activation patterns differ across sleep states (Braun et al., 1997; Maquet, 2000). A key finding for our purposes here is that limbic areas, including the amygdala, are highly active in REM, as compared to both NREM sleep and waking (Braun et al., 1997; Maquet, 2000). Although most differences between REM and NREM reports fall away when the overall

greater length of REM reports is controlled for (Antrobus, 1983), motivation, presumed to be reliant on limbic structures, is greater in REM than NREM sleep, even when controlling for report length (Smith et al., 2004). A recent content-analysis study by McNamara et al. (McNamara et al., 2005) suggests a greater emotional intensity in REM, finding that REM reports contain a greater percentage of interactions that are aggressive than NREM reports. It seems likely that emotion and motivation, found to be more prominent in REM dreams, regardless of report length, may be the result of a pattern of regional brain activation specific to REM sleep.

In summary, the Dual Rhythm model of dreaming holds that during periods of high sensory thresholds, general cortical activation modulated by both circadian and REM/NREM cycles drives the dream creation process. Sleep mentation may also be further modified by changes in the pattern of regional cortical activation across the REM-NREM cycle (Braun et al., 1997; Maquet, 2000; McNamara et al., 2005; Smith et al., 2004). The current study is therefore designed to test the theoretical assumptions that:

1. The fundamental cognitive and visual characteristics of sleep mentation such as length, bizarreness, and vividness are primarily dependent on general cortical activation, driven by both circadian and REM-NREM cycles.
2. The emotional intensity of dreams is a function of a REM-specific brain activation pattern.

In the present experiment, mentation reports elicited near the estimated nadir of circadian-driven cortical activation were compared to reports collected during the late morning, when circadian-driven activation of the cortex is presumed to be high. It was hypothesized that reports collected in the late morning would contain significantly greater

amounts of content. Additionally, both REM and NREM reports collected in the late morning were expected to exhibit to a greater degree the cognitive and visual features traditionally ascribed to REM dreams, including Bizarreness, auditory imagery, overall "Dreamlike Quality", and increased perceptual vividness. It was further hypothesized that circadian-driven cortical activation increases in the late morning would lead to increased emotional intensity in REM, but not in NREM mentation.

Methods

Participants

Participants were 5 male and 15 female undergraduate students from the City College of New York (mean age=26.6, SD=7.5). Participants kept a sleep log for one week prior to the study. In order to qualify for inclusion, participants were required to have an average bedtime before midnight during this week, and no bedtime on any night was allowed to deviate by more than one hour from this average. Five additional participants are not included in the analyses presented here, due to failure to maintain a sufficient amount of sleep on the experimental night in order to complete the study.

Procedures

In the week prior to the study, as a part of the sleep log, participants were instructed to record the number of dreams that they recalled each night and to record notes on the content of those dreams. On the experimental night, participants were put to bed 3 hours later than their mean bedtime for the previous week, and were encouraged to sleep in as long as they could in the morning. Sleep data were recorded using a standard electroencephalographic (EEG), electro-oculographic (EOG), and electromyographic (EMG) montage.

Each subject was awoken once from a REM and NREM period near the nadir of the circadian body temperature cycle – estimated at 2.7 hours before their mean waking time (Czeisler et al., 1990) for the previous week – and once from a REM and NREM period a minimum of one hour after participants' mean wake time for the previous week, when circadian-driven cortical activation was assumed to be high (see Figure 1). Although the CBT nadir was estimated based on existing data rather than directly measured, we presume this estimate to be reasonably accurate. Subjects were carefully screened for having regularly occurring, early sleep times and the estimation relies on previous work with participants of comparable age who had similar sleep schedules (Czeisler et al., 1990). REM awakenings were performed 10 min. into REM periods and NREM awakenings were performed from stage 2 sleep, a minimum of 20 min. from the last awakening or REM period. At each time point, the order of REM/NREM awakenings was counterbalanced across participants.

For each awakening, the participants' name was called over an intercom once per second until he/she awoke and the following pre-recorded questions were played:

1. Tell me everything that was going through your mind just before I called.
2. Tell me one more time everything that was going through your mind just before I called.
3. Were you trying to do anything? (y/n)
4. Were you trying to find anything? (y/n)
5. Were you trying to solve any problem? (y/n)
6. Was anyone talking? Could you hear any speech? (y/n)

Participants were instructed that they should answer question 6 in the affirmative only if they actually recalled realistic auditory imagery. Data from questions 3 and 4 from some of the same participants were reported in a previous paper (Smith et al., 2004) and will not be discussed here. Data regarding question 2 are also not discussed in this paper.

Rating of Visual and Emotional Qualities of the Mentation

After giving oral responses to the above questions, participants completed a two-part form assessing the visual and emotional qualities of their mentation. To assess the visual qualities of their experience, participants were asked to list up to three of the most salient objects or persons in the mentation, and to indicate whether these were visual images. If any images were visual, participants rated the perceptual quality of these images by picking out the picture that most resembled their visual experience from a 4x4 array of photographs varying in brightness and clarity. Photographs were scaled such that photo selections could then be converted into separate scores for "Brightness" and "Clarity", for which a score of 100 represents brightness and clarity typical of waking visual experience (for more information on this scale see (Antrobus et al., 1995).

Participants then rated the presence and intensity of nine emotions using a nine-point Likert scale (Antrobus et al., 1995). Total emotional intensity was calculated by adding participants' ratings of the intensity of the nine separate emotions. Emotion scores were then log-transformed to remove a positive skew.

Scoring of Reports

Reports from question one were transcribed and scored for Word Information Count (WIC), Dreamlike Quality, and Bizarreness. Scorers were trained on the measurement scales, and were blind to condition.

Reports without mentation content were scored zero on all scales. Inclusion of these "no content" reports in the dataset is crucial in order to assess the total amount of content of various types recalled under each awakening condition. The exclusion of these mentation reports, a strategy favored by some investigators, results in the loss of important data about when various cognitive features are *not* experienced, and effectively skews the means for NREM reports to appear more REM-like. Separate analyses will be presented assessing the qualitative characteristics of reports while partialling out the influence of overall amount of content reported (WIC).

Word Information Count (WIC). WIC is a modified word count measure that eliminates repetition, non-words, and words that do not provide new information about the sleep mentation. WIC is a revised version of Total Recall Count (TRC), demonstrated by Antrobus (Antrobus, 1983) to be one of the best discriminators of REM and NREM reports. WIC scores were log-transformed. We presume log(WIC+1) to be an index of cognitive activation, and to indirectly reflect overall levels of cortical activation.

Dreamlike Quality. Dreamlike Quality is a global measure for which judges are instructed to rate reports on a scale of 1-10, according to how "dreamlike" the report seems (see also (Reinsel, Wollman, & Antrobus, 1992).

Bizarreness. Bizarreness is a count of bizarre elements of three types in the mentation: discontinuities, improbable combinations of elements, and indefinite identities of characters (Reinsel et al., 1992). Bizarreness scores were log-transformed to remove a positive skew.

Results

Inter-Rater Reliability

Inter-rater reliability correlations for the 2 judges that scored WIC and Dreamlike Quality were .91 and .86, respectively. Cronbach's alpha reliability for the 4 judges that scored Bizarreness was .82.

Mentation Recall

Mentation was reported by 80% of participants from the Nadir REM period, 100% from the Late REM period, and 70% from both the Nadir and Late NREM periods. Overall, then, some content was reported from 90% of REM, 70% of NREM, 75% of Nadir, and 85% of Late awakenings.

General Activation Level Effects

As predicted by the Dual Rhythm model, core cognitive characteristics of the mentation were most prominent during the late morning in both REM and NREM (See Table 1 and Figures 2-4). WIC ($F_{1,19}$=19.40, p<.001, η_p^2=.51), Dreamlike Quality ($F_{1,19}$=9.28, p<.01, η_p^2=.33), Bizarreness ($F_{1,19}$=6.60, p<.05, η_p^2=.26), and Speech ($F_{1,19}$=5.63, p<.05, η_p^2=.23) were all significantly greater in Late reports as compared to Nadir reports. Each of these features was also significantly greater in REM than NREM reports (WIC: $F_{1,19}$=12.73, p<.01, η_p^2=.40; Dreamlike Quality: $F_{1,19}$=9.10, p<.01, η_p^2=.32; Bizarreness: $F_{1,19}$=9.11, p<.01, η_p^2=.33; Speech: $F_{1,19}$=4.10, p=.05, η_p^2=.18). A lack of sleep stage x time of night interactions indicates that effects of circadian-driven activation were similar in REM and NREM. Therefore, although these cognitive features were expressed more in REM than NREM reports, circadian-driven activation amplified their expression in reports from *both* sleep stages.

There was no significant effect of circadian time or sleep stage on responses to the problem-solving question.

REM-Specific Effects

Emotion. As expected, emotional intensity exhibited a late-morning increase selectively in REM sleep (See Figure 5). Emotional Intensity was significantly greater for REM reports than for NREM reports ($F_{1,19}$=11.79, p<.01, η_p^2=.39) and there was a non-significant trend for emotional intensity to be greater in the Late reports as compared to the Nadir reports ($F_{1,19}$=2.92, p=.10, η_p^2=.13). Although the interaction of sleep stage with time of night did not reach significance, emotion exhibited a near-significant increase across night in REM ($F_{1,19}$=3.86, p=.06, η_p^2=.17), while remaining virtually constant in NREM (Table 1).

Visual imagery. Contrary to our hypotheses, Brightness and Clarity also increased across the night selectively in REM (See Figure 6). The interaction between sleep stage and time of night for both Brightness ($F_{1,19}$=4.27, p=.053, η_p^2=.18) and Clarity ($F_{1,19}$=3.34, p=.08, η_p^2=.15) approached statistical significance. While Brightness ($F_{1,19}$=6.53, p<.05, η_p^2=.26) and Clarity ($F_{1,19}$=5.03, p<.05, η_p^2=.21) increased from the circadian nadir to the late morning in REM, these vividness measures actually decreased slightly (n.s.) across time in NREM (Table 1). Brightness ($F_{1,19}$=11.47, p=.003, η_p^2=.38) and Clarity ($F_{1,19}$=12.10, p<.01, η_p^2=.39) were both significantly greater in REM than in NREM, but there was no significant main effect for time of night on either measure.

Relationship between WIC and other Variables

Almost any aspect of mentation reports will be greater in REM than NREM, simply because more information is delivered in REM reports, i.e. REM reports are

longer. Reports with greater amounts of total content are likely to contain, for example, a greater number of bizarre events, vivid images, and emotions (Antrobus, 1983). Researchers have often taken the view that word length is a nuisance variable in studies of dreaming that needs to be controlled for (i.e. (Domhoff, 2002). In the present study, however, we presume WIC to naturally be the key omnibus variable, in that it is an index of overall cognitive activation. Therefore "controlling for" the influence of WIC would amount to partialling out the influence of cortical activation, the process upon which most thought and imagery processes are dependent.

In order to identify any thought or imagery effects that are independent of general cortical activation as indexed by WIC, the WIC effect was removed by using a linear mixed model. All effects of both sleep stage and time of night on the other dependent measures then became statistically non-significant. We also note that some of these residual effects might be significant with a larger sample. Despite the small sample, however, a notable exception was that total emotional intensity was still greater in REM than NREM, even when controlling for WIC ($F_{1,19}$=4.35, p=.05, ω^2=.08).

Discussion

As hypothesized, these results demonstrate that the key cognitive features of dreaming are produced by overall levels of cortical activation, driven by both ultradian and circadian cycles. Length, Dreamlike Quality, and Bizarreness of dreams all increased along with late morning circadian activation in both REM and NREM reports. Therefore, as predicted by the Dual Rhythm model, circadian-driven and ultradian-driven general activation appear to sum, so that although the longest, most dreamlike reports are obtained in late-morning REM sleep, even NREM sleep supports long and dreamlike

reports when the neural substrate for dreaming receives sufficient circadian-driven activation. Late NREM reports in our sample were actually quite similar to Nadir REM reports. This pattern of reported thought, imagery and affect contradicts REM-exclusive theories of dreaming such as the activation-synthesis hypothesis, which assert that "dreamlike" mentation is generated only in REM sleep (Hobson et al., 2000).

Size of Effects

In contrast to a previous study (Antrobus et al., 1995), which found circadian effects about one-third the size of REM/NREM effects, here the effect of circadian time on WIC (η_p^2=.51) was actually larger than the effect of sleep stage on WIC (η_p^2=.40). This large effect of circadian activation on report length is likely due to our success in targeting the nadir of cortical activation during the middle of the night, creating a large contrast with a period of high cortical activation much later in the sleep phase -- at least one hour after subjects' normal waking time. The Antrobus et al. (1995) circadian effect may also have been smaller due to the shorter time period between report collection points.

REM-Specific Effects

As predicted by the Dual Rhythm model, although overall levels of cortical activation modulated dream production, the pattern of regional activation particular to REM sleep (Braun et al., 1997; Maquet, 2000) also modified dream content. As hypothesized, increased cortical activation in the late morning supported increased emotional intensity selectively in REM sleep. Our model attributes this increase to the heightened limbic activity characteristic of REM sleep (Braun et al., 1997; Maquet, 2000). Indeed, previous work from our laboratory has supported the idea that motivation,

presumed to be dependent on activation of limbic structures, is one dimension on which REM and NREM dreams do differ essentially, even when the influence of word count is partialled out (Smith et al., 2004).

Unexpectedly, vividness of visual imagery also exhibited a late-morning increase only in REM sleep. These results contradict those of two previous studies finding an increase in visual features across the night in NREM (Antrobus et al., 1995; Fosse et al., 2004). Although not anticipated, this selective increase in REM-dream vividness might also be attributed to a known REM-specific regional brain activation pattern. Neuroimaging studies have reported that extrastriate visual cortex is highly active in REM, as compared to NREM, sleep (Braun et al., 1998). However, interpretation of our vividness data is complicated by the fact that Late NREM reports were characterized by some very thought-like reports that contained no imagery, and some extremely visually vivid reports. The processes that might underlie this bimodal distribution are unclear, however. Future work with sample sizes large enough to carry out separate analyses on only those reports containing visual imagery would be necessary in order to resolve the conflict between our data and that of previous studies.

WIC as a Mediating Variable

Controlling for the influence of WIC resulted in many of the effects of sleep stage and time that we discuss here becoming non-significant. Considering that WIC is taken to be an indirect measure of overall cortical activation, this outcome is not surprising. It appears that the effects of both stage of sleep and time of night reported here are mediated by the increase in cortical activation common to both REM sleep and the rising phase of the circadian rhythm, as measured by WIC. Emotion, however, is the one

feature that was significantly greater in REM than NREM, even when controlling for WIC. Emotional intensity, which requires cortical activation for its expression but appears to be driven by subcortical limbic activation, is therefore uniquely a REM sleep process.

Our results here may have been strongly influenced by the fact that WIC reflects, in part, whether subjects recalled any mentation at all when awakened. That is, as described in the methods, WIC is calculated as the total amount of information reported from each condition, including instances where the WIC score is zero. An alternative dependent measure could have been the length of dreams in only those instances where at least some content is recalled. However, such an approach would exclude important information from the analyses regarding instances when no information was recalled resulting in a misleading picture of the amount of information recalled from each experimental condition. Again, though, note that when we controlled for the influence of WIC in analyses of Dreamlike Quality, Bizarreness, Brightness, and Clarity, both REM-NREM and circadian effects for these variables became non-significant, indicating that these effects were dependent on the total amount of information reported, as measured by WIC.

Additional Considerations

Circadian modulation of sleep stage features. The present study demonstrates that circadian-driven cortical activation increases the production of mentation, regardless of sleep stage. However, it is important to remember that some defining electrophysiological features of REM and NREM sleep are themselves under circadian control. REM sleep propensity, which increases across the night, is controlled by the

endogenous circadian clock (Czeisler et al., 1980; Wurts & Edgar, 2000), as is spindle frequency activity in stage 2 (De Gennaro & Ferrara, 2003) and alpha activity in REM (Dijk et al., 1997).

However, though circadian activation changes across the night are of course reflected in the EEG, our data support the idea that the essential differences between cognition in REM and NREM are maintained at all portions of the night. Differences between REM and NREM in both global and regional activation, then, seem likely to remain relatively stable across the night, remaining unchanged in the face of the circadian-driven activation changes observed in the EEG. However, no neuroimaging studies have examined the nature of global or regional activation in REM and NREM sleep during the late morning. Such studies would be necessary in order to confirm this assumption.

Homeostatic changes in slow wave activity across the night. Circadian nadir and late morning reports in this study were sampled from different points in the circadian cycle, but these report collection periods also differed in EEG characteristics under homeostatic control. Specifically, propensity for slow wave activity (SWA), which increases in an exponentially saturating function during wakefulness and then exponentially decays as a function of time asleep (Benington, 2004; Dijk, Beersma, & Daan, 1987), was greater during the nadir period as compared to the late morning period. This difference in SWA propensity between the nadir and late morning period could have been amplified by the 3 hours of sleep deprivation which subjects received. However, our NREM awakenings were carefully controlled, always being made after 20 minutes of clearly defined stage 2 sleep. The mechanism by which SWA propensity could affect

these stage 2 reports is unknown. However, because the exact nature of the relationship between sleep need and SWA remains unclear (Benington, 2004), future studies may be necessary to address the possibility that SWA propensity may have affected our results.

Conclusions

While sensory input is attenuated in sleep, dreaming is produced by cortical activation driven by ultradian and circadian activation cycles, and is then further modified by sleep-stage-specific regional activation patterns. Here, this Dual Rhythm model is strongly supported by the fact that important cognitive characteristics of dreaming fluctuated in concert with levels of circadian activation, independent of the presence of a REM-specific regional activation pattern. The dependence of dreaming on heightened cortical activation is, therefore, not exclusive to REM sleep. However, as hypothesized, the emotional intensity of dreaming does appear to be dependent upon a regional subcortical brain activation pattern specific to REM (Braun et al., 1997). Emotion increased with circadian-driven activation in the late morning exclusively in REM sleep, while remaining unaltered and at low levels even in the face of this additional activation in NREM.

Researchers have too long debated whether lengthy, vivid, bizarre "dreamlike" mentation depends exclusively on REM-specific brain mechanisms. While several features of dreaming are, indeed, dependent on brain processes unique to REM, the core characteristics of dreaming are produced by cortical activation driven by both circadian and REM-NREM rhythms.

III.

Homeostatic and Circadian Influences on Dreaming: NREM Mentation During a Daytime Nap

Previous empirical work on the neural basis of dreaming has focused largely on describing and explaining differences between mentation reported from REM, as opposed to NREM sleep (Braun et al., 1997; Dement & Kleitman, 1957b; Hobson et al., 2000). This approach has often been accompanied by the presumption that neural mechanisms specific to REM sleep are the primary generators of dreaming, an influential notion originating with the discovery that dreaming has a high probability of being reported from REM (Dement & Kleitman, 1957b). Unfortunately, the large magnitude of the REM/NREM dreaming effect appears to have dissuaded investigators from identifying other neural bases for systematic variations in the production of sleep mentation. In particular, a modulator of dream production other than the REM/NREM cycle is evident in observations that dreaming increases dramatically across the night within NREM, as well as within REM sleep (Antrobus et al., 1995; Casagrande et al., 1996; Pivik & Foulkes, 1968; Stickgold et al., 2001b; Wamsley et al., in press). The present study further examines the basis of changes in NREM dreaming across the diurnal cycle in an effort to specify the nature of this modulatory influence on the dreaming process.

It has long been known that dream reports change on a number of dimensions as the night progresses (Antrobus et al., 1995; Casagrande et al., 1996; Pivik & Foulkes, 1968; Stickgold et al., 2001b; Wamsley et al., in press). Later in the night, propensity for mentation recall, dream report length, and various qualitative features of dream reports increase, often dramatically. It has been proposed that such time-of-night mentation

effects are likely caused by an endogenously-driven, circadian activation rhythm (Antrobus et al., 1995; Nielsen, 2004). Indeed, increases in mentation production during the late morning hours are observed even when the influence of time since sleep onset is controlled for (Antrobus et al., 1995; Suzuki et al., 2004), strongly suggesting that the time-of-night effect on dreaming is controlled by internal clock-like mechanisms.

If reported sleep mentation is modulated, at least in part, by an endogenous circadian rhythm, it is reasonable to postulate that the time course of this rhythm would approximate the core body temperature (CBT) cycle. A number of other cognitive functions, such as alertness, dexterity, and working memory performance follow an endogenously-driven time course correlated with CBT (Monk et al., 1997; Wright, Hull, & Czeisler, 2002). Furthermore, some features of the sleep EEG itself also vary according to a circadian rhythm, reaching maximum levels in the late morning, coincident with the rising arm of the CBT rhythm (Czeisler & Khalsa, 2000; De Gennaro & Ferrara, 2003; Deboer, 2002; Dijk et al., 1997).

However, because studies of dreaming across the night rarely control for the influence of time since sleep onset, most evidence for 'time-of-night' effects on dreaming could potentially be explained via homeostatic-driven changes in arousal, changing in concert not with circadian time, but rather with time since sleep onset. That is, in studies of dreaming across the night, circadian and homeostatic influences on the dependent variables have typically been confounded, prohibiting meaningful conclusions regarding the cause of changes in dreaming across the night. In fact, there are good reasons to think that homeostatic changes in sleep need across the night might contribute to time-of-night mentation effects. Propensity for slow wave activity (SWA) has generally been taken to

be the physiological marker of homeostatic sleep need, building up following an exponentially saturating function during wakefulness, and discharging during subsequent sleep (Benington, 2004; Borbely et al., 1981). Distance from periods of REM sleep and, by implication, proximity to slow wave sleep, has been cited as a strong predictor of decreased dream recall within NREM (Nielsen, 2000). Though the mechanisms underlying a potential influence of slow wave propensity on dream recall outside of stages 3 and 4 remain unknown, some studies examining dream recall across the night are broadly more consistent with a homeostatic-based rather than a circadian-based explanation for time-of-night effects on dreaming. Pivik & Foulkes (Pivik & Foulkes, 1968) and Neilsen et al. (Nielsen, Germain, & Zadra, 1997) have both reported a sharp increase in dreaming early in the night, remaining relatively stable thereafter, a pattern which roughly mirrors the initial steep decline in SWA seen in the early night (Nielsen, 2004).

In a recent study (Wamsley et al., in press), we report that the amount of information recalled from NREM sleep increases dramatically in the late morning relative to the middle of the night near the circadian nadir of the CBT rhythm. This time-of-night effect on amount of information reported upon awakening was very large (η_p^2=.51), larger even than the effect of sleep stage on dream recall (η_p^2=.40) (Wamsley et al., in press). However, in this study, the influence of time since sleep onset was not controlled for, and so the large time-of-night effect may have been in part due to the discharge of homeostatic sleep need across the night. That is, in comparing reports collected from near the nadir of the CBT rhythm to reports collected in the late morning, we aimed to sample mentation from different circadian phases. Yet these conditions also

differed in regard to the amount of time subjects had been sleeping prior to data collection, and thus changes in SWA propensity across the night may have influenced the results. Previous studies which controlled for the influence of time since sleep onset through the use of full or partial forced desynchrony protocols have found relatively smaller effect sizes for circadian influences on dreaming (Antrobus et al., 1995; Suzuki et al., 2004).

In order to assess the relative contributions of circadian and homeostatic processes to diurnal variations in sleep mentation, here we examine dream reporting during a period of high circadian activation preceded by several hours of wakefulness, rather than after a full night of sleep. We compared the characteristics of mentation recalled from short daytime naps containing exclusively NREM sleep to nighttime NREM mentation previously collected from both the Circadian Nadir of the core body temperature (CBT) rhythm and the Late Morning, under an identical protocol (Wamsley et al., in press). We reasoned that, if sleep mentation is indeed driven by a circadian cycle approximating the time course of the CBT rhythm, mentation production should be even higher during an early afternoon nap than in the late morning hours, as CBT continues to rise throughout the day. Alternatively, to the extent that dreaming is driven by factors related to the homeostatic discharge of SWA across the sleep period, mentation production during NREM naps would be expected to be lower than in the late morning following a night's sleep, due to buildup of SWA propensity occurring during the hours of wakefulness preceding a nap period.

Methods

Participants

20 healthy undergraduate students (mean age=27.6, SD=9.6), kept a detailed sleep log during the week prior to the study. In order to qualify for participation, subjects were required to demonstrate an average bedtime before midnight, with no bedtime during the week deviating from that average by more than one hour. Participants were asked not to consume any caffeine on the morning of the study, or alcohol on the night prior to the study.

Data from these participants were compared to overnight mentation data previously collected from a similar group of participants (n=20) (Wamsley et al., in press). Table 2 describes the characteristics of Overnight vs. Nap participants. These two subject groups were not significantly different on age, sleep schedule, or dream recall variables. Selection criteria for the two groups were identical. Both studies were approved by the institutional review board of the City College of New York.

Procedures

Participants arrived at the laboratory at 11:00am, where they were familiarized with the lab and signed consent. Polysomnographic variables were measured using a standard EEG (C3-A2, C4-A1), EOG, and EMG montage. Signals were amplified using Grass Model 7 amplifiers and digitally converted for acquisition and analysis using Grass-Telefactor's *Gamma* software.

Data collection began at approximately 11:30am, as subjects reclined in a darkened, sound-attenuated sleep chamber. Just prior to the nap opportunity, subjects gave three reports on their waking mentation experiences after 3, 5, and 10 minutes of lying quietly awake in the darkened sleep chamber. The three-minute report was always

given first as a "practice" session, and order of the subsequent 5 and 10 minute waking reports was counterbalanced across subjects. The nap opportunity then began at approximately 12:00pm. All experimental awakenings from sleep were made from stage 2, following at least 20 minutes of continuous NREM. If participants were unable to initiate sleep within 45 minutes, to maintain sleep for a sufficient duration, or entered either SWS or REM less than 20 minutes following sleep onset, the study was terminated. Identical sleep stage criteria had previously been used to obtain NREM reports from Overnight subjects (Wamsley et al., in press). Figure 1 illustrates the three NREM report collection periods relative to presumed time courses for homeostatic and circadian influences on cortical activation. Nap reports were collected from a period of high circadian activation and also higher SWA propensity, relative to Late Morning reports collected after a full night of sleep.

The procedures for collecting waking and sleeping mentation reports were identical. In each case, subjects were contacted by calling their name over a microphone once per second until they responded. Upon awakening, subjects responded to the pre-recorded question *"Please tell me everything that was going through your mind just before I called."*

Subsequently, subjects filled out a written form assessing the visual and emotional qualities of their mentation. To assess the visual qualities of their experience, participants were asked to list up to three of the most salient objects or persons in the mentation, and to indicate whether these were visual images. If any images were visual, participants rated the perceptual quality of these images by picking out the picture that most resembled their visual experience from a 4x4 array of photographs varying in

brightness and clarity. Photographs were scaled such that photo selections could then be converted into separate scores for "Brightness" and "Clarity", for which a score of 100 represents brightness and clarity typical of waking visual experience (Antrobus et al., 1995). Participants then rated the presence and intensity of nine emotions using a nine-point Likert scale (Smith et al., 2004). Total Emotional Intensity was calculated by adding participants' ratings of the intensity of the nine separate emotions. Emotion scores were log-transformed to remove a positive skew.

Scoring of Mentation Reports

Verbal mentation reports were transcribed and scored for Word Information Count (WIC), Waking Verbal Generation (WVG), Dreamlike Quality, and Bizarreness. Scorers were trained on the measurement scales, and were blind to condition. Reports without mentation content were scored zero on all scales.

Word Information Count (WIC). WIC is a modified word count measure that eliminates repetition, non-words, and words that do not provide new information about the sleep mentation. WIC is a revised version of Total Recall Count (TRC), demonstrated by Antrobus (Antrobus, 1983) to be one of the best discriminators of REM and NREM reports. WIC scores were log-transformed ($\log WIC = \ln(x+1)$) to remove a positive skew.

Waking Verbal Generation (WVG). WVG was calculated by taking the mean log-transformed WIC score of the 5 min and 10 min pre-sleep waking reports. This variable was created in order to measure subjects' general propensity for reporting mental experiences, independent of their dream recall per se.

Dreamlike Quality. Dreamlike Quality is a global measure for which judges are instructed to rate reports on a scale of 1-10, according to how "dreamlike" the report seems (Reinsel et al., 1992).

Bizarreness. Bizarreness is a count of bizarre elements of three types in the mentation: discontinuities, improbable combinations of elements, and indefinite identities of characters (Reinsel et al., 1992). Bizarreness scores were log-transformed to remove a positive skew.

Results

Characteristics of Nap vs. Overnight Subjects

Nap and Overnight subjects were similar on age, habitual bedtime, habitual waking time, and trait dream recall as assessed by the sleep log (Table 2). Although Nap and Overnight subjects also did not differ significantly on WVG (Table 2), the amount of content which subjects reported from wakefulness was strongly predictive of the amount of sleep mentation they subsequently reported (as measured by WIC) and was significantly or near-significantly correlated with each of the qualitative measures considered here, with the exception of Clarity (WIC: r=.33, p=.04; Dreamlike Quality: r=.30, p=.06; Bizarreness: r=.33, p=.04; Emotional Intensity: r=.33, p=.04; Brightness r=.29, p=.07; Clarity: r=.07, n.s.). Accordingly, in order to eliminate the influence of individual differences in WVG, NREM nap reports were compared with Nadir and Late Morning overnight reports using a between-subjects ANCOVA model controlling for WVG as a covariate. WVG as a covariate had a significant or near-significant effect on the dependent variable in each analysis described below. WVG was not used as a covariate in the analysis of Clarity, however, as this variable did not have a significant

effect on Clarity ratings. Pairwise comparisons reported are post-hoc tests on estimated marginal means after removing the influence of WVG. Significance levels were set at $p<.05$ for all tests.

Total Amount of Recalled Information

The total amount of information reported from Nap awakenings was unexpectedly low (Table 3). WIC was significantly lower for Nap reports relative to Late Morning reports (t_{38}=2.21, p=.03, d=.49), being instead comparable to WIC for reports from the Circadian Nadir (Figure 2). In addition, the percentage of participants who recalled any mentation at all when awakened was lower during the nap period (40%) as compared to both Circadian Nadir (70%; χ^2=3.64, p=.057) and Late Morning night NREM reports (70%; χ^2=3.64, p=.057; Figure 2).

Other Mentation Characteristics

Mirroring the results for WIC, the Dreamlike Quality ratings of Nap reports were near-significantly lower than for Late Morning reports (t_{38}=1.66, p=.10, d=.54; Table 3, Figure 3) but similar to the Dreamlike Quality of Circadian Nadir NREM reports (p>.8; Table 3, Figure 3). No other qualitative measures differed significantly across the diurnal cycle (Table 3).

The confounding influence of report length has been a considerable problem in dream research, as longer dreams tend to have, for example, a greater number of bizarre events merely by virtue of their greater length. When the influence of report length is controlled for in analyses of qualitative dream characteristics, some apparent qualitative differences between REM and NREM dreams have been found to disappear (Antrobus, 1983). Here, when additional analyses were conducted controlling for the influence of

WIC as a second covariate, Dreamlike Quality, Bizarreness, Brightness, and Clarity did not differ significantly across the three report collection periods. Emotional intensity, however, demonstrated a near-significant tendency (t_{38}=1.75, p=.09, d=.57) to be *greater* in Nap as compared to Late Morning reports, indicating that, despite the generally low amount of content reported from the nap, content which was recalled tended to be emotionally intense relative to that of night reports.

Discussion

Cortical and subcortical activation supporting cognition in sleep may be achieved via the heightened activation characteristic of REM sleep, but also occurs outside of REM, presumably via an alternative source of activation to the dreaming process (Antrobus et al., 1995; Cavallero et al., 1992; Foulkes, 1967; Nielsen, 2000; Pivik & Foulkes, 1968; Solms, 2000). Here, hypothesizing that increases in NREM mentation across the night are due to circadian-driven increases in neural activity correlated with the CBT rhythm, we predicted that more mentation would be reported from a daytime nap as compared to periods of nocturnal sleep. Unexpectedly, nap reports demonstrated a relative paucity of mentation as compared to Late Morning reports collected after a night of sleep. Total amount of content reported from daytime naps, as measured by WIC, was instead similar to reports collected from NREM sleep near the nadir of the CBT rhythm. This relatively low mentation production characteristic of nap reports could not be accounted for by individual differences between subject groups, including differences in WVG or trait dream recall.

The present findings cannot be explained by an exclusively circadian influence on dreaming correlated with the CBT cycle. Although our present data could be accounted

for by a purely homeostatic-driven time course for dreaming, following changes in propensity for SWA across the day, this interpretation would be inconsistent with previous work demonstrating the presence of clear circadian effects on dreaming while controlling for time since sleep onset (Antrobus et al., 1995; Suzuki et al., 2004). Two general scenarios then present themselves as the most plausible accounts of our unanticipated results:

An Additive Influence of Circadian and Homeostatic Effects

Increased circadian activation during the early afternoon nap may have been counteracted by a concomitant increase in sleep need/SWA propensity. Since all subjects in the present study had relatively early habitual sleep phases, with an average wake time before 8:00am, participants were awake for approximately 4-5 hours prior to the experimental nap, providing ample time for the accumulation of sleep need and a concomitant increase in SWA propensity. It is unclear, however, what mechanism might account for an influence of SWA propensity on dream recall from stage 2 NREM sleep, where little slow wave activity is seen.

An Alternative Time Course for a Circadian Effect on Dreaming

We have presumed thus far that a circadian rhythm for dreaming might follow a time course similar to that of CBT, with a nadir several hours prior to habitual waking time and an acrophase in the early evening (Czeisler et al., 1990). However, a recent study employing an ultra-short sleep schedule forced desynchrony protocol provides evidence supporting a quite different time course for the circadian rhythm for dreaming (Suzuki et al., 2004), peaking at 8am and declining thereafter, mirroring the circadian rhythm for REM sleep propensity (Czeisler et al., 1980). Such a time course is broadly

consistent with the results we report here, though direct comparison of our data with that of Suzuki et al. (Suzuki et al., 2004) is difficult due to widely divergent methodology. Our protocol specifically avoids introducing the term "dreaming" to participants and relies on detailed verbal reporting. Suzuki et al. (Suzuki et al., 2004), in contrast, restricted their mentation collection to having subjects rate "how much they dreamed" on a scale of 0-3 at each awakening. This expedient approach was certainly practical given their repeated nap design, yet such divergent methods of collecting dream reports are likely to have a profound influence on the resultant data. Specifically, the method employed by Suzuki et al. (Suzuki et al., 2004) may have resulted in a report collection method sensitive to detecting only more vivid, "REM-like" sleep mentation. In this case, it would not be surprising for the particularly long and vivid dreaming measured by Suzuki et al. (Suzuki et al., 2004) to correlate strongly with circadian fluctuation in REM propensity.

Dreaming in NREM and 'Covert' REM Sleep. Suzuki et al.(Suzuki et al., 2004) have interpreted their data as indicative that dreaming in NREM-exclusive naps is the result of "covert" REM processes (Nielsen, 2000). However, REM sleep is not the only biological function following an endogenous rhythm with an 8am peak, and consequently, an ~8am peak for dreaming in NREM does not imply that dreaming in NREM naps must be attributed to REM-related processes. The endogenous rhythm for cortisol, for example, follows a similar time course (Uchiyama et al., 1998), and given its known influence on memory encoding and retrieval (Andreano & Cahill, 2006; Buchanan & Lovallo, 2001), this neuromodulatory hormone provides at least as plausible an

explanation for a late-morning peak in NREM dream recall as a mysterious influence of REM sleep on dreaming during NREM naps.

In the case of the present study, diurnal variation in REM propensity is a particularly unlikely explanation for the observed variations in dream reporting. Though close proximity to REM sleep may predict the report of mentation from NREM (Nielsen, 2000), we carefully controlled both nap and night awakenings such that mentation reports were always separated from the last REM period by at least 20 minutes. Additionally, NREM reports were not elicited when it appeared that subjects would shortly be entering a REM period. In contrast, studies of the influence of sleep architecture on dream reporting indicate that there is an increased likelihood of reporting dreaming from NREM when awakenings are made within 15 minutes of a REM period (Nielsen, 2000).

Relationship of Current Findings to Previous Studies of NREM Naps

Although several studies have examined the characteristics of mentation during a brief diurnal nap (Benbadis, Wolgamuth, Perry, & Dinner, 1995; Islas-Marroquin & Delgado-Brambila, 1998; Niedermeyer & Lentz, 1976; Palagini et al., 2004; Taub, 1971), no study has previously compared laboratory-collected nap mentation to night mentation reports collected under similar conditions. Across studies, average recall of dreaming from daytime naps containing exclusively NREM has been 37.4% (Benbadis et al., 1995; Islas-Marroquin & Delgado-Brambila, 1998; Niedermeyer & Lentz, 1976; Palagini et al., 2004; Taub, 1971), a figure comparable to the 40% recall from NREM naps that we report here. Yet recall rates have varied widely, one study reporting that only 16% of subjects recalled any mentation (Niedermeyer & Lentz, 1976), and another an astounding 97% (Palagini et al., 2004). This variability seems to be related to substantially different

methodologies for collecting dream content across these studies, as well as differences in definitions of 'dreaming'. Generally low figures for NREM nap recall (with the exception of Palagini et al. (Palagini et al., 2004)) stand in stark contrast to anecdotal reports of long, vivid dreaming during daytime napping and the observation that vivid lucid dreams are more likely to occur during a late morning nap as opposed to at the end of a night of sleep (LaBerge, Phillips, & Levitan, 1994). Non-laboratory reports of intense or lucid nap dreaming could be due to the presence of REM sleep in longer naps, or to sleep fragmentation, a reported predictor of dreaming during NREM (Takeuchi, Miyasita, Inugami, & Yamamoto, 2001; Takeuchi, Ogilvie, Murphy, & Ferrelli, 2003).

Conclusions

Within-stage changes in sleep mentation across the night indicate the presence of sources of activation to the dreaming process other than the REM/NREM cycle. Understanding these processes is crucial to the study of cognition in sleep, inasmuch as we hope to identify its neural basis. The present study is the first to examine dreaming during daytime NREM naps in comparison to night reports, providing initial data on the relative contribution of homeostatic vs. circadian factors to changes in NREM mentation across the diurnal cycle. The low mentation production observed during early afternoon napping indicates that a purely circadian influence following the endogenous core body temperature rhythm is inadequate to explain diurnal variations in sleep mentation within NREM. Time-of-night effects on NREM mentation may therefore be due to either *a)* the combined influence of circadian and homeostatic factors or *b)* an exclusively circadian contribution to mentation reporting with an acrophase during the late morning hours (Suzuki et al., 2004). Future work addressing these questions should employ constant

routine and forced desynchrony protocols, which are better able to parse circadian and homeostatic influences on sleep mentation.

IV.

The Expression of Hippocampally-Dependent Learning in NREM Sleep and its Relation to Sleep Mentation

Accumulating evidence suggests that the consolidation of declarative memory is facilitated by NREM (non-rapid eye movement) sleep, as the hippocampus mediates reactivation of cortical ensembles involved in recent learning (Gais & Born, 2004; Lee & Wilson, 2002; Maquet, 2001; Nadasdy et al., 1999; Peigneux et al., 2004; Wilson & McNaughton, 1994). This emerging idea that neural "replay" of memories occurs during sleep has naturally prompted speculation that dreaming may represent a cognitive component of memory consolidation (Kavanau, 2001; Maquet, 2001; Nielsen & Stenstrom, 2005; Paller & Voss, 2004; Payne & Nadel, 2004). So far, however, this assumption remains untested. The present study aims to test the hypotheses that a) recent declarative learning can be expressed during NREM sleep and b) experimentally induced hippocampal memory reactivation in sleep will be accompanied by observable effects within concomitant sleep mentation.

Hippocampally-Dependent Memories are Consolidated During NREM Sleep

During the encoding of "declarative" memories (memories of facts and events) the hippocampus is responsible for forming rapid associations between diverse cortical networks representing memory features (Eichenbaum, 2004; McClelland, McNaughton, & O'Reilly, 1995). Neurological models of memory consolidation are grounded in evidence that, although declarative memory is initially dependent on the hippocampus, over time repeated memory trace reactivation enables the cortex to support retrieval without the need of hippocampal involvement (Buzsaki, 1996; McClelland et al., 1995;

Squire, Stark, & Clark, 2004). This time-dependent role of the hippocampus in declarative memory has been widely supported by observations of memory deficits in hippocampally-damaged patients as well as by hippocampal lesion studies in animals (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Frankland & Bontempi, 2005; Spiers, Maguire, & Burgess, 2001; Squire et al., 2004).

The repeated reactivation of recent declarative memories thought to be crucial to consolidation (Buzsaki, 1996, 1998; Lee & Wilson, 2002; McClelland et al., 1995) may occur optimally during NREM sleep (Buzsaki, 1996). During the "closed-loop" state of NREM, the hippocampus is thought to mediate reactivation of cortical ensembles involved in recent experience (Buzsaki, 1996; Peigneux et al., 2004; Wilson & McNaughton, 1994). This reactivation may be the primary mechanism by which memory consolidation proceeds – each successive reinstatement of the cortical pattern slowly strengthens cortico-cortical connections which will eventually allow memory networks to be accessed without hippocampal involvement (Paller & Voss, 2004). Buzsaki (1996) has proposed that hippocampal sharp-wave/ripple (SPW-R)[1] activity during NREM may facilitate this sleep-dependent declarative memory reactivation. SPW-R activity is thought to preferentially recruit neurons involved in the encoding of recent experience, and to induce plasticity in the hippocampus and in cortical targets, thereby facilitating long-term memory storage (Buzsaki, 1998). Indeed, SPW-R-like events have been found to support synaptic reorganization in vitro (Behrens et al., 2005; Ben-Ari & Gho, 1988).

[1] SPW-R's, initiated by pyramidal cells in CA3 of the hippocampus, are high amplitude population bursts in which 40,000-60,000 medial temporal lobe cells participate (Buzsaki, 1998). Very high frequency (140-200 Hz) "ripple" activity is superimposed on this relatively slow population burst (Behrens et al., 2005; Buzsaki, 1998). During SPW-R's output layers of entorhinal cortex are selectively activated, suggesting that these events propagate activity out to the rest of the cortex (Chrobak & Buzsaki, 1994).

In the behaving animal, hippocampal firing patterns observed during waking exploration are re-expressed in later sleep, most often in NREM (Lee & Wilson, 2002; Nadasdy et al., 1999; Wilson & McNaughton, 1994). This neural "replay" of recent experience occurs preferentially during SPW-R events (Kudrimoti et al., 1999; Pennartz et al., 2004) and likely represents the metaphorical "transfer" of information from the hippocampus to the cortex which underlies memory consolidation. Evidence supporting this assumption includes observations of a close temporal relationship between neocortical oscillations and hippocampal SPW-R activity during sleep (Battaglia et al., 2004; Molle et al., 2006; Siapas, Lubenov, & Wilson, 2005; Siapas & Wilson, 1998; Sirota et al., 2003).

Behavioral studies in humans also suggest a role for NREM in the consolidation of declarative memories, demonstrating that declarative learning is selectively facilitated by post-learning NREM sleep (Gais & Born, 2004; Plihal & Born, 1999; Tucker et al., 2006). Using fMRI in humans, Peigneux et al. (2004) recently demonstrated that sleep-dependent improvement on declarative memory tasks in humans, as in animals, relies on the reactivation, during NREM, of activity patterns first seen in pre-sleep learning. Takashima et al.'s recent study (2006) adds to this literature by confirming that, over time, declarative memory retrieval in humans relies to a lesser degree on hippocampal networks and to a greater degree on neocortical structures, and that furthermore, amount of post-training slow wave sleep predicts the extent of this functional reorganization (Takashima et al., 2006).

Recent Declarative Memories and Mental Activity During Sleep

Although research on the role of sleep in consolidating declarative memories clearly suggests that memory processing might affect sleep mentation (Gais & Born, 2004; Maquet, 2001; Paller & Voss, 2004; Stickgold, Hobson, Fosse, & Fosse, 2001a), no empirical evidence as yet clearly supports or contradicts this position. The mere examination of subjective reports has not been able to provide an unambiguous test of the proposition that mentation from any sleep stage includes specifically hippocampally-dependent content. Though dreams clearly incorporate content related to recent experience (Arkin & Antrobus, 1991; Cartwright, 1991; De Koninck & Koulack, 1975; Dement, Kahn, & Roffwarg, 1965; Witkin & Lewis, 1965), studies of the effects of presleep stimuli on sleep mentation have not resulted in an understanding of the mechanism of these incorporations. Overall, direct incorporations of pre-sleep experimental manipulations into subsequent mentation reports are quite rare (Arkin & Antrobus, 1991).

A handful of studies have provided tentative evidence for a connection between sleep mentation and recent learning (Cipolli, Fagioli, Mazzetti, & Tuozzi, 2004, 2005; Fiss, Kremer, & Lichtman, 1977; Smith & Hanke, 2004). Smith & Hanke (2004) report preliminary evidence of dream content related to a pre-sleep declarative learning task, which was present to a greater degree in participants "cued" during sleep using a sound associated with this learning task. Fiss et al. (1977) reported that dreaming of stories presented to participants prior to sleep was associated with enhanced morning recall of those stories. Similarly, it has been reported that mental content from night awakenings is better remembered in the morning if it is 1) repeated throughout the night (Cipolli et al., 2005) or 2) related to a pre-sleep learning task (Cipolli et al., 2004).

However, despite apparent ties between recent episodic memory and sleep mentation, it is obvious that our dreams are rarely, if ever, exact replays of waking life experience. Instead, sleep mentation contains portions of recent episodic memories intermingled with other content (Fosse, Fosse, Hobson, & Stickgold, 2003). However, if sleep mentation is generated by the neural replay of recent memory facilitating consolidation, it does not necessarily follow that either the neural replay or the mental content in question would exactly replicate waking life experience. In fact, it is likely that the repeated, exact replay of recent experience would actually be a maladaptive strategy for memory consolidation (McClelland et al., 1995). On the contrary, it is thought that offline replay of recent memory must necessarily be gradual and "interleaved" with the replay of remote and semantic memories in order to lead to successful long-term storage (McClelland et al., 1995). Indeed, electrophysiological studies of memory reactivation in rodents support the notion that memory is not replayed during sleep in its original form. After learning a spatial task, pieces of firing sequences established in wakefulness are intermittently "replayed" during NREM sleep in the rodent hippocampus on a faster time scale than that at which the original experience occurred (Lee & Wilson, 2002; Nadasdy et al., 1999).

Within the small body of work on sleep-dependent memory processing and concomitant mentation, a connection between NREM dreaming and memory processing has not often been considered. This is likely due to a strong residual bias in both psychology and neuroscience towards the idea that dreamlike mentation can only be supported by REM sleep (Hobson et al., 2000). In reality, cognitive content is recalled on average from about 50% of NREM awakenings (Nielsen, 2000), though this NREM

mentation is sometimes characterized as being more "thought-like" than that from REM (Hobson et al., 2000). Yet given the demonstrated role of NREM sleep in processing recent declarative-type memories (Gais & Born, 2004; Lee & Wilson, 2002; Plihal & Born, 1999; Tucker et al., 2006; Wilson & McNaughton, 1994), and the relatively well-defined physiological models of how this consolidation might take place in NREM (Buzsaki, 1998), it seems that the search for the expression of recent episodic memory processing in sleep mentation should focus on NREM. The prudence of this approach is further supported by a group of studies demonstrating that episodic memories are more likely to be incorporated into NREM, as opposed to REM, mentation (Baylor & Cavallero, 2001). REM sleep appears to largely be tied to the processing of implicit procedural-type memory (Walker & Stickgold, 2004), the encoding of which is not necessarily accompanied by conscious awareness even during wakefulness. It therefore does not seem particularly likely that reactivation of implicit procedural memories during REM would be accompanied by conscious experience transparently related to previous waking experience.

Approach of the Present Research

The present study represents a first attempt to identify whether sleep mentation does, in fact, represent a cognitive correlate of sleep-dependent memory consolidation. Toward this end, we experimentally induced hippocampally-mediated memory retrieval during NREM sleep using a trace conditioning protocol, and then observed the effects of this manipulation on EEG and heart-rate conditioned responses (CRs), as well as on sleep mentation.

"Trace conditioning" has recently emerged as a well-characterized, simple model of hippocampally-dependent declarative memory (Clark, Manns, & Squire, 2002). In trace conditioning, a temporal gap between the offset of the conditioned stimulus (CS) and onset of the unconditioned stimulus (UCS; see Figure 10) renders the hippocampal complex necessary for both acquisition and expression of CRs (Buchel, Dolan, Armony, & Friston, 1999; Knight et al., 2004; McEchron, Tseng, & Disterhoft, 2000). Lesion studies in animals clearly demonstrate that an intact hippocampus is required for both acquisition and retrieval in trace fear conditioning tasks similar to the one employed here (Burman, Starr, & Gewirtz, 2006; Chowdhury, Quinn, & Fanselow, 2005; Fendt, Fanselow, & Koch, 2005; McEchron et al., 2000). Individual cells in the CA1 region of the dorsal hippocampus have been observed to exhibit conditioning-dependent firing adaptively timed to the duration of the trace interval separating the CS and UCS (McEchron, Tseng, & Disterhoft, 2003). Studies in humans compliment these findings, demonstrating that amnesiacs with bilateral hippocampal damage are impaired in acquiring trace conditioning tasks (McGlinchey-Berroth et al., 1997), and that conditioning-related activation occurs in the hippocampus of healthy volunteers during trace protocols (Buchel et al., 1999; Knight et al., 2004). Further supporting the characterization of trace conditioning as a declarative task, unlike delay conditioning, successful acquisition of trace conditioning is predicted by conscious awareness of stimuli relations (Carter et al., 2006; Clark et al., 2002; Han et al., 2003).

Unlike trace conditioning, "delay" classical conditioning requires neither hippocampal nor cortical contributions, as it is acquired at normal rates in decerebrate animals (Kotani, Kawahara, & Kirino, 2002). Furthermore, delay conditioning is

unrelated to awareness of stimuli relations (Clark et al., 2002). Several studies have reported evidence of classical delay-conditioned responses (CRs) in sleeping animals and humans when a CS is presented during post-training sleep (Beh & Barratt, 1965; Conduit & Coleman, 1998; Hennevin & Maho, 2005; Ikeda & Morotomi, 1997; Maho & Hennevin, 1999; McDonald et al., 1975). As during wakefulness, this expression of delay-conditioning during sleep would presumably not require hippocampal processing[2], whereas the similar expression of trace conditioning in sleep *would* necessarily depend on hippocampally-mediated reactivation of the recently learned association (Clark et al., 2002; McEchron et al., 2000).

Here, it is hypothesized that, as demonstrated for delay conditioning (Beh & Barratt, 1965; Hennevin & Maho, 2005; Ikeda & Morotomi, 1997), trace-conditioned responses will also be elicited during NREM in response to a CS cue. Expression of trace-conditioned responses during NREM would behaviorally confirm that hippocampally-mediated memory reactivation is functional during this sleep stage. Furthermore, due to the crucial involvement of the hippocampus and cortex in trace conditioning, as well as its demonstrated relationship with conscious awareness, it is anticipated that in trace-conditioned participants, physiological CRs will be accompanied by conditioning-dependent effects within concomitant sleep mentation. Support for this latter hypothesis would suggest that hippocampally-mediated memory reactivation contributes to the generation of mental activity in sleep.

Methods

[2] Note that, while it is clear that delay conditioning does not ***require*** hippocampal contributions, hippocampal activation may nonetheless be observed during acquisition of delay conditioning in the intact organism (Knight et al., 2004).

Participants (n=43) were undergraduate students from The City College of New York, recruited from psychology courses. Participants underwent discriminatory auditory fear conditioning prior to sleep, under either a *delay conditioning* or a *trace conditioning* protocol (Figure 10). 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) x 2(Cue Type: Conditioned Stimulus vs. Control Cue) mixed factorial design, in which Conditioning Type was a between-subjects factor and Cue Type was a within-subjects factor.

Six participants had to be excluded from final analyses due to technical difficulties including failure of subjects to maintain a sufficient amount of sleep, technical difficulties with the pre-sleep conditioning procedure, and the emergence of REM during stimulus presentation trials in sleep. The final sample consisted of n=18 Trace conditioning participants and n=19 Delay conditioning participants.

Pre-Sleep Procedures

Upon arriving at the laboratory at 9:30pm, participants were familiarized with the facilities and signed consent. Polysomnographic variables were measured using a standard EEG (C3-A2, C4-A1), EOG, EMG, and EKG montage. Signals were amplified using Grass Model 7 amplifiers and digitally converted for acquisition and analysis using Grass-Telefactor's *Gamma* software.

Approximately 30 minutes prior to an experimental bedtime of 12:00am, participants were trained using either:

1) A *"trace conditioning"* paradigm (hippocampally dependent) in which a neutral auditory stimulus predicted the subsequent occurrence of a startling auditory stimulus after a 15 second interval of silence.
2) A *"delay conditioning"* paradigm (<u>not</u> hippocampally dependent) in which a neutral auditory stimulus predicted the subsequent occurrence of a startling auditory stimulus which initiated exactly at the offset of the CS.

During the pre-sleep conditioning procedure, participants lay quietly in a sound-attenuated bedchamber. The UCS was the sound of a car horn (100dB, duration = 1 sec.), which always followed the conditioned stimulus (CS+). Participants were also intermittently exposed to a control stimulus (CS-), equal in intensity and duration to the CS+, but never paired with the UCS. The CS+ and CS- were 200Hz pulsed tones and 1200Hz pure tones (each 1 sec in duration) presented over a speaker mounted 4ft. above participants' beds. The assignment of which tone served as the CS+ was counterbalanced across participants in order to avoid any confounds related to stimulus characteristics.

Prior to conditioning, each of the three stimuli (the UCS, the CS+, and the CS-) were played twice in an unpaired fashion in order to habituate participants to the sounds. Participants 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".

During pre-sleep conditioning, there were 10 presentations each of the CS+ and the CS-, separated by randomly-determined intervals varying between 25 and 45 sec. (average ISI=35 sec.). The order of CS+ and CS- presentations was also randomly

determined, but stimulus order and ISI's were the same for every subject, regardless of condition. *For Delay-conditioned participants, the UCS was always administered immediately at the offset of the CS+ tone.*

For Trace-conditioned participants, the UCS always initiated exactly 15 seconds after termination of the CS+ tone. This relatively long trace interval was necessary in light of recent 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). 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 presleep training to 10 pairings of the CS+ and UCS (Buchel et al., 1999). To reiterate, previous research strongly supports the presumption that trace-conditioned responses, acquired under the particular training parameters described here, will necessarily require hippocampal processes for their expression (Burman et al., 2006; Chowdhury et al., 2005; Fendt et al., 2005; McEchron et al., 2000).

The 200Hz and 1200Hz tone were matched on subjective loudness, rather than objective intensity. Four pilot subjects provided an estimation of subjectively equivalent loudness levels for the tones using a matching procedure in which they adjusted the volume of the 200Hz tone until its perceived intensity was equivalent to that of the 1200Hz tone at 60 dB[3].

Following acquisition, a single probe trial was administered in which one presentation of the CS+ and one presentation of the CS- occurred without subsequent occurrence of the UCS. Heart rate and EEG responses were recorded throughout this procedure.

[3] Based on this procedure, baseline intensity for the 200Hz tone was set slightly higher than the intensity of the 1200Hz tone (to 64dB). In subject rooms, tone intensities (peak dB level) were measured using an analogue SPL meter positioned between the wall-mounted speaker and the subjects' pillow.

Procedures During Sleep

Subjects were put to bed approximately 30 minutes following conditioning. During the night, CS+ and CS- tones were played over the speaker in subjects' rooms. Two CS+ and two CS- trials were conducted for each participant, in an alternating fashion, with order of trials counterbalanced across subjects. Resultantly, mean time since sleep onset for CS+ and CS- trials was roughly equivalent (Table 4).

Stimulus delivery always began after at least 10 continuous minutes of stage 2 NREM sleep, at least 15 minutes from the last epoch of REM or wakefulness, and at least 20 minutes following initial sleep onset. In order to control for large individual differences and time of night effects on arousal and response thresholds, up to seven stimulus intensity levels were administered during sleep. At each data collection point, tones were presented every 25 seconds, beginning at the lowest intensity level[4] and increasing in intensity at 5dB increments until a stimulus elicited > 5 sec. of waking-frequency EEG (alpha or beta), or until seven intensity increases had been administered, at which point stimulus presentation was terminated. 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 in their room once per second until they responded. Participants were 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.

[4] Stimulus intensity began at 45dB for the 1200Hz tone and at 49dB for the 200Hz tone.

Participants also completed a visual analogue scale on which they were asked to indicate the emotional tone of their mentation just prior to awakening. The scale consisted of an 8-inch line on which the center indicated neutral/no emotion, and the poles were labeled as intensely positive emotion and intensely negative emotion. Scores on this scale may vary from –4 to +4 (Appendix A). Emotional Valence was calculated as the average emotion rating for each cue type, scores indicating the relative positivity or negativity of recalled emotions.

Data Scoring and Preprocessing

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 in response to experimental stimuli (CS+ and CS-). A "brief arousal" was defined as the intrusion of ≤5 seconds of waking-frequency EEG (alpha or beta) into the sleep record, followed by an immediate return to theta-frequency EEG. A stimulus-induced response in these categories was scored only if the EEG feature in question initiated within 2 seconds of stimulus onset. Subjects were classified as having awakened in response to a stimulus if >5 seconds of waking-frequency EEG appeared in the record following stimulus presentation, regardless of whether the subject then returned to sleep (which was often the case). Inter-rater reliability for determining the stimulus level inducing awakening was .95. Percentage agreements in determining the presence of sub-awakening arousals and sub-arousal K-complexes were 77.5% and 86.9%, respectively.

Heart rate responses. In wakefulness, HR responses to an auditory stimulus consist of three primary components: an initial deceleration during the first 3 beats,

followed by an acceleration peaking at approximately beats 4-6, and a subsequent more extended deceleration maximal from beats 9-12 (Keefe, Johnson, & Hunter, 1971). During stage 2 sleep, evoked HR responses are similar, though the initial deceleratory component (beats 1-3) is not consistently observed and the acceleratory component is much larger in size than during waking (Hord, Lubin, & Johnson, 1966; Johnson, 1970; Johnson & Lubin, 1967). In the present study, t-tests were used to examine conditioned HR responses in each of these three timeframes during both wakefulness and sleep. Based on previous research, conditioned responses were expected to most likely occur within the timeframe of the acceleratory response (beats 4-6) (Maschke et al., 2002; Moratti & Keil, 2005; Prescott, Durkin, Furchtgott, & Powell, 1992).

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. Heart rate responses are plotted on a beat-by-beat basis as change in beats per minute (BPM) rate from baseline (defined as the average BPM of the last 5 pre-stimulus beats).

Heart rate variability (HRV) was defined as the standard deviation of the R-R interval of the first 20 post-stimulus beats. HRV is affected by anxiety, stress (Gianaros, Van Der Veen, & Jennings, 2004; Inagaki, Kuwahara, & Tsubone, 2004; Stiedl et al., 2003; Stiedl & Spiess, 1997), and cognitive load (Gianaros et al., 2004). Short-term decreases in high-frequency HRV often accompany anxiety or stress-induced HR acceleration, and are thought to be primarily under sympathetic control, whereas increases in HRV are thought to be primarily parasympathetic, seen in conjunction with deceleratory HR responses (Inagaki et al., 2004; van Ravenswaaij-Arts et al., 1993).

HRV analyses were also carried out separately for stimulus intensity levels just prior to that those which a) caused awakening and b) caused the first arousal.

Additional cognitive variables. Mentation reports were transcribed prior to being scored by two blind raters. Amount of mentation content reported in response to question 1 was assessed using Word Information Count (WIC), a modified word count measure which ignores non-words, repetitions, and all other words not directly providing new information about the sleep mentation (Antrobus, 1983; Wamsley et al., in press). Inter-rater reliability for WIC was .97. For each mentation report, raters also assessed whether the report contained content potentially related to the experimental procedures in each of the following categories:

a) content related to the laboratory setting

b) specific mention of hearing a sound in the dream

c) specific mention of a car

Detailed written instructions provided to raters regarding these determinations are included in Appendix B. Raters agreed on these determinations in 97.3% of cases. For purposes of analysis, a given report was considered to include the above elements only in those cases where both raters agreed that the content element in question was present.

Results

Expression of Conditioned Responses in Wakefulness

Both Delay-conditioned and Trace-conditioned participants demonstrated clear HR conditioning during wakefulness. Consistent with previous research, in Delay subjects the CR consisted of a HR deceleration maximal during post-stimulus beats 4-6 (Maschke et al., 2002; Moratti & Keil, 2005; Prescott et al., 1992). Deceleration in

response to the CS+ was significantly greater than to the CS- during this timeframe, responses to the CS- being generally acceleratory (t_{18}=2.99, p<.01; Figure 11). Conversely, in Trace-conditioned subjects, the conditioned HR response consisted of an immediate and long-lasting acceleration to the CS+ persisting throughout the first 10 post-stimulus beats (t_{18}=2.14, p<.05; Figure 11).

In Trace-conditioned subjects, HRV for the first 20 post-stimulus beats was significantly elevated in response to the CS+ as compared to the CS- (t_{18}=2.13, p<.05; Figure 12), while there was no effect of cue type on HRV in Delay-conditioned participants (p>.6). In a 2(cue type) x 2(conditioning type) ANOVA on HRV scores, there was a trend towards a Conditioning Type x Cue Type interaction ($F_{1,35}$=3.02, p=.09; Figure 12).

Physiological Responses in Sleep

Awakening Thresholds. Awakening threshold was defined as the stimulus intensity level (1-7) first inducing >5 sec of waking EEG. Thresholds were similar for CS+ and CS- cues (p>.2 for main effect of cue), and similar for Trace and Delay participants (p>.5 for main effect of condition, no cue x conditioning type interaction). However, as anticipated, awakening thresholds varied substantially according to time of night, with thresholds for the 2nd set of trials, conducted later in the night, being significantly lower than for initial trials (threshold for trial 1=5.33±1.71 SD, for trial 2=4.17,±1.78 SD; 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).

EEG responses. Both Delay and Trace participants exhibited conditioned EEG responses during sleep. All participants were significantly more likely to exhibit sub-

awakening arousals[5] in response to the CS+, as opposed to the CS- cue (main effect of cue type: $F_{1,35}$=6.208, p=.02, η_p^2=.15; Figure 13). Here there was no interaction between cue type and conditioning type (p>.3), and no main effect of conditioning type (p>.7). Trace (t_{17}=2.13, p=.056), but not Delay (t_{18}=1.07, p=.30) participants were also more likely to exhibit K-complexes in response to the CS+ vs. the CS- cue, at stimulus intensities prior to any EEG arousal (cue type x conditioning type interaction: $F_{1,35}$=4.11, p<.05, η_p^2=.15; no significant main effects; Figure 14).

Heart rate responses. Though sub-awakening (Figure 15) and sub-arousal (Figure 16) heart rate responses with the expected components occurred in response to experimental stimuli, conditioned responses were not clearly evident in this measure. Delay-conditioned participants exhibited a near-significant conditioned HR acceleration at the stimulus level just below that which induced awakening (Figure 15). This near-significant difference in responsiveness to the CS+ vs. the CS- occurred during the early declaratory component (post-stimulus beats 1-3; t_{18}=1.78, p=.09; Figure 15). No other effects of cue type (CS+ vs. CS-) on HR components just below awakening or just below arousal approached significance in either conditioning group (p>.1 for all comparisons; Figures 15 & 16). Note that variance in mean BPM change from baseline within the timeframe of each HR component was quite high. Prior to analysis, these data were square-root transformed to reduce substantial skewness and kurtosis.

Heart Rate Variability. There were no effects of cue type on HRV during sleep in either Trace or Delay participants. For all effects in a 2(cue type) x 2(conditioning type)

[5]Defined as a ≤5 sec intrusion of alpha or beta EEG frequency in response to a stimulus intensity below that which caused awakening.

ANOVA on trials just below awakening, $p>.5$. For trials just below arousal, $p\geq.2$ for all effects.

Cognitive Responses in Sleep

Emotional Valence. Dreamed emotions were generally more negative in tone during CS+, as compared to CS-, trials across all participants, evident in a significant main effect of cue type on Emotional Valence in a 2(Cue Type) x 2(Conditioning Type) ANOVA ($F_{1,35}=4.64$, $p<.05$, $\eta_p^2=.12$; Figure 17). Here there was no main effect for Conditioning Type, and no Cue Type x Conditioning Type interaction.

Time elapsed since sleep onset positively correlated with emotional valence ratings, such that negative emotional ratings occurred predominantly for trials conducted earlier in the night ($r=.18$, $p<.05$). Additional analyses were therefore conducted to examine whether the effect of Cue Type (CS+ vs. CS-) on Emotional Valence was dependent on Trial (1st vs. 2nd) within Trace and Delay subjects. When Trial was added as a 3rd factor in an ANOVA including only subjects for whom all four trials during the night were successfully completed (n=25), a trend towards a 3-way Cue Type x Conditioning Type x Trial interaction was evident ($F_{1,23}=1.77$, $p=.19$; Figure 18). Within early night trials (all subjects included), not only does the CS+ elicit significantly more negative emotion ratings overall (main effect of Cue Type: $F_{1,34}=5.90$, $p<.05$, $\eta_p^2=.15$; Figure 18), but there is also a significant Conditioning Type x Cue Type interaction ($F_{1,34}=4.25$, $p<.05$, $\eta_p^2=.11$; Figure 18). This interaction reflects the fact that, within Trace-conditioned participants in the early night, the CS+ elicits significantly more negative emotion than the CS- ($t_{17}=2.67$, $p<.05$; Figure 18), though Emotional Valence ratings are unaffected by Cue Type in the Delay group ($p>.7$; Figure 18). In a separate

analysis examining only the 2nd trials of the night, there were no significant main effects and no Conditioning Type x Cue Type interaction ($p \geq .4$ for all comparisons; Figure 18).

Word Information Count. Response patterns for WIC also differed substantially between the 1st and 2nd pair of trials during the night. In a 2(Cue Type) x 2(Conditioning Type) ANOVA, there was no main effect of Cue or Conditioning Type on WIC, as well as no interaction. However, when trial was added as a third factor, a highly significant Cue x Conditioning x Trial 3-way interaction emerged ($F_{1,24}=17.83$, $p<.001$, $\eta_p^2=.43$; Figure 19). Although there was no effect of Cue Type on WIC within Trace participants on the 1st set of trials ($p>.4$), Delay participants reported more mentation following the CS+, as opposed to the CS- cue ($t_{18}=2.07$, $p=.05$; Figure 19). For these early trials, there was a trend towards a Cue x Conditioning Type interaction ($F_{1,35}=3.47$, $p=.07$, $\eta_p^2=.09$). On the 2nd trials of the night, there was a significant Cue x Conditioning Type interaction ($F_{1,24}=6.90$, $p<.05$, $\eta_p^2=.22$; Figure 19). Here, a near-significant trend emerged for Trace participants to recall more content from sleep in response to the CS+, as opposed to the CS- cue ($t_{13}=1.80$, $p=.09$). However, on these later trials the opposite trend was seen for Delay participants, for whom WIC scores were greater in response to the CS- ($t_{11}=1.94$, $p=.08$).

Relation of Sleep Mentation to Experimental Procedures. Reports very infrequently incorporated content potentially related to the experimental procedures. Overall, only 5% of 130 reports explicitly mentioned sounds, 3% explicitly mentioned cars, and 2% included mention of the laboratory context (Table 6). The low instance of these content elements precludes drawing meaningful conclusions regarding their

distribution across condition, as the expected cell counts are too low to support a valid approximation of the Chi-Square statistic.

Recall of Experimental Stimuli. Despite the fact that stimulus delivery frequently resulted in EEG arousal, subjects reported hearing tones on only 37.7% of trials overall. There was no effect of either Cue Type or Conditioning Type on the % of trials on which subjects correctly recalled the experimental stimuli ($p>.5$ for Cue and Conditioning type main effects and interaction; Table 5).

Arguing against a possible influence of demand characteristics, whether or not subjects reported hearing the stimulus on a particular trial did not influence their emotion ratings ($t_{125}=1.31$, $p=.2$) nor whether mentation was reported on that trial ($\chi_1=1.11$, $p=.3$).

Relationship between Physiological and Cognitive Measures. Sub-awakening arousals were positively associated with amount of sleep mentation reported ($r_{74}=.25$, $p<.05$). Arousals were unrelated to Emotional Valence. K-complexes and HR responses were unrelated to WIC and to Emotional Valence.

Discussion

Expression of Delay-Conditioning in Sleep

Delay-conditioned responses established during wakefulness were expressed during post-training NREM sleep. This was most clearly observed in a tendency for subjects to exhibit more short (<5 sec) arousals in response to the conditioned stimulus, as compared to the control cue.

At stimulus intensities just below awakening, increased HR acceleration in response to the CS+, as compared to the control cue, did not reach statistical significance (Figure 15). However, this response pattern, in which the CR during wakefulness

consists of an HR deceleration and subsequent CRs during sleep are conversely acceleratory, is consistent with the results of a single previous study examining expression of HR conditioning during sleep in a delay paradigm (Ikeda & Morotomi, 1997), which renders this near-significant finding more compelling than it otherwise would be. The high degree of variability observed in evoked HR responses, in conjunction with the low number of trials obtainable during this single experimental night, could have contributed to a lack of significant findings for this dependent measure.

Cognitive data suggest that physiological expression of delay conditioning in sleep may have been accompanied by conditioning-dependent effects of Cue Type on the amount of mentation reported. On the 1st trials of the night, Delay participants recalled more mentation in response to the CS+ as compared to the control cue, though in the later night a trend in the reverse direction emerged. Meanwhile, Cue Type appeared to have no effect on the Emotional Valence of mentation reports in Delay subjects. Despite a significant main effect of Cue Type on Emotional Valence, Cue Type did not significantly affect Emotional Valence in the Delay group on either the 1st or 2nd trial of the night.

Expression of Trace Conditioning in NREM

Trace-conditioned subjects also expressed conditioned responses during post-training NREM sleep. Here, CRs were expressed through a tendency to exhibit both more brief arousals and more K-complexes in response to the CS+, as compared to the control cue. Again, note that, based on previous research, these CRs observed in the trace-conditioned group can reasonably be presumed to rely on hippocampally-mediated memory reactivation (Buchel et al., 1999; Burman et al., 2006; Chowdhury et al., 2005;

Fendt et al., 2005; McEchron et al., 2000). Though the fact that only Trace-conditioned participants exhibited conditioned K-complex responses could be attributed to differential involvement of hippocampal and cortical structures in Trace vs. Delay conditioning, note that previous research has demonstrated conditioning of the K-response under a delay paradigm as well (Beh & Barratt, 1965).

As hypothesized, physiological trace-conditioned responses were accompanied by conditioning-dependent effects on the emotional valence of sleep mentation, such that the CS+ cue induced a negative emotional tone, relative to the control cue (Figure 17). Note, however, that the fact that this relationship was seen only on early trials was unanticipated.

Conversely, Trace-conditioned participants exhibited a trend towards a conditioning effect for *amount* of mentation recalled only later in the night, on the 2nd pair of trials. As with the physiological CRs, conditioning-dependent effects on sleep mentation in the trace group almost certainly relied on hippocampally-mediated memory reactivation, suggesting that hippocampal output may influence at least some qualitative features of mentation during NREM sleep.

The Effect of Time-of-Night on Conditioned Responses. Conditioned responses expressed in the Emotional Valence of sleep mentation, and in amount of mentation reported, were differentially dependent on time of night (Figures 18, 19). Conditioning-dependent effects seen in WIC and Emotional Valence measures may have relied on very different neural substrates for their expression. Presumably, conditioning effects on emotionality require output from the central nucleus of the amygdala for their expression (LeDoux, 2000; LeDoux, Iwata, Cicchetti, & Reis, 1988). Given the fact that a

conditioned Emotional Valence effect was seen only in the Trace group, where conditioned responses additionally require hippocampal involvement, it is reasonable to hypothesize that hippocampal-amygdala communication specific to trace acquisition was critical in the expression of this particular response. As results for WIC differed substantially from those for Emotional Valence, WIC responses may have relied on a different set of processes for their expression than amygdala-mediated emotional responses. Note that, for certain dependent measures (i.e. skin conductance), hippocampally-dependent, awareness-related, CRs may be seen even in delay-conditioned participants, though the expression of delay conditioning though other measures clearly proceeds independently of hippocampal involvement (Clark et al., 2002; Hamm & Weike, 2005). Therefore, in the present study, even in the *delay* group, mentation effects could have relied on hippocampal processes. In the present study, WIC could have represented a declarative-type response dependent primarily on the hippocampus, whereas Emotional Valence may have been additionally dependent on hippocampal-amygdala communication specific to the trace group.

A number of physiological variables likely differed between the 1st pair of trials, earlier in the night, and the 2nd pair of trials later in the night, including core body temperature (Czeisler et al., 1990; Wright et al., 2002), cortisol levels (Uchiyama et al., 1998), slow wave activity (Benington, 2004; Borbely et al., 1981) REM sleep propensity (Czeisler et al., 1980; Fosse, 2000; Wurts & Edgar, 2000), and the organization of the recently acquired memory traces, as consolidation of both declarative and non-declarative memory is presumed to be proceeding across the night (Peigneux et al., 2004; Plihal & Born, 1999; Walker & Stickgold, 2004). Changes in one or more of these physiological

variables across the night apparently exerted a differential effect on the neural substrate underlying expression of conditioning through Emotional Valence vs. expression of conditioning through WIC.

Given the fact that conditioning effects on EEG variables and near-significant conditioning effects on WIC were present on later trials, habituation or extinction processes seem an unlikely explanation for the lack of Emotional Valence CRs later in the night. It should be noted, however, that habituation of heart rate responses (McDonald & Carpenter, 1975) and extinction of conditioned responses (Coenen & Drinkenburg, 2002) can occur during NREM sleep, though these processes may require a larger number of stimulus presentations than the present study employed (Coenen & Drinkenburg, 2002; McDonald & Carpenter, 1975).

Hippocampal Memory and REM Sleep

The present study did not examine REM sleep, due to strong evidence that declarative-type memories are re-expressed primarily in NREM (Baylor & Cavallero, 2001; Plihal & Born, 1999; Wilson & McNaughton, 1994). Hippocampal output to the cortex may be blocked during REM sleep as a result of elevated acetylcholine levels (Hasselmo, 1999), thereby prohibiting the expression of trace conditioning in REM. Indeed, the single previous study examining the expression of trace-conditioning in post-learning sleep reported that CRs were seen in NREM, but not in REM sleep (McDonald et al., 1975). Nonetheless, hippocampal memory reactivation has been observed during REM sleep (Louie & Wilson, 2001). Future studies examining the expression of trace-conditioning in REM may be able to assist in clarifying the functioning of hippocampal memory systems in this sleep stage.

Conclusions

Evidence of declarative memory consolidation in sleep has consisted primarily of behavioral studies demonstrating that NREM enhances performance on declarative tasks (Gais & Born, 2004; Plihal & Born, 1999; Tucker et al., 2006), complimented by observations that learning-related neural activity is re-expressed during NREM in humans and animals (Nadasdy et al., 1999; Peigneux et al., 2004; Wilson & McNaughton, 1994). The present study adds to this literature, firstly, by confirming that hippocampally-dependent learning can be retrieved during NREM sleep. Furthermore, the observation that trace-conditioned responses were accompanied by conditioning-dependent mentation effects suggests that hippocampally-mediated memory reactivation may contribute to sleep mentation. This constitutes the first experimental evidence in support of this hypothesis. Future work on sleep-dependent memory consolidation should consider the possibility that mentation during NREM is, at least in part, the result of the hippocampal output to the cortex underlying memory reorganization in sleep. Conversely, studies of NREM mentation should regard hippocampal output as a potentially important consideration in modeling cognition during this sleep stage.

V.

Conclusions

Cognition and information processing in NREM sleep have historically received little research attention, largely due to a residual misconception that these sleep stages represent a period of global neural and cognitive quiescence. In more recent years, however, new data on neural activity in NREM at both the single-cell (Kudrimoti et al., 1999; Lee & Wilson, 2002; Wilson & McNaughton, 1994) and whole-systems level (Battaglia et al., 2004; Braun et al., 1997; Buzsaki, 1996, 1998; Huber et al., 2004; Nofzinger et al., 2002; Siapas & Wilson, 1998; Steriade, 2006; Steriade & Timofeev, 2003), has rendered this presumption finally untenable. In fact, NREM sleep may actually support one of the most important information processing functions of the human brain – the transformation of recent declarative memories from an initial labile form supported by the hippocampus into more stable memory traces integrated with existing cortical networks (Ellenbogen et al., 2006; Gais & Born, 2004; McClelland et al., 1995; Orban et al., 2006; Peigneux et al., 2004; Plihal & Born, 1999).

That cognition occurs during even the "deepest" stages of NREM has been recognized for decades (Foulkes, 1967; Foulkes, 1962), but little attempt has been made to understand the neurophysiology supporting its generation and influencing its content. Presumably, in any sleep stage, general cortical activation must reach some critical threshold level in order for cognition to occur. Research presented here demonstrates that, although the REM cycle is one important source of this activation, the report of cognition in both REM and NREM is also independently mediated by changes across the diurnal cycle. Remarkably, this time of night effect, perhaps due to a combination of

circadian and homeostatic factors, modulates the reporting of mentation as strongly as the REM cycle. This work provides initial data regarding the nature of activation sources supporting generation of mental activity outside of REM sleep.

Evidence is then presented here that mentation in NREM sleep is influenced by the cued reactivation of hippocampally-dependent recent learning. This is the first empirical evidence in support of the hypothesis that NREM mentation represents a cognitive correlate of processes underlying consolidation of hippocampally-dependent memory. The experience of dreaming, like waking perception, is likely to depend on complex interactions within and between a large number of distributed cortical networks, and therefore it is unreasonable to presume that mental content in NREM is fully determined by hippocampal output to the cortex. Indeed, in the present study, expression of recent learning was not observed in the actual content of reports, but only in their qualitative characteristics. Nonetheless, evidence that hippocampal output may have some influence on NREM mentation has potentially profound implications for the study of both memory and dreaming. One the one hand, it suggests that examining sleep mentation during NREM may provide a useful methodology for understanding the reactivation of hippocampally-dependent memory on the cognitive level, perhaps providing insight into how recent experiences reactivated via the hippocampus are interleaved with other content and integrated into cortical networks (McClelland et al., 1995; Paller & Voss, 2004). On the other hand, of course, it provides a potential new perspective on the age-old question "what is a dream?"

Finally, note that evidence suggesting sleep mentation results from or contributes to memory consolidation may induce speculation that this constitutes a *function* for

dreaming. Extreme caution should be employed in inferring that evidence of a relationship between sleep mentation and memory consolidation informs us about function in any meaningful sense. Even in the unlikely case that the processes underlying declarative memory consolidation were found to be precisely identical to the set of processes generating dream content, it would still remain unclear whether dreaming actually contributes to memory processing, or is merely an epiphenomenon of it. The hypothesis that dreaming *causally contributes* to the consolidation of memories is likely an untestable one.

Table 1

Mean Report Characteristics at Each Awakening

	REM		NREM	
	Nadir	Morning	Nadir	Morning
WIC				
Mean	2.06	3.42	1.18	1.86
SE	.35	.22	.23	.33
Dreamlike Quality				
Mean	4.1	5.5	1.7	3.18
SE	.73	.73	.26	.67
Bizarreness				
Mean	.46	.69	.06	.30
SE	.15	.14	.04	.11
Emotional Intensity				
Mean	1.35	1.85	.75	.76
SE	.25	.19	.23	.25
Brightness				
Mean	58.1	79.6	46.8	39.1
SE	9.04	4.20	8.92	9.98
Clarity				
Mean	42.8	61.9	37.3	31.6
SE	7.69	5.25	7.45	8.33

Note. Mean report characteristics for REM and NREM dreams at the Nadir and in the late morning (N=20). WIC, Bizarreness, and Emotion scores were log-transformed (ln(x+1)) to remove a positive skew.

Table 2

Characteristics of Nap vs. Overnight Subjects

	Nap Subjects (n=20)	Overnight Subjects (n=20)
Mean Age	27.6 *(±9.6)*	26.7 *(±7.5)*
Mean Wake Time	7:48 *(±.27hrs)*	7:10 *(±.22hrs)*
Mean Bedtime	11:48 *(±.16hrs)*	11:38 *(±.15hrs)*
Dream Recall	2.5 *(±1.5)*	3.2 *(±1.6)*
WVG	21.39 *(±3.50)*	27.38 *(±5.94)*

Note. Mean *(±S.E.)* characteristics of Nap vs. Overnight subjects. Dream recall values represent the mean number of nights which subjects reported recalling a dream during the week prior to the study. There were no significant differences between groups on any variable (p>.2 for all comparisons).

Table 3

Characteristics of Sleep Mentation Reports across the Diurnal Cycle

	Circadian Nadir	Late Morning	Nap
% Recall	70%	70%	40%
WIC	3.7 *(±1.18)*	15.73 *(±5.23)*	7.15 *(±2.54)*
Dreamlike Quality	2.15 *(±.44)*	3.38 *(±.67)*	2.08 *(±.61)*
Bizarreness	.4 *(±.19)*	.03 *(±.03)*	.15 *(±.09)*
Emotional Intensity	2.80 *(±1.07)*	3.10 *(±1.17)*	4.90 *(±1.72)*
Brightness	46.8 *(±8.92)*	39.13 *(±9.98)*	30.95 *(±8.83)*
Clarity	37.34 *(±7.45)*	31.56 *(±8.34)*	20.29 *(±6.18)*

Note. Mean *(±S.E.)* characteristics of sleep mentation reports across the diurnal cycle.

Table 4.

Time Since Sleep Onset by Cue Type and Conditioning Type

	Min. Since Sleep Onset	*p*-value
Cue Type		
CS-	209 ± 14	>.8
CS+	214 ± 14	
Conditioning Type		
Delay	203 ± 14	>.9
Trace	219 ± 14	

Note. Minutes since sleep onset ±*SE*.

Table 5.

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 each subject recalled the experimental stimuli.

Table 6.

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+)

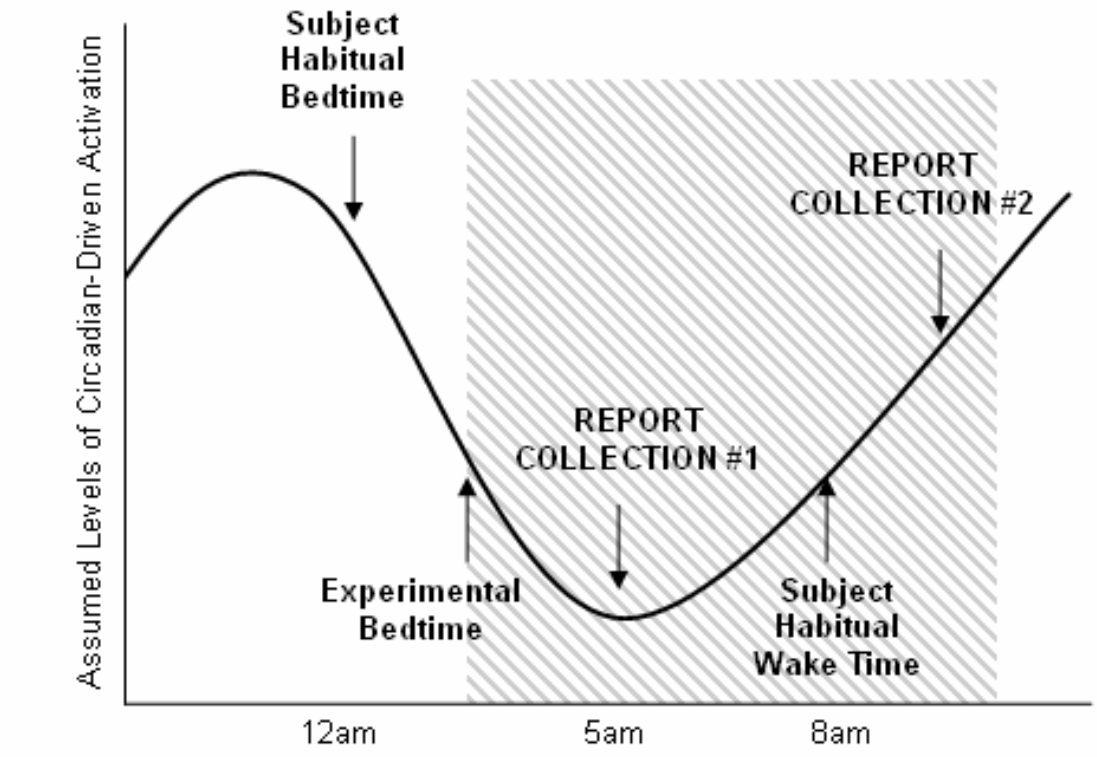


Figure 1. Experimental timeline for a hypothetical subject with a mean bedtime of 12am and a mean wake time of 8am for the week previous to the study.

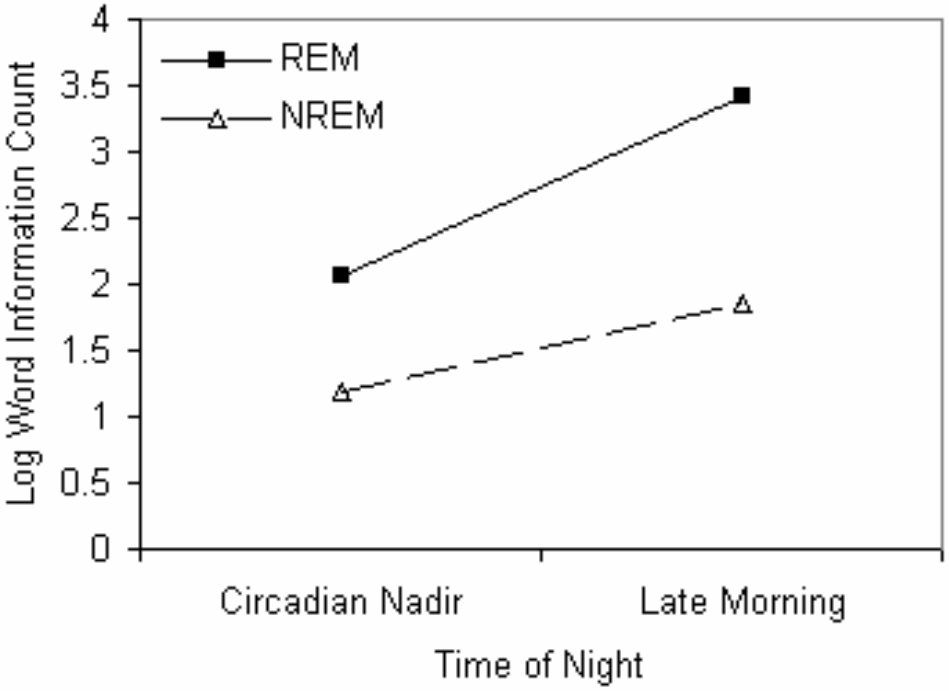


Figure 2. Word Information Count for REM and NREM reports at the circadian nadir and in the late morning.

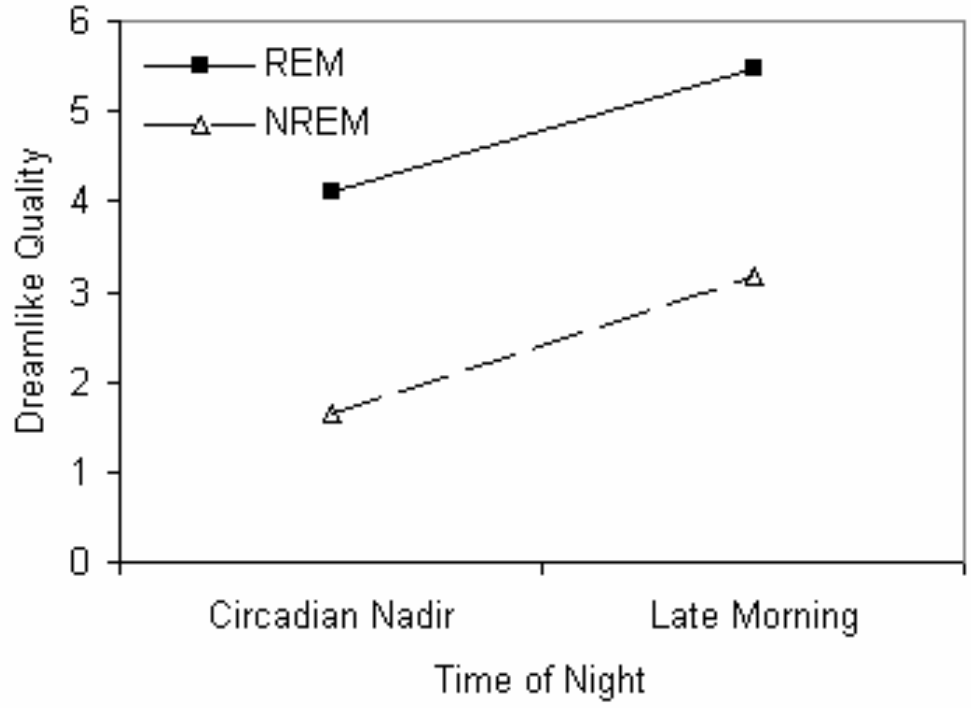


Figure 3. Dreamlike Quality of REM and NREM reports at the circadian nadir and in the late morning.

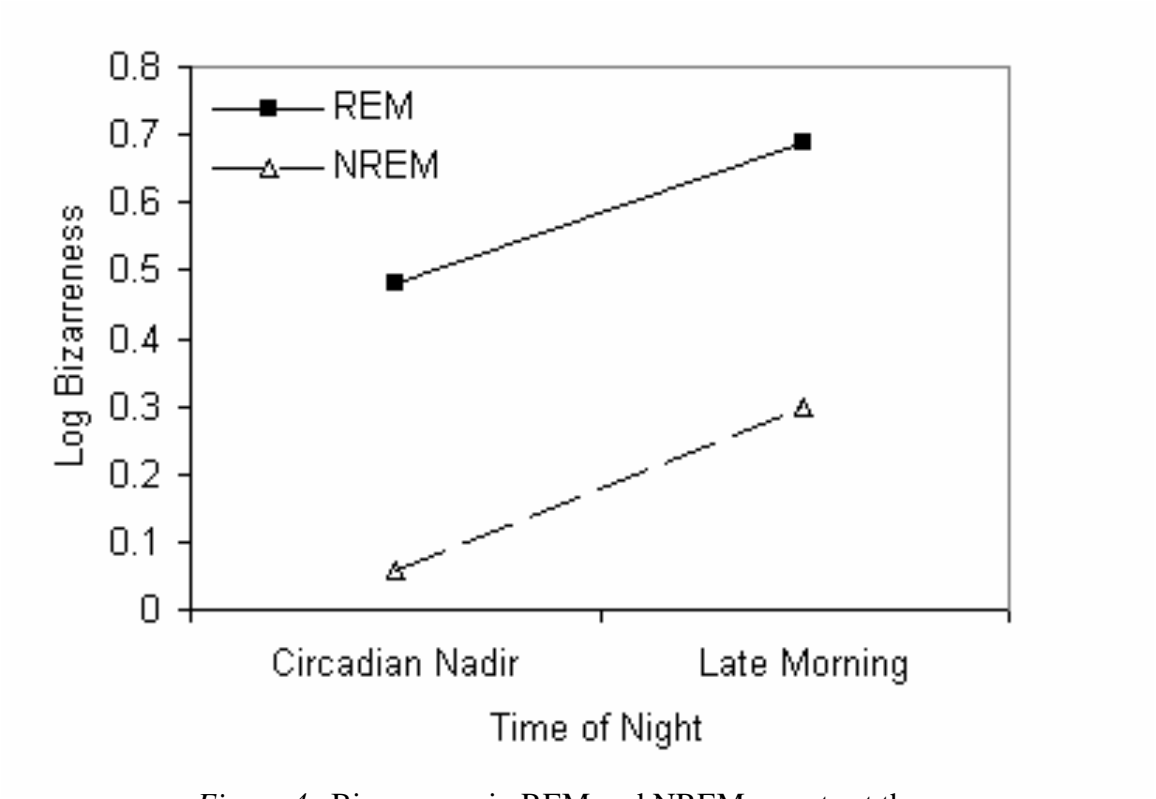


Figure 4. Bizarreness in REM and NREM reports at the circadian nadir and in the late morning.

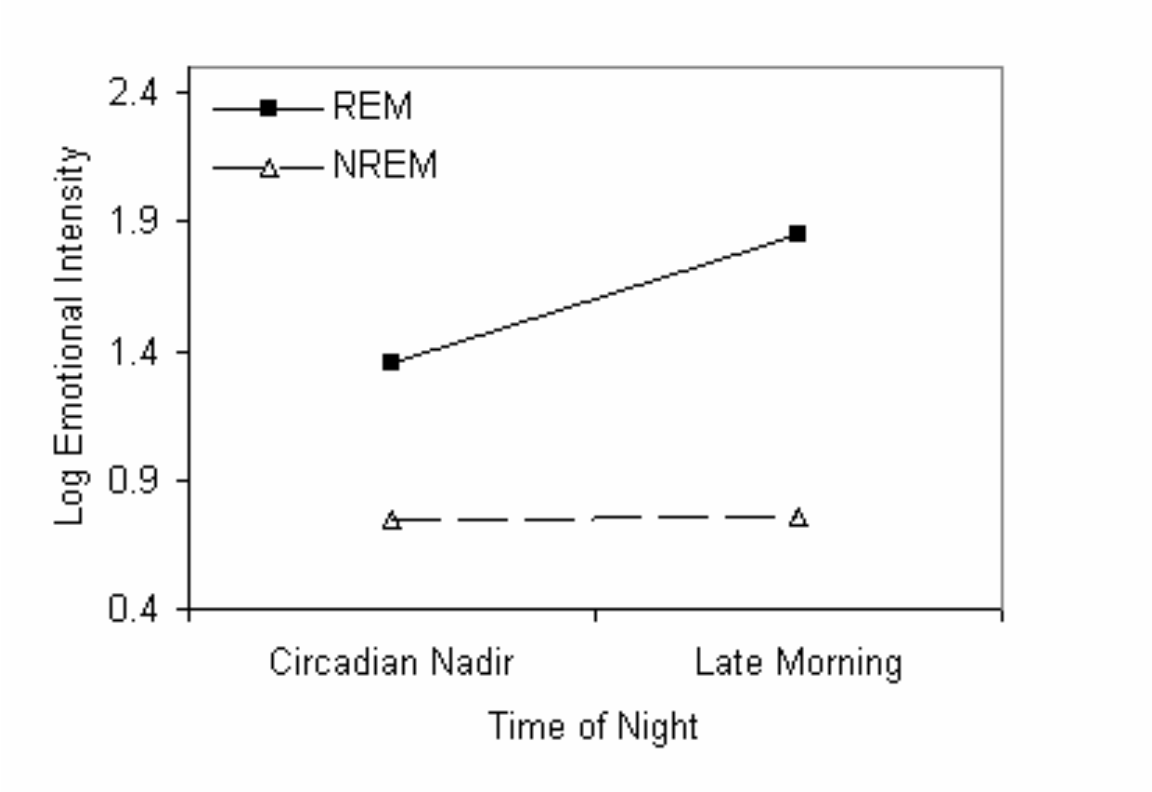


Figure 5. Emotional intensity of REM and NREM reports at the circadian nadir and in the late morning.

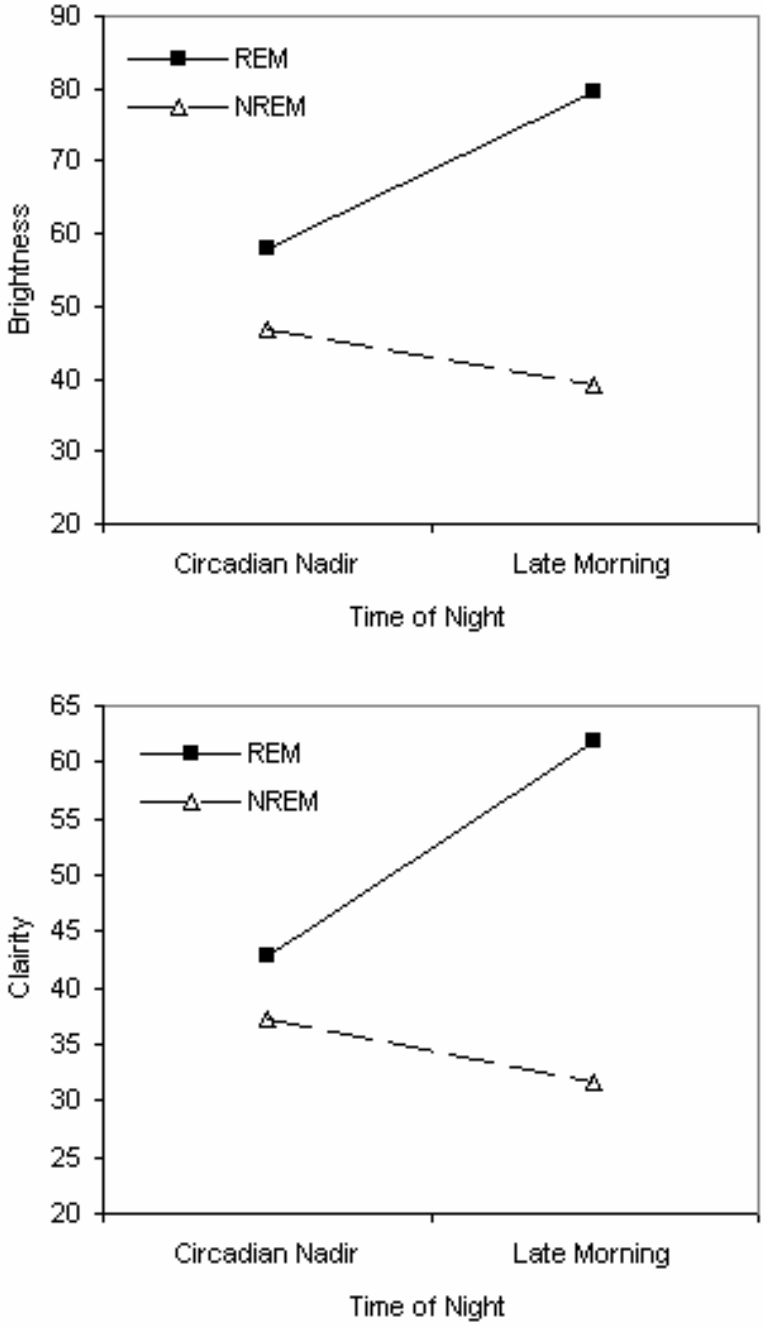


Figure 6. Brightness and Clarity of REM and NREM reports at the circadian nadir and in the late morning.

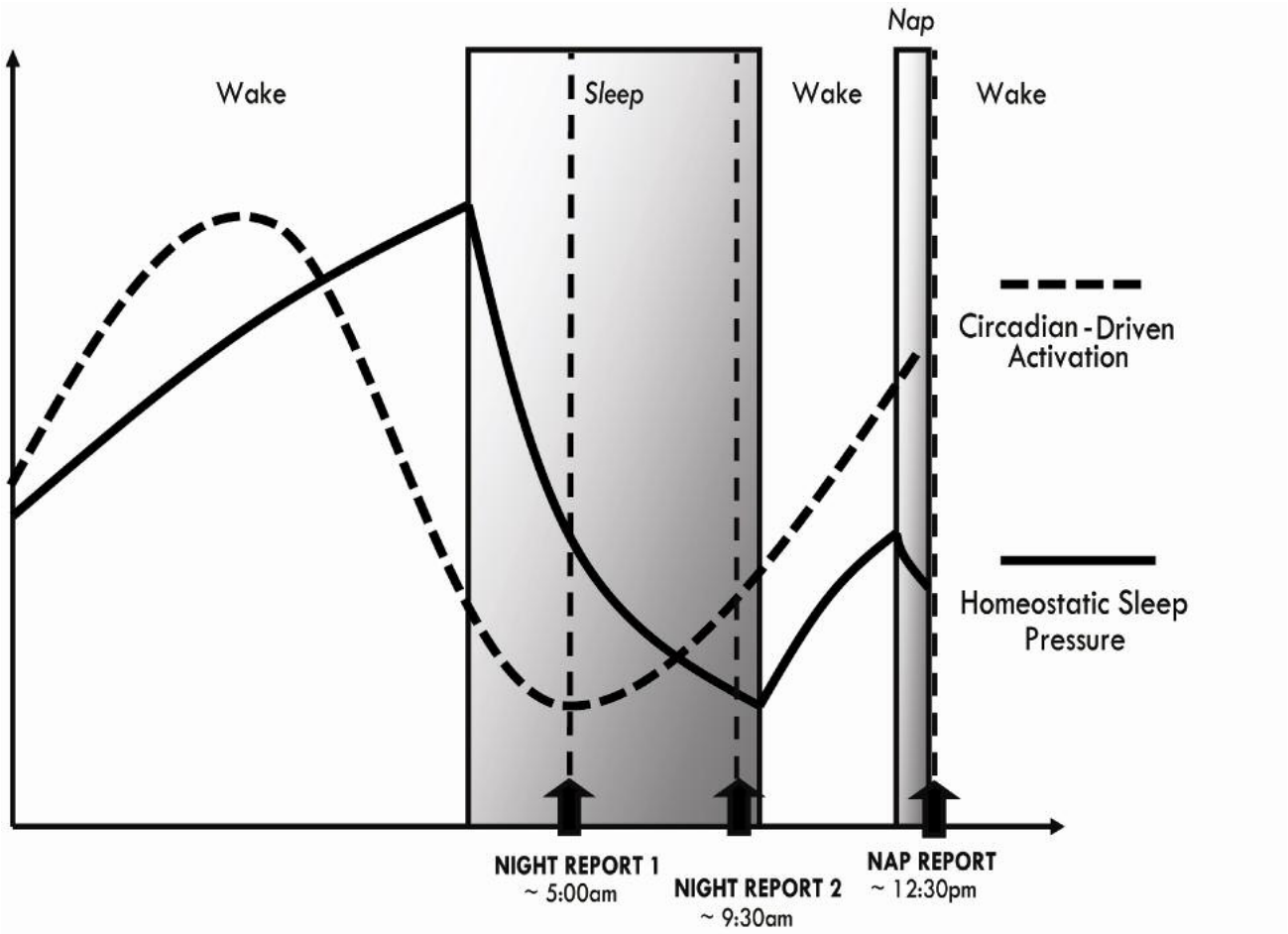


Figure 7. Report collection periods in relation to the presumed time courses for both circadian-driven activation and homeostatic sleep need.

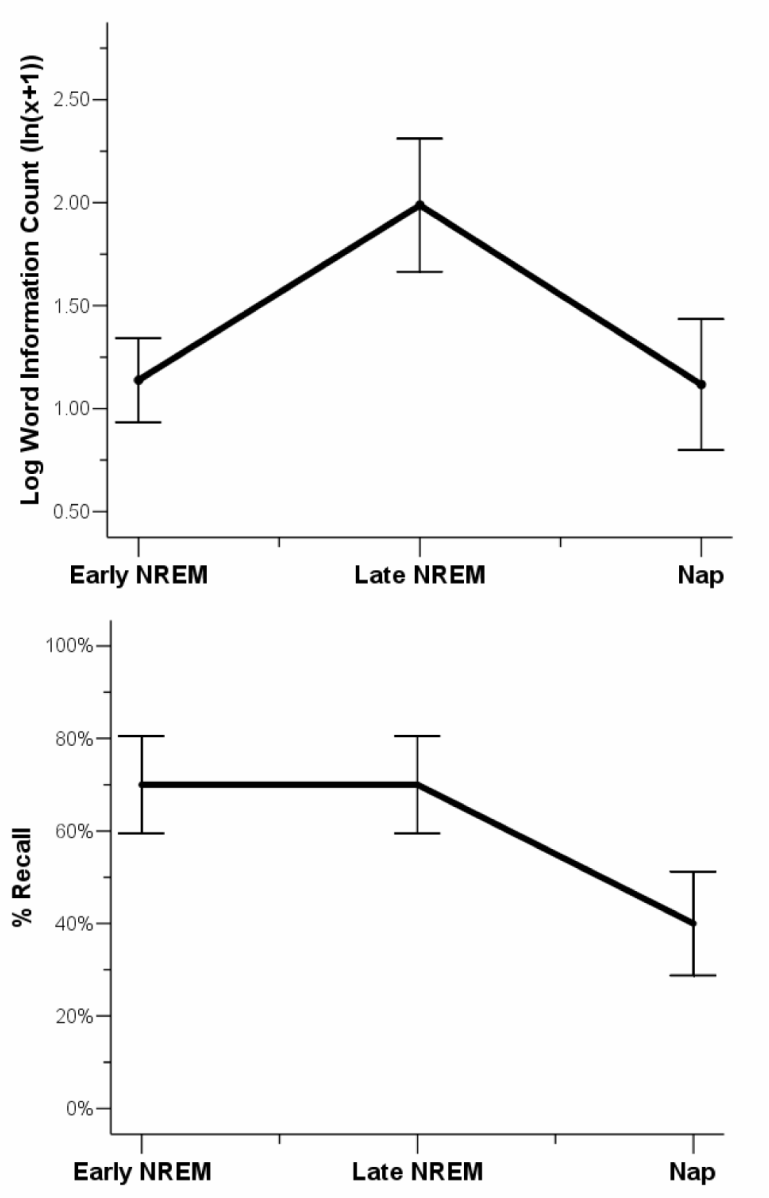


Figure 8. Top: Mean Word Information Count (± SE) from each report collection period. Bottom: % Dream Recall (± SE) from each report collection period.

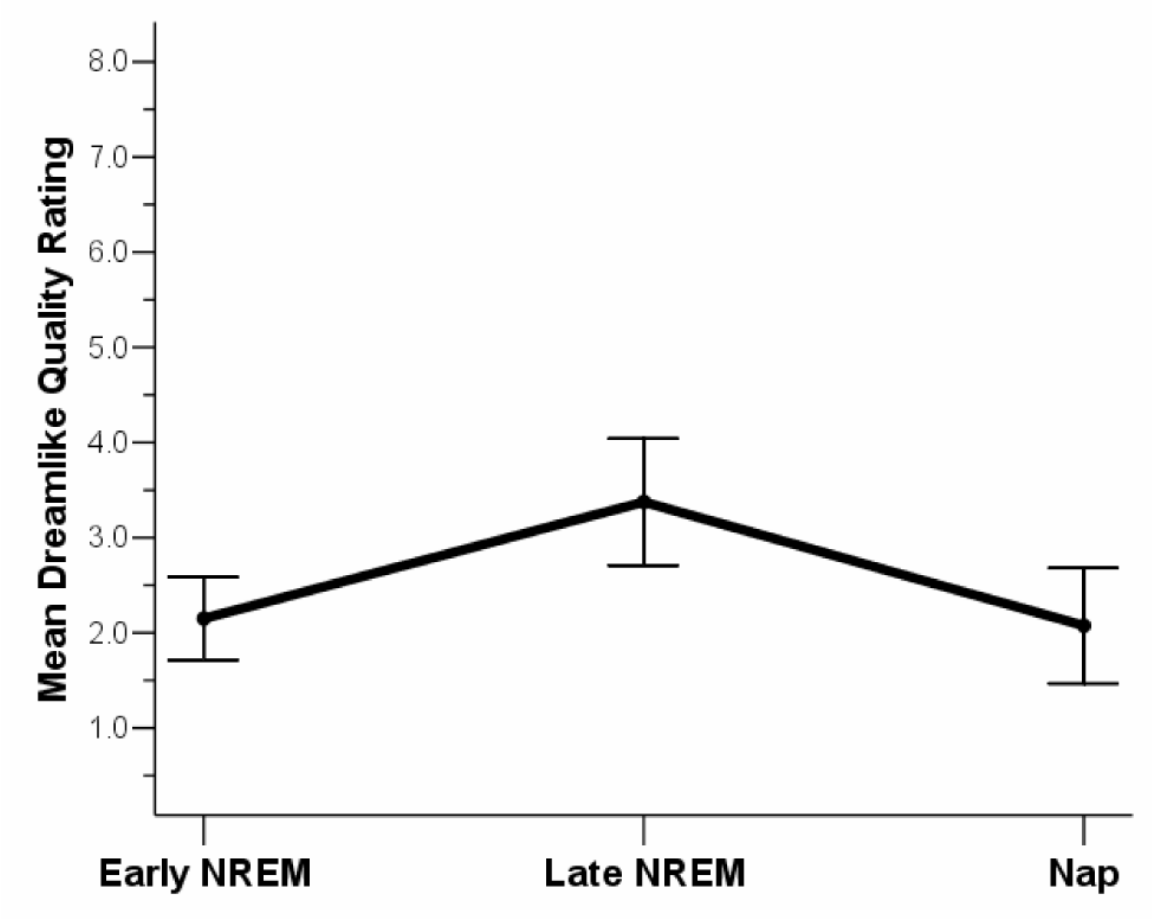


Figure 9. Dreamlike Quality ratings (± SE) for NREM reports across the diurnal cycle.

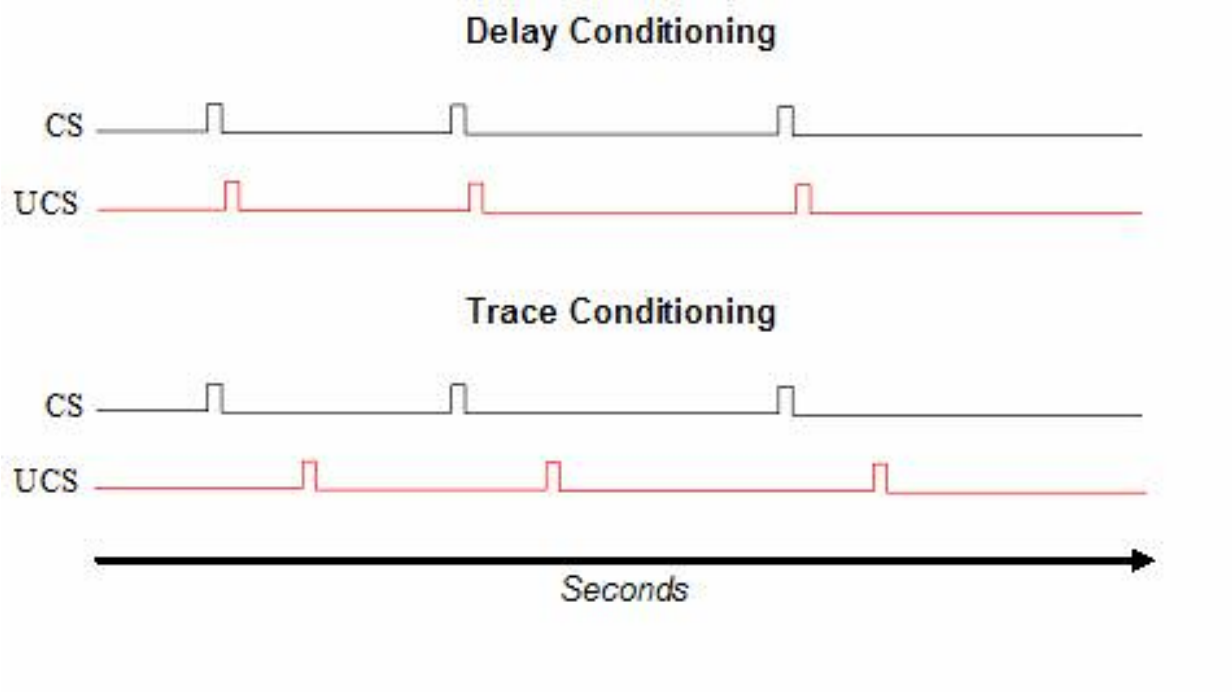


Figure 10. In Delay Conditioning (top) the UCS is initiated immediately at the offset of the CS. In Trace Conditioning (bottom), a trace interval is present between the offset of the CS and the onset of the UCS.

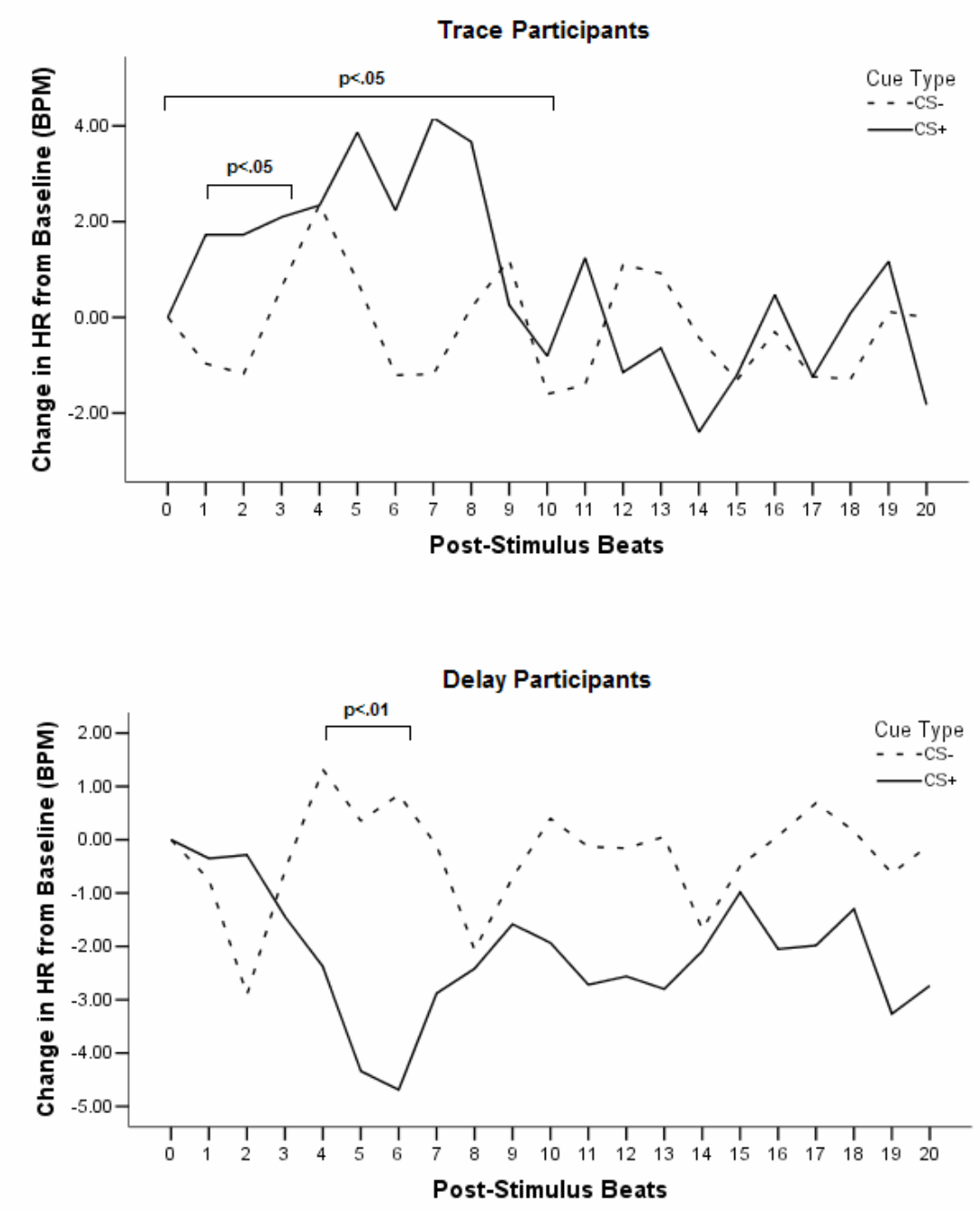


Figure 11. Heart rate responses to the CS+ and CS- during the waking probe trial. HR is plotted as change in BPM from baseline values across the first 20 post-stimulus beats. In Trace-conditioned participants (Top) the conditioned HR response consisted of an extended acceleration from beats 1-10, whereas Delay participants exhibited a conditioned deceleration maximal during beats 4-6.

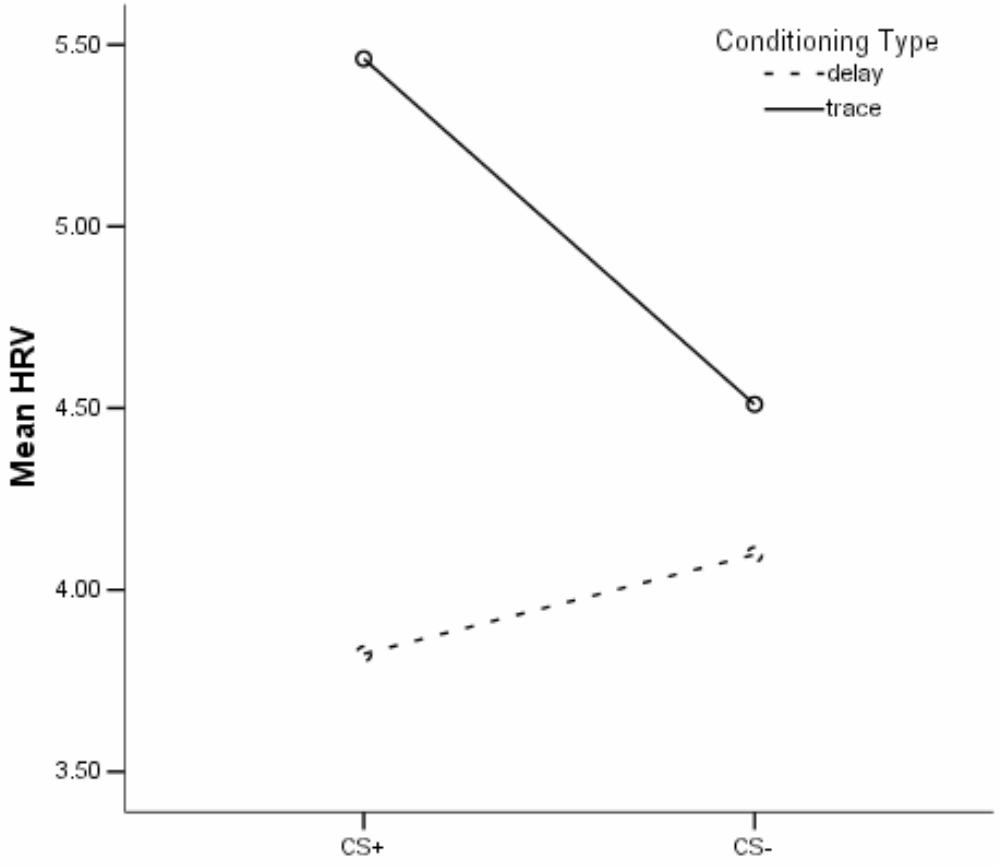


Figure 12. Heart-Rate Variability responses in wakefulness. In Trace, but not Delay, participants HRV was significantly elevated in response to the CS+ relative to the CS-.

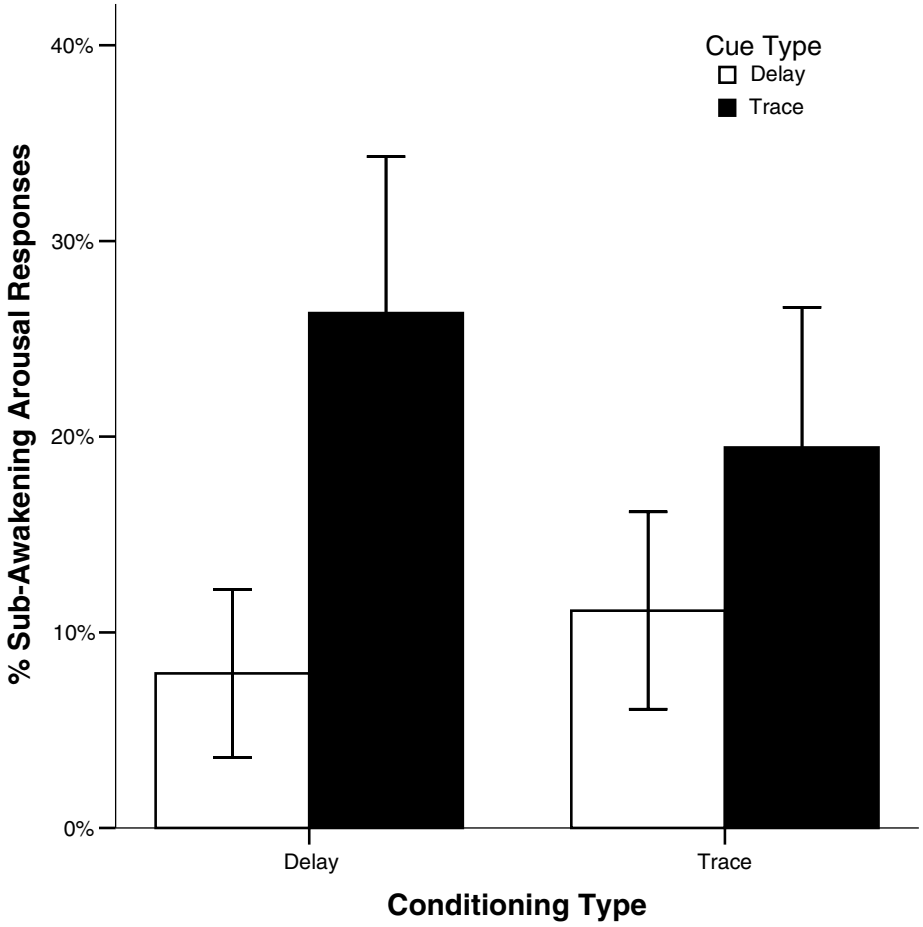


Figure 13. Sub-awakening arousals occurred more often in response to the CS+ than to the CS- in both Trace and Delay Participants. Significant main effect of cue type: $F_{1,35}$=6.208, p=.02, η_p^2=.15.

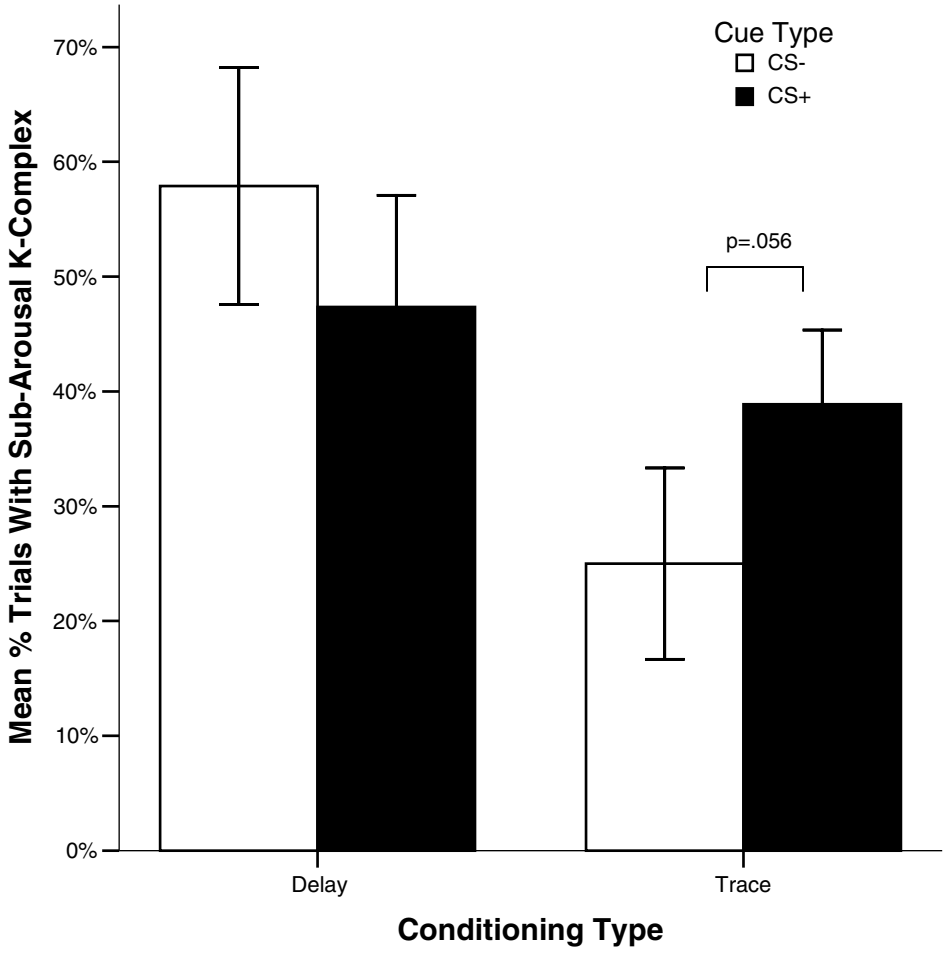


Figure 14. In the Trace group only, K-Complexes were more likely to occur in response to the CS+ than to the control cue, prior to any sign of EEG arousal.

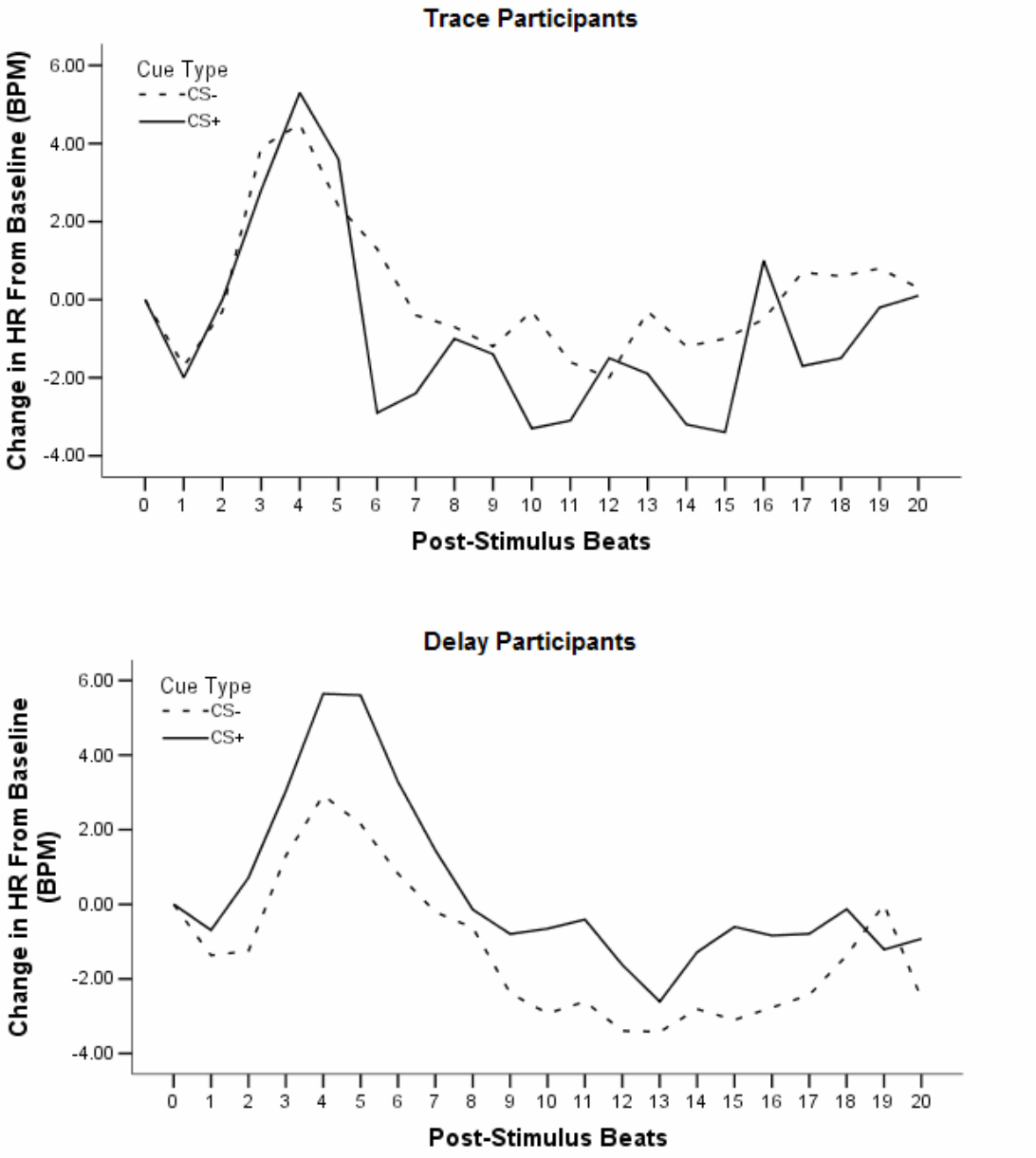


Figure 15. Heart-Rate responses to the CS+ and CS- ***just prior to awakening.*** Delay participants exhibited a near-significant acceleratory CR during post-stimulus beats 1-3.

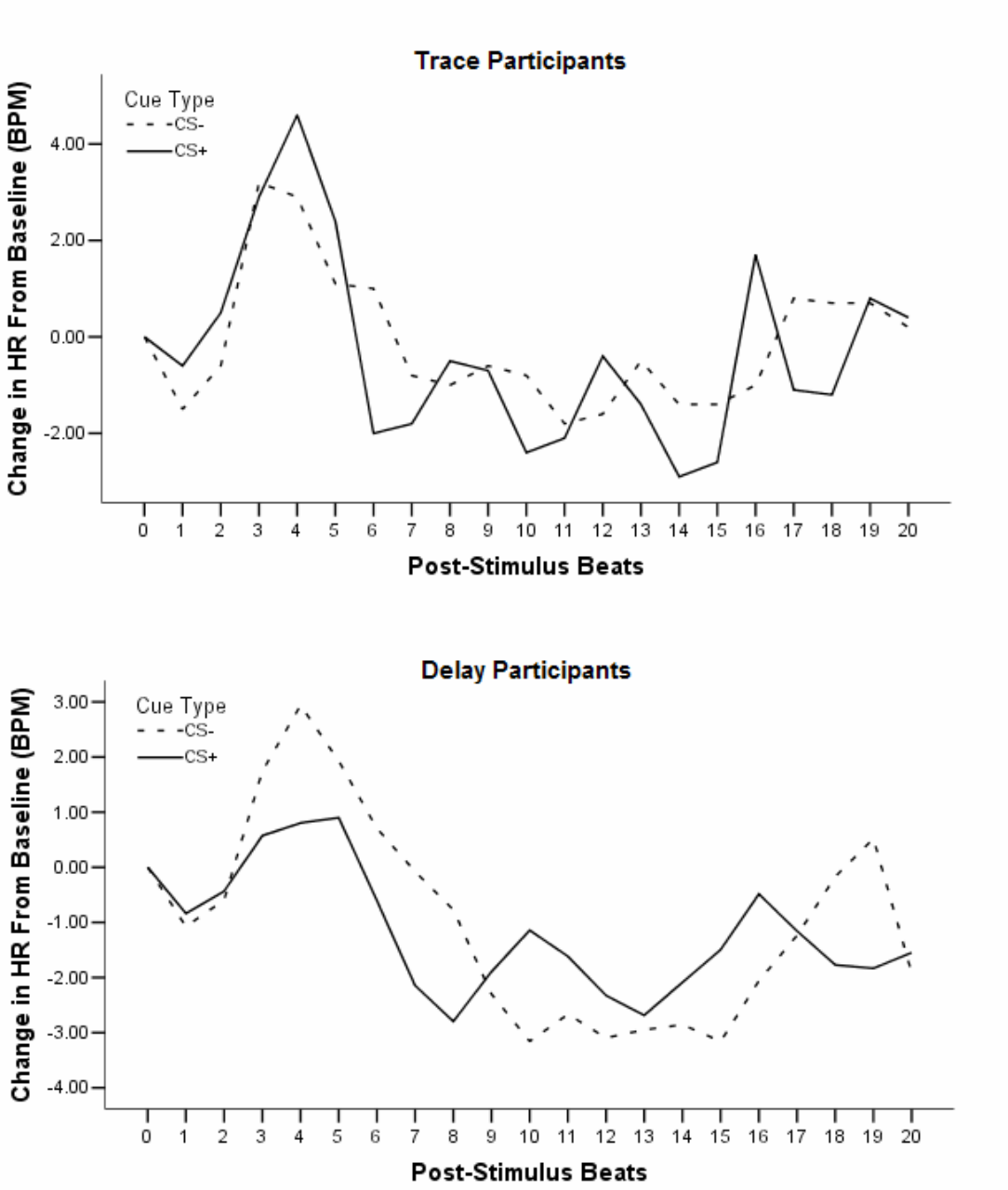


Figure 16. Heart-Rate responses ***just prior to arousal.*** HR responses did not differ significantly in response to the CS+ as compared to the CS- cue in either conditioning group.

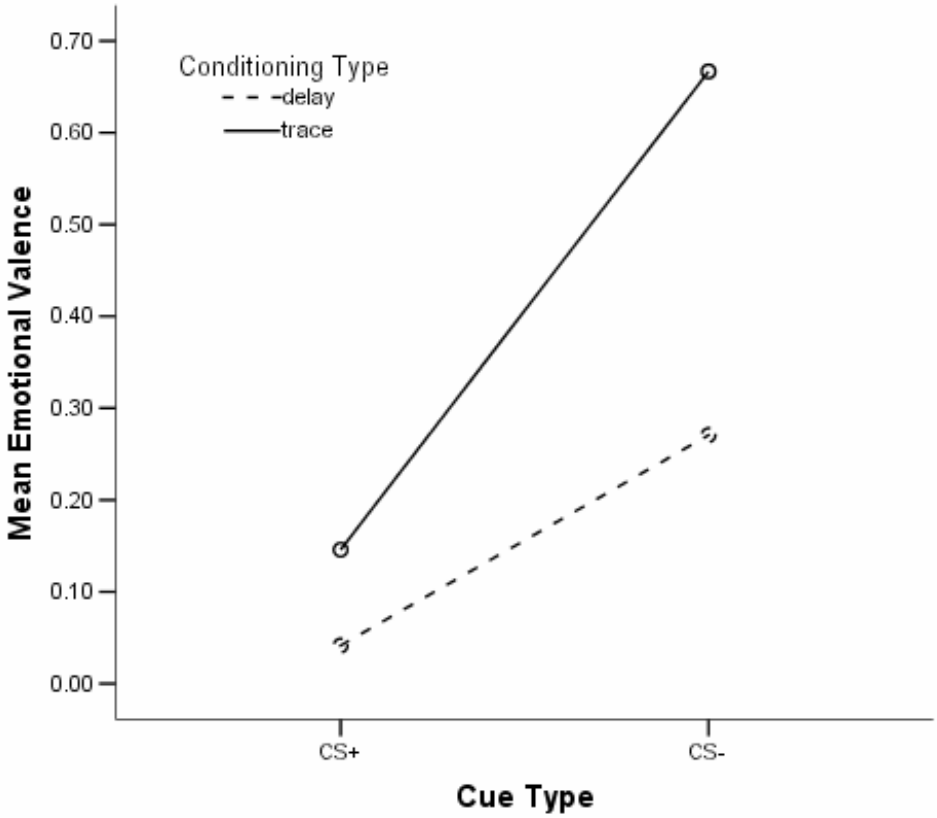


Figure 17. Mean Emotional Valence ratings in response to CS+ and CS- cues for Delay and Trace participants. Emotional Valence was overall more negative in tone during CS+ trials.

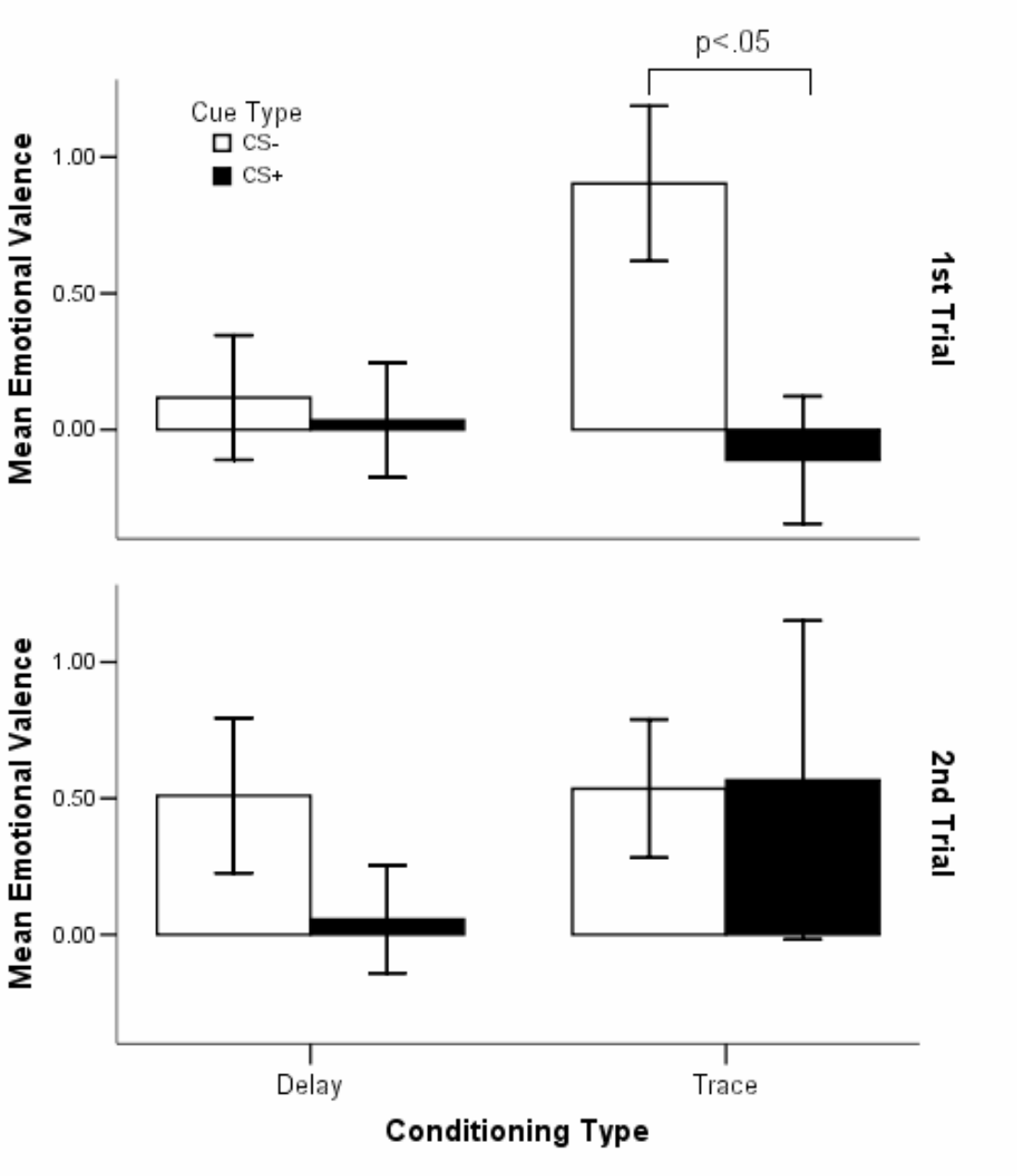


Figure 18. Emotional Valence in Trace and Delay participants during the 1st and 2nd trials of the night. Emotional Valence was significantly more negative in response to the CS+ as compared to the CS- only in Trace Conditioning participants and then only during the 1st trials, earlier in the night.

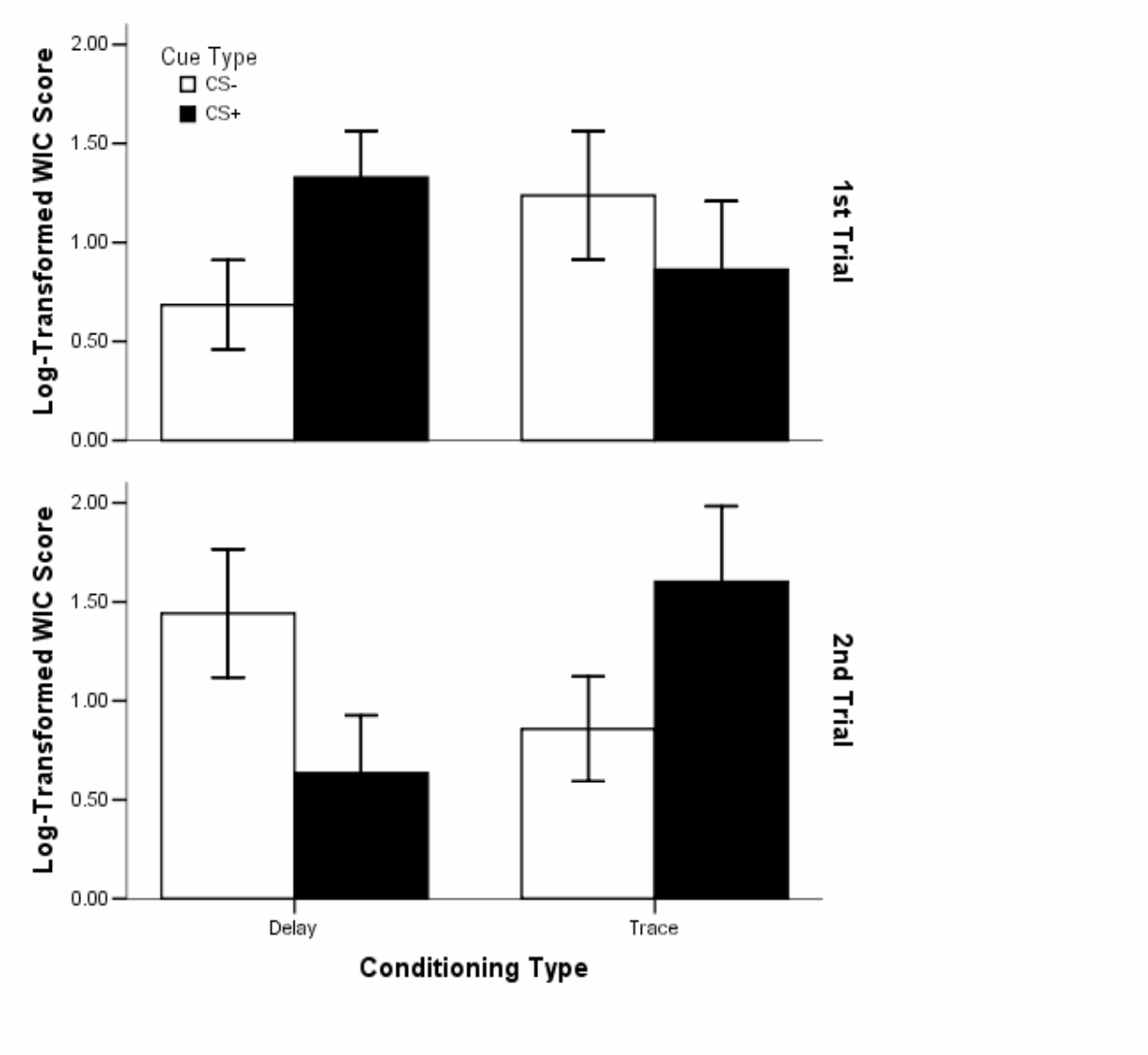


Figure 19. Word Information Count in Trace and Delay participants during the 1st and 2nd pair of trials. Early in the night subjects recalled more mentation in response to the CS+ only in the Delay group. On later trials, there was a trend for Trace subject to recall more mentation in response to the CS+, while the opposite trend was observed in Delay participants.

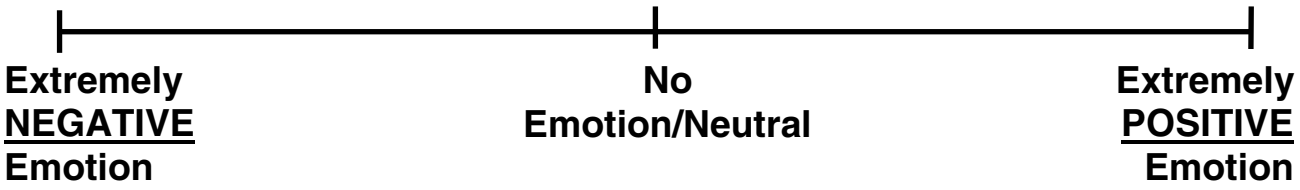
Appendix A

Visual Analogue Emotional Valence Scale
(size reduced from original)

Subject #:___
Awakening #: ___

Please place an "X" at the appropriate point on the line.

Just before I was awakened and called to give my report, I felt:



Appendix B

Content Relatedness
Instructions to Scorers

Your goal in scoring the 'content relatedness' of this set of reports is to determine whether the dream content of each report might bear some relation to various aspects of subjects' pre-sleep experience in the laboratory.

Please **provide a YES or NO answer for the following four questions regarding the content of each report.** *In scoring for sounds, please ignore any description of HEARING THE EXPERIMENTAL STIMULI FROM "REAL LIFE". Restrict your scoring to evaluating sounds which appear to be a part of the subject's dreams/thoughts during sleep. You will notice, however, that subjects sometimes do report apparently dreamed sounds in response to question #2, which aims to ask about hearing the experimental stimuli. So in determining your answers look at responses to both question 1 and 2. There are never any sounds in subjects' rooms other than the experimental stimuli. Subjects who report hearing things like talking, cell phones, and music in response to question 2 could not have really heard these sounds in real life.*

Never score a "yes" answer based on any type of symbolic interpretation of the dream content. For example, if a subject mentions an intimidating male character dressed in white, this should not be symbolically interpreted as being a doctor.

THE FOUR QUESTIONS:

1. Was a LOUD SOUND mentioned in the report??:
Hearing a sound must be explicitly mentioned in the dream report. Score this as a "yes" if the sound is either explicitly described as being loud, OR the described sound can be reasonably assumed to be "loud" if it occurred in real life **(loud is defined as ≥80 dB/the sound of a ringing telephone or a doorbell)**. For example, if the dreamer describes someone shouting, a fire alarm going off, or a lion roaring, these should be assumed to be "loud" sounds even if the subject does not specifically mention that the sound was loud.

2. Was ANY (non-loud) SOUND mentioned in the report??:
Hearing a sound must be explicitly mentioned in the dream report. Score this as a "yes" if a sound is explicitly mentioned in the report, but there is **no particular reason to think that this sound would be a "loud" sound**. Therefore, this category is mutually exclusive with the previous question.

3. Was the LABORATORY CONTEXT mentioned in the report??:
Score this as a "yes" if the subject mentions any of the following:

- The sleep laboratory or any equipment therein (electrodes, monitoring devices, the experimental sleep chambers, etc.)

- The experimenter (Erin, who may also be referred to as "you" in the report)
- The experimental procedure overall (coming to the lab, getting instructions about the experiment, reporting dreams) and/or specifically the conditioning procedure undergone prior to sleep
- Other scientific laboratories, experiments, doctors or researchers, even if these are not clearly specific to the present study
- Also answer 'yes' if the subject themselves indicates that they were dreaming about the experiment, even if they then fail to describe any of the specific content listed above

It is possible that the subject may mention that they were in the laboratory, but then say it somehow looked different or was in a different location than the 'real' laboratory. This should be counted.

4. Was A CAR mentioned in the dream report??:

Answer 'yes' to this question if a car is specifically mentioned. Mere mention of "driving" should not be counted unless the car they are in or another car is also specifically mentioned. In other words, we are looking for the OBJECT of a car to be mentioned, not just the ACTION of driving, which is extremely common in dream reports.

References

Andreano, J. M., & Cahill, L. (2006). Glucocorticoid release and memory consolidation in men and women. *Psychological Science, 17*(6), 466-470.

Antrobus, J. (1983). REM and NREM sleep reports: comparison of word frequencies by cognitive classes. *Psychophysiology, 20*(5), 562-568.

Antrobus, J. (1991). Dreaming: cognitive processes during cortical activation and high afferent thresholds. *Psychological Review, 98*(1), 96-121.

Antrobus, J., Kondo, T., Reinsel, R., & Fein, G. (1995). Dreaming in the late morning: summation of REM and diurnal cortical activation. *Consciousness and Cognition, 4*(3), 275-299.

Arkin, A., & Antrobus, J. S. (1991). The effects of external stimuli applied prior to and during sleep on sleep experience. In A. Arkin, J. S. Antrobus & S. Ellman (Eds.), *The Mind in Sleep, 2nd Edition*. New York: Wiley.

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science, 118*(3062), 273-274.

Atienza, M., Cantero, J. L., & Escera, C. (2001). Auditory information processing during human sleep as revealed by event-related brain potentials. *Clinical Neurophysiology, 112*(11), 2031-2045.

Bastuji, H., Perrin, F., & Garcia-Larrea, L. (2002). Semantic analysis of auditory input during sleep: studies with event related potentials. *International Journal of Psychophysiology, 46*(3), 243-255.

Battaglia, F. P., Sutherland, G. R., & McNaughton, B. L. (2004). Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. *Learning and Memory, 11*(6), 697-704.

Baylor, G. W., & Cavallero, C. (2001). Memory sources associated with REM and NREM dream reports throughout the night: a new look at the data. *Sleep, 24*(2), 165-170.

Beh, H. C., & Barratt, P. E. (1965). Discrimination and Conditioning During Sleep as Indicated by the Electroencephalogram. *Science, 147*, 1470-1471.

Behrens, C. J., van den Boom, L. P., de Hoz, L., Friedman, A., & Heinemann, U. (2005). Induction of sharp wave-ripple complexes in vitro and reorganization of hippocampal networks. *Nature Neuroscience, 8*(11), 1560-1567.

Ben-Ari, Y., & Gho, M. (1988). Long-lasting modification of the synaptic properties of rat CA3 hippocampal neurones induced by kainic acid. *Journal of Physiology, 404*, 365-384.

Benbadis, S. R., Wolgamuth, B. R., Perry, M. C., & Dinner, D. S. (1995). Dreams and rapid eye movement sleep in the multiple sleep latency test. *Sleep, 18*(2), 105-108.

Benington, J. H. (2004). Homeostatic and Circadian Influences. In C. Kushida (Ed.), *Sleep Deprivation: Basic Science, Physiology & Behavior*. New York: Dekker.

Bontempi, B., Laurent-Demir, C., Destrade, C., & Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature, 400*(6745), 671-675.

Borbely, A. A., Baumann, F., Brandeis, D., Strauch, I., & Lehmann, D. (1981). Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalography and Clinical Neurophysiology, 51*(5), 483-495.

Braun, A. R., Balkin, T. J., Wesensten, N. J., Gwadry, F., Carson, R. E., Varga, M., et al. (1998). Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. *Science, 279*(5347), 91-95.

Braun, A. R., Balkin, T. J., Wesenten, N. J., Carson, R. E., Varga, M., Baldwin, P., et al. (1997). Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. *Brain, 120*, 1173-1197.

Broughton, R. (1975). Biorhythmic variations in consciousness and psychological functions. *Canadian Psychological Review, 16*, 217-239.

Buchanan, T. W., & Lovallo, W. R. (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology, 26*(3), 307-317.

Buchel, C., Dolan, R. J., Armony, J. L., & Friston, K. J. (1999). Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *Journal of Neuroscience, 19*(24), 10869-10876.

Burman, M. A., Starr, M. J., & Gewirtz, J. C. (2006). Dissociable effects of hippocampus lesions on expression of fear and trace fear conditioning memories in rats. *Hippocampus, 16*(2), 103-113.

Buzsaki, G. (1996). The hippocampo-neocortical dialogue. *Cerebral Cortex, 6*(2), 81-92.

Buzsaki, G. (1998). Memory consolidation during sleep: a neurophysiological perspective. *Journal of Sleep Research, 7 Suppl 1*, 17-23.

Carrier, J., & Monk, T. (1999). Effects of sleep and circadian rhythms on performance. In F. Turek & P. Zee (Eds.), *Regulation of Sleep and Circadian Rhythms*. New York: Dekker, Inc.

Carter, R. M., O'Doherty, J. P., Seymour, B., Koch, C., & Dolan, R. J. (2006). Contingency awareness in human aversive conditioning involves the middle frontal gyrus. *Neuroimage, 29*(3), 1007-1012.

Cartwright, R. (1991). Dreams that work: The relation of dream incorporation to adaptation to stressful events. *Dreaming, 1*(1), 3-9.

Cartwright, R. D. (2004). The role of sleep in changing our minds: a psychologist's discussion of papers on memory reactivation and consolidation in sleep. *Learning and Memory, 11*(6), 660-663.

Casagrande, M., Violani, C., Lucidi, F., Buttinelli, E., & Bertini, M. (1996). Variations in sleep mentation as a function of time of night. *International Journal of Neuroscience, 85*(1-2), 19-30.

Cavallero, C., Cicogna, P., Natale, V., Occhionero, M., & Zito, A. (1992). Slow wave sleep dreaming. *Sleep, 15*(6), 562-566.

Chowdhury, N., Quinn, J. J., & Fanselow, M. S. (2005). Dorsal hippocampus involvement in trace fear conditioning with long, but not short, trace intervals in mice. *Behavioral Neuroscience, 119*(5), 1396-1402.

Chrobak, J. J., & Buzsaki, G. (1994). Selective activation of deep layer (V-VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. *Journal of Neuroscience, 14*(10), 6160-6170.

Cicogna, P., Natale, V., Occhionero, M., & Bosinelli, M. (2000). Slow wave and REM sleep mentation. *Sleep Research Online, 3*(2), 67-72.

Cicogna, P. C., Natale, V., Occhionero, M., & Bosinelli, M. (1998). A comparison of mental activity during sleep onset and morning awakening. *Sleep, 21*(5), 462-470.

Cipolli, C., Fagioli, I., Mazzetti, M., & Tuozzi, G. (2004). Incorporation of presleep stimuli into dream contents: evidence for a consolidation effect on declarative knowledge during REM sleep? *Journal of Sleep Research, 13*(4), 317-326.

Cipolli, C., Fagioli, I., Mazzetti, M., & Tuozzi, G. (2005). Consolidation effect of the processing of declarative knowledge during human sleep: evidence from long-term retention of interrelated contents of mental sleep experiences. *Brain Research Bulletin, 65*(2), 97-104.

Clark, R. E., Manns, J. R., & Squire, L. R. (2002). Classical conditioning, awareness, and brain systems. *Trends in Cognitive Sciences, 6*(12), 524-531.

Coenen, A. M., & Drinkenburg, W. H. (2002). Animal models for information processing during sleep. *International Journal of Psychophysiology, 46*(3), 163-175.

Conduit, R., & Coleman, G. (1998). Conditioned Salivation and Associated Dreams from REM Sleep. *Dreaming, 8*(4), 243-262.

Czeisler, C., & Khalsa, B. (2000). The human circadian timing system and sleep-wake regulation. In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and Practice of Sleep Medicine* (pp. 353-375). Philadelphia: WB Saunders Company.

Czeisler, C. A., Johnson, M. P., Duffy, J. F., Brown, E. N., Ronda, J. M., & Kronauer, R. E. (1990). Exposure to bright light and darkness to treat physiologic maladaptation to night work. *New England Journal of Medicine, 322*(18), 1253-1259.

Czeisler, C. A., Zimmerman, J. C., Ronda, J. M., Moore-Ede, M. C., & Weitzman, E. D. (1980). Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep, 2*(3), 329-346.

De Gennaro, L., & Ferrara, M. (2003). Sleep spindles: an overview. *Sleep Medicine Reviews, 7*(5), 423-440.

De Koninck, J. M., & Koulack, D. (1975). Dream content and adaptation to a stressful situation. *Journal of Abnormal Psychology, 84*(3), 250-260.

Deboer, T. (2002). Electroencephalogram theta frequency changes in parallel with euthermic brain temperature. *Brain Research, 930*(1-2), 212-215.

Dement, W., & Kleitman, N. (1957a). Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroencephalography and Clinical Neurophysiology. Supplement, 9*(4), 673-690.

Dement, W., & Kleitman, N. (1957b). The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. *Journal of Experimental Psychology, 53*(5), 339-346.

Dement, W. C., Kahn, E., & Roffwarg, H. P. (1965). The Influence of the Laboratory Situation on the Dreams of the Experimental Subject. *Journal of Nervous and Mental Disease, 140*, 119-131.

Dijk, D. J., Beersma, D. G., & Daan, S. (1987). EEG power density during nap sleep: reflection of an hourglass measuring the duration of prior wakefulness. *Journal of Biological Rhythms, 2*(3), 207-219.

Dijk, D. J., Shanahan, T. L., Duffy, J. F., Ronda, J. M., & Czeisler, C. A. (1997). Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *Journal of Physiology, 505 (Pt 3)*, 851-858.

Domhoff, G. W. (2002). *The Scientific Study of Dreams*. Washington, D.C.: American Psychological Association.

Eichenbaum, H. (2004). Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron, 44*(1), 109-120.

Ellenbogen, J. M., Hulbert, J. C., Stickgold, R., Dinges, D. F., & Thompson-Schill, S. L. (2006). Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. *Current Biology, 16*(13), 1290-1294.

Fendt, M., Fanselow, M. S., & Koch, M. (2005). Lesions of the dorsal hippocampus block trace fear conditioned potentiation of startle. *Behavioral Neuroscience, 119*(3), 834-838.

Fiss, H., Kremer, E., & Lichtman, J. (1977). The mnemonic function of dreaming. *Sleep Research, 6*, 122-136.

Fosse, M. J., Fosse, R., Hobson, J. A., & Stickgold, R. J. (2003). Dreaming and episodic memory: a functional dissociation? *Journal of Cognitive Neuroscience, 15*(1), 1-9.

Fosse, R. (2000). REM mentation in narcoleptics and normals: an empirical test of two neurocognitive theories. *Consciousness and Cognition, 9*(4), 488-509.

Fosse, R., Stickgold, R., & Hobson, J. A. (2004). Thinking and hallucinating: reciprocal changes in sleep. *Psychophysiology, 41*(2), 298-305.

Foulkes, D. (1967). Nonrapid eye movement mentation. *Experimental Neurology*, Suppl 4:28-38.

Foulkes, D., & Schmidt, M. (1983). Temporal sequence and unit composition in dream reports from different stages of sleep. *Sleep, 6*(3), 265-280.

Foulkes, W. D. (1962). Dream reports from different stages of sleep. *Jounal of Abnormal and Social Psychology, 65*, 14-25.

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience, 6*(2), 119-130.

Gais, S., & Born, J. (2004). Declarative memory consolidation: mechanisms acting during human sleep. *Learning and Memory, 11*(6), 679-685.

Gianaros, P. J., Van Der Veen, F. M., & Jennings, J. R. (2004). Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: Implications for the cortical and subcortical regulation of cardiac autonomic activity. *Psychophysiology, 41*(4), 521-530.

Goodenough, D. R., Lewis, H. B., Shapiro, A., Jaret, L., & Sleser, I. (1965). Dream Reporting Following Abrupt and Gradual Awakenings from Different Types of Sleep. *Journal of Personality and Social Psychology, 56*, 170-179.

Hamm, A. O., & Weike, A. I. (2005). The neuropsychology of fear learning and fear regulation. *International Journal of Psychophysiology, 57*(1), 5-14.

Han, C. J., O'Tuathaigh, C. M., van Trigt, L., Quinn, J. J., Fanselow, M. S., Mongeau, R., et al. (2003). Trace but not delay fear conditioning requires attention and the anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the United States of America, 100*(22), 13087-13092.

Hasselmo, M. E. (1999). Neuromodulation: acetylcholine and memory consolidation. *Trends in Cognitive Sciences, 3*(9), 351-359.

Hennevin, E., & Maho, C. (2005). Fear conditioning-induced plasticity in auditory thalamus and cortex: To what extent is it expressed during slow-wave sleep? *Behavioral Neuroscience, 119*(5), 1277-1289.

Hobson, J. A., & McCarley, R. W. (1977). The brain as a dream state generator: an activation-synthesis hypothesis of the dream process. *American Journal of Psychiatry, 134*(12), 1335-1348.

Hobson, J. A., Pace-Schott, E. F., & Stickgold, R. (2000). Dreaming and the brain: toward a cognitive neuroscience of conscious states. *Behavioral and Brain Sciences, 23*(6), 793-842; discussion 904-1121.

Hord, D. J., Lubin, A., & Johnson, L. C. (1966). The evoked heart rate response during sleep. *Psychophysiology, 3*(1), 47-54.

Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature, 430*(6995), 78-81.

Ikeda, K., & Morotomi, T. (1997). Reversed discriminatory responses of heart rate during human REM sleep. *Sleep, 20*(11), 942-947.

Inagaki, H., Kuwahara, M., & Tsubone, H. (2004). Effects of psychological stress on autonomic control of heart in rats. *Experimental Animals, 53*(4), 373-378.

Islas-Marroquin, J., & Delgado-Brambila, H. A. (1998). Studies on nap sleep in young students. Relationships between polygraphic data and the occurrence of dreams in replacing naps. *Archives of Medical Research, 29*(2), 149-153.

Johnson, L. C. (1970). A psychophysiology for all states. *Psychophysiology, 6*(5), 501-516.

Johnson, L. C., & Lubin, A. (1967). The orienting reflex during waking and sleeping. *Electroencephalography and Clinical Neurophysiology, 22*(1), 11-21.

Kavanau, J. L. (2001). Memory failures, dream illusions and mental malfunction. *Neuropsychobiology, 44*(4), 199-211.

Keefe, F. B., Johnson, L. C., & Hunter, E. J. (1971). EEG and autonomic response pattern during waking and sleep stages. *Psychophysiology, 8*(2), 198-212.

Knight, D. C., Cheng, D. T., Smith, C. N., Stein, E. A., & Helmstetter, F. J. (2004). Neural substrates mediating human delay and trace fear conditioning. *Journal of Neuroscience, 24*(1), 218-228.

Kotani, S., Kawahara, S., & Kirino, Y. (2002). Classical eyeblink conditioning in decerebrate guinea pigs. *European Journal of Neuroscience, 15*(7), 1267-1270.

Kudrimoti, H. S., Barnes, C. A., & McNaughton, B. L. (1999). Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. *Journal of Neuroscience, 19*(10), 4090-4101.

LaBerge, S., Phillips, L., & Levitan, L. (1994). An hour of wakefulness before morning naps makes lucidity more likely. *NightLight, 6*(3).

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23*, 155-184.

LeDoux, J. E., Iwata, J., Cicchetti, P., & Reis, D. J. (1988). Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *Journal of Neuroscience, 8*(7), 2517-2529.

Lee, A. K., & Wilson, M. A. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron, 36*(6), 1183-1194.

Louie, K., & Wilson, M. A. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron, 29*(1), 145-156.

Lovatt, D. J., & Warr, P. B. (1968). Recall after sleep. *American Journal of Psychology, 81*(2), 253-257.

Maho, C., & Hennevin, E. (1999). Expression in paradoxical sleep of a conditioned heart rate response. *Neuroreport, 10*(16), 3381-3385.

Maquet, P. (2000). Functional neuroimaging of normal human sleep by positron emission tomography. *Journal of Sleep Research, 9*(3), 207-231.

Maquet, P. (2001). The role of sleep in learning and memory. *Science, 294*(5544), 1048-1052.

Maschke, M., Schugens, M., Kindsvater, K., Drepper, J., Kolb, F. P., Diener, H. C., et al. (2002). Fear conditioned changes of heart rate in patients with medial cerebellar lesions. *Journal of Neurology, Neurosurgery and Psychiatry, 72*(1), 116-118.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological Review, 102*(3), 419-457.

McDonald, D. G., & Carpenter, F. A. (1975). Habituation of the orienting response in sleep. *Psychophysiology, 12*(6), 618-623.

McDonald, D. G., Schicht, W. W., Frazier, R. E., Shallenberger, H. D., & Edwards, D. J. (1975). Studies of information processing in sleep. *Psychophysiology, 12*(6), 624-629.

McEchron, M. D., Tseng, W., & Disterhoft, J. F. (2000). Neurotoxic lesions of the dorsal hippocampus disrupt auditory-cued trace heart rate (fear) conditioning in rabbits. *Hippocampus, 10*(6), 739-751.

McEchron, M. D., Tseng, W., & Disterhoft, J. F. (2003). Single neurons in CA1 hippocampus encode trace interval duration during trace heart rate (fear) conditioning in rabbit. *Journal of Neuroscience, 23*(4), 1535-1547.

McGlinchey-Berroth, R., Carrillo, M. C., Gabrieli, J. D., Brawn, C. M., & Disterhoft, J. F. (1997). Impaired trace eyeblink conditioning in bilateral, medial-temporal lobe amnesia. *Behavioral Neuroscience, 111*(5), 873-882.

McGrath, M. J., & Cohen, D. B. (1978). REM sleep facilitation of adaptive waking behavior: a review of the literature. *Psychological Bulletin, 85*(1), 24-57.

McNamara, P., McLaren, D., Smith, D., Brown, A., & Stickgold, R. (2005). A "Jekyll and Hyde" within: aggressive versus friendly interactions in REM and non-REM dreams. *Psychological Science, 16*(2), 130-136.

Molle, M., Yeshenko, O., Marshall, L., Sara, S. J., & Born, J. (2006). Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *Journal of Neurophysiology, 96*(1), 62-70.

Monk, T. H., Buysse, D. J., Reynolds, C. F., 3rd, Berga, S. L., Jarrett, D. B., Begley, A. E., et al. (1997). Circadian rhythms in human performance and mood under constant conditions. *Journal of Sleep Research, 6*(1), 9-18.

Moratti, S., & Keil, A. (2005). Cortical activation during Pavlovian fear conditioning depends on heart rate response patterns: an MEG study. *Brain Research. Cognitive Brain Research, 25*(2), 459-471.

Nadasdy, Z., Hirase, H., Czurko, A., Csicsvari, J., & Buzsaki, G. (1999). Replay and time compression of recurring spike sequences in the hippocampus. *Journal of Neuroscience, 19*(21), 9497-9507.

Niedermeyer, E., & Lentz, W. (1976). Dreaming in non-REM sleep: A preliminary study of brief diurnal sleep in the clinical EEG laboratory. *Waking and Sleeping, 1*, 49-51.

Nielsen, T., Germain, A., & Zadra, A. (1997). Physiological correlates of dream recall vary across REM periods: Eye movement density vs. heart rate. *Sleep Research, 26*, 249.

Nielsen, T. A. (2000). A review of mentation in REM and NREM sleep: "covert" REM sleep as a possible reconciliation of two opposing models. *Behavioral and Brain Sciences, 23*(6), 851-866; discussion 904-1121.

Nielsen, T. A. (2004). Chronobiological features of dream production. *Sleep Medicine Reviews, 8*(5), 403-424.

Nielsen, T. A., & Stenstrom, P. (2005). What are the memory sources of dreaming? *Nature, 437*(7063), 1286-1289.

Nofzinger, E. A., Buysse, D. J., Miewald, J. M., Meltzer, C. C., Price, J. C., Sembrat, R. C., et al. (2002). Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. *Brain, 125*(Pt 5), 1105-1115.

Orban, P., Rauchs, G., Balteau, E., Degueldre, C., Luxen, A., Maquet, P., et al. (2006). Sleep after spatial learning promotes covert reorganization of brain activity. *Proceedings of the National Academy of Sciences of the United States of America, 103*(18), 7124-7129.

Palagini, L., Gemignani, A., Feinberg, I., Guazzelli, M., & Campbell, I. G. (2004). Mental activity after early afternoon nap awakenings in healthy subjects. *Brain Research Bulletin, 63*(5), 361-368.

Paller, K. A., & Voss, J. L. (2004). Memory reactivation and consolidation during sleep. *Learning and Memory, 11*(6), 664-670.

Payne, J. D., & Nadel, L. (2004). Sleep, dreams, and memory consolidation: the role of the stress hormone cortisol. *Learning and Memory, 11*(6), 671-678.

Peigneux, P., Laureys, S., Fuchs, S., Collette, F., Perrin, F., Reggers, J., et al. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron, 44*(3), 535-545.

Pennartz, C. M., Lee, E., Verheul, J., Lipa, P., Barnes, C. A., & McNaughton, B. L. (2004). The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. *Journal of Neuroscience, 24*(29), 6446-6456.

Perrin, F., Garcia-Larrea, L., Mauguiere, F., & Bastuji, H. (1999). A differential brain response to the subject's own name persists during sleep. *Clinical Neurophysiology, 110*(12), 2153-2164.

Pivik, T. (1991). Tonic states and phasic events in relation to sleep mentation. In J. S. Antrobus & S. Ellman (Eds.), *The Mind in Sleep, 2nd Edition*. New York: Wiley.

Pivik, T., & Foulkes, D. (1968). NREM mentation: relation to personality, orientation time, and time of night. *Journal of Consulting and Clinical Psychology, 32*(2), 144-151.

Plihal, W., & Born, J. (1999). Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology, 36*(5), 571-582.

Prescott, L., Durkin, M., Furchtgott, E., & Powell, D. A. (1992). Concomitant heart rate and eyeblink Pavlovian conditioning in human subjects as a function of interstimulus interval. *Psychophysiology, 29*(6), 646-656.

Reinsel, R., Wollman, M., & Antrobus, J. S. (1992). Bizarreness in dreams and waking fantasy. In J. S. Antrobus & M. Bertini (Eds.), *Neuropsychology of Sleep and Dreaming*. Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Rosanova, M., & Ulrich, D. (2005). Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *Journal of Neuroscience, 25*(41), 9398-9405.

Shapiro, A., Goodenough, D. R., Biederman, I., & Sleser, I. (1964). Dream Recall and the Physiology of Sleep. *Journal of Applied Physiology, 19*, 778-783.

Siapas, A. G., Lubenov, E. V., & Wilson, M. A. (2005). Prefrontal phase locking to hippocampal theta oscillations. *Neuron, 46*(1), 141-151.

Siapas, A. G., & Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron, 21*(5), 1123-1128.

Sirota, A., Csicsvari, J., Buhl, D., & Buzsaki, G. (2003). Communication between neocortex and hippocampus during sleep in rodents. *Proceedings of the National Academy of Sciences of the United States of America, 100*(4), 2065-2069.

Skaggs, W. E., & McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science, 271*(5257), 1870-1873.

Smith, C., & Hanke, J. (2004). Memory processing reflected in dreams from rapid eye movement sleep. *Sleep, 27*(Suppl.1), A60.

Smith, M. R., Antrobus, J. S., Gordon, E., Tucker, M. A., Hirota, Y., Wamsley, E. J., et al. (2004). Motivation and affect in REM sleep and the mentation reporting process. *Consciousness and Cognition, 13*(3), 501-511.

Solms, M. (2000). Dreaming and REM sleep are controlled by different brain mechanisms. *Behavioral and Brain Sciences, 23*(6), 843-850; discussion 904-1121.

Spiers, H. J., Maguire, E. A., & Burgess, N. (2001). Hippocampal amnesia. *Neurocase, 7*(5), 357-382.

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*, 279-306.

Steriade, M. (2006). Grouping of brain rhythms in corticothalamic systems. *Neuroscience, 137*(4), 1087-1106.

Steriade, M., & Timofeev, I. (2003). Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron, 37*(4), 563-576.

Stickgold, R., Hobson, J. A., Fosse, R., & Fosse, M. (2001a). Sleep, learning, and dreams: off-line memory reprocessing. *Science, 294*(5544), 1052-1057.

Stickgold, R., Malia, A., Fosse, R., Propper, R., & Hobson, J. A. (2001b). Brain-mind states: I. Longitudinal field study of sleep/wake factors influencing mentation report length. *Sleep, 24*(2), 171-179.

Stiedl, O., Meyer, M., Kishimoto, T., Rosenfeld, M. G., & Spiess, J. (2003). Stress-mediated heart rate dynamics after deletion of the gene encoding corticotropin-releasing factor receptor 2. *European Journal of Neuroscience, 17*(10), 2231-2235.

Stiedl, O., & Spiess, J. (1997). Effect of tone-dependent fear conditioning on heart rate and behavior of C57BL/6N mice. *Behavioral Neuroscience, 111*(4), 703-711.

Suzuki, H., Uchiyama, M., Tagaya, H., Ozaki, A., Kuriyama, K., Aritake, S., et al. (2004). Dreaming during non-rapid eye movement sleep in the absence of prior rapid eye movement sleep. *Sleep, 27*(8), 1486-1490.

Takashima, A., Petersson, K. M., Rutters, F., Tendolkar, I., Jensen, O., Zwarts, M. J., et al. (2006). Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. *Proceedings of the National Academy of Sciences of the United States of America, 103*(3), 756-761.

Takeuchi, T., Miyasita, A., Inugami, M., & Yamamoto, Y. (2001). Intrinsic dreams are not produced without REM sleep mechanisms: evidence through elicitation of sleep onset REM periods. *Journal of Sleep Research, 10*(1), 43-52.

Takeuchi, T., Ogilvie, R. D., Murphy, T. I., & Ferrelli, A. V. (2003). EEG activities during elicited sleep onset REM and NREM periods reflect different mechanisms of dream generation. Electroencephalograms. Rapid eye movement. *Clinical Neurophysiology, 114*(2), 210-220.

Taub, J. M. (1971). Dreams recalled spontaneously following afternoon naps and nocturnal sleep. *Journal of Abnormal Psychology, 78*(2), 229-231.

Tracy, R. L., & Tracy, L. N. (1974). Reports of mental activity from sleep stages 2 and 4. *Perceptual and Motor Skills, 38*(2), 647-648.

Tucker, M. A., Hirota, Y., Wamsley, E. J., Lau, H., Chaklader, A., & Fishbein, W. (2006). A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiology of Learning and Memory, 86*(2), 241-247.

Uchiyama, M., Ishibashi, K., Enomoto, T., Nakajima, T., Shibui, K., Hirokawa, G., et al. (1998). Twenty-four hour profiles of four hormones under constant routine. *Psychiatry and Clinical Neurosciences, 52*(2), 241-243.

van Ravenswaaij-Arts, C. M., Kollee, L. A., Hopman, J. C., Stoelinga, G. B., & van Geijn, H. P. (1993). Heart rate variability. *Annals of Internal Medicine, 118*(6), 436-447.

Vogel, G. (1991). Sleep onset mentation. In J. S. Antrobus & S. Ellman (Eds.), *The Mind in Sleep, 2nd Edition*. New York: Wiley.

Walker, M. P., & Stickgold, R. (2004). Sleep-dependent learning and memory consolidation. *Neuron, 44*(1), 121-133.

Wamsley, E. J., Hirota, Y., Tucker, M. A., Smith, M., Doan, T., & Antrobus, J. S. (in press). Circadian and Ultradian Influences on Dreaming: A Dual Rhythm Model. *Brain Research Bulletin*.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science, 265*(5172), 676-679.

Witkin, H. A., & Lewis, H. B. (1965). The relation of experimentally induced presleep experiences to dreams. A report on method and preliminary findings. *Journal of the American Psychoanalytic Association, 13*(4), 819-849.

Wittmann, L., Palmy, C., & Schredl, M. (2004). NREM sleep dream recall, dream report length and cortical activation. *Sleep and Hypnosis, 6*(2), 54-58.

Wolpert, E. A. (1960). Studies in psychophysiology of dreams. II. An electromyographic study of dreaming. *Archives of General Psychiatry, 2*, 231-241.

Wright, K., Hull, J., & Czeisler, C. (2002). Relationship between alertness, performance, and body temperature in humans. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, 283*, R1370-R1377.

Wurts, S. W., & Edgar, D. M. (2000). Circadian and homeostatic control of rapid eye movement (REM) sleep: promotion of REM tendency by the suprachiasmatic nucleus. *Journal of Neuroscience, 20*(11), 4300-4310.