Circadian and ultradian NREM-REM sleep modulation of Dream Recall: Effects of age and spectral activity

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SUMMARY

This thesis deals with the electrophysiological correlates of sleep prior to dream recall and the age-related effects on dream processing. The dual NREM/REM sleep cycle and the circadian modulation of REM sleep sum to generate dream processing. However, little is known about the age-related effects on dream recall during both NREM and REM sleep, which comprises the first aim of this thesis. To address this question, seventeen young (20-31 years) and 15 older (57-74 years) healthy volunteers underwent continuous polysomnography recording and hormonal assessments during a 40-h multiple nap protocol (150 minutes of wakefulness and 75 minutes of sleep; 10 naps in total) under constant routine conditions. The analysis of NREM/REM sleep prior to dream recall focused on the last 15 minutes of each nap prior to dream recall. Number of dreams, dream recall and the emotional aspect of dreaming was investigated using the sleep mentation questionnaire. The results indicate that older participants had less dream recall after both NREM and REM sleep, although no differences were observed between the age-groups with respect to the emotional domain of dreaming. Interestingly, older volunteers had fewer dreams after naps scheduled during the biological day (outside the time window of melatonin secretion), which was closely associated with the circadian rhythm of REM sleep (Chapter 2). This implies that aging can be associated to decreased amplitude in the circadian modulation of REM sleep, with repercussions on dream recall.

Since dreaming crucially relies on the ultradian NREM/REM sleep, it is very likely that differences in the spectral composition of sleep prior to dreaming may pinpoint the cortical networks associated to dream generation. Surprisingly, frequency and

regional specific differences in EEG activity prior to dreaming remains both controversial and with mixed results, due to the use of different sleep recordings and dream assessments. To answer this issue, NREM/REM sleep EEG power density associated with and without dream recall was investigated in young participants. NREM sleep was associated with lower EEG power density for dream recall in frontal delta and centro-parietal sigma activity, while REM sleep was associated with low frontal alpha activity, and with high occipital alpha and beta activity (Chapter 3). Thus, specific EEG frequency- and topography changes can modulate differences between dream recall and no recall after NREM and REM sleep awakening.

In the next logical step, we investigated how age-related changes in sleep structure can impact on dream processing, an issue that remains largely unknown. During NREM sleep prior to dream recall, older participants had higher frontal EEG delta activity and higher centro-parietal sigma activity than the young volunteers. Contrariwise, before no recall, older participants had less frontal-central delta activity and less sigma activity in frontal, central and parietal derivations than the young participants. REM sleep was associated to age-related changes, such that older participants had less frontal-central alpha and beta activity, irrespective of dream recall and no recall (Chapter 4). Taken together, age-related differences in dream recall seem to be directly associated to specific frequency and topography EEG activity patterns, particularly during NREM sleep. Thus, aging can result in specific changes for dream processing, most likely through its effects on sleep. The results in this thesis indicate that the circadian and ultradian NREM/REM sleep modulation on dream recall can help to better understand the mechanistic framework of this complex cognitive process.

CHAPTER 1

GENERAL INTRODUCTION

Dreaming comprises a complex ongoing cognitive process that has stimulated fascinating debates over the centuries. However, the mechanistic framework that underlies this process still remains elusive. One aspect, nevertheless, is certain: to understand dreams, one needs to look at sleep. Human sleep is not a uniform event, but shows ultradian changes within each sleep episode (1). Each sleep cycle lasts about 90-100 min and normally comprises a non-rapid eye movement (NREM) and a rapid eye movement (REM) sleep episode. Sleep is controlled by the interplay of two internal oscillators: the circadian pacemaker and the sleep homeostat (2). These two facets of sleep regulation play a key role in the prediction of sleep propensity in humans on a wide array of dimensions: sleep timing and duration, REM sleep, NREM sleep, REM density, sleep spindles, slow wave sleep, and so on (2). The relative contribution of these oscillators crucially relies on their non-additive contribution, and on the repercussions that one process has on each other. Surprisingly, in the 50 years since discovery of a link between dreaming and the endogenous biorhythmic events defining REM sleep (3), there has been little convergence between chronobiology and dreaming, despite the overwhelming research in both domains (4). More surprising is the scarcity of information about specific sleep characteristics, such as spectral sleep electroencephalographic (EEG) activity and regional cortical topography correlates of dreaming.

Another question of great importance is how aging can affect dream recall. Aging is a critical factor in modern-day society, as the fraction of older persons has doubled in the last hundred years and life expectancy is increasing. Healthy aging is known

to cause various physiological and psychological changes, and among the most common are sleep problems, although the underlying driving forces remain rather unknown. Circadian rhythms can be phase advanced with aging (5), which, in turn, could result in earlier circadian-coupled peak in dream intensification during sleep and a decrease in retrospectively estimated dream recall (4). However, there still remains no consensus on how changes in sleep and circadian rhythmicity with aging can impact on dream recall.

These wide gaps of uncertainties make the understanding of circadian rhythms, sleep, and dreams of critical interest. Thus, the overarching aim of this thesis was to investigate the interplay of these factors.

SLEEP-WAKE CYCLE

The cyclic structure of sleep and wakefulness is a feature common to most species of the animal kingdom (6). Sleep and wakefulness can be determined by dynamic fluctuations of electrical brain activity, as measured by electroencephalographic (EEG) recordings. The EEG mirrors electrical potentials of cortical neurons registered from the scalp surface (i.e. EEG) in a voltage-time domain. Sleep undergoes ultradian changes (1), in which each sleep cycle lasts approximately 90-100 min and includes a NREM and REM sleep episode. Visual scoring of sleep EEG is defined according to Rechtschaffen and Kales (7). NREM sleep is characterised by a gradual reduction in frequency and an increase in the amplitude of EEG waves from stage 1 (transition between wakefulness and sleep) to stage 3 and 4 (Slow Wave Sleep, SWS). NREM phasic events typically include sleep spindles and K-complexes (e.g. during stage 2) or vertex sharp transients (stage 1). REM sleep is characterised by rapid eye movements (measured in the

electrooculogram; EOG), loss of muscle tone in the electromyogram (EMG) and low voltage with mixed EEG frequency pattern. Based on Rechtschaffen and Kales (7), the visual scoring subdivides sleep EEG into discrete units (NREM sleep stages 1 to 4; REM sleep) and thus enables a limited quantification of the continuous changes in sleep EEG. The most common method to quantify human EEG is by Fast Fourier transform (FFT), which results in a power spectrum that allows analyses in the frequency domain (8). The FFT algorithm (9) transforms and integrates digitised EEG signals into sinusoid functions of varying frequency and amplitude per time window (e.g. 4-s epochs during sleep). Sleep EEG power density results in a 0.25 Hz resolution, and the contribution of each 0.25-Hz frequency bin to the total EEG power density during a certain time (e.g. across the night) can then be analysed. Power density in frequencies between 0.75-4.5 Hz (Slow Wave Activity, SWA) quantifies slow EEG activity. Other frequency bands include theta (4.75-7.5Hz), alpha (8 to 11.5 Hz), spindle (12-15Hz) and beta bands (15 to 30 Hz).

The underlying processes that drive sleep and wakefulness converge to two oscillators: the circadian and sleep homeostatic processes.

CIRCADIAN PROCESS

The circadian system modulates a wide array of physiological and behavioural patterns (10). The master pacemaker driving circadian rhythms - the suprachiasmatic nuclei (SCN) - acts as the central pacemaker for generation and/or synchronization of circadian rhythms (11, 12). These rhythms are self-sustained and persist in the absence of environmental time cues with remarkable precision (13).

Under normal conditions, circadian rhythms are entrained to the 24-h day, thus enabling behavioural and physiological rhythms to aptly time daily changes in the environment.

In order to obtain circadian entrainment, the SCN synchronises to the external light–dark cycle through retinal light input (light being the main synchronizer or “zeitgeber”) (14). A specialized non-visual retinohypothalamic tract then provides direct neuronal connection to the SCN from novel photoreceptors in the retinal ganglion cells that measure luminance (15, 16). The SCN innervates several brain areas mostly located within the thalamus and hypothalamus, with indirect projections via the dorsomedial hypothalamus (DMH) to the ventrolateral preoptic nucleus of the hypothalamus (VLPO) and to arousal-promoting cell groups (17). **Figure 1** illustrates the structural inputs, the neuroanatomical connections of the SCN, and some of the behavioural and neuroendocrine outputs of the circadian timing system.

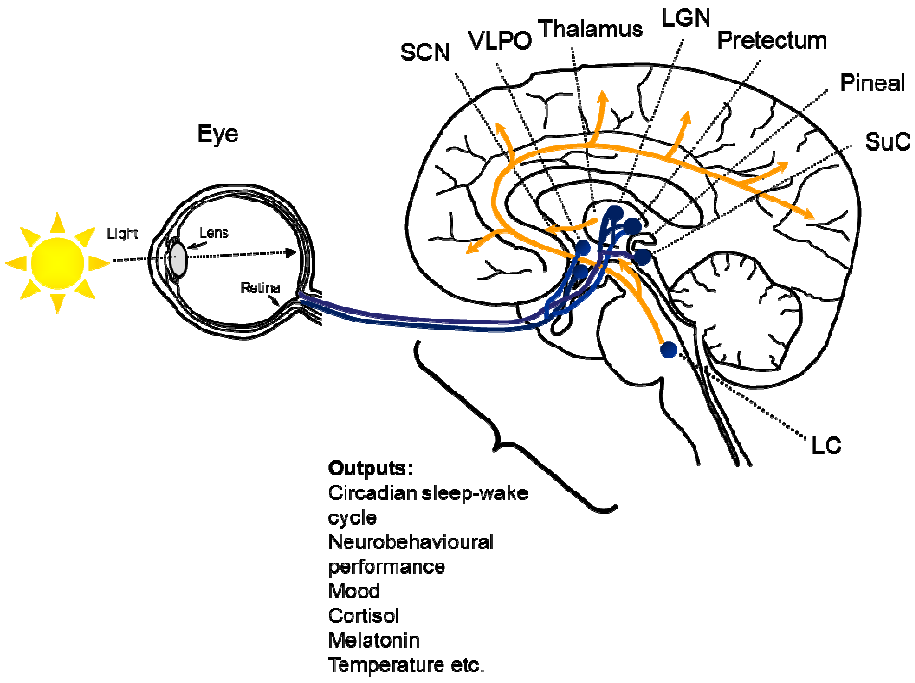

Figure 1 – Light input (dark lines) projects to several non-visual areas of the brain, including the suprachiasmatic nuclei (SCN), which project multisynaptically to the pineal gland and to other areas such as lateral geniculate nucleus (LGN), pretectum and superior colliculus (SuC). It also reaches sleep-promoting neurons of the ventrolateral preoptic nucleus (VLPO) and the noradrenergic locus coeruleus (LC) system, involved in the circadian regulation of arousal (18).

The VLPO, together with the wake-maintaining posterior lateral hypothalamus, can generate a “flip-flop” switch for sleep–wake control (19). According to this model, monoaminergic nuclei, such as the histaminergic tuberomammilary neurons (TMN), locus coeruleus (LC) and the serotonergic dorsal and median raphé nuclei (DR) promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep promoting neurons of the VLPO. With increasing reduction of the circadian drive for arousal in the later part of the waking period, there is a substantial increase in the neuron firing rate of VLPO, through GABA neurons that project to wake-promoting areas. During sleep, the VLPO inhibits monoaminergic-mediated arousal regions through GABAergic and galaninergic projections. This leads to a progressive synchronization in the thalamo-cortical network by means of a synchronous discharge of the thalamic reticular nucleus (19, 20). As a result, this strongly enhances the generation of sleep spindles and deeper stages of NREM sleep (21). Intermediate states between sleep and wakefulness are, thus, avoided through the reciprocal inhibition of VLPO neurons and monoaminergic cell groups, which reinforce their own firing rates in a parallel manner.

A hallmark of the circadian sleep regulation is the peak of REM sleep during the early hours of the morning, which may represent a circadian sleep-promoting signal to ensure normal sleep duration. The circadian activation of REM sleep may occur by indirect projections from the SCN to the mesopontine tegmental nuclei, directly implicated with REM sleep generation (22). Interestingly, even though the SCN

plays a major role in sleep regulation, it has rather limited monosynaptic outputs to sleep-regulatory centres, like VLPO and the lateral hypothalamus (23). Hence, the circadian sleep regulation might be mediated by multisynaptic projections from the SCN to sleep-wake centres, such as the subparaventricular zone and the dorsomedial hypothalamic nucleus (24), which sends a GABAergic projection to the VLPO, thus ensuring a putative mechanism for the circadian sleep regulation (25). The circadian regulation of sleep also involves the synthesis and secretion of melatonin in the pineal gland (26). Melatonin is synthesized in a circadian fashion, in which maximum levels are secreted during the night, with the onset of production in the later part of the day, while the lowest levels occur during the day. The increase in melatonin secretion leads to an inhibition of the firing rate of SCN neurons, with a subsequent decline of the circadian force for arousal, thus enhancing sleep (17). However, sleep propensity depends not only on the circadian rhythmicity, but also on sleep satiety or sleep pressure, as indexed by the level of homeostatic sleep drive (27, 28). Thus, it is pivotal to understand the functional role of the sleep homeostatic process on the regulation of human sleep-wake cycles.

SLEEP HOMEOSTATIC PROCESS

Sleep homeostasis implies the enhancement of sleep propensity when sleep is curtailed and its reduction when there is an excess of sleep (2, 29). This is clearly demonstrated by sleep deprivation protocols which challenge homeostatic sleep mechanisms (8, 30-32). Extended time awake during sleep deprivation increases low-frequency EEG activity in the range of 0.75–8Hz during NREM sleep, particularly in frontal brain areas (32-34). Similarly, NREM sleep EEG activity in the spindle activity (12–15 Hz) is modified with increased sleep pressure such that high

spindle frequency activity (>13.5 Hz) decreases, while low spindle activity (<13.5 Hz) increases (35). This increase can be reversed by short nap episodes, through which the high sleep pressure is attenuated (36, 37). The sensitivity of these frequency ranges to changes in the duration of prior wakefulness and sleep implies that they can act as correlates of the homeostatic sleep process.

While the neuroanatomical and molecular substrates of the circadian sleep regulation are rather well-known, the substrates of sleep homeostasis remain fairly unidentified (38). One likely candidate that may account for the inter-individual variability in sleep homeostasis regulation is the adenosinergic system (39-41). During wakefulness, increased metabolic and neural activity leads to higher extra-cellular adenosine concentrations, whereas, during sleep, there is a substantial decline in adenosine concentrations. This suggests that adenosine may be related to sleep regulation by inhibition of neuronal activity. Similarly, in humans, a genetic variant of adenosine deaminase, which is associated with reduced metabolism of adenosine to inosine, enhances slow-wave sleep and SWA during sleep (39).

The neuroanatomical underpinnings for the sleep homeostatic process also remain fairly unknown. Converging lines of evidence support that local adenosine levels rise in certain cortical areas during wakefulness and decline during sleep (42, 43). Given that these changes are predominantly in the basal forebrain than in other cortical regions (44), local release of adenosine in this structure has been proposed as a signal for the homeostatic regulation of NREM sleep (45). Alternatively, adenosine may disinhibit and/or actively induce sleep-promoting neurons in the VLPO (46, 47). Furthermore, adenosine may contribute to global cortical inhibition, due to reduced activating input from ascending cholinergic and monoaminergic pathways and, as a result, of long-lasting hyperpolarizing potentials during NREM sleep (48).

THE TWO-PROCESS MODEL OF SLEEP REGULATION

Despite the usual controversy regarding whether it is the circadian or the homeostatic process that underpins sleep, there is mounting evidence in support of the interaction of these two systems for sleep regulation (2, 49, 50). Indeed, it is the combination of these two oscillatory processes that best explains the timing of human sleep/wake behaviour in humans living in the absence of time cues (51). Given this important interface, the circadian and sleep homeostatic processes have been conceptualized in the two process model of sleep regulation to better understand the timing and architecture of sleep (52, 53). According to this model (**Figure 2**), the homeostatic sleep drive accumulates with each waking hour and is dissipated by sleep in an exponential manner. This process has properties very different from those of the circadian oscillator, which opposes the increasing homeostatic drive for sleep that builds near the end of the habitual wake day (54). A similar process may happen during the end of the sleep episode, when sleep pressure dramatically decreases. In order to counteract a possible arousal during these early morning hours, the circadian oscillator may “tick in” through a sleep-promoting signal that opposes this decrease in the homeostatic sleep pressure, thus ensuring a longer sleep episode.

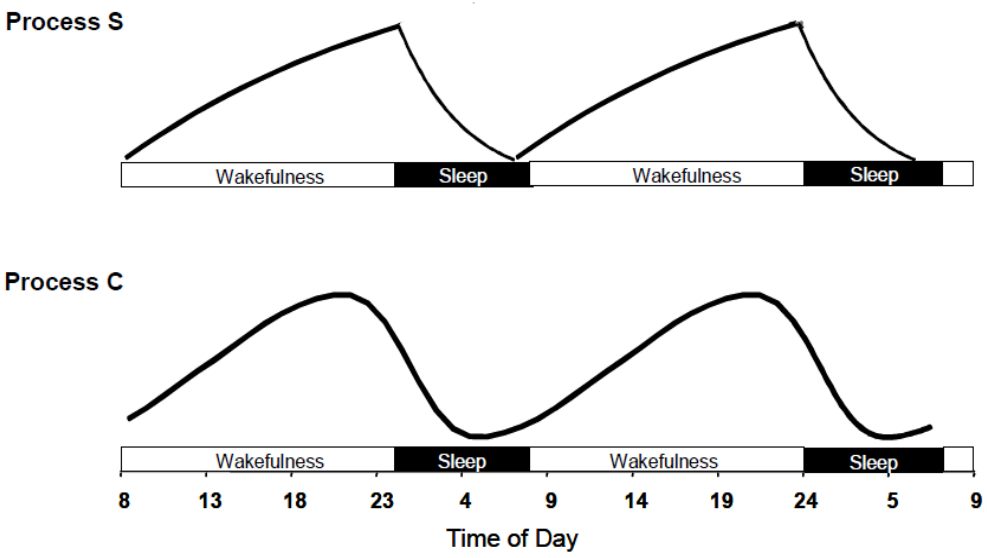

Figure 2 – Schematic diagram of the two process model of sleep regulation. The upper panel illustrates the homeostatic process (process S), whereby sleep pressure accumulates during wakefulness and exponentially declines during sleep. The lower bottom shows the circadian process (process C), which underlies sleep timing and propensity with a time-of-day dependency (52).

An indication of the strength of these processes on EEG activity builds-up from forced desynchrony studies, in which the sleep–wake cycle was either 28 or 42.85h (13, 55). Accordingly, the circadian rhythm of endogenous melatonin oscillated within a 24-h basis and with a similar period of the circadian rhythm of core body temperature, thus leading to a desynchronization of these rhythms (29, 56). Analysis of EEG power spectra revealed high alpha power during wakefulness, predominance of low frequencies and spindle range during NREM sleep, and lower values in the same frequency bins during REM sleep. During all stages of vigilance, low EEG components were predominantly modulated by the homeostatic factor. However, the circadian modulation of the EEG patterns differed across these states, such that the maximum circadian variance was shown for REM sleep in the alpha activity and for NREM sleep in the low spindle activity (57).

An interesting aspect in the EEG power spectra regards sleep spindles, which are primarily generated and modulated by a thalamocortical network, which comprises the interplay between reticular thalamic, cortical pyramidal, and thalamocortical cells (58). Initially, the progressive hyperpolarization of thalamocortical cells after sleep onset results in spindle oscillations, which are then replaced by slow wave oscillations when deepening of sleep proceeds and thalamocortical neurons achieve a voltage range at which slow wave oscillations are triggered (59). Thus, sleep spindles are deemed to play a key role in neuronal plasticity and sleep maintenance, basically by inhibiting sensory information that reaches the cerebral cortex (60). When the sleep episode coincides with the circadian phase of endogenous melatonin secretion and when it is highly consolidated, mild reductions in the frequency range of slow waves and theta activity are observed in NREM sleep, while profound variations occur in spindle activity (28, 50). Low frequency sleep spindle activity (12.25–13 Hz) exhibits a clear circadian modulation, with maximum levels during the circadian phase of melatonin secretion (57). This has been interpreted as evidence for the circadian modulation of the frequency of sleep spindles. Taken together, spectral hallmarks of sleep EEG activity exhibit a frequency-specific homeostatic and circadian modulation. These two independent oscillatory processes correspond to an essential component of cortical activation during sleep, which is likely to be related to the processing of external sensory stimuli and behavioural responses (29).

AGE-RELATED CHANGES IN SLEEP

Aging is associated with numerous changes in the sleep-wake cycle, such as shallower nocturnal sleep, increased number of arousals, less slow wave sleep and

more daytime naps (61, 62). Similarly, there appears to be attenuated amplitude of circadian markers, such as melatonin, core body temperature and cortisol (63). Older individuals tend to present earlier sleep times with a concomitant advanced circadian phase in relation to core body temperature minimum (64, 65), although the endogenous circadian period is quite stable (13). However, it is still unclear if it is the circadian or the homeostatic facet of sleep which undergoes maximal changes with aging. The sleep homeostat appears to remain operational after sleep deprivation in older individuals (66). On the circadian domain, although some aspects of circadian sleep regulation seem to be affected by age (67), it is unclear whether it is aging *per se* or the modified regulation of circadian signalling downstream or both that underlies these changes (38). To address these questions, it was hypothesized whether age-related changes in sleep result from an attenuated circadian arousal signal in the evening. The circadian pacemaker ensures sleep timing and consolidation by opposing increased homeostatic sleep pressure, particularly in the evening during the “wake maintenance zone” (38). If the circadian signal is dampened with age, this opposition would be unclear. Quantitative evidence for a dampened circadian arousal signal in older individuals was observed through increased sleep in the wake maintenance zone (**Figure 3**) (68), and lower levels of melatonin secretion. Older participants had a reduction in circadian modulation of REM sleep, together with less obvious day-night differences in spindle frequency. This implies that age-related changes in sleep propensity can be underpinned by a reduced circadian signal opposing the homeostatic sleep drive.

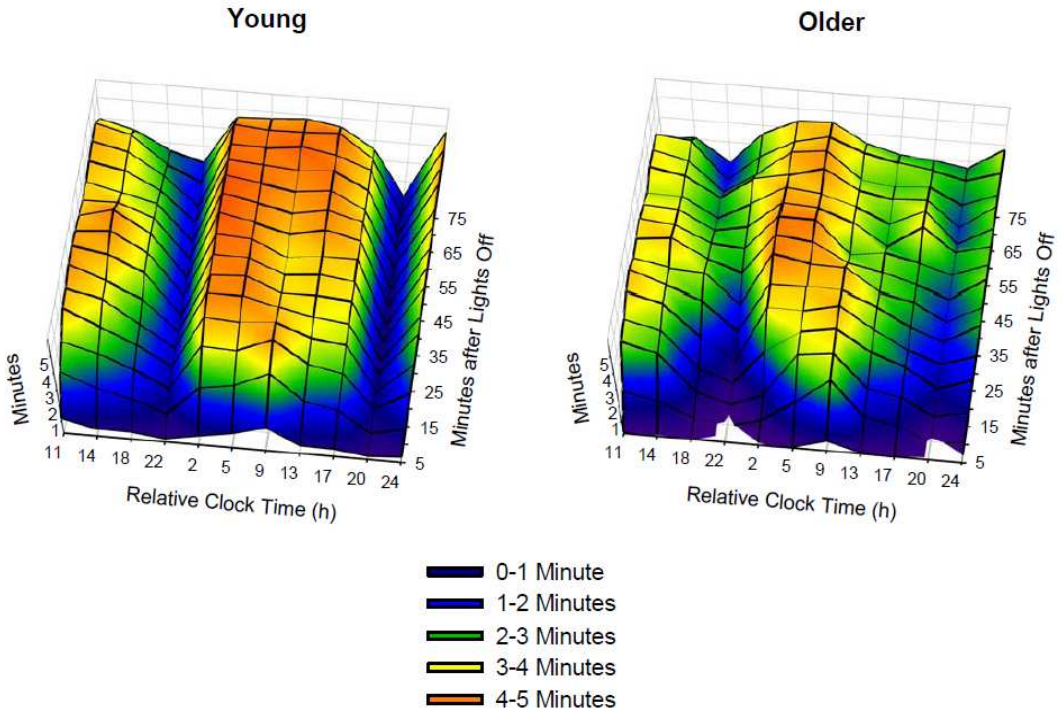

Figure 3 - Quasi three-dimensional plots of total sleep time for young (left panel, n=17) and older subjects (right panel, n=15). The x-axis represents the averaged mid-nap clock times for both groups and the y-axis the time course within the respective naps (0-75 min). The z-axis specifies the amount of sleep (TST) per 5-min bin of each nap (min). Blue and green colours depict less sleep, while yellow and orange colours illustrate more sleep (68).

When considering the sleep homeostat, there is evidence for two types of situations: (1) under high sleep pressure, older participants exhibit an attenuated frontal predominance of sleep EEG delta activity (66); (2) under low sleep pressure, in which sleep pressure is kept low through multiple-naps throughout the 40 hours of the constant routine protocol, there are slight age-related differences (69). However, the SWA response to low sleep pressure was more enduring in younger individuals, given that it lasted for the first 2 NREM sleep episodes, while for the older individuals it lasted only for the first NREM sleep episode. Given that both the circadian system and the sleep homeostat modulate sleep regulation, changes in these two processes can account for the age-related changes in sleep. Thus, the

next logical step is to know how the complex interplay of these systems can modulate cognitive processes, such as dreaming, in young and older individuals.

DREAM RECALL

Overview

Dreaming is a universal human experience which offers a unique view of consciousness and cognition. Definitions of dreaming range from the broadest "any mental activity occurring in sleep" and “dreams represent the conscious awareness of complex brain systems involved in the reprocessing of emotions and memories during sleep” (70) to narrower ones, such as "mental activity occurring in sleep characterized by vivid sensorimotor imagery that is experienced as waking reality, despite distinctive cognitive features as impossibility or improbability of time, place, person and actions; emotions, especially fear, elation and anger predominate over sadness, shame and guilt and sometimes reach sufficient strength to cause awakening; memory for even very vivid dreams is evanescent and tends to fade quickly upon awakening unless special steps are taken to retain it." (71). The functional relevance of dreaming remains a matter of debate. Some hypotheses, such as the mind-brain reductionism, suggest that dreaming is a random by-product of underlying REM sleep physiology (72). Recently, dream processing has been argued as a means for reactivation and consolidation of novel and individually-relevant features of prior wake experience (73-75). In this context, one might speculate that dreaming enables the replay of isolated elements (from their original context) for the integration of new features into existing cognitive representations linked to specific brain areas (76). Furthermore, dreams may enable enactment of affective processes by providing, for instance, an internal activation, arising from the

individuals affective and emotional history and serving an emotion–regulation function (77-79). As a consequence, dreaming may stimulate the resolution of emotional conflict and reduce next-day negative mood. When looked from any angle, the key to unravel dreaming is the understanding of NREM and REM sleep.

REM and NREM dreaming: Spectral EEG correlates

The neuroscientific explanation of dreaming was initially postulated to be driven by REM sleep. Subsequent to Aserinsky and Kleitman (3) discovery that higher rates of dream recall were strongly associated with REM sleep, it became a credible hypothesis that specific brain mechanisms linked to REM sleep might pinpoint the origin of dream processing. Considering this REM sleep-centric approach, the “activation-synthesis” hypothesis was proposed, which described the brainstem generators of REM sleep as the origin of dreaming (72). This hypothesis cascaded numerous studies thereof, which attempted to understand dream generation as a by-product of REM sleep (78, 80-82). However, this REM sleep-driven belief has changed given the compelling evidence of dreaming following NREM sleep (4, 83, 84), although NREM dreaming has also been credited as a memory from a previous REM episode, as argued by “covert” REM sleep theory (84). NREM dreaming differs to REM dreaming on a wide-range of characteristics. Dream reports are more probable and longer after REM than after NREM sleep awakenings, with REM/NREM differences in dream report length varying from REM:NREM ratios of 2:1 to as high as 5:1 (4). REM and NREM dreaming are also critically different with respect to its emotional tone. REM dream reports are more emotional, anxious, unpleasant, with clearly visualized different scenes and more socially unacceptable

content (violence/ hostility), while NREM dream reports are consistently more conceptual and thought-like (71).

If sleep EEG patterns can reflect specific brain activation related to dream generation, specific EEG activities prior to dreaming may shed light on the underlying factors that account for dreaming. Previous research on EEG spectral power and dream recall has produced a wide-range of results. It has been reported that beta frequency increases in NREM stage 2, during the transition from epochs without dream mentation to those with distinct mental activity (85). Contrariwise, Morel et al. (86) did not find a relationship between successful recall and EEG activity during stage 2 awakening, but found a significant association between successful recall and reduced levels of sigma activity (12–16 Hz) in post-stage 2 awakening. Evidence also indicates less NREM sleep EEG power density in the theta range (5-8.5Hz) prior to dream recall (87).

REM sleep mentation in young subjects has been linked to alpha activity (88), and to widespread 40-Hz oscillations, both of which may induce large functional states for cognitive processing (89). Faster oscillations during REM sleep may thus correspond to an “electrophysiological correlate” for dream processing (89). Interestingly, there seems to be evidence for an inverse relationship between SWA and sleep mentation (88), with higher levels of SWA associated to no-recall conditions during NREM sleep and, particularly, REM sleep. In fact, the inverse association was more robust for REM sleep, thus suggesting that SWA may be an “index” of sleep mentation. Early studies found similar inverse relationships for more broadly defined frequency bands, such as 4.0–14.0 Hz (90). These diverse results may be due to different methods of EEG quantification (88, 91) and/or different

approaches for dream recall (92). Thus, the precise spectral correlates of dream recall remain uncertain.

Neuronal network for dream generation: Is REM sleep a template for dreaming?

REM sleep is associated with increased regional brain activity in the pontine tegmentum, thalamus, basal forebrain, and limbic and paralimbic structures, including amygdaloid complexes, hippocampal formation and anterior cingulate cortex (ACC) (93-95). Activation of these regions suggests that memory consolidation, particularly emotional memories, may occur during REM sleep (96-99). Furthermore, several regions are hypoactive during REM sleep as compared to wakefulness, such as the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, posterior cingulate gyrus, precuneus, and the inferior parietal cortex (93-95, 100). Deactivations in regions that subserve important executive and attentional functions during wakefulness suggest that the functional neuroanatomy of REM sleep differs from wakefulness (93-95, 100). REM sleep is generated by cholinergic processes within brainstem structures (pedonculopontine tegmentum and laterodorsal tegmentum) that mediate cortical activation through a ventral pathway innervating the basal forebrain and a dorsal pathway innervating the thalamus (101). Rapid eye movements during REM sleep co-occur with “ponto-geniculo-occipital” (PGO) waves, particularly in the pons, the thalamic lateral geniculate and the occipital cortex. PGO waves are bioelectrical phasic potentials occurring during the transition from NREM sleep to REM sleep or during REM sleep itself (102). Potentially important functional roles have been attributed to PGO waves, including

promotion of brain development, brain plasticity (103), and a mechanism for internally-generated neural activity underlying dream processing (72).

NREM sleep comprises widespread cerebral deactivation, particularly with the deactivation of the pontine brainstem, orbito-frontal cortex and anterior cingular cortex (93, 104), while REM sleep can be associated with the regional activation of these same regions (94). NREM sleep decline of cerebral activation has been argued as reflecting progressive deactivation of the reticular activating system (RAS), which follows the deepening of NREM sleep and results in the disfacilitation of thalamocortical relay neurons, which allows for the emergence of thalamocortical oscillations (105, 106). NREM deactivation of ascending arousal systems, such as the pons and midbrain, would probably translate into overall lower levels of global forebrain activation (104, 107). Furthermore, the decreased activation of limbic-related cortical structures, such as the anterior cingulate (104, 108), may limit affective content in comparison to REM sleep. Taken together, REM and NREM sleep show specific activation patterns, with regional changes in brain activity and effective neural connectivity that can pinpoint to differences in dreaming.

Clinical-anatomical studies (109) and functional imagery studies (93-95, 110-113) further suggest that dreaming involves intense activity in selective group of forebrain structures. Data from neurological patients indicate that lesions in two brain areas result in complete loss of dreaming (109, 114). One area is at or near the parietal-temporal-occipital (PTO) junction, with both unilateral and bilateral lesions leading to cessation of dreaming. It is likely that the right PTO area is essential to dreaming due to its function of spatial thought, and the left PTO area is required for quasi-spatial (symbolic) thought (109, 114). The second type of lesion that leads to loss of dreaming is deep bilateral frontal lesions, which undermines the regulatory influences for elaborated volitional interest (109, 114). Patients with lesions in the

visual association cortex can also experience loss of visual imagery in dreams, as well as loss of the capacity to conjure visual imagery while awake, although visual imagery in dreams and wakefulness is preserved with lesions in the primary visual cortex (109). Lesions in various anterior limbic structures can result in the inability to distinguish dreams from reality, often in conjunction with increased frequency and vivacity of dreaming and with waking changes as visual hallucinations and delusions. Finally, lesions in the dorsolateral prefrontal cortex, essential for executive functioning, goal-directed behaviour, and self-monitoring, appear to have minimal effect on dreaming, indicating that these functions are not strongly involved in dreaming (109).

Imaging studies corroborate most of these lesion studies. Most studies show a very specific, selective pattern of activation of forebrain structures, suggesting that the brain is organized to carry out particular functions in a concerted manner (93-95, 100). These structures include REM-related *activation* of anterior and lateral hypothalamic areas, amygdaloid complex, septal-ventral striatal areas, and infralimbic, prelimbic, orbitofrontal, anterior cingulate, and occipital-temporal cortical areas (93-95, 100). Conversely, primary visual cortex and dorsolateral prefrontal cortex are *deactivated* during REM dreaming (110), which indicates diminished executive functioning in dreams. This suggests that specific forebrain mechanisms are involved in the generation of dream imagery, which is actively constructed through complex cognitive processes.

Neuronal networks that underpin NREM dreaming are currently unknown. Imaging studies of the dreaming brain at sleep onset, or during the rising morning phase of diurnal rhythm, when brainstem mechanisms that generate REM are uncoupled from the putative forebrain mechanisms that generate dreaming, may help to unravel specific neuronal networks for NREM dreaming (108).

Circadian activation of Dream Recall

Circadian changes in cortical activity may comprise a likely candidate for dream processing both within and outside REM sleep (115). This circadian modulation can be indexed by progressive across-night changes consistent with a sinusoidal 24-h rhythm, with clear differences between reports from the first third of the night to later samplings (4). Nonetheless, these differences may also be explained by linear, non-oscillatory factors, such as sleep homeostasis (115, 116). A definite conclusion, though, is still far from reach.

Evidence for the circadian influence on dreaming builds-up from a study in which relationships between circadian factors and dreaming were out of sync (117). To create a phase delay of dreaming relative to the hypothesized circadian influence, sleep onset and offset were delayed by 3 hours. REM and NREM dreaming would then occur 3 hours later than usual, thus coinciding with the rising phase of the circadian activation (**Figure 4**). REM and NREM dream reports were compared from the phase-delayed condition with control reports from non-delayed sleep. Delayed dream reports were longer and more visually intense, especially later at night. REM/NREM differences were observed, but REM and NREM reports were both affected by the circadian factor independent of sleep-stage difference. For visual imagery, in particular, the circadian effect size (0.23 or small) was about 30% of the ultradian NREM/REM effect size (0.70 or large). These findings may suggest that the ultradian NREM/REM sleep and circadian cortical and subcortical activation can be independent but additive in their effects on dreaming (117).

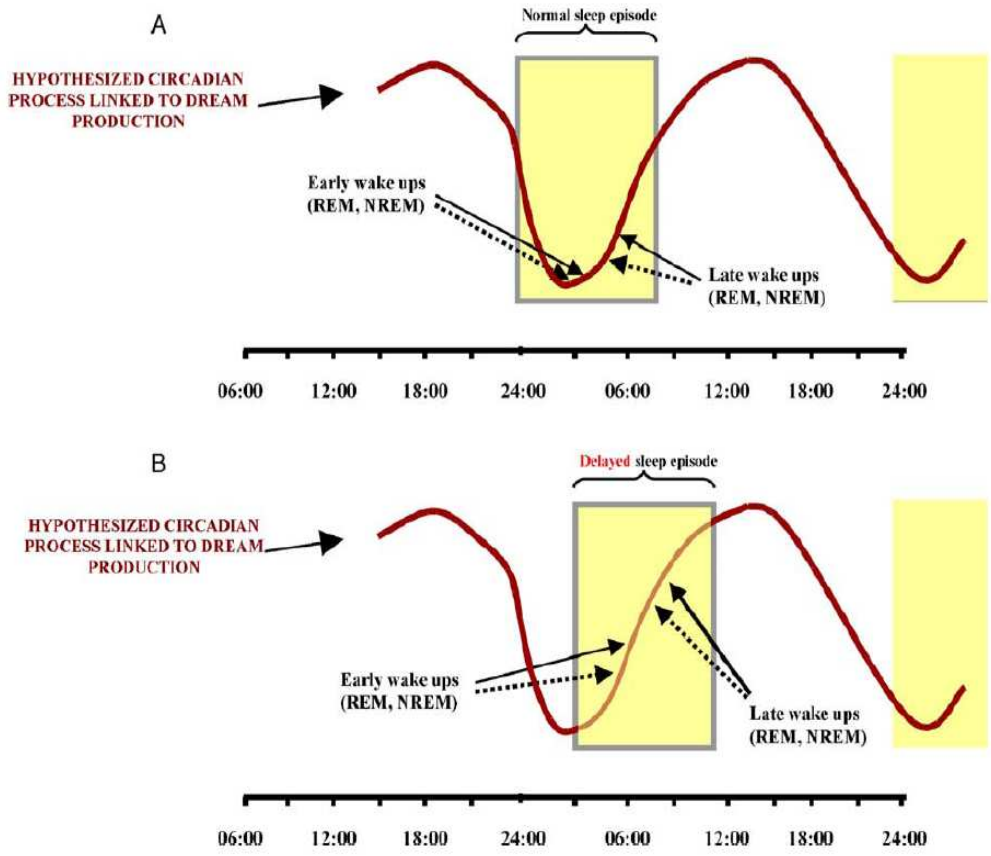

Figure 4 - Theoretical model underlying the partial forced desynchrony protocol to manipulate hypothesized circadian influences on dreaming. Awakenings for dream report in the no-delay condition (A) were made early and late in the sleep episode. Awakenings in the delayed sleep condition (B) were made at the same times relative to sleep onset, thus, at different phase relationships to the hypothesized circadian process. Dream vivification was increased for the late night reports in the delayed condition (117).

Further support for the circadian-driven activation of dreaming comes from an ultra-short multiple-nap protocol study (40/20 minutes of wake/sleep schedules) (118). Dreaming scores elicited for NREM reports were distributed sinusoidally across the 24-h day, with an acrophase at 08:00h. REM report scores were high during the diurnal period of 06:00–16:00h and then dropped. Interestingly, the NREM dream score peak coincided with the peak of REM stage duration, thus suggesting that the propensity for dreaming output from REM and NREM sleep are both influenced by

the same underlying circadian oscillator. This interface between circadian and ultradian NREM/REM sleep factors of dream processing has been the target of some interesting dream hypothesis: single or multi-oscillatory processes (4).

Circadian and ultradian NREM/REM sleep regulation of dreaming: How do they work together?

The general cortical activation for dreaming appears to be modulated by both the circadian and ultradian REM/NREM cycle during periods of high sensory thresholds, thus ensuing dream generation. This regulation may occur by either single or multi-oscillatory processes (4, 71). According to the single-oscillator model, dreaming is regulated by a single oscillatory process, whereby the simultaneous fluctuation in all features of dreaming is modulated by ultradian REM/NREM sleep rhythm. This model is supported by the parallel changes in dream content measures, either as a function of ultradian variation (REM/NREM differences) or circadian variation (within-night differences). Conversely, the multi-oscillator model postulates that dreaming is regulated by separate, partially independent, oscillators similar to the regulation of physiological variables, such as temperature and melatonin under circadian control. Dreaming would have temporal morphologies out of phase with those of other measures, as indexed by higher recall rates in REM sleep at the end of the night. While both models are corroborated by some type of evidence, it is obvious that different types of biological rhythms are implicated in dreaming.

A question in dream research: Aging and dreams

While dream function remains obscure, a reduction in dream recall is observed in a wide-range of circumstances, such as healthy aging (119-121) and also in clinical

settings (122-124). Aging can be associated with reduced circadian amplitude of core body temperature (CBT) rhythm, and phase advances of CBT and melatonin rhythm (67). Some (63, 68, 125, 126), but not all (127-129) studies report a decline in the amplitude of CBT, melatonin and cortisol. If aging is associated to less dream recall, a phase advance in circadian rhythms (5) would result in an earlier circadian peak in dream intensity during sleep. This might explain the resurgence in sleep paralysis events among 40–80-year-olds, and the decrease in retrospectively estimated dream recall with advanced age (119-121). However, it remains largely unclear whether dream recall and /or the emotional toning of dream is *in fact* modified with age, and if so, which are the possible candidates that underpin these changes.

OBJECTIVES AND STRUCTURE OF THESIS

The general objective of this thesis was to investigate the electrophysiological correlates of sleep prior to dream recall and the age-related effects on dream processing. In chapter 2, age-related changes in dream recall, number of dreams, and emotional domain characteristics of dreaming subsequent to NREM and REM sleep were investigated. Dream recall can decline with advancing age (119-121). Given that circadian rhythms may have decreased amplitude (68) and may be phase advanced in older subjects (5), it has been hypothesized that the circadian-coupled peak in dream intensification may be attenuated and/or occur earlier during the sleep episode as compared to young individuals. While there seems to be a strong link between dreaming and endogenous rhythmic events that define REM sleep, there are virtually no studies that link circadian rhythms, aging and dreaming, which was the target of chapter 2.

In chapter 3, NREM and REM sleep EEG power density associated with and without dream recall in young participants was investigated during a 40-hour multiple nap protocol under constant routine conditions. Dream recall can be associated to prior sleep EEG activity, which by itself supports the idea of different neural states triggering changes in dream recall. However, few studies have investigated frequency-specific EEG characteristics of dream recall from both REM and NREM sleep, all of which with limited EEG montages and mixed results (88, 91) and/or different approaches for dream recall (92). Of particular interest, chapter 3 focuses on how topographic distribution of EEG activity during NREM and REM sleep can underpin the cortical networks associated to dream recall.

In chapter 4, NREM and REM sleep EEG activity prior to dream recall and no recall was investigated in young and older participants. Thus, the topic of chapter 3 was extended to further investigate how aging can result in specific changes for dream processing, presumably through its effects on sleep structure.

The methodological rationale underlying chapters 2-4 was the assessment of dream recall through the sleep mentation questionnaire (130), which was carried out immediately after awakenings from each nap of the 40-h multiple nap paradigm (150 / 75 minutes of wake-sleep schedule; 10 naps in total) (**Figure 5**), under constant routine conditions (38).

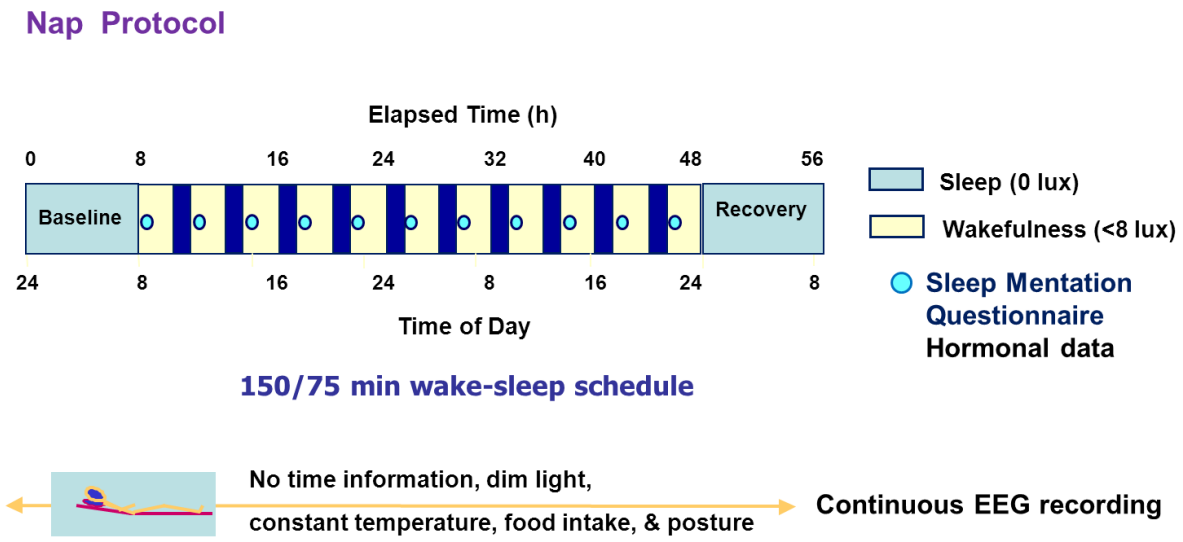

Figure 5 - Schematic representation of the multiple nap-protocol during 150 / 75 minutes of wake-sleep schedule (10 naps in total). Yellow areas indicate scheduled wakefulness and blue bars delineate the scheduled sleep episodes. Throughout the protocol, subjects are under constant posture, semi-recumbent during wakefulness and recumbent during sleep.

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CHAPTER 2

DOES THE CIRCADIAN MODULATION OF DREAM RECALL MODIFY WITH AGE?

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SUMMARY

Study objectives: The ultradian NREM-REM sleep cycle and the circadian modulation of REM sleep sum to generate dreaming. Here we investigated age-related changes in dream recall, number of dreams, and emotional domain characteristics of dreaming during both NREM and REM sleep.

Design: Analysis of dream recall and sleep EEG (NREM/REM sleep) during a 40-h multiple nap protocol (150 min of wakefulness and 75 min of sleep) under constant routine conditions.

Setting: Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Basel, Switzerland.

Participants: Seventeen young (20-31 years) and 15 older (57-74 years) healthy volunteers

Interventions: N/A.

Measurements and Results: Dream recall and number of dreams varied significantly across the circadian cycle and between age groups, with older subjects exhibiting fewer dreams ($P < 0.05$), particularly after naps scheduled during the biological day, closely associated with the circadian rhythm of REM sleep. No significant age differences were observed for the emotional domain of dream content.

Conclusions: Since aging was associated with attenuated amplitude in the circadian modulation of REM sleep, our data suggest that the age-related decrease in dream recall can result from an attenuated circadian modulation of REM sleep.

Keywords: Dream recall; sleep mentation; NREM/REM sleep; melatonin; ageing; circadian rhythms.

INTRODUCTION

Dreams have an internal structure that reflects ongoing large-scale neural networks,[1] which mainly comprise the ultradian NREM-REM sleep cycle and the circadian activation of REM sleep. These combine to generate the main characteristics of dreaming.[2] Accordingly, in periods of high sensory thresholds, the general cortical activation modulated by both circadian and NREM/REM sleep cycles creates an overall level of cortical activation that leads to dreaming. Therefore, circadian-driven changes in cortical activity can play a critical role in dream activation.[3-5]

In a study purported to control both ultradian and circadian components of dreaming, both sleep onset and offset were intentionally delayed by 3 hours.[3] As a consequence, REM and NREM dreams occurred later than usual in order to coincide with the rising phase of the hypothesized circadian influence on dreaming, near the time of core body temperature nadir. A comparison of both REM and NREM dream reports from the phase-delayed condition with control reports from non-delayed sleep indicated that delayed dream reports were more visually and emotionally intense, particularly when collected later at night. Thus, the relative influence of time of day in relation to sleep stage on dream characteristics appears to play a pivotal role in dreaming. Furthermore, the emotional domain of dreaming appears to be dependent on sleep-stage specific neural activation patterns.[6] It seems likely that motivation and emotionality, considered more prominent in REM dreams, may be linked to regional brain activation patterns specific to REM sleep.[7] One of the theoretical underpinnings for this assumption builds on recent imaging

findings confirming that general cortical activation, as measured by global cerebral blood flow, is greater in REM sleep than in NREM sleep.[8] Limbic areas such as the amygdala were described as more active in REM sleep than in NREM sleep wake.[1,8] While this does not necessarily imply that NREM sleep cannot be associated with dreaming, it may account for some of the differences in REM/NREM dream recall.[7]

Regarding age-related changes in dream recall, there is evidence for a dream recall decline with advancing age.[9-12] Given that circadian rhythms have decreased amplitude and may be phase advanced in older subjects,[13] it can be hypothesized that the circadian-coupled peak in dream intensification might be attenuated and occur earlier than in young subjects during the sleep episode. This may partly explain why dream recall is decreased in older individuals. Albeit the strong link between dreaming and endogenous rhythmic events that define REM sleep, there are few stringent studies that link circadian rhythms, aging and dreaming *per se*. Thus, in the current study, we investigated age-related changes in the circadian modulation of dream recall, number of dreams and emotional domain characteristics of dreaming, during both NREM sleep and REM sleep, under stringently controlled laboratory conditions.

METHODS

Study participants

All study participants were recruited via advertisements at different Swiss universities and in newspapers. Only candidates with a Pittsburgh sleep quality index (PSQI) score ≤ 5[14] and no extreme chronotype, (ratings between 14 and 21

points on the morning-evening M/E questionnaire[15]) were selected. All potential study participants were questioned about their sleep quality, life habits and health state. Exclusion criteria were smoking, medication or drug consumption, shift work within the last 3 months, and transmeridian flights during the month prior to the study. Volunteers underwent physical examination, interview, neuropsychological assessment (only for the older cohort to exclude motor, attention or memory impairments), and polysomnographically recorded adaptation night, in order to exclude sleep disorders. Inclusion criteria were sleep efficiency ≥ 80%, < 10 periodic leg movements per hour and an apnea-hypopnea index < 10. Only participants without any medication (with the exception of 4 young women using oral contraceptives) were included in the study. Young females started the study on day 1–5 after menses onset during the follicular phase of their menstrual cycle.

Seventeen healthy young (9 women, 8 men, age range 20–31 years, mean: 25.0 ± 3.3 SD) and 15 healthy older volunteers (7 women, 8 men, age range 57–74 years, mean: 65.1 ± 5.6 SD) were included in the study. All participants gave written informed consent. The study protocol, screening questionnaires and consent form were approved by the local ethics committee and conformed to the Declaration of Helsinki.

Study Design

One week prior to the study (baseline week), the participants were requested to abstain from excessive caffeine and alcohol consumption (one caffeine-containing beverage per day at most and < 5 alcoholic beverages per week). They were instructed to keep a regular sleep-wake schedule during the baseline week at home (bedtimes and wake times within ± 30 minutes of a self-selected target time between 22:00 and 02:00) prior to admission to the laboratory. Compliance was

checked by sleep logs and ambulatory activity measurements (wrist activity monitor, Cambridge Neurotechnology Ltd, UK). The timing of the sleep-wake schedule during the protocol was adjusted to individual habitual bedtimes. For each participant, habitual bedtime was calculated by centering the approximately 8-h sleep episodes during the baseline week at their midpoint. The inpatient part of the protocol comprised 2 baseline sleep episodes in the chronobiology laboratory, followed by a 40-h multiple nap protocol, with 10 alternating sleep-wake cycles of 75/150 minutes duration each and one recovery sleep episode (**Figure 1**). Baseline and recovery nights were scheduled at individual habitual bedtimes. Polysomnographic recordings and constant posture started in the afternoon after the first baseline night. Thereafter, participants remained under constant routine conditions (constant dim light levels < 8 lux during scheduled wakefulness, semi-recumbent posture in bed, food and liquid intake at regular intervals, no time cues).[16-18] During scheduled sleep episodes a minor shift (45 degrees up) in the supine posture was allowed, and the lights were off (0 lux). Older participants received a daily low-dose subcutaneous heparin injection (Fragmin, 0.2 mL, 2500 IE/UI, Pfizer AG, Switzerland) to prevent potential venous thrombosis.

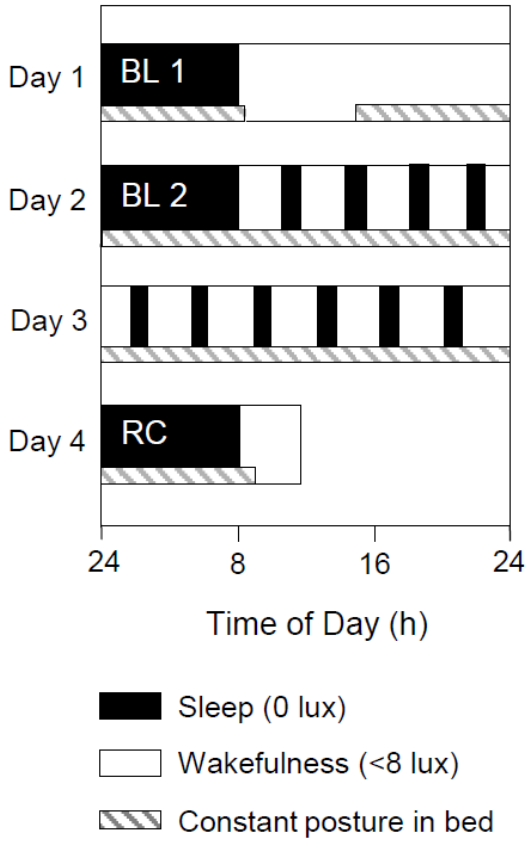

Figure 1—Overview of the 4-day inpatient part of the study protocol. Black bars (0 lux) indicate the sleep episodes and white bars the wake episodes (< 8 lux). The hatched bars indicate controlled posture (semi-recumbent during wakefulness and supine during sleep). BL = baseline night, RC = recovery night (modified from Munch et al., 2005[18]).

Polysomnographic Measures

Sleep was polysomnographically recorded with the VITAPORT ambulatory system (Vitaport-3 digital recorder, TEMEC Instruments B.V., Kerkrade, the Netherlands). Twelve EEGs channels, 2 electroculograms, a submental electromyogram, and an electrocardiogram were recorded. All signals were low-pass filtered at 30 Hz (fourth order Bessel type anti-aliasing, total 24 dB/Oct) at a time constant of 1.0 s. After online digitization by using a 12 bit AD converter (0.15V/bit) in the range of 610V

and a sampling rate at 128 Hz for the EEG, the raw signals were stored on a Flash RAMCard (Viking, USA) and later downloaded to a PC hard drive. Sleep stages were visually scored per 20-s epochs (Vitaport Paperless Sleep Scoring Software) according to standard criteria.[19]

A nap trial that contained only REM sleep in the *last* 15 minutes of a scheduled 75-minute nap was defined as a REM nap and a nap trial with NREM sleep in the *last* 15 minutes was defined as a NREM nap. "Wakefulness naps" were defined as nap trials not containing either NREM or REM sleep stages and were excluded from further analyses. This criterion was based on a prior definition of NREM and REM naps, in which 20-min naps were employed.[20] Since the current study included 75-min naps, *only* the last 15 min were considered for the REM sleep and NREM sleep stages, instead of 20 minutes, since the likelihood of having 20-min naps exclusively with REM sleep would be substantially reduced. Dreams from NREM and REM naps were expressed as dream recall, number of dreams, and dream characteristics on a point-scale of the Sleep Mentation Questionnaire ranging from 0 (less) to 3 (more), at each given nap (see methods section on dream recall).

Sleep stages were visually scored per 20-s epochs. NREM sleep (i.e., stages 1-4) and REM sleep were expressed as the percentage of total sleep time (i.e., stages 1-4 and REM sleep) per nap before averaging over subjects.

Subjective Sleepiness Ratings

Subjective sleepiness was assessed by the Karolinska Sleepiness Scale (KSS) on a point scale ranging from 1 (very alert) to 9 (very sleepy) every 30 min during scheduled wakefulness.[21] To test possible repercussions of age-related changes in

sleep inertia on dream recall, only the very first KSS rating taken (5 min after lights on) after each nap was considered for analysis.

Salivary Melatonin and Classification of Biological Day and Night

Saliva collections were scheduled during wakefulness at the same time intervals (every 30 min). A direct double-antibody radioimmunoassay was utilized for the melatonin assay (by gas chromatography–mass spectroscopy with an analytical least detectable dose of 0.65 pm/mL; Bühlmann Laboratory, Schönenbuch, Switzerland).[22] For mean melatonin levels, values of all samples between the upward- and downward-mean crossing points were averaged per subject and age group. The mean melatonin concentration was calculated for each subject. A nap was classified as a night nap (biological night) if the melatonin concentration of the last saliva sample prior to the nap was above the individual mean; otherwise, it was classified as a day nap (biological day).[18,23]

Dream Recall

Dream recall was assessed immediately at the end of each nap trial (10 naps in total) with the Sleep Mentation Questionnaire, which addresses main characteristics of dream recall, such as number of dreams, emotionality, vividness, pleasantness, hostility, and colourfulness. Questions were not asked about detailed dream content, as this could have influenced dream reports at successive nap trials. The dream recall questionnaire comprised the following questions:

Q1. “How much did you dream?” (1: greatly, 2: fairly, 3: relatively little¸ 4: not at all)

Q2. “How many different dreams can you remember having?” (none [0], 1, 2, 3, 4, 5, 6, more than 6). When the reply to Q1 and Q2 was 4 and 0, respectively, Q3-7 were not asked. Otherwise, Q2 was followed by Q3-7. Hence, participants were considered to have had dream recall if their response to Q1 and Q2 was *not*, respectively, 4 and 0.

Q3. “How emotional was your dream?” (1: greatly, 2: moderately, 3: little, 4: not at all)

Q4. How vivid was the dream?” (1: very vivid, 2: moderately, 3: little, 4: not vivid)

Q5. “How pleasant was the dream?” (1: very pleasant, 2: moderately pleasant, 3: moderately unpleasant, 4: very unpleasant)

Q6. “How much hostility was in your dream?” (1: greatly, 2: fairly, 3: relatively little, 4: not at all)

Q7. “Did you dream in colour?” (1: greatly, 2: fairly, 3: relatively little, 4: not at all)

The participants’ responses to Q1 and Q2 were averaged separately for REM naps and NREM naps. Likewise, participants’ mean scores for Q3-Q7 after REM and NREM naps were calculated.

For analysis of the dream variables, the point scale from 1 (more) to 4 (less) of this dream questionnaire was inverted from 0 (less) to 3 (more) for statistical comparisons. Afterwards, for the analysis of dream characteristics, an emotional composite score was built with the following 5 items: emotionality, vividness, pleasantness, hostility, and colourfulness. Since dream characteristics rely on number of dreams, the emotional composite score was adjusted to the individual mean values of number of dreams.

Statistical Analysis

For all analysis, the statistical packages SAS (SAS Institute Inc., Cary, NC, USA; Version 6.12) and Statistica (Stat-Soft Inc., 2000–2004, STATISTICA for Windows, Tulsa, OK, USA) were utilized. Visually scored sleep stages per nap sequence and the dream characteristics after naps and baseline sleep episode were tested with a Mann–Whitney *U* test for the age group comparisons, since the data did not reach the criterion for a parametric distribution. For the comparison of recall, number, and the emotional composite score of dreams across naps with baseline values in the young cohort and in the older cohort, the Wilcoxon matched pairs test was utilized. For group differences of dream variables both in relation to baseline and within naps, the mixed-model analyses of variance for repeated measures, r-ANOVA (PROC Mixed), with factors “age” (young and older) and “time” (10 naps) was performed. For group differences of dream variables during the biological day and biological night, PROC Mixed was utilized considering factors “age” (young and older) and “condition” (subjective day/night). REM and NREM sleep duration were included as *covariates* in this model, in which the same factors were utilized. For group differences of the KSS in relation to the naps, PROC Mixed was performed considering factors “age” (young and older) and “time” (10 naps). For dream recall after NREM and REM naps averaged across the 10 naps, PROC Mixed was performed considering factors “age” (young and older) and “type” (NREM and REM naps). Contrasts were assessed with the LSMEANS statement and all P-values for the r-ANOVA were based on the Kenward-Roger corrected degrees of freedom. For the adjustment for post-hoc multiple comparisons, the Tukey-Kramer test for unbalanced data was utilized in the PROC Mixed.

RESULTS

Age-related changes in dream recall after baseline sleep and nap episodes

baseline sleep episode

Baseline dream values, conducted immediately after baseline night, encompassed dream recall, number of dreams, and dream emotionality on the sleep mentation questionnaire. No significant age-related differences were observed with respect to dream recall (older: 1.1 ± 0.9, young: 1.7 ± 0.9, Mann-Whitney *U* test, $P > 0.1$) and number of dreams (older: 0.9 ± 0.9, young: 1.3 ± 1.1, Mann-Whitney *U* test, $P > 0.1$). However, older individuals exhibited a comparatively lower emotional composite score (older: 0.78 ± 0.6, young: 1.0 ± 0.7, Mann-Whitney *U* test; $P < 0.1$). Dream recall, number of dreams and the emotional composite score expressed as percentage of dream recall averaged across the 10 naps in relation to baseline recall (relative values) are shown in Table 1. Baseline values were deemed as 100% for both age groups. Comparison between baseline and nap values for the young group yielded a significant decrease for dream recall and an increase for number of dreams (Wilcoxon paired test, $P < 0.05$), with no differences for the emotional composite score. For the older cohort, a trend for lesser dream recall was elicited for the naps in comparison to baseline (Wilcoxon paired test $P < 0.1$), with no further differences for the other dream variables. Comparison between age groups yielded no significant differences for any of the aforementioned dream variables (Mann-Whitney *U* test, $P > 0.1$). Therefore, when adjusted for baseline levels, both age groups recalled dreams similarly, and the emotional composite score of their dreams did not significantly differ. No gender differences were seen in baseline values or in the remainder of this data set.

Naps

In a second step, age-group specific differences were compared with r-ANOVA with factors “age” and “time (naps).” For dream recall, significant differences were elicited for main effects “age” (r-ANOVA, $F_{1,60}$ = 17.3, P < 0.001) and “time” (r-ANOVA, $F_{9,250}$= 5.1, P < 0.001). Likewise, number of dreams yielded significant differences for main effects “age” (r-ANOVA, $F_{1,80}$ = 12.8, P < 0.001) and “time” (r-ANOVA, $F_{9,246}$=3.2, P < 0.001). For the emotional composite only the main factor “time” yielded significance (r-ANOVA, $F_{9,205}$ = 4.1, P < 0.001). The interaction “age” × “time” yielded no significant differences for any of the dream variables.

In this step, dream recall was deemed as the amount of recall at each of the given 10 naps on a same point-scale questionnaire value (0-3) for each dream variable in both age groups, with the emotional composite score adjusted to the individual mean number of dreams. Averaging these data for young and older subjects and for subjective day and night, respectively when endogenous melatonin levels are lowest and highest (**Figure 2**), indicated that dream recall (r-ANOVA: main effect “age”; $F_{1,60}$= 11.51, P < 0.05) and number of dreams (r-ANOVA: main effect “age”; $F_{1,60}$ = 8.21, P < 0.05) were significantly higher in young individuals during subjective day in detriment to older subjects. However, no significant interactions were elicited for either of these variables. Regarding the emotional composite score, there was a significant interaction (age × subjective day/ night) between young and older individuals (r-ANOVA: interaction “age”; × “condition” $F_{1,56}$ = 4.32, P < 0.05), with younger subjects exhibiting a higher emotional composite score during the subjective day than the subjective night. **Figure 3** illustrates the time course of dream recall, number of dreams, and emotional composite score for both age groups.

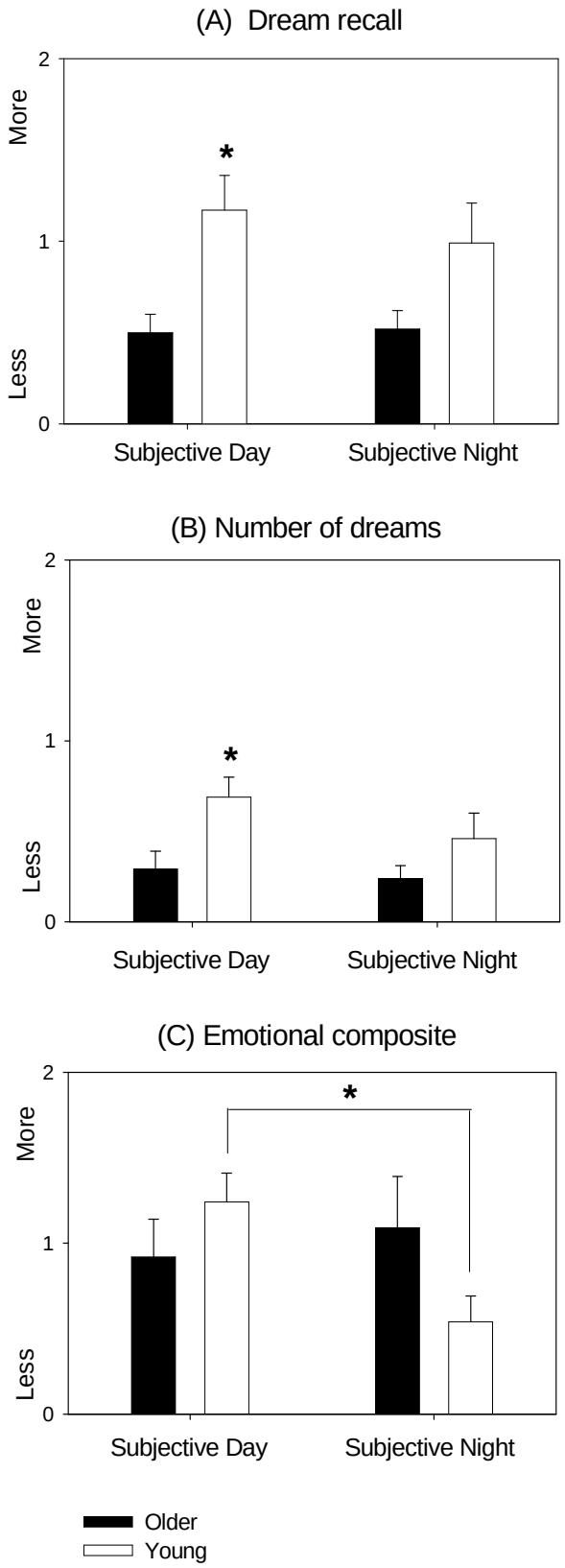

Figure 2 — Dream recall, number of dreams, and emotional composite score averaged for young (white bars, n = 17) and older subjects (black bars, n = 15) for subjective day and subjective night. Scores are presented as mean values ± SEM. *P < 0.05; ^{o}P < 0.1.

Time course of salivary melatonin

The time course of melatonin concentrations throughout the naps is illustrated in **Figure 3 (last panel)**. Older participants had significantly lower nighttime salivary melatonin levels in relation to the young cohort (*t*-test 2-tailed for independent samples; 11.4 ± 6.1 older vs.18.9 ± 12.6 pg/mL young group; mean ± SEM; $P < 0.05$). When considering dream recall, the significant age-related differences were mostly observed in naps 1, 2, 3, and 9 for dream recall and dream characteristics. Interestingly, these significant differences occurred exclusively during the biological day, when saliva melatonin was at the lowest levels.

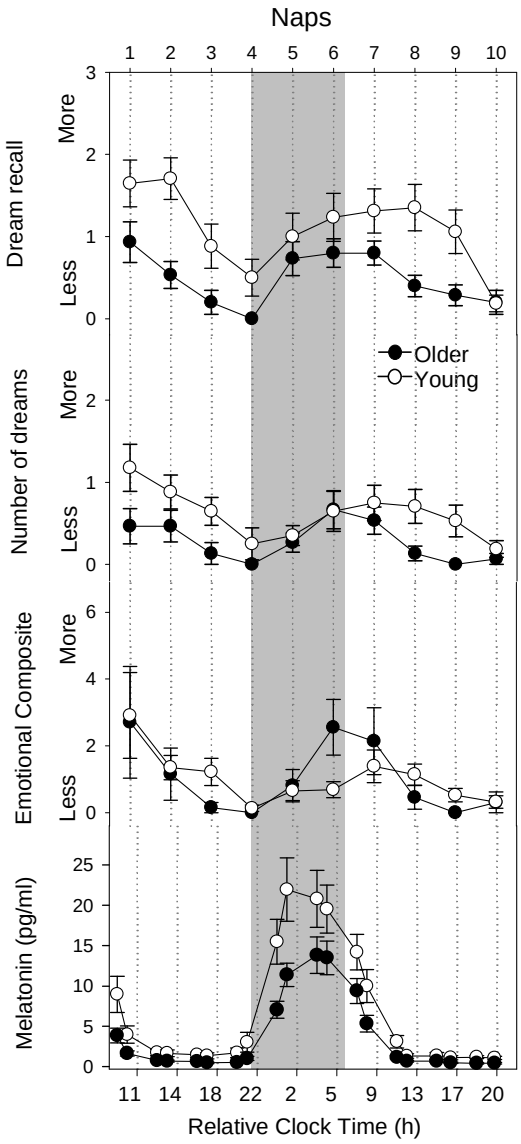

Figure 3—Time course of dream recall, number of dreams, emotional composite score and mean ± SEM. values of melatonin secretion in both age groups during the 40-h nap protocol between young (white circles, *n* = 17) and older volunteers (black circles, *n* = 15). The grey bar illustrates biological night. Scores are presented as mean values ± SEM.

Time course of TST, NREM Sleep, and REM sleep within naps

The analysis of total sleep time (TST) revealed that the young cohort slept significantly less during naps 4 and 10 (wake maintenance zone) and more during naps 5 and 8 (Mann-Whitney *U* test; $P < 0.05$; **Figure 4, first panel**). Older subjects exhibited comparatively more NREM sleep during naps 1, 4, 7 and 10 than the young cohort ($P < 0.05$; **Figure 4, second panel**). On the other hand, older volunteers had significantly less REM sleep than young volunteers during naps 2, 7, and 8 ($P < 0.05$; **Figure 4, third panel**) and a tendency during the first nap ($P < 0.1$). Nonetheless, both age groups exhibited an apparent circadian modulation of REM sleep. For more detailed information on age-related changes on sleep structure and sleep EEG characteristics, please see Münch et al. 2005.[18]

In order to discriminate the contributions of REM and NREM sleep duration during the last 15 minutes of a given nap on dream recall, these sleep parameters were included as covariates for both age groups and averaged across the naps. The analysis of covariance of REM and NREM sleep duration revealed that NREM sleep significantly modulated dream recall ($F_{1,250} = 11.8$, $P < 0.001$), albeit not number of dreams ($F_{1,286} = 0.14$, $P > 0.1$) or the emotional composite score ($F_{1,244} = 1.6$, $P > 0.1$). REM sleep significantly modulated dream recall ($F_{1,258} = 21.4$, $P < 0.001$), number of dreams ($F_{1,291} = 58.7$, $P < 0.001$) and the emotional composite score ($F_{1,244} = 7.3$, $P < 0.05$). In addition, all these dream variables varied significantly across the circadian

cycle (r-ANOVA, main factor: “time” (naps): $P < 0.05$), with a circadian modulation closely associated with the time course of REM sleep throughout the naps.

Time course of sleep inertia

The very first sleepiness rating (KSS) after each nap, as an index for sleep inertia, of both age groups exhibited a clear circadian modulation, with highest sleepiness levels occurring at around naps 5 to 7 (time of day: day 1: 22:00 to day 2: 05:00) (**Figure 4, fourth panel**). Although older subjects appeared to be comparatively less sleepy, no significant age-related effects were observed (2-way r-ANOVA, factor “age,” $F_{1,59.5} = 1.57$; $P = 0.21$). The time course of KSS ratings yielded significance for naps (2-way r-ANOVA, factor “time” [naps], $F_{9,259} = 7.16$; $P < 0.001$) as well as for the interaction “age” × “time” (2-way r-ANOVA; $F_{9,259} = 2.06$, $P = 0.03$). Sleep inertia after nap 8 was significantly higher in younger subjects, whereas after nap 10 (wake maintenance zone), older subjects experienced more sleep inertia than young individuals.

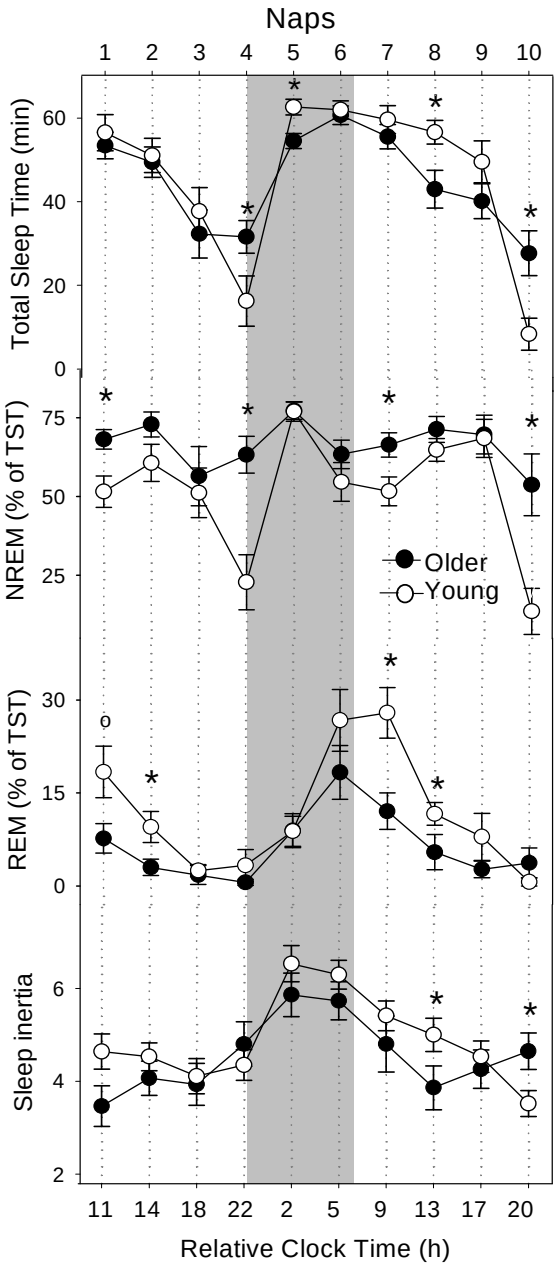

Figure 4—The first panel shows total sleep time (TST), the second depicts NREM sleep, the third shows the REM sleep and the last panel represents the Karolinska Sleepiness Scale (KSS) ratings across the 40-h nap protocol between young (white circles, *n* = 17) and older volunteers (black circles, *n* = 15). The grey bar illustrates the biological night. Mean ± SEM. *P < 0.05.

Dream Recall from NREM and REM Naps

Taken together, the young (n = 17) and older (n = 15) cohorts had a total of 170 and 150 scheduled naps, respectively. According to our criteria, naps among the young cohort included 48.3% NREM naps, 27.9% REM naps, and 23.8% wakefulness naps. The older cohort had 61.2% NREM naps, 14.3% REM naps, and 24.5% wakefulness naps. When comparing the types of naps between age groups, older subjects had significantly fewer REM naps than young subjects (Mann-Whitney *U* test; $P < 0.05$), while having more NREM naps instead (Mann- Whitney *U* test; $P < 0.1$). There were no significant age-related differences for wakefulness naps. Dream recall analysis from REM and NREM naps revealed an overall recall rate of 84% and 57% for REM and NREM naps, respectively.

Age-group specific differences were compared by r-ANOVA with factors “age” and “type” (NREM sleep/REM sleep). For dream recall, the main effects “age” (r-ANOVA, $F_{1,79} = 7.9$, $P < 0.05$) and “type” (r-ANOVA, $F_{2,79} = 19$, $P < 0.001$) yielded significant differences. Similarly, for number of dreams, significant differences were elicited for main effects “age” (r-ANOVA, $F_{1,79} = 5.6$, $P < 0.05$) and “type” (r-ANOVA, $F_{2,79} = 9.8$, $P < 0.001$). The interaction “age” × “type” yielded significant differences only for dream recall (r-ANOVA, $F_{2,79} = 3.1$, $P < 0.05$). With respect to the emotional composite score, factor “type” was significant (r-ANOVA, $F_{2,75} = 5.1$, $P < 0.05$).

Older individuals had significantly less dream recall after NREM naps (older: 0.36 ± 0.09, young: 1.11 ± 0.2, r-ANOVA main factor “age,” $P < 0.05$) and a tendency for less dream recall after REM naps (older: 1.23 ± 0.13, young: 1.73 ± 0.25, r-ANOVA main factor “age,” $P < 0.1$) (**Figure 5A**). Additionally, both older (r-ANOVA interaction “age” × “time” [naps], $P < 0.001$), and young individuals (r-ANOVA interaction “age” × “time” [naps], $P < 0.05$) had significantly less dream recall after NREM naps than after REM naps (**Figure 5A**). A trend for fewer dreams was yielded for older individuals after REM naps (older: 0.67 ± 0.2, young: 1.03 ± 0.21, r-

ANOVA main factor “age,” P < 0.1) (**Figure 5B**). Furthermore, both older and young individuals had significantly fewer dreams after NREM naps than REM naps (P < 0.05) (Figure 5B). No age-related differences were observed for the emotional composite score after NREM and REM naps (**Figure 5C**). However, young individuals exhibited a significantly higher emotional composite score after REM naps than NREM naps (P < 0.001) (**Figure 5C**).

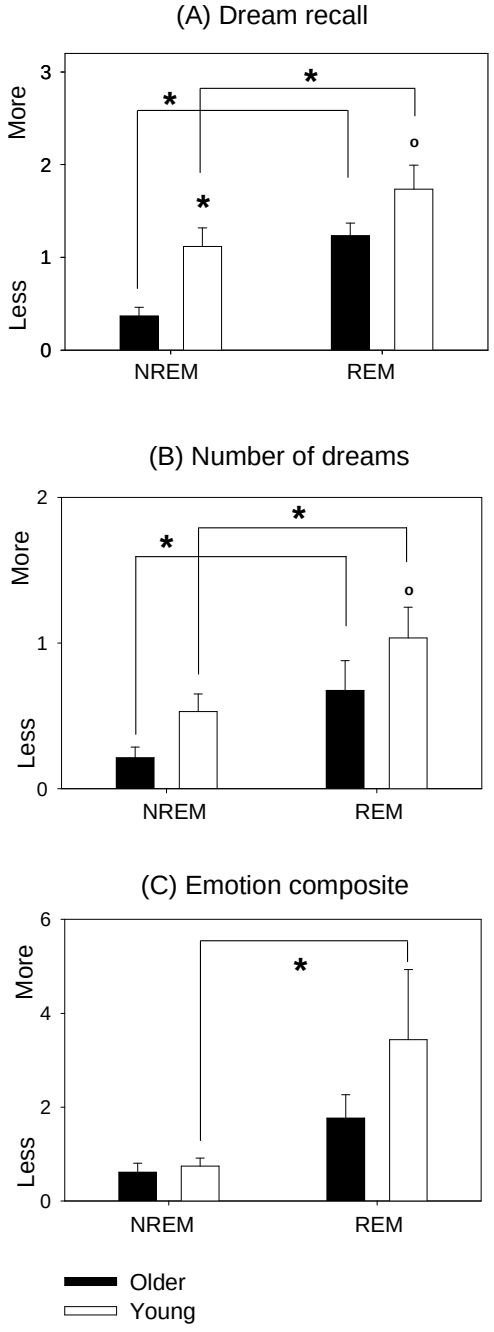

Figure 5—Dream recall, number of dreams and the emotional composite score for NREM and REM naps in young (white bars) and older volunteers (black bars). Scores are presented as mean values ± SEM. *P < 0.05.

DISCUSSION

The time course of dream recall across a 40-h nap protocol followed the clear circadian profile of sleep propensity. This circadian modulation of dream recall showed an age-dependent attenuation, as indexed by less dream recall in older subjects, particularly during naps scheduled during the biological day when endogenous melatonin levels were low. The emotional composite score, which encompasses emotionality, vividness, pleasantness, hostility and colourfulness of dream content, yielded no age-related differences. In other words, older subjects did not exhibit a decrease in the emotional domain of dreaming as compared to the young cohort, when adjusted for number of dreams. Our data indicate that the observed age-related decline in dream recall and number of dreams are related to the concomitant age-related decrease in circadian REM sleep propensity.

Is aging *per se* accountable for lower dream recall?

Dream recall and number of dreams decreased with age, which corroborates with previous findings that support fewer dreams with increasing age.[10,11] It is assumed that, while sensory input is attenuated in sleep, dreaming is generated by cortical activation driven by ultradian and circadian activation cycles.[2] This is strongly supported by the fact that dreaming can fluctuate in concert with the circadian activation, irrespective of REM sleep-specific regional activation pattern.[24] However,

this assumption is controversial, since one could argue that dreaming processes are likely to be dependent on regional subcortical brain activation *specific* to REM sleep.[7] It might be that the age-related changes in both sleep structure and consolidation, caused by reduction in the circadian force that opposes homeostatic pressure,[18,25] may account for age-related effects in dream recall. Since dreaming depends on circadian dependent brain activation, this assumption can be further supported by the fact that, throughout the 40-h multiple-nap protocol, the older cohort showed a diminished circadian rhythm of REM sleep. As dream recall is robustly connected with REM sleep, it can be hypothesized that an attenuated circadian modulation of REM sleep in older individuals can have repercussions on dreaming process.

Is dream recall modulated in a circadian manner?

In this study, dream recall and number of dreams varied significantly across the naps, with an age-related difference, particularly in naps 1, 2, 8, and 9, during the biological day—the time of lowest levels of saliva melatonin (respectively, time of day: day 1, 11:00, 14:00, and day 2, 13:00 and 17:00). As illustrated in the results, the age-related changes in dream recall were more apparent when a similar age difference was observed for the REM sleep, which occurred during the biological day. A possible hypothesis is that sleeping outside the time window of endogenous melatonin secretion leads to fewer sleep spindles,[23] which in turn may reflect higher brain activation and, thus, an increased likelihood for dream mentation. Nevertheless, the reason for higher dream recall when melatonin levels are lowest remains to be clarified.

Older participants appeared to exhibit less sleep inertia than young individuals, mostly in nap 8 (time of day: day 2, 13:00). Evidence suggests that cognitive performance during or shortly after awakening can play a key role for dream recall, since, within this state, cognitive functioning can be impaired by the effects of sleep inertia.[26] Another point to be addressed is that older subjects are more likely to experience sleepiness and increased total sleep time during the wake maintenance zone,[18] since the circadian arousal signal in the evening can fail to adequately oppose the increasing homeostatic sleep pressure in older individuals.[25] However, when considering only the very first KSS rating after the naps, older subjects did not appear to be sleepier than young individuals. Taken together, our results indicate that, although older subjects were *less* sleepy, they still had fewer dreams, which argues against an age-related decrease in dream recall caused by sleep inertia.

One aspect to be considered is that in older subjects circadian rhythms may have a decrease in amplitude and/or be phase advanced.[27,28,13] Evidence that the circadian pacemaker plays a pivotal role in sleep regulation has led to the hypothesis that age differences in sleep can be mediated by changes in the circadian timing system.[27,28] Accordingly, an age-related reduction in the amplitude of the circadian signal can imply an attenuation of the circadian drive for sleep in the morning hours. This can lead to an internal circadian advance, relative to the core body temperature and melatonin rhythm, of the propensity to awaken in older people.[28] This may partly explain the overall decrease in retrospectively estimated dream recall with advanced age. For instance, if dream intensification is phase advanced, spontaneous morning dream recall should be lower.[29] In our study, older individuals appeared to exhibit a higher emotional composite score earlier (around 05:00h) than young subjects (after 05:00h). Taken together, it can be speculated that older individuals have a phase advance and a decrease in amplitude in their dream recall.

What do age effects in dream recall of NREM and REM sleep mirror?

Older individuals recalled fewer dreams after both NREM and REM naps than young individuals. The emotional composite score did not yield age-related differences with respect to NREM and REM naps, although the young cohort exhibited significantly more emotion scores after REM naps. Furthermore, both age groups recalled more dreams after REM naps, with a comparative decrease in the older cohort. Taken together, it can be inferred that dream recall was higher after REM naps, although it also occurred after NREM sleep.

The initial association between REM sleep and dreams[30] stimulated studies designed to clarify the relationship between sleep physiology and dreams. A theoretical assumption emerged, according to which dreaming was viewed as an exclusive REM sleep domain.[31] Nonetheless, various studies have challenged the REM sleep-dreaming perspective, by demonstrating dream recall from NREM sleep stages.[32,33,20] As a result, this has raised the question of to what extent REM sleep-specific physiology constitutes a satisfactory explanation of dreaming. Hence, one of the current debates has shifted to how characteristics of NREM and REM dreams differ and to what might be the neurobiological basis of these differences.[34]

It is well-established that the regional activation pattern of REM sleep can modulate dream recall.[35,8] As hypothesized, dreaming is selectively enhanced during REM sleep, probably due to the heightened limbic activity characteristic of REM sleep.[35,8,1] This adds to the activation of the dorsolateral prefrontal cortex, associated with higher cognitive functions in REM sleep. Thus, the cortical activation appears to be biased toward dreaming processes in this state.[36] This can explain the higher propensity for dreaming in REM sleep, which in our study was demonstrated by the fact that REM sleep significantly modulated dream recall,

number of dreams and the emotional composite score. In the realm of age effects, our data indicated no age-related changes in the emotional domain of dreaming. In other words, older subjects do not necessarily have less emotional dreams than young subjects. Thus, it can be argued that the apparent decrease of these dream characteristics, as described previously,[9-11] is likely to happen since older individuals report less dream recall and number of dreams.

As indicated in the covariate analysis, NREM sleep strongly modulated dream recall, albeit not with respect to number of dreams and the emotional composite score. Within a theoretical framework, it is possible that the intrinsic thalamocortical rhythms associated with NREM sleep, such as higher levels of sleep spindles and delta waves, may interfere with ongoing cognitive activity during NREM sleep, leading to fewer dreams in this state.[24] Likewise, one could argue that dream recall after NREM sleep can be attributed to prior REM sleep.[2] In our study, only the last 15 minutes of each nap were utilized to determine if a given nap was NREM or REM, thus not excluding the possibility of having REM sleep before a NREM nap. Does this imply that NREM sleep is not associated with dreaming? Perhaps not. For instance, dreaming scores elicited for NREM dream recall can be distributed sinusoidally across the 24-h day, with an acrophase at 08:00h[20]. REM dream scores were high for the entire diurnal period and then dropped markedly. Since NREM dreaming curve paralleled the REM sleep curve, as indexed by time-in-stage prior to awakening, it is likely that the dreaming output from REM and NREM sleep are influenced by the same underlying circadian oscillator.[37] Thus, it might be that these cycles sum in such a fashion that NREM sleep can support dream recall when there is circadian activation for dreaming. Taken together, NREM dream recall contradicts REM sleep exclusive dream theories, which assert that dreams are generated solely in REM sleep.[24]

In the context of a multilevel sleep-dependent memory reprocessing, dreams represent the conscious awareness of complex brain systems involved in the reprocessing of emotions and memories during sleep,[36] which can provide a functional role for REM dreaming (particularly for REM sleep-facilitated retention of emotional memories). Thus, it is tempting to speculate that the age-related dampening of the circadian rhythm of REM sleep may lead to decrements in REM sleep replay of emotional memory.

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CHAPTER 3

CORTICAL ACTIVATION PATTERNS HERALD SUCCESSFUL DREAM RECALL AFTER NREM AND REM SLEEP

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SUMMARY

Dreaming pertains to both REM and NREM sleep, however frequency and regional specific differences in EEG activity remains controversial. We investigated NREM and REM sleep EEG power density associated with and without dream recall in 17 young subjects during a 40-hour multiple nap protocol under constant routine conditions. NREM sleep was associated with lower EEG power density for dream recall in the delta range, particularly in frontal derivations, and in the spindle range in centro-parietal derivations. REM sleep was associated with low frontal alpha activity and with high alpha and beta activity in occipital derivations. Our data indicate that specific EEG frequency- and topography changes underlie differences between dream recall and no recall after both NREM and REM sleep awakening. This dual NREM-REM sleep modulation holds strong implications for the mechanistic understanding of this complex ongoing cognitive process.

Keywords: Dream recall; EEG spectral analysis; Cortical activity; Emotional memory; Constant routine; Sleep–wake cycle.

INTRODUCTION

Dreaming is a universal human experience which offers a unique view of consciousness during sleep, although the “whys” and “hows” remain controversial. A critical issue of debate concerns whether dream mentation from REM and NREM sleep can be explained by a one-generator dream model or two-generator dream model. One-generator models stem from a cognitive perspective whereby physiological activity is related to dreaming from a general perspective, with cortical activation being related to the length or complexity of dream reports (Cicogna & Bosinelli, 2001; Foulkes, 1985). In contrast, the most representative neurocognitive two-generator model (Hobson, Pace-Schott, & Stickgold, 2000) proposes dream mentation as a direct function of different physiological profiles characterizing REM and NREM sleep. REM sleep high cholinergic and low aminergic neuromodulation determines dreamlike features (i.e, emotionality, bizarreness), whereas intermediate levels of cholinergic and aminergic NREM sleep neuromodulation underlies less dream mentation (Hobson et al., 2000). If this holds true, cognition occurs throughout sleep, although *dream recall* differs due to differential activity patterns (Antrobus 1983; Cavallero et al. 1990; Foulkes 1993; Rosenlicht et al. 1994). Considering that both one- and two-generator models are supported by some empirical evidence (Nielsen, 2000), the psychophysiological correlates of dream recall – sleep EEG activity as a reflection of specific anatomical pathways - may help to underpin this ongoing cognitive process. Evidence suggests that dream recall relates to increased activity in REM sleep (Armitage et al. 1989), reduced alpha activity in NREM stage 2 and REM sleep (Esposito et al.,2004), and in theta ranges (Lehmann et al. 1981). This supports the idea of different neural states

triggering changes in dream recall. However, strikingly few studies have investigated frequency- and topography-specific EEG characteristics of dream recall from REM and NREM sleep, and all with limited EEG montages (Armitage et al. 1989; Watermann et al., 1993; Esposito et al., 2004).

Here we quantified NREM and REM sleep EEG activity prior to awakening in young volunteers, with and without subjectively rated amount of dream recall, under stringent controlled laboratory conditions, during a 40-h multiple nap protocol. Our two main predictions were as follows:

1. Dream recall and no recall differ in a frequency-specific manner, such that alpha and theta activity will be reduced during dream recall;

2. Dream recall and no recall differ in a very topographic-specific manner, although the direction of these differences cannot be predicted.

METHODS

Study participants

Study volunteers were recruited through advertisements at different Swiss universities. Only candidates with Pittsburgh sleep quality index (PSQI) score < 5 (Buysse et al. 1989) and intermediate chronotype rating (>14 and <21 points on morning-evening M/E questionnaire (Torsvall and Åkerstedt 1980) were enrolled. All potential participants were questioned about sleep quality, life habits and health state. Exclusion criteria were smoking, medication or drug consumption, shift work within the last 3 months, and transmeridian flights during the month prior to study. Each volunteer underwent medical exam and polysomnographically recorded adaptation night to exclude sleep disorders. Inclusion criteria were sleep efficiency >80%, < 10 periodic leg movements / hour and an apnea-hypopnea index < 10.

Only participants without medication (with the exception of 4 young women using oral contraceptives) were included in the study. Young females started the study on day 1–5 after menses onset during the follicular phase of their menstrual cycle. Seventeen healthy young (9 women, 8 men, age range 20–31 years) were included in the study. All participants gave written informed consent. The study protocol, screening questionnaires and consent form were approved by the local ethics committee and conformed to the Declaration of Helsinki.

Study Design

One week prior to the study (baseline week), the participants were requested to abstain from excessive caffeine and alcohol (one caffeine-containing beverage per day at most and < 5 alcoholic beverages per week). They were instructed to keep a regular sleep-wake schedule during baseline week at home (bedtimes and wake times within ± 30 minutes of self-selected target time between 22:00h and 02:00h) prior to admission to the laboratory. Compliance was verified by sleep logs and ambulatory activity measurements (wrist activity monitor, Cambridge Neurotechnology Ltd, UK). The timing of the sleep-wake schedule during the protocol was adjusted to habitual individual bedtimes. For each participant, habitual bedtime was calculated by centring 8-h sleep episodes during baseline week at their midpoint.

The “in-lab” part of the study comprised 2 baseline sleep episodes in the chronobiology laboratory, followed by a 40-h multiple nap protocol, with 10 alternating sleep-wake cycles of 75/150 minutes duration each and one recovery sleep episode (**Figure 1**). Baseline and recovery nights were scheduled at individual habitual bedtimes. Polysomnography recordings and constant posture started in the afternoon after the first baseline night. Thereafter, participants

remained under constant routine conditions (constant dim light levels < 8 lux during scheduled wakefulness, semi-recumbent posture in bed, food and liquid intake at regular intervals, no external time cues). During scheduled sleep episodes, subjects stayed in recumbent position and lights were off (0 lux).

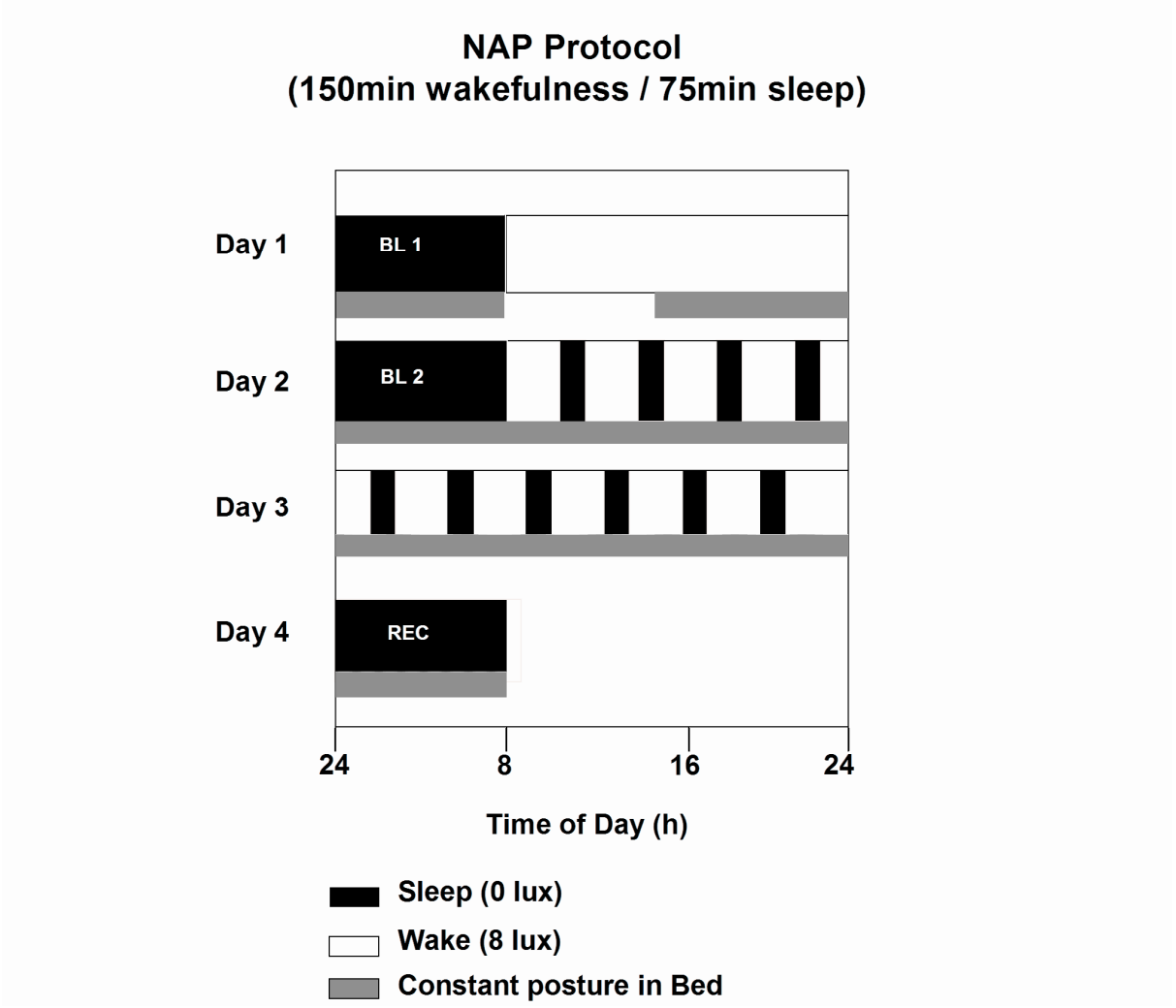

Figure 1 — Overview of the 4-day "in-lab" part of the study. Black bars (0 lux) indicate sleep and white bars wakefulness (< 8 lux). Gray bars indicate controlled posture (semi-recumbent during wakefulness and supine during sleep). BL = baseline night, REC = recovery night (modified from Munch et al., 2005). Herein, data comprise 40-h between BL 2 and recovery night (multiple-nap protocol).

Polysomnographic Measures

Sleep was polysomnographically recorded with the VITAPORT ambulatory system (Vitaport-3 digital recorder, TEMEC Instruments B.V., Kerkrade, the Netherlands). Twelve EEGs channels, 2 electroculograms, a submental electromyogram and an electrocardiogram were recorded. All EEG signals were filtered at 30 Hz (fourth-order Bessel-type antialiasing low-pass filter, total 24 dB/Oct), and a time constant of 1.0 second was used prior to online digitization (range 610 µV, 12 bit AD converter, 0.15 µV/bit; storage sampling rate at 128 Hz). The raw signals were stored online on a Flash RAM Card (Viking, USA) and downloaded offline to a PC hard drive. Sleep stages were visually scored per 20-s epochs (Vitaport Paperless Sleep Scoring Software) according to standard criteria (Rechtschaffen and Kales 1968).

EEG artefacts were detected by an automated artefact algorithm (CASA, 2000 PhyVision B.V., Gemert, Netherlands). Spectral analysis was conducted using a Fast Fourier transformation (FFT; 10% cosine 4-s window) which yielded a 0.25 Hz bin resolution. NREM sleep (stages 1-4) and REM sleep were expressed as the percentage of total sleep time per nap before averaging over subjects. EEG power spectra were calculated during REM sleep and NREM sleep in the frequency range from 0 to 20 Hz. Finally, artefact free 4-s epochs were averaged over 20-s epochs. Here, we report log-transformed EEG data derived from 12 topographical derivations (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, Oz) referenced against linked mastoids (A1, A2) in the range of 0.5–20 Hz on log-transformed data.

A nap trial that contained only REM sleep in the *last* 15 minutes of a scheduled 75-minute nap was defined as a REM nap and a nap trial with NREM sleep (stags 1-4) in the *last* 15 minutes was defined as a NREM nap (Chellappa et al. 2009).

“Wakefulness naps” were defined as nap trials not containing either NREM or REM sleep stages and were excluded from further analyses.

The amount of REM and/or NREM sleep stages during the 15 minutes *prior to* the selected last 15 minutes of a given nap was calculated and the ratio of NREM/REM sleep in both of these two 15-min intervals was compared to illustrate if these ratios remain similar or not in both intervals across the 40-h nap protocol (see supplementary figure 1).

Dream Recall

Dream recall was assessed immediately at the end of each nap trial (10 naps in total) with the Sleep Mentation Questionnaire, which addresses numerous characteristics of dream recall, such as number of dreams, emotionality, vividness, pleasantness, hostility, and colourfulness, on a likert-point scale, whereby 1: greatly, 2: fairly, 3: little¸ 4: not at all (Chellappa et al. 2009). Because the 40-h protocol assesses dream recall at a very high sampling frequency (in addition to collecting physiological variables and carrying out performance tests), we did not access dream content, as this could have seriously influenced and, therefore, biased dream reports at successive nap trials. Instead we selected the previously validated, readily comprehensible, sleep mentation questionnaire (Chellappa et al. 2009), whereby subjectively rated amount of dream experiences could be quantified as either dream or no dream recall. For this categorized classification of dream recall, only the first question [Q1. “How much did you dream?” (1: greatly, 2: fairly, 3: little¸ 4: not at all)] was considered for all the analysis of our dataset. Participants were considered to have had dream recall if their response to Q1 was not 4.

Salivary Melatonin and Classification of Biological Day and Night

Saliva collections were scheduled during wakefulness every 30 minutes. A direct double-antibody radioimmunoassay was utilized for the melatonin assay (validated by gas chromatography–mass spectroscopy with an analytical least detectable dose of 0.65 pm/mL; Bühlmann Laboratory, Schönenbuch, Switzerland) (Weber et al. 1997). For mean melatonin levels, values of all samples between the upward- and downward-mean crossing points were averaged per subject. The mean melatonin concentration was calculated for each subject. A nap was classified as a night nap (biological night) if the melatonin concentration of the last saliva sample prior to the nap was above the individual mean; otherwise, it was classified as a day nap (biological day) (Knoblauch et al. 2005; Münch et al. 2005). This classification was carried out since throughout the 10 scheduled naps, not every scheduled nap had comparable levels of dream recall. Naps were classified into two categories of naps – biological day or night naps – given that by comprising more naps, the comparison of dream recall between these two nap categories would be viable. On average, there were 6.9 ± 0.4 day naps and 3.1 ± 0.2 night naps per subject.

Statistical Analysis

For all analysis, the statistical packages SAS (SAS Institute Inc., Cary, NC, USA; Version 6.12) and Statistica (Stat-Soft Inc., 2000–2004, STATISTICA for Windows, Tulsa, OK, USA) were utilized. The ratio of NREM/REM sleep of the last 15 minutes of a scheduled nap and the 15 minutes prior to the abovementioned time interval of the same nap were compared with one-way ANOVA (Factor: ‘time’). For recall–no recall comparisons during NREM and REM sleep, the mixed-model analyses of variance for repeated measures, r-ANOVA (PROC MIXED), was performed with

factors ‘dream recall´ (recall or no recall) and ‘derivation’ (frontal=F3, F4 and Fz; central= C3, C4 and Cz; parietal= P3, P4 and Pz; occipital= O1, O2 and Oz, thus 4 levels of the repeated measures factor 'derivation'). Alpha adjustment for multiple comparisons was applied in PROC MIXED using Tukey-Kramer test. For day–night comparisons during NREM and REM sleep (please see supplementary material), averaged EEG power density across biological daytime naps was compared with averaged values across biological night-time naps for both recall and no recall conditions. Spectral results averaged for each recall and no recall nap for each subject, as well as for the biological day/night comparisons. Three-way rANOVA (PROC GLM) with the factors dream recall (recall or no recall), ‘biological condition’ (biological day and night) and ‘derivation’ (frontal=F3, F4 and Fz; central= C3, C4 and Cz; parietal= P3, P4 and Pz; occipital= O1, O2 and Oz) was performed. Alpha adjustment for multiple comparisons was applied in PROC MIXED using Tukey-Kramer test. For factor ‘derivation’, the corresponding three derivations (i.e. Frontal=F3, F4 and Fz) were averaged per subject, given that there were no lateralisation effects for dream recall and no recall. Gender was included as *covariate* in this model, in which the same factors were utilized. All *p*-values derived from rANOVAs were based on Huynh-Feldt’s (H-F) corrected degrees of freedom (significance level: $p < 0.05$).

RESULTS

Sleep stages during naps

Sleep stages during the 10 scheduled naps (indexed as percentage of baseline night) indicate that, respectively, NREM sleep stage 1 comprised 21.7$\pm$8.6%, stage 2 was 44.6$\pm$17.3%, stage 3 was 13.5$\pm$4.1%, stage 4 was 9.0$\pm$5.9% and REM sleep

was 15.6±7.5% (all values mean ± SEM, % total sleep time - TST). Time course analysis of TST, NREM sleep, and REM sleep within the naps yielded less TST during naps 4 and 10 (respectively, time of day: Day 1, 22:00h, and Day 2, 20:00h) (wake maintenance zone) and more TST during naps 5 and 8 (respectively, time of day: Day 2, 02:00h, and Day 2, 13:00h). Less NREM sleep was elicited during nap 4 (time of day: Day 1, 22:00h) and nap 10 (time of day: Day 2, 20:00h), while REM sleep was significantly higher during nap 1 (time of day: Day 1, 11:00h), nap 6 (time of day: Day 2, 05:00h) and nap 7 (time of day: Day 2, 09:00h) (1-way ANOVA, factor 'time', $p < 0.05$). Time of day corresponds to mean values across subjects. For detailed information on sleep during the naps, please see (Münch et al. 2005; Münch et al. 2007). Sleep stages derived from visual scoring for dream recall averaged across the last 15 minutes of all naps indicated no differences for total sleep time, sleep efficiency, NREM 1-4 sleep stages and slow-wave sleep. No recall yielded a tendency for more NREM sleep (Wilcoxon matched pair test, $p<0.1$), while dream recall was associated with significantly more REM sleep (Wilcoxon matched pair test, $p<0.05$).

NREM sleep EEG power spectra prior to dream recall and no-dream recall

Overall dream recall rate during NREM sleep was 57±9.6%. No differences were observed for gender effects, as well as in all further analysis of this data set. A significant interaction between the factors 'derivation' (frontal, central, parietal, and occipital) and 'recall' (dream recall vs. no dream recall) was found in the delta (1-3Hz) (two-way r-ANOVA on log-transformed values, $F_{3,57}=7.81$; $p<0.05$) and spindle (12-15.5Hz) (two-way r-ANOVA on log-transformed values, $F_{3,57}=3.65$; $p<0.05$), but not in theta (4.75-7.75Hz), alpha (8-9.75Hz) and beta ranges (16.5-20Hz).

Accordingly, delta activity was attenuated prior to dream recall particularly in fronto-central brain regions ($p<0.001$), with a concomitant spindle decrease in centro-parietal brain regions ($p=0.013$), as compared to no recall **(Figure 2)**. For enhanced visual illustration, a global cortical visual plot with the entire topography is provided in **Figure 3**, for the EEG power density in the delta and spindle range after dream recall and no recall, and for the EEG anterior-posterior topography gradient (EEG recall and no recall spectra expressed as relative ratio of recall/no recall values). Dream recall was related to less delta, particularly in fronto-central derivations, and spindle activity in centro-parietal derivations (two-way r-ANOVA conducted on log-transformed data, factors "derivation' and 'recall', $F_{3,54;}$ $p<0.05$).

REM sleep EEG power spectra prior to dream recall and no-dream recall

Overall dream recall percentage during REM sleep was 74$\pm$13.5%. A significant interaction between factors 'derivation' and 'recall' occurred for the alpha (10-12Hz) (two-way r-ANOVA on log-transformed values, $F_{3,59}=13.35$; $p<0.001$) and beta (14-19Hz) (two-way r-ANOVA on log-transformed values, $F_{3,59}=3.99$; $p=0.03$), but not for delta (1-3.5Hz) and theta (4.75-7.75Hz) ranges. While delta and theta ranges during dream recall yielded no significant differences, alpha and beta ranges were lower in the frontal derivation ($p<0.001$) and higher in the occipital derivation ($p=0.013$) **(Figure 4)**. For enhanced visual illustration, a global cortical visual plot with the EEG anterior-posterior topography is provided in **Figure 5** for the frequencies (alpha and beta ranges) in which significant differences were elicited between recall and no recall. Accordingly, dream recall was related to lower alpha activity in frontal derivation and higher in occipital derivation, together with higher beta activity in the occipital derivation.

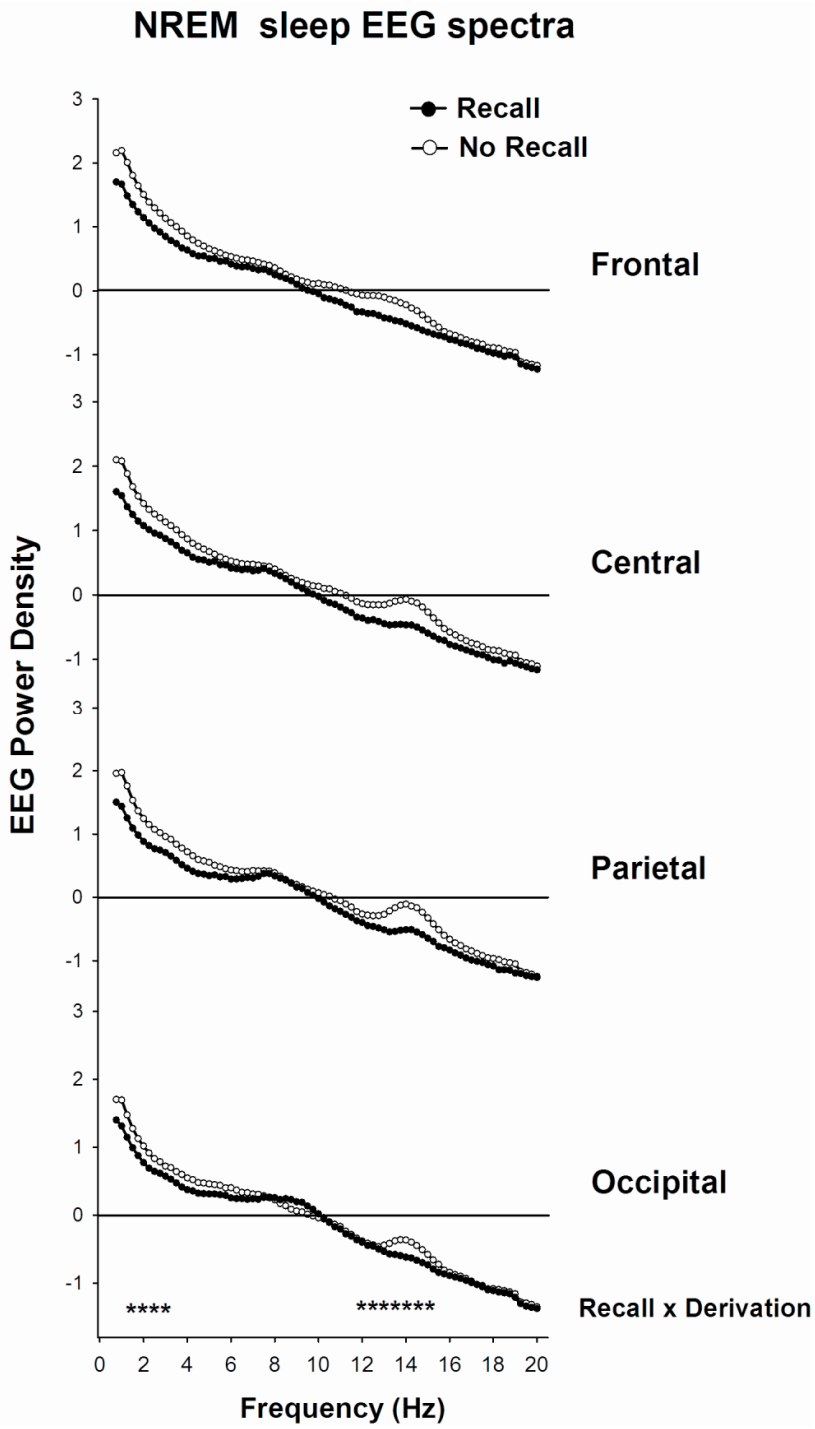

Figure 2 – Absolute NREM sleep EEG spectra (log-transformed) during recall (black circles) and no recall (white circles) (n = 17) in the frequency range between 0.75 and 20 Hz for frontal, central, parietal and occipital derivations. Stars near the abscissa indicate frequency bins with a significant interaction 'recall' x 'derivation' ($p < 0.05$).

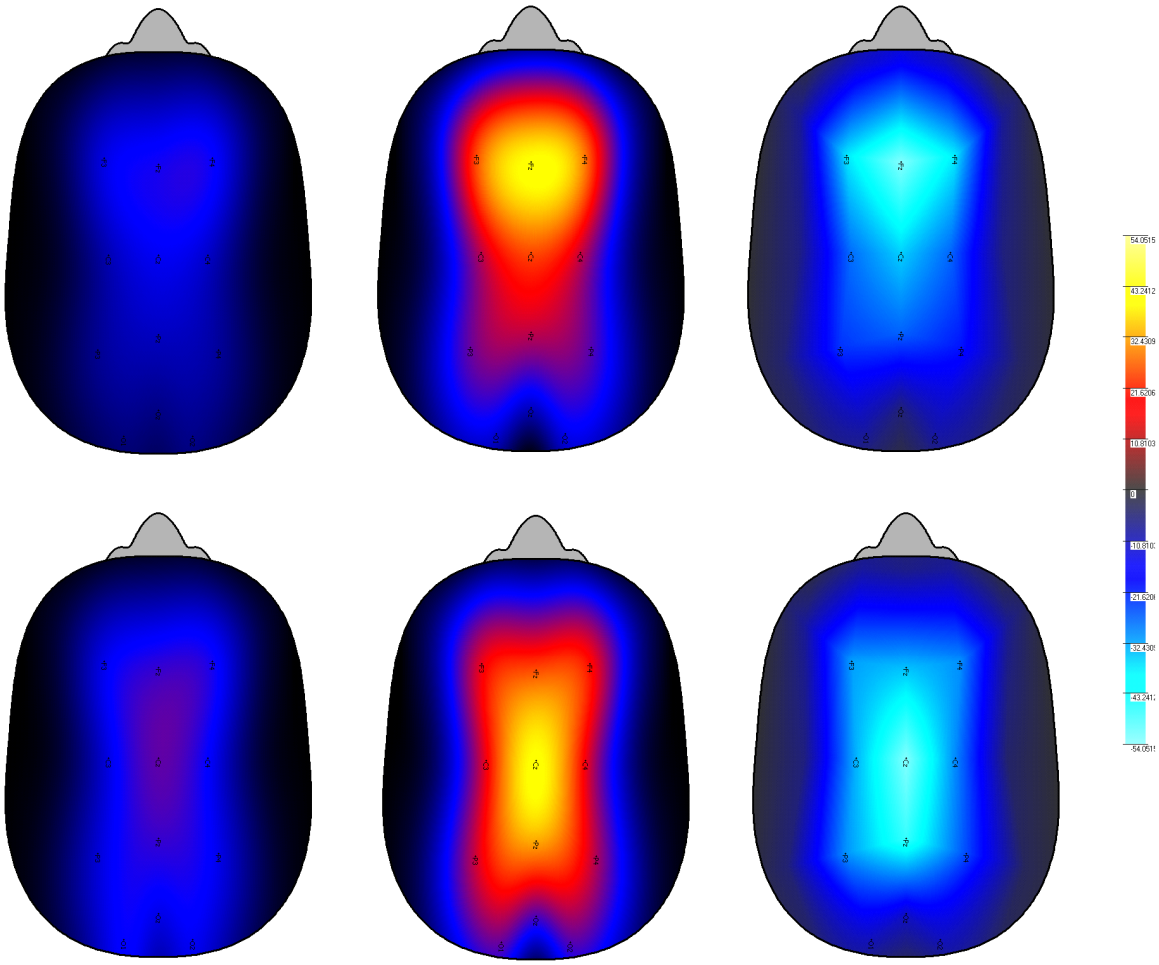

Figure 3 – Top panel illustrates the topographical NREM sleep EEG power density in delta activity (1-3Hz) during dream recall and no recall. Top panels left, middle and right depict, respectively, NREM delta activity during dream recall, no recall, and the relative NREM delta activity (relative ratio of dream recall / no recall). Bottom panel illustrates the topographical NREM sleep EEG power density in spindle activity (12-15.5Hz) during dream recall and no recall. Bottom panels left, middle and right depict, respectively, NREM spindle during dream recall, no recall, and the relative NREM spindle activity (ratio of dream recall / no recall). *Scales: Light blue indicates minimum EEG activity and yellow indicates maximum.*

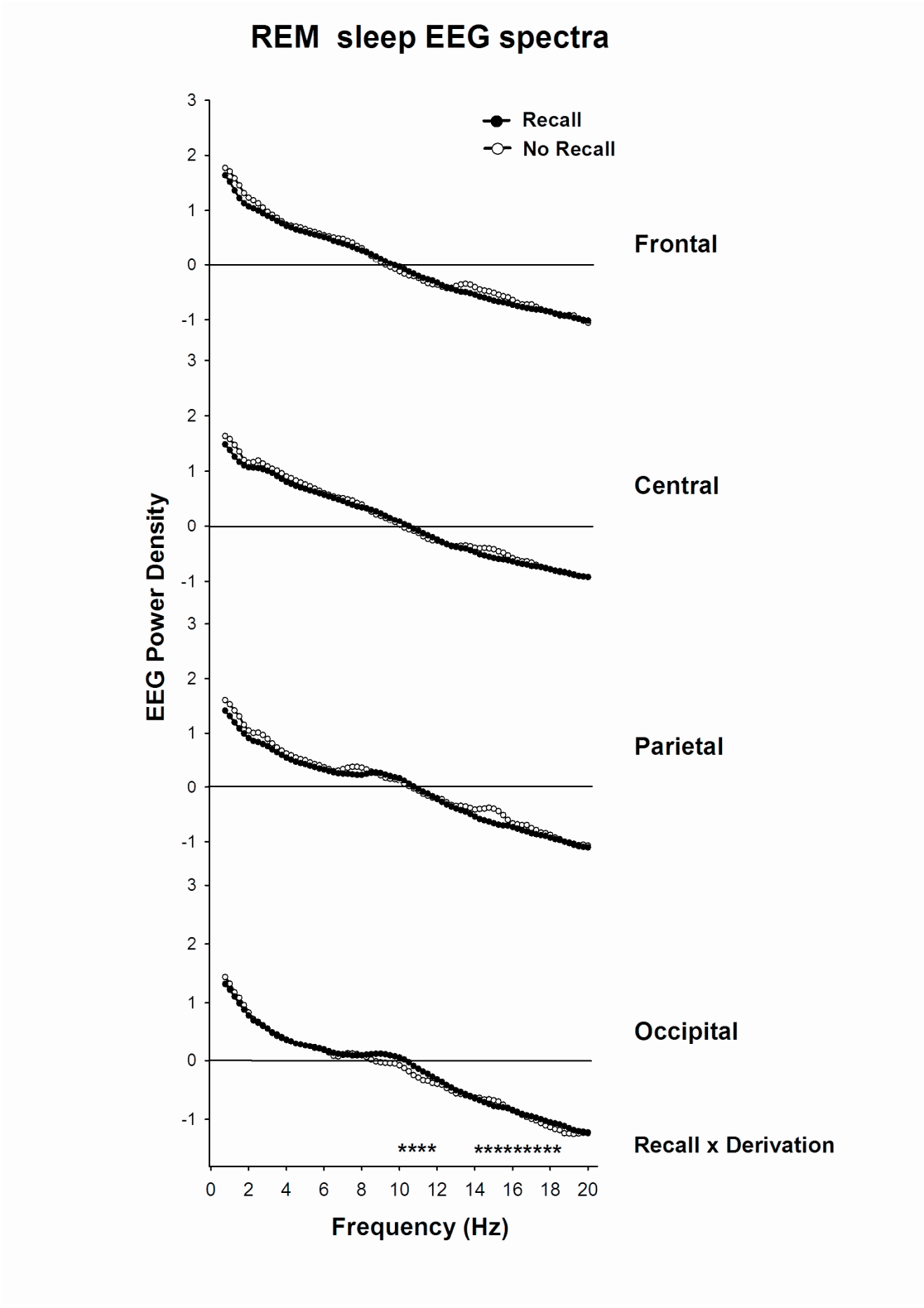

Figure 4 – Absolute REM sleep EEG spectra (log-transformed) during recall (black circles) and no recall (white circles) in the frequency range between 0.75 and 20 Hz for frontal, central, parietal and occipital derivations. Stars near the abscissa indicate the frequency bins with a significant interaction 'recall' x 'derivation' ($p < 0.05$).

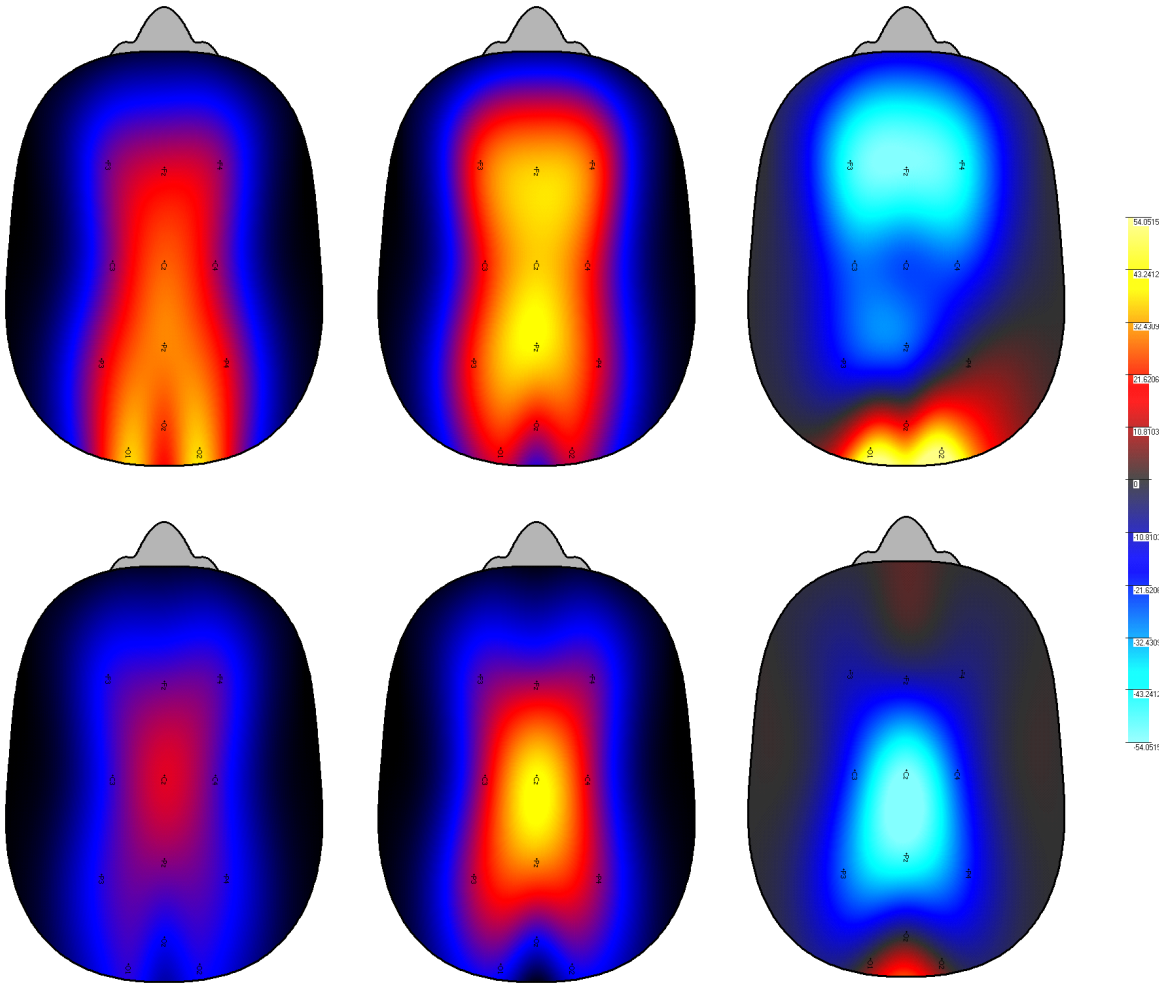

Figure 5 - Top panel illustrates the topographical REM sleep EEG power density in alpha activity (10-12Hz) during dream recall and no recall. Top panels left, middle and right depict, respectively, REM alpha activity during dream recall, no recall, and the relative REM alpha activity (relative ratio of dream recall / no recall). Bottom panel illustrates the represent topographical REM sleep EEG power density in beta activity (14-19Hz) during dream recall and no recall. Bottom panels left, middle and right depict, respectively, REM beta during dream recall, no recall, and the relative REM beta activity (ratio of dream recall / no recall). *Scales: Light blue indicates minimum EEG activity and yellow indicates maximum.*

DISCUSSION

Our data yielded distinct frequency- and topography specific spectral EEG correlates for subjectively rated amount of dream recall during NREM and REM sleep. Dream recall was preceded by lower frontal delta NREM EEG activity and lower spindle NREM EEG activity in centro-parietal brain regions, together with higher REM alpha and beta activity in the occipital cortex.

NREM sleep is not a challenge for dream recall

NREM dreaming challenges the concept that REM-specific physiology underlies all sleep mentation (Cavallero et al. 1992). However, it remains controversial if NREM dreams are the repercussion of “covert” REM sleep (Nielsen 2000). For instance, dreaming scores elicited for NREM dream recall can be distributed sinusoidally across the 24-h day, with a NREM dreaming curve parallel to the REM sleep curve, as indexed by time-in-stage prior to awakening, which suggests that the dreaming output from REM and NREM sleep may be influenced by the same underlying circadian oscillator (Suzuki et al. 2004). In our study, percentage of NREM sleep and REM sleep during 15 minutes prior to awakening and 15 minutes prior to this time window had similar levels (supplemental figure 1), although this does not rule out that NREM sleep preceding recall may contain REM-like signs, such as lower EMG and increased rapid eye movements. Furthermore, our EEG findings for dream recall in NREM naps, such as decreased delta and spindle power, seem consistent with the idea that dreaming is more likely if sleep contains fewer of the classical defining signs of NREM sleep (delta waves, spindles). In other words, dreaming in NREM sleep could be more likely if this sleep stage is relatively more

'REM-like' (Nielsen 2000) or, alternatively, that dreaming in NREM sleep waxes and wanes with variations in underlying REM propensity (Nielsen 2004).

NREM dream recall was associated with lower frontal delta and centro-parietal spindle activity. The intrinsic thalamocortical network during NREM sleep, as indexed by higher levels of sleep spindles and delta waves, can strongly interfere with ongoing mental activity (Steriade et al. 1993). At the transition from wakefulness to sleep, the neuronal membrane potential in the cortex and thalamus (relay station for most sensory signals to the cerebral cortex) reduces, resulting in NREM sleep oscillations - sleep spindles and slow-waves - which lead to impaired synaptic responsiveness (Timofeev et al. 2001). This neuronal network most likely explains why dream recall was dramatically reduced during delta and spindle activity.

Interestingly, we did not find differences for EEG beta activity (16.5-20Hz) during NREM sleep before dream and no dream recall. Beta frequency increases in NREM stage 2, during the transition from epochs without dream mentation to those with distinct mental activity (Williamson et al. 1986), which hints to the fact that dream recall *per se* is likely to be mediated by high-frequency activity. This suggests that a functional stage-shift model is more appropriate than the dream recall arousal theory (Hobson et al. 2000). In other words, if the resemblance of sleep EEG patterns is nearer to those during wakefulness, there is a higher likelihood of dream recall. However, these differences usually happen in frequencies above 20Hz.

NREM sleep frequency-specific differences are further supported by biological day-night differences, in which dream recall was linked to lower delta and spindle activity, while no recall was related to higher spindle activity during the biological day (supplementary figure 2). Young subjects exhibit a well-defined circadian modulation of spindle frequency phase-locked with melatonin secretion (Knoblauch

et al. 2005), with, respectively, lower and higher spindle activity during the biological night and day. One assumption is that the circadian modulation of spindle frequency facilitates consolidated night sleep and day wakefulness (Knoblauch et al. 2005). Within this framework, daytime fast spindle frequencies can represent a circadian waking signal.

REM sleep spectral characteristics of dream recall

Dream recall rate after REM awakening was higher in comparison to NREM sleep. During REM sleep, heightened activation of forebrain structures essential to motivation and emotion— lateral hypothalamic areas, infralimbic, prelimbic, and limbic areas (amygdaloid complex) - imposes vivid recall (Braun et al. 1997; Solms 2000). Furthermore, motivational states with active limbic processes in REM sleep are rendered compatible with visual-spatial images in occipital and parietal cortices (Smith et al. 2004). Thus, cortical activation is biased toward REM dreaming.

We demonstrate that the offline facilitation of dream recall can be associated with lower REM alpha activity, suggesting the relationship of specific alpha activity to sleep mentation (Takeuchi et al., 2003). Esposito et al. 2004 demonstrated that recall was associated with lower alpha power in a non-topographic manner, which may reflect cognitive elaboration active prior to awakening. In our study, lower alpha activity was observed *only* in frontal derivations. REM sleep activation of sub-cortical and cortical limbic structures, which mediates emotion, can be associated with relative frontal cortex inactivation, which mediates directed thought (Braun et al. 1997). Within this context, our results might indicate that REM dreaming comprises emotion-driven cognition with possible deficient analytic thinking.

Another key finding was the association of dream recall with higher alpha and beta activity in the occipital cortex. The activation synthesis model (Hobson and McCarley, 1977) proposes PGO (ponto-geniculo-occipital) activity as a generator of the internal signal and sensory input of REM sleep, whereby the brainstem is the key initiator of dreaming, assigning the forebrain a secondary role. The forebrain then receives tonic and phasic signals from the midbrain reticular formation via thalamus, and phasic eye movement signals from the pontine reticular formation via lateral geniculate nucleus. The forebrain then compares pseudo-sensory information from the brainstem with stored sensorimotor information, resulting in dreams (Hobson and McCarley, 1977).

These frequency specific differences are further supported by the biological day-night differences, in which dream recall was related to higher alpha activity during the biological day (supplementary figure 3). Circadian modulation of sleep EEG is such that REM sleep propensity peak coincides with rising core body temperature during late morning hours (Dijk et al. 1997; De Gennaro and Ferrara 2003). This can imply why dream recall maybe linked to REM alpha activity – as an "electrophysiological correlate" - during the biological day (Llinás and Ribary 1993).

Study limitations

Our 40-h protocol assesses dream recall at a very high sampling frequency (in addition to collecting physiological variables and carrying out performance tests), thus we did not access dream content, as this could have seriously influenced and, therefore, biased dream reports at successive nap trials. For a similar reason, it may not be appropriate to speculate as to how dream content is encoded in memory during sleep and if its retrieval is facilitated after awakening (Anderson et

al. 2010). Taken together, caution should be exercised when extrapolating upon how dream content and its possible EEG activity patterns may be associated, for instance, in the context of episodic memories.

Dreaming is regulated in a very specific manner

Recapitulating our two predictions, there are clear *specific*-frequency and topography dissimilarities in dream recall during NREM and REM sleep. In view of these, we suggest that (1) differences in subjective rated amount of dream recall are related to on frequency ranges, such that higher frequencies are associated with REM sleep, while NREM dreaming can be associated with attenuated NREM sleep oscillations; (2) dreaming may be related to frontal deactivation and occipital activation. Dream variations are linked to oscillations within a specific type of rhythm, such as the REM/NREM ultradian rhythm, regulated by either single or multi-oscillatory processes (Nielsen 2004). If single processing is correct, REM/NREM rhythm may lead to simultaneous fluctuations in dreaming, with parallel changes in dreaming as a function of ultradian (REM/NREM differences) or circadian variations (within-night differences). If multi-processing is correct, dreaming may be regulated by separate, partially independent oscillators, as numerous physiological variables (temperature and melatonin), under circadian control. Dreaming would then have temporal morphologies seemingly out of phase with those of other measures, which can be indexed by higher recall rates in REM sleep in the end of a night.

While our results suggest that dream mentation is NREM–REM sleep driven with frequency and topography specificity, it remains unclear if these results can exclusively fit into one of these two models. Indeed, our present findings cannot be interpreted in favour of either hypothesis of dreaming (one vs. two generators),

given that we focused exclusively on dream recall and no recall, and not on measures of dream length and perceptual/emotional features of dream content. Therefore, given that the two alternative hypotheses stem from differences in the quantitative and qualitative characteristics of verbally-reported dreams, our findings do not lean exclusively toward either of these models. In the broader context, this dual NREM-REM sleep modulation of dreaming may hold implications for the mechanistic understanding of this complex cognitive activity.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

RESULTS

Sleep stages during naps

Comparisons of the NREM/REM sleep ratios (expressed as percentage of REM sleep) between the last 15 minutes (interval 5) of a scheduled nap indicated that during naps 6 (time of day: Day 2, 05:00h), 7 (time of day: Day 2, 09:00h) and 8 (time of day: Day 2, 13:00h), subjects had a lower percentage of NREM/REM sleep ratio (1-way ANOVA, factor 'time', $p < 0.05$) (**Supplementary Figure 1**). Given that dreaming from NREM sleep may reflect dream recall from a REM sleep period immediately prior to the NREM sleep episode, a similar analysis was conducted for the 15 minutes *prior to* the targeted last 15 minutes (interval 4) of a given nap. Comparisons of the NREM/REM sleep ratios for intervals 4 and 5 yielded no significant differences for the NREM/REM sleep ratios (**Supplementary Figure 1**).

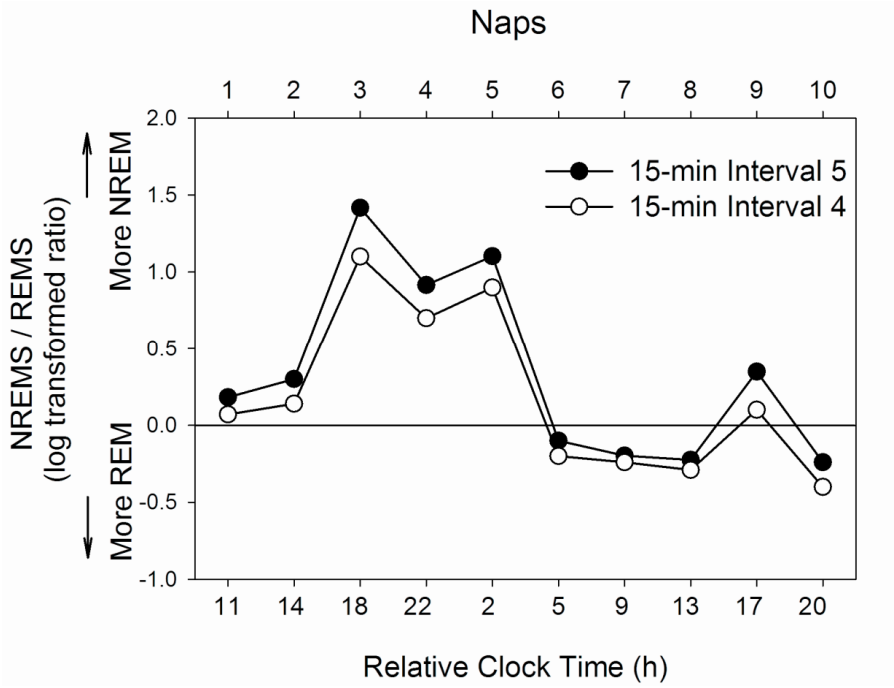
Day-night differences in recall and no recall in NREM EEG sleep spectra

Supplementary Figure 2 illustrates the EEG recall and no recall spectra during the biological day and night expressed as a relative ratio of day / night (where 0= night spectra). A three-way r-ANOVA ('derivation', 'recall' and 'biological day / night') performed on this relative EEG values yielded, respectively, significant differences for the delta (1-3Hz) and low sigma (12-14Hz) frequency ranges ($p<0.05$; Alpha adjustment for multiple comparisons was performed with Tukey-Kramer test). Day-night differences during dream recall indicated lower relative values in delta and low sigma ranges for all derivations. With respect to day-night differences during no

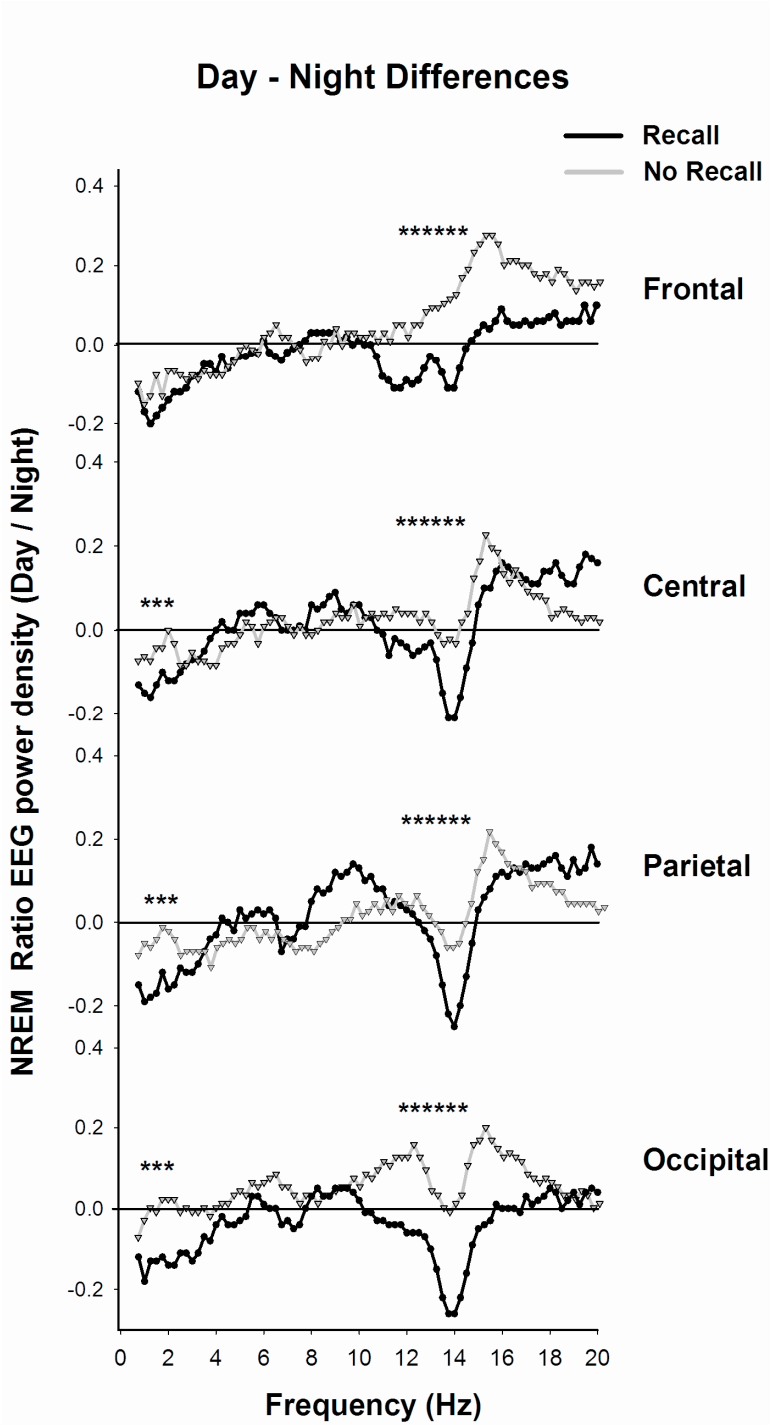
recall, we observed higher relative values in high sigma range (14.5-15.5Hz) in frontal, central and parietal derivations.

Day-night differences in recall and no recall in REM EEG sleep spectra

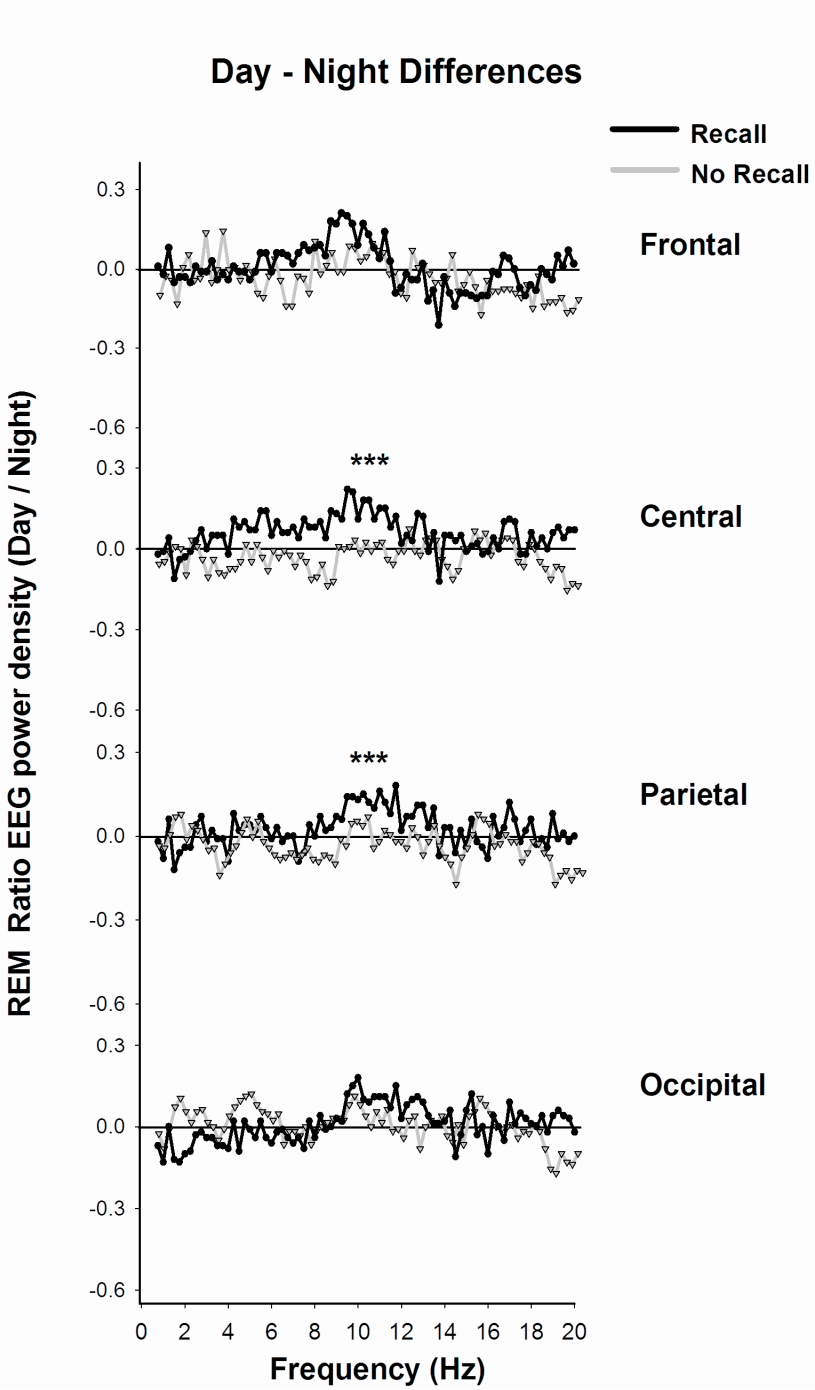
The EEG recall and no recall spectra during the biological day and night expressed as a relative ratio of biological day / night (where 0= night spectra) is illustrated in **Supplementary Figure 3**. A three-way r-ANOVA ('derivation', 'recall' and 'biological day / night') performed on these relative EEG values of all derivations yielded significant differences for the alpha range (10-12Hz) ($p<0.05$; Alpha adjustment for multiple comparisons was performed with Tukey-Kramer test). Day-night differences during dream recall indicated significantly higher values for the alpha range, particularly in centro-parietal derivations during the biological day.



Supplementary Figure 1 - Comparisons of the NREM/REM sleep ratios (log transformed, where 0= REM sleep) between the last 15 minutes (interval 5) of a scheduled nap (black circles) and the 15 minutes *prior to* the targeted last 15 minutes (interval 4) of a given nap (white circles).



Supplementary Figure 2 – NREM sleep EEG power density (log transformed) in dream recall (black lines with triangles) and no recall (grey lines with triangles) during the biological day and night, expressed as relative biological ratio of day / night (where 0= night spectra). Values are depicted for the frequency range between 0.75 and 20 Hz for frontal, central, parietal and occipital derivations. Stars indicate the frequency bins with significant interaction of 'derivation' x 'recall' x 'biological day / night' (p<0.05).



Supplementary Figure 3 – REM sleep EEG power density (log transformed) in dream recall (black lines with triangles) and no recall (grey lines with triangles) during the biological day and night, expressed as relative ratio of biological day / night (where 0= night spectra). Values are depicted for the frequency range between 0.75 and 20 Hz for frontal, central, parietal and occipital derivations. Stars indicate the frequency bins with significant interaction of 'derivation' x 'recall' x 'biological day / night' (p<0.05).

CHAPTER 4

AGE EFFECTS ON SPECTRAL EEG ACTIVITY PRIOR TO DREAM RECALL

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SUMMARY

Aging is associated with marked changes in sleep timing, structure and electroencephalographic (EEG) activity. Older people exhibit less slow-wave and spindle activity during non-rapid eye movement (NREM) sleep, together with attenuated levels of rapid eye movement (REM) sleep as compared to young individuals. However, the extent to which these age-related changes in sleep can impact on dream processing remains largely unknown. Here we investigated NREM and REM sleep EEG activity prior to dream recall and no recall in 17 young (20-31 y) and 15 older volunteers (57-74 years) during a multiple nap protocol across 40 hours. Dream recall was assessed immediately after each nap. During NREM sleep prior to dream recall, older participants displayed higher frontal EEG delta activity (1-3Hz) and higher centro-parietal sigma activity (12-15Hz) than the young volunteers. Conversely, before no recall, older participants had less frontal-central delta activity and less sigma activity in frontal, central and parietal derivations than young participants. REM sleep was associated to age-related changes, such that older participants had less frontal-central alpha (10-12Hz) and beta (16-19Hz) activity, irrespective of dream recall and no recall. Our data indicate that age-related differences in dream recall seem to be directly coupled to specific frequency and topography EEG patterns, particularly during NREM sleep. Thus, the spectral correlates of dreaming can help to understand the cortical pathways of dreaming.
Keywords: Dream recall; Aging; NREM sleep; REM sleep; EEG spectral analysis.

INTRODUCTION

The reduction NREM slow-wave and spindle frequency activity, together with attenuated levels of REM sleep and an increase in involuntary awakenings during sleep, represent the hallmarks of age-related changes in sleep (Münch et al., 2005, Dijk et al., 1999). Given the magnitude of age effects on sleep structure and sleep EEG power density, the question arises as to how it can impact on dream generation. Dreaming is a complex mental activity, driven by the interplay of the ultradian nonREM-REM sleep cycle and the circadian modulation of REM sleep. REM dreaming is elicited by selective activation of wake-activated structures in the brainstem, limbic subcortex and cortex (Braun et al., 1997, Maquet P et al., 1996, Nofzinger, 2005). Dreamlike recalls can also be obtained after NREM sleep, sleep onset, or even relaxed awakening, which suggests that differences in recall may underlie dissimilarities in cortical activation (Antrobus, 1983, Cavallero et al., 1990, Foulkes, 1993, Rosenlicht et al., 1994), in sleep architecture and EEG composition (Antrobus et al., 1995, Casagrande et al., 1996). In young participants, dream recall has been associated with increased alpha and beta activity during REM sleep, and decreased delta and sigma activity during NREM sleep prior to dream recall (Chellappa et al., 2011). Dream recall progressively declines with advancing age and becomes less intense, perceptually and emotionally (Zanasi et al., 2005). One candidate for this attenuated dream recall with aging is the diminished circadian rhythm of REM sleep (Chellappa et al., 2009). The idea of REM sleep as a hallmark for age differences in dreams also builds up from recent evidence whereby patients suffering from mild degenerative dementia dream much less than healthy aged persons, possibly due to a REM sleep decrease (Guenole et al., 2010). However, the extent to which age differences in NREM and REM sleep can interfere with

dream recall remains unknown. Thus, we investigated frequency and topographical changes in EEG activity during NREM and REM sleep prior to dream recall and no recall in young and older participants under stringent controlled laboratory conditions.

METHODS

Study participants

Study volunteers were recruited through advertisements at different Swiss universities and in newspapers. Only candidates with a Pittsburgh sleep quality index (PSQI) score $\leq$5 (Buysse et al., 1989) and without extreme chronotypes ratings [between 14 and 21 points on the morning-evening M/E questionnaire (Torsvall and Åkerstedt, 1980)] were enrolled in the study. All participants were questioned about sleep quality, life habits and health state. Exclusion criteria were smoking, medication or drug consumption, shift work within the last 3 months, and transmeridian flights during the month before the study. All volunteers underwent a physical examination, an interview, a neuropsychological assessment, and a polysomnographically recorded adaptation night in order to exclude sleep disorders. Inclusion criteria were: sleep efficiency >80%, periodic leg movements per hour < 10 and an apnea-hypopnea index < 10. Only participants without medication (with the exception of 4 young women using oral contraceptives) were included in the study. Young females started the study on day 1-5 after menses onset during the follicular phase of their menstrual cycle. Seventeen healthy young (9 women, 8 men, age range 20–31 years) and 15 healthy older volunteers (7 women, 8 men, age range 57–74 years) were included in the study. All participants gave written

informed consent. The study protocol, screening questionnaires and consent form were approved by the local ethics committee and conformed to the Declaration of Helsinki.

Study Design

One week prior to the study (baseline week), the participants were requested to abstain from excessive caffeine and alcohol (one caffeine-containing beverage per day at most and < 5 alcoholic beverages per week). They were instructed to keep a regular sleep-wake schedule during the baseline week at home (bedtimes and wake times within ± 30 minutes of self-selected target time between 22:00h and 02:00h) prior to admission to the laboratory. Compliance was checked by sleep logs and ambulatory activity measurements (wrist activity monitor, Cambridge Neurotechnology Ltd, UK). The timing of the sleep-wake schedule during the protocol was adjusted to habitual individual bedtimes. The “in-lab” part of the study comprised 2 baseline sleep episodes in the chronobiology laboratory, followed by a 40-h multiple nap protocol, with 10 alternating sleep-wake cycles of 75/150 minutes duration each and one recovery sleep episode. Baseline and recovery nights were scheduled at individual habitual bedtimes. Polysomnography recordings and constant posture started in the afternoon after the first baseline night. Thereafter, participants remained under constant posture conditions (constant dim light levels < 8 lux during scheduled wakefulness, semi-recumbent posture in bed, food and liquid intake at regular intervals, no time cues). During scheduled sleep episodes a minor shift (45 degrees up) in the supine posture was allowed, and lights were off (0 lux). Older participants received a daily low-dose subcutaneous heparin injection

(Fragmin, 0.2 mL, 2500 IE/UI, Pfizer AG, Switzerland) to prevent potential venous thrombosis.

Polysomnographic Measures

Sleep was polysomnographically recorded with the VITAPORT ambulatory system (Vitaport-3 digital recorder, TEMEC Instruments B.V., Kerkrade, the Netherlands). Twelve EEGs channels, 2 electrooculograms, a submental electromyogram and an electrocardiogram were recorded. All signals were low pass filtered at 30 Hz (fourth order Bessel type anti-aliasing, total 24 dB/Oct) at a time constant of 1.0 s. After online digitization by using a 12 bit AD converter (0.15V/bit) and a sampling rate at 128 Hz for the EEG, the raw signals were stored on a Flash RAM Card (Viking, USA) and later downloaded to a PC hard drive. Sleep stages were visually scored per 20-s epochs (Vitaport Paperless Sleep Scoring Software). EEG artefacts were detected by an automated artefact algorithm (CASA, 2000 PhyVision B.V., Gemert, the Netherlands). Spectral analysis was conducted using a Fast Fourier transformation (FFT; 10% cosine 4-s window) which yielded a 0.25 Hz bin resolution. NREM sleep (stages 2-4) and REM sleep were expressed as the percentage of total sleep time per nap before averaging over participants. EEG power spectra were calculated during REM sleep and NREM sleep in the frequency range from 0 to 20 Hz. Finally, artefact free 4-s epochs were averaged across 20-s epochs. Here, we report EEG data derived from 12 derivations (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, Oz) referenced against linked mastoids (A1, A2) in the range of 0.75–20 Hz.

A nap trial that contained only REM sleep in the *last* 15 minutes of a scheduled 75-minute nap was defined as a REM nap, and a nap trial with NREM sleep in the *last* 15 minutes was defined as a NREM nap (Chellappa et al., 2009). “Wakefulness naps” were defined as nap trials not containing either NREM or REM sleep stages and were excluded from further analyses. According to our criteria, naps among the young group included 48.3% NREM naps, 27.9% REM naps, and 23.8% wakefulness naps. The older group had 61.2% NREM naps, 14.3% REM naps, and 24.5% wakefulness naps. Older participants had significantly fewer REM naps than young volunteers (Mann-Whitney U test; $p< 0.05$), at the cost of a tendency for more NREM naps (Mann-Whitney U test; $P < 0.1$) (Chellappa et al., 2009). The criterion of 15 minutes was based on a prior definition of NREM and REM naps, in which 20-min naps were employed (Suzuki et al., 2004). Given that our study included 75-min naps (Münch et al., 2005), *only* the last 15 min were considered for the REM sleep and NREM sleep stages, instead of 20 minutes, since the likelihood of having 20-min naps exclusively with REM sleep would be substantially reduced.

Dream Recall

Dream recall was assessed immediately at the end of each nap trial (10 naps in total) with the Sleep Mentation Questionnaire, which addresses numerous characteristics of dream recall, such as number of dreams, emotionality, vividness, pleasantness, hostility, and colourfulness (Chellappa et al., 2009). For the classification of dream recall, only the first question [“How much did you dream?” (1: greatly, 2: fairly, 3: little¸ 4: not at all)] was considered for the analysis. Participants were considered to have successful dream recall if their response to Q1 was not 4. The main advantage of a 40-h multiple nap protocol was the numerous time points

(10 in our study). Thus, dream recall could be assessed without possible effects of total sleep deprivation or selective sleep stage deprivation prior to recall.

Statistical Analysis

For all analysis, the statistical package SAS (SAS Institute Inc., Cary, NC, USA; Version 9.1) was utilized. Visually scored sleep stages were expressed as percentages of total sleep time or in minutes. The analysis of sleep-stage differences was carried out with the mixed-model analyses of variance for repeated measures (PROC Mixed) with factors 'age' (young x older) and 'time' (10 naps). For the accumulation curves, sleep stages (wake, NREM stage 2 and slow wave sleep) were collapsed into 5-min intervals of the 75 minutes comprising the naps. A general linear model (PROC GLM) was carried out with factors 'age' (young x older), 'time' and 'recall' (dream recall x no recall), with the Duncan's multiple range test and corrections for multiple comparison. For comparisons during NREM and REM sleep, mixed-model analyses of variance for repeated measures (PROC Mixed) was used with factors 'age´ (young x older), 'derivation' (frontal = F3, F4 and Fz; central = C3, C4 and Cz; parietal = P3, P4 and Pz; occipital = O1, O2 and Oz) and 'recall' (recall x no recall). Alpha adjustment for multiple comparisons was applied using Tukey-Kramer test. For factor 'derivation', the corresponding three derivations (i.e. frontal = F3, F4 and Fz) were averaged per subject, given that there were no lateralisation effects for dream recall. All *p*-values derived from r-ANOVAs were based on Huynh-Feldt's (H-F) corrected degrees of freedom (significance level: $p < 0.05$). Post-hoc measurements were obtained using Tukey-Kramer test.

RESULTS

Sleep stages during the last 15 minutes of naps prior to dream recall

Total sleep time (TST) in the last 15 minutes (averaged across all 10 naps per subject) did not significantly differ between age groups. Analysis of sleep stages collapsed for all 10 naps revealed that older participants had more NREM sleep than the young, with significantly more stage 2, less slow-wave sleep (stages 3 and 4) and REM sleep (Mann-Whitney *U* test, $p<0.05$). Analysis of the time course of TST, NREM sleep, NREM stage 2 and REM sleep during the last 15 minutes of the naps yielded more TST for older participants during naps 4 and 10 (2-way r-ANOVA, factors 'age' vs. 'time'; $F_{9,269}=3.45$, $p<0.05$). Older participants had a tendency for more NREM sleep during nap 10 ($F_{9,227}=1.69$, $p=0.04$) and significantly more NREM sleep stage 2 during naps 1, 2, 7 and 10 than young participants ($F_{9,228}=1.79$, $p=0.04$). REM sleep was significantly reduced in older participants during naps 7 and 8 as compared to the young ($F_{9,226}=1.83$, $p=0.04$) (**Figure 1**). No gender differences were seen across sleep architecture or in the remainder of this data set.

→ Please insert Table 1 and Figure 1

The accumulation curves of NREM naps yielded a significant interaction between factors 'age' and 'time' for wake, NREM stage 2 and slow wave sleep ($F_{4,64}=1.7$; $p<0.05$). Older participants had more accumulated wakefulness, more NREM stage 2 and less slow wave sleep (SWS) than young participants, particularly after 60 minutes of sleep onset. The interaction of factors 'age' and 'recall' elicited significant differences only for accumulated NREM stage 2 ($F_{1,16}=7.33$; $p=0.02$). Similarly, the

3-way interaction of factors ‘age’ vs. ‘recall’ vs. ‘time’ yielded significant differences only for NREM stage 2 ($F_{4,64}$=2.11; p=0.04). Older participants had more accumulated NREM stage 2 during dream recall than the young, particularly after 60 minutes of sleep onset, while they had less accumulated NREM stage 2 during *no* recall compared to young participants (**Figure 2**).

→ Please insert Figure 2

Dream recall differences in NREM EEG sleep spectra

A three-way r-ANOVA with factors ‘age’, ‘recall’ and ‘derivation’ yielded a significant main effect for factor ‘age’ in the frequency range of 1-3 Hz (delta range) and 12-15Hz (sigma range) (p at least < 0.05). Main effect ‘derivation’ was significant for delta (1-3Hz) ($F_{3,149}$=42.3, p<0.01), theta (5-7.75Hz) ($F_{3,148}$=16.4, p<0.01), sigma (12-15Hz) ($F_{3,148}$=25.5, p<0.01) and beta activity (16-19Hz) ($F_{3,148}$=19.2, p<0.01). Main effect ‘recall’ was significant for delta (1-3Hz) ($F_{1,160}$=25.4, p<0.01), sigma (12-15Hz) ($F_{1,160}$=25.2, p<0.01) and beta activity (16-19Hz) ($F_{1,162}$=14.2, p<0.01). A significant interaction of factors ‘age’ vs. ‘derivation’ vs. ‘recall’ was elicited for delta (1-3Hz) ($F_{8,149}$=4.4, p=0.02) and sigma activity (12-15Hz) ($F_{8,149}$=2.3, p=0.01). Older participants had more delta and sigma activity prior to dream recall than to *no* recall, while in the young, delta and sigma activity was attenuated before dream recall compared with *no* recall (p at least <0.05) (**Figure 3**). The topographical distribution of EEG activity was such that, during dream recall, older participants had more frontal delta activity (1-3 Hz) than the young participants, while during *no* recall, older volunteers had less fronto-central delta activity (**Figures 4 and 5)**. Similarly, during dream recall, older participants had more centro-parietal sigma activity (12-

15 Hz) than the young participants, while during *no* recall, older volunteers had less sigma activity in frontal, central and parietal derivations than the young (**Figures 4 and 5)**.

→ **Please insert Figures 3, 4 and 5**

Dream recall differences in REM EEG sleep spectra

A three-way r-ANOVA with factors ‘age’, ‘recall’ and ‘derivation’ yielded a significant effects for factor ‘age’ in the frequency range of 10-12 Hz (alpha range) and 16-19Hz (beta range) (p at least < 0.05). Main effect ‘derivation’ was significant for alpha (10-12Hz) ($F_{3,167}$=10.5, p<0.01) and beta (16-19Hz) ($F_{3,167}$=25.6, p<0.01) activity. Main effect ‘recall’ was significant for alpha (10-12Hz) ($F_{1,155}$=5.7, p<0.01) and beta activity (16-19Hz) ($F_{1,155}$=14.7, p<0.01). The interaction of factors ‘age’ vs. ‘derivation’ vs. ‘recall’ did not reach significance for any frequency range. Comparison of dream recall and *no* recall yielded no differences for alpha (10-12Hz) and beta activity (16-19Hz) for the older participants and also for the young. However, there was a clear age effect, such that older participants had less alpha and beta activity as compared to the young, irrespective of dream recall and *no* recall (**Figure 6**). The topographic distribution of this age-related effects was such that, during dream recall and *no* recall, older participants had less fronto-central alpha (10-12Hz) and beta activity (16-19Hz) in comparison to young participants (2-way r-ANOVA with factors ‘age’ vs. ‘derivation’; p at least<0.05) (**Supplemental Figure 1**).

→ **Please insert Figure 6**

DISCUSSION

Our data indicate clear age-related changes in specific frequency- and topography NREM sleep EEG activity between dream recall and no recall. These differences are such that, in comparison to the young, older volunteers had more frontal delta and central-parietal sigma activity before dream recall, while they had less frontal-central delta and sigma activity before no recall. Conversely, REM sleep EEG activity showed an age effect *per se*, which was not related to dream recall and no recall. These age-related changes for REM sleep were such that older volunteers had less frontal-central alpha and beta activity than the young, irrespective of recalling dreams or not.

The intrinsic thalamocortical network related to NREM sleep, as indexed by higher levels of sleep spindles and delta waves, can strongly interfere with ongoing mental activity, such as dreaming (Hobson and Pace-Schott, 2002). At the transition from wakefulness to sleep, the neuronal membrane potential in the thalamus and cortex reduces, resulting in NREM sleep oscillations (sleep spindles and slow waves), associated with impaired synaptic responsiveness (Timofeev et al., 2001). This neuronal network can explain the reduced delta and sigma activity before dream recall than no recall in young participants. Aging is unambiguously associated with a reduction of SWS, which indicates reduced NREM sleep intensity (Münch et al., 2005). This may imply an age-related decrease in the hyperpolarized state of thalamocortical and cortical neurons (Steriade et al., 1993), resulting in less synchronization and shorter periods of SWS. Thus, it is not surprising that before no recall, older participants had less delta activity as compared to the young. However, the higher delta activity before dream recall in older volunteers is paradoxical. Older participants had more NREM stage 2, which comprises the NREM sleep stage most

connected to dream recall (Takeuchi et al., 2003), which could result in higher delta and sigma activity before dream recall. Furthermore, since aging is associated with reduced sleep consolidation (Dijk et al., 2001), particularly of NREM sleep, there may be an attenuated protective effect of NREM sleep on the probability of awakening. This may result in more micro-arousals or awakenings, thus facilitating the recollection of dreams. Indeed, NREM dreaming has been related to intrusion of arousals, such that external stimuli can influence mentation during NREM sleep, but not REM sleep (Manni, 2005), and this information may be "reconstructed" as mental activity, such as dreams (Takeuchi et al., 2003). An alternative explanation builds up from differences between REM and SWS mentation. Young people show higher mentation recall following REM sleep than during SWS, although they do exhibit SWS mentation, which suggests that REM and SWS dreaming can involve different quantities of accessible mnemonic traces and of emotionality (Cicogna et al., 2000). Since our older participants have less accumulated SWS during both dream recall and *no* recall, it is likely that in order to achieve dream mentation, they accumulate more NREM sleep stage 2, which, in turn, enables for dream recall.

The increased sigma activity before dream recall in older participants could be driven by differences in the circadian modulation of spindle frequency. Spindles are under circadian control such that the circadian pacemaker promotes spindles during the night, possibly to mediate sleep consolidation (Dijk and Czeisler, 1995). Young people have a clear-cut circadian modulation of higher EEG spindle frequency, phase-locked with the circadian rhythm of melatonin (Knoblauch et al., 2005). This modulation is such that they have less fast spindle frequencies during the night and more during the day. In contrast, older people have less distinctive day-night differences. Since fast spindle frequencies during the day could represent a

circadian waking signal, less well-defined day-night differences in spindle frequency may represent a reduction of this signal in the evening with more “sleep intrusions”. This may explain the higher sigma activity during dream recall in older volunteers.

REM sleep has an undisputable role in dreaming, and is associated to increased alpha activity (Esposito et al., 2004), which may reflect cognitive elaboration prior to awakening. In our study, older volunteers had decreased alpha and beta activity irrespective of dream recall and no recall. The percentage of REM sleep undergoes a decline during middle-aged adulthood, and remains stable in people above 60 years (Ohayon et al., 2004). Shorter REM sleep duration does not imply less EEG activity; however, the reduction of REM sleep in older participants may have resulted in an overall decrease of EEG activity, irrespective of recalling dreams or not. Dream recall and no recall were associated to less frontal-central alpha and beta activity in older participants. Since REM sleep involves activation of sub-cortical and cortical limbic structures (emotion-driven) and inactivation of frontal cortex (directed thought-driven) (Braun et al., 1997), one may speculate that REM dreaming in older people may impinge more on the analytic thinking domain then the “emotional tone” of dreaming (Chellappa et al., 2009). Taken together, age differences in dream recall seem to be directly coupled to specific frequency and topography-EEG activity patterns, particularly during NREM sleep. The understanding of these spectral correlates of dreaming may help to unravel the cortical pathways of dream generation.

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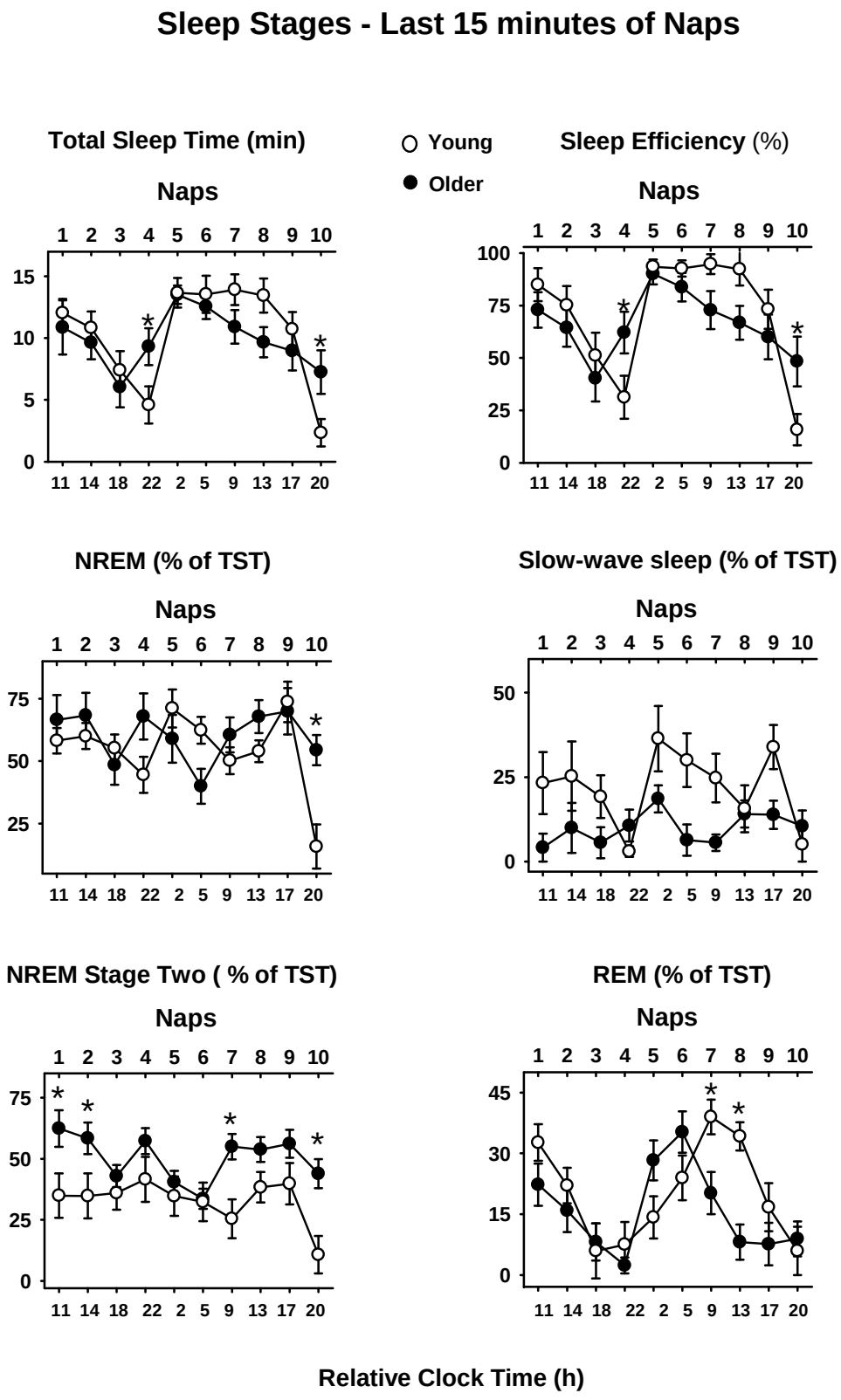


Figure 1 - Time course of sleep stages of the last 15 minutes of naps. White circles: young volunteers (n = 17), black circles: older volunteers (n = 15; mean ± S.E.M.), *p < 0.05.

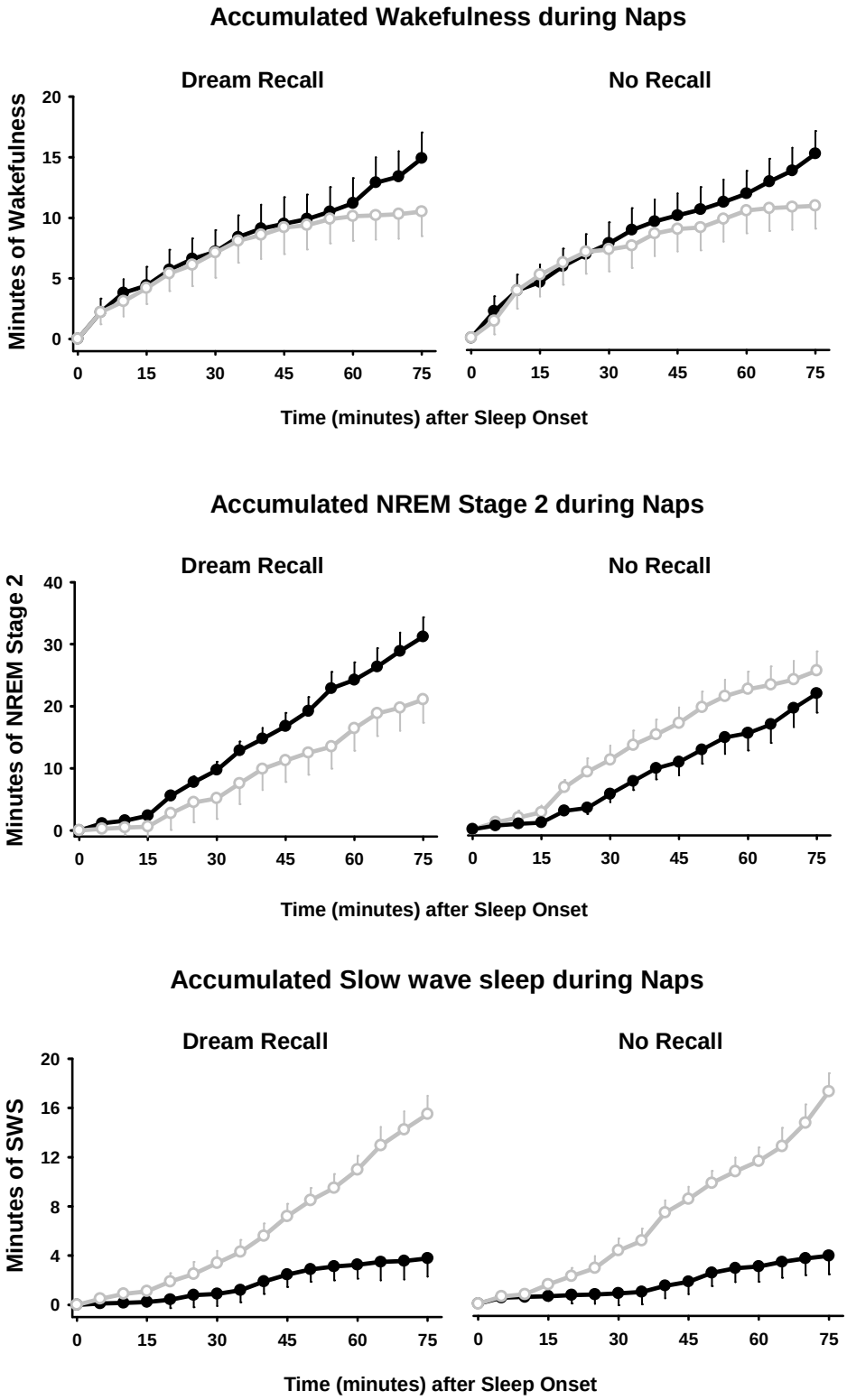


Figure 2 - Accumulation curves for wakefulness (upper panel), NREM sleep stage 2 (middle panel) and NREM slow wave sleep (SWS) (bottom panel) after sleep onset during the naps (10 naps in total) in older (black lines) and young (grey lines) participants. Data are plot relative to elapsed time (minutes) after sleep onset. Mean values are shown for each 5- min bin.

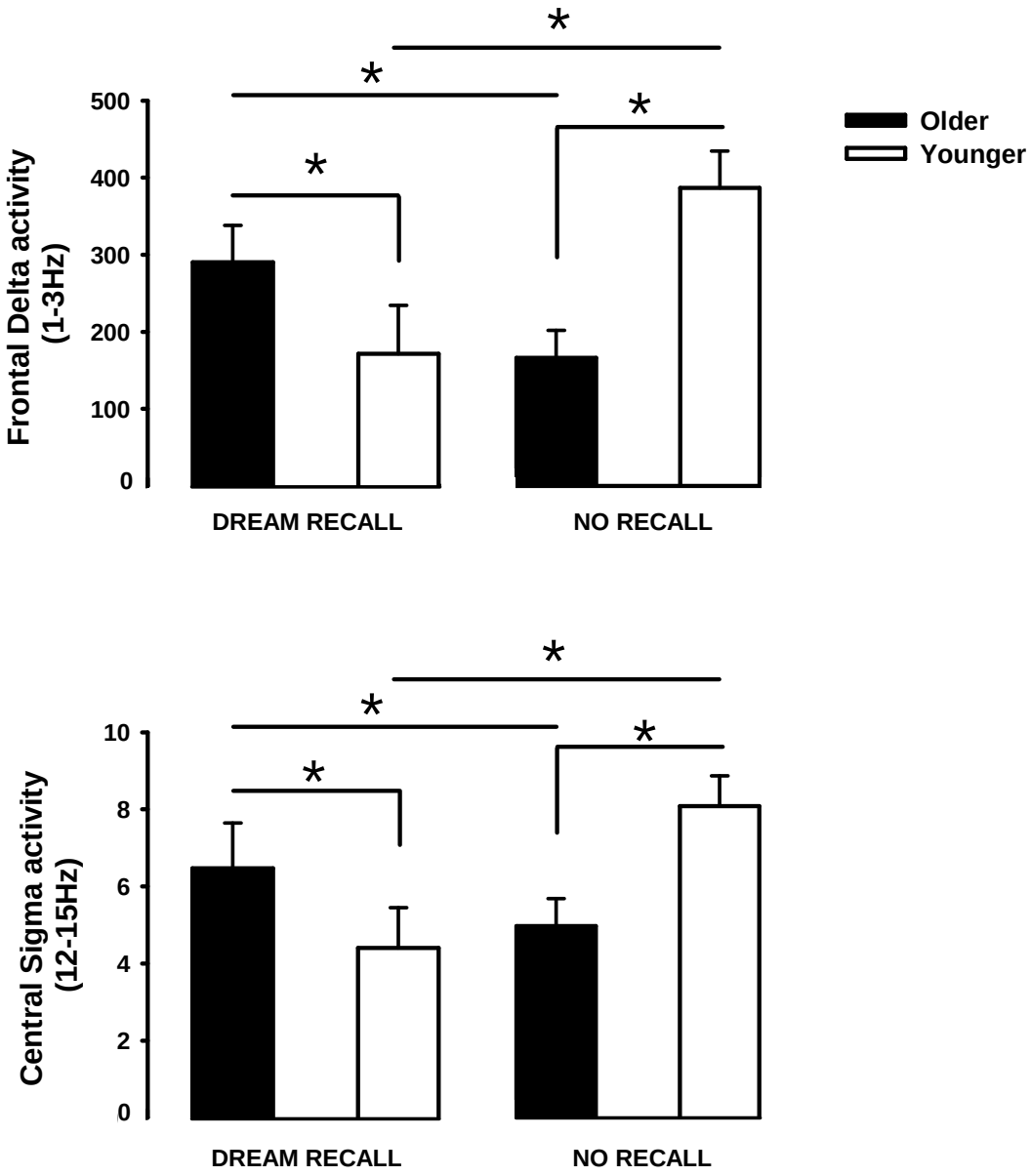


Figure 3 – NREM sleep dream recall and no recall between older and young participants. Upper panel illustrates frontal delta activity (1-3Hz) and bottom panel depicts central sigma activity (12-15Hz) during dream recall and no recall between older (black bars) and young participants (white bars) (mean ± standard error of mean; * $p < 0.05$).

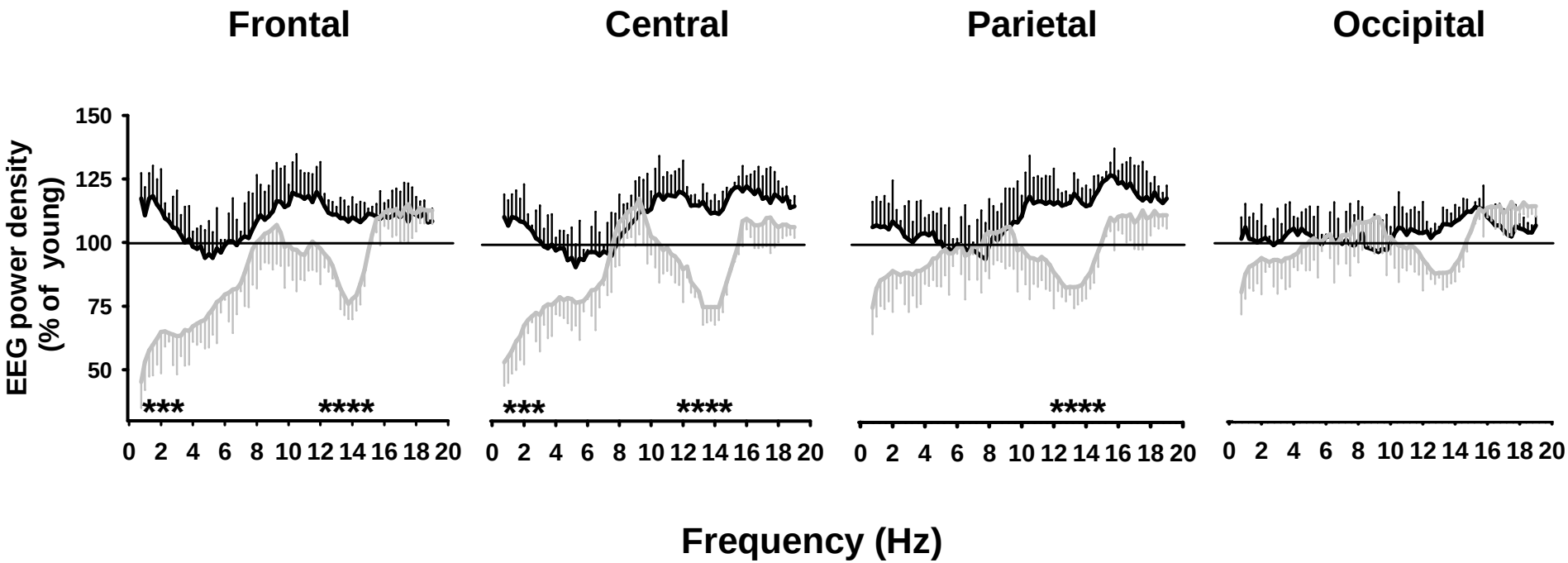


Figure 4 – NREM sleep EEG power density during dream recall (black lines) and no recall (grey lines) for frontal, central, parietal and occipital derivations. EEG power density values per 0.25Hz bin during non-REM sleep in older participants are expressed as percentage of the corresponding average values in young participants. Horizontal line represents 100% of EEG activity in young participants. Mean values are shown for each 0.25-Hz frequency bin in the range of 0.75–20 Hz. Horizontal stars near the abscissa at the bottom indicate frequency bins with a significant interaction 'age' x 'derivation' x 'recall' ($p < 0.05$).

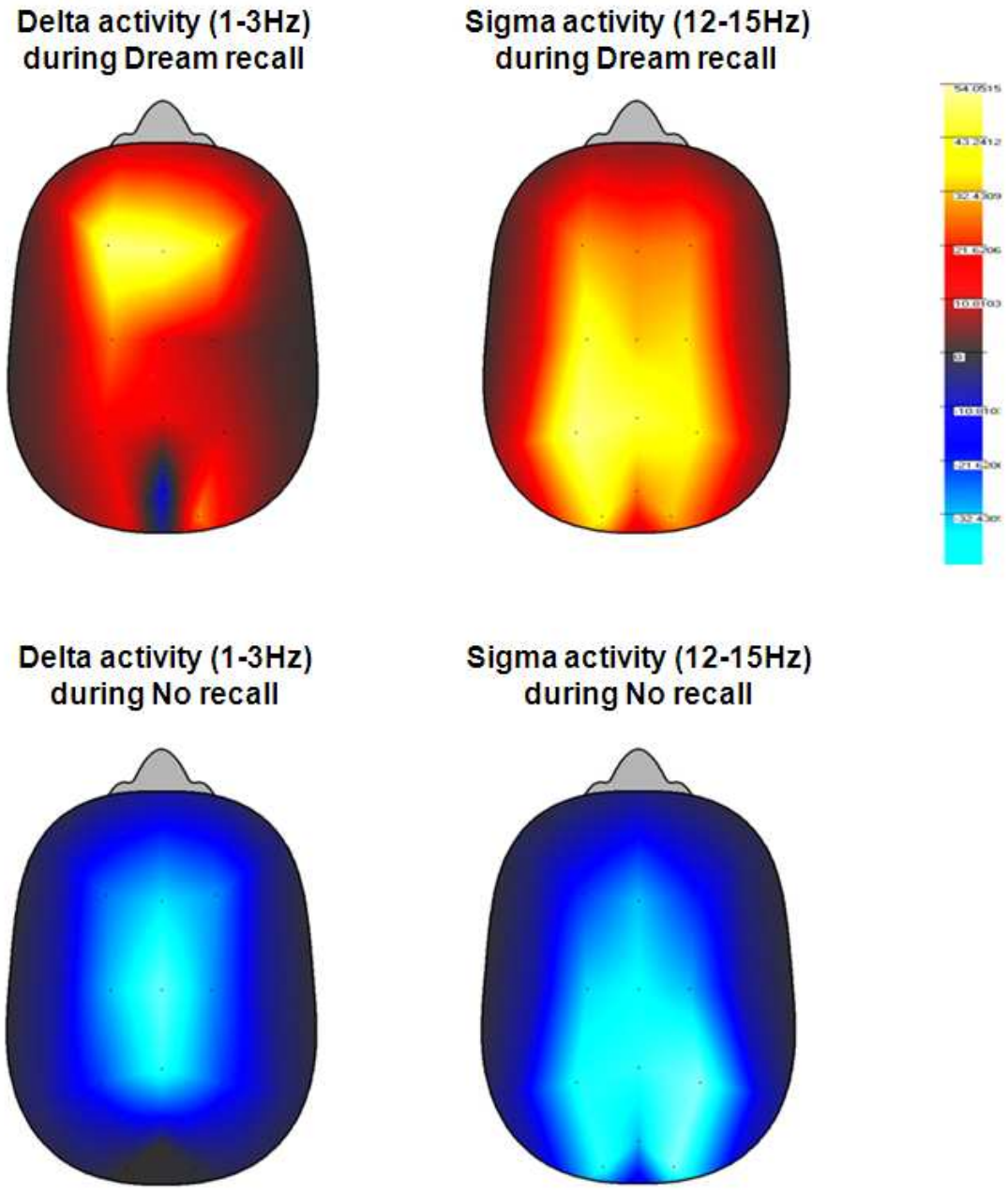


Figure 5 - Top panel: Left and right panels illustrates, respectively, the topographical distribution of NREM delta (1-3Hz) and sigma (12-15 Hz) activity during dream recall in older and young participants (NREM EEG spectra, indexed as a ratio of older / young). **Bottom panel:** Left and right panels illustrates, respectively, the topographical distribution of NREM delta (1-3Hz) and sigma (12-15 Hz) activity during No recall in older and young participants (NREM EEG spectra, indexed as a ratio of older / young). *Scales*: Light blue indicates *less* EEG activity and yellow indicates *more* EEG activity.

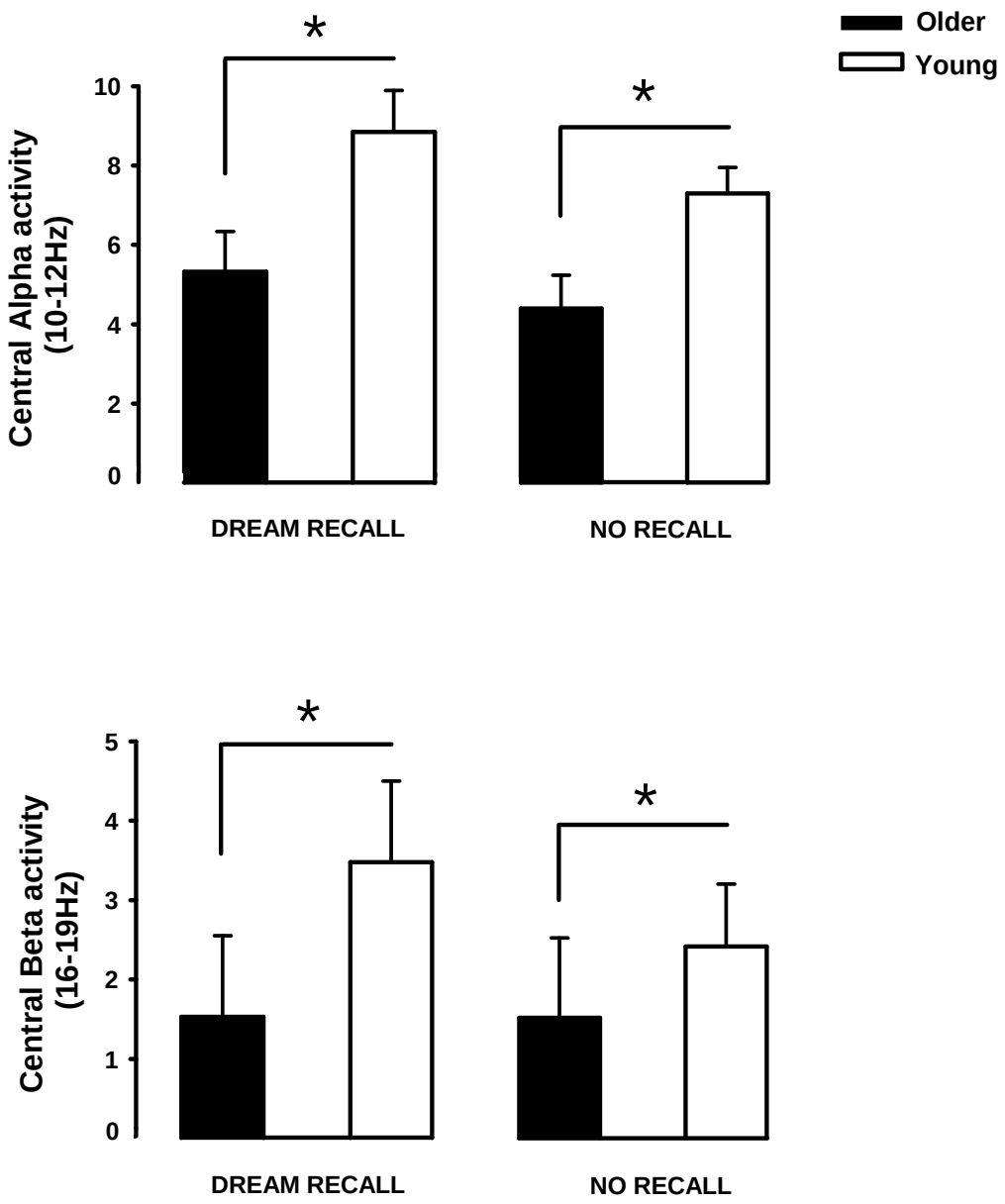
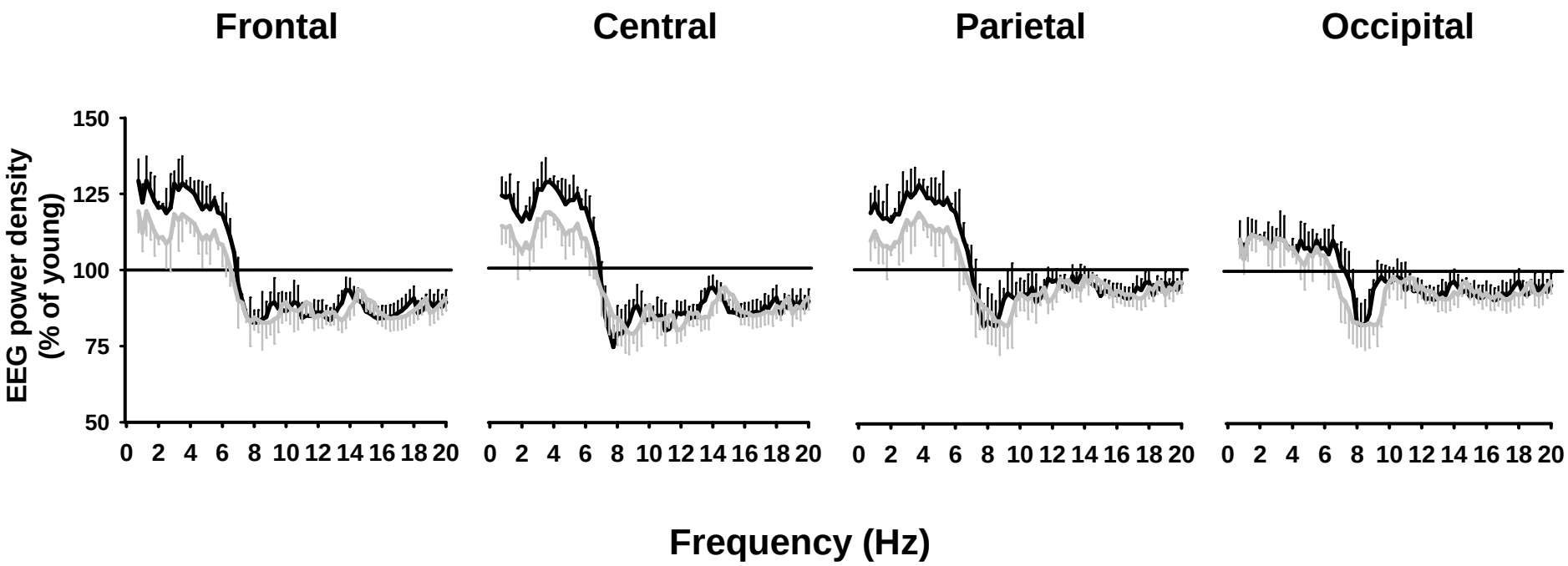


Figure 6 – REM sleep dream recall and no recall between older and young participants. Upper panel illustrates central alpha activity (10-12Hz) and bottom panel depicts central beta activity (16-19Hz) during dream recall and no recall between older (black bars) and young participants (white bars) (mean $\pm$ standard error of mean; * $p < 0.05$).



Supplemental Figure 1 – REM sleep EEG power density during dream recall (black lines) and no recall (grey lines) for frontal, central, parietal and occipital derivations. EEG power density values per 0.25Hz bin during REM sleep in older participants are expressed as percentage of the corresponding average values in the young. Horizontal line represents 100% of EEG activity in young participants. Mean values are shown for each 0.25-Hz frequency bin in the range of 0.75–20 Hz.

Table I – Averaged sleep stages (across 10 naps per subject) for older and young subjects during the last 15 minutes of naps prior to dream recall.

Sleep variables	Older	Young	*p*
TST (min)	9.8 ± 1.3	11.3 ± 1.1	n.s.
Sleep efficiency (%)	66.1 ± 8.9	71.4 ± 6.4	n.s.
Stage 1 (%)	14.4 ± 3.8	18.4 ± 4.7	n.s.
Stage 2 (%)	53.4 ± 7.6	32.2 ± 6.9	<0.05
Stage 3 (%)	5.1 ± 1.1	9.8 ± 2.7	<0.05
Stage 4 (%)	2.1 ± 1.7	9.4 ± 1.5	<0.05
SWS (%)	7.2 ± 1.0	19.2 ± 2.3	<0.05
NREM sleep (%)	61.6 ± 2.5	50.4 ± 6.1	<0.05
REM sleep (%)	6.2 ± 1.3	17.6 ± 2.7	<0.05

TST = total sleep time (min; stages 1–4 +REM sleep); Sleep efficiency (% of TST); SWS= slow-wave sleep (% of TST; stage 3 + 4); NREM sleep = NREM (% of TST; stage 2–4); REM sleep = REM (% of TST); *p*-values between dream recall and no recall (Mann-Whitney *U* test); n.s.= not significant. (Mean ± SEM).

CHAPTER 5

GENERAL DISCUSSION

In this thesis, the circadian and ultradian NREM/REM sleep regulation of dream recall was investigated in young and older participants. Dream recall fluctuated across the circadian cycle in concert with the circadian rhythm of REM sleep. Dreaming changed between the age groups, such that older participants had fewer dreams, especially during the biological day, with no differences in the emotional domain of dreaming. In young participants, dream recall subsequent to NREM sleep was associated with less frontal delta activity and centro-parietal sigma activity. Conversely, dream recall following REM sleep was associated with less frontal alpha activity and high occipital alpha and beta activity. With respect to aging, older participants had higher frontal delta activity (1-3Hz) and centro-parietal sigma activity (12-15Hz) during NREM sleep prior to dream recall. REM sleep was associated to age-related changes, such that older participants had less frontal-central alpha (10-12Hz) and beta (16-19Hz) activity, regardless of dream recall and no recall.

The circadian system and aging: Effects on dream recall

Dream recall decreased with aging, which goes in line with previous studies (1-3). Older people may exhibit an attenuated amplitude (4) and/or phase advance (5, 6) of the circadian rhythms of core body temperature and melatonin. Furthermore, given the key role of the circadian pacemaker in the sleep regulation, age-related effects on sleep may be mediated by changes in the circadian timing system (7). For instance, an age-related decrease in the amplitude of the circadian signal can result in a

dampening of the circadian drive for sleep in the morning hours (4). This, in turn, can lead to an internal circadian advance, relative to the rhythm of core body temperature and melatonin, of the propensity to awaken in older people (8). In this context, there might be a global decrease in retrospectively estimated dream recall with aging. Interestingly, in this study (Chapter 2), older participants had an earlier peak of emotionality score than the young participants, which could suggest that older individuals have a phase advance of their dream recall. The age-related decline in dream recall could also be due to an attenuated REM sleep. The percentage of REM sleep undergoes a steep decline during middle-aged adulthood, and remains rather unchanged in subjects older than 60 years of age (9). The idea of REM sleep as a hallmark for age-related changes for dreaming partially builds-up from studies where patients with mild degenerative dementia dream much less than healthy aged people, possibly due to REM sleep decrease and atrophy of associative sensory areas of the cerebral cortex (10). Given that older participants had an attenuated circadian rhythm of REM sleep, this may have resulted in a reduction in dream recall.

The ultradian NREM/REM sleep modulation of dream recall

In young participants, dream recall was linked to specific frequency- and topography spectral EEG activity during NREM and REM sleep. Dreaming was associated with less frontal delta and centro-parietal sigma activity during NREM sleep. The intrinsic thalamocortical network during NREM sleep, as indexed by higher levels of sleep spindles and delta waves, can strongly interfere with ongoing mental activity (11). At the transition from wakefulness to sleep, the neuronal membrane potential in the cortex and thalamus, which comprises the relay station for most sensory signals to the cerebral cortex, reduces, resulting in NREM sleep oscillations - sleep spindles

and slow-waves - which lead to impaired synaptic responsiveness (12). This neuronal network most likely explains why dream recall was dramatically reduced during delta and spindle activity.

Dream recall following REM sleep was higher than after NREM sleep. Furthermore, the offline facilitation of dream recall was associated with lower REM alpha activity. Dream recall has been associated with alpha activity in a non-topographic manner (13), which may reflect cognitive elaboration active prior to awakening. Interestingly, in this study (Chapter 3), less alpha activity was observed only in frontal derivations. Given that REM sleep activates limbic structures (emotion-driven) and can be associated with frontal cortex inactivation (directed thought-driven (14)), these results suggest that REM dreaming comprises emotion-driven cognition with deficient analytic thinking. Dream recall subsequent to REM sleep was also associated with higher occipital alpha and beta activity. PGO (ponto-geniculo-occipital) activity has been proposed as a generator of the internal signal and sensory input of REM sleep, whereby the brainstem is the key initiator of dreaming, conveying a secondary role to the forebrain (15). This structure, in turn, receives tonic and phasic signals from the midbrain reticular formation via thalamus, and phasic eye movement signals from the pontine reticular formation via lateral geniculate nucleus. The forebrain then compares pseudo-sensory information from the brainstem with stored sensorimotor information, resulting in dreams (15). Taken together, this may explain the vivid imagery linked to REM dreaming. As can be noticed, dreaming in young people undergoes a distinctive ultradian NREM/REM sleep modulation. The next logical question is whether a similar situation happens in healthy aging.

In Chapter 4, aging was associated to specific frequency- and topography EEG activity prior to dream recall, such that during NREM sleep, older people have higher frontal delta and centro-parietal sigma activity prior to dream recall. This

counterintuitive finding could be due an increase in NREM sleep stage 2, which is the NREM sleep stage mostly connected to dream recall (16). Alternatively, since aging is associated with reduced sleep consolidation (17), there may be have been an increase in micro-arousals or awakenings, thus facilitating dream recollection. Conversely, increased sigma activity prior to dream recall in older people can reflect circadian-driven differences in spindle frequency. Spindles are under circadian control (18, 19), such that the circadian pacemaker actively promotes spindle activity during the night, and it can mediate the circadian modulation of sleep consolidation (18). Sleep spindles and their circadian modulation can decline with age (18-20). Young people show a distinct circadian modulation of spindle frequency phase-locked with melatonin secretion rhythm (20), such that they have lower spindle frequency during the biological night and higher during the biological day. Contrariwise, older people have less distinctive differences between the biological day and night (20). Given that in the young fast spindle frequencies during the day can indicate a circadian waking signal, a less well-defined day-night difference in spindle frequency in older people could reflect an attenuation of this signal, resulting in with more sleep intrusions. This, in turn, could increase the likelihood of dream recall. The lack of clear differences between REM sleep spectral composition prior to dream recall and no recall in older people may reflect a global attenuation of REM sleep, given that older people may undergo a reduced circadian modulation of REM sleep (4). However, since aging was associated with less frontal alpha and beta activity (irrespective of dreaming or not), one could speculate that REM dreaming in older people does not modify the “emotional tone” of dreaming, but rather the analytic thinking domain, due to a possible inactivation of frontal cortex (which mediates directed thought) (14).

PERSPECTIVES

How do we dream? In this thesis, there is compelling evidence in favour of a strong circadian and ultradian NREM/REM sleep modulation for dreaming, as indexed by the association of dream recall to the circadian modulation of REM sleep (Chapter 2), the biological day and night differences in dream recall (Chapter 3), and the remarkable differences in NREM and REM sleep EEG activity prior to dreaming (Chapters 3 and 4). Moreover, the circadian and the ultradian NREM/REM sleep modulation of dream recall does not seem to remain unchanged throughout one's life span, particularly when considering advanced age (Chapter 4).

Why do we dream? This very old question has some very new and exciting answers. Dreaming has been argued as a means for reactivation and consolidation of novel and individually-relevant features of prior wake experience (21-23). This consolidation, however, does not seem to be exclusive to REM sleep. Very recently (23), dreaming about a learning experience during NREM sleep was associated with improved performance on a hippocampus-dependent spatial memory task. This suggests that sleep-dependent memory consolidation in humans is facilitated by the offline reactivation of recently formed memories, and, quite interestingly, that dream experiences reflect this memory processing.

The "How" and "Why" question marks on dreaming will likely remain for a long time. But in view of the results in this thesis, it is clear that a better comprehension of the circadian and ultradian NREM/REM sleep factors underlying dreaming may help to unearth the mechanistic understanding of this complex cognitive activity.

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