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Nightmare disorder in light of neuropsychological and polysomnographic investigations

- PhD thesis -

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Glossary of abbreviations

REM – rapid eye movement

NREM – non-rapid eye movement

PTSD – post traumatic stress disorder

TNF-α – tumor necrosis factor alpha

IL-1β – interleukin 1-beta

GHRH – growth hormone releasing hormone

NO – nitric oxide

VIP – vasoactive intestinal polypeptide

ATP – adenosine tripjosphate

SCN – suprachiasmatic nucleus

GABA - gamma-aminobutyric-acid

VLPO – ventrolateral preoptic area

EEG – electroencephalography

SWA – slow wave activity

SWS – slow wave sleep

PGO – ponto-geniculo-occipital

fMRI – functional magnetic resonance imaging

CAP – cyclic alternating pattern

BOLD – blood oxygenation dependent level

ERP – event related potential

MMN – mismatch negativity

LTD – long term depression

RBD – REM Behavior Disorder

NMs – nightmare subjects

CTLs – control subjects

Abstract

Nightmare disorder, affecting approximately four percent of the adult population is a rather prevalent, but scarcely investigated sleep disorder. Frequent nightmares are very often co-morbid with different mental complaints however, the causal relationship between mental disorders and frequent nightmares lacks empirical support. More conclusive empirical findings point to the close association between nightmare frequency and altered sleep quality, suggesting that nightmare disorder belongs to the domain of sleep medicine.

The present paper consists of three parts: The first part is a general review of the neurobiological and psychophysiological aspects of sleep and dreaming. The aim of this extensive introduction is to provide a comprehensive context for the empirical studies presented in the second part of the thesis. The studies presented in the second part introduce our novel findings and propose some theoretical speculations regarding nightmare disorder. The third part of the thesis resumes the main findings, conclusions and possible future directions of the present research.

In the theoretical part of the thesis (Part 1), I will show that sleep is not a homogeneous process, but a continuously changing state characterized by prolonged and more transient fluctuations of arousability and environmental awareness. I will also aim to relate these changes regarding the depth, stability and specific oscillatory patterns of sleep with the presence and quality of ongoing mental, dream experiences.

In *Study 1*, testing some of the assumptions of the neurocognitive model of Levin and Nielsen's (2007), we addressed the issue of impaired prefrontal and fronto-limbic functions in subjects with frequent nightmares. We showed that nightmare subjects in comparison with controls were characterized by impaired behavioural performance in specific neuropsychological tasks involving executive control processes.

Although the personality correlates of frequent nightmares were characterized in several studies, only few investigations addressed the issue of altered sleep physiology in nightmare sufferers. Therefore, in *Study 2, 3 and 4* based on the data of whole-night laboratory sleep recordings, we examined the electrophysiological background of altered sleep quality, in a group of nightmare sufferers and health controls. In order to rule out the confounding effects of waking affective distress, we controlled the effects of the levels of trait anxiety and depressive symptoms by statistical models.

Nightmare subjects exhibited impaired sleep efficiency, reduced slow wave sleep, longer REM sleep, as well as increased sleep fragmentation especially during NREM sleep. Altered NREM sleep architecture was independent of anxiety and depressive symptoms, but increased REM sleep durations seemed to be the function of heightened negative affect *(Study 2).*

Nightmare subjects showed alterations regarding the microstructure of sleep, exhibiting increased arousal responses composed of high-frequency oscillations (*Study 3*).

And finally, quantitative EEG analysis showed increased relative low alpha power (7.75-9) in NREM sleep and increased high alpha power (10-14.5 Hz) in REM sleep in nightmare subjects, in comparison with controls. We suggest that increased alpha power during NREM and alpha power incorporating higher frequencies in REM sleep, reflect the coexistence of sleep-like and wake-like cortical activity in NMs *(Study 4).*

Our findings contribute to the understanding of the sleep pathophysiology of nightmare disorder, and points to the importance of some previously unemphasized aspects of this sleep disorder.

Kivonat [Abstract in Hungarian]

A felnőtt populáció hozzávetőlegesen négy százalékát jellemző rémálom zavar egy igen gyakori, ugyanakkor kevéssé vizsgált alvászavar. A gyakori rémálmok és a mentális panaszok közti komorbiditás kifejezetten magasnak tekinthető, ugyanakkor a rémálom gyakoriság és a mentális zavarok közti ok-okozati összefüggést nem nyert empirikus alátámasztást. Meggyőzőbbek azok az empirikus vizsgálatok, amelyek a rémálom gyakoriság és a rossz alvásminőség kapcsolatára és egyúttal arra a tényre hívták fel a figyelmet, miszerint a rémálom zavar az alvásmedicina hatáskörébe tartozik.

A dolgozat három részből áll: Az első, összefoglaló részben bemutatom az alvás és álmodás neurobiológiai és pszichofiziológiai vonatkozásait. A bevezető rész célja, hogy a dolgozat második részében bemutatott empirikus vizsgálatok számára tágabb elméleti keretet biztosítson. A második részben bemutatom az empirikus kutatások eredményeit, és az eredményekkel kapcsolatos elméleti felvetéseket. A dolgozat lezáró részében összefoglalom a kutatássorozat főbb eredményeit, következtetéseit és a kutatások kiegészítésének lehetőségeit.

A disszertáció elméleti részében (Part 1) bemutatom, hogy az alvás nem tekinthető egységes állapotnak; sokkal inkább egy változékony jelenségnek, amelyet az éberség és a környezeti ingerekre való fogékonyság tekintetében hosszabb és rövidebb átmeneti állapotok sora jellemez. Az alvás állapotainak, az alvás mélységének, stabilitásának és specifikus mintázatainak változásait az alvás alatti mentális (álom)élmény megjelenésével és jellegével is igyekszem majd összefüggésbe hozni.

Az *1. vizsgálatban*, Levin és Nielsen (2007) neurokognitív modelljében megfogalmazott hipotézis tesztelése végett, megvizsgáltuk a gyakori rémálmoktól szenvedő személyek prefrontális és fronto-limbikus hálózatokat aktiváló feladatokban nyújtott teljesítményét. Kimutattuk, hogy a rémálmoktól szenvedő személyek, a végrehajtó funkciókat igénybe vevő egyes neuropszichológiai feladatokban a kontroll csoporthoz képest gyengébb teljesítményt nyújtanak.

Míg a gyakori rémálmokkal együtt járó személyiségváltozókat számos vizsgálat vette górcső alá, a rémálom zavar alvásfiziológiai vonatkozásait rendkívül kevés kutatás tette vizsgálata tárgyává. Hogy ezt a hiányosságot valamelyest bepótoljuk, a *2. 3. és 4. vizsgálatunkban* egész éjszakás laboratóriumi alvásfelvételek alapján, összehasonlítottuk a rémálom zavarban szenvedő illetve kontroll személyek alvásának elektrofiziológiai sajátosságait. Az ébrenléti affektív zavarok hatásának kontrollálása érdekében, az alanyok vonásszorongás és depresszív tüneteinek értékeit is figyelembe vettük a statisztikai elemzések során.

A rémálom zavarral jellemezhető személyek a kontroll csoportoz képest rosszabb alváshatékonyságot, lecsökkent lassú hullámú alvás és megnövekedett REM fázis arányt, továbbá gyakori, elsősorban NREM fázis során bekövetkező rövid ébredéseket mutattak. Míg a NREM fázist érintő eltérések függetlennek bizonyultak a vonásszorongás és a depresszív tünetek szintjétől, a megnövekedett REM arányt a negatív affektivitás mértéke magyarázta *(2. vizsgálat)*. A rémálom zavarban szenvedő személyek továbbá az alvás mikrostruktúrája tekintetében is jelentős eltéréseket mutattak. A magasabb frekvencia komponensű éberségi (arousal) reakciók megemelkedett száma jellemezte az alvásuk NREM fázisát *(3. vizsgálat).* Végezetül, a kvantitatív EEG elemzések NREM fázisban tendencia szintű növekedést jeleztek a rémálom zavaros személyek esetében az alacsony alfa (7.75-9 Hz) sáv relatív spektrum értékében, míg REM fázis során szignifikánsan megemelkedett relatív spektrum értékeket a magas alfa (10-14.5 Hz) tartományban. Elképzelésünk szerint a rémálom zavarban tapasztalható fokozott alfa aktivitás, amely REM fázisban gyorsabb frekvenciakomponensekkel jellemezhető, egyfajta „hibrid”, az ébrenlét és az alvás „keveredéséből” fakadó tudatállapotot tükröz *(4. vizsgálat)*.

Eredményeink hozzájárulnak a rémálom zavar patofiziológiai aspektusainak megértéséhez, és felhívják a figyelmet e sajátos alvászavar eddig kevéssé hangsúlyozott vonatkozásaira.

Introduction

Dreams, the mental phenomena of the sleeping state have always been a fascinating topic for scientific inquiry. Although the study of cortical and mental activity during different states of alertness – in our case during the heterogeneous states of sleep – may contribute to our knowledge about the brain, as well as the neural underpinnings of mental activity, dream researchers still have to face various methodological challenges. The difficulties of dream research are caused by the specific nature of dreaming, the very same issue that scientist are trying to understand! For instance, the reconstructive nature of dream reports, influenced by the diverse expectations and belief systems of the dreamers as well as the difficulties in dream recall led researchers to collect dreams in sleep laboratories. While laboratory dream collection seems to be a much more controlled experimental method in contrast to home dream logs, the artificial and novel environment of the laboratory, the repeated awakenings during the night and the experimental procedure involving "forced dream mentations" that evidently influence the nature of dreaming might produce a quite salient heisenbergian problem.

Although these obstacles have yet to be overcome, remarkable progress has been made in the last decades due to the rapidly developing field of the neuroscience of sleep. The description of different sleep states (Rechtschaffen & Kales, 1968), and the differentiation of the activated state of Rapid Eye Movement (REM) sleep from the less activated and deeper stages of Non-REM (NREM) (Aserinsky & Kleitman, 1953) sleep has given rise to a wide variety of inspiring investigations in the field of experimental and clinical sleep research; however, to some extent, it has also constrained our view of the nature of the sleeping process. While the importance of different sleep stages, of the so-called macrostructure of sleep can not be overemphasized, recent lines of research indicate that the sleep process is characterized by more subtle dynamics including short, transient changes and fluctuations between different states of arousal and environmental alertness (Halász & Bódizs, 2013). Accordingly, the mental experience during sleep seems to be related to the underlying neural dynamics comprising sleep state transitions, exceeding the traditional view of dreaming as a correlate of REM sleep. While novel quantitative electroencephalographic techniques with different levels of analyses contributed to the understanding of the subtle dynamics of neural oscillations, brain imaging methods have enriched our knowledge of large-scale neural functions and information processing during different sleep states.

The growing field of the neuroscience of sleep has also unraveled some of the previously hidden aspects concerning the neural background of different sleep disorders helping clinicians and experimental sleep scientists to relate the dysfunctional sleep profiles with altered or, in some cases, severely impaired waking functions. This way, in light of the brain imaging findings regarding prolonged wakefulness, the cognitive and affective effects of sleep deprivation or even sleep fragmentation can be interpreted as the result of dysfunctional neural networks.

While in this review I will mainly focus on the latest neuroscientific findings of sleep and dream research, I will try to elucidate the relevance of the mental level, without attempting to resolve the so called hard-problem of conscious processes (Chalmers, 1995), but instead by considering the neural and the mental level as different levels of analysis.

As a graduate student in psychology, I was fascinated by the intensity and complex associative nature of (mainly my own) dreams, and I initially focused on the phenomenological and psychological aspects of dreaming. However, presumably like other beginners in dream research, I soon had to face the obstacles bound up with the investigation of such a specific subjective phenomenon. In order to somehow reduce the diversity of my topic of interest, I started to study a specific dream disturbance: nightmare disorder. Nightmares are a specific example of the intensification of the dream experience regarding content, as well as perceptual and emotional aspects. Although frequent (weekly occurrence of) nightmares seem to be a rather prevalent symptom (Janson et al., 1995; Levin & Fireman, 2002; Li, Zhang, Li, & Wing, 2010; Ohayon, Morselli, & Guilleminault, 1997) it is quite interesting that nightmares were conceptualized among the unusual events during the night (Koffel & Watson, 2009); and their inclusion into past and current dream theories seems to be somewhat ponderous. Even in the influential and integrative dream theory of Sigmund Freud (Freud, 2004/1905), the topic of frightening dreams is elucidated with only a few evasive remarks, in sharp contrast with the extensive elaboration of other aspects of dreaming. A somewhat similar attitude was present within modern sleep research communities that often considered nightmares as trivial secondary symptoms of an underlying mental disorder, or solely examined nightmares within the frames of post traumatic stress disorder (PTSD). Nevertheless, in recent years several attempts have been made to integrate the phenomenon of (frequent) nightmares into the rapidly expanding knowledge of cognitive neuroscience (Levin & Nielsen, 2007; Walker & van Der Helm, 2009), evolutionary psychology (Revonsuo, 2000) and the neurophysiology of sleep (Germain & Nielsen, 2003; Nielsen, 2000; Nielsen et al., 2010; Nielsen & Zadra, 2011). In this thesis, I would like to continue these endeavors by

attempting to place this specific sleep disorder to a less neglected shelf of sleep science. In the theoretical part of the thesis, I will review the most influential and conclusive results and models regarding the neural orchestration of sleep and concomitant mental experience in order to integrate nightmare disorder into our current knowledge of sleep regulation, sleep-related information processing and mental activity.

Part 1. The neurobiology of sleep and dreaming: A theoretical review

Chapter 1. The topsoil of oneiric experience: the indispensable state of sleep

In order to understand the mental experience during sleep one major and crucial step is to understand the basic mechanisms that govern different states of alertness, in our first distinction, the wakeful and the sleeping state. The cyclic alternation of these apparently opposite active and inactive states seem to characterize almost all animals, with the exception of some fish species whose behavioral prerequisites of sleep including the typical body posture, specific sleeping site, behavioral rituals before sleep, physical quiescence, elevated threshold for arousal and reactivity, rapid state reversibility, and circadian organization of rest–activity cycles (Campbell & Tobler, 1984; McNamara, Barton, & Nunn, 2010) are not evident (Kavanau, 2010; Tobler, 2005). While the neurophysiological properties of sleep in non-mammalian species require further investigations, a growing body of data suggests that the behavioral aspects of sleep are universal across species and present even in insects (Donlea, Ramanan, & Shaw, 2009; Ganguly-Fitzgerald, Donlea, & Shaw, 2006; Tobler & Stalder, 1988). The universality of sleep suggests that it is an essential function of animal organisms that requires thorough investigations in order to complete our knowledge about waking behavior and underlying neural functions.

While the evolutionary advantage of the active wakeful state, including motility, low thresholds for environmental stimulation and in some cases complex information processing is obvious, the inactive state of sleep with reduced environmental awareness seems to be a rather risky behavior for survival. In spite of the risks of predation and the time costs interfering with foraging and mating behaviors, animal species exhibit relatively long durations of sleep. Nevertheless, there seems to exist a trade-off between the hours spent asleep and the amount of time needed for efficient wakeful behaviors (Capellini, Barton, McNamara, Preston, & Nunn, 2008).

Although environmental factors can alter the duration of sleep and the proportion of different sleep stages, for instance, simulated predator encounters reduce NREM as well as REM sleep in rats (Lesku et al., 2008), if the necessary conditions for sleep are restored, we see a marked rebound effect with increased sleep pressure, indicating that sleep is a homeostatic process that needs to be accomplished (Borbély & Achermann, 1999). Therefore, sleep seems to be a behavioral program that animals can not sacrifice. This fact is especially

evident in case of certain cetaceans whose sleeping state is apparently maladaptive in the water environment. In spite of the constant need of swimming and breathing with lungs, these species did not dispose of sleep during the course of evolution, but "developed" the so-called alternating unihemispheric sleep (Siegel, 2005). And finally, sleep deprivation is a devastating condition resulting in severe physiological and cognitive dysfunctions (Bonnet, 2000).

Despite the differences in sleep architecture and sleep patterns among animal species, the regulation and the antagonistic influences of sleep-promoting versus wake-promoting effects as well as the homeostatic and so-called restorative functions (Halász & Bódizs, 2013) seem to be universal features of the sleep process. While the elucidation of the specific functions of sleep are far beyond the scope of this review, in light of converging data, we can postulate that sleep is the price that organisms have to pay for the development of plastic neuronal networks subserving such emergent processes as complex information-processing, learning, decision-making or volitional control (Krueger, Obál, Kapás, & Fang, 1995; Krueger & Obal, 2003).

In the following sections, I will summarize the most influential model, the two-process model of sleep regulation (Borbély & Achermann, 1999). Additionally, I will present the basic neural circuitry that orchestrates the alternation between wakefulness and sleep (Lu, Sherman, Devor, & Saper, 2006), and finally, I will briefly summarize the global as well as the local aspects of homeostatic sleep regulation that provide the role of sleep in "fine-tuning" the efficiency of neural networks supporting waking cognitive functions.

1.1. The regulation of sleep and wakefulness

The pressure to fall asleep, experienced in the subjective level as sleepiness is unequivocally related to the time spent awake. This led researchers even at the beginning of the twentieth century to search for substances that accumulate in the cerebrospinal fluid during wakefulness and induce sleep (Borbély & Tobler, 1989). A large body of research with a new impetus from the 1960's resulted in the isolation of several substances that play an important role in the regulation of sleep.

The criteria for sleep regulatory substances were considered to be the following: 1) the substance enhances sleep pressure after injection to the cerebrospinal fluid; 2) if inhibited, sleep is reduced; 3) its level in the brain varies with sleep propensity; 4) it acts on sleep regulatory circuits; 5) its level is altered in case of pathological sleep (Borbély & Tobler, 1989; Krueger & Obal, 2003). These criteria were met for the tumor necrosis factor alpha

(TNF-α), interleukin-1 beta (IL-1β), growth hormone-releasing hormone (GHRH), adenosine, and prostaglandine D_2 for the regulation of NREM sleep, while for REM sleep pressure, prolactine, nitric oxide (NO), and vasoactive intestinal polypetides (VIP) seemed to be the candidate substances (Krueger, 2011). (The difference between NREM and REM enhancing substances clearly indicates that sleep is not a homogeneous process, an issue that I will address in the following chapter.) Nevertheless, these sleep regulatory substances do not act in isolation but exhibit interrelated cascades of excitatory and inhibitory influences on other substances and receptors that finally lead to the intensification of sleep pressure (Bódizs, 2000). Moreover, their effects are not restricted to sleep propensity; for instance TNF-α and IL-1β are important chain links of the immune reaction, while adenosine as the decomposition product of adenosine triphosphate (ATP) is intimately related to brain energy metabolism and exhibits its sleep enhancing effect after increased energy consumption and, consequently, energy deficit in the neural tissue, thereby mediating the relationship between energy demanding wakefulness and the restorative properties of sleep (Porkka-Heiskanen & Kalinchuk, 2011).

Nevertheless, the extent of sleepiness and sleep pressure is not only dependent on prior wakefulness, but also on the biological rhythms of the organism. This fact is reflected by the conserved circadian fluctuations of alertness in spite of extended waking hours and accumulated sleep depth. The 24-hour cycle of circadian rhythmicity is generated by a complex, genetically transmitted network (Florez & Takahashi, 1995; Takahashi, Shimomura, & Kumar, 2008) that orchestrates the secretion of certain substances (eg., melatonin, cortisol), as well as the fluctuation of other biological variables (eg., body temperature, autonomic nervous system activity) that are important for the regulation of sleep-wake cycles (Bódizs, 2000). The integration of the internal and external cues indexing the circadian rhythm, the so-called master clock, is localised in the suprachiasmatic nucleus (SCN) of the hypothalamus. The anatomical as well as the physiological properties of the SCN make it en efficient neural network synchronizing internal homeostasis with the solar day (Antle & Silver, 2005).

The circadian rhythm determines the peaks of alertness, and consequently efficient waking performance as well as the "valleys" of behavioural performance covering the domains of sensory, motor and higher order cognitive functions (Dijk, Duffy, & Czeisler, 1992). Therefore, the tendency to fall asleep is the function of an interaction between the homeostatic and exponentially increasing influence of wake time and the non-linear fluctuation of circadian rhythmicity, a process that was quantified in the influential two-

process model of Borbély and Achermann (Borbély & Achermann, 1999; Borbély, 1982). While the two processes act antagonistically during the day (especially in the morning hours), they have synergistic influences during the night when the cumulative effect of sleep pressure (process S) "encounters" the circadian timing of low levels of vigilance (process C) (Borbély, 1982).

While the two-process model provides important clues to understand the tendency of falling asleep, it does not reveal the neural circuitry underlying well-defined state transitions between wakefulness and sleep in the behavioural level. The opposite effect of wake and sleep promotion and the regulation of these reciprocal antagonistic states was elegantly described by the flip-flop model, the pioneering work of Saper that we will briefly discuss in the following section (Saper, Fuller, Pedersen, Lu, & Scammell, 2010).

1.2. The wake-sleep antagonism: the flip-flop model

Although the influence of sleep promoting hypothalamic structures as well as the arousing nature of brainstem and hypothalamic neural pathways were described in the first part of the twentieth century (Halász & Bódizs, 2013), the regulation of the alternation between awake and sleeping states was only thoroughly explored and modelled recently (Saper, Chou, & Scammell, 2001). Saper and colleagues (2001) as well as Takahashi and colleagues (2006; 2010) showed that the ventrolateral preoptic area (VLPO) of the hypothalamus exhibits inhibition on the ascending reticular system by the neurotransnmitters of gamma-aminobutyric-acid (GABA) and galanin. Reciprocally, the neuronal groups of the monoaminergic ascending reticular system exert inhibitory control over the neurons of the VLPO. During wakefulness serotonergic, noradrenergic, cholinergic and histaminergic brainstem nuclei fire at high rate inhibiting VLPO neurons as well as disinhibiting their own activity. In the course of the transition from wakefulness to sleep, these wake-promoting neurons decrease their firing rates, that results in the disinhibition, and hence, increased firing patterns of sleep-promoting VLPO neurons (Saper et al., 2010; Takahashi, Kayama, Lin, & Sakai, 2010; Kazumi Takahashi, Lin, & Sakai, 2006). Moreover, the VLPO neurons act in concert with the firing of the neurons in the suprachiasmatic nucleus, both structures receiving inputs from retinal ganglionic cells. This ensures the timing of sleep to be synchronized with the circadian rhythms of the organism. The reciprocally antagonistic nature of sleep- and wake-promoting influences was denominated the flip-flop switch model of sleep regulation (Saper et al., 2001; Saper et al., 2010). **Figure 1.** illustrates the schematic representation of the

flip-flop model showing the reciprocal interaction of sleep-promoting and wake-promoting neuronal groups.

The flip-flop model describes a bistable system that has two mutually exclusive states, wakefulness and sleep, and although animal data clearly shows the relevance of these brainstem and hypothalamic centres in the orchestration of wake/sleep cycles, the model can neither account for the specific cortical oscillations that occur during the transitions between different states of vigilance (Bódizs, Sverteczki, & Mészáros, 2008), the heterogeneity of sleep architecture with alternating NREM and REM periods (Halász & Bódizs, 2013) or the coexistence of wake-like and sleep-like oscillations in the cortex (Nobili et al., 2011), all of them being essential sleep phenomena that I will summarize in chapter 2.

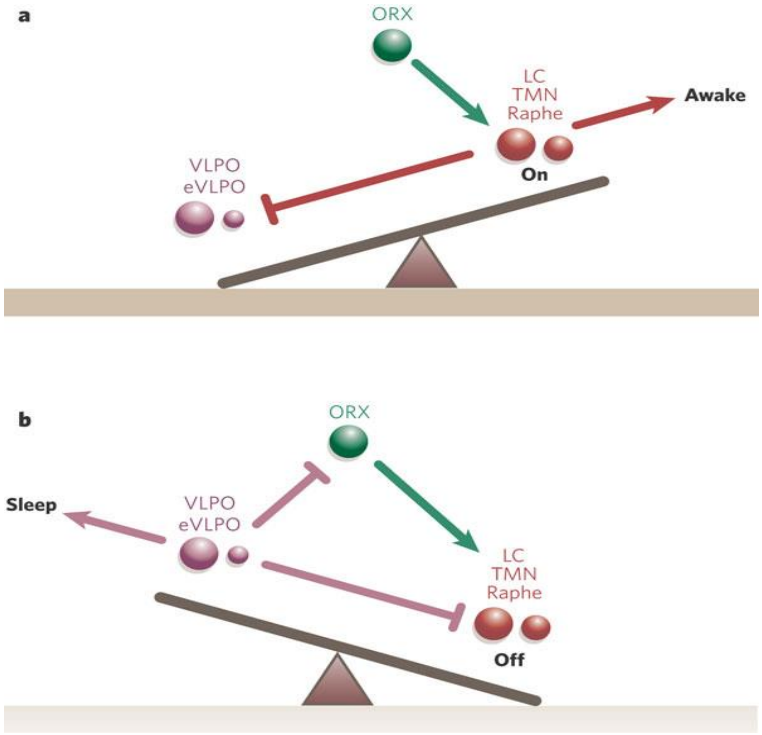

Figure 1. The schematic representation of the flip-flop model. Figure **a** illustrates the activation of wake-promoting and the inhibition of sleep inducing neural structures. In contrast, figure **b** shows the inhibition of arousal, wake-promoting systems and the activation of sleep-promoting VLPO neurons. Abbreviations: ORX – orexin, VLPO – ventrolateral preoptic area, LC – locus courelous, TMN – tuberomamillary nucleus. (Extracted from Saper, Scammel, & Lu, 2005).

1.3. Delta and slow oscillations

Sleep is defined as partly driven by a homeostatic process, that results in increasing sleep need after prolonged wakefulness and gradually dissipates after falling asleep (Borbély & Achermann, 1999). While the role of brainstem/hypothalamic structures in the initiation and maintenance of sleep is of utmost importance, the intensity as well as the graded dissipation of sleep, especially of NREM sleep is reflected in the oscillatory patterns of cortical neurons. The prominent oscillation of NREM sleep, the so-called delta (1-4 Hz) activity is easily observed by scalp electroencephalography (EEG) (Blake & Gerard, 1937). The sleep-specific activity of ten thousands of cortical pyramidal neurons of layers 3, 5 and 6 reflected in high amplitude slow waves can be regarded as an indicator of sleep intensity or sleep depth (Achermann & Borbély, 2011). Increased sleep pressure results in larger amplitude delta waves with steeper slopes (Bersagliere & Achermann, 2010). The propensity of delta waves is also easily quantified by spectral power measures (Achermann & Borbély, 2011).

In line with the homeostatic nature of sleep, delta power or slow wave (0.75-4.5 Hz) activity (SWA) is increased in the first stage of NREM sleep and continuously diminishes throughout the night. The exponential increase during wakefulness and the exponential decline during sleep shown for the delta range seems to be a specific marker of sleep regulation, since, for instance, it is not evident in slower (<1Hz) oscillatory activity (Bersagliere & Achermann, 2010).

While the homeostatic nature of delta power reflects a universal feature of NREM sleep, interesting individual as well as age-related differences were reported regarding the build-up and dissipation of delta activity (Jenni, Achermann, & Carskadon, 2005; Rusterholz, Dürr, & Achermann, 2010). Developmental and age-related region-specific changes in the topographical distribution of NREM SWA, especially during adolescence, indicate that this characteristic sleep oscillation reflects the maturation and functional reorganization of cortical networks (Campbell & Feinberg, 2009; Feinberg & Campbell, 2010).

Although the homeostatic nature of NREM delta activity was primarily described as a whole brain process, it was clearly shown that SWA during sleep also shows region-specific characteristics with prominent activity at frontal derivations (Finelli, Borbély, & Achermann, 2001). The frontal predominance of delta power is also evident after sleep deprivation

(Marzano, Ferrara, Curcio, & Gennaro, 2010), and suggests that it is related to the high energy demand and recovery need of the prefrontal cortex. The topographical differences in sleep-related slow activity raised a difficult question regarding the neural levels of sleep; in the words of James Krueger (2010): "What exactly is it that sleeps?"[1]

1.4. Local aspects of sleep and the synaptic downscaling hypothesis

The frontal dominance of delta activity (Finell et al, 2001) and its relationship to extended wakefulness (Marzano et al, 2001), as well as to enhanced waking cognitive performance after sleep (Marshall & Born, 2007) suggests that the appearance of homeostatic neural oscillations is associated with the local, experience-dependent activity of certain neural populations. This idea was originally put forward by (Krueger & Obál, 1993) and was later extended and tested in several experiments by Tononi and colleagues who formulated the local sleep theory and synaptic downscaling hypothesis (Krueger & Tononi, 2011; Tononi & Cirelli, 2006, 2012). The local expression of homeostatic delta power was evidenced after a visuo-motor adaptation task (requiring sensorimotor processes in the right hemisphere) that has led to local increases in delta activity over right parietal areas (Huber, Ghilardi, Massimini, & Tononi, 2004). Similarly, unilateral somatosenory stimulation of the hand has led to enhanced delta power in the corresponding hemisphere (Kattler, Dijk, & Borbély, 1994). Complementary to this finding, an arm immobilization procedure resulted in reduced delta activity over the cortical area that represented the passive arm (Huber et al., 2006).

Prolonged wakefulness not only results in enhanced delta activity during sleep, but also in increased theta activity in the wakeful state (Cajochen, Brunner, Kräuchi, Graw, & Wirz-Justice, 1995; Tinguely, Finelli, Landolt, Borbély, & Achermann, 2006). Moreover, increased theta power during wakefulness is related to enhanced delta power after falling asleep, suggesting that slowing of EEG oscillations are not restricted to the behavioral state of sleep. In line with the local sleep theory, a recent experiment has shown that experience-dependent plasticity in specific functional circuits, in this case a verbal task and a visuo-motor task leads to increased EEG theta activity during waking in region-specific, left frontal and posterior parietal areas, respectively. Moreover, region specific increases in waking theta

[1] Krueger, J. M. (2010). What exactly is it that sleeps? The evolution, regulation, and organization of an emergent network property. In: McNamara, P., Barton, R. A., Nunn, C. L. (eds). The Evolution of Sleep. Phylogenetic and Functional Perspectives. Cambridge University Press, New York, 2010.

activity were related to region specific increases in slower (delta) sleep oscillations (Hung et al., 2013).

Apart from these human studies, a large body of animal experiments and molecular findings indicate that the pressure of SWA is related to local synaptic processes, to long term potentiation and to the net increase in synaptic strength. According to these results, delta activity mediates the renormalization of neural circuits by facilitating synaptic depression, and thus, the increase of signal-to-noise ratio (see for an extensive review: Hanlon, Vyazovskiy, Faraguna, Tononi, & Cirelli, 2011).

The influential findings of the local sleep theory refute the homogeneity of sleep and provide strong and plausible explanations for the coexistence of sleep-like and wake-like neuronal processes. Krueger and Obál (1993) presented a feasible theoretical explanation for the apparent discrepancy between the neuronal (local) and behavioral (global) levels of sleep. They speculated that cortical columns oscillate between awake-like and sleep-like functional states, and in this way, functionally awake as well as functionally "sleeping" cortical columns coexist in the cerebral cortex. Krueger emphasized that the probability of a column to be in a sleep-like state is increased if the column was excessively stimulated previously (Krueger, 2010). In this view, sleep homeostasis and sleep regulation act on the level of the cortical columns that were exposed to stimulation-inducing plastic changes. According to Krueger and Obál (1993, 2003), global, behavioral sleep is a statistical phenomenon, the result of a high number of cortical columns entering the sleep-like mode.

These models suggest that local, sleep-like oscillations can occur during the behavioral state of wakefulness, without "switching" the whole brain into a sleeping mode. In the following chapters, I will examine the other side of the coin to show that wake-like oscillations may occur during sleep, without resulting in awakening.

Chapter 2. The structure of sleep: changing dynamics during the night

The macrostructural changes of sleep clearly indicate that sleep is not a homogeneous process. After falling asleep, in the so-called descending branch, the intensity of sleep increases, reaching the deepest stage of sleep. In parallel with the changes of oscillatory activity reflected by scalp EEG, there is a graded loss of perceptual awareness, as well as a reduction in the complexity of conscious mental processes. Nevertheless, approximately 90 minutes after falling asleep, in the so-called ascending branch, sleep progresses into the cortically activated state of REM sleep prior to which we can see the reduction of slow oscillations and enhanced arousal responses (Terzano et al., 1985). In accordance with the activated state of REM sleep, the level of conscious mental processes increases and the excitability of neurons in the modulatory pathways of the ascending reticular system (Steriade, McCormick, & Sejnowski, 1993), as well as the effective connectivity of widespread cortical EEG responses (Massimini et al., 2010) resemble those of the waking state. The cyclic alternation of the descending and ascending branches, reaching slow wave sleep (SWS) and REM sleep/wakefulness, respectively, build up the macrostructure, the NREM-REM cycles of sleep.

2.1. Thalamo-cortical oscillations during NREM sleep

Several in vivo and in vitro studies demonstrated that reduced transmission of incoming sensory signals in the descending branches of sleep are caused by the hyperpolarization of thalamo-cortical neurons (Steriade et al, 1993). The hyperpolarization of these neurons is provided by the thalamic reticular cells receiving inputs from thalamic neurons that project back to the cortex, and from cortical neurons that project to the thalamus (**Figure 2.**). This way, due to their anatomical and functional organization, the reticular cells have an essential role in organizing the information flow between the thalamus and the cortex (Steriade & Llinás, 1988; Llinas & Steriade, 2006). More specifically, the activation of the reticular nucleus of the thalamus that forms a sheet of GABAergic inhibitory interneurons at the outer surface of the thalamus hyperpolarizes thalamic relay neurons. The hyperpolarization of the relay cells leads to the opening of voltage-gated calcium channels that set the neuron's membrane potential for firing action potentials. The cascade of the opening of calcium channels results in a burst of action potentials until the opening of potassium channels hyperpolarize the cells, resetting them for another burst of calcium current

induced action potentials. Forming a loop in the thalamic network, the hyperpolarization of the relay neurons facilitates the activation of the inhibitory reticular neurons. The hyperpolarization and rebound bursts of action potentials, these rhythmic and synchronous firing patterns of thalamic relay neurons generate excitatory postsynaptic potentials in the dendrites of cortical neurons reflected by spindle and delta oscillations in the scalp EEG (Steriade et al., 1993). Spindling occurs if the hyperpolarization is moderate, and delta oscillations appear when thalamo-cortical cells are more hyperpolarized (Steriade, Dossi, & Nuñez, 1991). This suggests that in the course of the descending branch of sleep, there is a graded change in the hyperpolarization of thalamo-cortical neurons, leading to the gating of incoming sensory stimuli during the deepening phases of sleep. And finally, the synchronization of a large number of cortical neurons in the delta as well as the slower (<1 Hz) frequency ranges seems to organize thalamic activity, grouping and synchronizing the oscillations of the spindle and delta frequency ranges (Steriade, 2006). While delta activity is of cortical and thalamo-cortical origin, slow oscillation below 1 Hz seems to be exclusively generated in cortical neurons (Steriade et al., 1991).

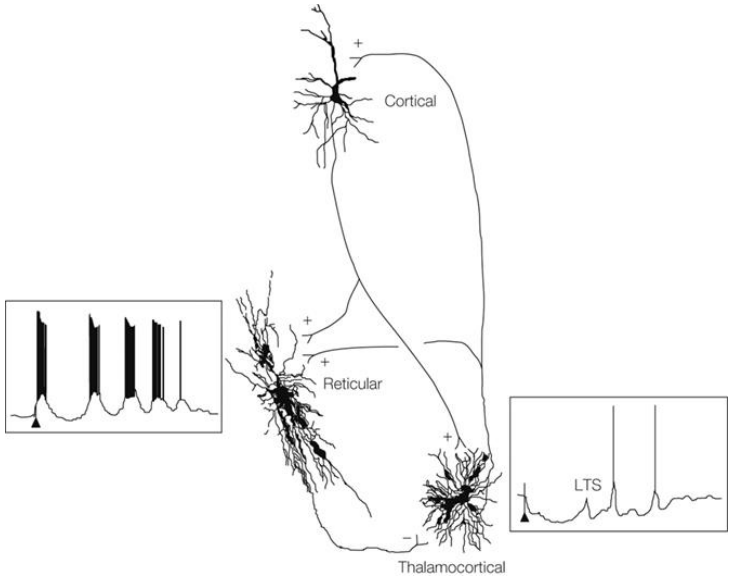

Figure 2. The neural groups (cortical, reticular and thalamocortical neurons) and their connections implicated in the emergence of delta and spindle activity during NREM sleep. Stimuéation of the cortical neurons results in spindle waves in reticular and low threshold spikes (LTS) in thalamocortical neurons. (Extracted from Steriade, 2005.)

2.2. The regulation of NREM/REM cycles

In the transition from NREM to REM sleep, activating influences of the upper brainstem, hypothalamus and basal forebrain abolish low-frequency rhythms and increase mixed and high frequency oscillations reflected by more tonic patterns, as well as enhanced arousal responses in the scalp EEG (Halász & Bódizs, 2013). These activating influences originating from the brainstem depolarize thalamo-cortical cells (Steriade, 1993; 2006). The increased firing rates of thalamo-cortical neurons reinstate the physiological state of these networks into the so-called "transmission mode" when incoming excitatory postsynaptic potentials can "force" the neuron to exhibit action potentials that reflect the incoming stimulus (Saper, 2000). Therefore, in the ascending branches and less deep stages of sleep, there is a relative increase of sensory processing (see Chapter 3).

The neurobiological background of the initiation of REM sleep was modelled by McCarley and Massaquoi (McCarley & Massaquoi, 1992). In their influential model, called the limit cycle reciprocal interaction model, based on the results of in vivo and in vitro experiments, they proposed that NREM/REM cycles are regulated by the interaction of monoaminergic (primarily serotonin and noradrenalin) REM-off and cholinergic REM-on neurons. According to the model, after falling asleep, the activation of monoaminergic neurons ceases due to inhibitory recurrent collaterals. The suppression of mainly serotonergic and noradrenergic influence from the dorsal raphe and locus coeruleus nuclei, respectively, disinhibits cholinergic influences from the laterodorsal tegmental and pedunculopontine (LTD/PPT) nuclei. Positive feedback projections reinforce cholinergic influences, but at the same time facilitate REM-off monoaminergic activity leading to the transition to a new NREM/REM cycle (McCarley & Massaquoi, 1992). Nevertheless, REM sleep can be disrupted by different excitatory influences transmitted by monoaminergic influences. In the extension of the model, these excitatory influences are also taken into account. According to the authors, excitatory influences can emerge from circadian, sensory and forebrain (cognitive and emotional) pathways that result in the activation of REM-off neurons (Massaquoi & McCarley, 1992). This way, the model can account for the perturbations and frequent arousals that may occur during REM periods, especially in case of disordered sleep.

The model states that pontine cholinergic influences are one of the essential neural substrates of REM sleep, but recently other neurotransmitters, such as glutamatergic neurons in the LTD were also reported to be involved in the generation of REMs (Krenzer et al., 2011). REMs are related to biphasic, sharp field potentials called ponto-geniculo-occipital

(PGO) waves, that were recorded in animals (Calvo, Datta, Quattrochi, & Hobson, 1992; Datta, Calvo, Quattrochi, & Hobson, 1992), but recently, supposedly the human analogue of PGO waves were also evidenced with different methods including magnetoencephalography (Ioannides et al., 2004), positron emission tomography (PET) (Peigneux et al., 2001), functional magnetic resonance imaging (fMRI) (Miyauchi, Misaki, Kan, Fukunaga, & Koike, 2009) and deep brain electrodes (Fernández-Mendoza et al., 2009). These ascending influences result in widespread cortical activations, as well as motor atonia induced by GABA/glycinergic inhibition of spinal alpha motoneurons. For long decades, increased cortical activation and motor atonia characterizing the paradoxical state of REM sleep were considered as the neural correlates of dream experiences, but in light of different lines of research, the equation between REM sleep and dreaming turned out to be an oversimplification (Domhoff, 2011).

2.3. NREM and REM sleep periods and concomitant mental phenomena

While the discovery of REM related dream mentation in the 1950's (Aserinsky & Kleitman, 1953) marked the beginning of the study of the neurophysiological background of dreaming, a large body of data indicates that mental experiences are not limited to REM periods, although sleep-state dependent modulation of the qualitative aspects of dreaming were reported in different studies (Bosinelli, Cavallero, & Cicogna, 1982; Cicogna, Natale, Occhionero, & Bosinelli, 2000). NREM mentation, in contrast to REM dream reports, was characterized as perceptually less intense, with reduced movement, speech, active self representation, hallucinatory nature and narrative structure (Foulkes, 1985; Hobson, 1988). Interesting differences regarding the content of dreams also emerged between the two states, with more aggression in REM compared to NREM dreams (McNamara, McLaren, Smith, Brown, & Stickgold, 2005; Uguccioni et al., 2013). Although dream reports from REM and NREM sleep are different – perceptually vivid and hallucinatory-like mental experiences in REM and less vivid, rather thought-like mentations in NREM sleep, – these qualitative differences progressively decrease during the night in consistence with the observation that late-night NREM EEG patterns are more similar to REM periods in comparison to early-night NREM oscillatory activity (Fosse, Stickgold, & Hobson, 2004).

While dream reports form REM sleep were consistently rated as complex, long, visually intense and bizarre, findings regarding NREM mentations are more heterogeneous since NREM dreams are more variable regarding these qualitative aspects (Cavallero et al.,

1992). Moreover, although several researchers claim that dream generation is specifically dependent on the physiological properties of REM sleep (Nielsen, 2000; Stuart & Conduit, 2009; Takeuchi, Miyasita, Inugami, & Yamamoto, 2001), others, for instance with pharmacological REM-suppression, showed that REM sleep is not necessary for the specific qualitative aspects of dreaming (Oudiette et al., 2012).

One methodological problem concerning the comparison of NREM and REM dream reports is that these states might not only differ in dream generation but also regarding the accessibility and retrieval of dream memories (Conduit, Crewther, & Coleman, 2004). Another difference is related to the heterogeneity of the microstructure of NREM sleep that is composed of markedly different oscillatory patterns and fluctuations of arousal reactions, while REM sleep seems to be a more - although far from fully - homogeneous process. Spontaneous and induced arousals were indeed related to increased visual imagery reports in NREM sleep (Conduit, Bruck, & Coleman, 1997; Jakobson, Fitzgerald, & Conduit, 2012), suggesting that the intensity of dreaming during NREM sleep is intimately related to cortical activation and to the reduction of (deep) sleep-promoting processes. Although the understanding of the generation of dreams in relation to the underlying neural networks requires further investigations, it is tempting to speculate that NREM dreams emerge from the activation of ascending alerting mechanisms, while REM dreams are the result of intrinsic activation patterns related to the specific physiology of REM sleep. However, the role of the arousing influences in this state cannot be excluded either.

2.4. The microstructure of NREM sleep: Phasic events and the cyclic alternating pattern

NREM sleep is characterized by the appearance of transient, phasic events such as vertex sharp waves, sleep spindles, K-complexes, delta bursts or mixed and high frequency (alpha and beta) activities that build-up the structure of sleep. Autonomic activity during these phasic elements indicate that the above events – except sleep spindles – are related to intrinsically or extrinsically induced arousing influences (Halász, Terzano, Parrino, & Bódizs, 2004). Therefore, these activities can be considered as the sleeping brain's response to stimulation.

Probably the most thoroughly investigated phasic events during sleep are the K-complexes that are predominant during the descending phases of sleep and are considered to be the 'forerunners' of delta activity in SWS (De Gennaro, Ferrara, & Bertini, 2000). Recent findings regarding the neural correlates of evoked K-complexes indicate that these phasic

events are underlain by the activation of subcortical (brainstem, thalamus) and cortical structures (anterior cingulate, middle frontal gyri), as well as by modality specific activations reflecting the type of stimulation (Jahnke et al., 2012; Riedner, Hulse, Murphy, Ferrarelli, & Tononi, 2011). In light of earlier and recent findings, spontaneously occurring and evoked K-complexes seem to be so-called 'Janus faced' features of sleep, that constitute a short arousal response related to low-level information processing of environmental stimuli, and subsequently, a global sleep-protecting response that reinforces the thalamic-basal forebrain gate against arousing influences (Halász et al., 2004; Halász & Bódizs, 2013; Jahnke et al., 2012; Parrino, Ferri, Bruni, & Terzano, 2012).

Although K-complexes can appear in isolation, basically they belong to a diverse phasic phenomena denominated as microarousals. The thorough characterization of microarousals during NREM sleep was provided by the Parma sleep group that introduced the concept of the cyclic alternating pattern (CAP) (Terzano et al., 1985). CAP sequences are characterized by phasic electrocortical activities that are different from background EEG and recur in quasi-periodic burst sequences with inter-burst intervals up to 1 minute. CAP sequences, apart from changes in EEG, exhibit alterations in autonomic activity reflecting sympathetic activations (Ferri et al., 2000). These sequences composed of different oscillatory activities show an alternating pattern of activated, arousal responses (A phases) and deactivated tonic periods (B phases) (Terzano et al., 1985).

These transient bursts of phasic events are categorized into different subtypes based on their frequency distributions. The subtype A1 is a burst of synchronized delta waves generated at anterior sites with frequency components predominantly between 0.25-2.5 Hz (Ferri, Bruni, Miano, & Terzano, 2005). Subtype A2 is a mixture of synchronized delta oscillations and higher (alpha and beta) frequency activity, while in A3, desynchronized high frequency oscillations are the predominant activities. Higher frequency components of A2 and A3 are generated in posterior sites, and reflect the transient instability of sleep depth in response to afferent inputs, while A1 and the slow component of A2 are characterized by anterior predominance. Although the vegetative components indicate a clear activation during A1 episodes these events seem to be strongly related to sleep-promotion (anti-arousals), reflecting the effort of the cortex to preserve the stability of sleep (Parrino et al., 2012; Halász & Bódizs, 2013). In line with the role of sleep in offline memory processing and cognitive functions, synchronized phasic bursts (A1 subtype) were related to enhancements of cognitive performance, while desynchronized microarousals (A2 and A3) were associated with slightly impaired cognitive functions after awakening (Aricò et al., 2010; Ferri et al., 2008).

The characterization of the microstructure of sleep proved to be a comprehensive tool in studying developmental changes and pathological alterations, as well as pharmacological treatments of sleep instability (Parrino et al., 2012; Terzano & Parrino, 2000). The study of sleep microstructure definitely complements our knowledge about sleep architecture and sleep regulation. The temporal dynamics of microarousals seem to be intimately related to the alternation of NREM/REM cycles and to the descending and ascending phases of sleep (for an extensive review see Halász and Bódizs, 2013); moreover, transient events of arousals were hypothesized to be associated with the hyperpolarization-depolarization sequences of the cortical slow oscillatory (< 1 Hz) rhythm as well as to the ultraslow oscillation of the default mode network (Dang-Vu et al., 2008; Parrino et al., 2012), a remarkable suggestion that needs to be ascertained by further investigations.

And finally, microarousals seem to be related to the intensification of mental experiences during NREM sleep. Sleep deprivation resulted in reduced CAP rate and a marked reduction in the A3 subtype during the recovery night (De Gennaro et al., 2002), and a similar restriction of sleep almost completely abolished dream reports from NREM sleep during the night when subjects were allowed to recover from prolonged wakefulness (De Gennaro et al., 2010). Moreover, arousals induced by auditory stimulation increased the visual intensity of dream reports during NREM sleep (Conduit, Bruck, & Coleaman, 1997). These findings indicate that phasic events during NREM sleep, involving transient cortical activations that facilitate the processing of extrinsically (environmental) or intrinsically driven arousing stimuli are paralleled by the intensification of mental experiences.

2.5. Phasic and tonic REM sleep

Although REM sleep is also characterized by transient phasic electrocortical events such as sawtooth waves, short lasting alpha and beta bursts (Rechtschaffen and Kales, 1968), the fine-grained characterization of these phenomena, as well as their relationship to neural and mental events, is still an unresolved issue of sleep research. REM sleep is generally not categorized into different states in conventional sleep staging algorithms. However, the distinction between phasic and tonic REM periods is widely accepted among sleep researchers. Phasic REM periods are characterized by bursts of eye movements, whereas no eye movements occur in tonic periods (Hobson, Lydic, & Baghdoyan, 1986). Since rapid eye movements are considered to be the markers of PGO activity, the neuroanatomical background of phasic and tonic REM periods might be different (Hobson et al, 1986).

Earlier findings indicate that the two states also differ in terms of mental state. Phasic periods were related to more active and emotionally intense dream reports as opposed to tonic REM periods (Dement & Wolpert, 1958; Pivik & Foulkes, 1966).

According to some more recent data, phasic, in contrast to tonic REM, seems to be a more sleep-like state, with increased arousal thresholds (Ermis, Krakow, & Voss, 2010) and enhanced theta, as well as reduced alpha and beta power (Waterman, Elton, Hofman, Woestenburg, & Kok, 1993). However, other findings regarding the spectral profile of these two states are somewhat inconsistent (Jouny, Chapotot, & Merica, 2000). In spite of the increased sleep-like theta activity and reduced alpha and beta power, others found gamma power enhancements during phasic REM periods (Gross & Gotman, 1999; Jouny et al., 2000; Nishida et al., 2005), indicating that, although being more sleep-like, phasic REM periods are also characterized by increased, intrinsically driven cognitive processing, presumably related to dream experiences. In contrast, tonic periods are more open to external events: infrequent auditory stimuli elicited stronger REM-P3 (a REM evoked response resembling waking P300) and P-210 waves in tonic than in phasic periods (Sallinen, Kaartinen, & Lyytinen, 1996), and more recently, an fMRI study (Wehrle et al., 2007) showed that auditory stimulation elicited residual activation in the auditory cortex during tonic, relatively reduced activity during phasic REM periods. While brain activity during tonic periods was influenced by external stimulation, phasic REM was characterized by a lack of cortical reactivity to auditory stimulation. Moreover, during phasic REM, strong interregional correlations emerged with thalamic BOLD time series signals in several areas including brainstem, limbic, parahippocampal and middle frontal structures. The authors conclude that phasic REM sleep is a functionally more isolated state in comparison woth tonic REM periods, in which residual alertness is maintained (Wehrle et al., 2007).

These findings indicate that REM sleep is far from being a uniform state, and that fluctuations of arousability are not confined to NREM sleep. Variations between internally and externally oriented cognitive processes between the “shores” of sleep and wakefulness seem to characterize REM sleep, but in contrast to NREM sleep, here, transient phasic events with eye movements belong to the sleep-like state, while more extended tonic periods resemble a long-lasting aroused state with increased sensory processing.

Future studies might address how these states differ regarding the content of mental experiences, reflecting diverse and presumably functionally different information-processing during REM sleep.

Chapter 3. Sleep and information processing

The formation of long-term memories relies on the reactivation and system-level reconsolidation of newly acquired information into distributed neural networks facilitating voluntary retrieval and qualitative changes of the original memory representations (Squire & Bayley, 2007). Sleep seems to be an ideal state for long-term memory formation because of the reduction of environmental stimuli and on-line encoding processes. Therefore, reactivated and temporarily instable memories are not prone to interference and may undergo a process of reconsolidation (Rasch & Born, 2007).

In the last two decades, a large body of research data has shown that sleep is an essential state for the consolidation and long-term storage of previously acquired memories (Marshall & Born, 2007). Sleep-dependent memory reprocessing seems to be supported by a widely distributed, complex neural network comprising subcortical, limbic and cortical structures, and by molecular and cellular changes initiated during specific sleep stages (Diekelmann & Born, 2010; Ribeiro, Goyal, Mello, & Pavlides, 1999). The coalescence of different neural oscillations in hippocampal, thalamo-cortical and neocortical structures during sleep, especially SWS, seems to promote the reactivation and redistribution of memory elements into broadly distributed neocortical networks (Marshall & Born, 2007).

The role of sleep in off-line memory consolidation and cognitive performance is elucidated by studies on the effects of sleep deprivation, as well as by findings reporting cognitive impairments in relation to fragmented sleep (McCoy & Strecker, 2011). Since fragmented sleep reflects the impairment of sleep-promoting and the enhancement of arousing influences (Halász et al, 2004; Parrino et al, 2012), it might be suggested that there is a trade-off between off-line memory reprocessing and on-line – although reduced – processing of afferent stimuli during sleep. Internally and externally focused information processing seem to be different mechanisms that parallel the fluctuations of sleep-like and wake-like oscillations during sleep. In the following sections, I will summarize some of the main findings regarding these "different directions" of information-processing during sleep.

3.1. Processing of afferent inputs during sleep: Event Related Potential (ERP) studies

Since behavioral responsiveness can not be measured, ERP studies are one of the possible ways to examine to what extent the brain processes information after falling asleep. The more thoroughly investigated evoked components during different stages of sleep were

the N350, N400, N550, P300 and the MMN (mismatch negativity) (Bastuji, Perrin, & Garcia-Larrea, 2002). Although the presence of these evoked responses was mainly investigated by auditory stimulation, research suggests that this is not the only modality that can be used in order to measure information-processing during sleep (Colrain, Webster, & Hirst, 1999).

N350 and N550 seem to reflect the vertex sharp transients and K-complexes, respectively. While N350 is elicited during sleep onset, N550 is seen during deeper NREM sleep (Colrain & Campbell, 2007). Both components can appear spontaneously and can be elicited with external stimuli. Nevertheless, they also seem to be independent of the modality of the stimuli, since respiratory occlusions elicit strikingly similar responses as sound stimuli (Colrain et al., 1999). Furthermore, the probability of the stimulus seems to influence the amplitude of N350 and N550, while the personal relevance of the stimulus does not exert an effect on these evoked responses. Both potentials seem to be related to the protection of sleep, involving short-lasting, low-level information processing, and subsequently, a global inhibitory response. Nevertheless, the topographical difference between the centro-parietally localized N350 and the fronto-central N550, indicates that they are functionally independent processes (Bastuji et al., 2002). These neural events emerging at different points in the descending phase of sleep – N350 during sleep onset and N550 during Stage 2 and SWS – reflect the synchronized activity of large numbers of pyramidal neurons that prevent the high-level processing of sensory stimuli (Bastuji et al., 2002).

Nevertheless, other findings indicate that the sleeping brain is able to accomplish more refined processing of external stimuli. P300 is most often elicited within the frames of the "oddball paradigm" involving the presentation of a frequent, "standard" stimuli that appear with high probability, and the presentation of a "target" stimuli that appear at odd and unpredictable intervals during the sessions, and differ from the standard stimuli in some parameter (pitch, color, location, relevance etc.) (Polich, 2007). P300 is considered to reflect an updating mechanism of working memory, involving the memory representation of the standard stimulus, the detection of stimulus change through the comparison of the novel stimulus with the previous memory representation, and finally, an updating mechanism revising the memory representation in working memory (Polich, 2007). In accordance with the reduction of prefrontal attentional mechanisms during the course of sleep, the amplitude of P300 gradually declines during sleep onset, and there is no compelling evidence that it can be elicited in NREM sleep (Cote, 2002). Nevertheless, according to the study of Perrin and colleagues (1999) the subject's own name elicited an evoked response during Stage 2 and REM sleep resembling the P300 response to own names during wakefulness (Perrin, García-

Larrea, Mauguière, & Bastuji, 1999). Whether the processing of the own name is an exception or whether it reflects the capability of the sleeping brain to process stimuli of intrinsic (psychological) relevance is still a question of debate (Colrain & Campbell, 2007).

Semantic processing during sleep is evidenced by the N400 potential that is enhanced in response to incongruous semantic stimuli relative to a given context. N400 was present during Stage 2 as well as REM sleep in response to semantically discordant words, as opposed to congruous ones (Fabien Perrin, Bastuji, & Garcia-Larrea, 2002).

MMN was not found in earlier reports during sleep (Sallinen et al., 1996), but later studies showed, that it can be elicited by deviant tones during REM sleep. However, the sensory memory on which the MMN response relies seems to be shorter than in wakefulness (Mercedes Atienza, Cantero, & Dominguez-Marin, 2002). MMN was detected during REM sleep even to small changes in a complex auditory pattern if and only if subjects during previous training learned to behaviorally discriminate the two patterns. This finding suggests that complex sound processing might also take place in REM sleep by reactivating previously learned patterns from long-term memory (Atienza & Cantero, 2001). In contrast to findings in REM sleep, MMN was not detected in NREM sleep (Sculthorpe, Ouellet, & Campbell, 2009).

In sum, ERP studies indicate that external information processing is preserved to some extent during sleep, especially during the more active state of REM sleep. While event related potentials reflect evoked power changes and/or phase-resetting in the EEG that are phase-locked to the event, the non-phase-locked EEG changes (induced power), in response to external stimuli are scarcely investigated. External stimuli can alter the ongoing pattern of EEG even after longer time scales after the presentation of the stimuli. Therefore, induced changes in power measured by Short-Term Fourier Transformation or Wavelet analyses might provide valuable information regarding the processing of external events. Changes in EEG oscillations in response to external stimulation might be reflected by changes in the ongoing mental experience as well. Somatosensory stimulations were shown to be incorporated to some extent into the content of dream experiences (Nielsen, 1993), and the pleasantness of different olfactory stimuli were reflected in the emotional tone of dreams (Schredl et al., 2009). Nevertheless, the characterization of the neural background of the processing and mental incorporation of external stimuli warrants further investigations.

3.2. Memory-consolidation during sleep

As the detailed presentation of the waste literature regarding sleep-related memory consolidation is far beyond the scope of this section, here I shall resume the more conclusive findings of the field.

The beneficial influence of post-learning sleep on memory reprocessing was evidenced by behavioral studies on animals (Smith, 1995) and humans (Plihal & Born, 1997), as well as brain-imaging (Peigneux et al., 2003) studies. Moreover, neurophysiological (Louie & Wilson, 2001), cellular (Frank, Issa, & Stryker, 2001) or molecular studies (Ribeiro et al., 1999; Ribeiro et al., 2002) also supported the intimate relationship between learning and post-learning sleep.

The two most influential models of sleep-related memory enhancements are 1) the synaptic downscaling hypothesis (Huber et al., 2004) (see section 1.4) that provides a general framework for sleep related neural plasticity facilitating post-sleep cognitive performance and 2) the model of memory reactivation and hippocampal-neocortical transfer during sleep (Buzsáki, 1998; Marshall & Born, 2007). These two models are not mutually exclusive since the first emphasizes the importance of a general neural state (slow oscillations) while the latter focuses on the activation and reorganization of specific (memory) representations coded by different neural networks.

The synaptic downscaling hypothesis postulates that due to the effects of long-term depression (LTD) and the general reduction of synaptic strength during SWS, stronger and thus more relevant synaptic connections remain, while weaker synaptic connections are abolished (Hanlon et al., 2011). This way, the synaptic downscaling leads to the increase of the signal-to-noise ratio, and to the consolidation of the more activated representations during waking, while irrelevant, less activated representations during wakefulness are prone to be forgotten (Hanlon et al., 2011). In line with the preferential enhancement of relevant memories, recent studies showed that sleep after learning selectively enhanced memories of future relevance (Wilhelm et al., 2011), and reduced memory for irrelevant items that were instructed to be forgotten (Racsmány, Conway, & Demeter, 2010; Saletin, Goldstein, & Walker, 2011).

In contrast to the more indirect effects of synaptic downscaling on the strengthening of memory traces, other researchers suggest an active and trace-specific role for sleep in memory consolidation. These lines of thought suggest that during sleep, memory elements are first reactivated (Louie & Wilson, 2001; Peigneux et al., 2003) and then go through a process of reconsolidation making representations more enduring and resistant to interference (Walker & Stickgold, 2010). Temporally structured replay of waking firing patterns of hippocampal and

neocortical neuronal ensembles reported in the REM state of rats (Euston, Tatsuno, & McNaughton, 2007; Louie & Wilson, 2001) and human studies that show overlapping patterns of neural activations during task-acquisition and post-learning REM sleep (Maquet et al., 2000; Peigneux et al., 2003; Bergmann, Mölle, Diedrich, Born, & Siebner, 2012; van Dongen et al. 2012) provide evidence for the assumption of selective memory reactivations. The heterogeneity of sleep is reflected in this domain as well: different kinds of memories seem to benefit from different sleep stages. While NREM sleep and more specifically SWS is associated to the reactivation and consolidation of declarative memories, REM sleep was linked to procedural and emotional memory consolidation (Diekelmann & Born, 2010).

Instead of mere reactivation and consolidation, sleep seems to facilitate the neural redistribution of memory representations. According to the model of the so-called sleep-related reconsolidation, sleep alters memory representations by fostering the information transfer between the hippocampus and the neocortex. Research indicates that the "dialogue" between hippocampal and neocortical structures facilitates the redistribution of new, reactivated memories in the hippocampus into broadly distributed neocortical networks (Marshall & Born, 2007; Ribeiro & Nicolelis, 2004; Stickgold & Walker, 2007).

Studies investigating the electrophysiological background of sleep-related memory consolidation point to the role of slow oscillations and sleep spindles. Improved memory performance was related to slow oscillations (< 1Hz activity presumably generated in the neocortex) that were experimentally boosted by transcranial direct current stimulation on frontocortical sites after a declarative learning task (Marshall, Mölle, Hallschmid, & Born, 2004), and enhanced number of post-learning sleep spindles were related to improved performance in different declarative memory tasks (Clemens, Fabo, & Halasz, 2005; Z. Clemens, Fabó, & Halász, 2006). Moreover, the topographical distribution of spindles were in coherence with the neural requisites of the pre-sleep learning tasks, showing fronto-central spindle predominance after verbal tasks, and parietal after visuo-spatial ones (Clemens et al., 2005; 2006).

Sleep spindles and slow oscillations seem to be two intricately related neural phenomena, since spindles are predominantly exhibited in the Up-state of slow oscillations reflecting phases of cortical depolarization (Mölle, Marshall, Gais, & Born, 2002). Moreover, learning related increases in spindle density are grouped in these Up-states of slow oscillations (Mölle, Eschenko, Gais, Sara, & Born, 2009). According to the results of Clemens and colleagues (2007, 2011) neocortical slow oscillations and thalamo-cortical spindles are also temporally coupled to hippocampal ripples (Clemens et al., 2007, 2011). And finally,

recent studies suggest that the Up-state of slow oscillations are also connected in time to the burst-like activity of Locus Coeruleus neurons that release the neurotransmitter noradrenalin (Eschenko, Magri, Panzeri, & Sara, 2011; Eschenko & Sara, 2008). These findings opened an intriguing avenue of future research, since the release of noradrenalin is intimately related to learning processes during waking, and thus to memory reconsolidation (Marshall & Born, 2007). This way, during sleep, synchronized activity of different neural populations in different neural structures (brainstem, hippocampus, thalamus and neocortex) might organize the consolidation as well as the neural reorganization of previously acquired memory representations.

Our knowledge about the neurophysiological markers of sleep-dependent memory reprocessing has significantly increased in light if these novel findings. Nevertheless, we should note that results about sleep-dependent improvements in memory consolidation, as well as learning related alterations in neural oscillations are still based mainly on correlational methods. This is an important point, given that the spectral power of NREM sleep is highly individual-specific, and, for instance, certain characteristics of sleep spindles were strongly related to general intelligence (Bódizs et al., 2005; Fogel & Smith, 2011). Therefore, the association between learning, post-learning sleep spindles and post-sleep performance can be mediated by the underlying cognitive abilities of the subjects (Lustenberger, Maric, Dürr, Achermann, & Huber, 2012).

A promising but methodologically challenging technique is the cueing procedure (Rudoy, Voss, Westerberg, & Paller, 2009) that involves the association of the learned material with other stimuli (generally odor or sound) that is presented during subsequent sleep in order to reactivate the newly acquired representations. Targeted memory reactivations with sound cues resulted in enhanced memory for the items associated with the cue (Rudoy et al., 2009), and visuo-spatial memory reactivation with odor cues (Diekelmann, Büchel, Born, & Rasch, 2011) protected previously acquired memories against interference. These and other findings showed that the cueing technique is an efficient method for the study of the causal relationship between sleep and memory consolidation (Oudiette & Paller, 2013). Main results emerged exclusively after cue induced memory reactivations during SWS, while cueing in other sleep stages was not efficient (Diekelmann et al., 2011). Nevertheless, previous studies mainly focused on declarative memory tasks that seem to "benefit" from post-learning SWS. The effect of cued memory reactivations during REM sleep might be evident in different memory tasks (See chapter below). Moreover, SWS might be a state when incoming sensory stimulation scarcely elicits transient arousals that disturb sleep-specific slow wave activity. In

contrast, cueing during more active phases of sleep might direct attention towards the external environment indexed by arousals and the disruption of sleep-specific thalamo-cortical oscillations that interfere with the consolidation of memory representations. Sleep-like slow oscillatory activity and, presumably, increased sleep spindling after the presentation of the cue might reflect increased processing of reactivated memories, while arousals and wake-like oscillatory activity after cue presentation might index the monitoring of the environment in a more "online-mode" with the disruption of off-line memory reprocessing.

3.3. Sleep and affective processing

Several lines of research indicate that sleep plays an important role in affective information processing. For instance, chronic sleep restriction and sleep fragmentation is associated with a wide variety of mental symptoms characterized by emotional dysregulation (Benca et al., 1997; Benca, Obermeyer, Thisted, & Gillin, 1992; Peterson & Benca, 2006). Although the relationship between sleep and emotions seems to be bidirectional (Kahn, Sheppes, & Sadeh, 2013), in this section I will only focus on the effects of sleep (and the lack of sleep) on daytime emotional processing.

In addition to the devastating effects of chronic sleep restriction, even one night of sleep deprivation was shown to enhance dissociative symptoms (Giesbrecht, Smeets, Leppink, Jelicic, & Merckelbach, 2007), as well as to increase physiological emotional reactivity (Franzen, Buysse, Dahl, Thompson, & Siegle, 2009). One night of sleep deprivation alters the subjective evaluation of neutral stimuli biased towards more negative responses (Tempesta et al., 2010) and impairs the accurate recognition of human emotions (van der Helm, Gujar, & Walker, 2010). A latter study showed that sleep deprivation is not only related to increased emotional reactivity in response to negative stimuli, but amplifies the reactivity toward positive stimuli as well (Gujar, Yoo, Hu, & Walker, 2011).

The neural background of increased emotional reactivity after sleep deprivation is presumably due the reduction of fronto-limbic connectivity and inefficient prefrontal inhibition on amygdalar activity (Yoo, Gujar, Hu, Jolesz, & Walker, 2007), the functional alteration of a widespread emotion processing network comprising limbic (amygdala, hippocampus), fronto-limbic (anterior cingulate) and neocortical structures (ventromedial prefrontal and orbitofrontal cortex) (Walker & van Der Helm, 2009). A whole night of sleep or even a short nap seems to enhance the processing and regulation of emotional memories by reducing the subjective intensity of the previously presented emotional stimuli (Gujar,

McDonald, Nishida, & Walker, 2011). These ameliorating effects of sleep were understood as mainly relating to REM sleep (van der Helm et al., 2011). REM periods were associated not only with the consolidation of emotional memories (Nishida, Pearsall, Buckner, & Walker, 2009; Wagner, Gais, & Born, 2001), but also with enhanced processing of fear extinction memories after aversive-conditioning and subsequent fear-extinction learning sessions (Spoormaker et al., 2010; Spoormaker et al., 2012). These findings cohere with animal data, showing the dependency of fear- and fear-extinction memory consolidation on the specific neurophysiological properties of REM sleep (Datta & O'Malley, 2013; Popa, Duvarci, Popescu, Léna, & Paré, 2010).

Although relatively few studies have addressed the issue of REM-related memory reprocessing, researchers speculate that REM sleep facilitates the neural reorganization of emotional memories originally processed by the amygdala and related subcortical structures into a widely distributed neocortical network. According to these lines of thought, the reprocessing of emotional memories during sleep leads to the attenuation of the affective intensity of the original event (Levin & Nielsen, 2007; Walker & van der Helm, 2009). The mechanism of sleep and especially REM-related emotional information processing is still unclear. Synchronized neural activity between the amygdala and the neocortex (Paré, Collins, & Pelletier, 2002), low noradarenergic tone facilitating affective "recalibration" and regulation (Walker & van der Helm, 2009) and medial prefrontal inhibition on amygdala activity (Levin & Nielsen, 2007) were considered to be the neural underpinnings of REM related emotional reprocessing and affective regulation. Future studies transcending the traditional correlational methods might address the plausibility of these assumptions.

Chapter 4. New advances in dream research: the neuroscience of dreaming

The discovery of REM sleep and concomitant mental phenomena in 1953 (Aserinsky & Kleitman, 1953) initiated a series of research that related eye-movements to mental oneiric experience. However, these findings were far from being conclusive, and due to the lack of advanced neuroscientific methods, after approximately a decade, the attempts to characterize the neural underpinnings of dreaming began to fade away from the horizon of dream research. The specific features of dream experiences were understood as relating to the neurophysiological properties of REM sleep (Hobson, 1988) and the fine-graded changes and transient events of different sleep stages were not taken into consideration for the purpose of bridging the abyss between the neural and the mental level.

This section will summarize the most recent brain imaging and electrophysiological findings regarding the neural background of dreaming. I will discuss some of the most relevant differences between waking and dreaming consciousness, and show that dreaming is a form of mental (reality) simulation with a first person perspective, that might have adaptive roles in testing alternative behaviors and preparing the organism for future scenarios. I will discuss the emotional aspects of dreaming, and finally, introduce the topic of the empirical studies: the intense dream experiences in nightmare disorder, the most prevalent disorder of dreaming.

4.1. The emergence of dreams: different routes of activation

Until the development of brain imaging techniques, the most influential model for the emergence of dreams was the activation-synthesis model of dreaming proposed by Hobson and McCarley (Hobson & McCarley, 1977). According to their theory, dreams arise from the activation of primary sensory cortices triggered by ascending cholinergic brainstem/pontine bursts in REM sleep (PGO activity). The chaotic activation of sensory areas results in hallucinatory perceptual experiences that are "interpreted" as real events, and synthesized into a narrative structure by forebrain, higher-order neural networks. This way, dreams are considered to be the mental epiphenomena of cortical activation and synthesis, induced primarily by REM specific PGO bursts. A second postulate of the model is that the qualitative aspects of dreaming (bizarreness, discontinuities, lack of self-reflection and logical reasoning) are related to the deactivation of monoaminergic neurotransmission, and to the imbalance of cholinergic and monoaminergic influences. According to this theory, the deactivation of

serotonergic and noradrenergic ascending pathways reduces the signal-to-noise ratio and produces the failure to inhibit irrelevant associations, as well as the impairment of selective attention and more focused higher-order cognitive processes (Hobson, Hoffman, Helfand, & Kostner, 1987).

Among the several critical remarks against the activation-synthesis hypothesis the strongest turned out to be the observation that REM sleep and bursts of eye movements (the visible signs of PGO activity) are not a necessary condition for dream experiences (Solms, 2011). For instance, the cessation of REM sleep in pathological cases did not cause the cessation of dreaming, while specific lesions in cortical areas, especially in the temporo-parietal junction, resulted in the complete loss of dream experiences that were not explained by impaired performance in memory acquisition and recall (Solms, 2000). In contrast to the assumptions of the activation-synthesis hypothesis, subjects with lesions in the primary visual cortex did not report the cessation of visual dreaming, suggesting that dream experiences might not arise from a "bottom-up" direction resembling the neural underpinnings of perception (Solms, 2000). The more pronounced activation of secondary sensory areas, as well as of associative cortical structures during REM sleep, suggest that higher-order cortical structures and the "top-down" pathways seem to play a major role in the generation of dreams (Braun et al., 1997). Finally, specific antidepressants that cause the suppression of REM sleep do not decrease dream reports or seem to influence the qualitative aspects of dreaming (Oudiette et al., 2012).

As we have seen in the previous sections, arousals activating the cortex can occur in NREM sleep as well, and cortical activations involving wake-like oscillatory patterns can give rise to mental experiences during sleep (Conduit et al, 1997). These activating influences can originate from different sources and might result in different patterns of cortical activations. Since neuroimaging during sleep is still a methodologically challenging task, our knowledge about the cerebral functions during this state is mainly restricted to the differences between NREM and REM periods.

4.2. Brain imaging findings in NREM and REM sleep

In coherence with the decreased levels of vigilance and conscious awareness, there is a marked attenuation in brain energy metabolism after falling asleep. During the transition from wakefulness into light NREM sleep, reduction in pontine, thalamic, frontal and parietal cerebral blood flow were reported, but cerebral blood flow in midbrain structures resembled

that of waking levels (Kajimura et al., 1999). Relative to wakefulness, cerebral blood flow is reduced to 5-10 % during Stage 2 (Maquet et al., 1992) and to 25–40 % during SWS (Braun et al., 1997). More recent studies investigated the transient events during NREM sleep by sleep EEG coupled fMRI recording, and showed that transient events during NREM sleep, such as spindles and slow oscillations were associated with increased activity in hippocampal, thalamocortical and neocortical structures (Dang-Vu et al., 2008; Schabus et al., 2007). These findings are in line with the previously discussed considerations (see sections 2.4 and 3.2) that transient, phasic events are related to information-processing during NREM sleep.

Brain imaging data during REM sleep are mainly restricted to epochs containing bursts of eye movements, the so-called phasic periods of REM sleep. Cerebral blood flow during REM sleep resembles levels of wakefulness, with increased blood flow in the pons, thalamus, amygdala, hippocampus, anterior cingulate and the ventromedial prefrontal cortex (Maquet et al., 1996). Nevertheless, the distribution of regional brain activity differs from wakefulness: while limbic and paralimbic regions show enhanced activations, the dorsolateral prefrontal, the parietal and the posterior cingulate cortex as well as the precuenus seem to be deactivated during REM periods (Maquet et al., 1996). The intense activation of the amygdala and related ventromedial prefrontal structures, and the selective deactivation of the dorsolateral prefrontal cortex was supposed to be the background of the pronounced emotional tone and the impairment of self-reflective and executive functions characterizing dream experiences (Muzur, Pace-Schott, & Hobson, 2002).

While these important studies completed our understanding about the region-specific cortical activations that characterize and differentiate sleep stages and wakefulness, future studies might address the neural activation patterns heralding spontaneous and evoked transient events, as well as their relationship to information processing during NREM and REM sleep.

4.3. The electrophysiological correlates of dream recall

While brain imaging studies focused mainly on the neural activation patterns of different states of vigilance, a few sleep EEG studies aimed at characterizing the electrophysiological correlates of successful dream recall. Marzano and colleagues (Marzano et al., 2011) showed that enhanced frontal theta power during REM, and reduced alpha activity in right temporal sites during NREM sleep were related to successful dream recall after morning awakenings. Another study found different electrophysiological markers

associated with dream recall: Chelappa and colleagues reported reduced delta and spindle activity during NREM and increased high alpha and beta activity during REM sleep prior to successful dream recall, indicating that microarousals and wake-like oscillations during sleep might be associated with dream experiences (Chellappa, Frey, Knoblauch, & Cajochen, 2011). This resembles the findings of an earlier study that examined spectral power and dreaming during anesthesia, and reported fewer spindles and increased high frequency activity in relation to dream reports (Leslie et al., 2009). Although the discrepancies between these studies and that of Marzano and colleagues might have been related to methodological differences, they may also indicate that dream generation can stem from different kinds of cortical activations. Theta activity during REM sleep is predominant during phasic REM periods, while high alpha and beta oscillations are more dominant during tonic REM sleep (Waterman et al., 1993). Similarly, different oscillatory patterns can characterize NREM sleep in the ascending and descending slopes, but, unfortunately, these studies treated NREM and REM periods as homogeneous processes.

Dream reports were also related to arousal processes during sleep, especially NREM sleep (Conduit et al., 1997; De Gennaro et al., 2010), and to the bursts of eye movements during REM sleep (Stuart & Conduit, 2009; Takeuchi et al., 2001). Arousal processes involving wake-like oscillations during sleep might increase the intensity, as well as the recall of oneiric experience, but on the other hand, sleep-specific oscillations associated with "internal" information-processing may also increase dream generation. For instance, rhinal-hippocampal connectivity was associated with high dream recall in a group of epileptic patients (Fell et al., 2006), and dreaming about a previously practiced task was related to improved performance of the task at retest sessions (Oudiette et al., 2011; Wamsley, Tucker, Payne, Benavides, & Stickgold, 2010).

Although dream generation is obviously not equivalent to dream recall, recent studies on subjects suffering from REM behaviour disorder, sleep walking or sleep terrors clearly indicate that specific movements (dream-enacting behaviours) during sleep correspond significantly to dream reports after awakenings (Leclair-Visonneau, Oudiette, Gaymard, Leu-Semenescu, & Arnulf, 2010; Oudiette et al., 2009; Uguccioni et al., 2013).

4.4. Dream consciousness: Simulations of reality

Dreams are defined as the mental experiences during sleep, from vague thought-like events to the most complex and visually intense forms of oneiric experience. The theoretical

assumptions about the nature, as well as the function of dreams are so diverse that they resemble the multiplicity of dream experiences. Since dreams are the products of conscious processes during sleep, an exclusive explanation for their function might be misleading. Somewhat similar to attempting to explain waking consciousness as having only one function! More effective approaches focus on the differences between dreaming and waking consciousness (Hobson, 2009), or in contrast, on the similarities between these states (Domhoff, 2011), as well as on the building blocks of dream scenarios, including memory elements (Nielsen, Kuiken, Alain, Stenstrom, & Powell, 2004; Nielsen & Stenstrom, 2005), external stimulation (Schredl et al., 2009) or waking emotional concerns (Cartwright, Agargun, Kirkby, & Friedman, 2006).

Researchers focusing on the relationship between sleep and memory consolidation suggest that dreams are the mental reflection of memory reprocessing during sleep. Although sleep seems to be related to memory reactivation during sleep (Wamsley et al., 2010, 2010) – with the exception of trauma-related recurrent nightmares, – dreams rarely replay the previously experienced events in their original form (M. J. Fosse, R. Fosse, Hobson, & Stickgold, 2003). These authors suggest that dreams do not reflect merely the reactivation, but instead the integration of recently encoded memories into distributed general semantic networks (Stickgold, 2002).

Contrarily, other researchers suggest that dreams play a role in the anticipation of future events, providing mental simulation of potential future threats (Revonsuo, 2000) or, more generally, the mental (and neural) activation of basic behavioral programs (Hobson, 2009). These considerations resemble earlier assumptions suggesting that the function of dreaming is the genetic programming of the behavioral and mental repertoire of the personality (Jouvet, 1991), or more recent assumptions relating the nature and functions of dreaming to the functions of mammalian play (Bódizs, 2000).

Reintegration of past, and anticipation of future events are not exclusive processes but seem to be the two sides of the same coin since the integration and constant updating of self-relevant memory representations facilitate the preparation of flexible reactions in response to future events. Moreover, remembering the past and imagining the future seem to be underlain by a very similar neural machinery (Schacter et al., 2012; Schacter, Addis, & Buckner, 2007). Dream scenarios are influenced by past events, current emotional concerns and future expectations (Nielsen & Stenstrom, 2005), and thus might constitute a model, a simulation of the reality depicting alternative events, behavioral reactions and possible outcomes, but these models are characterized by a much higher degree of freedom regarding their associative

complexity in comparison to wakeful thoughts and day-dreaming. Consequently, dreaming is a mental space, where recently reactivated and integrated memories related to skills, episodic and sometimes highly intense emotional events can be used as the building blocks of self-centered reality simulations. In parallel with the processing of internally generated mental representations, dreams might also incorporate external stimuli transmitted by sensory afferents that may also modulate and to some extent constrain the ongoing mental simulation. These considerations implicate that dreams can facilitate the preparation of the organism for future events and the rehearsal of relevant behavioral programs. Although there is some pilot data, indicating a beneficial role of dreams in this regard (Erlacher & Schredl, 2010; Wamsley et al., 2010), future studies with larger sample sizes are warranted to support or refute these assumptions.

4.5. Dream disturbances in parasomnias and sleep-wake transitions

Alterations in the qualitative aspects, such as the bizarreness, vividness and emotional tone of dreaming seems to be related to atypical sleep patterns (Nielsen & Zadra, 2011). Although dreaming might occur outside of REM sleep (Oudiette, 2012), the most intense forms of dreaming generally appear during this sleep stage (Fosse et al., 2004). Accordingly, an earlier study showed increased negative dream affect and dream bizarreness in narcolepsy - a sleep disorder characterized by increased REM propensitys (Schredl, 1998). A more recent study showed that narcoleptic patients in comparison with controls report longer and more complex dreams in the first REM period (Cipolli et al., 2008; Mazzetti et al. 2010).

Sleep paralysis is a relatively frequent condition in narcoleptic patients with cataplexy (DSM-IV, 2000). During sleep paralysis the subject may be partially aware of the surrounding environment, however is unable to move in spite of the intention to do it, and often experiences highly negative, hallucinatory-like mental experiences (Terzaghi, Ratti, Manni, & Manni, 2012). Sleep paralysis seems to be a "hybrid state" between REM sleep and wakefulness: while the former is responsible for motor atonia and hallucinatory-like dream experiences, the latter is reflected by increased sensory processing. Accordingly, polysomnographic data indicates that sleep paralysis is characterized by the mixture of REM-like (theta activity, sawtooth waves, muscle atonia) and wake-like EEG activity (alpha power) (Dyken, Wenger, & Yamada, 2006; Terzaghi et al., 2012).

Intense, complex and aggressive dream experiences are frequent phenomena in REM behavior disorder (RBD), characterized by dream enacting behaviors (Uguccioni et al., 2013).

In RBD, due to the failure of the inhibition of spinal motoneurons, activity in the motor cortex – presumably related to dreamed movements (Leclair-Visonneau et al., 2010) – elicits diverse movements during REM sleep (ICSD-II, 2005). Moreover, dysphoric dreams can be present in NREM parasomnias as well, such as sleepwalking and sleep terrors (Zguccioni et al., 2013). Recently, sleep terrors were also characterized by the coexistence of sleep-like and wake-like cortical activity (Terzaghi et al., 2012).

Although, the cortical correlates of such abnormal sleep phenomena warrants further investigations, these findings indicate that the dissociation and imbalance in the components of different sleep/wake states might constitute the physiological background of atypical mental experiences during sleep. This seems to be the case for non-clinical mental phenomena during sleep, such as lucid dreaming (Tyson, Ogilvie, & Hunt, 1984; Voss, Holzmann, Tuin, & Hobson, 2009) or mental experiences during wake-sleep transitions (Nielsen & Zadra, 2011). The analysis of electroencephalographic oscillations based on polysomnographic recordings not only fosters our understanding about the neurophysiology of sleep disorders, but also might help to understand the atypical oneiric experiences that occur during sleep-state transitions and abnormal sleep patterns.

Although nightmare disorder in comparison with the above parasomnias, is a rather prevalent sleep disorder (Spoormaker et al., 2006) it was scarcely investigated from the perspective of experimental sleep research or sleep medicine. In the following chapter I present a series of studies that aimed to fill this gap by examining waking cognitive functions and altered sleep patterns in nightmare disordered with.

Part 2. Nightmare disorder: Empirical investigations

Chapter 1. The intensification of dreaming: nightmare disorder

Nightmares are highly intense and negatively toned mental experiences during REM or light NREM sleep (DSM-IV, 2000). These perceptually vivid, real-like experiences often depict long and complex dream scenarios involving fear, anxiety or other negative emotions (Nielsen & Zadra, 2011), and usually, but not mandatorily, end in abrupt awakenings (Spoormaker et al., 2006). Nightmare disorder is described as the condition of experiencing nightmares on a weekly basis. Moreover, after awakening from a nightmare, the subject is fully alert and can recall the nightmarish experience. The nightmares cause emotional and cognitive difficulties during waking, and finally, the nightmares do not occur exclusively during the course of another mental disorder (DSM-IV, 2000).

Although the etiology of nightmares is still far from being clarified, recent data has questioned the general view that considers frequent nightmares as secondary symptoms of an underlying mental disorder (Spoormaker et al., 2006). This assumption led to the under-diagnosis of nightmares, and more unfortunately, to the under-treatment of this condition (Schredl, 2010). Nightmares are indeed overrepresented in psychiatric populations, especially in PTSD, where trauma-related recurrent nightmares constitute one of the marked features of the disorder (Swart, van Schagen, Lancee, & van den Bout, 2013). However, the high co-morbidity of mental complaints and nightmares does not implicate a causal relationship between these phenomena. While frequent nightmares and mental complaints may exacerbate the severity of "the waking", as well as of the "the sleep" symptoms, research indicates that nightmare disorders and waking mental disorders stem form different pathological and etiological processes (see the introduction of Study 2 for a more detailed description and: Coolidge, Segal, Coolidge, Spinath, & Gottschling, 2010; Lancee, Spoormaker, & van den Bout, 2010; Spoormaker & Montgomery, 2008).

Nightmares are clearly a specific case for the intensification of the dreaming process. Accordingly, subjects characterized by frequent nightmares in certain life-periods, also report vivid, bizarre, complex and unusual, but not necessarily nightmarish dreams in non-symptomatic periods (Hartmann, 1989). This indicates that subjects who are prone to nightmares are characterized by intense dream experiences. Several personality measures

involving mainly neuroticism and dissociative tendencies were – although moderately – related to nightmares (Levin & Nielsen, 2007). In an integrative attempt, Hartmann aimed at characterizing the personality of frequent nightmare sufferers by the concept of thin-boundaries. Thin-boundaries describe a personality profile characterized by high vulnerability, openness, and the inability to distinguish between intrapsychic, mental states, as well as by the immersion in waking imaginative and dream experiences (Hartmann, 1989).

While Hartmann's approach focuses on trait-like aspects, other researchers also pointed to the state-specific factors of frequent nightmarish experiences (Levin, Fireman, Spendlove, & Pope, 2011; Schredl, 2003). In their multi-level, integrative model, Levin and Nielsen (2007) conceptualize nightmares as the results of increased trait-specific affect distress and state-specific affect load. Moreover, they present a neurocognitive model that describes nightmares as the mental reflections of unsuccessful fear-extinction processes. According to their model, nightmares reflect the intensification of emotional memories supported by amygdalar and subcortical activations. Due to impaired hippocampal functions, the network fails to provide novel spatio-temporal contexts for emotional memories, and because of dysfunctional (medial) prefrontal functions, the amygdalar activity processing emotional reactions is not efficiently inhibited. Levin and Nielsen argue that the failure to provide novel contexts and to reduce the emotional intensity reactivated by emotional memories results in impaired fear-extinction during sleep (Levin & Nielsen, 2007). Levin and Nielsen's neurocognitive model is based mainly on experimental findings and clinical observations regarding subjects with PTSD, and although the authors view nightmarish experiences as a continuum from "normal", non-pathological dysphoric dreaming to the most severe cases of traumatic nightmares, it is still not clarified whether the assumptions of the model can be generalized in relation to nightmare sufferers without PTSD.

Another important feature of nightmare disorder is altered subjective sleep quality (Lancee et al., 2010). Levin and Nielsen's above model would implicate that sleep disruption is caused by emotional over-activation. The activation of limbic and paralimbic structures during sleep were suggested to be related to arousals and sleep disruption (Nofzinger and Maquet, 2011). However, the extent and nature of sleep disruption in nightmare sufferers was only scarcely elucidated by objective sleep assessments (See the introduction of Study 2, 3 and 4; and Spoormaker et al., 2006).

Impaired emotional information processing and the nature of disrupted sleep in subjects with frequent nightmares remained issues that we aimed to examine within the framework of my PhD thesis.

1.1. Main objectives and thesis points

While the altered neural circuitry underlying impaired information-processing and disrupted sleep in PTSD was elucidated in several studies (see Levin & Nielsen, 2007; Walker & van der Helm, 2009 for more extensive reviews), the neurocognitive characterization of nightmare subjects without co-morbid PTSD (idiopathic nightmare sufferers) has not been accomplished to date. We have seen that several studies suggest a role for sleep, especially REM sleep, in emotion regulation (Pace-Schott et al., 2009; Spoormaker et al., 2012; Walker & van der Helm, 2009; Yoo et al., 2007), and nightmares were conceptualized as the mental reflection of impaired emotional regulation during sleep (Levin & Nielsen, 2007). If we assume that nightmare subjects are characterized by altered emotional information-processing due to impaired prefrontal inhibitory functions, we may expect that these subjects will show impaired information-processing in response to emotionally toned stimuli during the waking state as well. Therefore, one of our aims was to test these assumptions by comparing the performance of a group of nightmare subjects with that of healthy controls in different neuropsychological tasks involving executive control processes in the presence or absence of emotional stimuli. In line with the hypotheses presented by Levin and Nielsen regarding impaired inhibitory functions, we applied a series of neuropsychological tests that are known to activate prefrontal and fronto-limbic neural circuitry.

Our second aim was to characterize the polysomnographic features of nightmare disorder based on full-night, undisturbed laboratory sleep recordings. Although frequent nightmares were related to poor subjective sleep quality in several studies (Krakow, 2006; Li et al., 2010; Schredl, Schafer, Weber, & Heuser, 1998; Schredl, 2003), objective sleep parameters were scarcely investigated and only with studies involving low sample sizes (Fisher, Byrne, Edwards, & Kahn, 1970; Germain & Nielsen, 2003; Newell, Padamadan, & Drake, 1992). This is a considerable shortcoming in the field of sleep research in light of the extensive literature regarding macrostructural, as well as more fine-grained polysomnographic analyses of different sleep disorders (Bruni et al., 2008; Chou et al., 2011; Guilleminault, Kirisoglu, da Rosa, Lopes, & Chan, 2006; Nardone et al., 2013; Riemann et al., 2010; Terzano et al., 2006). Therefore, in our subsequent studies we examined the objective sleep parameters of a group of nightmare and control subjects with different methods, involving standard sleep scoring, sleep-microstructure and quantitative EEG analyses. Since important findings regarding the relationship between nightmare disorder and our dependent variables of

interest might be masked by the confounding effects of waking psychopathological symptoms, we selected groups of nightmare subjects without prior or present history of waking psychopathology. Furthermore, we controlled the effects of sub-clinical psychopathological symptoms with statistical methods in all of the studies presented below.

1.1.1. Main objectives

1. To examine the behavioral performance of a group of nightmare subjects (NMs) and healthy control subjects (CTLs) in an Emotional Go/NoGo task, Emotional and non-Emotional Stroop task, and Verbal Fluency task.

2. To examine the sleep architecture (sleep macrostructure) in NMs in comparison with that of CTLs, based on full-night sleep polysomnography.

3. To analyze the nature of arousal processes (sleep microstructure) during NREM and REM sleep in NMs and CTLs. In NREM sleep, this was accomplished by the scoring of the CAP, while in REM sleep, by the visual scoring of arousals.

4. To examine the characteristic EEG oscillatory patterns in NMs and CTLs based on the respective relative spectral power analyses of their NREM and REM sleep periods.

5. In order to investigate the relationship between nightmare frequency and disturbed sleep, we aimed to control for the effects of waking anxious and depressive symptoms.

1.1.2. Thesis points

1. Impaired executive functions in subjects with frequent nightmares (Study 1).

NMs exhibited lower performance, reflected by increased reaction times in and Emotional Go/NoGo task that involved emotional stimuli as distractors, and by increased reaction times in Emotional Stroop tasks. Regarding non-emotional, Color-Word Stroop tasks no significant differences emerged between the two groups. NMs showed impaired performance in the Verbal Fluency task, reflected by slightly lower fluency and a considerably higher number of perseveration errors.

2. Impaired executive functions in NMs are not unequivocally mediated by waking anxiety (Study 1).

Although higher reaction times in the Emotional Go/NoGo task were mediated by higher anxiety scores in NMs, increased reaction times in the Emotional Stroop task, and lower performance in Verbal Fluency task were not influenced by the trait measure of anxiety.

3. NMs, in comparison with CTLs, are characterized by altered sleep architecture reflecting impaired sleep continuity (Study 2).

NMs exhibited impaired objective sleep quality in comparison with CTLs. Reduced sleep efficiency, increased wakefulness after falling asleep, and reduced percentage of SWS characterized the sleep macrostructure of NMs. NMs showed a trend of increased sleep latency and a higher rate of Stage 1 sleep. Furthermore, NMs were characterized by an increased number of nocturnal awakenings in Stage 2 sleep. These differences were independent of the effects of higher levels of waking anxious and depressive symptoms in the nightmare group.

4. Increased REM percentage in NMs is mediated by enhanced negative emotionality (Study 2).

NMs, in comparison with controls, exhibited increased rates of REM sleep, but this difference turned out to be the function of heightened trait anxiety and depressive symptoms in the nightmare group.

5. NMs are characterized by abnormal arousal processes during NREM sleep (Study 3).

The NMs group exhibited reduced amounts of synchronized CAP A1 subtype and increased amounts of A2 and A3 subtypes, as well as longer duration of CAP A phases in comparison with CTLs. These differences were not influenced by the confounding factors of anxious and depressive symptoms. REM arousals did not differentiate the two groups.

6. NMs are characterized by wake-like oscillatory activity during sleep, especially in REM sleep, and, to some extent, during NREM sleep (Study 4).

NMs, in comparison with CTLs, exhibited increased relative high alpha (10-14.5 Hz) power in REM, and a trend of enhanced fronto-central low alpha (7.75-9 Hz) power in NREM sleep. High REM alpha and low NREM alpha were strongly correlated in the nightmare-, but not in the control group, suggesting that enhanced alpha activity is a characteristic feature of the pathophysiology of nightmare disorder modulated in a sleep-state dependent manner, exhibiting higher frequency components in REM, and lower ones in NREM sleep. High REM alpha activity peaked at posterior locations, resembling the topographical distribution and frequency range of wake-like alpha activity.

Chapter 2. Studies

Study 1

Simor, P., Pajkossy, P., Horváth, K., & Bódizs, R. (2012). Impaired executive functions in subjects with frequent nightmares as reflected by performance in different neuropsychological tasks. *Brain and Cognition*, *78*(3), 274–283.

Study 2

Simor, P., Horváth, K., Gombos, F., Takács, K. P., & Bódizs, R. (2012). Disturbed dreaming and sleep quality: altered sleep architecture in subjects with frequent nightmares. *European archives of psychiatry and clinical neuroscience*, *262*(8), 687–696.

Study 3

Simor, P., Bódizs, R., Horváth, K., & Ferri, R. (2013). Disturbed dreaming and the instability of sleep: altered nonrapid eye movement sleep microstructure in individuals with frequent nightmares as revealed by the cyclic alternating pattern. *Sleep*, *36*(3), 413–419.

Study 4

Simor, P., Horváth, K.,Ujma, P., Gombos, F., Bódizs, R. (2013) Fluctuations between sleep and wakefulness: wake-like features indicated by increased EEG alpha power during different sleep stages in nightmare disorder. Biological Psychology (in press).

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Impaired executive functions in subjects with frequent nightmares as reflected by performance in different neuropsychological tasks

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ABSTRACT

Nightmare disorder is a prevalent parasomnia characterized by vivid and highly unpleasant dream experiences during night time sleep. The neural background of disturbed dreaming was proposed to be associated with impaired prefrontal and fronto-limbic functioning during REM sleep. We hypothesized that the impaired prefrontal and fronto-limbic functioning in subjects with frequent nightmares would be reflected at the behavioral level during waking tasks as well. 35–35 Subjects with frequent nightmares and matched controls participated in *Study 1*, involving an Emotional Go/NoGo, an Emotional Stroop task, and a Verbal Fluency task. Nightmare subjects exhibited longer reaction times in the Emotional Go/NoGo and Emotional Stroop tasks. Moreover, they committed more perseveration errors and showed less fluent word generation in the Verbal Fluency task. Nightmare subjects showed an overall slowing irrespective of the valence of the stimuli. While the effects of sleep quality and waking anxiety were associated to these deficits in some cases, these factors could not solely explain the difference between the two groups. In *Study 2*, 17 subjects with frequent nightmares and 18 controls were compared by a Color-word and an Emotional, block design Stroop task in order to avoid the slow effects of emotional interference potentially caused by previous items. Nightmare subjects were characterized by an overall slowing in the Emotional Stroop task, irrespective of the valence of the stimuli. In the Color-word Stroop task, nightmare subjects were not significantly slower in comparison with controls. Our results suggest that individuals with frequent nightmares are impaired in executive tasks involving the suppression of task-irrelevant semantic representations.

1. Introduction

Idiopathic nightmare sufferers frequently – at least once a week – experience visually vivid, intense and disturbing dreams that involve fear, anxiety, anger, sadness, disgust or other unpleasant emotions (Nielsen & Zadra, 2010). According to the *International Classification of Sleep Disorders*, 2nd edition (ICSD-II, 2005) these dream disturbances end in abrupt awakenings. However, research on the nature of bad dreams (disturbing dreams that do not awaken the dreamer) suggests that the awakening criterion for nightmare disorder is unnecessarily narrow (Blagrove, Farmer, & Williams, 2004; Spoormaker, Schredl, & van den Bout, 2006; Zadra & Donderi, 2000). Others proposed that *disturbed dreaming* forms a continuum from normal dysphoric dreaming to post-traumatic nightmares where the pressure for awakening varies as a function of situational and dispositional factors as well (Levin, Fireman, Spendlove, & Pope, 2011; Levin & Nielsen, 2007).

Disturbed dreaming is associated with a variety of psychopathological conditions (Agargun et al., 2007; Besiroglu, Agargun, & Inci, 2005; Krakow et al., 2002; Roberts & Lennings, 2006; Semiz, Basoglu, Ebrinc, & Cetin, 2008). These findings provide valuable data on the comorbidity of mental disorders and dream disturbances, but cannot reveal the mechanisms and emergence of disturbed dreaming *per se* because of the confounding effects of waking pathology. While the psychiatric perspective assumes that nightmares and bad dreams are "mere" symptoms of an underlying mental disorder, recent findings suggest the nature of this relationship to be more complex (Lancee, Spoormaker, & van den Bout, 2010; Spoormaker & Montgomery, 2008). For instance, some studies have failed to detect a direct association between psychopathology and nightmare frequency (Levin & Fireman, 2002; Levin & Nielsen, 2007), especially when mental disorders were examined among a sample of frequent nightmare reporters (instead of the inverse, investigating nightmare frequency in psychiatric populations) (Lancee et al., 2010). The association between nightmares and mental complaints seems to be mediated by *nightmare distress*, the affective and cognitive impact of nightmares on daytime

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functioning (Belicki, 1992; Blagrove et al., 2004). Furthermore, nightmare frequency was shown to be a stable disposition with high genetic heritability, which was independent of the genetic influences of general waking anxiety (Coolidge, Segal, Coolidge, Spinath, & Gottschling, 2010).

These findings suggest that instead of the prevailing view of being a symptom of waking dysfunctions, frequent nightmares should be conceptualized as a specific sleep disorder (Spoormaker et al., 2006). Despite their relatively high prevalence (4–5%) in the general population (Nielsen & Zadra, 2000), the underlying mechanisms of nightmare disorder were only scarcely investigated (Germain & Nielsen, 2003; Nielsen, Paquette, Solomonova, Lara-Carrasco, Popova, et al., 2010; Nielsen, Paquette, Solomonova, Lara-Carrasco, Colombo, et al., 2010).

Recent findings indicate that sleep is intimately related to the processing and probably to the regulation of affect-laden memories (Walker, 2009). Studies examining sleep-dependent emotional memory consolidation indicate that emotional processing may especially benefit from REM sleep (Nishida, Pearsall, Buckner, & Walker, 2009; Wagner, Gais, & Born, 2001; Wagner, Hallschmid, Rasch, & Born, 2006). Moreover, REM sleep involves the intense activation of an emotional network comprising the amygdala, the anterior cingulate and the ventromedial prefrontal cortex (Desseilles et al., 2006; Maquet et al., 2005; Muzur, Pace-Schott, & Hobson, 2002). Nightmares generally – but not exclusively – occur during REM sleep (Spoormaker et al., 2006) suggesting that disturbed dreaming is an example of dysfunctional emotional processing during REM sleep. In their integrative model, Levin and Nielsen (2007) proposed that nightmares may be the consequence of the inefficient down-regulation of amygdalar over-activation, and a failure to provide new spatiotemporal contexts for the fearful emotional memories processed during REM sleep. According to the model, the former dysfunction is related to impairments in the ventromedial prefrontal and the anterior cingulate cortex, while the latter is related to impaired hippocampal functioning. Furthermore, these impairments are related to the failure in creating adaptive fear-extinction memories leading to emotional dysregulation during sleep (Levin & Nielsen, 2007; Levin & Nielsen, 2009; Nielsen & Levin, 2007).

Recent findings on healthy subjects support the idea that sleep and especially REM sleep has an important role in the generalization and consolidation of fear-extinction memories, respectively (Pace-Schott et al., 2009; Spoormaker et al., 2010). Nevertheless, no prior studies have examined fronto-limbic abnormalities and/or related executive functions in subjects with frequent nightmares. We hypothesized that if nightmare subjects were characterized by impaired prefrontal and fronto-limbic functions during REM sleep, alterations in these networks would be reflected during waking tasks as well. Therefore, the aim of our experiments was to test the neurocognitive model of Levin and Nielsen (2007) through different neuropsychological assessments of executive functions.

2. Study 1

In order to examine the behavioral effects of impaired prefrontal and fronto-limbic functioning in subjects with frequent nightmares, we applied a series of neuropsychological tasks that were previously shown to rely on these brain areas. Executive functions or cognitive control processes involving the manipulation of items in working memory or the inhibition of prepotent but inappropriate response tendencies are considered to activate mainly prefrontal and related neural structures (Botvinick, Cohen, & Carter, 2004; Bush, Luu, & Posner, 2000; Dillon & Pizzagalli, 2007; Garavan, Ross, Murphy, Roche, & Stein, 2002; Rueda, Posner, & Rothbart, 2005). In case of emotional information, such functions seem to activate more specifically the ventrolateral and the ventromedial prefrontal, as well as the rostral anterior cingulate cortex (Bremner et al., 2004; Bush et al., 2000; Chiu, Holmes, & Pizzagalli, 2008; Lane et al., 1998; Wingenfeld et al., 2009).

In light of these findings and based on Levin and Nielsen's (2007) neurocognitive model presuming fronto-limbic impairments as the neural background of disturbed dreaming, we anticipated that the nightmare (NM) group – in comparison with the controls (CTL) – would show worse performance in different executive tasks, and especially in those that require the processing of negative emotional information. In order to test this hypothesis we applied three well-characterized paradigms, the Emotional Go/NoGo task, the Emotional Stroop task and the Letter-and Category Fluency task.

The Go/NoGo task is a frequently used paradigm to assay motor response inhibition to perceptual stimuli (Aron et al., 2007). The task involves the presentation of a series of "Go" cues to which subjects have to press a button as quickly as possible, and "NoGo" cues that require the inhibition of this motor response. In the emotional version of this task (Reynolds & Jeeves, 1978), emotionally salient (e.g. happy and/or angry faces) perceptual stimuli are interspersed with emotionally neutral stimuli (neutral faces). The Emotional Go/NoGo task assesses response inhibition in the context of affective information processing, allowing the investigation of perturbations in emotional processing. Previous studies indicate that the Emotional Go/NoGo task activates the ventrolateral prefrontal cortex in relation to response inhibition, while the ventromedial prefrontal cortex and the rostral anterior cingulate cortex are activated in relation to the processing of negative emotional information (Chiu et al., 2008; Dolcos, Kragel, Wang, & McCarthy, 2006; Dolcos & McCarthy, 2006; Hare & Casey, 2005). Since the proper functioning of these networks are reflected by the behavioral measures of reaction time and accuracy (Hare & Casey, 2005; Waters & Valvoi, 2009), *we hypothesized that NM subjects – in comparison with CTLs – would be characterized by longer reaction times and more false alarms, especially in the condition involving the inhibition of negative emotional information (Neutral Go/AngryNoGo).*

The Emotional Stroop task is a widely used tool to investigate attentional bias and emotional interference caused by emotionally salient stimuli (MacLeod, Mathews, & Tata, 1986). The task involves the presentation of neutral and emotionally charged stimuli (e.g. neutral and emotionally negative words) with different colors, and participants are asked to press the button corresponding to the color of the word as quickly as possible. Since the semantic content of the words are irrelevant for the task, subjects may suppress distracting semantic representations, and focus only on the perceptual information (the color) of the presented words. Emotionally charged words may produce stronger interference, since they capture the attention more effectively than neutral words, and may also require additional cognitive processes in order to suppress the semantic content and also to regulate evoked emotional reactions. Consequently, reaction times are generally longer for affect-laden words, especially in subjects who are characterized by emotional dysregulation (Becker, Rinck, Margraf, & Roth, 2001; Bremner et al., 2004; Hope, Rapee, Heimberg, & Dombeck, 1990; Mattia, Heimberg, & Hope, 1993). Brain imaging studies indicate that the Emotional Stroop task is associated with enhanced activation in the amygdala, the anterior cingulate cortex and the middle frontal gyrus (Bremner et al., 2004; Bush et al., 2000; Whalen et al., 1998; Wingenfeld et al., 2009). In light of these findings, *we expected that NM subjects – in contrast to CTLs – would exhibit worse performance in the Emotional Stroop task, reflected by longer reaction times and/or more errors in the trials involving negative emotional stimuli. In other words, we expected enhanced emotional interference in the nightmare in comparison with the control group.*

The Letter-and Category Fluency task is a classical neuropsychological task generally used to measure executive functions in different clinical settings (Baldo & Shimamura, 1998; Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001; Curtis et al., 1998; Lezak, 2004; Moritz et al., 2002). The task requires participants to generate as many different words as they can in 60 s, starting with a given letter (Letter Fluency) or belonging to a semantic category (Category Fluency). The task is considered to engage different cognitive processes such as working memory, cognitive flexibility and inhibitory control (Baldo, Schwartz, Wilkins, & Dronkers, 2006). Lower fluency and perseveration errors (repetitions) reflect executive dysfunctions. Performance in the Letter-and Category Fluency task was related to the frontal and the temporal cortex, respectively (Baldo et al., 2006), but other findings indicate that both areas are implicated in the letter-based and category-based word generation (Baldo & Shimamura, 1998; Schwartz, Baldo, Graves, & Brugger, 2003). Since the task is sensitive to a wide range of executive functions underlain by the prefrontal cortex, *we anticipated worse performance in the NM group in contrast to CTLs*.

Furthermore, since performance in these three tasks may be influenced by waking anxiety and sleep quality, we aimed to control the confounding effects of these factors as well.

2.1. Methods and materials

2.1.1. Participants

Participants (all native Hungarians) were selected from a large pool of undergraduate students attending to different introductory psychology courses at the Budapest University of Technology and Economics. First they completed an on-line questionnaire assessing dream quality and a variety of personality factors. Findings on the relationship between dream quality and personality were reported (Simor, Köteles, & Bódizs, 2011) and will be reported elsewhere. Dreaming-related questionnaires included the Dream Quality Questionnaire (DQQ) (Bódizs, Simor, Csóka, Bérdi, & Kopp, 2008), the Hungarian version of the Van Dream Anxiety Scale (VDAS-H) (Agargun et al.,1999; Simor, Kovács, et al., 2009) and a 7-point Likert scale with two items; one assessing the frequency of nightmares with awakenings, and the other the frequency of bad dreams without awakenings (0 – Almost never; 1 – once or twice a year; 2 – every 2–3 month; 3 – once in a month; 4 – twice a month; 5 – once a week; 6 – more than once a week). Subjects of the nightmare group were selected on the basis of the *International Classification of Sleep Disorders*, 2nd edition criteria and Levin and Nielsen's (2007) model of disturbed dreaming, including disturbed dreamers without abrupt awakenings. Moreover, after the first selection, participants kept a 2-week daily dream-log, and rated the emotional quality of their reported dreams based on the items of the DQQ (Bódizs et al., 2008). Subjects reporting one or more nightmares or bad dreams per week in the retrospective questionnaires and in the dream-logs were enrolled in the NM group, while individuals having less than two nightmares and bad dreams during the last year, and no nightmares and bad dreams at all in the 2-week dream-log period were enrolled in the CTL group. Subjects were thoroughly interviewed about their negative dream experiences and the content of their reported dreams. Those subjects who reported the onset of negative dream experiences in relation to a traumatic event or indicated that their reported dreams were related to a prior trauma (such as physical attack, accident, and sudden death of a close relative) were excluded from the study. Finally, 35 (21 female and 14 male) NM (M_{age} = 20.5 ± 1.8 y) and 35 (21 female and 14 male) CTLs (M_{age} = 20.1 ± 1.34 y) were selected. (The difference in age was not significant between the two groups: $F_{1,68}$ = 1.5 p = 0.23) None of the subjects reported prior neurological, psychiatric or sleep disorders or prior history of any chronic disease. NM subjects scored higher on the Nightmare Frequency Scale (NM: 5.52 ± 1.46 vs. CTL: 1.54 ± 0.66; $F_{1,68}$=, p < 0.0001), on the Bad Dream Frequency Scale (NM: 5.61 ± 1.48 vs. CTL: 1.77 ± 0.8; $F_{1,68}$=, p < 0.0001), on the Negative Dream Affect Scale of the DQQ (NM: 8.7 ± 0.75 vs. CTL: 4.4 ± 0.79; $F_{1,68}$ = 557.03, p < 0.0001) and on the VDAS-H (NM: 19.5 ± 7.6 vs. CTL: 0.26 ± 0.78; $F_{1,68}$ = 221.6, p < 0.0001), indicating at least moderately severe dream disturbances (Bódizs et al., 2008; Simor, Kovács, et al., 2009).

The study protocol was approved by the local ethical review board of the Budapest University of Technology and Economics. Subjects were told that the aim of the study was the investigation of the relationship between dreaming and cognitive processes. The subjects received partial credit points in the introductory psychology course as compensation for their participation. Written informed consent was obtained.

2.1.2. Procedures

Subjects completed the psychometric measures and neuropsychological tasks in a noise-attenuated room. The order of the tasks was fixed for all subjects.

2.1.2.1. Psychometric measures. The Dream Quality Questionnaire (Bódizs et al., 2008) includes 11 items assessing the tendency of experiencing nightmares with recurrent or non-recurrent content; the vividness, bizarreness and emotional load of dreams; the effect of dreams on daytime mood and the frequency of having night-terror-like symptoms. The measure contains three main components: the negative, positive and the neutral emotional aspects of dreams. According to previous results the DQQ proved to be a valid instrument measuring the above qualities of dreaming (Bódizs et al., 2008). Since the present study focused on the aspects of disturbed dreaming, we only analyzed the data regarding the Negative Dream Affect Scale of the DQQ.

The Van Dream Anxiety Scale (VDAS) (Agargun et al., 1999) provides information about nightmare frequency and dream anxiety (nightmare distress) caused by frightening dreams. The items of the self-rating scale are concerned with nightmare frequency and the maleficent effects of nightmares on daytime functioning. Items are weighted on a 0–4 scale and summed to yield a global VDAS score of 0–52. The Hungarian version of the scale proved to be a reliable (α = 0.96) and valid instrument in order to measure dream anxiety (Simor, Kovács, et al., 2009). Internal consistency of the VDAS was excellent in previous studies (α = 0.91) (Simor, Köteles, Sándor, Petke, & Bódizs, 2011).

In order to control for the effects of sleep quality, the Hungarian version of the *Groningen Sleep Quality Scale* (GSQS) (Simor, Köteles, Bódizs, & Bárdos, 2009) was used. The 14-item questionnaire measures the extent of subjective sleep fragmentation by a binary scale. The internal reliability and validity measures of the scale indicated that the questionnaire was an adequate tool for assessing subjective sleep quality (Simor, Köteles, et al., 2009).

The *STAI* (Spielberger, Gorsuch, & Lusgene, 1970) is a widely used self-report instrument that differentiates between the temporary condition of state anxiety and the longstanding quality of trait anxiety. We used the 20-item Hungarian version of STAI trait anxiety questionnaire (STAI-T) in order to assess general levels of anxiety (Sipos, Sipos, & Spielberger, 1994). The questionnaire proved to be a valid tool for the measurement of trait anxiety, showing excellent internal consistency in different studies (Köteles et al., 2011).

2.1.2.2. Emotional Go/NoGo task. In a computerized version of the Emotional Go/NoGo task we used pictures of faces with neutral, angry and happy facial expressions. 56 faces were selected from multiple open-source face-databases and were rated previously by 30 subjects. (These subjects where different from our study participants.) They indicated which expressions they thought a

particular face has and also estimated the typicality of that particular facial expression for the given emotion. We selected seven faces for every category with the best inter-rater agreement and highest typicality-ratings. These faces appeared on a screen against a black background during the task.

The task consisted of four blocks with 60 trials in each. In every trial, a randomly selected picture from one of the three facial-expression categories was presented. The four blocks differed in respect of which facial expression constituted a Go or a NoGo cue. In the first block during a Go trial a neutral face, whereas during a NoGo trial an angry face was presented. By contrast, in the second block neutral faces were designated as NoGo trials, and angry faces were set to Go trials. The design of the third and fourth block was analogous to the first two blocks except that here the angry faces were replaced by happy faces. Thus, in the four blocks, both angry and happy faces were associated with both Go and NoGo trials.

From the 60 trials in every block, 42 constituted a Go trial whereas 18 were NoGo trials. Every picture was presented for 1000 ms, and the pictures were separated by a pause of 500 ms. Subjects were asked to give accurate responses as fast as possible. Subjects underwent a practice phase of 10 trials before the task. The order of the four conditions was randomized across the subjects.

2.1.2.3. Letter-and Category Fluency task. In the Letter Fluency task, participants had to generate as many words as they could in 60 s beginning with the letter *F*. They were asked to avoid repetitions of a previously mentioned word or word stem, and to avoid proper names. Subjects were subsequently asked to generate words beginning with the letters A and S. The words were written down by an assistant blind to the group membership of the subjects.

In the Category Fluency task, subjects were given 60 s to generate words belonging to the semantic categories *Hungarian male names*, and then, *Hungarian female names*. Similarly, they were asked to avoid repetitions and nicknames of a previously mentioned name. Fluency was calculated by summing the number of the correct solutions. Perseveration was calculated by the number of repetitions/(number of correct + number of incorrect (repetitions, errors) responses).

2.1.2.4. Emotional Stroop task. During the Emotional Stroop task subjects were sitting in front of a computer screen, where different words were presented against a black background. The font color was randomly set to one of the following four colors: red, blue, green and yellow. Subjects had to indicate the color of the word – as fast as possible – by pressing a key on the keyboard assigned to the specific color. The task consisted of four blocks, with the same 30 words presented in each block following a fully randomized sequence, and the words were separated by a pause lasting randomly between 300 and 1200 ms.

Half of the words had intense negative valence, whereas the other half were neutral. Subjects practiced with 10 neutral words before performing the task. The words were selected from a 480-word pool, each rated by 54 subjects in a pilot study on the following dimensions: arousal, valence and dominance. (The subjects who rated the words were different from our study subjects). The selected 30 words were matched in respect to valence (neutral or negative) and word frequency.

2.1.2.5. Data analysis. Mean scores of the two groups (NM vs. CTL) in the GSQS and the STAI-T questionnaire were compared with the Welch test and with independent *t*-test, respectively. (We applied the Welch test if the criterion for the homogeneity of variance were violated.) Reaction times of the correct responses in the Emotional Go/NoGo task were compared using repeated measures ANOVAs with Group (NM, CTL) as a between-subject factor and Valence (angry vs. happy faces) as a within-subject factor. In order to measure the differences in accuracy, sensitivity scores (*D*-prime value: $D' = Z(\text{hit rate}) - Z(\text{false alarm rate})$ of the two groups in the Go/NoGo task were compared with oneway ANOVA. To compare mean reaction times for correct responses in the Emotional Stroop task we used repeated measures ANOVA with Group as a between-subject factor and Valence (neutral vs. negative words) as a within-subject factor. The number of errors in the Emotional Stroop task between the two groups was compared with oneway ANOVA. To control the possible mediating effects of sleep quality and waking anxiety on the neuropsychological task performance, we also analyzed the same between-and within subject effects by using the GSQS and the STAI-T scores as covariates in the repeated measures ANCOVAs. In order to compare performance in the Letter-and Category Fluency task controlling for the effects of anxiety and sleep quality we applied a MANOVA analysis with Fluency and Perseveration scores as the dependent variables, Group as a between-subject factor, and subsequently a MANCOVA with the same variables but also with the STAI-T and GSQS score as covariates in the model.

2.2. Results

2.2.1. Psychometric tests

The NM group scored higher ($M = 5.29 \pm 3.2$) than the CTL group ($M = 2.06 \pm 2.2$) on the GSQS, showing worse subjective sleep quality ($t_{60} = 24.37$, $p < 0.0001$), and on the STAI-T, showing higher levels of dispositional anxiety ($M = 49.2 \pm 9.1$ vs. $M = 34.2 \pm 8$ $t_{68} = 7.29$, $p < 0.0001$).

2.2.2. Emotional Go/NoGo task

In the condition where emotional stimuli were the targets and neutral stimuli the distractors (*Angry Go/Neutral NoGo vs. Happy Go/Neutral NoGo*) a significant main effect of Valence emerged ($F_{1,68} = 47.67$, $p < 0.0001$) due to slower reaction times (ms) for Angry targets vs. Happy targets ($M_{\text{angry targets}} = 472.2 \pm 71.36$ vs. $M_{\text{happy targets}} = 425 \pm 55.73$). Neither the effect of Group (NM vs. CTL) nor the interaction of Group $\times$ Valence reached significance ($F_{1,68} = 0.96$, $p = 0.34$; $F_{1,68} = 0.01$, $p = 0.92$; respectively). After controlling for the effects of sleep quality (using the GSQS as covariate), the effect of Valence ($F_{1,67} = 15.7$, $p < 0.0001$) remained significant; but after controlling for trait anxiety (using the STAI-T as the only covariate), Valence showed only a trend ($F_{1,67} = 3.66$, $p = 0.06$). The main effect of Group and the interaction between Group and Valence remained non-significant after controlling for sleep quality ($F_{1,67} = 1.43$, $p = 0.31$; $F_{1,67} = 0.19$, $p = 0.89$; respectively) or trait anxiety ($F_{1,67} = 0.7$, $p = 0.79$; $F_{1,67} = 0.09$, $p = 0.77$; respectively).

In the condition involving inhibition in response to emotional stimuli (*Neutral Go/Angry NoGo vs. Neutral Go/Happy NoGo*) a significant effect of Valence emerged ($F_{1,68} = 11.53$, $p = 0.001$) due to longer reaction times for Neutral targets with Angry distractors vs. Neutral targets with Happy distractors ($M_{\text{angry distractors}} = 485.24 \pm 62.02$ vs. $M_{\text{happy distractors}} = 467.08 \pm 55.35$).

The main effect of Group yielded a trend difference ($F_{1,68} = 3.78$, $p = 0.056$) due to longer reaction times in the NM ($M_{\text{angry distractors}} = 497.32 \pm 64.19$; $M_{\text{happy distractors}} = 479.64 \pm 52.69$) compared to the CTL group ($M_{\text{angry distractors}} = 472.59 \pm 58.03$; $M_{\text{happy distractors}} = 454.13 \pm 55.79$). Contrary to our hypothesis, the interaction between Group and Valence was not significant ($F_{1,68} = 0.01$, $p = 0.93$). After controlling for sleep quality, the main effect of Valence ($F_{1,67} = 3.89$, $p = 0.053$) and Group ($F_{1,67} = 3.52$, $p = 0.064$) showed a trend, but after controlling for anxiety, both effects became non-significant ($F_{1,67} = 0.07$, $p = 0.74$; $F_{1,67} = 1.04$, $p = 0.31$; respectively).

In order to compare the sensitivity index between NM and CTL group, we compared the mean *D*-prime (D') values between the two groups. Mean scores of D' values (that were very high, ranging

from 3.5 to 3.9 in the different conditions) for each condition were not significantly different between the NM and the CTL group ($F_{1,68} = 0.24$, $p = 0.62$; $F_{1,68} = 1.11$, $p = 0.29$; $F_{1,68} = 0.01$, $p = 0.94$; $F_{1,68} = 0.1$, $p = 0.92$).

2.2.3. Emotional Stroop task

In the Emotional Stroop task there was a significant main effect of Valence ($F_{1,68} = 7.14$, $p < 0.01$) due to longer mean reaction times (in ms) in response to negative ($M = 688.3 \pm 59.06$) in contrast to neutral words ($M = 678.76 \pm 77.53$). NM group showed significantly ($F_{1,68} = 10.39$, $p = 0.002$) longer reaction times ($M_{neutral} = 707.14 \pm 86.44$; $M_{negative} = 709.58 \pm 60.67$) than the CTL group for both types of stimuli ($M_{neutral} = 651.19 \pm 56.41$; $M_{negative} = 667.63 \pm 50.1$) (see Fig. 1). The interaction of Group × Valence showed a marginal effect ($F_{1,66} = 3.92$, $p = 0.052$). Parsing of this interaction (by examining the performance of the two groups separately) revealed a significant within-subject effect of Valence in the CTL group ($F_{1,34} = 31.96$, $p < 0.0001$), but not in the NM group ($F_{1,34} = 0.14$, $p = 0.71$). Contrary to our expectations, mean reaction times in the NM group were not different for neutral and negative words. In contrast, the CTLs were faster in response to neutral words than to negative words. After controlling for sleep quality and/or anxiety (by using GSQS and subsequently STAI-T as covariates), the main effect of Group remained significant ($F_{1,66} = 6.11$, $p = 0.016$) and the interaction of Group × Valence showed a significant effect ($F_{1,66} = 5.2$, $p = 0.026$). In contrast, the effect of Valence was no longer significant ($F_{1,66} = 0.19$, $p = 0.89$). The effect of Valence was not significant even after controlling for sleep quality and anxiety independently. Nevertheless, the interaction of Valence × sleep quality was significant ($F_{1,66} = 4.15$, $p = 0.04$), indicating longer reaction times for negative words in case of more fragmented sleep. The mean number of errors (ranging between 0.9 and 1.2) of the neutral and the negative trials in the Emotional Stroop task did not differ significantly between the NM and CTL group ($F_{1,68} = 0.18$, $p = 0.67$; $F_{1,68} = 0.49$ $p = 0.49$, respectively).

2.2.4. Letter-and Category Fluency task

The between subject Group had a significant main effect on Perseveration scores ($F_{1,68} = 11.47$, $p < 0.001$) because of the significantly higher scores of perseveration errors in the NM ($M = 0.4 \pm 0.32$) compared with the CTL group ($M = 0.18 \pm 0.23$).

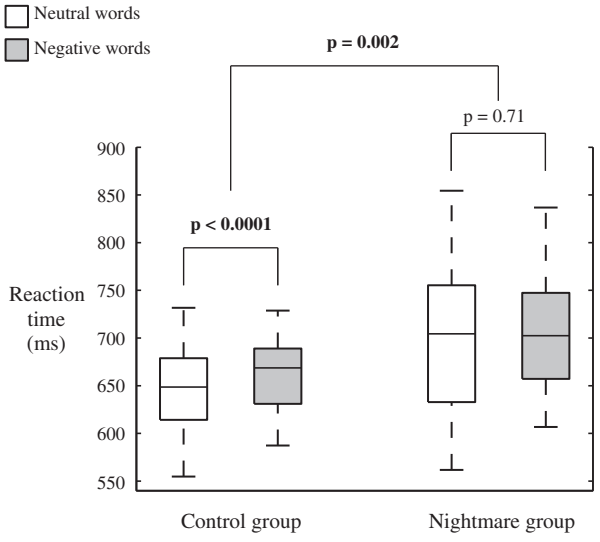

Fig. 1. Reaction times in the mixed design Emotional Stroop task by Group and Valence (neutral vs. negative stimuli). The NM group was significantly slower in both conditions ($p = 0.002$). While in the CTL group a significant difference occurred in response to neutral and negative words ($p < 0.0001$), the NM group did not differ in those ($p = 0.71$).

Regarding Fluency the effect of Group was not significant ($F_{1,68} = 0.04$, $p = 0.85$). After controlling for trait anxiety and sleep quality, the effect of Group on Perseveration remained significant ($F_{1,66} = 7.3$, $p = 0.009$) and Fluency showed a trend difference between the groups (see Table 1). While sleep quality was not related to the performance in the Fluency task, higher levels of trait anxiety were associated with lower fluency scores. (Subsequent analysis indicated that the STAI-T scores correlated negatively with the Fluency scores: Pearson $r = -0.26$, $p = 0.03$).

2.3. Discussion of Study 1

In our first study we aimed to characterize executive control processes in a group of young subjects with frequent nightmares and healthy controls by two tasks involving affect-laden stimuli (Go/NoGo and Stroop) and one without emotional information. We showed that NM subjects by comparison with the CTL group exhibited worse performance in these executive tasks. Moreover, lower performance in these tasks cannot be attributed exclusively to the effects of waking anxiety or disturbed sleep.

In the Emotional Go/NoGo task, subjects of both groups showed increased response time when the stimuli included negative emotional information (angry faces) as targets, as well as distractors; suggesting that identifying or suppressing threatening stimuli requires additional attentional resources in comparison with neutral or positive emotional stimuli.

The performance of the NM and CTL group did not differ regarding identifying emotional faces among neutral distractors, but NM subjects exhibited slightly increased response time to neutral target faces embedded among emotional distractors. This finding dovetails with previous studies indicating that this identifying process requires enhanced attentional resources (Chiu et al., 2008), and resembles the findings of a similar study examining children with anxiety disorders (Waters & Valvoi, 2009). Interestingly, this relative slowing in the NM group was also present in case of neutral targets embedded among positive (happy faces) distractors. This indicates that the lower performance of disturbed dreamers was independent of the valence of the distractors. Nevertheless, the general slowing pattern in NM subjects was influenced by trait anxiety but not by poor sleep quality.

Accuracy did not differ between NM and CTL subjects, probably because the task was relatively easy for the subjects as evidenced by the high *D*-prime values.

In sum, the results of the Emotional Go/NoGo task partially supported our first hypothesis anticipating worse performance in NM in comparison with CTL subjects. While accuracy was not different in any condition between the two groups, NM subjects were slightly slower in responding to neutral stimuli among emotional distractors, suggesting that individuals with frequent nightmares require additional cognitive efforts for emotion-modulated response inhibition. Nevertheless, the disadvantage for NM subjects disappeared if we controlled the effects of trait anxiety, suggesting

Table 1
Results of the multivariate analysis of variance of the letter-and category fluency task. Tests of between-subjects effects. Independent variables: Group (NM = 1, CTL = 2), STAI-T (Spielberger Trait Anxiety Inventory), GSQS (Groningen Sleep Quality Scale).

Independent variables	Dependent variables	F-value	Significance
Group	Fluency	3.39	$p = 0.07$
	Perseveration	7.3	$p = 0.009$
STAI-T	Fluency	6.04	$p = 0.017$
	Perseveration	0.56	$p = 0.46$
GSQS	Fluency	0.57	$p = 0.46$
	Perseveration	0.26	$p = 0.61$

that not nightmare disorder *per se*, but the higher levels of waking anxiety are associated to weaker performance in the Emotional Go/NoGo task.

In accordance with previous studies (Becker et al., 2001; Hope et al., 1990; Mattia et al., 1993), we found significantly longer reaction times for negative words in contrast to neutral words in the Emotional Stroop task. However, only CTL subjects showed this relative slowing in response to negative words, whereas NM subjects were characterized by similar reaction times for negative and neutral words contrary to our expectations. The NM in comparison with the CTL group showed significantly longer reaction times for negative and neutral words as well. This finding partially supports our second hypothesis claiming longer reaction times in NM subjects, but the specific sensitivity of NM subjects in response to negative words was not supported. On the contrary, NM subjects exhibited an overall slowing pattern in the Emotional Stroop task, irrespective of the valence of the stimuli. Furthermore, this slowing was not a function of trait anxiety or disturbed sleep, but an independent characteristic of the NM group. This finding is in accordance with previous studies examining individuals with Borderline Personality Disorder (Wingenfeld et al., 2009) and Post-traumatic Stress Disorder (Bremner et al., 2004) – two conditions associated with disturbed dreaming (Mellman, David, Bustamante, Torres, & Fins, 2001; Simor, Csóka, & Bódizs, 2010) – showing similar patterns of overall slowing in Emotional Stroop paradigms. Nevertheless, our findings indicating emotional interference in CTL but not in NM subjects still require further considerations. We assumed that the lack of emotional interference in the NM group was due to the design of our Emotional Stroop task. Since we applied a mixed set of neutral and negative words that were presented randomly in the same block, a slow effect of emotional interference might have confounded our results. Emotionally charged, negative words may exert a slow effect, and thus, interfere with the processing of subsequent neutral trials as well (McKenna & Sharma, 2004; Phaf & Kan, 2007). Therefore, the emotional interference caused by the negative words might have increased the response time not only for the negative but for some neutral words as well. If NM subjects were specifically sensitive to negative emotional information, in this group, a slow effect of emotional interference might have influenced response time for the neutral trials as well. Given these considerations, in our second study (see Section 3) we applied an Emotional Stroop task with block design.

In contrast to reaction times, accuracy did not differ between the two groups, both committing a low number of errors.

Finally, we found that poor sleep quality was related to less efficient processing of negative words. This finding is in accordance with previous studies showing increased sensitivity for emotional information in sleep deprived subjects (Franzen, Buysse, Dahl, Thompson, & Siegle, 2009; Tempesta et al., 2010). Increased sensitivity and attentional bias for negative words might require additional cognitive resources in order to suppress the semantic content of the stimuli.

In sum, NM subjects showed impaired performance in the Emotional Stroop task, reflected by an overall increase in response time. This general slowing was not explained by trait anxiety or by disturbed sleep. Nevertheless, the lack of emotional interference in the NM group called for further investigations.

Results of the Letter-and Category Fluency task supported our third hypothesis expecting worse performance in NM compared to CTL subjects. NM subjects, compared to CTLs were characterized by slightly less fluent word generation and a notably higher number of perseverations, even after controlling for the effects of sleep quality and trait anxiety. While trait anxiety was associated to lower performance in word generation, the higher number of perseverations in the NM group was independent of the effects of anxiety.

3. Study 2

In our first study NM subjects in comparison with CTLs exhibited longer reaction times in the Emotional Stroop task irrespective of the emotional nature of the stimuli. Nevertheless, the presentation of neutral and negative words in mixed design might have confounded our results due to the slow effect of negative emotional stimuli (McKenna & Sharma, 2004). In order to test this assumption we examined a new nightmare group and healthy controls by using an Emotional block design Stroop task. *We hypothesized that both groups would be slower in response to negative words than to neutral ones, but NM subjects would exhibit increased emotional interference (increased response time for negative vs. neutral words) in comparison with CTLs*.

Moreover, in order to test if NM subjects show lower performance in the Stroop task regardless of the emotional nature of the stimuli, we applied the Color-word Stroop task (Stroop, 1992). This classic Stroop task has been widely used for evaluating executive functions (Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000; Zysset, Müller, Lohmann, & Von Cramon, 2001). In the Color-word Stroop task subjects are required to press a button corresponding to the color of the stimuli. In the incongruent condition, subjects are asked to press the button corresponding to the color of the stimulus which is a color word different from the stimulus (e.g. the word "blue" in yellow font); in the congruent condition the color word is presented with a matching color; and in the neutral condition subjects are asked to respond to a control (e.g. XXXXX) stimulus. In the incongruent condition the semantic representation of the word must be inhibited in favor of the perceptual characteristic of the stimulus. Brain imaging studies of the Color-word Stroop task indicate that the conflict resolution in this condition is associated with enhanced activation in the dorsolateral prefrontal cortex and in the dorsal anterior cingulate cortex (Banich et al., 2000; Bush et al., 2000; Milham & Banich, 2005; Milham et al., 2002). Since the task requires executive functions relying on prefrontal structures, *we anticipated that NM subjects – compared to CTLs – would exhibit worse performance in the incongruent condition of the Color-word Stroop task*. Similarly to Study 1, we controlled the effects of trait anxiety and sleep quality.

3.1. Methods and Materials

3.1.1. Participants

19 (7 female and 12 male) NM (M_{age} = 19.9 ± 1.3 y) and 17 (8 female 9 male) CTL subjects (M_{age} = 19.8 ± 1.3 y) were selected by the procedure described in study 1 (see Section 2.1.1). (Both groups comprised a new sample as none of these subjects participated in Study 1.) The difference in male–female ratio was not significant between the groups ($\chi^2 = 0.39$, $p = 0.53$). None of the subjects reported having prior neurological, psychiatric or sleep disorders or prior history of any chronic disease. None of them reported traumatic experiences such as physical attack, accident, and the sudden death of a close relative. NM subjects scored higher on the Nightmare Frequency Scale (NM: 4.21 ± 1.84 vs. CTL: 1.59 ± 0.71; $F_{1,34} = 30.28$, $p < 0.0001$), on the Bad Dream Frequency Scale (NM: 5.74 ± 1.24 vs. CTL: 1.65 ± 0.86; $F_{1,34} = 128.96$, $p < 0.0001$), on the Negative Dream Affect Scale of the DQQ (NM: 9.02 ± 1.47 vs. CTL: 5.5 ± 0.94; $F_{1,34} = 71.63$, $p < 0.0001$), and on the VDAS-H (NM: 15.1 ± 9.34 vs. CTL: 0.29 ± 0.85; $F_{1,34} = 42$, $p < 0.0001$), indicating at least moderately severe dream disturbances (Bódizs et al., 2008; Simor, Kovács, et al., 2009).

The study protocol was approved by the local ethical review board of the Budapest University of Technology and Economics. Subjects were told that the aim of the study was the investigation of the relationship between dreaming and cognitive processes. The

subjects received partial credit points in the introductory psychology course as compensation for their participation. Written informed consent was obtained.

3.1.2. Procedure

Subjects completed the Groningen Sleep Quality Scale (GSQS), the STAI-T questionnaire (see Section 2.1.2.1) and the Stroop tasks in a noise-attenuated room. The order of the tasks (first the Color-word and then the Emotional Stroop task) was fixed for all subjects.

3.1.2.1. Color-word Stroop task. We used a computerized version of the Color-word Stroop task. There were three conditions: neutral, congruent and incongruent. In all conditions words or letters were presented with various font colors, and subjects had to indicate the color of the stimuli by pressing – as fast as possible – one of the four predefined keys.

The task consisted of three blocks after a short practice phase. In each block, there were 32 trials of the control condition (a row of five "Xs"), followed by 32 trials of the congruent (e.g. "RED" with red font color), and 32 trials of the incongruent condition (e.g. "RED" with blue font color). This yielded a total of 96 trials for all three conditions. The trials were separated by a random pause that lasted between 300 and 1200 ms.

3.1.2.2. Emotional Stroop task (Block design). The Emotional Stroop task was similar to the one used in Study 1. We presented subjects with neutral and negative words with different font colors, and they had to indicate the color of the words by pressing a predefined key on the keyboard. However, in contrast to Study 1, we increased the number of the presented words to 32 neutral and 32 negative words. Moreover, we used a block design: first, 32 neutral words were presented which were followed by 32 negative words. This sequence was repeated three times. The order of the 32–32 neutral and negative words was randomized in every block, but the 32 neutral words came always before the 32 negative words. The duration of the inter-trial pause was set to a random value between 300 and 1200 ms.

3.1.2.3. Data Analysis. Mean reaction times for correct responses in the Emotional Stroop task were compared with repeated measures ANOVA with Group as a between-subject factor and Valence (Neutral vs. Negative) as a within subject factor. Similarly, in the Color-word Stroop task Group served as a between-subject factor and Condition (Control vs. Congruent vs. Incongruent) as a within-subject factor. The number of errors between the two groups was compared by oneway ANOVA. To control the possible mediating effects of sleep quality and waking anxiety on the neuropsychological task performance, we also analyzed the same between-and within subject effects by using the GSQS and the STAI-T scores as covariates in the repeated measures ANCOVAs. Since the set of stimuli in the Emotional Stroop task in contrast to the Color-word Stroop task includes longer words (e.g. bicycle vs. red), differences in word reading abilities may influence reaction times. Therefore, in order to control the confounding effects of word reading speed, a repeated measure ANOVA was used with Group as a between-subject factor, and Word length (words with two vs. three syllables) as a within-subject factor.

3.2. Results

3.2.1. Psychometric tests

The NM group scored higher ($M = 4.32 \pm 3.25$) than the CTL group ($M = 2.65 \pm 2.37$) on the GSQS, but the difference was not significant ($t_{34} = 1.74$, $p = 0.086$). STAI-T scores were significantly higher in the NM group ($M = 45.63 \pm 8.97$ vs. $M = 38 \pm 11.8$; $t_{34} = 2.19$, $p = 0.036$).

3.2.2. Color-word Stroop task

In the Color-word Stroop task a significant effect of Condition ($F_{2,33} = 56.07$, $p < 0.0001$) emerged due to longer reaction times (ms) for Incongruent ($M = 797.25 \pm 105.03$) vs. Congruent ($M = 717.07 \pm 103.44$; $F_{1,34} = 61.96$, $p < 0.0001$) and Incongruent vs. Control ($M = 701.7 \pm 109.57$; $F_{1,34} = 79.85$, $p < 0.0001$) trials. Although NM subjects were slightly slower in each condition, the effect of Group was not significant ($F_{2,32} = 2.04$, $p = 0.16$; $F_{1,32} = 2.18$, $p = 0.15$, respectively). Similarly, the interaction between Group and Condition did not reach significance. The main effect of Condition remained significant after controlling for sleep quality ($F_{2,32} = 18.14$, $p < 0.0001$) or trait anxiety ($F_{2,32} = 4.06$, $p < 0.027$). CTL subjects committed more errors in the Incongruent condition compared to NM subjects ($M = 2.12 \pm 2.5$ vs. $M = 0.58 \pm 0.96$; $F_{1,34} = 6.2$, $p = 0.018$), while there were no significant differences in the other two conditions regarding the number of errors.

3.2.3. Emotional Stroop task

In the Emotional Stroop task a significant effect of Valence emerged due to longer reaction times (ms) in response to negative words than to neutral words ($M = 731.93 \pm 110.82$ vs. $M = 709.52 \pm 110.52$; $F_{1,32} = 25.48$, $p < 0.001$). The effect of Group was also significant ($F_{1,34} = 4.18$, $p = 0.049$) because of longer reaction times in the NM group for both neutral and negative words ($M_{Neutral} = 743.56 \pm 113.36$; $M_{Negative} = 768.09 \pm 109.43$) compared with the CTL group ($M_{Neutral} = 665.12 \pm 93.87$; $M_{Negative} = 691.53 \pm 100.53$) (see Fig. 2). Contrary to our expectation, the interaction between Group and Valence was not significant, since both groups were significantly slower in response to negative than to neutral words (NM: $F_{1,18} = 14.29$, $p = 0.001$; CTL: $F_{1,16} = 11.39$, $p = 0.004$). After controlling for the effects of sleep quality, the effects of Valence ($F_{1,33} = 8.43$, $p = 0.007$) and Group ($F_{1,33} = 4.96$, $p = 0.033$) remained significant; but after controlling for the effects of trait anxiety the effect of Valence lost its significance ($F_{1,33} = 0.09$, $p = 0.768$), while the main effect of Group remained significant ($F_{1,33} = 4.18$, $p = 0.049$). There were no significant differences regarding the number of errors between NM and CTL subjects.

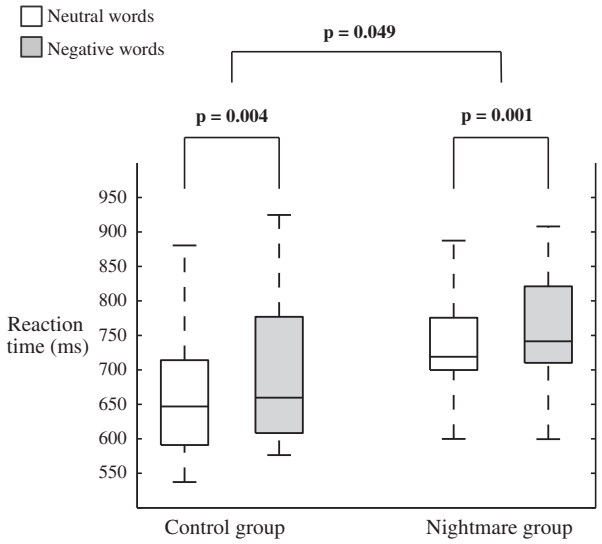

Fig. 2. Reaction times in the block design Emotional Stroop task by Group and Valence (neutral vs. negative stimuli). The NM group was significantly slower in both conditions ($p = 0.049$). In both groups subjects responded significantly slower to negative words (CTL: $p = 0.004$; NM: $p = 0.001$).

3.2.4. Word reading

Neither the main effect of Word length ($F_{1,34} = 0.001$, $p = 0.974$), nor the interaction between Group and Word length ($F_{1,34} = 1.05$, $p = 0.312$) had a significant effect on response time.

3.3. Discussion of Study 2

In coherence with our previous findings (*Study 1*), results of *Study 2* revealed increased reaction times in the NM as compared to the CTL subjects in the Emotional Stroop task. While in the Emotional Stroop task with mixed design (*Study 1*) NM subjects did not show emotional interference, in the blocked version (*Study 2*) both groups were characterized by longer reaction times in response to negative stimuli. This discrepancy suggests that the lack of emotional interference in the NM group of *Study 1* might have been masked by the influence of negative stimuli on subsequent responses to neutral trials. Nevertheless, in the blocked version, the NM group exhibited longer reaction times in response to neutral words as well, showing an overall slowing pattern in the Emotional Stroop task, irrespective of the emotional nature of the stimuli. Therefore, contrary to our expectation, NM subjects were not characterized by increased emotional interference. Moreover, slower reactions for negative vs. neutral words (emotional interference) in both groups disappeared after the statistical control of trait anxiety, whereas the overall slowing in NM subjects was independent of poor sleep quality or trait anxiety.

In contrast to the findings in the Emotional Stroop task, NM subjects were not characterized by worse performance in the Color-word Stroop task, since mean reaction times did not significantly differ between the two groups in either condition. Indeed, CTLs in contrast to NM subjects exhibited more errors in the incongruent condition, the task requiring enhanced cognitive control in order to suppress the interfering semantic representation of the color word.

4. Discussion and conclusions

While in the last decades nightmare disorder was mainly investigated and substantially characterized from a clinical point of view, the mechanisms and the neurocognitive aspects of this disorder were only scarcely investigated (Germain & Nielsen, 2003; Levin & Nielsen, 2007; Nielsen, Paquette, Solomonova, Lara-Carrasco, Popova, et al., 2010; Nielsen, Paquette, Solomonova, Lara-Carrasco, Colombo, et al., 2010; Spoormaker, 2008). Levin and Nielsen (2009) provided a neurocognitive framework with testable hypotheses in order to model the mechanism of disturbed dreaming. They proposed that impaired prefrontal and fronto-limbic functions unable to regulate emotional activation during REM sleep are one of the crucial aspects of disturbed dreaming. The assumption of the impaired neural network in NM subjects was derived from the integration of previous research on emotional information processing in waking and brain imaging findings on REM sleep (Levin & Nielsen, 2007; Levin & Nielsen, 2009; Nielsen & Levin, 2007).

In the present studies we applied four different, well-characterized neuropsychological tasks that were shown to be associated with prefrontal and fronto-limbic functioning. We hypothesized that impaired prefrontal and fronto-limbic functions in relation to emotional dysregulation would be reflected in waking tasks as well, especially in those that require the processing of emotional information.

NM subjects exhibited lower performance in the emotional executive tasks, reflected by slightly increased response time in the Emotional Go/NoGo task involving emotional stimuli as distractors, and by increased response time in the Emotional Stroop task. While the slowing pattern in the Emotional Go/NoGo seemed to be the result of higher levels of trait anxiety in the NM group, the slowing in the Emotional Stroop task was not related to anxiety. This latter finding is in coherence with recent findings indicating that disturbed dreaming is not a "mere symptom" of waking psychopathology (Coolidge et al., 2010; Lancee et al., 2010; Spoormaker & Montgomery, 2008). Interestingly, lower performance in NM subjects in comparison with CTLs was independent of the emotional valence of the stimuli. Nightmare subjects exhibited longer response times in the Emotional Go/NoGo in case of positive emotional distractors and also in case of neutral words in the Emotional Stroop task, suggesting that impaired executive functions were not restricted to the processing of negative emotional information. These findings resemble earlier results examining executive functions in the context of affective stimuli in other populations characterized by emotional dysregulation (Bremner et al., 2004; Waters & Valvoi, 2009; Wingenfeld et al., 2009).

NM subjects showed impaired performance in the Letter-and Category Fluency task reflected by slightly lower fluency and a considerably higher number of perseverations. While the task aims to measure executive functions without involving emotional components, we suppose that even so, the task may evoke emotional reactions that might interfere with optimal performance. Although the task is apparently easy, according to our results it is rather difficult; moreover, subjects may get puzzled by their unexpectedly low performance. Even though earlier reports suggest that performance in Verbal Fluency tasks is not related to conditions of emotional dysregulation (Airaksinen, Larsson, & Forsell, 2005; Airaksinen, Larsson, Lundberg, & Forsell, 2004; Gruzelier, Seymour, Wilson, Jolley, & Hirsch, 1988), we found that fluency was related to higher levels of anxiety. Nevertheless, earlier investigations reporting the lack of associations between affective processes and fluency examined populations with severe psychopathological conditions, while our subjects comprised healthy university students and NM subjects without a prior history of mental disorders. We speculate that subclinical levels of trait anxiety influenced the rate of word generation due to performance anxiety and the unexpected difficulties of the task. However, it is also possible that other uncontrolled factors related to anxiety influenced task performance. While fluency was associated to trait anxiety, NM subjects exhibited a higher number of perseveration errors independently of the effects of anxiety, demonstrating that disturbed dreamers are characterized by prefrontal, executive deficits (especially dysfunctional inhibitory control).

NM subjects did not exhibit worse performance in the Color-word Stroop task. This executive task is associated with enhanced activation of the dorsolateral prefrontal and of the dorsal anterior cingulate cortex (Banich et al., 2000; Bush et al., 2000; Milham & Banich, 2005; Milham et al., 2002), structures that were not implicated in emotional regulation and in the mechanism of disturbed dreaming. Moreover, we speculate that in contrast to the Letter- and Category Fluency task – where subjects have to generate words aloud, in front of an assistant – the computerized Color-word Stroop task does not trigger negative emotional or cognitive reactions due to test or social anxiety. In line with this assumption, performance in the Color-word Stroop task was not influenced by trait anxiety scores.

In sum, our results support the assumption of executive dysfunctions in subjects with frequent nightmares, as evidenced by impaired performance in several neuropsychological tasks that involve the processing of emotional information, as well as the regulation of emotional reactions. We should note, however, that the overall slowing pattern of NM subjects in the Emotional Stroop task calls for further investigation, since this group was slower in response to neutral stimuli (neutral words) as well, that apparently do not involve emotional components. In contrast, they were not impaired in either condition of the Color-word Stroop task. NM subjects might have been slower in response to the neutral words

because of slower word-reading, since these stimuli were generally longer than the color words (e.g. bicycle vs. red). However, this explanation seems unlikely since response time was not related to word length.

Another explanation is that NM subjects in comparison with controls are more sensitive to distracting neutral stimuli that elicit a broader network of semantic associations. Different, emotionally neutral words, such as *trumpet, river, novel, and mirror* might elicit a broad range of semantically related representations compared to the repeating presentation of the words: red, green, blue and yellow. These, "internal associations" may involve personally relevant semantic representations that interfere with the representation of the color of the stimuli. We speculate that subjects with frequent nightmares were more prone to be distracted by the spontaneous generation of semantic representations elicited by the words presented on the computer screen. This would partly explain lower performance in the Fluency task as well, since strategic (letter or category based) word generation relies on the suppression of semantically related spontaneous representations interfering with the task (Perret, 1974). This is also consistent with Hartmann and colleagues' (1991) findings that individuals with thin boundaries – a psychological construct related to nightmare frequency and to more bizarre dream images – are characterized by a tendency toward immersion in internally generated associations and imaginative processes (Hartmann, 1989; Hartmann et al., 1991; Kunzendorf, Hartmann, Cohen, & Cutler, 1997). While this explanation seems plausible, it is not clear whether the general slowing may be the result of the above described hyperassociative process or the emotional context elicited by the self-relevant associations. Therefore, these considerations require further investigations.

Regarding the limitations of our study we should note that while we applied well characterized neuropsychological paradigms in order to examine prefrontal and fronto-limbic functioning in subjects with frequent nightmares, our results are only based on behavioral data that do not provide a precise picture about the underlying neural networks that are supposed to be dysfunctional in disturbed dreamers. Brain imaging or sophisticated electrophysiological methods would facilitate our understanding about altered fronto-limbic networks in nightmare reporters. Furthermore, examining a student sample is advantageous because of the relative homogeneity of our subjects, but care should be taken in generalizing our results to other populations. We should also note that other uncontrolled psychological variables such as depression might underlie the general slowing in the NM group. And finally, while we controlled for subjective sleep quality; more objective measures (e.g. polysomnography) of sleep architecture would be necessary in order to rule out the possible confounding effects of disrupted sleep on information processing.

In spite of these limitations, to the best of our knowledge this is the first investigation examining neuropsychological functions in subjects with frequent nightmares, and providing empirical data regarding the neurocognitive aspects of disturbed dreaming.

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References

Agargun, M. Y., Besiroglu, L., Cilli, A. S., Gulec, M., Aydin, A., Inci, R., et al. (2007). Nightmares, suicide attempts, and melancholic features in patients with unipolar major depression. *Journal of Affective Disorders, 98*(3), 267–270.

Agargun, M. Y., Kara, H., Bilici, M., Sava, A., Telci, M., Semiz, B., et al. (1999). The van dream anxiety scale: A subjective measure of dream anxiety in nightmare sufferers. *Sleep Hypnosis, 4*, 204–211.

Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: Evidence of episodic memory dysfunction. *Journal of Psychiatric Research, 39*(2), 207–214.

Airaksinen, E., Larsson, M., Lundberg, I., & Forsell, Y. (2004). Cognitive functions in depressive disorders: Evidence from a population-based study. *Psychological Medicine, 34*(1), 83–91.

American Academy of Sleep Medicine, Task Force Chair HP. ICSD-II. (2005). *International classification of sleep disorders: Diagnostic and coding manual* (2nd ed.). Chicago: American Academy of, Sleep Medicine.

Aron, A. R., Durston, S., Eagle, D. M., Logan, G. D., Stinear, C. M., & Stuphorn, V. (2007). Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. *Journal of Neuroscience, 27*(44), 11860–11864.

Baldo, J. V., Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society, 12*(06), 896–900.

Baldo, J. V., & Shimamura, A. P. (1998). Letter and category fluency in patients with frontal lobe lesions. *Neuropsychology, 12*(2), 259–267.

Baldo, J. V., Shimamura, A. P., Delis, D. C., Kramer, J., & Kaplan, E. (2001). Verbal and design fluency in patients with frontal lobe lesions. *Journal of the International Neuropsychological Society, 7*(5), 586–596.

Banich, M. T., Milham, M. P., Atchley, R., Cohen, N. J., Webb, A., Wszalek, T., et al. (2000). FMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. *Journal of Cognitive Neuroscience, 12*(6), 988–1000.

Becker, E. S., Rinck, M., Margraf, J., & Roth, W. T. (2001). The Emotional Stroop effect in anxiety disorders: General emotionality or disorder specificity? *Journal of Anxiety Disorders, 15*(3), 147–159.

Belicki, K. (1992). Nightmare frequency versus nightmare distress: Relations to psychopathology and cognitive style. *Journal of Abnormal Psychology, 101*(3), 592–597.

Besiroglu, L., Agargun, M. Y., & Inci, R. (2005). Nightmares and terminal insomnia in depressed patients with and without melancholic features. *Psychiatry Research, 133*(2–3), 285–287.

Blagrove, M., Farmer, L., & Williams, E. (2004). The relationship of nightmare frequency and nightmare distress to well-being. *Journal of Sleep Research, 13*(2), 129–136.

Bódizs, R., Simor, P., Csóka, S., Bérdi, M., & Kopp, M. S. (2008). Dreaming and health promotion: A theoretical proposal and some epidemiological establishments. *European Journal of Mental Health, 3*(1), 35–62.

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences, 8*(12), 539–546.

Bremner, J. D., Vermetten, E., Vythilingam, M., Afzal, N., Schmahl, C., Elzinga, B., et al. (2004). Neural correlates of the classic color and Emotional Stroop in women with abuse-related posttraumatic stress disorder. *Biological Psychiatry, 55*(6), 612–620.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences, 4*(6), 215–222.

Chiu, P. H., Holmes, A. J., & Pizzagalli, D. A. (2008). Dissociable recruitment of rostral anterior cingulate and inferior frontal cortex in emotional response inhibition. *Neuroimage, 42*(2), 988–997.

Coolidge, F. L., Segal, D. L., Coolidge, C. M., Spinath, F. M., & Gottschling, J. (2010). Do nightmares and generalized anxiety disorder in childhood and adolescence have a common genetic origin? *Behavior Genetics, 40*(3), 349–356.

Curtis, V. A., Bullmore, E. T., Brammer, M. J., Wright, I. C., Williams, S. C. R., Morris, R. G., et al. (1998). Attenuated frontal activation during a verbal fluency task in patients with schizophrenia. *American Journal of Psychiatry, 155*(8), 1056–1063.

Desseilles, M., Dang Vu, T., Laureys, S., Peigneux, P., Degueldre, C., Phillips, C., et al. (2006). A prominent role for amygdaloid complexes in the variability in heart rate (VHR) during rapid eye movement (REM) sleep relative to wakefulness. *Neuroimage, 32*(3), 1008–1015.

Dillon, D. G., & Pizzagalli, D. A. (2007). Inhibition of action, thought, and emotion: A selective neurobiological review. *Applied and Preventive Psychology, 12*(3), 99–114.

Dolcos, F., Kragel, P., Wang, L., & McCarthy, G. (2006). Role of the inferior frontal cortex in coping with distracting emotions. *NeuroReport, 17*(15), 1591–1594.

Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *Journal of Neuroscience, 26*(7), 2072–2079.

Franzen, P. L., Buysse, D. J., Dahl, R. E., Thompson, W., & Siegle, G. J. (2009). Sleep deprivation alters pupillary reactivity to emotional stimuli in healthy young adults. *Biological Psychology, 80*(3), 300–305.

Garavan, H., Ross, T. J., Murphy, K., Roche, R. A. P., & Stein, E. A. (2002). Dissociable executive functions in the dynamic control of behavior: Inhibition, error detection, and correction. *Neuroimage, 17*(4), 1820–1829.

Germain, A., & Nielsen, T. A. (2003). Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. *Biological Psychiatry, 54*(10), 1092–1098.

Gruzelier, J., Seymour, K., Wilson, L., Jolley, A., & Hirsch, S. (1988). Impairments on neuropsychologic tests of temporohippocampal and frontohippocampal functions and word fluency in remitting schizophrenia and affective disorders. *Archives of General Psychiatry, 45*(7), 623–629.

Hare, T. A., & Casey, B. J. (2005). The neurobiology and development of cognitive and affective control. *Cognition, Brain, and Behavior, 9*(3), 273–286.

Hartmann, E. (1989). Boundaries of dreams, boundaries of dreamers: Thin and thick boundaries as a new personality measure. *Psychiatric Journal of the University of Ottawa, 14*(4), 557–560.

Hartmann, E., Elkin, R., & Garg, M. (1991). Personality and dreaming: The dreams of people with very thick or very thin boundaries. *Dreaming, 1*(4), 311–324.

Hope, D. A., Rapee, R. M., Heimberg, R. G., & Dombeck, M. J. (1990). Representations of the self in social phobia: Vulnerability to social threat. *Cognitive Therapy and Research, 14*(2), 177–189.

Köteles, F., Szemerszky, R., Freyler, A., & Bárdos, G. (2011). Somatosensory amplification as a possible source of subjective symptoms behind modern health worries. *Scandinavian Journal of Psychology, 52*(2), 174–178.

Krakow, B., Schrader, R., Tandberg, D., Hollifield, M., Koss, M. P., Yau, C. L., et al. (2002). Nightmare frequency in sexual assault survivors with PTSD. *Journal of Anxiety Disorders, 16*(2), 175–190.

Kunzendorf, R. G., Hartmann, E., Cohen, R., & Cutler, J. (1997). Bizarreness of the dreams and daydreams reported by individuals with thin and thick boundaries. *Dreaming, 7*(4), 265–271.

Lancee, J., Spoormaker, V. I., & van den Bout, J. (2010). Nightmare frequency is associated with subjective sleep quality but not with psychopathology. *Sleep and Biological Rhythms, 8*(3), 187–193.

Lane, R. D., Reiman, E. M., Axelrod, B., Yun, L. S., Holmes, A., & Schwartz, G. E. (1998). Neural correlates of levels of emotional awareness: Evidence of an interaction between emotion and attention in the anterior cingulate cortex. *Journal of Cognitive Neuroscience, 10*(4), 525–535.

Leung, H. C., Skudlarski, P., Gatenby, J. C., Peterson, B. S., & Gore, J. C. (2000). An event-related functional MRI study of the Stroop color word interference task. *Cerebral Cortex, 10*(6), 552–560.

Levin, R., & Fireman, G. (2002). Nightmare prevalence, nightmare distress, and self-reported psychological disturbance. *Sleep, 25*(2), 205–212.

Levin, R., Fireman, G., Spendlove, S., & Pope, A. (2011). The relative contribution of affect load and affect distress as predictors of disturbed dreaming. *Behavioral Sleep Medicine, 9*(3), 173–183.

Levin, R., & Nielsen, T. A. (2007). Disturbed dreaming, posttraumatic stress disorder, and affect distress: A review and neurocognitive model. *Psychological Bulletin, 133*(3), 482–528.

Levin, R., & Nielsen, T. (2009). Nightmares, bad dreams, and emotion dysregulation: A review and new neurocognitive model of dreaming. *Current Directions in Psychological Science, 18*(2), 84–88.

Lezak, M. D. (2004). *Neuropsychological assessment*. USA: Oxford University Press.

MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology, 95*(1), 15–20.

Maquet, P., Ruby, P., Maudoux, A., Albouy, G., Sterpenich, V., Dang-Vu, T., et al. (2005). Human cognition during REM sleep and the activity profile within frontal and parietal cortices: A reappraisal of functional neuroimaging data. *Progress in Brain Research, 150*, 219–227.

Mattia, J. I., Heimberg, R. G., & Hope, D. A. (1993). The revised Stroop color-naming task in social phobics. *Behaviour Research and Therapy, 31*(3), 305–313.

McKenna, F. P., & Sharma, D. (2004). Reversing the Emotional Stroop effect reveals that it is not what it seems: The role of fast and slow components. *Journal of Experimental Psychology. Learning, Memory, and Cognition, 30*(2), 382–392.

Mellman, T., David, D., Bustamante, V., Torres, R., & Fins, A. (2001). Dreams in the acute aftermath of trauma and their relationship to PTSD. *Journal of Traumatic Stress, 14*, 241–247.

Milham, M. P., & Banich, M. T. (2005). Anterior cingulate cortex: An fMRI analysis of conflict specificity and functional differentiation. *Human Brain Mapping, 25*(3), 328–335.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., et al. (2002). Attentional control in the aging brain: Insights from an fMRI Study of the Stroop task. *Brain and Cognition, 49*(3), 277–296.

Moritz, S., Birkner, C., Kloss, M., Jahn, H., Hand, I., Haasen, C., et al. (2002). Executive functioning in obsessive-compulsive disorder, unipolar depression, and schizophrenia. *Archives of Clinical Neuropsychology, 17*(5), 477–483.

Muzur, A., Pace-Schott, E. F., & Hobson, J. A. (2002). The prefrontal cortex in sleep. *Trends in Cognitive Sciences, 6*(11), 475–481.

Nielsen, T., & Levin, R. (2007). Nightmares: A new neurocognitive model. *Sleep Medicine Reviews, 11*(4), 295–310.

Nielsen, T., Paquette, T., Solomonova, E., Lara-Carrasco, J., Colombo, R., & Lanfranchi, P. (2010). Changes in cardiac variability after REM sleep deprivation in recurrent nightmares. *Sleep, 33*(1), 113.

Nielsen, T. A., Paquette, T., Solomonova, E., Lara-Carrasco, J., Popova, A., & Levrier, K. (2010). REM sleep characteristics of nightmare sufferers before and after REM sleep deprivation. *Sleep Medicine, 11*(2), 172–179.

Nielsen, T. A., & Zadra, A. L. (2000). Dreaming disorders in principles and practices in sleep medicine. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practices of sleep medicine* (3rd ed., pp. 2000). Philadelphia: WB Saunders.

Nielsen, T., & Zadra, A. L. (2010). Idiopathic nightmares and dream disturbances associated with sleep-wake transitions. A. In M. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (5th ed., pp. 1106–1115). New York: Elsevier.

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex, 19*(5), 1158–1166.

Pace-Schott, E. F., Milad, M. R., Orr, S. P., Rauch, S. L., Stickgold, R., & Pitman, R. K. (2009). Sleep promotes generalization of extinction of conditioned fear. *Sleep, 32*(1), 19–26.

Perret, E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia, 12*(3), 323–330.

Phaf, R. H., & Kan, K. J. (2007). The automaticity of Emotional Stroop: A meta-analysis. *Journal of Behavior Therapy and Experimental Psychiatry, 38*(2), 184–199.

Reynolds, D. M., & Jeeves, M. A. (1978). A developmental study of hemisphere specialization for recognition of faces in normal subjects. *Cortex, 14*(4), 511–520.

Roberts, J., & Lennings, C. J. (2006). Personality, psychopathology and nightmares in young people. *Personality and Individual Differences, 41*(4), 733–744.

Rueda, M. R., Posner, M. I., & Rothbart, M. K. (2005). The development of executive attention: Contributions to the emergence of self-regulation. *Developmental Neuropsychology, 28*(2), 573–594.

Schwartz, S., Baldo, J., Graves, R. E., & Brugger, P. (2003). Pervasive influence of semantics in letter and category fluency: A multidimensional approach. *Brain and Language, 87*(3), 400–411.

Semiz, U. B., Basoglu, C., Ebrinc, S., & Cetin, M. (2008). Nightmare disorder, dream anxiety, and subjective sleep quality in patients with borderline personality disorder. *Psychiatry and Clinical Neurosciences, 62*(1), 48–55.

Simor, P., Csóka, S., & Bódizs, R. (2010). Nightmares and bad dreams in patients with borderline personality disorder: Fantasy as a coping skill? *European Journal of Psychiatry, 24*(1), 28–37.

Simor, P., Köteles, F., & Bódizs, R. (2011). Submersion in the experience: The examination of the Tellegen Absorption scale in an undergraduate university sample. *Mentálhigiéné és Pszichoszomatika, 12*(2), 101–123.

Simor, P., Köteles, F., Bódizs, R., & Bárdos, G. (2009). A questionnaire based study of subjective sleep quality: The psychometric evaluation of the hungarian version of the Groningen sleep quality scale. *Mentálhigiéné és Pszichoszomatika, 10*(3), 249–261.

Simor, P., Köteles, F., Sándor, P., Petke, Z., & Bódizs, R. (2011). Mindfulness and dream quality: The inverse relationship between mindfulness and negative dream affect. *Scandinavian Journal of Psychology, 52*(4), 369–375.

Simor, P., Kovács, I., Vargha, A., Csóka, S., Mangel, B., & Bódizs, R. (2009). Nightmares, dream anxiety and psychopathology: the validation of the Hungarian version of the Van Anxiety Scale. *Psychiatria Hungarica, 24*(6), 428–438.

Sipos, K., Sipos, M., & Spielberger, C. D. (1994). The hungarian version of the state-trait anxiety inventory (STAI). In F. Mérei & F. Szakács (Eds.), *Pszichodiagnosztikai vademecum I/2* (pp. 123–148). Budapest: Nemzeti Tankönyvkiadó.

Spielberger, C., Gorsuch, R., & Lusgene, R. (1970). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.

Spoormaker, V. I. (2008). A cognitive model of recurrent nightmares. *International Journal of Dream Research, 1*(1), 15–22.

Spoormaker, V. I., & Montgomery, P. (2008). Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature? *Sleep Medicine Reviews, 12*(3), 169–184.

Spoormaker, Victor. I., Schredl, M., & van den Bout, J. (2006). Nightmares: From anxiety symptom to sleep disorder. *Sleep Medicine Reviews, 10*(1), 19–31.

Spoormaker, V. I., Sturm, A., Andrade, K. C., Schröter, M. S., Goya-Maldonado, R., Holsboer, F., et al. (2010). The neural correlates and temporal sequence of the relationship between shock exposure, disturbed sleep and impaired consolidation of fear extinction. *Journal of Psychiatric Research, 44*(16), 1121–1128.

Stroop, J. R. (1992). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology: General, 121*(1), 15–23.

Tempesta, D., Couyoumdjian, A., Curcio, G., Moroni, F., Marzano, C., De Gennaro, L., et al. (2010). Lack of sleep affects the evaluation of emotional stimuli. *Brain Research Bulletin, 82*(1–2), 104–108.

Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning and Memory, 8*(2), 112–119.

Wagner, U., Hallschmid, M., Rasch, B., & Born, J. (2006). Brief sleep after learning keeps emotional memories alive for years. *Biological Psychiatry, 60*(7), 788–790.

Walker, M. P. (2009). The role of sleep in cognition and emotion. *Annals of the New York Academy of Sciences, 1156*(1), 168–197.

Waters, A. M., & Valvoi, J. S. (2009). Attentional bias for emotional faces in paediatric anxiety disorders: An investigation using the Emotional Go/No Go task. *Journal of Behavior Therapy and Experimental Psychiatry, 40*(2), 306–316.

Whalen, P. J., Bush, G., McNally, R. J., Wilhelm, S., McInerney, S. C., Jenike, M. A., et al. (1998). The emotional counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biological Psychiatry, 44*(12), 1219–1228.

Wingenfeld, K., Rullkoetter, N., Mensebach, C., Beblo, T., Mertens, M., Kreisel, S., et al. (2009). Neural correlates of the individual Emotional Stroop in borderline personality disorder. *Psychoneuroendocrinology, 34*(4), 571–586.

Zadra, A., & Donderi, D. C. (2000). Nightmares and bad dreams: Their prevalence and relationship to well-being. *Journal of Abnormal Psychology, 109*(2), 273–281.

Zysset, S., Müller, K., Lohmann, G., & Von Cramon, D. Y. (2001). Color-word matching Stroop task: Separating interference and response conflict. *Neuroimage, 13*(1), 29–36.

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ORIGINAL PAPER

Disturbed dreaming and sleep quality: altered sleep architecture in subjects with frequent nightmares

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Abstract Nightmares are intense, emotionally negative mental experiences that usually occur during late-night sleep and result in abrupt awakenings. Questionnaire-based studies have shown that nightmares are related to impaired sleep quality; however, the polysomnographic profile of nightmare subjects has been only scarcely investigated. We investigated the sleep architecture of 17 individuals with frequent nightmares and 23 control subjects based on polysomnographic recordings of a second night spent in the laboratory after an adaptation night. Nightmare subjects in comparison with control subjects were characterized by impaired sleep architecture, as reflected by reduced sleep efficiency, increased wakefulness, a reduced amount of slow wave sleep, and increased nocturnal awakenings, especially from Stage 2 sleep. While these differences were independent of the effects of waking psychopathology, nightmare subjects also exhibited longer durations of REM sleep that was mediated by heightened negative affect. Our results support that nightmares are related to altered sleep architecture, showing impaired sleep continuity and emotion-related increase in REM propensity.

Keywords Nightmares · Sleep · Dreaming · EEG · Polysomnography · Sleep quality

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Introduction

Nightmares are vivid, intense, and emotionally negative dream experiences that provoke abrupt awakenings especially, but not exclusively, from rapid eye movement (REM) sleep [1, 2]. Nightmares affect 2–4 % of the population on a weekly basis [2–4]; however, this rate is even higher if the awakening criterion is excluded from the definition of nightmares [5]. Indeed, research suggests that the inclusion of bad dreams without awakenings in the spectrum of dream disturbances provides a more accurate explanation regarding the relationship between dysphoric dreaming and waking negative affect [6]. Others proposed that disturbed dreaming forms a continuum from subclinical dysphoric dreaming through idiopathic nightmares to the most intense post-traumatic nightmares, where the pressure for awakening varies as a function of situational and dispositional factors as well [7, 8].

Even though nightmares often show high comorbidity with different mental disorders and clinical symptoms [7, 9–14], the direct relationship between nightmare frequency and waking psychopathology is far from being uncontroversial [15, 16]. The association between nightmare

frequency and mental symptoms seems to be mediated by nightmare distress, the affective and cognitive impact of nightmares on waking functioning [6, 17]. Nevertheless, Lancee et al. [18], investigating a population with frequent nightmares, found that the mediating role of nightmare distress for the link between nightmares and waking psychopathology is only applicable to populations with high comorbidity. Moreover, their results indicate that nightmares are independent from other mental complaints, disproving the common view of nightmares as a secondary symptom of an underlying anxiety disorder. The independence of nightmares from anxiety symptoms was supported by other studies as well. Clinical observations on post-traumatic stress disorder (PTSD) suggest that symptoms of disturbed sleep (including nightmares) may persist even after the remission of waking symptoms [19]. Furthermore, a prospective study of nightmare frequency (based on dream logs) found that the prevalence of nightmares was not related to daily variations of anxiety [20]; and finally, nightmare frequency was shown to be a stable disposition with high genetic heritability, which was independent of the genetic influences of general waking anxiety [21].

Several questionnaire-based studies demonstrated that nightmares are related to poor sleep quality both in adults [5, 18, 22] and children [23]. Nightmares may deteriorate sleep quality by frequent nocturnal awakenings as well as by the fear of falling asleep or difficulties of returning to sleep [24]. According to a study based on self-reports of sleep-disordered patients, 25 % reported frequent nightmare complaints. In addition, 63 % of the nightmare sufferers indicated that their nightmares were related to disrupted sleep. Furthermore, these patients exhibited significantly worse values on sleep and health-related indexes [25]. Examining a non-clinical sample, Schredl [22] showed that while the relationship between nightmares and poor sleep quality was partly explained by trait-like effects of neuroticism and state-like effects of current stress, nightmare frequency still remained as an independent factor contributing to complaints of insomnia. Similarly, nightmares and negatively toned dreams are prevalent in patients with insomnia [26, 27], and nightmare frequency is related to the severity of insomnia symptoms [28].

Retrospective and self-report measures are an important first step in investigating the relationship between disturbed dreaming and sleep quality; however, these methods are prone to subjective biases, and cannot provide a detailed picture about sleep architecture. Nevertheless, studies examining the relationship between nightmares and sleep quality with more objective methods are scarce. An early study found that nightmare sufferers (without comorbid PTSD) were characterized by decreased total sleep time, increased amount of nocturnal awakenings, decreased slow wave sleep (SWS), and increased REM density [29]. Interestingly, a more recent polysomnographic study could not reproduce these findings, but reported higher number of periodic limb movements in PTSD and in idiopathic nightmare sufferers in comparison with controls [30]. Nonetheless, this study had relatively low sample sizes and subjects were recruited through media advertisements. These factors may limit statistical power and the representative value of the sample, respectively. Two recent studies [31, 32] investigated the effects of a partial REM deprivation procedure in a group of nightmare sufferers and healthy controls. Subjects slept 3 days in the sleep laboratory: the first night was an adaptation night, whereas on the second night subjects were woken up from the beginning of every REM sleep episode after the second (REM episode). The third night served as a REM recovery night. Nightmare sufferers exhibited decreased REM pressure, and a trend of enhanced sympathetic activation measured by heart rate variability during the first, and markedly, during the third night. According to these studies, nightmare sufferers were not characterized by impaired sleep quality. While these investigations offer valuable data about the *reactive*, rebound effects of REM sleep deprivation in nightmare sufferers, they could not report the macrostructure of a standard night of sleep that would be reflected by the second night spent in the laboratory without experimental manipulations.

In light of the reported associations between subjective sleep quality and nightmare frequency, and given the scarcity of polysomnographic investigations of this population, the aim of our study was to examine sleep architecture in subjects with frequent nightmares. We focused on the macrostructural characteristics of the second night spent after an adaptation night in the laboratory. We considered that sleep indexes of the second night would provide more valid picture about sleep quality compared to the first night that might be influenced by the novelty of the experimental situation, a phenomenon known as the first-night effect [33]. Moreover, in order to investigate the primary relationship between disturbed dreaming and sleep architecture, we controlled for the possible confounding effects of waking psychopathological symptoms.

We hypothesized that:

(1) Nightmare subjects (NMs) will rate their sleep more fragmented in comparison with the control subjects (CTLs).
(2) NMs will be characterized by fragmented sleep as reflected by decreased sleep efficiency, increased duration of wakefulness after sleep onset, and decreased slow wave sleep.
(3) NMs in contrast to CTLs will be characterized by higher rate of nocturnal awakenings, especially from REM sleep.

(4) Sleep fragmentation in NMs will be independent from the effects of waking anxious and depressive symptoms.

Methods

Participants

Participants (all native Hungarians) were selected from a large pool of undergraduate students from the Budapest University of Technology and Economics and the Semmelweis University. First, they completed an online questionnaire assessing dream quality and a variety of personality factors. Subjects were told that the aim of the study was to investigate the relationship between sleep, dreams, and personality. Findings on the relationship between dream quality and personality have already been [34, 35] and will be reported elsewhere. Dreaming-related questionnaires included the Dream Quality Questionnaire (DQQ) [34], the Hungarian version of the Van Dream Anxiety Scale (VDAS-H) [36], and a 7-point Likert scale with two items; one assessing the frequency of nightmares with awakenings, and the other assessing the frequency of bad dreams without awakenings (0—almost never; 1—once or twice a year; 2—every 2–3 month; 3—once in a month; 4—twice a month; 5—once a week; 6—more than once a week). NMs were selected on the basis of the *International Classification of Sleep Disorders*, 2nd edition criteria [37] and Levin and Nielsen's [7] model of disturbed dreaming, including disturbed dreamers without abrupt awakenings. Subjects reporting one or more nightmares and/or bad dreams per week in the retrospective questionnaires were assigned to the NMs group, while individuals having less than two nightmares and bad dreams during the last year were assigned to CTLs. Subjects were thoroughly interviewed about the frequency and content of their negative dream experiences. Those subjects who reported the onset of negative dream experiences in relation to a traumatic event or indicated that the content of their dreams were somehow related to a prior trauma (such as physical attack, accident, sudden death of a close relative, etc.) were excluded from the study. Finally, 17 (7 females and 10 males) NMs ($M_{age} = 20.65 \pm 1.73$) and 23 (12 females and 11 males) CTLs ($M_{age} = 21.35 \pm 1.61$) were included for polysomnography. (The difference in age was not significant between the two groups: $U(38) = 134$; $Z = -1.719$; $p = .086$). None of the subjects reported prior neurological, psychiatric, or sleep disorders or prior history of any chronic disease. NMs scored higher on the Negative Dream Affect Scale of the DQQ (NM: 7.8 ± 1.81 vs. CTL: 4.04 ± 1.69; $t(38) = -6.83$; $p < .001$) and on the VDAS-H (NM: 19.53 ± 7.21 vs. CTL: $.26 \pm .62$; $t(16.17) = -10.99$; $p < .001$; equal variances not assumed), indicating at least moderately severe dream disturbances [34, 36].

The study protocol was approved by the Ethical Committee of the Semmelweis University. The subjects received monetary compensation (approximately 20 Euros in Hungarian Forints) for their participation in the sleep laboratory investigations. Written informed consent was obtained.

Psychometric tests

The *STAI* [38] is a widely used self-report instrument that differentiates between the temporary condition of state anxiety and the longstanding quality of trait anxiety. We used the 20-item Hungarian version of the STAI trait anxiety questionnaire (STAI-T) to assess general levels of anxiety [39]. The questions are scored on a 4-point Likert scale. The scale has proven to be valid and reliable tool for the measurement of trait anxiety, showing excellent internal consistency in different studies [40].

We used the short form of the Hungarian version of the *Beck Depression Inventory* (BDI-H) [41] in order to measure the extent of waking depressive symptoms in our subjects. The 9-item BDI-H is a one-dimensional scale assessing different symptoms of depression including social withdrawal, indecision, sleep disturbance, fatigue, intense worry about bodily symptoms, work inhibition, pessimism, lack of satisfaction, self-accusation. The items are scored on a 4-point Likert scale. The instrument showed good internal consistency, and high specificity and sensitivity for screening depression [41].

The Hungarian version of the *Groningen Sleep Quality Scale* (GSQS) was used for measuring subjective sleep quality [42]. The 14-item questionnaire measures the extent of subjective sleep fragmentation by a binary scale. The internal reliability and validity measures of the scale indicated that the questionnaire was an adequate tool for assessing subjective sleep quality [42].

Procedure

Polysomnographic recordings were performed in the sleep research laboratory of the Semmelweis University for 2 consecutive nights. (The first night served as the adaptation night). Subjects were not allowed to drink alcohol and take drugs (except contraceptives) on the day and the previous day of the examination. They were asked to avoid napping and consuming caffeine on the afternoon of the sleep recordings. Subjects completed the short version of the Beck Depression Inventory upon arrival. (The STAI-T was completed previously during the selection procedure.) The timing of lights off was between 11.00 PM and 1.00 AM

depending on each participant's preferred bedtime. Morning awakenings were scheduled after 9 h of undisturbed sleep except if participants woke up earlier spontaneously. In the morning, participants were asked to complete the Groningen Sleep Quality Scale and to report their dreams. One of the NMs reported a nightmare and two of them had bad dreams in the laboratory.

Polysomnography

During the standard polysomnographic examination on both nights, subjects were fitted with 19 EEG (Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2) electrodes according to the 10–20 electrode placement system [43] as well as with 2 EOG electrodes (bipolar channel) monitoring vertical and horizontal eye movements, 2–2 EMG electrodes (bipolar channels) for chin and for the anterior tibialis muscles, 2 ECG electrodes according to standard lead I, in addition to the thoracic and abdominal respiration sensors. Gold-coated Ag/AgCl EEG cup electrodes were fixed with EC2 Grass Electrode Cream (Grass Technologies, USA) and referred to the mathematically linked mastoids. Impedances were kept below 8 kΩ. Signals were collected, prefiltered (.33–1,500 Hz, 40 dB/decade anti-aliasing hardware input filter), amplified, and digitized with 4,096 Hz/channel sampling rate (synchronous) with 12 bit resolution by using the 32 channel EEG/polysystem (Brain-Quick BQ 132S, Micromed, Italy). A further 40-dB/decade anti-aliasing digital filter was applied by digital signal processing which low-pass filtered the data at 450 Hz. After this, the digitized and filtered EEG was subsequently undersampled at 1,024 Hz.

Wakefulness and sleep stages of the second night were identified manually according to the criteria of Rechtschaffen and Kales [44] by two experienced sleep researchers who were blind to the group membership of the subjects. A program developed by our laboratory was used to output the following sleep architecture variables: Wake time after sleep onset (WASO), Sleep efficiency (Sleep time/Time in bed), Sleep latency (period between lights off and the first epoch scored as Stage 2 sleep), absolute and relative (to the sleep time) duration of Non-REM (NREM) sleep, Stage 1, Stage 2, SWS (including Stage 3 and 4), REM sleep, and REM latency (period between sleep onset and the first epoch scored as REM sleep). We computed the measure of REM density (the frequency of eye movements (EM) during the REM phase) which was quantified as the total number of EM in REM/duration of REM sleep (in seconds). The scoring of eye movements was based on visual detection of the EOG by a trained researcher who was blind to the group membership of the subjects. Rapid left and right EMs and saccades in the same direction of gaze with the minimum amplitude of 50(μV) were counted as separate eye movements. The number of awakenings from different stages (Stage 2, SWS, REM) was also computed.

Statistical analyses

All statistical procedures were carried out with the Statistical Package for the Social Sciences (SPSS) version 19 (IBM). Mean scores of the psychometric tests were compared with independent samples *t* test, and, if the criterion for homogeneity of variance was violated, we applied the Welch test. For those psychometric variables that were not normally distributed (according to the Shapiro–Wilk test), the Mann–Whitney *U* test was used. Several sleep variables (Sleep efficiency, WASO, Sleep latency, Relative Stage 1 duration, REM latency, number of awakenings) were characterized by positively skewed distributions. These variables were transformed to a natural logarithmic scale in order to normalize their distribution. Sleep variables as dependent factors were entered to multivariate analysis of variance (MANOVA) with group as an independent factor. To control the possible effects of the BDI-H and STAI-T on the group differences in sleep variables, multivariate analysis of covariance (MANCOVA) was conducted with the BDI-H and STAI-T scores as covariates. Since the EOG recordings of 3 subjects (2 CTL and 1 NM) were too noisy hindering the detection of EMs for the whole sample, the group difference in REM density was analyzed with univariate ANOVA without and with STAI-T and BDI-H as covariates. To compare the number of awakenings across groups, *t*-tests and univariate analysis of covariance (ANCOVA) were carried out. Pearson correlation coefficients were computed in order to analyze the relationship between waking depressive and anxiety symptoms and the absolute duration of sleep stages.

Results

Psychometric measures

Besides the group differences regarding the VDAS-H and the DQQ Negative Dream Affect scale (see "Participants" section), NMs reported increased levels of depressive symptoms and waking anxiety as evidenced by higher scores on the BDI-H (NM: 15.59 ± 3.83 vs. CTL: 10.87 ± 1.63; $t(21.39) = -4.321$; $p < .001$; equal variances not assumed) and STAI-T questionnaires (NM: 49.94 ± 7.66 vs. CTL: 33.3 ± 8.14; $t(38) = -5.971$; $p < .001$). These scores reflect mild, sub-clinical depression [41] and moderate levels of trait anxiety [39] in NMs. No significant difference was found between the two

groups regarding subjective sleep fragmentation measured by the Groningen Sleep Quality Scale (NM: 3.76 ± 3.05 vs. CTL: 2.78 ± 2.17; $U(38) = 158$; $Z = -1.041$; $p = .298$).

Sleep architecture

In order to normalize their distribution, some of the sleep variables (see Table 1) were logarithmized. The MANOVA revealed that NMs differed significantly from CTLs in the sleep variables ($F(9, 30) = 2.25$; $p = .046$). According to the univariate tests, NMs had significantly longer WASO and their sleep tended to be less efficient. Moreover, their relative NREM and SWS duration were significantly shortened, whereas their relative REM duration was significantly longer in comparison with the CTLs. Sleep latency, relative duration of Stage 1 and Stage 2, and REM latency did not differ between the two groups. Means of the groups, p values, and effect sizes are shown in Table 1.

In order to control for the confounding effects of anxiety and depression scores, we carried out MANCOVA with STAI-T and BDI-H scores as covariates in the model. NMs still differed significantly from CTLs ($F(9, 28) = 2.311$; $p = .043$). Significant group differences emerged for WASO, sleep efficiency, and SWS duration. NMs spent more time awake after falling asleep, their sleep was less efficient, and they spent less time in SWS in comparison with the CTLs. Moreover, these group differences were independent of the effects of questionnaire measures of depressive and anxiety symptoms. In contrast, by the inclusion of the two covariates the difference in relative NREM and REM duration did not remain significant, whereas sleep latency and the relative duration of Stage 1 sleep showed a marginal association with group. NMs had longer Stage 1 sleep, as well as they fell asleep more slowly. While the decreased relative NREM duration and the increased relative REM duration in NMs seem to be mediated by waking anxiety and depressive symptoms, longer duration of Stage 1 sleep and sleep latency were not a function of depressive symptoms and/or waking anxiety. Effect sizes and p values can be observed in Table 1.

Furthermore, we conducted univariate ANOVA to analyze the group differences regarding REM density without and with the control for STAI-T and BDI-H scores. Significant differences were found neither without ($F(1, 38) = .006$; $p = .937$) nor with the control for the psychometric variables ($F(1, 35) = .193$; $p = .663$).

Nocturnal awakenings

In addition, to clarify whether an increased number of awakenings are responsible for the altered duration of different sleep stages, the numbers of awakenings were also compared between the groups. Because these variables were not normally distributed, ln (x + 1) transformation was applied to normalize their distribution. Although the transformed variables still deviated from normality, the kurtoses of the distributions, which could have great effect on the robustness of the F test, were in acceptable range (−.6 to .4). Group comparisons revealed that NMs woke up significantly more, particularly from Stage 2 sleep. Group differences were more pronounced after controlling for waking the STAI-T and BDI scores. The number of awakenings from REM and SWS did not differ significantly between the two groups. Detailed results are shown in Table 2.

Table 1 Differences in sleep architecture between NMs and CTLs

	Mean ± SD[b]		ANOVA ($df = 1, 38$)			ANCOVA ($df = 1, 36$)[c]		
	NMs	CTLs	F	p	Partial η^2	F	p	Partial η^2
Sleep efficiency[a]	91.496 ± 6.38	95.024 ± 4.698	3.663	.063	.088	8.222	.007	.186
WASO (min)[a]	27.039 ± 19.515	17.565 ± 24.668	5.494	.024	.126	11.462	.002	.241
Sleep latency (min)[a]	17.274 ± 24.826	7.29 ± 6.992	2.162	.15	.054	3.264	.079	.083
Relative NREM sleep duration (%)	71.031 ± 3.849	74.83 ± 4.608	7.614	.009	.167	.243	.625	.007
Relative stage 1 duration (%)[a]	3.354 ± 2.276	2.822 ± 1.877	.88	.354	.023	3.407	.073	.086
Relative stage 2 duration (%)	52.673 ± 4.214	54.252 ± 5.765	.912	.346	.023	.546	.465	.015
Relative SWS duration (%)	15.004 ± 3.998	18.148 ± 4.517	5.212	.028	.121	5.343	.027	.129
Relative REM duration (%)	28.969 ± 3.849	25.026 ± 4.411	8.685	.005	.186	.517	.477	.014
REM latency (min)[a]	74.098 ± 23.676	83.478 ± 39.302	.224	.639	.006	.724	.4	.02

[a] Variables were ln (x) transformed for statistical comparisons

[b] Non-logarithmized values are displayed

[c] Group effects with STAI-T and BDI-H as covariates

Table 2 Differences in the number of awakenings between NMs and CTLs

	Mean ± SD[b]		Independent sample t test ($df = 38$)			ANCOVA ($df = 1; 36$)[d]		
	NMs	CTLs	t	p	Cohen's d[c]	F	p	Partial η^2
Number of awakenings from sleep[a]	10.118 ± 5.83	7.43 ± 4.698	−1.614	.115	.522	7.988	.008	.182
Number of awakenings from stage 2 sleep[a]	7.47 ± 5.467	4.7 ± 3.686	−2.073	.045	.677	6.174	.018	.146
Number of awakenings from SWS[a]	.82 ± 1.286	.52 ± .73	−.741	.463	.234	2.043	.162	.054
Number of awakenings from REM sleep[a]	1.82 ± 1.59	2.22 ± 2.152	.351	.728	.115	.068	.796	.002

[a] All variables were ln (x + 1) transformed for statistical comparisons

[b] Non-logarithmized values are displayed

[c] Absolute values are displayed

[d] Group effects with STAI-T and BDI-H as covariates

Associations between the absolute duration of sleep stages and questionnaire measures of waking depression/anxiety

Due to the difference between the results of the ANOVA and the ANCOVA, we analyzed further the associations of the lengths of different sleep stages with the STAI-T and BDI-H scores by computing Pearson correlation coefficients between the variables. Correlations were computed across the two groups. In order to examine these associations, we used the absolute length of the sleep stages. While in the previous analysis we used the relative amount of different sleep stages, here we decided to analyze the absolute amounts (length) because these values are independent of the duration of sleep, and therefore, from each other. Only absolute REM sleep duration showed significant correlations with STAI-T and BDI-H scores. None of the other variables correlated significantly with the psychometric scales. p and r values are shown in Table 3.

Table 3 Pearson correlation coefficients between psychometric tests and absolute duration of sleep stages across groups

	STAI-T		BDI-H	
	r ($n = 40$)	p	r ($n = 40$)	p
Absolute NREM sleep duration	−.192	.235	−.268	.094
Absolute stage 1 duration	−.013	.938	−.241	.133
Absolute stage 2 duration	−.167	.604	−.053	.745
Absolute SWS duration	−.072	.659	−.165	.310
Absolute REM duration	.447	.004	.429	.006

Discussion

We compared the sleep architecture of young subjects with frequent nightmares and healthy controls as reflected by the second night spent in the sleep laboratory. Sleep architecture clearly differentiated the two groups. NMs exhibited worse sleep quality than CTLs, showing reduced sleep efficiency, increased wakefulness after falling asleep, and reduced percentage of SWS. Moreover, NMs showed a trend regarding longer sleep latency and increased proportion of Stage 1 sleep. Furthermore, NMs were characterized by an increased number of nocturnal awakenings in Stage 2 sleep. Even though reduced SWS was characteristic in alcohol dependence and major depression [45], these differences between the two groups were independent of the confounding effects of sub-clinical waking psychopathology, suggesting that the relationship between nightmares and impaired sleep continuity is not a function of waking depressive symptoms or anxiety.

In contrast to our first hypothesis, NMs in comparison with CTLs did not rate their sleep as more fragmented according to the self-report measure of subjective sleep quality. While several studies applying retrospective questionnaires reported impaired subjective sleep quality in relation to nightmares [5, 18, 22, 24, 25], to the best of our knowledge, subjective sleep quality of NMs was not previously assessed in laboratory conditions. The incidence of disturbed dreaming is relatively low under laboratory and clinical settings even in traumatized subjects with severe post-traumatic nightmares [2, 46], and it is possible that the laboratory settings may influence—in this case, beneficially—the subjective quality of sleep as well. By all means, this finding indicates that our subjects were adequately adjusted to the artificial settings of the sleep laboratory and for the second night they had overcome the somewhat disturbing effects of polysomnography.

Interestingly, while NMs reported adequate subjective sleep quality, objective sleep quality was impaired in this group. In consistence with our second and third hypothesis, we found reduced sleep efficiency, increased WASO, decreased SWS, and more nocturnal awakenings in NMs in comparison with CTLs. Moreover, a trend for longer sleep

latency and increased Stage 1 sleep also reflects impairments of sleep regulation in NMs. We should note that while NMs showed consistent differences in these measures of sleep continuity, the alterations were only slightly below the normal range for this age group [47].

NMs also exhibited slightly longer durations of relative REM sleep and consequently slightly shortened relative NREM sleep in contrast to CTLs; although after controlling for depression and anxiety, the differences between the groups were not significant. Shortened REM latency, increased REM duration, and increased REM density are considered to be stabile biological markers of affective dysregulation in depression and other mood disorders [48–50]. However, we did not find increased REM density in NMs which may indicate the dissimilarity of frequent nightmares from depression. Furthermore, brain imaging as well as behavioral research indicates that REM sleep is intimately related to the activation of emotion-processing networks [51, 52]. Frequent nightmares are often comorbid with disorders of emotional regulation [7], and nightmares are experiences involving intense negative emotions. Therefore, it is plausible that in NMs the relative increase in REM pressure in the second half of the night was mediated by the heightened negative affect. Accordingly, we found that depressive symptoms and trait anxiety as measured by the BDI-H and the STAI-T, respectively, showed medium-size correlations with the length of REM sleep.

In sum, we found impaired sleep continuity with reduced SWS and increased REM pressure in NMs, but while alterations in sleep continuity were independent associates with disturbed dreaming, heightened REM activity seemed to be a function of comorbid affective dysregulation. Our results cohere with earlier reports of Fisher and colleagues [29], but are inconsistent to the results of a more recent study by Germain and Nielsen [30], which did not find altered sleep architecture in idiopathic nightmare sufferers. Nevertheless, in this study, three groups (post-traumatic nightmare sufferers, idiopathic nightmare sufferers, and healthy controls) were compared with relatively low sample sizes limiting statistical power for testing group differences. Moreover, their nightmare subjects were elder in comparison with the subjects of the present study and were recruited by media advertisements instead of the questionnaire-based selection process that we applied. And finally, the authors did not control for the confounding effects of waking psychopathology that might have influenced sleep parameters.

Spoormaker [2] and Lancee et al. [18] proposed that nightmares should be viewed as a sleep disorder instead of a secondary symptom of an underlying mental complaint. This assumption may be supported by genetic twin studies carried out on NMs [21, 53]. Our results demonstrating that impaired sleep continuity in subjects with frequent nightmares is independent of the effects of waking depressive symptoms or trait anxiety clearly support this claim. Indeed, our analyses showed that the statistical control for the effects of waking psychopathological symptoms resulted in a better model explaining the group differences of altered sleep architecture regarding NREM sleep. Nevertheless, waking symptoms of psychopathology have a profound impact on REM sleep in NMs due to the higher levels of depression and anxiety scores that characterize them. Thus, it could be possible that nightmare disorder is the consequence of the combination of two at least partly independent factors, the impaired NREM continuity and the increased REM pressure stemmed from the increase of depressive and anxious symptoms that NMs experience.

Instead of the prevailing view that nightmare disorder affects mainly REM sleep [31, 37], our results indicate that NMs have impaired sleep regulation during NREM sleep. Longer sleep latency, increased number of nocturnal awakenings, and reduced SWS reflect a more aroused, more alert brain state resulting in less restorative and less efficient sleep. Since the majority of awakenings occurred in the second Stage of NREM sleep, it is highly probable that the reduced amount of SWS in NMs is due to these relatively short nocturnal awakenings that may hinder the appearance of slower neural oscillations during NREM sleep and prevent sleep to reach deeper stages. It is well known that SWS appears predominantly in the first third of the night [47]. Later as sleep progresses, the neural apparatus may not recover the deficit of slow activity because of the heightened pressure of REM sleep related to comorbid affective dysregulation.

Disrupted sleep in NMs may resemble sleep patterns found in chronic insomnia stemmed from hyperarousal processes during sleep [54, 55]. The possible overlap between nightmares and insomnia is supported by an epidemiologic study that showed higher prevalence (18.3 %) of nightmares in subjects complaining about insomnia symptoms [26] compared to the population (2–4 %). Moreover, one study [30] reported similar patterns of elevated periodic limb movements in PTSD and idiopathic nightmare disorder indicating sleep-related hyperarousal in PTSD and idiopathic nightmares sufferers [30]. Therefore, it is feasible that impaired sleep continuity in our NMs originates from heightened arousal; however, future studies with more refined quantitative analysis on the neural oscillations as well as the arousal processes during sleep should examine the overlapping patterns or dissimilarities between these pathological states.

Our results indicate that NMs are not aware of their impaired sleep continuity. This is an interesting finding since the opposite is reported in samples of subjective insomnia patients, who tend to overestimate the amount of

wake time disrupting sleep [55]. Sleep state misperception in insomniacs is related to the dissociation between sleep-inducing and arousing mechanisms—with abnormally increased cortical arousal—and consequently to enhanced levels of sensory and cognitive processing during sleep [55, 56]. While it is possible that the "harmony" of sleep-promoting and arousing mechanisms is also impaired in NMs, we speculate that in their case, cortical hyperarousal is not resulting in increased sensory processing of external information. In contrast, NMs may engage cortical resources toward internally generated sensorial, emotional, and cognitive processes that constitute the raw material for intense dream experiences [30, 57].

Nightmares are thought to impair sleep quality by frequent nocturnal awakenings as well as by fear of falling or returning to sleep [24]. However, an inverse mechanism could be also plausible. Fragmented sleep, with frequent arousals and awakenings, reflecting impaired sleep continuity, may also trigger the appearance of dysphoric dreams, especially in case of comorbid trait-like effects of affective dysregulation or state-like effects of current stress. In addition, the high number of awakenings and the more superficial sleep may promote the recall of dreams including dysphoric ones. Furthermore, impaired sleep quality may also have deleterious effects on affective processes during waking. For instance, a recent longitudinal study with adolescents showed that poor sleep quality is predictive of impaired emotional information processing abilities [58]. Impaired emotion processing may compromise emotional regulation, and thus lead to heightened negative affect.

While our study does not allow for inferences on the mechanism of nightmare generation, it clearly indicates that impaired sleep continuity is an integral part of this disorder. Therefore, we consider that the interrelation between disturbed dreaming and altered sleep regulation requires further investigations. Apart from the short nocturnal awakenings, examining microarousals that do not lead to awakenings in NREM sleep would provide a more detailed picture about impaired sleep regulation in NMs. Moreover, examining the sleep stages with more refined quantitative methods would foster our understanding of the presumably altered neural oscillatory activity in this population.

Since we were interested in the "undisturbed" sleep architecture of individuals with frequent nightmares, we did not wake up our subjects in order to collect dream reports. Consequently, our study does not provide any information regarding sleep parameters during nightmares. Moreover, only 3 of our subjects reported dysphoric dream experiences in consistence to earlier results showing the attenuation of nightmares in laboratory settings [2]. Ambulant sleep recordings or polysomnographic measurements with more adaptation nights would be more adequate methods in order to examine sleep parameters in NMs. Additionally, we did not acquire data on circadian rhythms that might be related to altered sleep patterns in NMs. A recent study indicates that nightmares are related to eveningness chronotype in females [59]; therefore, it is possible that the predominance of this among NMs influenced our results. Nevertheless, it seems unlikely that sleep disruptions were the result of eveningness chronotype since subjects went to bed at their preferred bedtime and sleep pressure might have been increased for the second night if sleep curtailment occurred for the first night. And finally, examining a student sample may be advantageous because of the relative homogeneity of our subjects, but on the other hand, we must be careful in generalizing our results to other populations. In spite of these limitations, our study provides relevant empirical data on the relationship between nightmares and altered sleep architecture contributing to our understanding of this scarcely investigated but peculiar oneiric experience.

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References

1. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th text revision edn. American Psychiatric Publishing, Washington, DC
2. Spoormaker VI, Schredl M, van den Bout J (2006) Nightmares: from anxiety symptom to sleep disorder. Sleep Med Rev 10(1): 19–31
3. Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S (1979) Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 136(10):1257–1262
4. Schredl M (2010) Nightmare frequency and nightmare topics in a representative German sample. Eur Arch Psychiatry Clin Neurosci 260(8):565–570
5. Li SX, Zhang B, Li AM, Wing YK (2010) Prevalence and correlates of frequent nightmares: a community-based 2-phase study. Sleep 33(6):774–780
6. Blagrove M, Farmer L, Williams E (2004) The relationship of nightmare frequency and nightmare distress to well-being. J Sleep Res 13(2):129–136
7. Levin R, Nielsen TA (2007) Disturbed dreaming, posttraumatic stress disorder, and affect distress: a review and neurocognitive model. Psychol Bull 133(3):482–528
8. Zadra A, Pilon M, Donderi DC (2006) Variety and intensity of emotions in nightmares and bad dreams. J Nerv Ment Dis 194(4): 249–254
9. Agargun MY, Besiroglu L, Cilli AS, Gulec M, Aydin A, Inci R, Selvi Y (2007) Nightmares, suicide attempts, and melancholic features in patients with unipolar major depression. J Affect Disord 98(3):267–270

10. Agargun MY, Kara H, Ozer OA, Selvi Y, Kiran U, Kiran S (2003) Nightmares and dissociative experiences: the key role of childhood traumatic events. Psychiatry Clin Neurosci 57(2): 139–145
11. Roberts J, Lennings CJ (2006) Personality, psychopathology and nightmares in young people. Pers Individ Dif 41(4):733–744
12. Simor P, Csóka S, Bódizs R (2010) Nightmares and bad dreams in patients with borderline personality disorder: fantasy as a coping skill? Eur J Psychiat 24(1):28–37
13. Krakow B, Schrader R, Tandberg D, Hollifield M, Koss MP, Yau CL, Cheng DT (2002) Nightmare frequency in sexual assault survivors with PTSD. J Anxiety Disord 16(2):175–190
14. Tanskanen A, Tuomilehto J, Viinamäki H, Vartiainen E, Lehtonen J, Puska P (2001) Nightmares as predictors of suicide. Sleep 24(7):844–847
15. Spoormaker VI, van den Bout J (2005) Depression and anxiety complaints; relations with sleep disturbances. Eur Psychiatry 20(3):243–245
16. Levin R, Fireman G (2002) Nightmare prevalence, nightmare distress, and self-reported psychological disturbance. Sleep 25(2): 205–212
17. Belicki K (1992) Nightmare frequency versus nightmare distress: relations to psychopathology and cognitive style. J Abnorm Psychol 101(3):592–597
18. Lancee J, Spoormaker VI, Van den Bout J (2010) Nightmare frequency is associated with subjective sleep quality but not with psychopathology. Sleep Biol Rhythms 8(3):187–193
19. Spoormaker VI, Montgomery P (2008) Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev 12(3):169–184
20. Wood JM, Bootzin RR (1990) The prevalence of nightmares and their independence from anxiety. J Abnorm Psychol 99(1):64–68
21. Coolidge FL, Segal DL, Coolidge CM, Spinath FM, Gottschling J (2010) Do nightmares and generalized anxiety disorder in childhood and adolescence have a common genetic origin? Behav Genet 40(3):349–356
22. Schredl M (2003) Effects of state and trait factors on nightmare frequency. Eur Arch Psychiatry Clin Neurosci 253(5):241–247
23. Li SX, Yu MW, Lam SP, Zhang J, Li AM, Lai KY, Wing YK (2011) Frequent nightmares in children: familial aggregation and associations with parent-reported behavioral and mood problems. Sleep 34(4):487–493
24. Krakow B, Tandberg D, Scriggins L, Barey M (1995) A controlled comparison of self-rated sleep complaints in acute and chronic nightmare sufferers. J Nerv Ment Dis 183(10):623–627
25. Krakow B (2006) Nightmare complaints in treatment-seeking patients in clinical sleep medicine settings: diagnostic and treatment implications. Sleep 29(10):1313–1319
26. Ohayon MM, Morselli PL, Guilleminault C (1997) Prevalence of nightmares and their relationship to psychopathology and daytime functioning in insomnia subjects. Sleep 20(5):340–348
27. Schredl M, Schafer G, Weber B, Heuser I (1998) Dreaming and insomnia: dream recall and dream content of patients with insomnia. J Sleep Res 7(3):191–198
28. Schredl M (2009) Nightmare frequency in patients with primary insomnia. Int J Dream Res 2(2):85–88
29. Fisher C, Byrne J, Edwards A, Kahn E (1970) A psychophysiological study of nightmares. J Am Psychoanal Assoc 18(4): 747–782
30. Germain A, Nielsen TA (2003) Sleep pathophysiology in post-traumatic stress disorder and idiopathic nightmare sufferers. Biol Psychiatry 54(10):1092–1098
31. Nielsen TA, Paquette T, Solomonova E, Lara-Carrasco J, Popova A, Levrier K (2010) REM sleep characteristics of nightmare sufferers before and after REM sleep deprivation. Sleep Med 11(2):172–179
32. Nielsen T, Paquette T, Solomonova E, Lara-Carrasco J, Colombo R, Lanfranchi P (2010) Changes in cardiac variability after REM sleep deprivation in recurrent nightmares. Sleep 33(1):113–122
33. Agnew HWJ, Webb WB, Williams RL (1966) The first night effect: an EEG study of sleep. Psychophysiology 2(3):263–266
34. Bódizs R, Simor P, Csóka S, Bérdi M, Kopp MS (2008) Dreaming and health promotion: a theoretical proposal and some epidemiological establishments. Eur J Ment Health 3(1):35–62
35. Simor P, Köteles F, Sándor P, Petke Z, Bódizs R (2011) Mindfulness and dream quality: the inverse relationship between mindfulness and negative dream affect. Scand J Psychol 52(4): 369–375
36. Simor P, Kovacs I, Vargha A, Csoka S, Mangel B, Bodizs R (2009) Nightmares, dream anxiety and psychopathology: the validation of the Hungarian version of the Van Anxiety Scale. Psychiatr Hung 24(6):428–438
37. American Academy of Sleep Medicine (2005) The international classification of sleep disorders: diagnostic and coding manual, 2nd edn. American Academy of Sleep Medicine, Westchester
38. Spielberger C, Gorsuch R, Lusgene R (1970) Manual for the state-trait anxiety inventory. Consulting Psychologists Press, Palo Alto
39. Sipos K, Sipos M, Spielberger CD (1994) A State-Trait Anxiety Inventory (STAI) magyar változata. In: Mérei F, Szakács F (eds) Pszichodiagnosztikai Vademecum I/2. Nemzeti Tankönyvkiadó, Budapest, pp 123–148
40. Köteles F, Szemerszky R, Freyler A, Bárdos G (2011) Somatosensory amplification as a possible source of subjective symptoms behind modern health worries. Scand J Psychol 52(2): 174–178
41. Rózsa S, Szádoczky E, Füredi J (2001) A Beck Depresszió Kérdőív rövidített változatának jellemzői a hazai mintán. Psychiatria Hungarica 16(4):379–397
42. Simor P, Köteles F, Bódizs R, Gy B (2009) A questionnaire based study of subjective sleep quality: the psychometric evaluation of the Hungarian version of the Groningen Sleep Quality Scale. Mentálhigiéné és Pszichoszomatika 10(3):249–261
43. Jasper H (1958) Report of the committee on methods of clinical examination in electroencephalography. Electroenceph Clin Neurophysiol 10:370–375
44. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. UCLA, Brain Information Service, Los Angeles
45. Brower KJ, Hoffmann R, Conroy DA, Arnedt JT, Armitage R (2011) Sleep homeostasis in alcohol-dependent, depressed and healthy control men. Eur Arch Psychiatry Clin Neurosci 261(8): 559–566
46. Woodward SH, Arsenault NJ, Murray C, Bliwise DL (2000) Laboratory sleep correlates of nightmare complaint in PTSD inpatients. Biol Psychiatry 48(11):1081–1087
47. Rechtschaffen A, Siegel JM (2000) Sleep and dreaming. In: Kandel ER, Schwartz JH, Jessel TM (eds) Principles of neuroscience, 4th edn. McGraw-Hill, New York
48. Benca RM, Okawa M, Uchiyama M, Ozaki S, Nakajima T, Shibui K, Obermeyer WH (1997) Sleep and mood disorders. Sleep Med Rev 1(1):45–56
49. Riemann D, Berger M, Voderholzer U (2001) Sleep and depression–results from psychobiological studies: an overview. Biol Psychol 57(1–3):67–103
50. Buysse DJ, Tu XM, Cherry CR, Begley AE, Kowalski J, Kupfer DJ, Frank E (1999) Pretreatment REM sleep and subjective sleep quality distinguish depressed psychotherapy remitters and nonremitters. Biol Psychiatry 45(2):205–213
51. Gujar N, McDonald SA, Nishida M, Walker MP (2011) A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. Cereb Cortex 21(1):115–1123

52. Maquet P, Ruby P, Maudoux A, Albouy G, Sterpenich V, Dang-Vu T, Desseilles M, Boly M, Perrin F, Peigneux P, Laureys S (2005) Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. Prog Brain Res 150:219–227
53. Hublin C, Kaprio J, Partinen M, Koskenvuo M (1999) Nightmares: familial aggregation and association with psychiatric disorders in a nationwide twin cohort. Am J Med Genet 88(4): 329–336
54. Krystal AD, Edinger JD, Wohlgemuth WK, Marsh GR (2002) NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. Sleep 25(6):630–640
55. Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, Nissen C (2010) The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 14(1):19–31
56. Feige B, Al-Shajlawi A, Nissen C, Voderholzer U, Hornyak M, Spiegelhalder K, Kloepfer C, Perlis M, Riemann D (2008) Does REM sleep contribute to subjective wake time in primary insomnia? A comparison of polysomnographic and subjective sleep in 100 patients. J Sleep Res 17(2):180–190
57. Nielsen TA, Stenstrom P (2005) What are the memory sources of dreaming? Nature 437(7063):1286–1289
58. Soffer-Dudek N, Sadeh A, Dahl RE, Rosenblat-Stein S (2011) Poor sleep quality predicts deficient emotion information processing over time in early adolescence. Sleep 34(11):1499–1508
59. Nielsen T (2010) Nightmares associated with the eveningness chronotype. J Biol Rhythms 25(1):53–62

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Disturbed Dreaming and the Instability of Sleep: Altered Nonrapid Eye Movement Sleep Microstructure in Individuals with Frequent Nightmares as Revealed by the Cyclic Alternating Pattern

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Study Objectives: Nightmares are disturbing mental experiences during sleep that usually result in abrupt awakenings. Frequent nightmares are associated with poor subjective sleep quality, and recent polysomnographic data suggest that nightmare sufferers exhibit impaired sleep continuity during nonrapid eye movement (NREM) sleep. Because disrupted sleep might be related to abnormal arousal processes, the goal of this study was to examine polysomnographic arousal-related activities in a group of nightmare sufferers and a healthy control group.

Design: Sleep microstructure analysis was carried out by scoring the cyclic alternating pattern (CAP) in NREM sleep and the arousal index in rapid eye movement (REM) sleep on the second night of the polysomnographic examination.

Setting: Hospital-based sleep research laboratory.

Participants: There were 17 in the nightmare (NMs) group and 23 in the healthy control (CTLs) group.

Interventions: N/A.

Measurements and Results: The NMs group exhibited reduced amounts of CAP A1 subtype and increased CAP A2 and A3 subtypes, as well as longer duration of CAP A phases in comparison with CTLs. Moreover, these differences remained significant after controlling for the confounding factors of anxious and depressive symptoms. The absolute number and frequency of REM arousals did not differ significantly between the two groups.

Conclusions: The results of our study indicate that NREM sleep microstructure is altered during nonsymptomatic nights of nightmares. Disrupted sleep in the NMs group seems to be related to abnormal arousal processes, specifically an imbalance in sleep-promoting and arousing mechanisms during sleep.

Keywords: Arousals, cyclic alternating pattern (CAP), dreaming, nightmare, sleep microstructure

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INTRODUCTION

According to the International Classification of Sleep Disorders,[1] nightmares are disturbing mental experiences that often awaken the dreamer from late-night rapid eye movement (REM) sleep. The co-occurrence of disturbed dreaming and psychopathologic symptoms[2] has contributed to the assumption that nightmares are the secondary symptom of an underlying mental disorder. Although comorbid psychopathology may increase the severity and daytime effects of disturbed dreaming, research suggests that frequent nightmares should be considered as a specific sleep disorder that are independent in its origins from other mental complaints.[3-6] A growing body of research indicates that nightmares are related to impaired subjective sleep quality in large cohorts of adults, children, and university students.[7-9] Furthermore, negatively toned dreams are more frequent among individuals with insomnia and other sleep disordered persons,[10,11] and nightmare frequency seems to be related to the severity of sleep complaints.[10,12]

Early sleep electroencephalography (EEG) studies revealed altered sleep architecture in idiopathic nightmare sufferers reflected by decreased total sleep time and slow-wave sleep (SWS), as well as an increase in nocturnal awakenings.[13,14] A later study[15] with a relatively small sample size failed to confirm these findings but reported enhanced motor activation in NREM and REM sleep in idiopathic and posttraumatic nightmare sufferers, suggesting that increased arousal and the release of motor inhibition are related to negative dream experiences. Another study[16] reported heightened sympathetic arousal in nightmare sufferers during NREM and REM periods after a partial REM deprivation procedure. A more recent polysomnographic study[17] found that nightmare sufferers, in comparison with control patients, exhibited reduced sleep efficiency, increased wakefulness after sleep onset, decreased SWS, and higher number of nocturnal awakenings, especially from Stage 2 sleep. Nightmare sufferers also showed increased duration of REM sleep that was mediated by questionnaire measures of heightened daytime negative affect.

It is important to note that altered sleep architecture was not related to the occurrence of nightmares in these studies. In fact, because nightmares have almost never been reported in laboratory settings even in frequent nightmare sufferers, these findings indicate that impaired sleep regulation is an inherent, presumably traitlike feature of nightmare sufferers' sleep pathophysiology. Nightmares are assumed to arise mainly from REM sleep[5]; however, Simor and colleagues[17] showed that sleep instability in nightmare sufferers is more pronounced in NREM sleep. Impaired NREM sleep continuity, frequent awakenings from Stage 2 sleep, decreased SWS, and enhanced motor and

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sympathetic activation may reflect dysfunctional arousal processes, an imbalance of sleep-promoting and arousing mechanisms during sleep.

Cyclic alternating pattern (CAP)[18,19] is a spontaneous rhythm of NREM sleep characterized by EEG oscillations corresponding to recurrent activation events and unstable sleep depth. Since its discovery,[19] CAP has been extensively applied to the study of human sleep, in normal and pathologic conditions, in a wide age range from newborns to adults and elderly,[18,20] and is now considered to be a comprehensive tool to study sleep instability.[18] The analysis of CAP has already been shown to be useful in the understanding of neurophysiologic mechanisms of different NREM sleep parasomnia in children[20-22] and also in REM sleep parasomnia of adults.[23,24]

Thus, we considered that the fine grained microstructural analysis examining the nature of arousals in NREM sleep that can be carried out by CAP analysis would shed more light on the anomalies of sleep-wake regulation of nightmare sufferers. Moreover, to verify whether abnormal arousal processes are specific to NREM sleep or are also present in REM sleep, we analyzed arousal processes in REM sleep as well. We expected increased NREM sleep instability in nightmare sufferers, reflected by enhanced CAP rate, especially of the subtypes A2 and A3. Furthermore, based on the independence of nightmare-related NREM alterations from daytime distress,[17] we hypothesized that increased arousal processes during NREM sleep would be independent of the confounding effects of waking anxiety and/or depressive symptoms. Based on previous findings, we also hypothesized increased microarousals in nightmare sufferers during REM sleep, but we expected this enhancement to be mediated by waking psychopathological symptoms.

METHODS

Participants

Participants (all native Hungarians) were selected from a large pool of undergraduate students from the Budapest University of Technology and Economics and the Semmelweis University. The selection procedure of nightmare sufferers (NMs) and a control group (CTLs) was described previously in detail.[17] In brief, individuals were selected based on their scores on three different dreaming-related questionnaires: the Dream Quality Questionnaire (DQQ),[25] the Hungarian version of the Van Dream Anxiety Scale (VDAS-H),[26] and a 7-point Likert scale assessing the frequency of nightmares. Individuals reporting one or more nightmares per week in the retrospective questionnaires were assigned to the NMs group, whereas individuals having fewer than two nightmares during the past year were assigned as CTLs. Those individuals who reported the onset of negative dream experiences in relation to a traumatic event or indicated that the content of their dreams was related to a previous trauma (such as physical attack, accident, sudden death of a close relative, etc.) were excluded from the study. Finally, 17 NMs (7 females and 10 males) ($M_{age} = 20.65 \pm 1.73$) and 23 CTLs (12 females and 11 males) ($M_{age} = 21.35 \pm 1.61$) underwent polysomnographic studies. (The difference in age was not significant between the two groups: $U(38) = 134$; $Z = -1.719$; $P = 0.086$). NMs scored higher on the Negative Dream Affect Scale of the DQQ ($M_{NMs} = 7.8$; $SD_{NMs} = 1.81$ versus $M_{CTLs} = 4.04$; $SD_{CTLs} = 1.69$; $t(38) = -6.83$; $P < 0.001$) and on the VDAS-H ($M_{NMs} = 19.53$; $SD_{NMs} = 7.21$ versus $M_{CTLs} = 0.26$; $SD_{CTLs} = 0.62$; $t(16.17) = -10.99$; $P < 0.001$; equal variances not assumed), indicating at least moderately severe dream disturbances.[25,26]

None of the individuals reported previous neurological, psychiatric, or sleep disorders or history of any chronic disease. The study protocol was approved by the Ethical Committee of the Semmelweis University. The individuals received monetary compensation for their participation in the sleep laboratory investigations. Written informed consent was obtained.

Psychometric Tests

The State-Trait Anxiety Inventory (STAI)[27] is a widely used self-report instrument that differentiates the temporary condition of state anxiety and the long-standing quality of trait anxiety. We used the 20-item Hungarian version of the STAI-T (Trait Anxiety) to assess general levels of anxiety.[28]

We used the short form of the Hungarian version of the Beck Depression Inventory (BDI-H)[29] to measure the extent of waking depressive symptoms in our study participants. The 9-item BDI-H is a one-dimensional scale assessing different symptoms of depression including social withdrawal, indecision, sleep disturbance, fatigue, intense worry about bodily symptoms, work inhibition, pessimism, lack of satisfaction, and self-accusation.

The Hungarian version of the Groningen Sleep Quality Scale (GSQS) was used for measuring subjective sleep quality.[30] The 14-item questionnaire measures the extent of subjective sleep fragmentation by a binary scale.

Procedure

Polysomnographic recordings were performed in the sleep research laboratory of the Semmelweis University for 2 consecutive nights. (The first night served as the adaptation night). Study participants were not allowed to drink alcohol or take drugs (except contraceptives) on the day of and the day before the examination. They were asked to avoid napping and consuming caffeine on the afternoon of the sleep recordings. Study participants completed the short version of the BDI-H upon arrival. (The STAI-T was completed previously during the selection procedure.) The timing of lights off was between 11:00 and 01:00 depending on each participant's preferred bedtime. Morning awakenings were scheduled after 9 hours of undisturbed sleep except if participants woke up earlier spontaneously. In the morning, participants were asked to complete the GSQS and to report their dreams. Three of the NMs reported negatively toned dreams in the laboratory.

Polysomnography

During the standard polysomnographic examination on both nights, participants were fitted with 19 EEG electrodes (Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2) according to the 10-20 electrode placement system[31] as well as with two electrodes (bipolar channel) monitoring vertical and horizontal eye movements; electromyography (EMG) electrodes (bipolar channels) for the chin and for the anterior tibialis muscles, 2 ECG electrodes according to standard lead I; in addition to the thoracic and abdominal respiration sensors. Gold-coated Ag/AgCl EEG cup electrodes were fixed with EC2 Grass Electrode

Cream (Grass Technologies, West Warwick, USA) and referred to the mathematically-linked mastoids. Impedances were kept below 8 kΩ. Signals were collected, prefiltered (0.33-1,500 Hz, 40dB/decade anti-aliasing hardware input filter), amplified, and digitized with 4,096 Hz/channel sampling rate (synchronous) with 12-bit resolution by using the 32-channel EEG/polysystem (Brain-Quick BQ 132S, Micromed, Treviso, Italy). A further 40 dB/decade antialiasing digital filter was applied by digital signal processing, which low-pass filtered the data at 450 Hz. Finally, the digitized and filtered EEG was undersampled at 1,024 Hz.

CAP Scoring

Sleep stages and conventional measures of sleep macrostructure were previously scored according to standard criteria[32] by two experienced sleep researchers who were blind to the group membership of the participants. CAP was scored according to the criteria published by Terzano et al.[33] CAP is a periodic EEG activity of NREM sleep characterized by sequences of cycles composed of a phase A (transient electrocortical event) and a phase B (recurring EEG background activity). Phase A activities can be classified into three subtypes. This classification is based on the reciprocal proportion of high-voltage slow waves (EEG synchrony) and low-amplitude fast rhythms (EEG desynchrony). Subtype A1 shows a predominance of synchronized EEG activity; if present, EEG desynchrony occupies less than 20% of the entire A phase duration. Subtype A1 specimens include delta bursts, K-complex sequences, vertex waves, and polyphasic bursts with less than 20% of EEG desynchrony. Subtype A2 is scored in the presence of 20-50% of desynchronized EEG activity, with predominance of polyphasic bursts. Subtype A3 EEG activity is predominantly rapid low-voltage rhythms with more than 50% of phase A occupied by EEG desynchrony. Subtype A3 include EEG arousals and K-alpha and polyphasic bursts (with at least 50% of EEG desynchrony). CAP cycles are based on the presence of two successive phases A and B. CAP sequences are defined as three or more A phases separated from each other by no more than 60 s. CAP rate is defined as the percentage of total NREM time occupied by CAP sequences. The remaining NREM sleep is called non-CAP (NCAP). All CAP events were visually detected and marked on recordings and CAP parameters (CAP rate, rate and duration of CAP A subtypes, duration of A and B phases as well as the frequency (number/h) of A subtypes: A1, A2, A3 index) were extracted by means of the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy).

REM Arousals

Arousals during REM sleep were detected visually according to the criteria of the American Sleep Disorders Association[34] by a blind rater trained on sleep arousal scoring. REM arousals were scored as abrupt increases of EEG frequencies including theta, alpha, or beta activities for at least 3 sec as well as an increase (for at least 1 sec) of EMG activity in chin muscle tone. The absolute number of REM arousals as well as the frequency of REM arousals (the REM arousal index: the number of REM arousals/h) was used for statistical analyses.

Statistical Analyses

Statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS) version 19.0. Mean scores of the psychometric tests were compared with independent samples *t* test; if the criterion for homogeneity of variance was violated, we applied the Welch test. For those psychometric variables that were not normally distributed (according to the Shapiro-Wilk test), the Mann-Whitney U test was used. Those variables that were characterized by positively skewed distributions were transformed to a natural logarithmic scale to normalize their distribution. CAP variables as dependent factors were entered into a multivariate analysis of variance (MANOVA) model with group membership as an independent factor. To control for the confounding effects of daytime waking distress, we carried out a multivariate analysis of covariance (MANCOVA) with the same dependent and independent factors as well as the BDI-H and STAI-T scores as covariates in the model. Similar analyses were carried out for REM arousals. Significance level was set at $P < 0.05$ and the Bonferroni corrected value ($P < 0.005$) was considered in case of multiple comparisons of different independent variables.

RESULTS

Psychometric Variables and Sleep Architecture

A detailed description of psychometric assessments and differences regarding standard sleep architecture has been previously reported elsewhere.[17] Nonetheless, for clarity we provide a brief summary of these results. NMs in comparison with CTLs were characterized by significantly higher scores on the STAI-T and BDI-H questionnaires, indicating mild anxiety and depressive symptoms. NMs and CTLs did not significantly differ regarding subjective sleep fragmentation. In contrast, objective sleep measures showed increased wakefulness and Stage 1 sleep, as well as decreased SWS, reduced sleep efficiency, and more nocturnal awakenings in NMs. NMs also showed increased REM sleep; however, this was mediated by heightened waking affect measured by the psychometric assessments.

CAP Analysis

The comparison of CAP parameters with MANOVA revealed a significant main effect for Group ($F(12,27) = 5.53$; $P < 0.001$; Partial $\eta^2 = 0.71$), indicating that NMs and CTLs show different patterns regarding the microstructure of NREM sleep. Descriptive statistics and univariate tests of CAP indices are summarized in Table 1. Although the overall CAP rate was similar, the distributions of CAP A subtypes showed marked differences between the two groups (Figure 1). NMs exhibited a significantly lower percentage of A1 and higher rates of A2 as well as a trend of increase in the number of A3 subtypes. If the time spent in NREM sleep was controlled, the increase of A2 subtype (A2 index) remained significant, the increase in A3 index showed a trend, but the decrease in A1 index was not significant. Apart from these differences, the mean duration of CAP A phases was significantly longer in NMs in comparison with the CTLs. The comparison of the other CAP parameters did not reveal significant differences (Table 1).

To control for the confounding effects of waking anxiety and depressive symptoms, we carried out a MANCOVA with STAI-T and BDI-H scores as covariates in the model. The difference between NMs and CTLs remained significant ($F(12,25) = 3.3$; $P = 0.006$; partial $\eta^2 = 0.61$). In accordance with the previous

Table 1—Comparison of CAP variables between NMs and CTLs

	Means ± SD	Mean ± SD	ANOVA (df = 1,38)		
	NMs (n = 17)	CTLs (n = 23)	F	P <	Partial η^2
CAP rate (%)	37.68 ± 12.62	34.46 ± 10.81	0.75	NS	0.19
A1 (%)	68.96 ± 8.26	78.81 ± 6.07	18.91	0.0001	0.33
A2 (%)	16.47 ± 3.53	9.75 ± 2.65	47.41	0.0001	0.56
A3 (%)	14.56 ± 7.04	11.43 ± 4.75	2.83	0.1	0.069
A mean duration (s)	7.86 ± 0.82	6.97 ± 0.5	17.84	0.0001	0.32
A1 mean duration (s)	5.84 ± 0.6	5.69 ± 0.45	0.87	NS	0.02
A2 mean duration (s)	9.53 ± 1.49	8.81 ± 1.6	2.09	NS	0.05
A3 mean duration (s)	15.35 ± 1.76	14.8 ± 3.25	0.39	NS	0.01
B mean duration (s)	22.68 ± 2.13	23.08 ± 2.67	0.26	NS	0.001
A1 index (n/h)	37.1 ± 13.78	39.61 ± 13.02	0.35	NS	0.01
A2 index (n/h)	8.22 ± 4.05	4.31 ± 1.94	16.51	0.0001	0.30
A3 index (n/h)	6.54 ± 4.66	4.15 ± 2.04	4.85	0.05	0.11

ANOVA, analysis of variance; CAP, cyclic alternating pattern; CTLs, healthy control individuals; df, degrees of freedom; NMs, nightmare sufferers; NS, not significant; SD, standard deviation.

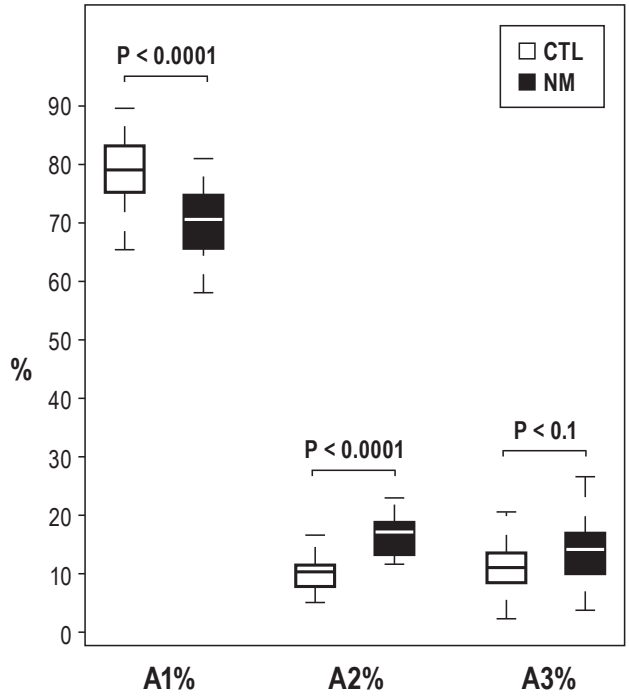

Figure 1—Group differences in the CAP subtypes: A1%, A2%, and A3%. Nightmare sufferers (NMs) show a significant decrease in A1% and a significant increase in A2% compared with healthy control individuals (CTLs).

Table 2—Analysis of covariance group (nightmare sufferers, healthy control individuals) effects with STAI-T (STAI-Trait Anxiety), Beck Depression Inventory (Hungarian version) as covariates

	ANCOVA (df = 1,36)		
	F	P <	Partial η^2
CAP rate (%)	1.413	NS	0.04
A1 (%)	11.783	0.005	0.25
A2 (%)	25.036	0.0001	0.41
A3 (%)	2.620	0.15	0.07
A mean duration (s)	9.366	0.005	0.21
A1 mean duration (s)	0.061	NS	0.001
A2 mean duration (s)	1.070	NS	0.03
A3 mean duration (s)	0.002	NS	0.001
B mean duration (s)	1.031	NS	0.03
A1 index (n/h)	0.000	NS	0.001
A2 index (n/h)	11.930	0.001	0.25
A3 index (n/h)	4.127	0.05	0.1

ANCOVA, analysis of covariance; CAP, cyclic alternating pattern; df, degrees of freedom; NS, not significant.

analysis, significant group differences emerged for A1% and A2% as well as a weak trend for A3%. A2 index and the mean duration of CAP A phases remained significantly increased in NMs in comparison with CTLs, and the increase of A3 index in NMs showed a trend (Table 2).

REM Arousals

A main effect for Group emerged F(2,37) = 3.93; P = 0.028; partial η^2 = 0.18 between NMs and CTLs; however, neither the number (M_{NMs} = 38.82; SD_{NMs} = 17.21 vs. M_{CLTs} = 33.43; SD_{CTLs} = 15.67; F(1,38) = 1.06; P = 0.31) nor the frequency of REM arousals (REM arousal index) (M_{NMs} = 21.71; SD_{NMs} = 7.79 versus M_{CLTs} = 23.2; SD_{CTLs} = 11.52; F(1,38) = 0.21; P = 0.65) differed significantly between the groups. Therefore, the significant main effect of Group in the MANOVA refers to the difference regarding the nonoverlapping part of the two dependent variables (number and frequency of REM arousals). Because the only non-overlapping factor between the number and the frequency of REM arousals is the duration of REM sleep, the significant main effect for Group likely reflects the difference in REM duration. This was supported by the fact that after including the relative duration of REM sleep as a covariate in the same model, the main effect of Group was not significant (F(2,36) = 0.17; P = 0.87). Accordingly, with the STAI-T and BDI-H scores

as covariates in the model, the effect of Group was not significant ($F(2,35) = 0.2$; $P = 0.82$) either. Nevertheless, the independent effect of the BDI-H was significant for the number ($F(3,36) = 5.19$; $P = 0.029$) and showed a trend for the frequency of REM arousals ($F(3,36) = 4.02$; $P = 0.053$). STAI-T showed a trend for REM arousal index ($F(3,36) = 3.54$; $P = 0.068$), but not for the absolute number of REM arousals ($F(3,36) = 1.72$; $P = 0.2$).

DISCUSSION

The results of our study indicate that the sleep of NMs is characterized by altered NREM microstructure in comparison with that of CTLs. Although the overall rate of CAP A phases was similar in the two groups, NMs showed a decrease in the rate of A1 and an increase in the rate and relative amount (sleep time was also considered) of A2 and A3 subtypes, as well as of the mean duration of A phases. Moreover, these differences were independent of the confounding effects of anxious and depressive symptoms measured by the psychometric tests. These findings confirm that the CAP analysis is a more than adequate method to unravel microstructural alterations in NMs.

The reduced absolute amount of A1 is consistent with decreased SWS in NMs, as A1 subtypes are more prominent in the descending phases of sleep. NMs also showed enhanced mean duration of CAP A phases that might be related to the increase in A2 and A3 in NMs, because the duration of these CAP subtypes was longer in comparison with the A1 subtype. The expression of A1 involves the synchronization of slow EEG activity especially in frontal areas,[35] which seems to facilitate the maintenance of sleep structure in states of transient instability[36] as well as the efficient offline information processing during sleep.[35] A2 and even more A3 subtypes seem to be generated in posterior areas with less (A2) or virtually no involvement (A3) of frontal cortical generators and comprise increased fast EEG activity, including alpha and beta waves.[37,38] Reduced amount of A1 and increased rate of A2 and A3 in NMs reflect dysfunctional sleep-wake regulation and the imbalance of sleep-promoting and arousing mechanisms during NREM sleep. This apparent shift toward arousal processes composed of desynchronized, low amplitude, and high frequency activities confirms that impaired sleep continuity in NMs is related to abnormal microarousal processes during sleep. Therefore, our findings complement earlier reports on poor sleep quality[4] and increased sympathetic[16] and motor activity in NMs.[15]

Our results partially resemble the findings by Parrino and colleagues[39] reporting altered sleep microstructure, especially enhanced A2 subtypes in patients with paradoxical insomnia. Nevertheless, despite the increased number of A2 subtypes, insomnia and nightmare sufferers seem to show different patterns regarding CAP parameters. Although the overall CAP rate was increased in patients with insomnia, the rate of CAP A1 and A3 subtypes was not altered in comparison with that of control patients.[39] In contrast, we found nonaltered overall CAP rate, but reduced A1 and slightly increased A3 subtypes in NMs, suggesting that not the frequency of CAP bursts *per se* but the cortical reactions in response to arousing stimuli are different in NMs. However, the partial overlap between disturbed dreaming and insomnia is in coherence with questionnaire-based findings reporting increased prevalence of nightmares among patients with insomnia.[10,40]

In addition to the maintenance of sleep structure, the generation of CAP A1 subtypes during sleep was related to next-day enhancements of waking performance in various cognitive tasks that require frontal lobe functions. In contrast, the rate of A2 and A3 subtypes was associated with reduced performance in attentional, memory, and executive tasks.[41] Decreased amount of A1 and increased rate of A2 and A3 in NMs are in conjunction with a recent study showing impaired executive functions in a group of NMs.[42] CAP A1 subtypes may be related to homeostatic, restorative properties of NREM sleep fostering the fine-tuning of neural networks that support offline information processing during sleep and cognitive functions during waking.[43] Moreover, these slow oscillations reflect the "effort" of the cortex to preserve sleep continuity by the reinforcement of the thalamic-basal forebrain gate against arousing impulses. In contrast, microarousals with higher frequencies generated in posterior areas reflect the failure of this gating process, when instead of the propagation of synchronized slow oscillations from anterior areas to posterior sites the cortex is shifted toward a more alert brain state.[18] In brief, our findings suggest that NMs are impaired in the buildup of slow synchronized activity that stabilizes and maintains deep sleep predominantly in the first part of the night. Moreover, NMs seem to be more prone to increased cortical activation in response to arousing stimuli.

Contrary to our hypothesis, NMs did not show arousal increments during REM sleep, but anxiety and depression scores seemed to be weakly related to the rate of REM arousals. This finding is in conjunction with previous studies indicating that the intensity of REM sleep is a biologic marker of affective dysregulation in depression and other mood disorders.[44,45] It is also consistent with the study by Simor and colleagues[17] showing that impaired sleep continuity in NREM sleep is an inherent feature of nightmare disorder independently of the comorbid psychopathologic symptoms, whereas increased duration of REM sleep is mediated by these factors.

Because we did not wake up our study participants during the night to collect dream reports, we cannot make direct inferences about the relationship between arousals and nightmare formation. In fact, only three of the 17 NMs reported that they experienced dysphoric dreams during the night, consistent with earlier reports on the attenuation of nightmares in laboratory settings.[5]

Disrupted sleep with reduced slow wave activity (especially in frontal areas) may have detrimental effects on cognitive functions relying on the prefrontal cortex,[46] the most vulnerable structure to sleep loss.[47,48] Because the prefrontal cortex has a crucial role in self-regulation, including the regulation of emotional responses,[49-51] we may speculate that dysfunctional restorative processes in prefrontal structures may increase the risk of heightened negative affect during waking and presumably during dreaming.[2] Nevertheless, despite our first results providing novel data on the neurophysiology of NREM sleep in NMs, the relationship between disrupted sleep and disturbed mental activity during sleep should be pursued by further investigations including experimental manipulations of sleep structure or mental activity.

Examining a relatively homogeneous sample may reduce the influence of different confounding factors; however, we should be careful with generalizing our data to other age groups and

populations. Due to the association between the distribution of different CAP subtypes and the performance in different neuropsychological tasks during waking,[41] the assessment of different cognitive and affective functions in the morning would have provided more information regarding the relationship between disrupted sleep and waking dysfunctions in NMs.

Despite these limitations, to the best of our knowledge this is the first study that provides empirical evidence on the relationship between nightmare disorder and altered sleep microstructure in NREM sleep, contributing to our understanding of the pathophysiology of disturbed dreaming.

ABBREVIATIONS

ANCOVA, analysis of covariance
ANOVA, analysis of variance
BDI-H, short form of the Hungarian version of the Beck Depression Inventory
CAP, cyclic alternating pattern
CTLs, control subjects
DQQ, Dream Quality Questionnaire
EEG, electroencephalography
GSQS, Groningen Sleep Quality Scale
MANCOVA, multivariate analysis of covariance
MANOVA, multivariate analysis of variance
NCAP, non-cyclic alternating pattern
NMs, nightmare subjects
NREM, non-rapid eye movement sleep
REM, rapid eye movement sleep
SPSS, Statistical Package for the Social Sciences
STAI, State-Trait Anxiety Inventory
STAI-T, State-Trait Anxiety Inventory-Trait component
SWS, slow-wave sleep
VDAS-H, the Hungarian version of the Van Dream Anxiety Scale

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DISCLOSURE STATEMENT

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REFERENCES

1. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005.
2. Levin R, Nielsen TA. Disturbed dreaming, posttraumatic stress disorder, and affect distress: a review and neurocognitive model. Psychol Bull 2007;133:482-528.
3. Coolidge FL, Segal DL, Coolidge CM, Spinath FM, Gottschling J. Do nightmares and generalized anxiety disorder in childhood and adolescence have a common genetic origin? Behav Genet 2010;40:349-56.
4. Lancee J, Spoormaker VI, van den Bout J. Nightmare frequency is associated with subjective sleep quality but not with psychopathology. Sleep Biol Rhythms 2010;8:187-93.
5. Spoormaker VI, Schredl M, van den Bout J. Nightmares: from anxiety symptom to sleep disorder. Sleep Med Rev 2006;10:19-31.
6. Wood JM, Bootzin RR. The prevalence of nightmares and their independence from anxiety. J Abnorm Psychol 1990;99:64-8.
7. Li SX, Zhang B, Li AM, Wing YK. Prevalence and correlates of frequent nightmares: a community-based 2-phase study. Sleep 2010;33:774-80.
8. Li SX, Yu MWM, Lam SP, et al. Frequent nightmares in children: familial aggregation and associations with parent-reported behavioral and mood problems. Sleep 2011;34:487-93.
9. Schredl M. Effects of state and trait factors on nightmare frequency. Eur Arch Psychiatry Clin Neurosci 2003;253:241-7.
10. Schredl M. Nightmare frequency in patients with primary insomnia. Int J Dream Res 2009;2:85-8.
11. Schredl M. Dreams in patients with sleep disorders. Sleep Med Rev 2009;13:215-21.
12. Krakow B. Nightmare complaints in treatment-seeking patients in clinical sleep medicine settings: diagnostic and treatment implications. Sleep 2006;29:1313-9.
13. Fisher C, Byrne J, Edwards A, Kahn E. A psychophysiological study of nightmares. J Am Psychoanal Assoc 1970;18:747-82.
14. Newell SA, Padamadan H, Drake ME Jr. Neurophysiologic studies in nightmare sufferers. Clin Electroencephalogr 1992;23:203-6.
15. Germain A, Nielsen TA. Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. Biol Psychiatry 2003;54:1092-8.
16. Nielsen T, Paquette T, Solomonova E, Lara-Carrasco J, Colombo R, Lanfranchi P. Changes in cardiac variability after REM sleep deprivation in recurrent nightmares. Sleep 2010;33:113-22.
17. Simor P, Horváth K, Gombos F, Takács K, Bódizs R. Disturbed dreaming and sleep quality: altered sleep architecture in subjects with frequent nightmares. Eur Arch Psychiatry Clin Neurosci 2012;262:687-96.
18. Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev 2012;16:27-45.
19. Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiologic component of normal NREM sleep. Sleep 1985;8:137-45.
20. Bruni O, Novelli L, Miano S, Parrino L, Terzano MG, Ferri R. Cyclic alternating pattern: A window into pediatric sleep. Sleep Med 2010;11:628-36.
21. Bruni O, Ferri R, Novelli L, Finotti E, Miano S, Guilleminault C. NREM sleep instability in children with sleep terrors: the role of slow wave activity interruptions. Clin Neurophysiol 2008;119:985-92.
22. Manni R, Terzaghi M, Sartori I, Veggiotti P, Parrino L. Rhythmic movement disorder and cyclic alternating pattern during sleep: a video-polysomnographic study in a 9-year-old boy. Mov Disord 2004;19:1186-90.
23. Kutlu A, Işeri P, Selekler M, Benbir G, Karadeniz D. Cyclic alternating pattern analysis in REM sleep behavior disorder. Sleep Breath 2012; http://dx.doi.org/10.1007/s11325-012-0675-5.
24. Terzano MG, Smerieri A, Del Felice A, Giglia F, Palomba V, Parrino L. Cyclic alternating pattern (CAP) alterations in narcolepsy. Sleep Med 2006;7:619-26.
25. Bódizs R, Simor P, Csóka S, Bérdi M, Kopp MS. Dreaming and health promotion: A theoretical proposal and some epidemiological establishments. Eur J Ment Health 2008;3:35-62.
26. Simor P, Kovács I, Vargha A, Csóka S, Mangel B, Bódizs R. [Nightmares, dream anxiety and psychopathology: the validation of the Hungarian version of the Van Anxiety Scale]. Psychiatr Hung 2009;24:428-38.
27. Spielberger C, Gorsuch R, Lushene R. Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press, 1970.
28. Sipos K, Sipos M, Spielberger C. A state-trait anxiety inventory (STAI) magyar változata. In: Mérei F, Szakács F, eds. Pszichodiagnosztikai Vademecum I/2. Budapest: Nemzeti Tankönyvkiadó, 1994:123-48.
29. Rózsa S, Szádoczky E, Füredi J. A Beck Depresszió Kérdőív rövidített változatának jellemzői a hazai mintán. Psychiatr Hung 16:379-97.
30. Simor P, Köteles F, Bódizs R, Bárdos G. A szubjektív alvásminőség kérdőíves vizsgálata: a Groningen Alvásminőség Skála hazai validálása. Mentálhigiéné es Pszichoszomatika 2009;10:249-61.
31. Jasper H. Report of the committee on methods of clinical examination in electroencephalography. Electroencephalogr Clin Neurophysiol 1958;10:370-5.
32. Rechtschaffen A, Kales A. A manual of standardized terminology, technique and scoring system for sleep stages of human sleep. Los Angeles: Brain Information Service. Brain Information Institute, UCLA, 1968.
33. Terzano MG, Parrino L, Smerieri A, Chervin R, Chokroverty S, Guilleminault C, et al. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med 2002;3:187-99.

34. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM Manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
35. Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. Regional scalp EEG slow-wave synchronization during sleep cyclic alternating pattern A1 subtypes. Neurosci Lett 2006;404:352-7.
36. Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. Dynamics of the EEG slow-wave synchronization during sleep. Clin Neurophysiol 2005;116:2783-95.
37. Ferri R, Bruni O, Miano S, Terzano MG. Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). Sleep Med 2005;6:29-36.
38. Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). Sleep Med Rev 2000;4:101-23.
39. Parrino L, Milioli G, De Paolis F, Grassi A, Terzano MG. Paradoxical insomnia: the role of CAP and arousals in sleep misperception. Sleep Med 2009;10:1139-45.
40. Schredl M, Schäfer G, Weber B, Heuser I. Dreaming and insomnia: dream recall and dream content of patients with insomnia. J Sleep Res 1998;7:191-8.
41. Aricò D, Drago V, Foster PS, Heilman KM, Williamson J, Ferri R. Effects of NREM sleep instability on cognitive processing. Sleep Med 2010;11:791-8.
42. Simor P, Pajkossy P, Horváth K, Bódizs R. Impaired executive functions in subjects with frequent nightmares as reflected by performance in different neuropsychological tasks. Brain Cogn 2012;78:274-83.
43. Ferri R, Huber R, Aricò D, et al. The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes. Neurosci Lett 2008;432:228-31.
44. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992;49:651-668.
45. Riemann D, Berger M, Voderholzer U. Sleep and depression–results from psychobiological studies: an overview. Biol Psychology 2001;57:67-103.
46. Mander BA, Reid KJ, Baron KG, et al. EEG measures index neural and cognitive recovery from sleep deprivation. J Neurosci 2010;30:2686-93.
47. Thomas M, Sing H, Belenky G, et al. Neural basis of alertness and cognitive performance impairments during sleepiness I: effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res 2000;9:335-52.
48. Wu JC, Gillin JC, Buchsbaum MS, et al. Frontal lobe metabolic decreases with sleep deprivation not totally reversed by recovery sleep. Neuropsychopharmacol 2006;31:2783-92.
49. Depue BE, Curran T, Banich MT. Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. Science 2007;317:215-9.
50. Dillon DG, Pizzagalli DA. Inhibition of action, thought, and emotion: a selective neurobiological review. Appl Prev Psychol 2007;12:99-114.
51. Dolcos F, Kragel P, Wang L, McCarthy G. Role of the inferior frontal cortex in coping with distracting emotions. Neuroreport 2006;17:1591-4.

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Fluctuations between sleep and wakefulness: Wake-like features indicated by increased EEG alpha power during different sleep stages in nightmare disorder

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ABSTRACT

Although a growing body of research indicates that frequent nightmares are related to impaired sleep regulation, the pathophysiology of nightmare disorder is far from being fully understood. We examined the relative spectral power values for NREM and REM sleep separately in 19 individuals with nightmare disorder and 21 healthy controls, based on polysomnographic recordings of the second nights' laboratory sleep. Nightmare subjects compared to controls exhibited increased relative high alpha (10–14.5 Hz) and fronto-central increases in high delta (3–4 Hz) power during REM sleep, and a trend of increased fronto-central low alpha (7.75–9 Hz) power in NREM sleep. These differences were independent of the confounding effects of waking emotional distress. High REM alpha and low NREM alpha powers were strongly related in nightmare but not in control subjects. The topographical distribution and spectral components of REM alpha activity suggest that nightmare disordered subjects are characterized by wake-like electroencephalographic features during REM sleep.

1. Introduction

Nightmares are intense and highly unpleasant mental experiences that occur usually – but not exclusively – during late-night Rapid Eye Movement (REM) sleep and often provoke abrupt awakenings (ICSD-II, 2005). Nightmares affect approximately 4% of the adult population on a weekly basis (Spoormaker, Schredl, & van den Bout, 2006). Even though nightmares are often co-morbid with a wide variety of mental complaints (Levin & Nielsen, 2007), research indicates that frequent nightmares are more appropriate to be conceptualized as a specific sleep disorder that are independent in its origins from waking psychopathological symptoms (Coolidge, Segal, Coolidge, Spinath, & Gottschling, 2010; Lancee, Spoormaker, & van den, 2010; Spoormaker et al., 2006). Frequent nightmares are related to impaired subjective sleep quality in different age-groups and populations (Li et al., 2011; Li, Zhang, Li, & Wing, 2010; Schredl, 2010), and negatively toned dreams are more frequent among subjects with different sleep disorders (Schredl, 2009a,b; Schredl, Schafer, Weber, & Heuser, 1998) in whom nightmares seem to increase the severity of sleep complaints (Krakow, 2006; Schredl, 2009a,b).

In consistence with questionnaire-based findings, early polysomnographic studies reported altered sleep architecture and sleep fragmentation in subjects with frequent nightmares (Fisher, Byrne, Edwards, & Kahn, 1970; Newell, Padamadan, & Drake, 1992). In addition, a recent study that also controlled for the confounding effects of co-morbid waking symptoms of depression and anxiety found decreased sleep efficiency, reduced slow wave sleep (SWS) and increased nocturnal awakenings in a group of young nightmare sufferers (Simor, Horváth, Gombos, Takács, & Bódizs, 2012). Others found enhanced periodic leg movements in nightmare sufferers with and without post-traumatic stress disorder suggesting that increased arousal and accompanying motor activation characterize the pathophysiology of nightmare disorder (Germain & Nielsen, 2003). Enhanced arousal during sleep was also evidenced by increased sympathetic (cardiac) activation in a group of nightmare subjects after a REM deprivation procedure (Nielsen et al., 2010).

A more recent study found altered sleep microstructure in nightmare sufferers during Non-REM (NREM) sleep (Simor, Bódizs, Horváth, & Ferri, 2013) revealed by the Cyclic Alternating Pattern (CAP) analysis that quantifies and categorizes electroencephalographic (EEG) oscillations corresponding to recurrent activation

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events and transient states of unstable sleep depth (Terzano et al., 1985). More specifically, nightmare subjects in comparison to controls exhibited increased arousal responses comprised of desynchronized, high or mixed frequency activities and a reduced amount of synchronized, low frequency oscillations during spontaneous recurrent events of instability in NREM sleep and these differences were independent of the effects of anxious and depressive symptoms, indexed by psychometric tests. Desynchronized arousal responses that are generated usually at posterior sites and incorporate alpha (8–13 Hz) and beta (13–30 Hz) frequency bands shift the cortex toward a more alert brain state, while the generally antero-posterior propagation of slow (0.25–2 Hz) synchronized oscillations reflects the "effort" of the cortex to preserve sleep depth by reinforcing the thalamic-basal forebrain gate against arousing impulses (Parrino, Ferri, Bruni, & Terzano, 2012). Therefore, these findings indicate that nightmare disorder is characterized by inefficient sleep regulation and increased arousal responses that reduce the threshold for awakening.

Interestingly, although nightmare disorder is considered to be a REM parasomnia (ICSD-II, 2005), anomalies in sleep continuity have been reported mainly during NREM sleep (Simor et al., 2013, 2012). Nevertheless, it is feasible that the above studies based on the visual scoring of sleep EEG could not capture the subtle alterations in the structure of neural oscillations during REM sleep. Power spectral analysis provides a fine-grained and sensitive examination of the electrophysiological oscillations during sleep, which seems to be an efficient tool to detect sleep alterations in different pathological conditions (Armitage, 1995; De la Fuente, Tugendhaft, & Mavroudakis, 1998; Feige, Scaal, Hornyak, Gann, & Riemann, 2007; Krystal, Edinger, Wohlgemuth, & Marsh, 2002; Lindberg et al., 2003; Moritz et al., 2002; Philipsen et al., 2005; Poulin, Stip, & Godbout, 2008). To the best of our knowledge, no previous studies have investigated the electrophysiological features of a whole night sleep in nightmare disorder. Therefore, our aim was to describe the EEG spectral profile of NREM and REM sleep in a group of nightmare subjects in comparison with that of controls.

2. Materials and methods

2.1. Participants

Participants (all native Hungarians) were selected from a large pool of undergraduate students from the Budapest University of Technology and Economics and Semmelweis University. Nightmare (NMs) and control subjects (CTLs) were enrolled after a stringent selection procedure described previously in detail (Simor et al., 2012). In brief, the enrollment was based on subjects' scores on three different dreaming-related questionnaires: the Dream Quality Questionnaire (DQQ) (Bódizs, Simor, Csóka, Bérdi, & Kopp, 2008), the Hungarian version of the Van Dream Anxiety Scale (VDAS-H) (Simor et al., 2009) and two seven-point Likert scales, one assessing the frequency of awakening nightmares, and the other assessing the frequency of bad dreams without awakenings (0 – almost never; 1 – once or twice a year; 2 – every 2–3 month; 3 – once in a month; 4 – twice a month; 5 – once a week; 6 – more than once a week). NMs were selected on the basis of the International Classification of Sleep Disorders, 2nd edition (2005) criteria and Levin and Nielsen's (2007) model of disturbed dreaming, including disturbed dreamers without abrupt awakenings. Subjects reporting one or more nightmares with awakening and/or bad dreams without awakening per week in the retrospective questionnaires were assigned to the NMs group, while individuals having less than two nightmares and/or bad dreams during the previous year were assigned as CTLs. Those subjects who reported the onset of negative dream experiences in relation to a traumatic event or indicated that the content of their dreams were related to a prior trauma (such as physical attack, accident, sudden death of a close relative, etc.) were excluded from the study. 21 NMs and 23 CTLs took part in polysomnographic examination; however, two NMs left the experiment after the first (baseline) night and two of the CTLs' recordings were considered too noisy for spectral analyses. Therefore, 19 NMs (10 males; $M_{age} = 20.87 \pm 1.57$) and 21 CTLs (11 male; $M_{age} = 21.57 \pm 1.47$) were included in the present study. There was no significant age difference between the two groups ($U(38) = 146$; $Z = -1.48$; $p = 0.138$). NMs scored higher on the Negative Dream Affect Scale of the DQQ ($M_{NMs} = 8.12$; $SD_{NMs} = 1.91$ vs. $M_{CTLs} = 4.03$; $SD_{CTLs} = 1.77$; $t(38) = -7.25$; $p < 0.0001$) and on the VDAS-H ($M_{NMs} = 20.58$; $SD_{NMs} = 7.5$ vs. M_{CTLs}: $0.23 \pm SD_{CTLs} = 0.62$; $t(18.22) = -11.73$; $p < 0.0001$; equal variances not assumed), indicating at least moderately severe dream disturbances (Bódizs, Sverteczki, & Mészáros, 2008; Simor et al., 2009).

None of the subjects reported prior neurological, psychiatric or sleep disorders or prior history of any chronic disease. The study protocol was approved by the Ethical Committee of the Semmelweis University. The subjects received monetary compensation for their participation in the sleep laboratory investigations. Written informed consent was obtained.

2.2. Procedure

Polysomnographic recordings were performed in the sleep research laboratory of the Semmelweis University for two consecutive nights. (The first night served as the adaptation night.) Subjects were not allowed to drink alcohol or take drugs (except contraceptives) on the day and the previous day of the examination. They were asked to avoid napping and consuming caffeine in the afternoon of the sleep recordings. The timing of lights off was between 11.00 PM and 1.00 AM depending on each participant's preferred bedtime. Morning awakenings were scheduled after 9 h of undisturbed sleep unless participants woke up earlier spontaneously. Five of the NMs reported negatively toned dreams in the laboratory.

In the morning – in order to measure subjective sleep quality – subjects were asked to complete the Hungarian adaptation of the Groningen Sleep Quality Scale (GSQS) (Simor, Köteles, Bódizs, & Bárdos, 2009). The one-dimensional 14-item questionnaire measures the extent of subjective sleep fragmentation.

In order to control for the confounding effects of waking emotional distress on sleep EEG the Hungarian versions of the Spielberger Trait Anxiety Inventory (STAI-T) (Spielberger, Gorsuch, & Lushene, 1970) and the short Beck Depression Inventory (BDI-H) (Rózsa, Szádoczky, & Füredi, 2001) were assessed. The STAI-T is a widely used self-report instrument that differentiates between the temporary condition of state anxiety and the longstanding quality of trait anxiety. We used the 20-item Hungarian version of the STAI-T to assess general levels of anxiety (Sipos, Sipos, & Spielberger, 1994).

The 9-item BDI-H is a one-dimensional scale assessing different symptoms of depression including social withdrawal, indecision, sleep disturbance, fatigue, intense worry about bodily symptoms, loss of work performance, pessimism, lack of satisfaction and self accusation (Rózsa et al., 2001).

2.3. Polysomnography

On both nights, subjects were fitted with 19 EEG electrodes (Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2) according to the 10–20 electrode placement system (Jasper, 1958) as well as with two EOG electrodes (bipolar channel) monitoring vertical and horizontal eye-movements; EMG electrodes (bipolar channels) for the chin and for the anterior tibialis muscles, two ECG electrodes according to standard lead I; in addition to the thoracic and abdominal respiration sensors. Gold-coated Ag/AgCl EEG cup electrodes were fixed with EC2 Grass Electrode Cream (Grass Technologies, USA) and referred to the mathematically-linked mastoids. Impedances were kept below 8 kΩ. Signals were collected, prefiltered (0.33–1500 Hz, 40 dB/decade anti-aliasing hardware input filter), amplified and digitized with 4096 Hz/channel sampling rate (synchronous) with 12 bit resolution by using the 32 channel EEG/polysystem (Brain-Quick BQ 132S, Micromed, Italy). A further 40 dB/decade anti-aliasing digital filter was applied by digital signal processing which low-pass filtered the data at 450 Hz. Finally, the digitized and filtered EEG was undersampled at 1024 Hz.

2.4. Spectral analyses

Sleep stages and conventional parameters of sleep macrostructure were scored according to Rechtschaffen and Kales standardized criteria (Rechtschaffen & Kales, 1968) by two experienced sleep researchers who were blind to the group membership of the participants. Overlapping (50%), artifact-free four-second-epochs of all EEG derivations were Hanning-tapered and Fourier transformed by using the FFT (Fast Fourier Transformation) algorithm in order to calculate the average power spectral densities (μV^2/0.25 Hz) for whole night NREM (stages 2–4) and REM sleep periods. Since the absolute power values may be biased due to differences in the thickness – and thus the conductivity – of the skull, leading to disproportionate discrepancies between males and females (Carrier, Land, Buysse, Kupfer, & Monk, 2001), we applied the relative spectral power values. Relative spectral power values were obtained for each frequency bin (width: 0.25 Hz) by dividing the absolute power of the given frequency bin with the total spectral power (the sum of the absolute power of the whole range of analysis between 0.75 Hz and 48.25 Hz). The relative power values reflect the relative contribution of a given frequency range to the total spectrum. Relative spectral power values were log-transformed by using a 10 base logarithm in order to normalize their distribution before performing statistical analyses.

2.5. Statistical analyses

Statistical analyses were carried out with the Statistical Package for the Social Sciences version 19.0 (SPSS, IBM) and MATLAB (version 7.10.0.499, R2010a, The MathWorks, Inc., Natick, MA). Group differences of mean scores regarding the

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Table 1
Descriptive statistics and group comparisons of the psychometric variables.

	NM		CTL		*t*-Test*	Mann–Whitney test*		
	Mean	SD	Mean	SD	*t*	*U*	*Z*	*p***
STAI-T	50.42	8.15	33.28	8.54	−6.475			<0.001
BDI-H	15.15	3.87	10.76	1.55		69.5	−3.545	<0.001
GSQS	4.16	3.61	2.9	2.23		162.5	−1.016	0.32

* df = 38.
** The *p* values correspond to the test that was carried out (independent sample *t*-test or Mann–Whitney test).

psychometric tests were compared with independent samples *t*-tests. If the psychometric parameters were not normally distributed, non-parametric (Mann–Whitney) tests were applied. Group comparisons of sleep architecture variables and relative spectral power values in each electrode and frequency bin were performed using multiple univariate analysis of covariance (ANCOVA). Relative spectral power values served as dependent variables, group membership was a fixed factor, and in order to control for the confounding effects of waking symptoms of anxiety and depressive states, STAI-T and BDI-H scores were used as covariates in the model. The sleep architecture variables that were not normally distributed were transformed to a natural logarithmic scale for statistical analysis. The level of significance was set at $p < 0.05$. Multiple comparisons inflate Type 1 error; however, statistical corrections (such as the Bonferroni or the Šidák correction) are too conservative for EEG data because they assume that the individual tests are independent from each other, which is not the case for EEG relative spectral power values. In order to address the issue of multiple comparisons we used the procedure of descriptive data analysis, delineating so called Rüger's areas (Abt, 1987; Duffy et al., 1990). The procedure is designed to handle data with strongly intercorrelated neighboring data points. Rüger's areas are defined as sets of conventionally significant ($p < 0.05$) results which are accepted or rejected as significant as a whole, instead of individual results of statistical tests. We took the results of our statistical tests as a two-dimensional matrix (with electrodes being one dimension, and frequency bins the other) and defined Rüger's areas along the dimension of frequency bins. A Rüger's area started when there was a significant result on any electrode in that frequency bin, continued into higher frequencies, and ended wherever there were no significant results on any electrode.

After defining these areas of significance, the number of significant results within the area was calculated, and it was investigated whether at least half of these results were significant at least at 1/2 of the conventional $p = 0.05$ significance level (that is, whether they were below 0.025) and at least one-third of them were significant at least at 1/3 of the conventional $p = 0.05$ significance level (that is, whether they were below 0.0167). If both of these conditions were fulfilled, the area as a whole was considered significant. With this method, a single significant statistical test with $p < 0.0167$ theoretically counts as a significant Rüger's area. However, we did not consider single-bin results as an area. This conservative method addresses the issue of multiple comparisons since the probability that all these requirements will be fulfilled by chance is low.

3. Results

3.1. Psychometric tests and sleep macrostructure

The sleep macrostructure of an overlapping sample has already been reported in details elsewhere (Simor et al., 2012). However, as the sample of the present study was slightly different due to the exclusion of recordings that were too noisy for spectral analysis and due to the broadening of the sample, we briefly describe the results. To analyze the group differences in terms of psychometric variables independent sample *t*-tests and Mann–Whitney tests (if the assumption of normality was violated) were conducted. To investigate the group main effect on sleep architecture, analysis of covariance was performed with STAI-T and BDI-H as covariates. Table 1 summarizes the descriptive statistics and the group comparisons of the psychometric variables, where NMs scored significantly higher both on the anxiety (STAI-T) and the depression (BDI-H) scales. In Table 2, the group differences regarding the sleep architecture can be observed. Even though no difference was found in subjective sleep quality of the two groups (GSQS), the objective sleep variables indicated impaired sleep architecture in NMs who had lower sleep efficiency and longer wake after sleep onset (WASO). Further, NMs were characterized by longer percentage of S1 sleep and lower proportion of SWS relative to the total sleep time.

3.2. Relative spectral power of NREM and REM sleep EEG

To analyze group differences in the EEG relative spectrum, analysis of covariance was carried out with relative power spectral density at the frequency bins as dependent variables and STAI-T and BDI-H as covariates. The differences between the relative spectra of NMs and CTLs can be observed in Fig. 1, where the data of the central midline (Cz) derivation are shown. Fig. 2A shows the proportion of the adjusted means of the two groups by electrode and by frequency band. Fig. 2B shows the *p*-values (only $p < 0.15$ are displayed) corresponding to the group main effects of the ANCOVA model. Significant Rüger's areas surviving the statistical correction by descriptive data analysis are indicated in the figure.

Clear differences can be observed both in NREM and REM sleep. Regarding NREM sleep, NMs showed significantly lower 1–1.25 Hz activity in various recording sites (F8, C3, Cz, T4, P3, Pz, O1, O2), whereas they had a higher 4–4.75 Hz activity on the Cz and the Pz electrodes compared to CTLs. Furthermore, increased frontocentral (Fz, F4, C3, Cz, C4) 7.75–9 Hz activity was found in NMs.

Table 2
Descriptive statistics and group comparisons of the sleep architecture variables.

	NM		CTL		ANCOVA[c]	
	Mean[b]	SD[b]	Mean[b]	SD[b]	*f*	*p*
Sleep efficiency (%)[a]	90.31	8.26	94.84	4.88	7.164	0.011
Sleep latency (min)[a]	24.79	24.33	12.73	9.35	2.586	0.117
WASO (min)[a]	30.75	27.81	17.86	25.81	10.704	0.002
Stage 1%[a]	3.91	2.88	2.65	1.65	4.198	0.048
Stage 2%	51.9	4.67	54.27	6.02	0.492	0.488
SWS %	15.85	4.55	18.34	4.67	5.355	0.027
REM %	28.34	4.4	25.01	4.63	0.437	0.513
REM latency (min)[a]	79.54	36.07	84.83	40.95	0.571	0.455

[a] These variables were transformed to a natural logarithmic scale for the statistical comparisons.
[b] Raw mean values and standard deviations are displayed.
[c] STAI-T and BDI-H controlled; df = 3,37.

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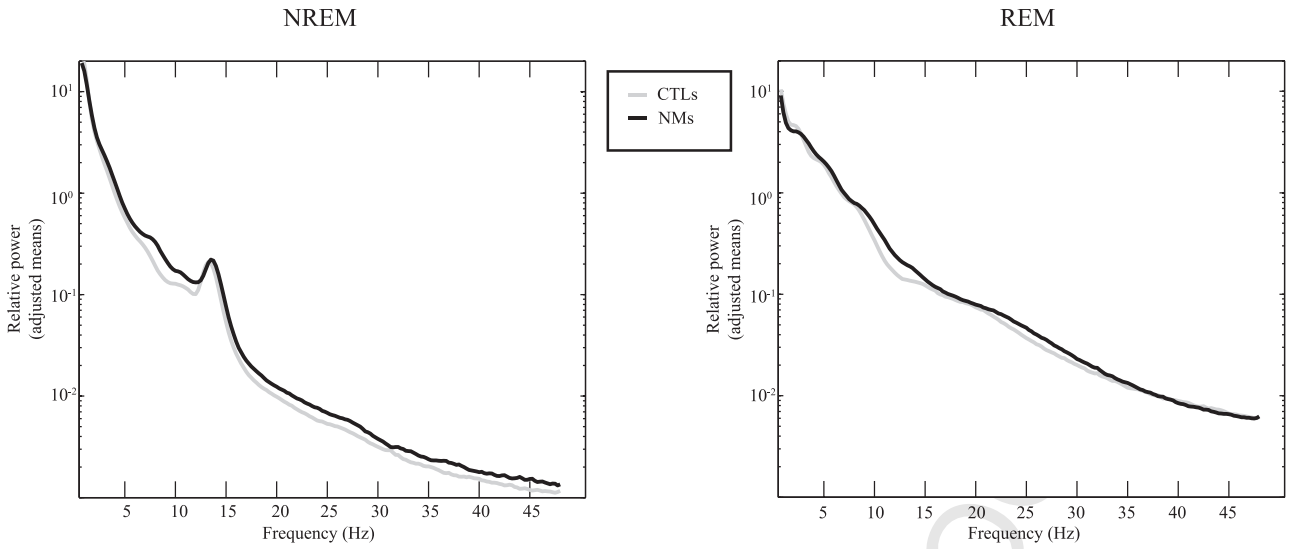

Fig. 1. Relative power spectra in NMs and CTLs. Group means of relative power spectra of NREM and REM sleep EEG at derivation Cz. The *y* axis shows the adjusted means (STAI = 41.43; BDI = 12.85) of the logarithmized raw data after back-transformation (10^x) for visualization. Significant differences before and after descriptive data analysis can be observed in Fig. 2. In sum, we found a tendency in the difference between the two groups regarding the NREM sleep EEG 7.75–9 Hz activity and a significant difference regarding the REM sleep EEG 3–4 and 10–14.5 Hz activity.

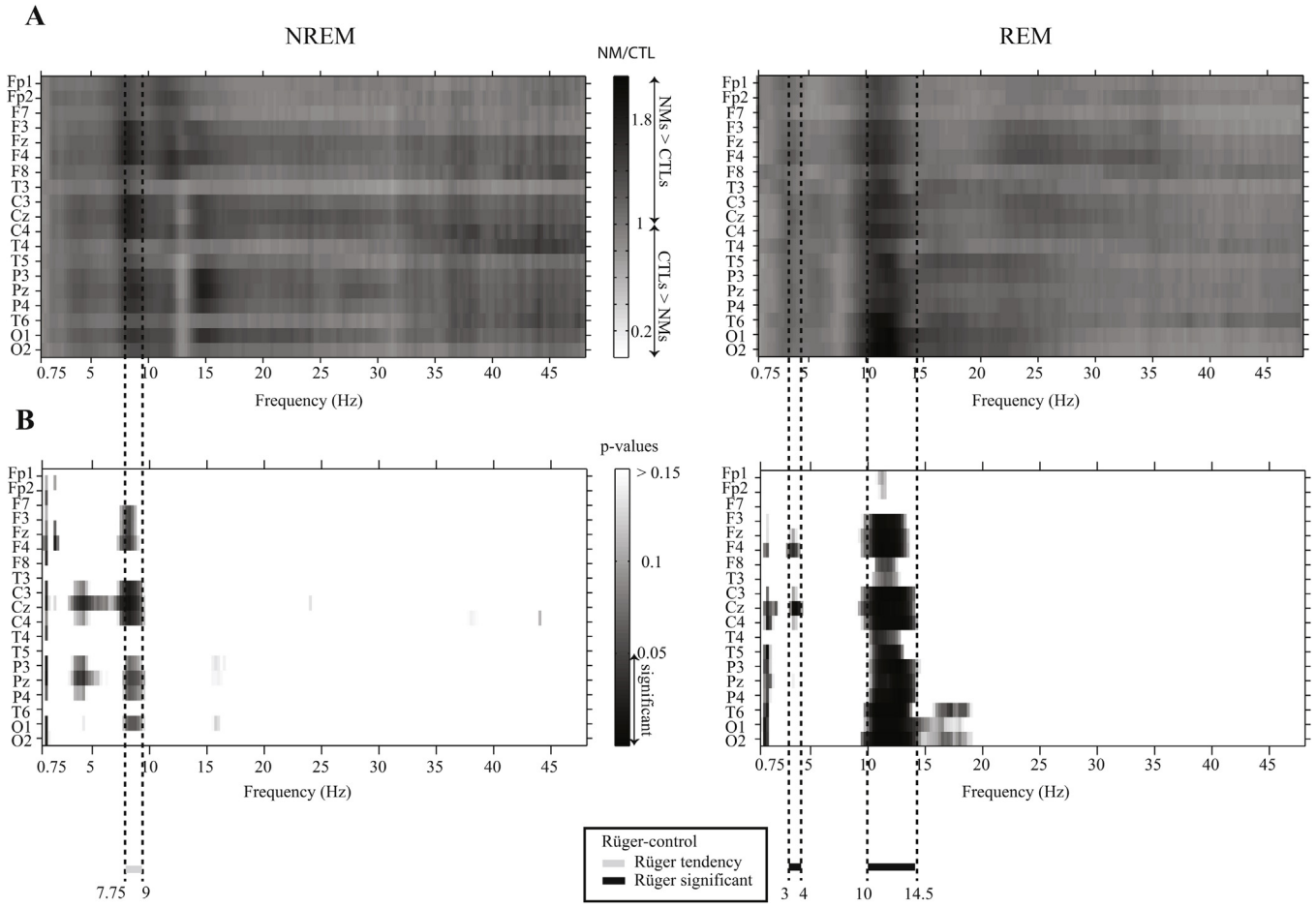

Fig. 2. Statistical difference between relative power spectra in NMs and CTLs. The proportion of NREM and REM sleep EEG relative power spectra in the two groups by electrodes (A) and the corresponding *p*-values of the ANCOVA group main effect (B). The proportion of adjusted means (STAI = 41.43; BDI = 12.85) are shown in A (the logarithmized raw data were back-transformed (10^x) for visualization). The horizontal lines below the graphs (gray line – tendency, black line – significant) and the vertical dashed lines indicate the frequency bins which were significant after the correction for multiple comparisons.

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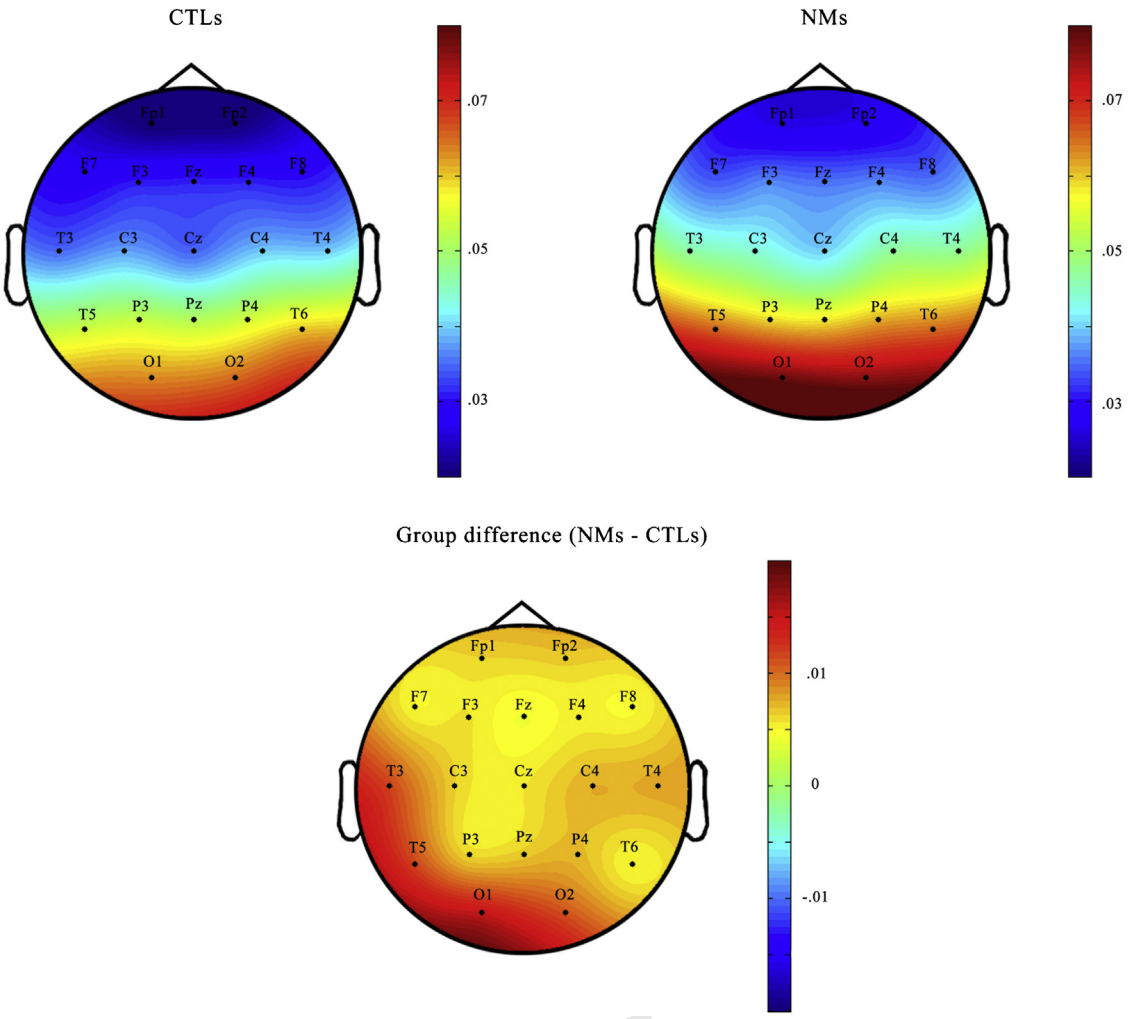

Fig. 3. Topographic distribution of REM high alpha activity. The topographic distribution of the REM sleep EEG 10–14.5 Hz activity in NMs and CTLs, as well as the difference between the two groups. Means of the raw relative power spectrum are displayed.

After the correction for multiple comparisons the differences in 1–1.25 Hz, 4–4.75 Hz frequency range were no more significant. Differences regarding the 7.75–9 Hz (low alpha range) showed a trend (one-quarter instead of one-half of the bins (20) were significant at the $p < 0.025$ level) (see Fig. 2B on the left).

Regarding REM sleep, NMs were characterized by a significantly higher 10–14.5 Hz EEG activity almost all over the scalp (F3, Fz, F4, F8, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2) in comparison with CTLs, in addition to a fronto-central (F4, Cz) increase in the 3–4 Hz activity range. Differences in both frequency ranges remained significant after correction for multiple comparisons.

To investigate further the topographic distribution of the 10–14.5 Hz activity in REM sleep that traditionally belongs to the high alpha range (Cantero, Atienza, & Salas, 2002), in Fig. 3 we plotted the relative power spectral density of this range for NMs and CTLs, as well as the difference between the two groups. The 10–14.5 Hz high alpha activity was prominent at the posterior sites, peaking at the occipital (O1, O2) derivations. According to Fig. 3, it is clear that the most significant differences between the groups emerged at the left temporo-occipital area.

To sum up, a slight increase in fronto-central high delta as well as a prominent and expanded high alpha increase were found in the REM sleep of NMs along with a tendency of more concentrated NREM alterations regarding the low alpha frequency components.

3.3. Relationship between NREM low and REM high alpha EEG in NMs and CTLs

In order to examine if the tendency-like increase in EEG low alpha activity in the NREM phase of sleep and the significant increase in high alpha EEG activity in REM sleep that were observed in NMs were related to each other, we performed a post hoc correlation analysis within the two groups separately. Relative spectral power values were averaged over the derivations and Pearson product–moment correlations were computed between NREM 7.75–9 Hz and REM 10–14.5 Hz activity. In the NMs group, a significant and strong correlation ($r(19) = 0.78$; $p = 0.0001$) emerged, whereas in CTLs no significant correlation was found ($r(21) = 0.22$; $p = 0.36$) between the low alpha frequency range of NREM and the high alpha frequency range of REM sleep.

In order to examine the relationship between NREM low/REM high alpha power with subjective sleep quality we performed Pearson product–moment correlations between these spectral measures and subjective sleep quality indexed by the GSQS scores. The spectral measures did not show significant correlations with

Table 3
Group and Gender effects on averaged relative spectral power values for different frequency domains.

Frequency domain (relative spectral power)	ANCOVA[a]		
	Group F (p)	Gender F (p)	Group × Gender F (p)
NREM sleep			
Delta	2.69 (ns)	4.55 (0.04)	1.60 (ns)
Theta	2.15 (ns)	8.58 (0.006)	0.01 (ns)
Alpha	3.45 (0.07)	8.56 (0.006)	7.32 (0.01)
Sigma	0.84 (ns)	0.74 (ns)	0.31 (ns)
Beta	1.69 (ns)	0.19 (ns)	0.30 (ns)
Gamma	0.001 (ns)	1.07 (ns)	0.22 (ns)
REM sleep			
Delta	3.01 (ns)	2.87 (ns)	0.16 (ns)
Theta	0.59 (ns)	1.82 (ns)	0.67 (ns)
Low alpha	0.14 (ns)	0.95 (ns)	0.02 (ns)
High alpha	9.45 (0.004)	5.74 (0.02)	1.06 (ns)
Beta	0.03 (ns)	0.46 (ns)	0.85 (ns)
Gamma	0.63 (ns)	1.92 (ns)	1.22 (ns)

a Controlled for STAI-T and BDI-H; df = 5,34; ns – not significant; Bonferroni corrected level of significance: $p < 0.0042$.

the subjective sleep quality neither across nor within the two groups.

3.4. Temporal dynamics in NREM and REM relative spectral power

In order to examine the temporal dynamics of altered NREM and REM sleep in NMs, we calculated the relative spectral power for the first three NREM/REM cycles separately. After the control for multiple comparisons significant differences emerged in the first and the second NREM period. NMs showed reduced power in the 1–1.25 Hz frequency range in several recording sites (F7, C3, Cz, T5, P3, O1, O2) in the first, and increased power in the low alpha band, between 7.25 Hz and 9.25 Hz in the second NREM period in fronto-central derivations (Fp1, Fp2, F7, F3, Fz, F4, C3, Cz, C4). Regarding REM sleep significant group differences were found only in the high alpha range in all the REM periods. Nevertheless, the significant frequency ranges showed slight variations among the first three REM cycles (8.75–13.75 Hz, 9–16 Hz and 10–14.25 Hz in the first, second and third REM period, respectively).

3.5. Gender differences

We examined the influence of gender as well as the Group × Gender interactions on relative spectral power data. In order to reduce the number of parameters, we averaged relative spectral power values over scalp derivations and summed up frequency bins to generate six frequency band windows for NREM and REM sleep separately. Frequency domains included delta (0.75–4 Hz), theta (4.25–7.5 Hz), alpha (7.75–10.75 Hz), sigma (11–15 Hz), beta (15.25–31 Hz) and gamma (31.25–48.25 Hz) for NREM, and delta (0.75–4 Hz), theta (4.25–7.5 Hz), low alpha (7.75–9.75 Hz), high alpha (10–15 Hz), beta (15.25–31 Hz) and gamma (31.25–48.25 Hz) relative spectral power values for REM sleep. Multiple univariate ANCOVAs were performed with the above frequency bands for NREM and REM sleep as dependent, Group and Gender as independent and STAI-T and BDI-H scores as covariate variables in the models. To address the issue of multiple comparisons, we corrected the α-level with the number of frequency bands (Bonferroni correction). This way, after the correction for multiple comparisons the error rate was set to $p = 0.05/\#\text{measures}$, or $0.05/12 = 0.0042$.

Detailed results are presented in Table 3. Regarding NREM sleep the effect of Gender was significant for the theta and alpha and delta frequency bands. Females exhibited higher values in the theta (Estimated Marginal Mean $(EMM)_{females}$: 0.47; SE: 0.02 vs. EMM_{males}: 0.39; SE: 0.02) and alpha ($EMM_{females}$: 0.15; SE: 0.01 vs. EMM_{males}: 0.11; SE: 0.01) and slightly lower values in delta ($EMM_{females}$: 5.45; SE: 0.04 vs. EMM_{males}: 5.6; SE: 0.05) power in comparison with male subjects. In coherence with the bin-wise analysis, the effect of Group showed a trend in the alpha range, and a significant effect emerged for the interaction of Group and Gender, the latter due to increased alpha power in female NMs (Raw Mean: 0.18; SD: 0.08) in contrast to male NMs (Raw Mean: 0.08; SD: 0.03). Nevertheless, none of these differences survived the Bonferroni correction for multiple comparisons.

In REM sleep the effect of Group (EMM_{NMs}: 0.45; SE: 0.03 vs. EMM_{CTLs}: 0.29; SE: 0.03) and Gender ($EMM_{females}$: 0.42; SE: 0.02 vs. EMM_{males}: 0.33; SD: 0.03) were significant for the high alpha frequency band, but only the effect of Group survived the correction for multiple comparisons. The interaction of Group and Gender was not significant for any of the examined frequency domains.

4. Discussion

To the best of our knowledge, the present study is the first to describe alterations in EEG spectral power in nightmare disorder. The most prominent finding is that subjects with frequent nightmares exhibited increased relative spectral power in the high alpha range (10–14.5 Hz) compared to healthy controls during REM sleep. In addition, increased REM high delta (3–4 Hz) activity and a tendency of increased NREM low alpha (7.75–9 Hz) activity were observed in NMs in contrast to CTLs. Separate analyses of the first three NREM/REM cycles revealed time dependent effects for the low alpha power in NREM sleep, showing significantly increased power in NMs only in the second NREM period. In contrast, high alpha power was increased in all the first three REM periods in NMs. Since these differences were statistically independent of the confounding effects of waking emotional distress indicative of subclinical psychopathological states, altered sleep microstructure seems to be an inherent feature of the neurophysiology of nightmare disorder.

We suggest that increased high alpha power in the REM periods of NMs is a wake-like feature during REM sleep which might contribute to the pathophysiology of nightmare disorder. Alpha oscillations during REM sleep might reflect relatively short periods of sleep instability (micro-arousals) that facilitate the connection between the sleeping brain and the external environment (Cantero, Atienza, & Salas, 2000; Halász, 1998; Halász, Terzano, Parrino, & Bódizs, 2004). Alpha oscillations were shown to be modulated differently in the different states of alertness (Cantero

et al., 2002): while higher alpha components are dominant during wakefulness, REM sleep is characterized by the preponderance of slower (7.5–10.5 Hz) alpha oscillations in healthy subjects (Cantero, Atienza, Gómez, & Salas, 1999). Moreover, there are clear differences in the topographical distribution of the alpha activity between wakefulness and REM sleep. Posterior dominance of alpha power is characteristic of relaxed wakefulness, whereas in REM the distribution seems to be more homogeneous (Cantero et al., 1999, 2002). Therefore, the increased high alpha activity peaking at posterior locations in the REM periods of NMs may reflect a "hybrid state" with the occurrence of wake-type alpha oscillations during REM sleep.

In addition to the increased high alpha activity in REM sleep, the alpha activity in NREM sleep was also higher in NMs, but at lower frequencies (7.75–9 Hz), which may indicate increased alertness during NREM. A growing body of research suggests that alpha activity reflects an "internal" preparatory state that facilitates alertness and readiness for sensorimotor and cognitive processing (Linkenkaer-Hansen, Nikulin, Palva, Ilmoniemi, & Palva, 2004; Palva, Linkenkaer-Hansen, Näätänen, & Palva, 2005; Palva & Palva, 2007; Sadaghiani et al., 2010; Schürmann & Başar, 2001). A recent study by McKinney and colleagues (McKinney, Dang-Vu, Buxton, Solet, & Ellenbogen, 2011) extended this concept to the sleeping state by showing that the continuous variation of alpha power is a sensitive marker of sleep fragility and environmental awareness during NREM sleep. In light of these findings, we suggest that the slightly enhanced alpha power in NMs sleep reflects disturbed sleep regulation and increased alertness toward environmental stimuli during NREM sleep, especially in the first part (second sleep cycle) of the night. Furthermore, we showed that the increase in different alpha components during NREM and REM sleep were related, but only within the NMs group, suggesting that enhanced alpha power is a peculiar characteristic of the sleep pathophysiology of nightmare disorder; however, its frequency range seems to be modulated in a sleep state-dependent manner.

In addition to group differences, gender also had an effect on spectral power measures. In coherence with previous findings on gender differences (Carrier et al., 2001), females exhibited higher values in NREM theta and alpha power. Nevertheless, a trend of Group and Gender interaction emerged for increased NREM alpha power. Females were shown to report more nightmares and bad dreams in both the general and clinical population, which might be related to trait-like differences in emotional reactivity (Levin & Nielsen, 2007). Although in our principal analyses we treated male and female NMs as a whole group, our findings revealed gender differences especially in NREM sleep spectral power. This suggests that proneness to nightmarish experiences may stem from different pathophysiological background in men and women.

Wake-like features in neural oscillations might have important consequences on mental experiences during sleep. Enhanced processing of the environment, including external (e.g. noise) as well as internal (e.g. proprioceptive) information may lead to insomniac complaints – like in sleep-state misperception (Riemann et al., 2010), but perhaps also to the intensification of dream experiences. We propose that the appearance of wake-type alpha oscillations during sleep – especially during the activated cortical state of REM sleep – might promote the intensification of sensorial, emotional and cognitive processes shaping the *oneiric* experience and result in perceptually vivid, realistic and emotionally absorbing dream images. Moreover, transient states of wake-like functioning may strengthen the memory traces for these dream experiences. It is worth noting that high, but not low alpha EEG oscillations involving the thalamo-cortical feed-back loops were hypothesized to reflect search and retrieval in semantic long-term memory during wakefulness (Klimesch, 1999). Thus, the significantly increased REM sleep high alpha EEG activity in NMs could reflect a permanent REM sleep-related intensification of cognitive activity possibly resulting in frequent nightmare experiences. These assumptions are in line with earlier studies showing the association between alpha activity in REM sleep and vivid dream experiences (Robert, Harry, Tyson, Melodie, & Daniel, 1982; Tyson, Ogilvie, & Hunt, 1984). Furthermore, nightmares seem to belong to a wide domain of unusual dream experiences like sleep paralysis, vivid dreaming, lucid dreaming or terrifying hypnagogic hallucinations, which usually occur during sleep–wake transitions (Nielsen & Zadra, 2011). Nevertheless, the question how the valence of these vivid dream experiences in NMs shifts toward the negative domain remains unanswered.

Our findings showing increased low NREM alpha/high REM alpha power in NMs might indicate that altered relative spectral power in NMs resembles sleep patterns found in insomnia; however, in case of insomniac subjects, conclusive findings emerged only during NREM sleep, showing decreased delta, and increased alpha, beta and sigma power (Krystal et al., 2002; Spiegelhalder et al., 2012), while there has been no convincing evidence on REM sleep alterations (Riemann et al., 2010). Moreover, in our sample neither NREM low alpha power, nor REM high alpha power correlated with subjective sleep quality scores. These results make unlikely that increased low NREM and high REM alpha power in NMs are related to concomitant symptoms of insomnia. Nevertheless, since nightmares and insomniac symptoms were reported to be associated in several studies (Li et al., 2011, 2010; Schredl, 2009a,b) proneness to insomniac complaints or subclinical insomniac symptoms might also play a role in shaping NMs' sleep.

The neural mechanism of increased alpha power during sleep is far from being fully understood; however, research suggests that alpha activity is related to an alertness network comprising the dorsal anterior cingulate cortex, anterior insula, and thalamus relaying sensory stimuli to cortical processing (Sadaghiani et al., 2010). Furthermore, these fluctuations between sleep and wakeful states might be modulated by ascending monoaminergic pathways that increase the responsiveness of cortical and thalamic neurons to sensory information (Steriade, McCormick, & Sejnowski, 1993). The effect of different monoaminergic neurotransmitters on sleep EEG and dream intensity awaits further investigations; however, clinical research showed that an α-1 adrenergic antagonist agent (prazosin) reduced nightmares in patients with post-traumatic stress disorder (Dierks, Jordan, & Sheehan, 2007; Peskind, Bonner, Hoff, & Raskind, 2003; Raskind et al., 2007, 2003; Taylor & Raskind, 2002), while selective serotonin and norepinephrine reuptake inhibitors seem to increase the vividness and nightmarish quality of dreaming (Tribl, Wetter, & Schredl, 2012).

NMs also exhibited increased power in 3–4 Hz high delta activity during REM sleep. Increased power in the high delta range during REM sleep is not easy to interpret; however, it is possible that it is related to an increased homeostatic sleep pressure (Marzano, Ferrara, Curcio, & Gennaro, 2010), the demand of the cortex to exhibit the thalamo-cortically generated "bursting mode" of hyperpolarization and rebound sequences (Steriade & Llinás, 1988) that could not be completely expressed due to inefficient sleep regulation and reduced slow wave sleep (Simor et al., 2012). An alternative view of the increased REM sleep 3–4 Hz activity in NMs might be related to the findings of Germain and Nielsen (2001), who reported a strong relationship between sleep onset hypnagogic imagery and EEG delta power. Given the similarities between sleep onset and REM sleep (Bódizs, Sverteczki, et al., 2008), as well as our major finding showing the intrusion of alpha-wave associated wakefulness-like processes into the course of REM sleep this hypothesis seems to be viable. We should note however, that increments in delta power were only evident at two recording sites (F4, Cz), therefore this finding should be treated carefully.

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In contrast to our previous results showing impaired sleep regulation by decreased slow wave sleep (Simor et al., 2012) and reduced number of delta bursts (CAP A1) during arousal events (Simor et al., 2013), relative spectral power analysis did not reveal significant decrease in slow oscillatory activity surviving the correction for multiple comparisons. However, the quantitative EEG analysis is based on artifact free epochs (since movement related artifacts are excluded from the analyses), while sleep staging and CAP analysis include these periods as well. Therefore it is possible that decreased slow oscillatory activity in NMs is principally apparent during transient events of arousal and is less evident during the "restored" background activity that spectral power measures analyze. Furthermore, due to the moderate presence of sweating artifacts in some of our subjects our analysis was restricted to the frequency range above 0.75 Hz, thus our study does not provide information about the slow oscillatory activity under this frequency bin which might be altered in NMs. Nevertheless, decreases in NREM slow delta (1–1.25 Hz) and increases in NREM low theta (4–4.75 Hz) – although were non-significant after the statistical correction – might similarly reflect impaired sleep regulation in NMs.

Regarding the limitations of our study we should note, that since we did not wake up our subjects during the night in order to collect dream reports, we cannot make direct inferences about the association between sleep EEG oscillations and nightmare formation. Hence, the direct relationship between sleep–wake transitions and mental experiences needs to be investigated further. Since nightmares do not occur every night and reports of nightmares are scarce in the sleep laboratory environment, assessments with more nights or ambulatory (home) recordings would provide a more efficient way to examine the neurophysiological background of nightmarish experiences. Examining a relatively homogeneous sample may reduce the influence of different confounding factors, even though we should be careful with generalizing our data to other age groups and populations. Further studies with larger sample sizes involving older subjects might help to resolve these limitations. Although we statistically controlled the effects of waking psychopathological symptoms on sleep EEG patterns, more research is warranted in order to examine the influence of more severe, co-morbid psychopathological symptoms on spectral power measures. Moreover, the influence of anxious or other pathological mood states should be investigated in further studies comparing nightmare and non-nightmare subsamples with high and low waking emotional distress.

In spite of these shortcomings, our study reports novel data regarding the pathophysiology of nightmare disorder and provides testable hypotheses for further investigations examining the relationship between neural oscillations and mental experiences during sleep.

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References

Abt, K. (1987). Descriptive data analysis: A concept between confirmatory and exploratory data analysis. *Methods of Information in Medicine*, *26*(2), 77–88.

American Academy of Sleep Medicine. (2005). *The international classification of sleep disorders: Diagnostic and coding manual* (2nd ed.). Westchester: American Academy of Sleep Medicine.

Armitage, R. (1995). Microarchitectural findings in sleep EEG in depression: Diagnostic implications. *Biological Psychiatry*, *37*(2), 72–84.

Bódizs, R., Simor, P., Csóka, S., Bérdi, M., & Kopp, M. S. (2008). Dreaming and health promotion: A theoretical proposal and some epidemiological establishments. *European Journal of Mental Health*, *3*(1), 35–62.

Bódizs, R., Sverteczki, M., & Mészáros, E. (2008). Wakefulness–sleep transition: Emerging electroencephalographic similarities with the rapid eye movement phase. *Brain Research Bulletin*, *76*(1–2), 85–89.

Cantero, J. L., Atienza, M., Gómez, C., & Salas, R. M. (1999). Spectral structure and brain mapping of human alpha activities in different arousal states. *Neuropsychobiology*, *39*(2), 110–116.

Cantero, J. L., Atienza, M., & Salas, R. M. (2000). Spectral features of EEG alpha activity in human REM sleep: Two variants with different functional roles? *Sleep*, *23*(6), 746–750.

Cantero, J. L., Atienza, M., & Salas, R. M. (2002). Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: Different electroencephalographic phenomena within the alpha band. *Neurophysiologie Clinique/Clinical Neurophysiology*, *32*(1), 54–71.

Carrier, J., Land, S., Buysse, D. J., Kupfer, D. J., & Monk, T. H. (2001). The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). *Psychophysiology*, *38*(2), 232–242.

Coolidge, F. L., Segal, D. L., Coolidge, C. M., Spinath, F. M., & Gottschling, J. (2010). Do nightmares and generalized anxiety disorder in childhood and adolescence have a common genetic origin? *Behavior Genetics*, *40*(3), 349–356.

De la Fuente, J. M., Tugendhaft, P., & Mavroudakis, N. (1998). Electroencephalographic abnormalities in borderline personality disorder. *Psychiatry Research*, *77*(2), 131–138.

Dierks, M. R., Jordan, J. K., & Sheehan, A. H. (2007). Prazosin treatment of nightmares related to posttraumatic stress disorder. *The Annals of Pharmacotherapy*, *41*(6), 1013–1017.

Duffy, F. H., Jones, K., Bartels, P., Albert, M., McAnulty, G. B., & Als, H. (1990). Quantified neurophysiology with mapping: Statistical inference, exploratory and confirmatory data analysis. *Brain Topography*, *3*(1), 3–12.

Feige, B., Scaal, S., Hornyak, M., Gann, H., & Riemann, D. (2007). Sleep electroencephalographic spectral power after withdrawal from alcohol in alcohol-dependent patients. *Alcoholism, Clinical and Experimental Research*, *31*(1), 19–27.

Fisher, C., Byrne, J., Edwards, A., & Kahn, E. (1970). A psychophysiological study of nightmares. *Journal of the American Psychoanalytic Association*, *18*, 747–782.

Germain, A., & Nielsen, T. A. (2001). EEG power associated with early sleep onset images differing in sensory content. *Sleep Research Online*, *4*(3), 83–90.

Germain, A., & Nielsen, T. A. (2003). Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. *Biological Psychiatry*, *54*(10), 1092–1098.

Halász, P. (1998). Hierarchy of micro-arousals and the microstructure of sleep. *Neurophysiologie Clinique/Clinical Neurophysiology*, *28*(6), 461–475.

Halász, P., Terzano, M., Parrino, L., & Bódizs, R. (2004). The nature of arousal in sleep. *Journal of Sleep Research*, *13*(1), 1–23.

Jasper, H. (1958). Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology*, *10*, 370–375.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews*, *29*(2), 169–195.

Krakow, B. (2006). Nightmare complaints in treatment-seeking patients in clinical sleep medicine settings: Diagnostic and treatment implications. *Sleep*, *29*(10), 1313–1319.

Krystal, A. D., Edinger, J. D., Wohlgemuth, W. K., & Marsh, G. R. (2002). NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep*, *25*(6), 630–640.

Lancee, J., Spoormaker, V. I., & van den, B. (2010). Nightmare frequency is associated with subjective sleep quality but not with psychopathology. *Sleep and Biological Rhythms*, *8*(3), 187–193.

Levin, R., & Nielsen, T. A. (2007). Disturbed dreaming, posttraumatic stress disorder, and affect distress: A review and neurocognitive model. *Psychological Bulletin*, *133*(3), 482–528.

Li, S. X., Yu, M. W. M., Lam, S. P., Zhang, J., Li, A. M., Lai, K. Y. C., et al. (2011). Frequent nightmares in children: Familial aggregation and associations with parent-reported behavioral and mood problems. *Sleep*, *34*(4), 487–493.

Li, S. X., Zhang, B., Li, A. M., & Wing, Y. K. (2010). Prevalence and correlates of frequent nightmares: A community-based 2-phase study. *Sleep*, *33*(6), 774–780.

Lindberg, N., Tani, P., Appelberg, B., Naukkarinen, H., Rimón, R., Porkka-Heiskanen, T., et al. (2003). Human impulsive aggression: A sleep research perspective. *Journal of Psychiatric Research*, *37*(4), 313–324.

Linkenkaer-Hansen, K., Nikulin, V. V., Palva, S., Ilmoniemi, R. J., & Palva, J. M. (2004). Prestimulus oscillations enhance psychophysical performance in humans. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *24*(45), 10186–10190.

Marzano, C., Ferrara, M., Curcio, G., & Gennaro, L. D. (2010). The effects of sleep deprivation in humans: Topographical electroencephalogram changes in non-rapid eye movement (NREM) sleep versus REM sleep. *Journal of Sleep Research*, *19*(2), 260–268.

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McKinney, S. M., Dang-Vu, T. T., Buxton, O. M., Solet, J. M., & Ellenbogen, J. M. (2011). Covert waking brain activity reveals instantaneous sleep depth. *PLOS ONE*, *6*(3), e17351.

Moritz, S., Birkner, C., Kloss, M., Jahn, H., Hand, I., Haasen, C., et al. (2002). Executive functioning in obsessive–compulsive disorder, unipolar depression, and schizophrenia. *Archives of Clinical Neuropsychology*, *17*(5), 477–483.

Newell, S. A., Padamadan, H., & Drake, M. E., Jr. (1992). Neurophysiologic studies in nightmare sufferers. *Clinical EEG (Electroencephalography)*, *23*(4), 203–206.

Nielsen, T., Paquette, T., Solomonova, E., Lara-Carrasco, J., Colombo, R., & Lanfranchi, P. (2010). Changes in cardiac variability after REM sleep deprivation in recurrent nightmares. *Sleep*, *33*(1), 113–122.

Nielsen, T., & Zadra, A. (2011). Idiopathic nightmares and dream disturbances associated with sleep–wake transitions. In M. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (5th ed., pp. 1106–1115). New York: Elsevier.

Palva, S., Linkenkaer-Hansen, K., Näätänen, R., & Palva, J. M. (2005). Early neural correlates of conscious somatosensory perception. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *25*(21), 5248–5258.

Palva, S., & Palva, J. M. (2007). New vistas for alpha-frequency band oscillations. *Trends in Neurosciences*, *30*(4), 150–158.

Parrino, L., Ferri, R., Bruni, O., & Terzano, M. G. (2012). Cyclic alternating pattern (CAP): The marker of sleep instability. *Sleep Medicine Reviews*, *16*(1), 27–45.

Peskind, E. R., Bonner, L. T., Hoff, D. J., & Raskind, M. A. (2003). Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. *Journal of Geriatric Psychiatry and Neurology*, *16*(3), 165–171.

Philipsen, A., Feige, B., Al-Shajlawi, A., Schmahl, C., Bohus, M., Richter, H., et al. (2005). Increased delta power and discrepancies in objective and subjective sleep measurements in borderline personality disorder. *Journal of Psychiatric Research*, *39*(5), 489–498.

Poulin, J., Stip, E., & Godbout, R. (2008). REM sleep EEG spectral analysis in patients with first-episode schizophrenia. *Journal of Psychiatric Research*, *42*(13), 1086–1093.

Raskind, M. A., Peskind, E. R., Hoff, D. J., Hart, K. L., Holmes, H. A., Warren, D., et al. (2007). A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biological Psychiatry*, *61*(8), 928–934.

Raskind, M. A., Peskind, E. R., Kanter, E. D., Petrie, E. C., Radant, A., Thompson, C. E., et al. (2003). Reduction of nightmares and Other PTSD Symptoms in combat veterans by prazosin: A placebo-controlled study. *American Journal of Psychiatry*, *160*(2), 371–373.

Rechtschaffen, A., & Kales, A. (1968). *A manual of standardized terminology, technique and scoring system for sleep stages of human sleep*. Los Angeles Brain Information Service. Brain Information Institute, UCLA.

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., et al. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Medicine Reviews*, *14*(1), 19–31.

Robert, D. O., Harry, T., Tyson, P. D., Melodie, L. L., & Daniel, B. J. (1982). Lucid dreaming and alpha activity: A preliminary report. *Perceptual and Motor Skills*, *55*(3), 795–808.

Rózsa, S., Szádoczky, E., & Füredi, J. (2001). A Beck Depresszió Kérdőív rövidített változatának jellemzői a hazai mintán. *Psychiatria Hungarica*, *16*(4), 379–397.

Sadaghiani, S., Scheeringa, R., Lehongre, K., Morillon, B., Giraud, A.-L., & Kleinschmidt, A. (2010). Intrinsic connectivity networks, alpha oscillations, and tonic alertness: A simultaneous electroencephalography/functional magnetic resonance imaging study. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(30), 10243–10250.

Schredl, M. (2009a). Nightmare frequency in patients with primary insomnia. *International Journal of Dream Research*, *2*(2), 85–88.

Schredl, M. (2009b). Dreams in patients with sleep disorders. *Sleep Medicine Reviews*, *13*(3), 215–221.

Schredl, M. (2010). Nightmare frequency and nightmare topics in a representative German sample. *European Archives of Psychiatry and Clinical Neuroscience*, *260*(8), 565–570.

Schredl, M., Schafer, G., Weber, B., & Heuser, I. (1998). Dreaming and insomnia: Dream recall and dream content of patients with insomnia. *Journal of Sleep Research*, *7*(3), 191–198.

Schürmann, M., & Başar, E. (2001). Functional aspects of alpha oscillations in the EEG. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *39*(2–3), 151–158.

Simor, P., Bódizs, R., Horváth, K., & Ferri, R. (2013). Disturbed dreaming and the instability of sleep: Altered NREM sleep microstructure in subjects with frequent nightmares as revealed by the cyclic alternating pattern. *Sleep*, *36*(3), 413–419.

Simor, P., Horváth, K., Gombos, F., Takács, K. P., & Bódizs, R. (2012). Disturbed dreaming and sleep quality: Altered sleep architecture in subjects with frequent nightmares. *European Archives of Psychiatry and Clinical Neuroscience*, *262*(8), 687–696.

Simor, P., Köteles, F., Bódizs, R., & Bárdos, G. (2009). A szubjektív alvásminőség kérdőíves vizsgálata: A Groningen Alvásminőség Skála hazai validálása. *Mentálhigiéné es Pszichoszomatika*, *10*(3), 249–261.

Simor, P., Kovács, I., Vargha, A., Csóka, S., Mangel, B., & Bódizs, R. (2009). Nightmares, dream anxiety and psychopathology: The validation of the Hungarian version of the Van Anxiety Scale. *Psychiatria Hungarica: A Magyar Pszichiátriai Társaság Tudományos Folyóirata*, *24*(6), 428–438.

Sipos, K., Sipos, M., & Spielberger, C. (1994). A state-trait anxiety inventory (STAI) magyar változata. *Pszichodiagnosztikai Vademecum*, *2*.

Spielberger, C., Gorsuch, R., & Lushene, R. (1970). Manual for the STAI. *Consulting Psychologists Tests*.

Spiegelhalder, K., Regen, W., Feige, B., Holz, J., Piosczyk, H., Baglioni, C., et al. (2012). Increased EEG sigma and beta power during NREM sleep in primary insomnia. *Biological Psychology*, *91*(3), 329–333.

Spoormaker, V. I., Schredl, M., & van den Bout, J. (2006). Nightmares: From anxiety symptom to sleep disorder. *Sleep Medicine Reviews*, *10*(1), 19–31.

Steriade, M., & Llinás, R. R. (1988). The functional states of the thalamus and the associated neuronal interplay. *Physiological Reviews*, *68*(3), 649–742.

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science (New York, N.Y.)*, *262*(5134), 679–685.

Taylor, F., & Raskind, M. A. (2002). The alpha1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *Journal of Clinical Psychopharmacology*, *22*(1), 82–85.

Terzano, M. G., Mancia, D., Salati, M. R., Costani, G., Decembrino, A., & Parrino, L. (1985). The cyclic alternating pattern as a physiologic component of normal NREM sleep. *Sleep*, *8*(2), 137–145.

Tribl, G. G., Wetter, T. C., & Schredl, M. (2012). Dreaming under antidepressants: A systematic review on evidence in depressive patients and healthy volunteers. *Sleep Medicine Reviews*, *17*(2), 133–142.

Tyson, P. D., Ogilvie, R. D., & Hunt, H. T. (1984). Lucid, prelucid, and nonlucid dreams related to the amount of EEG alpha activity during REM sleep. *Psychophysiology*, *21*(4), 442–451.

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Part 3. Conclusions and future directions

The above studies presented novel results regarding the neurocognitive and electrophysiological aspects of nightmare disorder however, they also raise several questions that need to be addressed in future investigations.

In our first study, we showed that NMs exhibited lower performance in well-characterized neuropsychological tasks, involving executive functions. We hypothesized that the specific performance profile of NMs, reflects their failure to inhibit task-irrelevant, semantic associations. Although this assumption is in accordance with the considerations regarding the personality characteristics of nightmare subjects, it might be tested in further investigations, applying other neuropsychological tasks, in which the extent and nature of task-irrelevant stimuli can be manipulated systematically. Moreover, although we selected neuropsychological tasks that were shown to involve the neural (prefrontal and fronto-limbic) circuitry of interest, future studies might apply high-density EEG and neuroimaging methods, in order to examine the neural underpinnings of altered information-processing in nightmare disorder. Although subjective sleep quality did not seem to influence impaired performance in NMs, objective sleep alterations (evidenced by Study 2, 3 and 4, but not assessed in Study 1) might have been associated to lower performance in NMs. Therefore, future studies might clarify the relationship between disrupted sleep and subsequent daytime (executive) performance in NMs.

Study 2, 3 and 4 showed that altered sleep patterns, such as impaired sleep architecture (Study 2), increased arousal processes in NREM (Study 3) and increased wake-like oscillatory activity in REM sleep (Study 4), characterize the pathophysiology of nightmare disorder. Moreover, these alterations were not the results of waking anxious and depressive symptoms.

Nevertheless, we do not claim that these are the only factors that facilitate frequent nightmares. We have seen that arousals and transient cortical activations during are related to the intensification of the mental experience during sleep. First of all, transient microarousals, and wake-like oscillatory activities during sleep might provide the "topsoil" of perceptually vivid, intense, real-like imagery, as well as enhanced memory coding and recall of these dream experiences. A personality profile characterized by thin-boundaries would be more susceptible to the intensity of these experiences. Subjects with thin boundaries might get absorbed and emotionally involved in these intense, night-time

perceptual experiences. Furthermore, trait-specific neurotic tendencies and emotional dysregulation (neuroticism, anxiety) and/or increased state-specific stressors might activate fear-related memories and other emotional concerns, shifting the dream experience towards the negative emotional domain.

Although intense dreaming do not necessarily involve negative emotionality, alpha activity during REM and so-called "hybrid states" involving the mixture of sleep-like and wake-like processes often result in intense, and highly disturbing mental experiences, such as in the case of sleep paralysis (Dyken et al., 2006; Takeuchi, Miyasita, Sasaki, Inugami, & Fukuda, 1992; Terzaghi, Ratti, Manni, & Manni, 2012). Another unusual dream experience, lucid dreaming is also characterized by intense dreaming, as well as the coexistence of wake-like and sleep-like phenomena however, these experiences usually do not involve negative affect (Tyson et al., 1984; Voss et al., 2009). This might explain the efficacy of lucid dreaming in the treatment of nightmares (Spoormaker & van den Bout, 2006). Future studies might elucidate the similarities, as well as the neurophysiological differences between nightmarish and lucid experiences. Moreover, the effects of lucid dream therapy on nightmare subjects' sleep parameters would shed more light on the relationship between disrupted sleep and frequent nightmares.

Although our most recent, preliminary findings indicate that relative high alpha power in REM sleep is also related to the severity of nightmares in our group of nightmare subjects (Simor, 2013), the casual relationship between altered sleep and mental experience is far from being clarified. Future studies, might apply affect-laden, pre-sleep stimulation, targeted memory activation during sleep with odor or sound cues, or even external stimulation during sleep in order to examine further these issues. These procedures might allow to model the relationship between specific electrophysiological patterns (eg. arousals), emotional memory activation and dream experience.

Another unanswered issue is the neurophysiological mechanism of increased high alpha power in NMs' sleep: is it related to a REM-specific processes (phasic REM), or it reflects increased environmental processing related to the promotion of wake-like states? Our preliminary findings suggest the latter (Simor, 2013), but further research is warranted to explore this question. And finally, neuroimaging methods coupled with sleep EEG would enrich our knowledge about the neurofunctional background of altered sleep physiology in nightmare disorder. In sum, our studies provide an important "first step" in unraveling the neurocognitive and electrophysiological aspects of nightmare disorder, but further studies, involving experimental manipulations before and/or during sleep might

provide valuable answers and presumably new questions regarding the nature of this prevalent, and hopefully less and less neglected sleep disorder.

References

Achermann, P., & Borbély, A. A. (2011). Sleep homeostasis and models of sleep regulation. In *M. H. Kryger, T. Roth and W. C. Dement (Eds):Principles and Practice of Sleep Medicine* (pp. 431– 444). Missouri: Elsevier Saunders.

Antle, M. C., & Silver, R. (2005). Orchestrating time: arrangements of the brain circadian clock. *Trends in neurosciences*, *28*(3), 145–151.

Antony, J. W., Gobel, E. W., O'Hare, J. K., Reber, P. J., & Paller, K. A. (2012). Cued memory reactivation during sleep influences skill learning. *Nature neuroscience*, *15*(8), 1114–1116.

Aricò, D., Drago, V., Foster, P. S., Heilman, K. M., Williamson, J., & Ferri, R. (2010). Effects of NREM sleep instability on cognitive processing. *Sleep Medicine*, *11*(8), 791–798.

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

Association, A. P., & DSM-IV, A. P. A. T. F. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR.* American Psychiatric Publishing, Inc.

Atienza, M., & Cantero, J. L. (2001). Complex sound processing during human REM sleep by recovering information from long-term memory as revealed by the mismatch negativity (MMN). *Brain research*, *901*(1-2), 151–160.

Atienza, M., Cantero, J. L., & Dominguez-Marin, E. (2002). Mismatch negativity (MMN): an objective measure of sensory memory and long-lasting memories during sleep. *International journal of psychophysiology: official journal of the International Organization of Psychophysiology*, *46*(3), 215–225.

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

Benca, R. M., Obermeyer, W. H., Thisted, R. A., & Gillin, J. C. (1992). Sleep and psychiatric disorders: a meta-analysis. *Archives of General Psychiatry*, *49*(8), 651-668.

Benca, R. M., Okawa, M., Uchiyama, M., Ozaki, S., Nakajima, T., Shibui, K., & Obermeyer, W. H. (1997). Sleep and mood disorders. *Sleep Medicine Reviews*, *1*(1), 45–56.

Bergmann, T. O., Mölle, M., Diedrichs, J., Born, J., & Siebner, H. R. (2012). Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. *NeuroImage*, *59*(3), 2733–2742.

Bersagliere, A., & Achermann, P. (2010). Slow oscillations in human non-rapid eye movement sleep electroencephalogram: effects of increased sleep pressure. *Journal of sleep research*, *19*, 228–237.

Blake, H., & Gerard, R. W. (1937). Brain potentials during sleep. *American Journal of Physiology*, *119*, 692–703.

Bódizs, R. (2000). Alvás, álom, bioritmusok. Budapest: Medicina.

Bódizs, R., Kis, T., Lázár, A. S., Havrán, L., Rigó, P., Clemens, Z., & Halász, P. (2005). Prediction of general mental ability based on neural oscillation measures of sleep. *Journal of sleep research*, *14*(3), 285–292.

Bódizs, R., Sverteczki, M., & Mészáros, E. (2008). Wakefulness-sleep transition: emerging electroencephalographic similarities with the rapid eye movement phase. *Brain research bulletin*, *76*(1-2), 85–89.

Bonnet, M. H. (2000). Sleep deprivation. *Principles and practice of sleep medicine*, *2*, 50-67.

Borbély, A. A. (1982). A two process model of sleep regulation. *Human neurobiology*, *1*(3), 195–204.

Borbély, A. A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of biological rhythms*, *14*(6), 557–568.

Borbély, A. A., & Tobler, I. (1989). Endogenous sleep-promoting substances and sleep regulation. *Physiological reviews*, *69*(2), 605–670.

Bosinelli, M., Cavallero, C., & Cicogna, P. (1982). Self-representation in dream experiences during sleep onset and REM sleep. *Sleep*, *5*(3), 290–299.

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

Bruni, O., Ferri, R., Novelli, L., Finotti, E., Miano, S., & Guilleminault, C. (2008). NREM sleep instability in children with sleep terrors: the role of slow wave activity interruptions. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *119*(5), 985–992.

Buzsáki, G. (1998). Memory consolidation during sleep: a neurophysiological perspective. *Journal of sleep research*, *7 Suppl 1*, 17–23.

Cajochen, C., Brunner, D. P., Kräuchi, K., Graw, P., & Wirz-Justice, A. (1995). Power density in theta/alpha frequencies of the waking EEG progressively increases during sustained wakefulness. *Sleep*, *18*(10), 890–894.

Calvo, J. M., Datta, S., Quattrochi, J., & Hobson, J. A. (1992). Cholinergic microstimulation of the peribrachial nucleus in the cat. II. Delayed and prolonged increases in REM sleep. *Archives italiennes de biologie*, *130*(4), 285–301.

Campbell, I. G., & Feinberg, I. (2009). Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(13), 5177–5180.

Campbell, S. S., & Tobler, I. (1984). Animal sleep: A review of sleep duration across phylogeny. *Neuroscience & Biobehavioral Reviews*, *8*(3), 269–300.

Capellini, I., Nunn, C. L., McNamara, P., Preston, B. T., & Barton, R. A. (2008). Energetic constraints, not predation, influence the evolution of sleep patterning in mammals. *Functional ecology*, *22*(5), 847–853.

Capellini, I., Barton, R. A., McNamara, P., Preston, B. T., & Nunn, C. L. (2008). Phylogenetic analysis of the ecology and evolution of mammalian sleep. *Evolution; international journal of organic evolution*, *62*(7), 1764–1776.

Cartwright, R., Agargun, M. Y., Kirkby, J., & Friedman, J. K. (2006). Relation of dreams to waking concerns. *Psychiatry Research*, *141*(3), 261–270.

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

Chalmers, D. J. (1995). Facing up to the problem of consciousness. *Journal of Consciousness Studies*, *2*(3), 200–219.

Chellappa, S. L., Frey, S., Knoblauch, V., & Cajochen, C. (2011). Cortical activation patterns herald successful dream recall after NREM and REM sleep. *Biological psychology*, *87*(2), 251–256.

Chou, K.-T., Chang, Y.-T., Chen, Y.-M., Su, K.-C., Perng, D.-W., Chang, S.-C., & Shiao, G.-M. (2011). The minimum period of polysomnography required to confirm a diagnosis of severe obstructive sleep apnoea. *Respirology*, *16*(7), 1096–1102.

Cicogna, P., Natale, V., Occhionero, M., & Bosinelli, M. (2000). Slow wave and REM sleep mentation. *Sleep research online: SRO*, *3*(2), 67–72.

Cipolli, C., Bellucci, C., Mattarozzi, K., Mazzetti, M., Tuozzi, G., & Plazzi, G. (2008). Story-like organization of REM-dreams in patients with narcolepsy-cataplexy. *Brain research bulletin*, *77*(4), 206–213.

Clemens, Z., Fabo, D., & Halasz, P. (2005). Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience*, *132*(2), 529–535.

Clemens, Z., Fabó, D., & Halász, P. (2006). Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. *Neuroscience letters*, *403*(1-2), 52–56.

Clemens, Z., Mölle, M., Eross, L., Barsi, P., Halász, P., & Born, J. (2007). Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. *Brain: a journal of neurology*, *130*, 2868–2878.

Clemens, Z., Mölle, M., Eross, L., Jakus, R., Rásonyi, G., Halász, P., & Born, J. (2011). Fine-tuned coupling between human parahippocampal ripples and sleep spindles. *The European journal of neuroscience*, *33*(3), 511–520.

Colrain, I. M., Webster, K. E., & Hirst, G. (1999). The N550 component of the evoked K-complex: a modality non-specific response? *Journal of sleep research*, *8*(4), 273–280.

Colrain, I. M, & Campbell, K. B. (2007). The use of evoked potentials in sleep research. *Sleep medicine reviews*, *11*(4), 277–293.

Conduit, R., Bruck, D., & Coleman, G. (1997). Induction of visual imagery during NREM sleep. *Sleep*, *20*(11), 948–956.

Conduit, R., Crewther, S. G., & Coleman, G. (2004). Poor recall of eye-movement signals from Stage 2 compared to REM sleep: implications for models of dreaming. *Consciousness and cognition*, *13*(3), 484–500.

Coolidge, F. L., Segal, D. L., Coolidge, C. M., Spinath, F. M., & Gottschling, J. (2010). Do Nightmares and Generalized Anxiety Disorder in Childhood and Adolescence have a Common Genetic Origin? *Behavior genetics*, *40*(3), 349–356.

Cote, K. A. (2002). Probing awareness during sleep with the auditory odd-ball paradigm. *International journal of psychophysiology: official journal of the International Organization of Psychophysiology*, *46*(3), 227–241.

Dang-Vu, T. T., Schabus, M., Desseilles, M., Albouy, G., Boly, M., Darsaud, A., … Maquet, P. (2008). Spontaneous neural activity during human slow wave sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(39), 15160–15165.

Datta, S., Calvo, J. M., Quattrochi, J., & Hobson, J. A. (1992). Cholinergic microstimulation of the peribrachial nucleus in the cat. I. Immediate and prolonged increases in ponto-geniculo-occipital waves. *Archives italiennes de biologie*, *130*(4), 263–284.

Datta, S., & O'Malley, M. W. (2013). Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *33*(10), 4561–4569.

De Gennaro, L., Ferrara, M., & Bertini, M. (2000). The spontaneous K-complex during stage 2 sleep: is it the „forerunner" of delta waves? *Neuroscience letters*, *291*(1), 41–43.

De Gennaro, L., Ferrara, M., Spadini, V., Curcio, G., Cristiani, R., & Bertini, M. (2002). The cyclic alternating pattern decreases as a consequence of total sleep deprivation and correlates with EEG arousals. *Neuropsychobiology*, *45*(2), 95–98.

De Gennaro, L., Marzano, C., Moroni, F., Curcio, G., Ferrara, M., & Cipolli, C. (2010). Recovery sleep after sleep deprivation almost completely abolishes dream recall. *Behavioural brain research*, *206*(2), 293–298.

Dement, W., & Wolpert, E. A. (1958). The relation of eye movements, body motility, and external stimuli to dream content. *Journal of experimental psychology*, *55*(6), 543–553.

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience*, *11*(2), 114–126.

Diekelmann, S., Büchel, C., Born, J., & Rasch, B. (2011). Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nature neuroscience*, *14*(3), 381–386.

Dijk, D. J., Duffy, J. F., & Czeisler, C. A. (1992). Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *Journal of Sleep Research*, *1*(2), 112–117.

Donlea, J. M., Ramanan, N., & Shaw, P. J. (2009). Use-dependent plasticity in clock neurons regulates sleep need in Drosophila. *Science*, *324*(5923), 105–108.

Dyken, M. E., Wenger, E. J., & Yamada, T. (2006). REM alpha rhythm: diagnostic for narcolepsy? *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*, *23*(3), 254–257.

Erlacher, D., & Schredl, M. (2010). Practicing a motor task in a lucid dream enhances subsequent performance: A pilot study. *The Sport Psychologist*, *24*(2), 157–167.

Ermis, U., Krakow, K., & Voss, U. (2010). Arousal thresholds during human tonic and phasic REM sleep. *Journal of sleep research*, *19*(3), 400–406.

Eschenko, O., Magri, C., Panzeri, S., & Sara, S. J. (2011). Noradrenergic Neurons of the Locus Coeruleus Are Phase Locked to Cortical Up-Down States during Sleep. *Cerebral Cortex*, *22(2),* 426-435.

Eschenko, O., & Sara, S. J. (2008). Learning-Dependent, Transient Increase of Activity in Noradrenergic Neurons of Locus Coeruleus during Slow Wave Sleep in the Rat: Brain Stem–Cortex Interplay for Memory Consolidation? *Cerebral Cortex, 18*(11), 2596-2603.

Euston, D. R., Tatsuno, M., & McNaughton, B. L. (2007). Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. *Science*, *318*(5853), 1147-1150.

Feinberg, I., & Campbell, I. G. (2010). Sleep EEG changes during adolescence: an index of a fundamental brain reorganization. *Brain and cognition*, *72*(1), 56–65.

Fell, J., Fernández, G., Lutz, M. T., Kockelmann, E., Burr, W., Schaller, C., … Helmstaedter, C. (2006). Rhinal-hippocampal connectivity determines memory formation during sleep. *Brain: a journal of neurology*, *129*(Pt 1), 108–114.

Fernández-Mendoza, J., Lozano, B., Seijo, F., Santamarta-Liébana, E., Ramos-Platón, M. J., Vela-Bueno, A., & Fernández-González, F. (2009). Evidence of subthalamic PGO-like waves during REM sleep in humans: a deep brain polysomnographic study. *Sleep*, *32*(9), 1117–1126.

Ferri, R., Parrino, L., Smerieri, A., Terzano, M. G., Elia, M., Musumeci, S. A., & Pettinato, S. (2000). Cyclic alternating pattern and spectral analysis of heart rate variability during normal sleep. *Journal of sleep research*, *9*(1), 13–18.

Ferri, R., Bruni, O., Miano, S., & Terzano, M. G. (2005). Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). *Sleep Medicine*, *6*(1), 29–36.

Ferri, R., Huber, R., Aricò, D., Drago, V., Rundo, F., Ghilardi, M. F., … Tononi, G. (2008). The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes. *Neuroscience letters*, *432*(3), 228–231.

Finelli, L. A., Borbély, A. A., & Achermann, P. (2001). Functional topography of the human nonREM sleep electroencephalogram. *The European journal of neuroscience*, *13*(12), 2282–2290.

Fisher, C., Byrne, J., Edwards, A., & Kahn, E. (1970). A psychophysiological study of nightmares. *Journal of the American Psychoanalytic Association*, *18*, 747–782.

Florez, J. C., & Takahashi, J. S. (1995). The circadian clock: from molecules to behaviour. *Annals of medicine*, *27*(4), 481–490.

Fogel, S. M., & Smith, C. T. (2011). The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neuroscience and biobehavioral reviews*, *35*(5), 1154–1165.

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

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

Foulkes, D. (1985). *Dreaming: A cognitive-Psychological Analysis.* Hillsdale, N. J. , Lawrence Erlbaum.

Frank, M. G., Issa, N. P., & Stryker, M. P. (2001). Sleep enhances plasticity in the developing visual cortex. *Neuron*, *30*(1), 275–287.

Franzen, P. L., Buysse, D. J., Dahl, R. E., Thompson, W., & Siegle, G. J. (2009). Sleep deprivation alters pupillary reactivity to emotional stimuli in healthy young adults. *Biological psychology*, *80*(3), 300–305.

Freud, S. (2004/1905) T*he Interpretation of Dreams*. Kessinger Publishing.

Ganguly-Fitzgerald, I., Donlea, J., & Shaw, P. J. (2006). Waking experience affects sleep need in Drosophila. *Science*, *313*(5794), 1775–1781.

Germain, A., & Nielsen, T. A. (2003). Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. *Biological Psychiatry*, *54*(10), 1092–1098.

Giesbrecht, T., Smeets, T., Leppink, J., Jelicic, M., & Merckelbach, H. (2007). Acute dissociation after 1 night of sleep loss. *Journal of abnormal psychology*, *116*(3), 599-606.

Gross, D. W., & Gotman, J. (1999). Correlation of high-frequency oscillations with the sleep-wake cycle and cognitive activity in humans. *Neuroscience*, *94*(4), 1005–1018.

Guilleminault, C., Kirisoglu, C., da Rosa, A. C., Lopes, C., & Chan, A. (2006). Sleepwalking, a disorder of NREM sleep instability. *Sleep medicine*, *7*(2), 163–170.

Gujar, N., McDonald, S. A., Nishida, M., & Walker, M. P. (2011). A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. *Cerebral Cortex*, *21*(1), 115-123.

Gujar, N., Yoo, S.-S., Hu, P., & Walker, M. P. (2011). Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(12), 4466–4474.

Halász, P., Terzano, M., Parrino, L., & Bódizs, R. (2004). The nature of arousal in sleep. *Journal of sleep research*, *13*(1), 1–23.

Halász, P., & Bódizs, R. (2013). *Dynamic Structure of NREM sleep*. London: Springer-Verlag.

Hanlon, E. C., Vyazovskiy, V. V., Faraguna, U., Tononi, G., & Cirelli, C. (2011). Synaptic potentiation and sleep need: clues from molecular and electrophysiological studies. *Current topics in medicinal chemistry*, *11*(19), 2472–2482.

Hartmann, E. (1989). Boundaries of dreams, boundaries of dreamers: Thin and thick boundaries as a new personality measure. *Psychiatric Journal of the University of Ottawa*, *14*(4), 557-560.

Hobson, J. A. (1988). *The Dreaming Brain*. New York: Basic Books.

Hobson, J. A., Hoffman, S. A., Helfand, R., & Kostner, D. (1987). Dream bizarreness and the activation-synthesis hypothesis. *Human neurobiology*, *6*(3), 157–164.

Hobson,J. A., Lydic, R., & Bhagdoyan, H. (1986). Evolving concepts of sleep cycle generation: from brain centers to neuronal populations. *Behavioral Brain Sciences*, *9*, 371-448.

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

Hobson, J. A. (2009). REM sleep and dreaming: towards a theory of protoconsciousness. *Nature reviews. Neuroscience*, *10*(11), 803–813.

Huber, R., Ghilardi, M. F., Massimini, M., Ferrarelli, F., Riedner, B. A., Peterson, M. J., & Tononi, G. (2006). Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nature neuroscience*, *9*(9), 1169–1176.

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

Hung, C.-S., Sarasso, S., Ferrarelli, F., Riedner, B., Ghilardi, M. F., Cirelli, C., & Tononi, G. (2013). Local experience-dependent changes in the wake EEG after prolonged wakefulness. *Sleep*, *36*(1), 59–72.

Ioannides, A. A., Corsi-Cabrera, M., Fenwick, P. B. C., del Rio Portilla, Y., Laskaris, N. A., Khurshudyan, A., … Kostopoulos, G. K. (2004). MEG tomography of human cortex and brainstem activity in waking and REM sleep saccades. *Cerebral cortex*, *14*(1), 56–72.

Jahnke, K., von Wegner, F., Morzelewski, A., Borisov, S., Maischein, M., Steinmetz, H., & Laufs, H. (2012). To wake or not to wake? The two-sided nature of the human K-complex. *NeuroImage*, *59*(2), 1631–1638.

Jakobson, A. J., Fitzgerald, P. B., & Conduit, R. (2012). Induction of visual dream reports after transcranial direct current stimulation (tDCs) during Stage 2 sleep. *Journal of sleep research*, *21*(4), 369–379.

Janson, C., Gislason, T., De Backer, W., Plaschke, P., Björnsson, E., Hetta, J., … Boman, G. (1995). Prevalence of sleep disturbances among young adults in the three European Countries. *Sleep*, *18*(7), 589–597.

Jenni, O. G., Achermann, P., & Carskadon, M. A. (2005). Homeostatic sleep regulation in adolescents. *Sleep*, *28*(11), 1446–1454.

Jouny, C., Chapotot, F., & Merica, H. (2000). EEG spectral activity during paradoxical sleep: further evidence for cognitive processing. *Neuroreport*, *11*(17), 3667–3671.

Jouvet, M. (1991). [Paradoxical sleep: is it the guardian of psychological individualism]. *Canadian journal of psychology*, *45*(2), 148–168.

Kahn, M., Sheppes, G., & Sadeh, A. (2013). Sleep and emotions: Bidirectional links and underlying mechanisms. *International journal of psychophysiology: official journal of the International Organization of Psychophysiology*.

Kajimura, N., Uchiyama, M., Takayama, Y., Uchida, S., Uema, T., Kato, M., … Takahashi, K. (1999). Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep. *The Journal of*

neuroscience: the official journal of the Society for Neuroscience, *19*(22), 10065–10073.

Kattler, H., Dijk, D. J., & Borbély, A. A. (1994). Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. *Journal of Sleep Research, 3(3),* 159-164.

Kavanau, J. (2010). Schooling by continuously active fishes: Clues to sleep's ultimate function. In. P. McNamara, R. A. Barton & C. L. Nunn (Eds.) *Evolution of Sleep. Phylogenetic and Functional Perspectives. (pp. 57-85).* New York: Cambridge University Press.

Koffel, E., & Watson, D. (2009). Unusual sleep experiences, dissociation, and schizotypy: Evidence for a common domain. *Clinical psychology review*, *29*(6), 548–559.

Krakow, B. (2006). Nightmare complaints in treatment-seeking patients in clinical sleep medicine settings: diagnostic and treatment implications. *Sleep*, *29*(10), 1313–1319.

Krenzer, M., Anaclet, C., Vetrivelan, R., Wang, N., Vong, L., Lowell, B. B., … Lu, J. (2011). Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. *PloS one*, *6*(10), e24998.

Krueger, J. M. (2010). What exactly is that sleeps? The evolution, regulation, and organization of an emergent network property. In. In. P. McNamara, R. A. Barton & C. L. Nunn (Eds.) *Evolution of Sleep. Phylogenetic and Functional Perspectives. (pp. 86-106).* New York: Cambridge University Press.

Krueger, J. M., Obál, F., Jr, Kapás, L., & Fang, J. (1995). Brain organization and sleep function. *Behavioural brain research*, *69*(1-2), 177–185.

Krueger, J. M., & Obál, F., Jr. (1994). *Sleep Factors. In N.A. Saunders C. E. Sullivan (Eds.) Sleep and Breathing (pp.79-112).* New York: Marcel Dekker, Inc.

Krueger, J. M., & Obal, F., Jr. (2003). Sleep function. *Frontiers in bioscience: a journal and virtual library*, *8*, 511–519.

Krueger, J. M., & Tononi, G. (2011). Local use-dependent sleep; synthesis of the new paradigm. *Current topics in medicinal chemistry*, *11*(19), 2490–2492.

Krueger, J. M. & Obál, F. (1993). A neuronal group theory of sleep function. *Journal of sleep research*, *2*(2), 63–69.

Lancee, J., Spoormaker, V. I., & van den Bout, J. (2010). Nightmare frequency is associated with subjective sleep quality but not with psychopathology. *Sleep and Biological Rhythms*, *8*(3), 187–193.

Leclair-Visonneau, L., Oudiette, D., Gaymard, B., Leu-Semenescu, S., & Arnulf, I. (2010). Do the eyes scan dream images during rapid eye movement sleep? Evidence from the rapid eye movement sleep behaviour disorder model. *Brain: a journal of neurology*, *133*(6), 1737–1746.

Lesku, J. A., Bark, R. J., Martinez-Gonzalez, D., Rattenborg, N. C., Amlaner, C. J., & Lima, S. L. (2008). Predator-induced plasticity in sleep architecture in wild-caught Norway rats (Rattus norvegicus). *Behavioural brain research*, *189*(2), 298–305.

Leslie, K., Sleigh, J., Paech, M. J., Voss, L., Lim, C. W., & Sleigh, C. (2009). Dreaming and Electroencephalographic Changes during Anesthesia Maintained with Propofol or Desflurane. *Anesthesiology*, *111*(3), 547–555.

Levin, R., & Fireman, G. (2002). Nightmare prevalence, nightmare distress, and self-reported psychological disturbance. *Sleep*, *25*(2), 205–212.

Levin, R., Fireman, G., Spendlove, S., & Pope, A. (2011). The Relative Contribution of Affect Load and Affect Distress as Predictors of Disturbed Dreaming. *Behavioral Sleep Medicine*, *9*(3), 173–183.

Levin, R., & Nielsen, T. A. (2007). Disturbed dreaming, posttraumatic stress disorder, and affect distress: a review and neurocognitive model. *Psychological Bulletin*, *133*(3), 482–528.

Li, S. X., Zhang, B., Li, A. M., & Wing, Y. K. (2010). Prevalence and correlates of frequent nightmares: a community-based 2-phase study. *Sleep*, *33*(6), 774-780.

Llinás, R. R., & Steriade, M. (2006). Bursting of thalamic neurons and states of vigilance. *Journal of neurophysiology*, *95*(6), 3297–3308.

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

Lu, J., Sherman, D., Devor, M., & Saper, C. B. (2006). A putative flip-flop switch for control of REM sleep. *Nature*, *441*(7093), 589–594.

Lustenberger, C., Maric, A., Dürr, R., Achermann, P., & Huber, R. (2012). Triangular relationship between sleep spindle activity, general cognitive ability and the efficiency of declarative learning. *PloS one*, *7*(11), e49561.

Maquet, P., Dive, D., Salmon, E., Sadzot, B., Franco, G., Poirrier, R., & Franck, G. (1992). Cerebral glucose utilization during stage 2 sleep in man. *Brain research*, *571*(1), 149–153.

Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., … Cleeremans, A. (2000). Experience-dependent changes in cerebral activation during human REM sleep. *Nature neuroscience*, *3*(8), 831–836.

Maquet, P., Péters, J., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., & Franck, G. (1996). Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature*, *383*(6596), 163–166.

Maquet, P., & Phillips, C. (1998). Functional brain imaging of human sleep. *Journal of sleep research*, *7 (Suppl 1)*, 42–47.

Marshall, L., & Born, J. (2007). The contribution of sleep to hippocampus-dependent memory consolidation. *Trends in cognitive sciences*, *11*(10), 442–450.

Marshall, L., Mölle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *The Journal of neuroscience*, *24*(44), 9985-9992.

Marzano, C., Ferrara, M., Curcio, G., & Gennaro, L. D. (2010). The effects of sleep deprivation in humans: topographical electroencephalogram changes in non-rapid eye movement (NREM) sleep versus REM sleep. *Journal of Sleep Research*, *19*(2), 260–268.

Marzano, C., Ferrara, M., Mauro, F., Moroni, F., Gorgoni, M., Tempesta, D., … De Gennaro, L. (2011). Recalling and forgetting dreams: theta and alpha oscillations during sleep predict subsequent dream recall. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *31*(18), 6674–6683.

Massaquoi, S. G., & McCarley, R. W. (1992). Extension of the Limit Cycle Reciprocal Interaction Model of REM cycle control. An integrated sleep control model. *Journal of sleep research*, *1*(2), 138–143.

Massimini, M., Ferrarelli, F., Murphy, M., Huber, R., Riedner, B., Casarotto, S., & Tononi, G. (2010). Cortical reactivity and effective connectivity during REM sleep in humans. *Cognitive neuroscience*, *1*(3), 176–183.

Mazzetti, M., Bellucci, C., Mattarozzi, K., Plazzi, G., Tuozzi, G., & Cipolli, C. (2010). REM-dreams recall in patients with narcolepsy-cataplexy. *Brain research bulletin*, *81*(1), 133–140.

McCarley, R. W., & Massaquoi, S. G. (1992). Neurobiological structure of the revised limit cycle reciprocal interaction model of REM cycle control. *Journal of sleep research*, *1*(2), 132–137.

McCoy, J. G., & Strecker, R. E. (2011). The cognitive cost of sleep lost. *Neurobiology of learning and memory*, *96*(4), 564–582.

McNamara, P., Barton, R. A., & Nunn, C. L. (2010). Introduction. In. P. McNamara, R. A. Barton & C. L. Nunn (Eds.) *Evolution of Sleep. Phylogenetic and Functional Perspectives. (pp. 1-11)*. New York: Cambridge University Press.

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

Medicine, E. A. (2005). *The international classification of sleep disorders: diagnostic and coding manual*. American Academy of Sleep Medicine.

Miyauchi, S., Misaki, M., Kan, S., Fukunaga, T., & Koike, T. (2009). Human brain activity time-locked to rapid eye movements during REM sleep. *Experimental brain research*, *192*(4), 657–667.

Mölle, M., Eschenko, O., Gais, S., Sara, S. J., & Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *European Journal of Neuroscience*, *29*(5), 1071–1081.

Mölle, M., Marshall, L., Gais, S., & Born, J. (2002). Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *The Journal of neuroscience*, *22*(24), 10941–10947.

Muzur, A., Pace-Schott, E. F., & Hobson, J. A. (2002). The prefrontal cortex in sleep. *Trends in Cognitive Sciences*, *6*(11), 475–481.

Nardone, R., Golaszewski, S., Höller, Y., Christova, M., Trinka, E., & Brigo, F. (2013). Neurophysiological insights into the pathophysiology of REM sleep behavior disorders: A review. *Neuroscience research*. pii: S0168-0102(13)00086-2. doi: 10.1016/j.neures.2013.03.009.

Newell, S. A., Padamadan, H., & Drake, M. E., Jr. (1992). Neurophysiologic studies in nightmare sufferers. *Clinical EEG (electroencephalography)*, *23*(4), 203–206.

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

Nielsen, T. A. (1993). Changes in the kinestetic content of dreams following somatosensory stimulation of leg muscles during REM sleep. *Dreaming, 3,* 99–113.

Nielsen, T., Paquette, T., Solomonova, E., Lara-Carrasco, J., Colombo, R., & Lanfranchi, P. (2010). Changes in cardiac variability after REM sleep deprivation in recurrent nightmares. *Sleep*, *33*(1), 113–122.

Nielsen, T., & Zadra, A. (2011). Idiopathic Nightmares and Dream Disturbances Associated with Sleep–Wake Transitions. In. M. Kryger, T. Roth & W. C. Dement (Eds.) *Principles and practice of sleep meidice* (5th ed., pp. 1106-1115). New York: Elsevier.

Nielsen, T. A., Kuiken, D., Alain, G., Stenstrom, P., & Powell, R. A. (2004). Immediate and delayed incorporations of events into dreams: further replication and implications for dream function. *Journal of sleep research*, *13*(4), 327–336.

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

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex*, *19*(5), 1158-1166.

Nishida, M., Uchida, S., Hirai, N., Miwakeichi, F., Maehara, T., Kawai, K., … Kato, S. (2005). High frequency activities in the human orbitofrontal cortex in sleep-wake cycle. *Neuroscience letters*, *379*(2), 110–115.

Nobili, L., Ferrara, M., Moroni, F., De Gennaro, L., Russo, G. L., Campus, C., … De Carli, F. (2011). Dissociated wake-like and sleep-like electro-cortical activity during sleep. *NeuroImage*, *58*(2), 612–619.

Nofzinger, E.A., Maquet, P. (2011). What brain imaging reveals about sleep generation and maintenance. In. M. Kryger, T. Roth & W. C. Dement (Eds.) *Principles and practice of sleep meidice* (5th ed., pp. 201-204). New York: Elsevier.

Ohayon, M. M., Morselli, P. L., & Guilleminault, C. (1997). Prevalence of nightmares and their relationship to psychopathology and daytime functioning in insomnia subjects. *Sleep*, *20*(5), 340–348.

Oudiette, D., Constantinescu, I., Leclair-Visonneau, L., Vidailhet, M., Schwartz, S., & Arnulf, I. (2011). Evidence for the re-enactment of a recently learned behavior during sleepwalking. *PloS one*, *6*(3), e18056.

Oudiette, D., Dealberto, M.-J., Uguccioni, G., Golmard, J.-L., Merino-Andreu, M., Tafti, M., … Arnulf, I. (2012). Dreaming without REM sleep. *Consciousness and cognition*, *21*(3), 1129–1140.

Oudiette, D., Leu, S., Pottier, M., Buzare, M.-A., Brion, A., & Arnulf, I. (2009). Dreamlike mentations during sleepwalking and sleep terrors in adults. *Sleep*, *32*(12), 1621–1627.

Oudiette, D., & Paller, K. A. (2013). Upgrading the sleeping brain with targeted memory reactivation. *Trends in cognitive sciences*, *17*(3), 142–149.

Pace-Schott, E. F., Milad, M. R., Orr, S. P., Rauch, S. L., Stickgold, R., & Pitman, R. K. (2009). Sleep promotes generalization of extinction of conditioned fear. *Sleep*, *32*(1), 19–26.

Paré, D., Collins, D. R., & Pelletier, J. G. (2002). Amygdala oscillations and the consolidation of emotional memories. *Trends in cognitive sciences*, *6*(7), 306–314.

Parrino, L., Ferri, R., Bruni, O., & Terzano, M. G. (2012). Cyclic alternating pattern (CAP): the marker of sleep instability. *Sleep Medicine Reviews*, *16*(1), 27–45.

Peigneux, P., Laureys, S., Fuchs, S., Delbeuck, X., Degueldre, C., Aerts, J., … Maquet, P. (2001). Generation of rapid eye movements during paradoxical sleep in humans. *NeuroImage*, *14*(3), 701–708.

Peigneux, P., Laureys, S., Fuchs, S., Destrebecqz, A., Collette, F., Delbeuck, X., … others. (2003). Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. *Neuroimage*, *20*(1), 125–134.

Perrin, F., García-Larrea, L., Mauguière, F., & Bastuji, H. (1999). A differential brain response to the subject's own name persists during sleep. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *110*(12), 2153–2164.

Perrin, F., Bastuji, H., & Garcia-Larrea, L. (2002). Detection of verbal discordances during sleep. *Neuroreport*, *13*(10), 1345–1349.

Peterson, M. J., & Benca, R. M. (2006). Sleep in mood disorders. *The Psychiatric clinics of North America*, *29*(4), 1009–1032.

Pivik, T., & Foulkes, D. (1966). „Dream deprivation": effects on dream content. *Science*, *153*(3741), 1282–1284.

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*, *9*(4), 534–547.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *118*(10), 2128–2148.

Popa, D., Duvarci, S., Popescu, A. T., Léna, C., & Paré, D. (2010). Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(14), 6516–6519.

Porkka-Heiskanen, T., & Kalinchuk, A. V. (2011). Adenosine, energy metabolism and sleep homeostasis. *Sleep medicine reviews*, *15*(2), 123–135.

Racsmány, M., Conway, M. A., & Demeter, G. (2010). Consolidation of Episodic Memories During Sleep. *Psychological Science*, *21*(1), 80-85.

Rasch, B., & Born, J. (2007). Maintaining memories by reactivation. *Current Opinion in Neurobiology*, *17*(6), 698–703.

Rechtschaffen, A., & Kales, A. (1968). A manual of standardized terminology, technique and scoring system for sleep stages of human sleep. Los Angeles Brain Information Service. *Brain Information Institute, UCLA*.

Revonsuo, A. (2000). The reinterpretation of dreams: an evolutionary hypothesis of the function of dreaming. *The Behavioral and brain sciences*, *23*(6), 877–901; discussion 904–1121.

Ribeiro, S., Goyal, V., Mello, C. V., & Pavlides, C. (1999). Brain gene expression during REM sleep depends on prior waking experience. *Learning & Memory*, *6*(5), 500–508.

Ribeiro, S., Mello, C. V., Velho, T., Gardner, T. J., Jarvis, E. D., & Pavlides, C. (2002). Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *22*(24), 10914–10923.

Ribeiro, S., & Nicolelis, M. A. L. (2004). Reverberation, storage, and postsynaptic propagation of memories during sleep. *Learning & memory*, *11*(6), 686–696.

Riedner, B. A., Hulse, B. K., Murphy, M. J., Ferrarelli, F., & Tononi, G. (2011). Temporal dynamics of cortical sources underlying spontaneous and peripherally evoked slow waves. *Progress in brain research*, *193*, 201–218.

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Medicine Reviews*, *14*(1), 19–31.

Rudoy, J. D., Voss, J. L., Westerberg, C. E., & Paller, K. A. (2009). Strengthening individual memories by reactivating them during sleep. *Science*, *326*(5956), 1079–1079.

Rusterholz, T., Dürr, R., & Achermann, P. (2010). Inter-individual differences in the dynamics of sleep homeostasis. *Sleep*, *33*(4), 491–498.

Saletin, J. M., Goldstein, A. N., & Walker, M. P. (2011). The Role of Sleep in Directed Forgetting and Remembering of Human Memories. *Cerebral Cortex*, *21*(11), 2534–2541.

Sallinen, M., Kaartinen, J., & Lyytinen, H. (1996). Processing of auditory stimuli during tonic and phasic periods of REM sleep as revealed by event-related brain potentials. *Journal of sleep research*, *5*(4), 220–228.

Saper, C. B, Chou, T. C., & Scammell, T. E. (2001). The sleep switch: hypothalamic control of sleep and wakefulness. *Trends in neurosciences*, *24*(12), 726–731.

Saper, C. B. (2000). Brainstem modulation of sensation movement and consciousness. In In: Kandel, E.R., Schwartz, J.H., Jessell T.M.(Eds.) *Principles of Neural Science, 4th ed. (pp. 871–909).* New York: McGraw-Hill.

Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J., & Scammell, T. E. (2010). Sleep state switching. *Neuron*, *68*(6), 1023–1042.

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, *437*(7063), 1257–1263.

Schabus, M., Dang-Vu, T. T., Albouy, G., Balteau, E., Boly, M., Carrier, J., … Maquet, P. (2007). Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(32), 13164–13169.

Schacter, D. L., Addis, D. R., & Buckner, R. L. (2007). Remembering the past to imagine the future: the prospective brain. *Nature reviews. Neuroscience*, *8*(9), 657–661.

Schacter, D. L., Addis, D. R., Hassabis, D., Martin, V. C., Spreng, R. N., & Szpunar, K. K. (2012). The future of memory: remembering, imagining, and the brain. *Neuron*, *76*(4), 677–694.

Schredl, M. (1998). Dream content in patients with narcolepsy: preliminary findings. *Dreaming*, *8*(2), 103-107.

Schredl, M. (2003). Effects of state and trait factors on nightmare frequency. *European archives of psychiatry and clinical neuroscience*, *253*(5), 241–247.

Schredl, M. (2010). Nightmares: An Under-Diagnosed and Undertreated Condition? *Sleep*, *33*(6), 733.

Schredl, M., Schafer, G., Weber, B., & Heuser, I. (1998). Dreaming and insomnia: dream recall and dream content of patients with insomnia. *Journal of sleep research*, *7*(3), 191–198.

Schredl, M., Atanasova, D., Hörmann, K., Maurer, J. T., Hummel, T., & Stuck, B. A. (2009). Information processing during sleep: the effect of olfactory stimuli on dream content and dream emotions. *Journal of sleep research*, *18*(3), 285–290.

Sculthorpe, L. D., Ouellet, D. R., & Campbell, K. B. (2009). MMN elicitation during natural sleep to violations of an auditory pattern. *Brain research*, *1290*, 52–62.

Siegel, J. M. (2005). Clues to the functions of mammalian sleep. *Nature*, *437*(7063), 1264–1271.

Simor, P. Aroused sleep, alert dreams: electrophysiological alterations in nightmare disorder. Learning & Perception, 3, 2 (Supplement), 26-27.

Smith, C. (1995). Sleep states and memory processes. *Behavioural Brain Research*, *69*(1-2), 137–145.

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

Solms, M. (2011). Neurobiology and the neurological basis of dreaming. *Handbook of clinical neurology*, *98*, 519–544.

Spoormaker, V. I., Sturm, A., Andrade, K. C., Schröter, M. S., Goya-Maldonado, R., Holsboer, F., … Czisch, M. (2010). The neural correlates and temporal sequence of the relationship between shock exposure, disturbed sleep and impaired consolidation of fear extinction. *Journal of Psychiatric Research*, *44*(16), 1121–1128.

Spoormaker, V. I, & Montgomery, P. (2008). Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature? *Sleep Medicine Reviews*, *12*(3), 169–184.

Spoormaker, V. I., Schredl, M., & van den Bout, J. (2006). Nightmares: from anxiety symptom to sleep disorder. *Sleep Medicine Reviews*, *10*(1), 19–31.

Spoormaker, V.I., Schröter, M. S., Andrade, K. C., Dresler, M., Kiem, S. A., Goya-Maldonado, R., … Czisch, M. (2012). Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. *Human brain mapping*, *33*(10), 2362–2376.

Spoormaker, V. I., & van den Bout, J. (2006). Lucid dreaming treatment for nightmares: a pilot study. *Psychotherapy and psychosomatics*, *75*(6), 389–394.

Squire, L. R., & Bayley, P. J. (2007). The neuroscience of remote memory. *Current opinion in neurobiology*, *17*(2), 185–196.

Steriade, M. (2005). Sleep, epilepsy and thalamic reticular inhibitory neurons. *Trends Neurosci.* 28, 317–324.

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

Steriade, M., Dossi, R. C., & Nuñez, A. (1991). Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: cortically induced synchronization and brainstem cholinergic suppression. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *11*(10), 3200–3217.

Steriade, M., & Llinás, R. R. (1988). The functional states of the thalamus and the associated neuronal interplay. *Physiological reviews*, *68*(3), 649–742.

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, *262*(5134), 679–685.

Stickgold, R., & Walker, M. P. (2007). Sleep-dependent memory consolidation and reconsolidation. *Sleep medicine*, *8*(4), 331–343.

Stickgold, R. (2002). EMDR: a putative neurobiological mechanism of action. *Journal of clinical psychology*, *58*(1), 61–75.

Stuart, K., & Conduit, R. (2009). Auditory inhibition of rapid eye movements and dream recall from REM sleep. *Sleep*, *32*(3), 399–408.

Swart, M. L., van Schagen, A. M., Lancee, J., & van den Bout, J. (2013). Prevalence of Nightmare Disorder in Psychiatric Outpatients. *Psychotherapy and Psychosomatics*, *82*(4), 267–268.

Takahashi, J. S., Shimomura, K., & Kumar, V. (2008). Searching for genes underlying behavior: lessons from circadian rhythms. *Science*, *322*(5903), 909–912.

Takahashi, K., Kayama, Y., Lin, J. S., & Sakai, K. (2010). Locus coeruleus neuronal activity during the sleep-waking cycle in mice. *Neuroscience*, *169*(3), 1115–1126.

Takahashi, K., Lin, J.-S., & Sakai, K. (2006). Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *26*(40), 10292–10298.

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

Takeuchi, T., Miyasita, A., Sasaki, Y., Inugami, M., & Fukuda, K. (1992). Isolated sleep paralysis elicited by sleep interruption. *Sleep*, *15*(3), 217–225.

Tempesta, D., Couyoumdjian, A., Curcio, G., Moroni, F., Marzano, C., De Gennaro, L., & Ferrara, M. (2010). Lack of sleep affects the evaluation of emotional stimuli. *Brain research bulletin*, *82*(1-2), 104-108.

Terzaghi, M., Ratti, P. L., Manni, F., & Manni, R. (2012). Sleep paralysis in narcolepsy: more than just a motor dissociative phenomenon? *Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *33*(1), 169–172.

Terzaghi, M., Sartori, I., Tassi, L., Rustioni, V., Proserpio, P., Lorusso, G., … Nobili, L. (2012). Dissociated local arousal states underlying essential clinical features of non-rapid eye movement arousal parasomnia: an intracerebral stereo-electroencephalographic study. *Journal of sleep research*, *21*(5), 502–506.

Terzano, M. G., Mancia, D., Salati, M. R., Costani, G., Decembrino, A., & Parrino, L. (1985). The cyclic alternating pattern as a physiologic component of normal NREM sleep. *Sleep*, *8*(2), 137–145.

Terzano, M. G., & Parrino, L. (2000). Origin and Significance of the Cyclic Alternating Pattern (CAP). REVIEW ARTICLE. *Sleep Medicine Reviews*, *4*(1), 101–123.

Terzano, M. G., Smerieri, A., Del Felice, A., Giglia, F., Palomba, V., & Parrino, L. (2006). Cyclic alternating pattern (CAP) alterations in narcolepsy. *Sleep Medicine*, *7*(8), 619–626.

Tinguely, G., Finelli, L. A., Landolt, H.-P., Borbély, A. A., & Achermann, P. (2006). Functional EEG topography in sleep and waking: state-dependent and state-independent features. *NeuroImage*, *32*(1), 283–292.

Tobler, I., & Stalder, J. (1988). Rest in the scorpion — a sleep-like state? *Journal of Comparative Physiology A*, *163*(2), 227–235.

Tobler, I. (2005). Phylogeny of sleep regulation. In. M. H. Kryger, T. Roth, & W. C. Dement *(Eds.) Principles and practice of sleep medicine* (pp. 70–90). Philadelphia: Elsevier.

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep medicine reviews*, *10*(1), 49–62.

Tononi, G., & Cirelli, C. (2012). Time to be SHY? Some comments on sleep and synaptic homeostasis. *Neural plasticity*, *2012*, 415250.

Tyson, P. D., Ogilvie, R. D., & Hunt, H. T. (1984). Lucid, prelucid, and nonlucid dreams related to the amount of EEG alpha activity during REM sleep. *Psychophysiology*, *21*(4), 442–451.

Uguccioni, G., Golmard, J.-L., de Fontréaux, A. N., Leu-Semenescu, S., Brion, A., & Arnulf, I. (2013). Fight or flight? Dream content during sleepwalking/sleep terrors vs rapid eye movement sleep behavior disorder. *Sleep medicine*, *14*(5), 391–398.

Van der Helm, E., Gujar, N., & Walker, M. P. (2010). Sleep deprivation impairs the accurate recognition of human emotions. *Sleep*, *33*(3), 335-342.

Van der Helm, E., Yao, J., Dutt, S., Rao, V., Saletin, J. M., & Walker, M. P. (2011). REM sleep depotentiates amygdala activity to previous emotional experiences. *Current biology: CB*, *21*(23), 2029–2032.

Van Dongen, E. V., Takashima, A., Barth, M., Zapp, J., Schad, L. R., Paller, K. A., & Fernández, G. (2012). Memory stabilization with targeted reactivation during human slow-wave sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(26), 10575–10580.

Voss, U., Holzmann, R., Tuin, I., & Hobson, J. A. (2009). Lucid dreaming: a state of consciousness with features of both waking and non-lucid dreaming. *Sleep*, *32*(9), 1191–1200.

Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning & Memory*, *8*(2), 112-119.

Walker, M. P., & Stickgold, R. (2010). Overnight alchemy: sleep-dependent memory evolution. *Nature Reviews Neuroscience*, *11*(3), 218–218.

Walker, M. P., & van Der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychological bulletin*, *135*(5), 731-748.

Wamsley, E. J., Tucker, M., Payne, J. D., Benavides, J. A., & Stickgold, R. (2010). Dreaming of a learning task is associated with enhanced sleep-dependent memory consolidation. *Current Biology*, *20*(9), 850–855.

Waterman, D., Elton, M., Hofman, W., Woestenburg, J. C., & Kok, A. (1993). EEG spectral power analysis of phasic and tonic REM sleep in young and older male subjects. *Journal of sleep research*, *2*(1), 21–27.

Wehrle, R., Kaufmann, C., Wetter, T. C., Holsboer, F., Auer, D. P., Pollmächer, T., & Czisch, M. (2007). Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods. *The European journal of neuroscience*, *25*(3), 863–871.

Wilhelm, I., Diekelmann, S., Molzow, I., Ayoub, A., Mölle, M., & Born, J. (2011). Sleep selectively enhances memory expected to be of future relevance. *The Journal of Neuroscience*, *31*(5), 1563–1569.

Domhoff, W. G. (2011). The neural substrate for dreaming: is it a subsystem of the default network? *Consciousness and cognition*, *20*(4), 1163–1174.

Yoo, S. S., Gujar, N., Hu, P., Jolesz, F. A., & Walker, M. P. (2007). The human emotional brain without sleep--a prefrontal amygdala disconnect. *Current Biology: CB*, *17*(20), R877–878.