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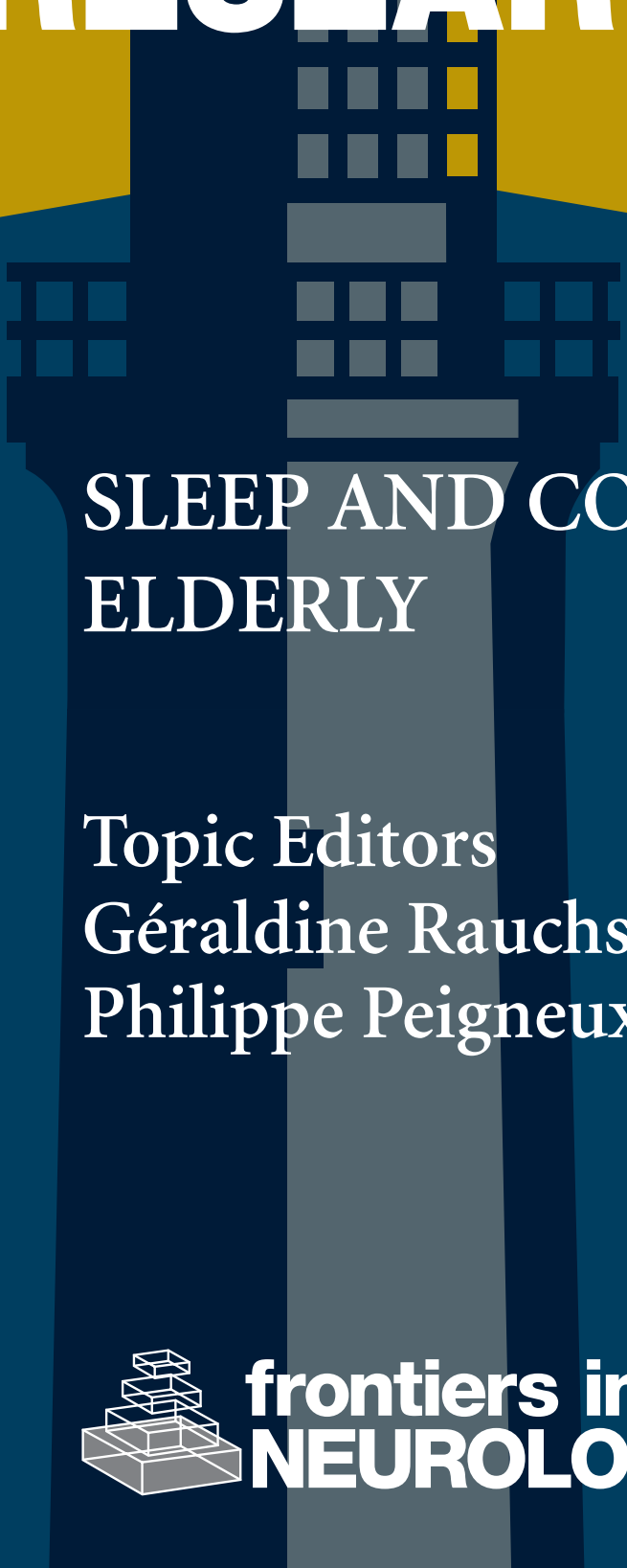

SLEEP AND COGNITION IN THE ELDERLY

Topic Editors
Géraldine Rauchs, Julie Carrier and Philippe Peigneux

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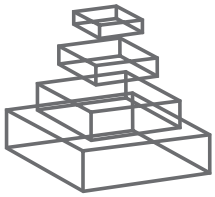

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Cover image provided by Ibbl sarl, Lausanne CH

ISSN 1664-8714
ISBN 978-2-88919-295-3
DOI 10.3389/978-2-88919-295-3

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SLEEP AND COGNITION IN THE ELDERLY

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frontiers in
NEUROLOGY

EDITORIAL
published: 10 June 2013
doi: 10.3389/fneur.2013.00071

Sleep and cognition in the elderly

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In the past decade, our understanding of sleep mechanisms and their role in cognitive processes including memory functions has markedly increased. However, most data have been gathered in young adults, neglecting the fact that sleep is an age-dependent evolutionary process featuring substantial physiological changes that may impact on daily cognitive functioning. Despite the importance of this topic from scientific and societal standpoints, studies jointly investigating aging, sleep, and cognition remain scarce, even considering patients with neurodegenerative diseases. With this special topic, we aim at providing the reader with an updated overview of those studies assessing the impact of age-related changes in sleep and sleep regulation on various domains of cognition. In this respect, this issue addresses changes in sleep and circadian rhythms in the elderly, and how they impact on cognitive performance and brain activity (Schmidt et al., 2012). Sleep-dependent memory consolidation and the age-related changes that may compromise this complex process are also discussed (Harand et al., 2012), as well as how pre-sleep learning can improve sleep continuity, stability, and organization in older adults (Conte et al., 2012). Considering mental productions during sleep, variations in dream recall frequency, and dream theme diversity across the lifespan are also investigated (Nielsen, 2012). From another perspective, the potential mechanisms underlying sleep changes in adults are investigated, focusing on the role of adenosine in protecting from neurobehavioral impairments after sleep deprivation in older adults (Landolt et al., 2012) and on age-related changes in slow oscillations during sleep-dependent memory consolidation processes (Fogel et al., 2012). Finally, common sleep-related pathologies are addressed. In the context of aging, insomnia complaints in older adults and its neural substrates are a crucial issue (Stoffers et al., 2012), but elderly are also a population at risk for obstructive sleep apnea, which might markedly impact on cognitive processes (Sforza and Roche, 2012). Also, less frequent in isolation in normal aging but commonly associated with dementia with Lewy bodies or Parkinson's disease, REM sleep behavior disorder may accelerate cognitive decline (Gagnon et al., 2012).

Altogether, the contributions in this issue show that a better understanding of age-related changes in sleep architecture and microstructure, of their potential impact on cognition and of their underlying mechanisms is essential to develop efficient care of sleep disturbances in the elderly. Such information is even more crucially needed to better apprehend and treat sleep disturbances in neurodegenerative diseases, such as Alzheimer's disease, where sleep disturbances, taken as downstream symptoms of the disease, can be evidenced years before the diagnosis. These sleep disturbances may significantly accelerate cognitive decline (e.g., Rauchs et al., 2008; Hot et al., 2011; Westerberg et al., 2012) and exacerbate the neuropathological processes leading to amyloid depositions (Kang et al., 2009; Ju et al., 2013). Hence it highlights the utmost importance of preserving sleep quality in older adults for optimal cognitive functioning and opposing to the course of neurodegenerative diseases.

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Received: 11 April 2013; accepted: 27 May 2013; published online: 10 June 2013.
*Citation: Rauchs G, Carrier J and Peigneux P (2013) Sleep and cognition in the elderly. Front. Neurol. **4**:71. doi: 10.3389/fneur.2013.00071*
This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in
NEUROLOGY

REVIEW ARTICLE
published: 26 July 2012
doi: 10.3389/fneur.2012.00118

Age-related changes in sleep and circadian rhythms: impact on cognitive performance and underlying neuroanatomical networks

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Circadian and homeostatic sleep-wake regulatory processes interact in a fine tuned manner to modulate human cognitive performance. Dampening of the circadian alertness signal and attenuated deterioration of psychomotor vigilance in response to elevated sleep pressure with aging change this interaction pattern. As evidenced by neuroimaging studies, both homeostatic sleep pressure and circadian sleep-wake promotion impact on cognition-related cortical and arousal-promoting subcortical brain regions including the thalamus, the anterior hypothalamus, and the brainstem locus coeruleus (LC). However, how age-related changes in circadian and homeostatic processes impact on the cerebral activity subtending waking performance remains largely unexplored. Post-mortem studies point to neuronal degeneration in the SCN and age-related modifications in the arousal-promoting LC. Alongside, cortical frontal brain areas are particularly susceptible both to aging and misalignment between circadian and homeostatic processes. In this perspective, we summarize and discuss here the potential neuroanatomical networks underlying age-related changes in circadian and homeostatic modulation of waking performance, ranging from basic arousal to higher order cognitive behaviors.

Keywords: aging, sleep-wake regulation, cognition, functional magnetic resonance imaging, circadian rhythms, sleep homeostasis

INTRODUCTION

Aging can be defined in terms of life and time (Martin, 1981) and it is often assumed that cognitive and health difficulties tend to increase as time advances. However, many researchers depart from this stereotype and put the concept of successful aging forward (for a review, see Lupien and Wan, 2004). Aging is considered as a multidimensional process in a way that environmental factors may protect for or conversely aggravate signs of aging in a non-linear manner with regard to physiological but also neurobehavioral processes. There is large and important heterogeneity both in cognitive and sleep-wake rhythm alterations that occur with normal aging, which have the potential to serve as a tool to better understand its underlying processes (Rowe and Kahn, 1987; Lupien and Wan, 2004; Eyler et al., 2011).

In the 1970s and 1980s, coupled oscillator models were shown to reproduce the basic features of the timing of human sleep and wake episodes, with one oscillator representing sleep/wake and the other representing the circadian pacemaker driving the temperature cycle (Wever, 1975; Kawato et al., 1982; Kronauer et al., 1982). Alternatively, the two process model of sleep regulation has been put forward at the same time by Borbely (1982) and Daan et al. (1984), and based on these models it was recently shown that a physiologically based model is able to account for many features of human sleep on self-selected schedules (Phillips et al., 2011). In this review we refer to the two process model, relying on a fined tuned interaction between the sleep-wake homeostatic and the circadian process to allow maintenance of sleep and wakefulness at appropriate times of day in order to explain time of day modulations in subjective sleepiness and cognitive performance.

There is ample evidence that the interplay of circadian and homeostatic processes also determines the temporal modulation of sleepiness and alertness levels across the day, which in turn affects performance for different cognitive domains (Cajochen et al., 2004; Dijk and von Schantz, 2005; Dijk and Archer, 2009). Disturbances or imbalance in the relationship between the circadian and homeostatic systems can lead to sleep and/or mood disorders and major difficulties in maintaining optimal cognitive performance during wake time.

Even in the absence of clinically significant sleep disorders, healthy aging is associated with a decline in night-time sleep quality and duration, decreases in sleep depth, sleep intensity, and sleep continuity (Bliwise, 2005). Concomitantly, a reduced amplitude of circadian rhythm output signals has been shown in older participants (Dijk et al., 1999; Duffy and Czeisler, 2002; Münch et al., 2005), suggesting that age-related changes in sleep may be partially due to a weaker circadian regulation of sleep and wakefulness. In parallel, it has been observed that older people may need less sleep (Klerman and Dijk, 2008) suggesting that in spite of marked changes in sleep physiology, excessive daytime sleepiness is not common during healthy aging (Duffy et al., 2009).

The underlying cerebral mechanisms of homeostatic and time of day-dependent modulation patterns in cognitive performance

remain largely unexplored, in particular in relation to the healthy aging process. Recent functional magnetic resonance imaging (fMRI) studies in young volunteers yielded evidence that this interaction also influences cognition-related cortical (mainly frontal) and subcortical (thalamic, hypothalamic, and brain stem locus coeruleus, LC) brain activity (Schmidt et al., 2009, 2012; Vandewalle et al., 2009). Furthermore, there is evidence that cortical and subcortical task-related BOLD activity declines in those individuals presenting higher vulnerability to sleep loss and circadian misalignment while it increases in those participants who are less susceptible (e.g., Chuah et al., 2006; Vandewalle et al., 2009).

Similar fMRI studies are not yet available in older individuals. However, post-mortem studies revealed neuronal loss in the SCN of older people (Hofman and Swaab, 2006). Also, neuron density within the LC decreases with age due to a progressive loss of noradrenergic neurons, both in animals and humans (Samuels and Szabadi, 2008). Furthermore, the number of LC neurons projecting to areas such as the frontal cortex and the hippocampus declines with age, resulting in fewer synapses (Samuels and Szabadi, 2008). Since the LC is also involved in the regulation of cognitive performance (Usher et al., 1999), it can be hypothesized that age-related changes in these arousal-promoting structures may crucially contribute to circadian-related alterations in cognitive abilities. At the cortical level, frontal brain regions are particularly prone to both the aging process and to the misalignment between circadian and homeostatic processes, even though recent evidence indicates dissociation between these influences on frontal-activation-related executive functions (Cain et al., 2011; Tucker et al., 2011; Bratzke et al., 2012).

In this review, we will discuss the influence of circadian and homeostatic regulation on waking performance, including recent insights into the underlying cerebral correlates of the observed behavioral modulations. The impact of the age factor on these brain networks will then be discussed, considering that it is most likely that cognitive decline is a multifactorial process and that reserve factors may compensate for age-related modifications both in sleep features and cognitive functions (Bartres-Faz and Arenaza-Urquijo, 2011).

CEREBRAL CORRELATES UNDERLYING CIRCADIAN AND HOMEOSTATIC REGULATION OF WAKING PERFORMANCE THROUGHOUT THE 24-H CYCLE

The specific timing and consolidation of sleep and wake episodes within the 24-h light-dark cycle are regulated by a coordinated action of homeostatic and circadian processes (Borbely, 1982; Daan et al., 1984; see also **Figure 1**). It is assumed that the circadian and homeostatic process represent independent drives on sleep-wake propensity but interact in a non-linear fashion across the 24-h light-dark cycle. Thus, circadian-based wake propensity is at its highest levels during the early evening hours (commonly after 12 h of wakefulness), when homeostatic sleep pressure is rather high, whereas circadian propensity for sleep reaches its maximum during the early morning (~2 h before habitual wake up time), when homeostatic sleep pressure is low (Dijk and Czeisler, 1994). At any given time, the magnitude of sleepiness, alertness, and fatigue is thus determined by the interacting influences of these two processes (**Figure 1**). After homeostatic sleep pressure has mostly dissipated over the first hours of the night, it is the high circadian-based propensity for sleep that prevents us from prematurely waking up in the early morning hours. Conversely, it is the very low circadian-based propensity for sleep (i.e., circadian wake-promoting signal) that prevents us from falling asleep in the early evening hours when homeostatic sleep pressure is at its highest level. In both cases, circadian and homeostatic systems ideally work in opposition to ensure a consolidated period of sleep or wakefulness (Dijk and Czeisler, 1994, 1995; Dijk and von Schantz, 2005).

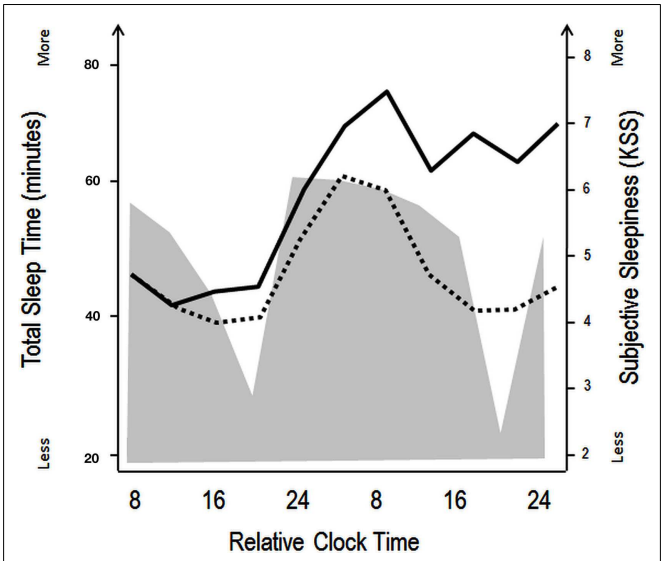

FIGURE 1 | Schematic illustration of the impact of circadian and homeostatic processes on sleep and wakefulness. The filled gray area illustrates variations in total sleep time during a constant routine protocol with regularly occurring naps (150 min of wakefulness followed by 75 min of naps), aiming at investigating circadian rhythm parameters under low homeostatic sleep pressure conditions. Black lines indicate superimposed subjective sleepiness as assessed by the Karolinska Sleepiness Scale over a similar nap (dashed line) and total sleep deprivation (straight line) protocol. The wake maintenance zone can be identified in the naps scheduled in the subjective evening hours, with minimal total sleep time (expressed in minutes). The sleep-promoting signal in the biological night is accompanied by rapid increases in subjective sleepiness in both the low (naps) and high (sleep deprivation) sleep pressure conditions. Over the course of the second biological day, subjective sleepiness decreases, even when homeostatic sleep pressure increases (in the sleep deprivation protocol, straight line), indicating that circadian wake promotion rises or that circadian sleep promotion diminishes [modified from Cajochen et al. (2001) and Münch et al. (2005)].

The impact of the circadian timing system goes beyond compelling the body to fall asleep and to wake up again (Blatter and Cajochen, 2007; Schmidt et al., 2007; Wright et al., 2012). Forced desynchrony, constant routine, and sleep deprivation studies have identified the respective contributions of homeostatic sleep pressure and circadian rhythmicity on neurobehavioral performance measures (Dijk et al., 1992; Johnson et al., 1992; Cajochen et al., 1999, 2004; Wyatt et al., 1999; Carrier and Monk, 2000; Horowitz et al., 2003; Rogers et al., 2003). Two important observations have been made from these controlled studies: (1) while performance deterioration is mostly seen when the wake episode is extended

into the biological night, modulations can also be seen throughout a usual waking day episode (<16 h of wakefulness) which can lead to significant deteriorations in the cognitive output and (2) the observed effects of the circadian and sleep-wake homeostatic system do not simply add up to characterize daily performance modulations. In particular, the circadian amplitude of cognitive performance modulation clearly depends on homeostatic sleep pressure levels (Dijk and Franken, 2005).

The proposal mentioned above that circadian and homeostatic systems interact at the neurobehavioral level has been supported by anatomical findings. In terms of circadian sleep-wake regulation, the SCN is the central circadian pacemaker regulating sleep-wake timing. The SCN sends an indirect projection – relayed via the dorsomedian hypothalamus – to the noradrenergic LC, which in turns sends wide projections to the entire cortex (Aston-Jones et al., 2001; Aston-Jones, 2005). Consequently, the LC has been proposed to be implicated in the circadian regulation of higher order cognitive behaviors (Gompf and Aston-Jones, 2008). On the other hand, the cerebral correlates and exact anatomical location of the sleep homeostat are still unknown. It most likely represents a diffuse system that includes the accumulation of at least one sleep-promoting substance, which enhances the activity of sleep-promoting, and reduces the activity of wake-promoting neurons (Landolt, 2008). Accordingly, sleep homeostasis has been related to plastic processes occurring during wakefulness that result in a net increase in synaptic strength in many brain circuits (Tononi and Cirelli, 2003). From this perspective, sleep would serve to downscale synaptic strength to a baseline level that is energetically sustainable with the aim of a homeostatic regulation of the total synaptic weight impinging on neurons.

Recent evidence from fMRI investigations in young morning and evening chronotypes indicate that homeostatic sleep pressure exerts an influence on attention-related cerebral activity in anterior hypothalamic structures, putatively implicated in the regulation of the circadian wake-promoting signal (Schmidt et al., 2009; see **Figure 2**). In particular, maintenance of optimal attentional performance in a vigilance task (PVT; psychomotor vigilance) after accumulated sleep pressure (i.e., during the subjective evening) was associated with higher activity in evening than morning chronotypes in the LC and in the anterior hypothalamus, two key structures crucially involved in the generation of the circadian wake-promoting signal. Furthermore, activity in the anterior hypothalamus decreased with increasing homeostatic sleep pressure as indexed by electroencephalographic (EEG) slow wave activity [SWA; EEG power density during non-rapid eye movement (Non-REM) sleep in the range of 0.75–4.5 Hz] in the first sleep cycle, suggesting that homeostatic and circadian interactions influence the neural activity underpinning diurnal variations in human behavior. Interestingly, this activation pattern was observed solely for the 10% of fastest reaction times that reflect the phasic ability to recruit the attentional network above normal levels (Drummond et al., 2005a).

Recently, a 24-h sleep deprivation study (Vandewalle et al., 2009) took advantage of a genetic trait (the hPER3 polymorphism; Viola et al., 2007) associated with differential vulnerability to the deleterious effects of sleep deprivation on neurobehavioral performance. This study revealed that from the morning (1.5 h of wakefulness) to the evening (14 h of wakefulness) of a normal waking day, the more resistant $PER3^{4/4}$ individuals did not exhibit significant changes in brain responses to a working memory task, whereas the more vulnerable $PER3^{5/5}$ participants presented decreased activity in the posterior dorso-lateral prefrontal cortex. When further challenging the sleep homeostat by 25 h of total sleep deprivation, the more vulnerable $PER3^{5/5}$ subjects presented various decreased task-related cortical activations in the morning after sleep loss. In contrast, $PER3^{4/4}$ still did not show decreased brain responses to the task, but rather recruited supplemental brain areas located in right inferior frontal, middle temporal, parahippocampal gyri, as well as in bilateral thalamic areas. Similarly, morning types, more vulnerable to the accumulation of time spent awake throughout a normal waking day (Kerkhof, 1991; Mongrain et al., 2006a,b) show decreased BOLD responses in brain areas involved in conflict resolution over a normal waking day while performing the Stroop paradigm (Schmidt et al., 2012). In contrast, evening chronotypes, less affected by accumulated homeostatic sleep pressure during the evening exhibited the reversed profile or presented stable BOLD responses from morning to evening hours in task-related brain regions (Schmidt et al., 2012).

AGE-RELATED MODULATION IN CIRCADIAN AND HOMEOSTATIC REGULATION OF SLEEP AND WAKING PERFORMANCE

It has been controversial whether age-related sleep changes result from alterations in circadian and homeostatic processes or in their precise interaction (see **Figure 3** for a schematic illustration of age-related changes on circadian and homeostatic sleep-wake regulation). The age-related decline in absolute levels of slow wave sleep (SWS) represents one of the most common reported features in the ageing and sleep literature (Bliwise, 2005). Studies demonstrated that older adults respond to sleep loss with an increase in EEG SWA (Dijk et al., 2001) indicating that, even though older persons present lower absolute SWS levels, the homeostatic response to increasing sleep need is basically operational. However, older adults also showed a shallower decline in homeostatic sleep pressure after sleep deprivation, particularly in frontal brain regions (Dijk et al., 1989; Münch et al., 2004). Together with the recently observed age-related reduction in asymptotic sleep duration under extended sleep conditions, these data favor the assumption that older adults have a generally lower homeostatic need for sleep (Klerman and Dijk, 2008). In the same perspective, healthy aging was associated with a reduction in daytime sleep propensity, while sleep continuity and SWS were reduced (Dijk et al., 2010).

From a circadian perspective, older adults present a reduced amplitude of circadian rhythmicity in endogenous core body temperature (Dijk and Duffy, 1999) and melatonin (Münch et al., 2005), suggesting that age-related changes in sleep can also be related to a weaker circadian regulation. Whether age merely affects the wake- or sleep-consolidating function of the circadian signal has been a topic of debate. Dijk and colleagues found evidence that sleep latencies were rather similar between age groups throughout the circadian cycle, even though the shortest sleep latency values located around the temperature nadir were slightly

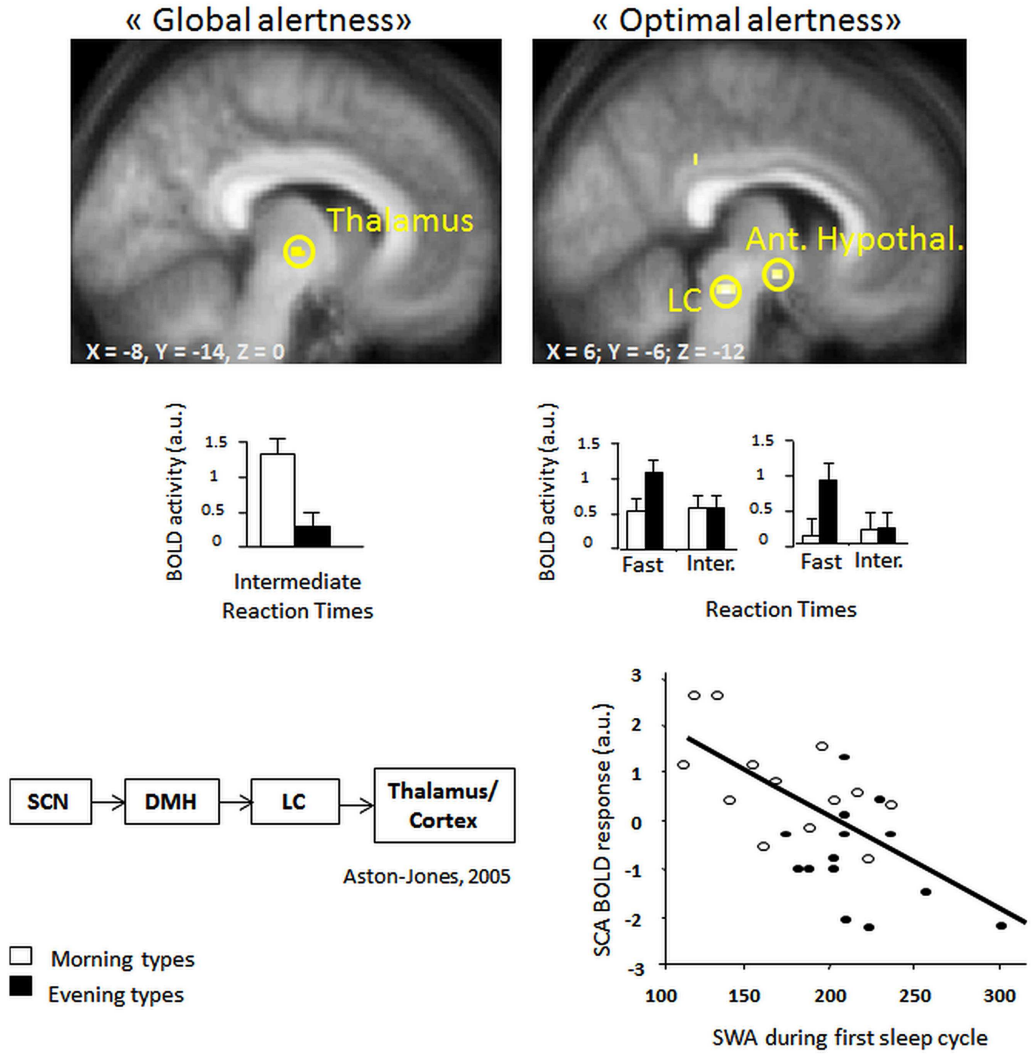

FIGURE 2 | (Left, top panel) higher task-related thalamic activation in morning as compared to evening types for intermediate reaction times ("global alertness") during the subjective evening hours [modified from Schmidt et al. (2009)] (right, top panel) Higher BOLD activity in locus coeruleus and anterior hypothalamic regions in evening as compared to morning types for "optimal alertness" (10% of fastest reaction times, as compared to intermediate reaction times). (Left, bottom panel) both regions have been implicated in circadian arousal regulation, as illustrated by the model of Aston-Jones et al. (2001). (right, bottom panel) Finally, optimal alertness-related activity in the anterior hypothalamus (i.e., suprachiasmatic area) is negatively related to the amounts of EEG slow wave activity at the beginning of the night, which can be considered as a reliable marker of homeostatic sleep pressure build-up [modified from Schmidt et al. (2009)].

longer in older participants (Dijk and Duffy, 1999; Dijk et al., 1999). Concomitantly, Duffy et al. (1998) reported that sleepiness and alertness levels in the older were less affected than in young adults, when the scheduled wake period occurred in the early morning hours coinciding with the maximal circadian drive for sleep. Finally, a nap study revealed that the circadian wake-promoting signal in the evening hours was weaker in older participants, with higher subjective sleepiness ratings and more sleep occurring during the wake maintenance zone in the late afternoon (Strogatz et al., 1987) in older than in young adults (Münch et al., 2005). Thus, the age-related lower homeostatic sleep need may account for the observed less consolidated and shorter sleep during night-time, while reduced circadian wake promotion during the biological day might favor daytime naps in older adults.

Cross-sectional studies indicate a preference for earlier habitual bedtime and getting-up time in older adults as compared to younger individuals (Carrier et al., 1997; Duffy et al., 1998; Duffy and Czeisler, 2002). This morningness preference has been associated with an advance in the circadian phase at the physiological level, which could theoretically be associated to differences in the intrinsic period of the circadian oscillator (Brown et al., 2011). In this perspective, Pagani et al. (2010) showed proportionality between the physiological period length of the human circadian clock *in vivo* and the period in human fibroblasts in young and older participants. Interestingly, measurement of human

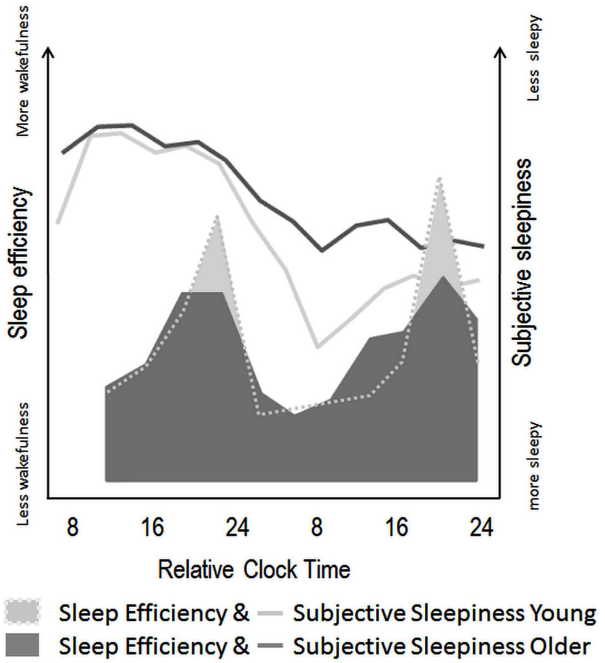

FIGURE 3 | Schematic illustration of age-related modifications in circadian and homeostatic sleep-wake regulation in humans. Filled areas illustrate variations in sleep efficiency over a nap protocol (10 episodes of 150 min of wake, followed by 75 min of scheduled sleep episodes) modified from Münch et al. (2005). Circadian sleep-wake promotion, as expressed by the amount of wakefulness throughout nap episodes seems attenuated in older (dark gray) as compared to young individuals (light gray area). Line plots indicate the superimposed time course of subjective sleepiness over a 40-h sleep deprivation protocol in young (light gray line) and older (dark gray line) adults [modified from Adam et al. (2006)]. These values indicate less pronounced effects of increasing homeostatic sleep pressure on subjective sleepiness in older, as compared to young individuals.

fibroblasts in the presence of human serum from older donors highlighted shortened period length and advanced phase of cellular circadian rhythms as compared with serum from young donors, indicating that a circulating factor might alter human chronotype (Pagani et al., 2011). However, *in vivo* under conditions of experimentally induced misalignment between the sleep-wake cycle and endogenous circadian rhythmicity, the investigation of the circadian period in melatonin secretion or core body temperature revealed very similar period lengths across age groups (Czeisler et al., 1999; Duffy and Czeisler, 2002). However, the phase angle of entrainment as indexed by the timing of the biological clock (i.e., circadian phase) in relation to the timing of sleep (i.e., usual bedtime) was different in young and older participants: while young morning types woke up later within their circadian cycle (i.e., longer phase angles; e.g., Duffy et al., 1999; see Emens et al., 2009 for naturalistic conditions), older morning types woke up earlier within the circadian cycle (i.e., shorter phase angles; Duffy et al., 1999).

These age-related alterations in circadian and homeostatic sleep regulation significantly impact on an individual's daytime cognitive performance level. Thus, from a clinical point of view, taking time of day and the individual's circadian preference into account when assessing cognitive functions across age groups is rather important and has been emphasized in a series of reports (Hasher et al., 2005). Indeed, studies carried out under normal day–night conditions have generally revealed that, whereas the cognitive performance of young evening type adults often improves over the day, old morning type adults markedly deteriorate (May et al., 1993, 2005; Yoon, 1997; May and Hasher, 1998; Hasher et al., 1999, 2002, 2005; May, 1999; Yoon et al., 2003; Schmidt et al., 2007; Yang et al., 2007). This effect has been referred to as the synchrony effect, or the beneficial impact of temporal matching between task timing and preferred time of day for diurnal activities (May et al., 1993). The synchrony effect applies to different cognitive domains, including short-term memory tasks such as word span measures (Yoon, 1997), performance on different long-term memory tasks (May and Hasher, 1998; Intons-Peterson et al., 1999; Winocur and Hasher, 2002), and executive functions, especially cognitive inhibition abilities (Intons-Peterson et al., 1998; May and Hasher, 1998; May, 1999; West et al., 2002). We have recently observed that adapting testing time according to the specific individual's sleep-wake schedule can attenuate synchrony effects in PVT and Stroop tasks (Schmidt et al., 2012), suggesting that part of the reported synchrony effects in aging may be accounted for by a series of confounders (e.g., differences in socio-professional timing constraints, the amount of accumulated sleep need or circadian phase position, all modulating arousal level at testing) rather than being inherent to the chronotypical profile of an individual. In the same vein, time of season may also affect cognitive functions, especially in clinical populations, such as bipolar I disorder (Rajajarvi et al., 2010). In the healthy population, there are indications that seasonal variation in mood can impact on cognitive performance (Merikanto et al., 2011).

Additionally, it is worth noting that the extent of age-related changes in circadian and sleep physiology substantially differs between individuals. For instance, the above mentioned polymorphism in the human clock gene PER3 may contribute to inter-individual differences in sleep and circadian physiology in older people (Viola et al., 2012). Homozygosity for the longer allele ($PER3^{5/5}$) was associated with a phase-advance in the circadian melatonin profile and an earlier occurrence of the melatonin peak within the sleep episode. Furthermore, older $PER3^{5/5}$ participants accumulated more nocturnal wakefulness, had increased EEG frontal delta activity (0.75–1.5 Hz), and decreased EEG frontal sigma activity (11–13 Hz) during (Non-REM) sleep compared with $PER3^{4/4}$ participants.

Finally, when looking at the impact of circadian and homeostatic modulations on neurobehavioral performance in aging, weaker variations in circadian output measures were observed for both subjective and objective vigilance measures in older study participants. Declines in PVT performance seem less susceptible to circadian and homeostatic misalignment in older people (Blatter et al., 2006). Intriguingly, a reversal of age-related differences in PVT performance speed has been reported when testing was scheduled to the early morning hours during SD, i.e., when elevated homeostatic sleep pressure and minimal circadian wake promotion coincide, such that the older reacted faster than the young participants (Adam et al., 2006; Duffy et al., 2009). More recently,

a forced desynchrony study similarly revealed that response speed on a sustained attention task and the ability to perform mental arithmetic are less deteriorated by the cumulative effects of repeated exposure to adverse circadian phase in older as compared to young individuals (Silva et al., 2010). In the same line, during a sleep fragmentation protocol, older participants were less sensitive to the imposed sleep disturbance in terms of performance decrements than young participants (Bonnet, 1989). Together, these data suggest an age-related attenuation of the wake-dependent homeostatic influence on cognitive performance (Silva et al., 2010). Alternatively, weakening of the circadian signal promoting wakefulness in the late biological day, also called the wake maintenance zone, may be responsible for the observed effects (Cajochen et al., 2006). However, in the above mentioned study (Silva et al., 2010), it was found that older participants had fewer lapses of attention in the circadian phase bins corresponding to the late biological day/early biological evening. It is also worth noting that optimal reaction time performance (i.e., the fastest 10% reaction times in the PVT) revealed that neither the wake-dependent homeostatic nor the circadian influence showed a significant interaction with age, suggesting that for both age groups, optimal reaction time performance is affected similarly by wake-dependent and circadian influences.

CEREBRAL UNDERPINNINGS OF THE CIRCADIAN AND HOMEOSTATIC REGULATION OF WAKING PERFORMANCE: AGE-RELATED INFLUENCES?

Overall, more disruption in sleep and circadian rhythm outputs have been linked to increased disease susceptibility (Hastings et al., 2003), which both occur more often with advanced age. However, with increasing age, circadian, and sleep-wake related neural areas or the connections within the functional neuroanatomical networks may compensate for initial dysfunction (van Someren et al., 2002).

Hypothalamic dysfunction may potentially trigger some age-related physiological and behavioral changes in sleep-wake patterns, but the effects of senescence on specific hypothalamic nuclei that mediate these alterations have still to be elucidated (Kessler et al., 2011). Even though controversial, post-mortem studies indicate neuronal degeneration of the SCN in senescence, which suggests that the circadian pacemaker in the human brain becomes progressively disrupted during aging (Hofman and Swaab, 2006). Although no age-related changes were found in the number or size of SCN cells in the rhesus (Roberts et al., 2012), changes in spontaneous SCN neuron firing activity have been reported in aged rodents, together with alterations in the expression of certain genes and peptides similarly to findings in non-human primates (see Bertini et al., 2010 for a review). Also, Nakamura et al. (2011) reported reduced amplitude of day–night differences in neural activity with increasing age in mice, together with an alteration in neural activity in the subparaventricular zone, one of the main neural outputs of the SCN. As parallel studies indicate that the molecular clockwork in the SCN as measured by PER2 exhibits only minor deficits at the same age of those presenting reduced day–night amplitude and neural activity in the subparaventricular zone, it is suggested that the circadian output measured at the level of neural activity rhythms in the SCN is degraded by aging, before disruption becomes evident in key components of the molecular clockwork (Roberts et al., 2012).

Circadian arousal regulation acts via indirect projections from the SCN to the arousal-promoting LC in the brainstem (Aston-Jones et al., 2001). Interestingly, the LC has the potential to impact on higher order cognitive performance and shows early vulnerability to the aging process, such that neuron density within the LC decreases with age due to a progressive loss of cell number and size of noradrenergic neurons both in animals and humans (Samuels and Szabadi, 2008). Furthermore, the loss of noradrenergic LC axons innervating the frontal cortex has been associated with modifications in the electrophysiological properties of the remaining LC terminals (Samuels and Szabadi, 2008). The SCN has also a weak direct projection to the wake-active orexin-producing neurons in the lateral hypothalamic area (Saper et al., 2001). Since the densest projection of orexin fibers terminates in the LC, it has also been suggested that the LC controls the activity of orexin neurons directly by inhibiting orexin firing and indirectly via the DMH. Interestingly, orexin secretion follows a circadian variation in rats (Zhang et al., 2004), monkeys (Zeitzer et al., 2003), and humans (Salomon et al., 2003), which might be the result of direct or indirect inputs from the SCN to the orexin circuits. Indeed lesions of the SCN suppress the daily orexin rhythm (Deboer et al., 2004; Adamantidis and de Lecea, 2008). On the other side, orexin levels increased in response to sleep deprivation in both control and SCN-lesioned animals, demonstrating that sleep homeostatic control of orexin occurs independently from the SCN (Deboer et al., 2004). It is known that orexin in the lateral hypothalamus influences many integrative homeostatic processes related to wakefulness and plays a crucial role in sleep architecture and state stabilization throughout the sleep-wake cycle (Saper et al., 2001). Kessler et al. (2011) observed that aged rats exhibited a loss of greater than 40% of orexin-immunoreactive neurons, suggesting that compromised orexin function could be an important mediator of age-related homeostatic disturbances of hypothalamic origin.

The cholinergic basal forebrain represents an additional important key area in the regulation of wakefulness-related cortical arousal that is selectively sensitive to both prolonged waking and aging (Cayetanot et al., 2005). Interestingly, the sleep-wake-dependent decline and rise in adenosine levels, a potential sleep-promoting substance, is more pronounced in the basal forebrain than in other cerebral regions (Strecker et al., 2000). Accordingly, it has been suggested that local release of adenosine in the basal forebrain provides a signal for the homeostatic regulation of Non-REM sleep (Landolt, 2008). Furthermore, age-related attenuation in basal forebrain function reduces its capacity to respond to increased neuronal activity during prolonged wakefulness (Cayetanot et al., 2005). In a similar perspective, cognitive stimulation in humans increases lactate expression in the prefrontal cortex of young, but not in an aged population (Urrila et al., 2004).

All of these cerebral systems involved in waking performance have the potential to modulate cognition through their widespread connections to the cerebral cortex and thus do not act in isolation. For instance, orexin neurons activate regions such as the prefrontal cortex and the basal forebrain cholinergic system, both

of which are strongly implicated in normal cognitive function and in age-related cognitive decline.

Older age has also been associated with lower blood flow and resting metabolism, particularly in the prefrontal cortex (Meltzer and Francis, 2001) as well as reduced regional brain responses to challenging tasks (see **Figure 4**; Dennis et al., 2008; see Buckner, 2004; Hedden and Gabrieli, 2004 for a review). Conversely, when performing at optimal levels, older adults present higher functional responses in frontal cortices. Besides quantitative changes, there may be also qualitatively different brain response patterns, such as "over-activation" in an homologous region in the opposite hemisphere from the region typically responsive in young adults, a phenomenon referred to as to "hemispheric asymmetry reduction" in older adults (Eyler et al., 2011). Overall, supplemental recruitment of cerebral structures might reflect compensatory activity or strategic differences with advanced age. A general hypothesis is that increased brain recruitment represents a general response to increasing task difficulty and conveyed global factors that affect aging (Buckner, 2004).

Task-related BOLD activity decreases have been observed in young adults under sleep deprivation, while other studies showed compensatory mechanisms resulting in activity increases (e.g., Drummond et al., 2000; Drummond and Brown, 2001; Chee and Choo, 2004; Habeck et al., 2004; Choo et al., 2005; Mu et al., 2005a,b; Chee et al., 2006; Chuah et al., 2006; Chee and Chuah, 2007; see Chee and Chuah, 2008 for a review). Thus, similarly to what has been hypothesized in the aging literature, it is suggested that increasing task difficulty elicits "compensatory" prefrontal activation in some, but not all studies, as a function of the investigated cognitive domain. Thus sleep deprivation and aging may elicit similar deficits in executive functions due to similar alterations in the prefrontal cortex (e.g., Harrison et al., 2007). Executive functions encompass a series of high-level processes, the main function of which is to facilitate adaptation to new or complex situations when highly practiced cognitive abilities or behaviors no longer suffice (Collette et al., 2006). While the frontal lobes play a major role in executive function (Shallice, 1982), additional posterior cerebral regions, including the parietal lobes (Collette et al., 2006) also play a key role in executive functioning. Horne and colleagues first hypothesized that the waking function of the prefrontal cortex and the frontal predominance of EEG delta activity in sleep may be linked (Horne, 1993; see also Blatter and Cajochen,

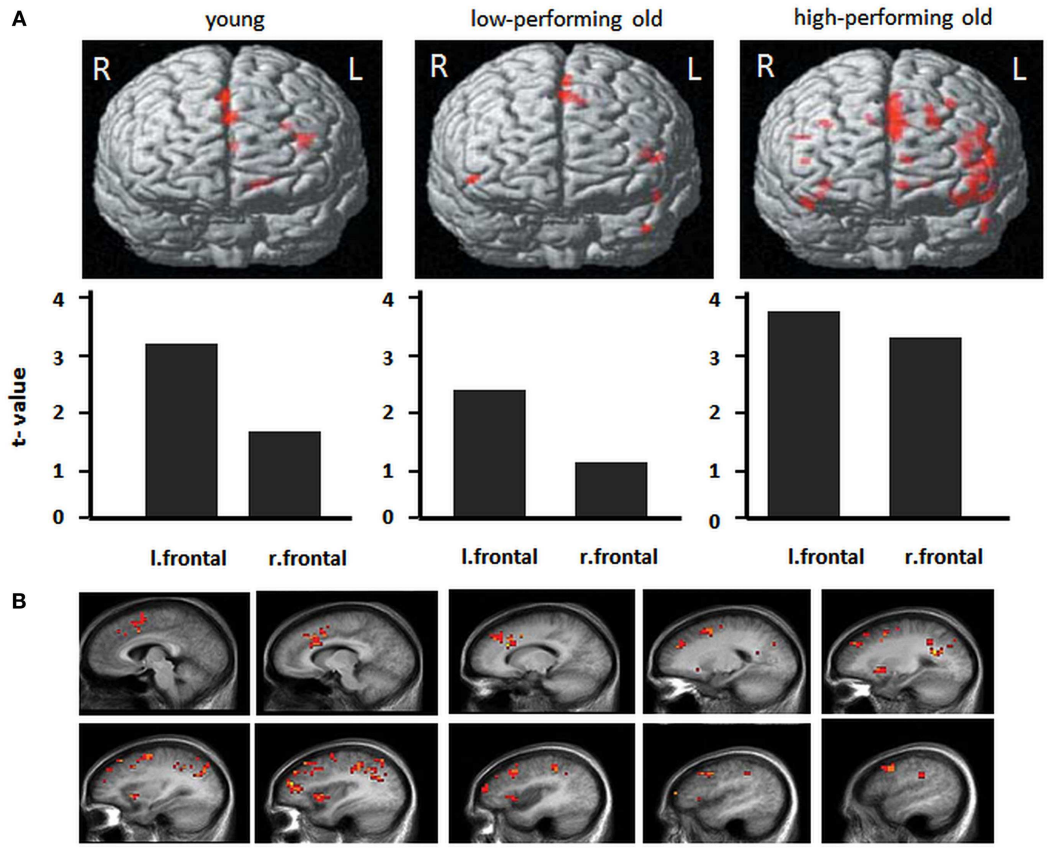

FIGURE 4 | Frontal activity changes in young and older populations. (A) Activations during a memory-encoding task in young adults, low-performing older adults and high-performing older adults. Low-performing older adults exhibit a similar pattern as do young adults, with lower overall levels of activation. High-performing older adults exhibit greater bilateral activation (with permission from Hedden and Gabrieli, 2004). **(B)** Total sleep deprivation-related patterns of cerebral activation during a verbal learning task. For each of these regions, the memorization of difficult words elicited greater activation after total sleep deprivation than after a night of sleep. Images show left hemisphere slices from 5 to 50 mm [adapted from Drummond et al. (2005b)].

2007). Since then, several studies have argued that cognitive functioning related to the prefrontal cortex is particularly vulnerable to sleep loss (Blatter and Cajochen, 2007). However, in a recent report, Tucker et al. (2011) observed heterogeneity in cognitive aspects impaired by sleep deprivation and aging when looking more specifically at the affected cognitive compounds during the performance of executive function tasks, raising questions about the similarity of the involved cognitive processes underlying sleep loss related and age-related modulations in cognitive performance.

CONCLUSION AND PERSPECTIVES

Healthy older individuals may experience twice as much time awake during a night sleep episode than young adults, suggesting that impaired sleep consolidation is associated with aging *per se*, rather than being a by-product of co-ailments linked to aging. Whether age-related sleep disruption derives from either the circadian and/or the homeostatic facet of sleep regulation is still somewhat uncertain. However, we propose that the strength of the circadian/homeostatic interaction on modulating sleep and cognitive processes are weakened in older healthy people. The cortical underpinnings that account for these age-related modulations are virtually unexplored. A combined investigation of these issues at the cerebral level would allow the elaboration of theoretical concepts in order to explain the underlying mechanisms of age-related changes in circadian and homeostatic modulations in cognitive performance. Hence, this leads to the next question: are age-related sleep disruptions a consequence of alterations in the circadian or homeostatic sleep regulation, or is it ultimately caused by an attenuated interaction between the circadian timing system and sleep-wake homeostatic process at the cerebral level? Here we surmise that some of the subcortical structures involved in the generation of circadian wake promotion may at least in part be compromised in healthy aging. Alternatively, upstream from these structures, more integrative cortical areas underlying higher order cognitive behaviors may also be selectively altered with aging. Quantitative evidence for such a hypothesis is building up from the vulnerability of frontal cortical brain regions to both the effects of elevated sleep pressure and aging. Whether there is a direct relationship between age-related decline in cognitive performance and sleep disruption still remains a matter of investigation. Prospective or intervention studies (e.g., sleep extension) would help to elucidate their relationships.

ACKNOWLEDGMENTS

Christina Schmidt and Christian Cajochen are funded by a research grant from the Swiss National Science Foundation (#310030_130689) and a post-doctoral fellowship from the AXA Research Fund.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 24 February 2012; paper pending published: 05 April 2012; accepted: 08 July 2012; published online: 26 July 2012.

Citation: Schmidt C, Peigneux P and Cajochen C (2012) Age-related changes in sleep and circadian rhythms: impact on cognitive performance and underlying neuroanatomical networks. Front. Neur. ***3****:118. doi: 10.3389/fneur.2012.00118*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in NEUROLOGY

HYPOTHESIS AND THEORY ARTICLE
published: 27 April 2012
doi: 10.3389/fneur.2012.00062

Reduced neurobehavioral impairment from sleep deprivation in older adults: contribution of adenosinergic mechanisms

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A night without sleep is followed by enhanced sleepiness, increased low-frequency activity in the waking EEG, and reduced vigilant attention. The magnitude of these changes is highly variable among healthy individuals. Findings in young men of low and high subjective caffeine sensitivity suggest that adenosinergic mechanisms contribute to inter-individual differences in sleep deprivation-induced changes in EEG theta activity, as well as optimal performance on the psychomotor vigilance task (PVT). In comparison to young subjects, healthy adults of older age typically feel less sleepy after sleep deprivation, and show fewer response lapses, and faster reaction times on the PVT, especially in the morning after the night without sleep. We hypothesized that age-related changes in adenosine signal transmission underlie reduced vulnerability to sleep deprivation in older individuals. To test this hypothesis, the combined effects of prolonged wakefulness and the adenosine receptor antagonist, caffeine, on an antero-posterior power gradient in EEG theta activity and PVT performance were analyzed in healthy older and caffeine-insensitive and -sensitive young men. The results show that age-related differences in sleep loss-induced changes in brain rhythmic activity and neurobehavioral functions are mirrored in young individuals of low and high sensitivity to the stimulant effects of caffeine. Moreover, the effects of sleep deprivation and caffeine on regional theta power and vigilant attention are inversely correlated across older and young age groups. Genetic variants of the adenosine A_{2A} receptor gene contribute to individual differences in neurobehavioral performance in rested and sleep deprived state, and modulate the actions of caffeine in wakefulness and sleep. Based upon this evidence, we propose that age-related differences in A_{2A} receptor-mediated signal transduction could be involved in age-related changes in the vulnerability to acute sleep deprivation.

Keywords: aging, electroencephalogram, attention, A_1 receptors, A_{2A} receptors, *ADORA2A*

INTRODUCTION

Sleep deprivation affects subjective and objective measures of alertness, attention, and vigilance, as well as higher cognitive capabilities such as perception, memory, and executive functions (Goel et al., 2009). There exist, however, considerable and systematic inter-individual differences in the susceptibility to the lack of sleep. Among young healthy people, these differences are robust, trait-like, and possibly related to genetically determined, neurobiological differences in the physiological processes underlying the homeostatic and circadian regulation of wakefulness and sleep (Landolt, 2008a; Dijk and Archer, 2010; Van Dongen et al., 2012). Evidence from pharmacological and microdialysis studies in animals and humans strongly suggests the involvement of the neuromodulator adenosine and adenosine receptors in the effects of sleep deprivation (Ticho and Radulovacki, 1991; Schwierin et al., 1996; Porkka-Heiskanen et al., 2000; Landolt et al., 2004; Wyatt et al., 2004; Christie et al., 2008). Adenosinergic mechanisms may, thus, contribute to individual susceptibility or resistance to performance impairment as a consequence of sleep loss.

To investigate this hypothesis, the combined effects of prolonged wakefulness and the adenosine receptor antagonist, caffeine, on sustained vigilant attention were studied in two groups of young healthy men with low and high (as evidenced by experiencing sleep disturbances after caffeine consumption in the afternoon) subjective caffeine sensitivity (Rétey et al., 2006). Performance on the psychomotor vigilance task (PVT), a reliable measure of sustained vigilant attention (Lim and Dinges, 2008), was assessed at regular intervals before, during, and after one night without sleep. After 11 and 23 h of prolonged wakefulness, subjects received 200 mg caffeine and placebo in double-blind, cross-over manner. This dose of caffeine equals roughly the caffeine content in a double-espresso. Sleep deprivation impaired PVT performance more in caffeine-sensitive individuals than in caffeine-insensitive individuals. This difference was counteracted

by caffeine. These findings suggest that adenosinergic mechanisms contribute to individual differences in waking-induced impairment of neurobehavioral performance.

Normal human aging is associated with profound changes in sleep–wake behavior. Older people may rise early without feeling refreshed, feel sleepy during the day, take naps, go to bed early, have difficulty falling asleep, show superficial sleep with little or no slow-wave sleep (SWS), and exhibit frequent sleep interruptions and early morning awakenings. These alterations in the quality of wakefulness and sleep may be secondary to health problems, or reflect changes and/or disruptions in homeostatic and circadian sleep–wake regulatory mechanisms (Dijk et al., 2010). The detailed characteristics of sleep and sleep disorders in older age and their possible underlying causes have been reviewed elsewhere (e.g., Bliwise and Carrier, 2012). Interestingly, convergent recent insights from animal experiments as well as controlled studies in healthy humans consistently show that older people may be less sleepy during the daytime and better tolerate sleep deprivation when compared to young adults (animal experiments: Wigren et al., 2009; Hasan et al., 2012; human studies: Bonnet and Rosa, 1987; Münch et al., 2004; Philip et al., 2004; Urrila et al., 2004; Adam et al., 2006; Blatter et al., 2006; Duffy et al., 2009; Dijk et al., 2010). Some authors suggested that an altered response of the adenosinergic system contributes to these age-related changes in the behavioral repercussions of prolonged wakefulness (Murillo-Rodriguez et al., 2004; Rytkönen et al., 2010). This hypothesis, however, has not been tested in humans.

In this article, we will address the question whether adenosinergic mechanisms may contribute to reduced neurobehavioral impairment from sleep deprivation in healthy older adults. First, the current understanding of how adenosine and adenosine receptors are involved in sleep–wake regulation will be recapitulated. Then, evidence will be summarized suggesting that the competitive adenosine receptor antagonist, caffeine, attenuates the physiological consequences of sleep loss on functional brain oscillations in non-rapid-eye-movement (NREM) sleep and wakefulness, as well as on neurobehavioral performance. Next, empirical data will be reviewed and presented which demonstrate that older age not only modulates functional characteristics of adenosine and its receptors, but also the repercussions of caffeine on sleep and waking EEG, as well as vigilant attention after sleep deprivation. Finally, a few possible research strategies will be proposed that could be pursued to investigate in more detail the roles for adenosine and adenosine receptors in reduced vulnerability of older adults to impaired neurobehavioral performance after the lack of sleep.

THE NEUROMODULATOR ADENOSINE CONTRIBUTES TO THE PHYSIOLOGICAL CONSEQUENCES OF SLEEP DEPRIVATION

The effects of the prior history of wakefulness and sleep on functional characteristics of recovery sleep and the quality of wakefulness have been conceptualized as sleep homeostasis in the two-process model of sleep regulation (Borbély, 1980, 1982). The duration of SWS and the amount of computer-detected EEG slow-wave activity (SWA) in NREM sleep are considered the principle markers of the sleep–wake dependent, homeostatic aspect of sleep regulation. Biochemically, one or more endogenous "sleep substances" may accumulate during wakefulness and dissipate during sleep, yet the biochemical "substrates" of sleep homeostasis remain poorly understood. It is widely accepted, however, that adenosine, nitric oxide, prostaglandin D_2, tumor necrosis factor, interleukin-1, growth-hormone-releasing hormone, and brain-derived neurotrophic factor are important chemicals that may be primarily involved in mediating the consequences of prolonged wakefulness. Especially with respect to adenosine, compelling and converging evidence has accumulated over the past two decades to support a role for this neuromodulator and its receptors in sleep homeostasis in animals and humans (Krueger et al., 2008; Landolt, 2008b; Porkka-Heiskanen and Kalinchuk, 2011).

The formation of adenosine in the brain changes in activity-dependent manner, and different mechanisms contribute to the appearance of adenosine in extra-cellular space. Increased energy demand during wakefulness leads to the break-down of energy-rich adenine nucleosides such as adenosine-tri-phosphate (ATP). Adenosine is formed in neurons by 5′-nucleotidase and transported through plasma and intra-cellular membranes by specialized transporters, including sodium-driven concentrative (CNT) and equilibrative nucleoside transporters (ENT; **Figure 1A**). The CNTs use energy to move adenosine into the cell, whereas the ENTs transport adenosine according to the extra-cellular/intra-cellular concentration gradient. Elevated intra-cellular adenosine concentrations following increased utilization of ATP in conditions of high energy demand lead to release of adenosine. In addition, extra-cellular adenosine is also formed through ecto-nucleotidase-mediated hydrolysis of ATP. Release of ATP from synaptic vesicles occurs along with several neurotransmitters, including the major excitatory neurotransmitter glutamate (Haydon and Carmignoto, 2006). Finally, ATP and glutamate are also released from astrocytes by a recently established process referred to as gliotransmission. The ATP may either be hydrolyzed to adenosine or activate purinergic receptors such $P2X_7$ receptors and affect sleep directly or indirectly, yet independently from adenosine (Krueger et al., 2008, 2010).

Molecular genetic manipulations in mice suggest that glial cells provide a significant source of extra-cellular adenosine in the brain (Haydon and Carmignoto, 2006). Mice expressing a dominant-negative (dn) SNARE domain in astrocytes have reduced gliotransmission (Pascual et al., 2005). A recent study in these mice suggests that adenosine derived from astrocytes is importantly involved in the homeostatic regulation of sleep pressure (Halassa et al., 2009). Both transgenic and wild-type mice spent similar proportions of the light-phase (i.e., the major sleep phase in mice) in NREM sleep, rapid-eye-movement (REM) sleep and wakefulness. By contrast, sleep pressure (or sleep intensity) as reflected in SWS/SWA was significantly reduced when dnSNARE was expressed exclusively in astrocytes. The differences were specific to NREM sleep and not present in REM sleep and wakefulness, and most pronounced in the 0.5- to 1.5-Hz range. Importantly, dnSNARE expression attenuated the sleep deprivation-induced increase in SWA in NREM sleep, particularly in the low-frequency range and in hours 2–4 of recovery sleep. Moreover, performance on a novel object recognition task was unimpaired after sleep deprivation in dnSNARE mice, while it was dramatically reduced in wild-type animals. Taken together, these data are consistent with an important role

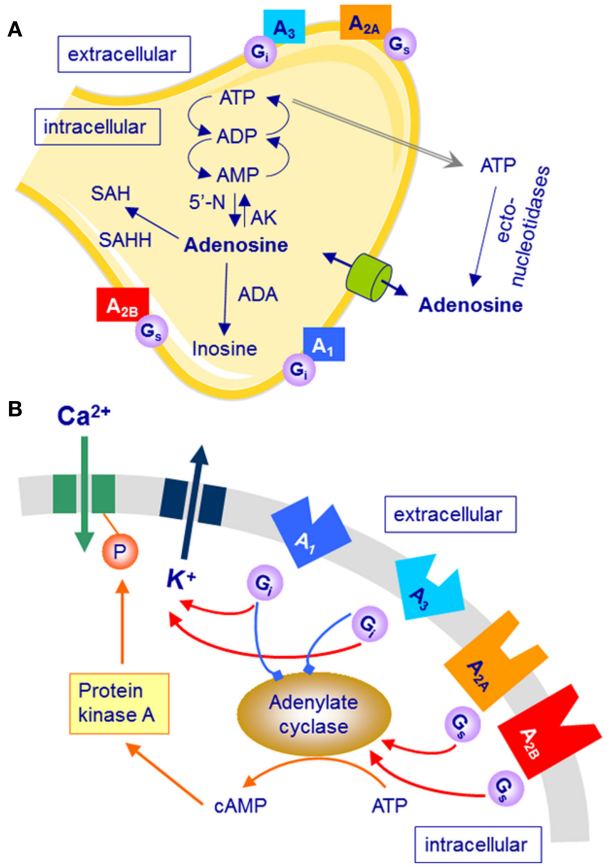

FIGURE 1 | Simplified schematic representation of adenosine formation, metabolism and transport, and G-protein coupled adenosine receptors (rectangles representing A_1, A_{2A}, A_{2B}, and A_3 receptors). Only selected mechanisms and pathways are shown. **(A)** Neurons, astrocytes, and microglia cells can release adenosine and adenosine-tri-phosphate (ATP; gray arrow). All cell types express adenosine receptors, adenosine transporters (cylinder), and ecto-nucleotidases that convert ATP into adenosine. ADP, adenosine-di-phosphate; AMP, adenosine-mono-phosphate; SAH, *S*-adenosyl-homocysteine; 5′-*N*, 5′-nucleotidase; AK, adenosine kinase; ADA, adenosine deaminase; SAHH, *S*-adenosyl-homocysteine hydrolase. **(B)** Activation of adenosine receptors either inhibits ($A_{1/3}$ receptors) or stimulates ($A_{2A/2B}$ receptors) adenylate cyclase and the cyclic AMP (cAMP) pathway.

for glia-dependent adenosine in regulating established markers of sleep homeostasis in mice.

Clearance of extra-cellular adenosine mostly occurs through the non-concentrative nucleoside transporters (Fredholm et al., 2005). The main intra-cellular metabolic pathways of adenosine are the formation of adenosine-mono-phosphate by adenosine kinase (AK), and the irreversible break-down to inosine by adenosine deaminase (ADA). Ecto-ADA also catalyzes the extra-cellular deamination of adenosine. Mainly due to the high activity of AK, baseline levels of extra-cellular adenosine usually remain low. The action of ADA, which appears to be more abundantly expressed in astrocytes than in neurons (Fredholm et al., 2005), may be particularly important when large amounts of adenosine have to be cleared. Both, a genetic variant of ADA in humans (Bachmann et al., 2012) and pharmacological inhibition of AK in rodents increase SWS/SWA (Okada et al., 2003; Palchykova et al., 2010).

ADENOSINE A_1 AND A_{2A} RECEPTORS MEDIATE EFFECTS OF ADENOSINE IN SLEEP–WAKE REGULATION

The cellular effects of adenosine are mediated via four subtypes of G-protein coupled adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 receptors. *In vitro* studies indicate that physiological concentrations of endogenous adenosine can activate A_1, A_{2A}, as well as A_3 receptors. Nevertheless, it is widely accepted that the high-affinity A_1 and A_{2A} receptors are primarily involved in mediating the effects of adenosine on vigilance and sleep, at least in humans (Sebastiao and Ribeiro, 2009).

ADENOSINE A_1 RECEPTORS AND THE EFFECTS OF PROLONGED WAKEFULNESS

The stimulation of A_1 receptors opens several types of K^+-channels, inhibits adenylate cyclase through activation of G_i proteins and inactivates transient voltage-dependent Ca^{2+}-channels (**Figure 1B**). The A_1 receptor is ubiquitously but not homogenously expressed in the central nervous system (Bauer and Ishiwata, 2009). *In vivo* imaging with the selective A_1 receptor antagonist, ^{18}F-CPFPX, recently developed for positron emission tomography (PET) revealed highest receptor occupancy in striatum and thalamus, as well as temporo-parietal and occipital cortex. Because of the inhibition of excitatory neurotransmission after pre- and post-synaptic A_1 receptor activation and the wide-spread distribution of this receptor subtype in the brain, it has been generally assumed that adenosine affects sleep–wake regulation primarily via this receptor subtype. Pharmacological and genetic studies in rats and mice, as well as molecular imaging in humans, partly support this assumption (Schwierin et al., 1996; Thakkar et al., 2003; Elmenhorst et al., 2007, 2009; Bjorness et al., 2009). For example, inducible knock-out of neuronal adenosine A_1 receptors reduced SWA (3.0–4.5 Hz range) in NREM sleep under baseline conditions, and attenuated the homeostatically regulated rise in SWA after sleep restriction (Bjorness et al., 2009). These knock-out mice also showed impaired working memory when sleep was curtailed. Moreover, prolonged wakefulness appears to up-regulate A_1 receptor binding in cortical and subcortical brain regions in animals and humans (Elmenhorst et al., 2007, 2009). Taken together, these data indicate a role for adenosine A_1 receptors in mediating the functional consequences of sleep deprivation.

ADENOSINE A_{2A} RECEPTORS AND THE EFFECTS OF PROLONGED WAKEFULNESS

Stimulation of A_{2A} receptors increases adenylate cyclase activity through activation of G_s (or G_{olf} in striatum) proteins, induces the formation of inositol phosphates, and activates protein kinase A (**Figure 1B**). Compared to the A_1 receptor, this adenosine receptor subtype is less widely distributed in the brain (Bauer and Ishiwata, 2009). Highest expression in the human central nervous system was found in basal ganglia (particularly in putamen and caudate nucleus) and thalamus. Recent studies in rodents, including experiments in knock-out mice, suggest that also A_{2A} receptors contribute to the effects of adenosine on sleep. Local administration of the selective A_{2A} receptor agonist, CGS21680, to the

subarachnoid space adjacent to basal forebrain and lateral pre-optic area increased *c-fos* expression in the ventro-lateral pre-optic (VLPO) area and promoted NREM sleep (Scammell et al., 2001). Direct activation of sleep-promoting VLPO neurons upon stimulation of A_{2A} receptors could underlie this effect (Gallopin et al., 2005). Interestingly, preliminary data showed that mice with A_{2A} receptor loss-of-function may have reduced sleep and attenuated responses to sleep deprivation (Hayaishi et al., 2004).

Taken together, both adenosine A_1 and A_{2A} receptor subtypes probably mediate functional effects of adenosine after sleep deprivation, and these effects appear to be site- and receptor-dependent.

CAFFEINE ATTENUATES FUNCTIONAL CONSEQUENCES OF SLEEP LOSS

Caffeine is the most widely consumed stimulant in the world. In the micro-molar plasma concentrations reached after moderate consumption, caffeine acts as a non-selective, competitive antagonist at both A_1 and A_{2A} receptors. It may be important to note, however, that caffeine fails to promote wakefulness in mice lacking functional A_{2A} receptors, whereas this effect is preserved in A_1 receptor-deficient mice (Huang et al., 2005). Other effects of caffeine can also be obtained *in vitro*, including inhibition of phosphodiesterase, blockade of $GABA_A$ receptors, and Ca^{2+} release. For these actions, however, drug doses are needed that are more than 100 times higher than those for adenosine receptor antagonism and toxic in humans (Fredholm, 1995).

CAFFEINE ATTENUATES EEG MARKERS OF PROLONGED WAKEFULNESS IN NREM SLEEP

Acute administration of caffeine in doses equivalent to one to two cups of coffee (100–200 mg) prolongs sleep latency, impairs sleep efficiency, and reduces the duration of SWS (for review, see Landolt, 2008b). Moreover, the stimulant induces changes in the NREM sleep EEG, which are opposite to those of sleep deprivation. Specifically, spectral power within the slow-wave range (∼1–2.5 Hz) was decreased, whereas power in the spindle frequency range (∼12–15 Hz) was increased. It is remarkable that these EEG alterations were still observed at night, even when caffeine was administered in the morning to either rested or sleep deprived subjects (Landolt et al., 1995, 2004). Supporting an important role for adenosine and adenosine receptors in the effects of sleep deprivation, these caffeine-induced EEG changes in NREM sleep in part mimicked the consequences of a nap in the afternoon, which induces a physiological reduction in NREM sleep pressure (Werth et al., 1996).

Regional EEG analyses revealed that SWA in NREM sleep is largest over frontal cortical areas, especially after sleep deprivation (Cajochen et al., 1999; Tinguely et al., 2006). These observations indicate that frontal parts of the cortex reflect the homeostatic process of sleep–wake regulation more sensitively than other cortical regions. To study a possible contribution of adenosinergic mechanisms to these regional differences, the interaction of sleep deprivation and caffeine on the spatial distribution of low-frequency (<1 Hz) EEG power in NREM sleep was investigated in young, self-rated caffeine-insensitive and -sensitive men (Rétey et al., 2006). It was found that the two groups responded differently to these challenges of sleep–wake regulation. Most interestingly, the changes induced by caffeine were opposite to the effects of prolonged wakefulness, and the efficacy of the stimulant was negatively correlated to the effects of sleep deprivation.

CAFFEINE ATTENUATES EEG MARKERS OF SLEEP DEPRIVATION IN WAKEFULNESS

During prolonged wakefulness, caffeine attenuated the increase of subjective sleepiness and EEG theta activity after sleep deprivation (Landolt et al., 2004). Spectral power in the theta band (∼5–9 Hz) of the waking EEG is considered an objective measure of sleep pressure. Similar to NREM sleep, theta power increased more in an anterior EEG derivation than in a posterior derivation, primarily in self-rated caffeine-sensitive individuals (Rétey et al., 2006). Moreover, caffeine attenuated the waking-induced fronto-occipital power gradient, and the effects of sleep deprivation and caffeine were inversely associated.

Taken together, these findings demonstrate that in those subjects in whom prolonged wakefulness-induced the largest increase in a fronto-occipital power ratio in the sleep and waking EEG, caffeine most potently reduced this ratio. Moreover, caffeine modified the EEG in state-specific manner in those frequencies, which most reliably reflect the functional consequences of sleep deprivation.

CAFFEINE IMPROVES IMPAIRED NEUROBEHAVIORAL PERFORMANCE AFTER SLEEP DEPRIVATION

Sustained vigilant attention as reliably quantified by performance on the PVT is also highly sensitive to wakefulness-induced impairment (Lim and Dinges, 2008). Optimal response speed on the PVT was recently found to be less impaired after prolonged wakefulness in self-rated caffeine-insensitive individuals than in caffeine-sensitive subjects (Rétey et al., 2006). Also this difference was reliably counteracted by caffeine, and the effects of sleep deprivation and caffeine were inversely associated. Because the interaction of caffeine with circadian aspects of waking performance is minor (Wyatt et al., 2004), this study strongly suggested that adenosinergic mechanisms contribute to waking-induced impairment of neurobehavioral functions. Based on this evidence, we hypothesized that increased age not only affects the susceptibility to sleep deprivation, but also the response to the stimulant effects of caffeine.

ADVANCED AGE ALTERS FUNCTIONAL ASPECTS OF THE ADENOSINERGIC SYSTEM

The striking age-related reductions in SWS/SWA may reflect an age-related decline in the build-up of homeostatic sleep pressure (or sleep need) during wakefulness, a lower efficiency in dissipating sleep pressure during sleep, or an altered interplay of homeostatic and circadian aspects of sleep–wake regulation. The currently available evidence does not provide unequivocal support for an exclusive one of these possibilities (Dijk et al., 1989, 1999, 2010; Landolt et al., 1996; Buysse et al., 2005; Cajochen et al., 2006; Münch et al., 2007). With respect to adenosine, microdialysis studies in rat basal forebrain revealed that extra-cellular adenosine levels were higher in old animals (21.5 months) when compared to young animals (3.5 months) in baseline and throughout sleep deprivation (Murillo-Rodriguez et al., 2004). Given the more superficial sleep in old rats and the suggested role for adenosine

in promoting SWS/SWA, these data indicated that the sensitivity of adenosine receptors declines with increasing age. In support of this hypothesis, autoradiography in rat brain slices and PET with ^{18}F-CPFPX in humans showed that adenosine A_1 receptor binding was significantly reduced with age in many cortical and subcortical brain regions (Meerlo et al., 2004; Meyer et al., 2007). No such studies were performed to date to investigate age-related changes in functional aspects of A_{2A} receptors in the brain.

In conclusion, the available literature indicates that sleep homeostasis is functional in older individuals, yet impaired adenosine receptor-mediated signal transduction may lead to reduced SWS/SWA at night, lower daytime sleep propensity, and reduced vulnerability to the neurobehavioral consequences of sleep deprivation.

ADVANCED AGE MODULATES THE EFFECTS OF CAFFEINE ON THE SLEEP EEG

Drapeau et al. (2006) investigated age-related changes in the acute effects of caffeine on sleep and the sleep EEG at night. They found that intake of 2 × 100 mg caffeine within 3 h prior to bedtime similarly lengthened sleep latency, reduced sleep efficiency, and shortened sleep duration in healthy middle-aged (mean age: 50.3 ± 1.6 years; $n = 12$) and young (23.8 ± 0.7 years; $n = 12$) adults. Moreover, caffeine reduced ∼1–4 Hz activity above frontal, central, and parietal brain areas, and increased high-frequency power (many bins within 15–32 Hz) in frontal and central EEG derivations in both age groups. Subtle differences in the reduction of low-delta (<1 Hz) activity in the prefrontal region indicated that the sleep EEG of the older subjects may be more sensitive to the effects of the xanthine. In a follow-up study in 12 middle-aged (53.8 ± 1.1 years) and 12 young (24.2 ± 1.0 years) men and women, these authors also investigated the action of 2 × 100 mg caffeine on daytime recovery sleep after 25 h of prolonged wakefulness (Carrier et al., 2009). Again, caffeine similarly decreased sleep efficiency, sleep duration, SWS and REM sleep, and reduced EEG synchronization in NREM sleep (reduced 4–12 Hz activity and enhanced 14–19 Hz activity) in both age groups. Nevertheless, the combined influence of older age and caffeine led to great difficulty in the middle-aged subjects to consolidate sleep during the daytime, at the time of a strong circadian waking signal in the morning and early afternoon.

These experiments indicate that the sleep EEG is slightly more vulnerable to caffeine-induced changes in middle-aged adults when compared to young adults. This observation may challenge the hypothesis of reduced sensitivity of adenosine receptors with increasing age.

ADVANCED AGE ATTENUATES THE EFFICACY OF CAFFEINE TO COUNTERACT THE CONSEQUENCES OF SLEEP DEPRIVATION

Given the assumption that reduced vulnerability to sleep loss may reflect attenuated adenosine signal transmission, it was hypothesized that the effects of caffeine during prolonged wakefulness would be reduced in older adults when compared to young adults. To test this hypothesis, the build-up of regional EEG theta activity, subjective sleepiness, and performance on the PVT during sleep deprivation was examined in healthy aged and caffeine-insensitive and -sensitive young men. It was predicted that older subjects would respond similarly to caffeine-insensitive subjects to the effects of both sleep deprivation and caffeine.

Inclusion criteria for all three groups were the same with respect to habitual sleep duration (7–8 h per night), daytime sleepiness (<10 on Epworth Sleepiness Scale), body-mass-index (20–25 kg/m^2), and habitual consumption of caffeine (one to three caffeinated beverages per day), and alcohol (<5 drinks per week). Physical examination confirmed good health in the older men. Before enrollment into the study, low sleep efficiency (<80%), sleep apnea (apnea/hypopnea index > 5), and nocturnal myoclonus (>5 periodic limb movements per hour of sleep) were excluded by polysomnography in the laboratory. No study participant had a history of neurologic or psychiatric disease. All subjects were non-smokers and denied taking any medication or consuming illicit drugs. They refrained from caffeine for 2 weeks prior to the study. They were also requested to abstain from ethanol and to maintain regular 8:16-h sleep–wake cycles for 5 days prior to the experiment. According to the reported habitual sleep times, sleep was scheduled from 23:00 to 07:00 (four young men, all older men) or from 24:00 to 08:00 (18 young men). Deviation of more than 1 h from these schedules was not allowed. Compliance with the pre-study instructions was verified by inspecting the records from activity monitors worn on the wrist of the non-dominant arm, and by determining the level of caffeine in saliva and breath ethanol concentration upon arrival in the sleep laboratory.

Because all experimental details were described in earlier publications (Adam et al., 2006; Rétey et al., 2006, 2007), they are not fully reported here. In brief, all volunteers participated in two blocks of four consecutive nights separated by 1 week. The first and second nights of each block served as adaptation and baseline nights. Then, subjects stayed awake for 40 h until bedtime of the recovery night. Standardized waking EEG recordings, administration of the Stanford Sleepiness Scale, and testing of PVT performance occurred at 3-h intervals throughout prolonged wakefulness. Two doses of 200 mg caffeine and placebo in the form of capsules were administered after 11 and 23 h of extended wakefulness (randomized, double-blind, cross-over design). During sleep deprivation, the subjects remained under continuous supervision of members of the research team. They were allowed to read, study, play games, watch films, and occasionally take a walk outside the laboratory.

AGED INDIVIDUALS SHOW REDUCED EFFECTS OF SLEEP DEPRIVATION AND CAFFEINE ON FRONTAL EEG THETA ACTIVITY

First, the effects of prolonged wakefulness on regional theta power in the waking EEG were quantified in the placebo condition. Averaged activity in the 6.25- to 8.25-Hz band recorded at 11:00, 14:00, and 17:00 after the night without sleep was expressed as a percentage of the corresponding value in baseline (Rétey et al., 2006). In all three groups, sleep deprivation increased theta activity in fronto-central (FC) and parieto-occipital (PO) derivations (**Figure 2**). Nevertheless, the repercussions of sleep loss differed among aged, insensitive and sensitive individuals, and between FC and PO derivations. In particular, the increase in FC was significantly reduced in older men when compared to caffeine-sensitive young subjects.

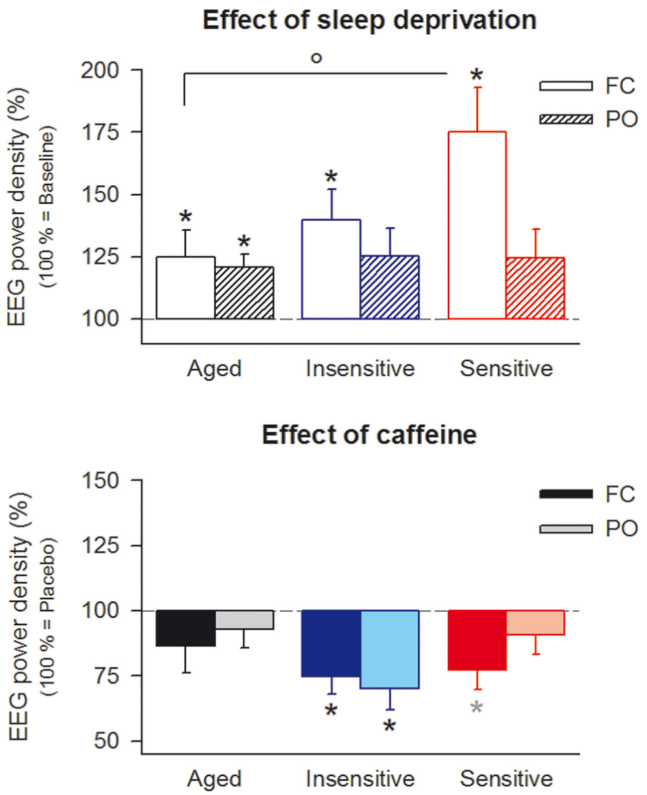

FIGURE 2 | Effects of sleep deprivation and caffeine on theta power (6.25–8.25 Hz) in the waking EEG (eyes open) in fronto-central (FC, open bars) and parieto-occipital (PO, striped bars) derivations in aged ($n = 10$, black bars) and caffeine-insensitive ($n = 10$, blue bars) and -sensitive ($n = 12$, red bars) young men. *Upper panel*: to quantify the effect of sleep deprivation, theta activity after sleep deprivation in the placebo condition was expressed as a percentage of the corresponding baseline value. Data represent means ± SEM. Three-way mixed-model ANOVA with the factors "*group*" (age, insensitive, sensitive), "*deprivation*" (sleep deprivation, baseline), and "*derivation*" (FC, PO) revealed significant main effects of "*deprivation*" ($F_{1,66.1} = 19.8$, $p < 0.001$) and "*derivation*" ($F_{1,48.8} = 4.8$, $p < 0.04$), as well as a significant "*group*" × "*derivation*" interaction ($F_{1,48.8} = 5.2$, $p < 0.009$). *$p < 0.04$ (two-tailed, paired *t*-tests), °$p < 0.04$ (two-tailed, unpaired *t*-tests). *Lower panel*: to quantify the effect of caffeine, theta activity after sleep deprivation in the caffeine condition was expressed as a percentage of the corresponding value in the placebo condition. Data represent means ± SEM. Three-way mixed-model ANOVA with the factors "*group*," "*treatment*" (caffeine, placebo), and "*derivation*" revealed a significant main effect of "*treatment*" ($F_{1,36.5} = 26.8$, $p < 0.001$), as well as a significant "*group*" × "*derivation*" interaction ($F_{1,28.6} = 4.8$, $p < 0.02$). *$p < 0.04$, *$p < 0.07$ (two-tailed, paired *t*-tests).

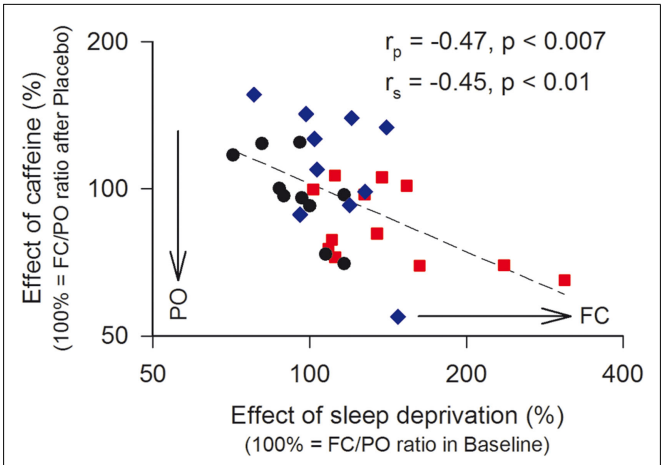

FIGURE 3 | Relationship between the effects of sleep deprivation and caffeine on FC/PO power ratios in the 6.25- to 8.25-Hz band of the waking EEG. To quantify the effect of sleep deprivation, the FC/PO ratio after sleep deprivation in the placebo condition was expressed as a percentage of the corresponding baseline value. To quantify the effect of caffeine, the FC/PO ratio after sleep deprivation in the caffeine condition was expressed as a percentage of the corresponding value in the placebo condition. Values above 100% indicate a shift of power in anterior direction (toward FC), whereas values below 100% indicate a shift of power in posterior direction (toward PO). Data are plotted on a double-logarithmic scale. Black dots: aged individuals; blue diamonds: caffeine-insensitive individuals; red squares: caffeine-sensitive individuals. A regression line was fitted through 32 individual data points. r_p: Pearson's product-moment correlation coefficient, r_s: Spearman rank correlation coefficient.

Caffeine attenuated the sleep deprivation-induced increase in theta activity in the waking EEG (**Figure 2**). When all three groups were considered, the reduction was more pronounced in the FC derivation and only significant in young subjects, especially in the caffeine-insensitive group. Regression analyses revealed an inverse relation between the effects of sleep deprivation and caffeine on the FC/PO ratio in theta power (**Figure 3**). This finding indicates that in those subjects in whom sleep deprivation-induced the largest increase in the FC/PO gradient in EEG theta activity, caffeine most potently reduced this gradient.

AGED INDIVIDUALS SHOW REDUCED EFFECTS OF SLEEP DEPRIVATION AND CAFFEINE ON NEUROBEHAVIORAL PERFORMANCE

Next, the evolution of subjective sleepiness and vigilant attention in placebo and caffeine conditions were quantified at 3-h intervals throughout sleep deprivation. Aged, as well as caffeine-insensitive and -sensitive young subjects maintained stable performance across the first 16–18 h of prolonged wakefulness (**Figure 4**). Afterward, sleepiness and lapses on the PVT increased, whereas slowest and fastest reaction times on the PVT decreased. The subjective and objective measures of vigilance in all three groups were worst in the placebo condition in the test sessions occurring between 24 and 32 h of prolonged wakefulness. The magnitude of impairment, however, differed in all variables. In general, young volunteers who reported high caffeine sensitivity were more impaired by sleep deprivation than aged and caffeine-insensitive young subjects.

Double-blind administration of caffeine improved subjective sleepiness in aged, insensitive, and sensitive men (**Figure 4**). By contrast, the stimulant attenuated the sleep loss-induced impairment in vigilant attention in caffeine-sensitive subjects only. Previous analyses revealed a significant negative correlation between the effects of sleep deprivation and caffeine on optimal PVT performance in young adults (Rétey et al., 2006). We investigated whether this relationship is also present when the older age group is included. To quantify the effect of caffeine on neurobehavioral performance, optimal PVT speed in the caffeine condition at 11:00, 14:00, and 17:00 after sleep deprivation was compared

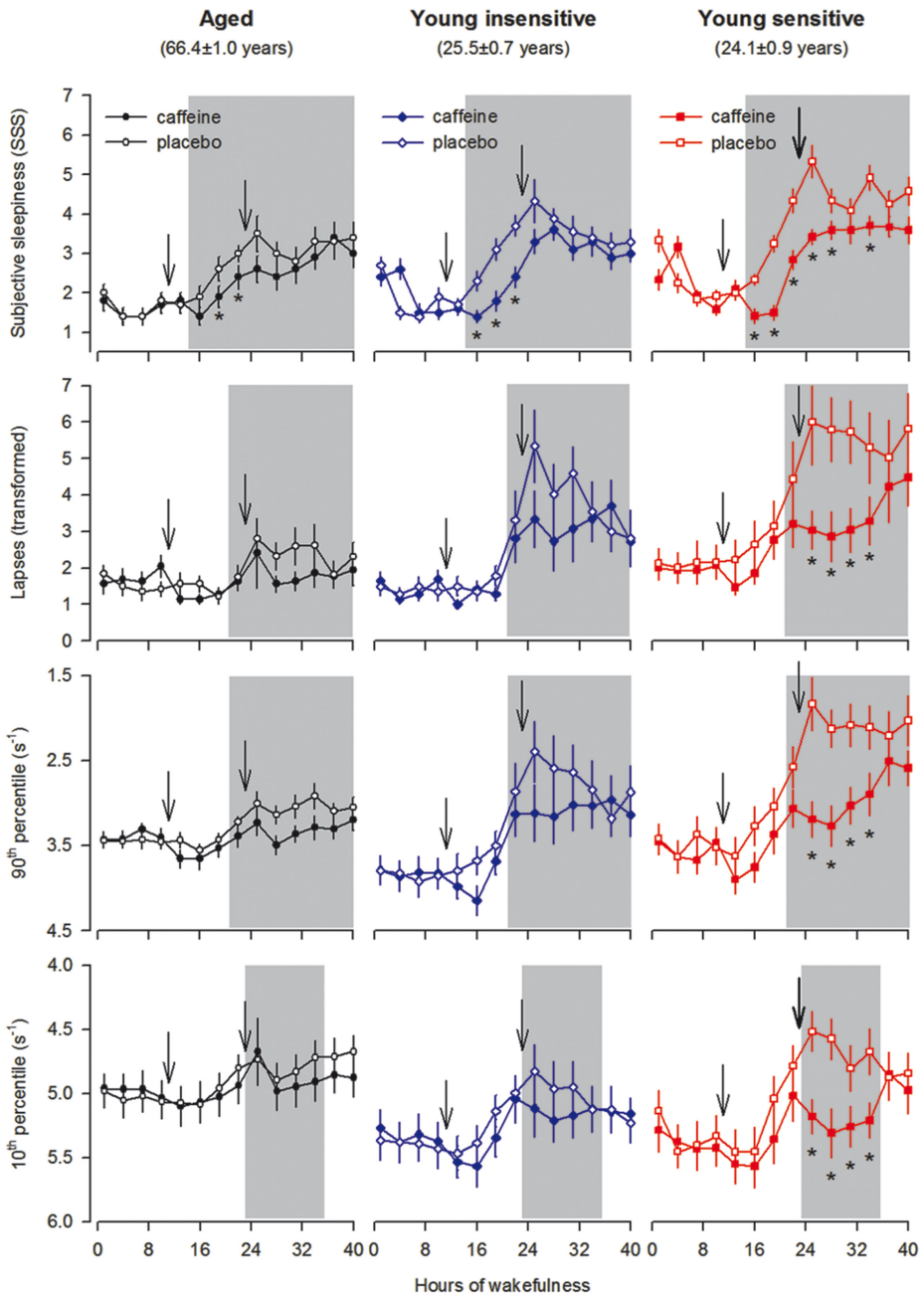

FIGURE 4 | Time course of subjective sleepiness [Stanford Sleepiness Scale (SSS)] and performance on the psychomotor vigilance task (PVT) across 40 h waking in aged ($n = 10$, black symbols) and caffeine-insensitive ($n = 10$, blue symbols) and -sensitive ($n = 12$, red symbols) young men. The SSS and 10-min PVT sessions were administered every 3 h beginning 30 min after awakening from the baseline night. Ticks on the *x*-axes were rounded to the previous hour. Data represent means ± SEM. Caffeine (200 mg) was administered 11 and 23 h into the scheduled waking period (arrows). Open symbols: placebo condition; filled symbols: caffeine condition. Gray shading indicates the test sessions, which showed a significant "*group*" × "*treatment*" interaction (see **Table 1** for further details of the statistical analyses). *$p < 0.05$ (false discovery rate).

to the corresponding value in the placebo condition. Indeed, a significant negative association between the effects of sleep deprivation and caffeine was found (**Figure 5**). In other words, including young and older individuals, those subjects with the largest impairment from sleep loss showed the largest benefit from caffeine.

NO DIFFERENCE IN CAFFEINE PHARMACOKINETICS IN AGED, INSENSITIVE, AND SENSITIVE INDIVIDUALS

There exist large inter-individual differences in caffeine metabolism in the liver that may be modified by age (Tanaka, 1998; Rasmussen et al., 2002; Carrier et al., 2009). Therefore, it was determined whether the different effects of caffeine on EEG and

Table 1 | Statistical analyses of subjective sleepiness and sustained vigilant attention across 40 h prolonged wakefulness.

Factors	*"Group"* (*F*; *p*)	*"Session"* (*F*; *p*)	*"Treatment"* (*F*; *p*)	*"Group"* × *"session"* (*F*; *p*)	*"Session"* × *"treatment"* (*F*; *p*)	*"Group"* × *"treatment"* (*F*; *p*)	*"Group"* × *"session"* × *"treatment"* (*F*; *p*)
SSS	17.1; 0.000	57.9; 0.000	102.1; 0.000	2.5; 0.000	2.6; 0.002	2.2; 0.138	0.7; 0.902
PVT							
Lapses	5.8; 0.009	17.0; 0.000	35.4; 0.000	2.4; 0.000	3.2; 0.002	8.4; 0.000	0.5; 0.973
Slowest	2.3; 0.136	26.2; 0.000	89.6; 0.000	2.9; 0.000	4.8; 0.002	12.3; 0.000	0.9; 0.556
Fastest	1.4; 0.267	21.1; 0.000	36.8; 0.000	1.7; 0.026	3.0; 0.001	10.4; 0.000	1.3; 0.174

To estimate the effects of sleep deprivation and caffeine, mixed-model ANOVA containing the random-effects factor "subject" and the fixed-effects factors "group" (aged, insensitive, sensitive), "session" (test sessions 1–14), and "treatment" (placebo, caffeine) were performed. The F- and p-values of the fixed-effects factors are reported; the reported p-values were controlled for the false discovery rate. Significant p-values are highlighted by gray shading. SSS, Stanford Sleepiness Scale. PVT, psychomotor vigilance task. Lapses = number of trials with a reaction time (RT) of longer than 500 ms. Slowest = slowest 10th percentile of RTs. Fastest = fastest 10th percentile of RTs.

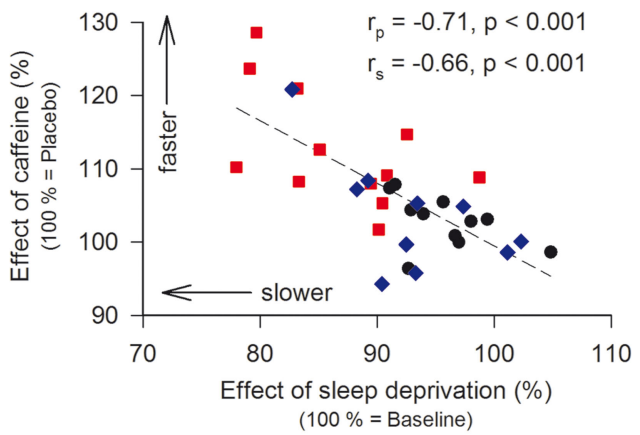

FIGURE 5 | Relationship between the effects of sleep deprivation and caffeine on the 10th percentile of speed (optimal performance) on the psychomotor vigilance task (PVT). To quantify the effect of sleep deprivation, the 10th percentile after sleep deprivation in the placebo condition was expressed as a percentage of the corresponding baseline value. To quantify the effect of caffeine, the 10th percentile after sleep deprivation in the caffeine condition was expressed as a percentage of the corresponding value in the placebo condition. Data are plotted on a linear scale. Black dots: aged individuals; blue diamonds: caffeine-insensitive individuals; red squares: caffeine-sensitive individuals. A linear regression line was fitted through 32 individual data points. r_p: Pearson's product-moment correlation coefficient, r_s: Spearman rank correlation coefficient.

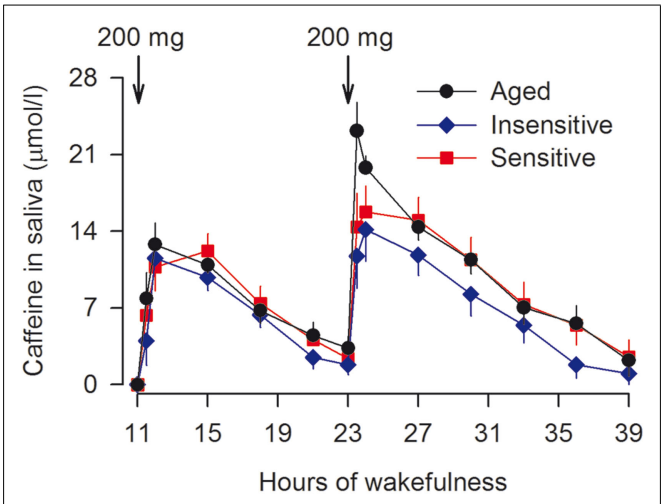

FIGURE 6 | Similar time course of saliva caffeine concentration in aged ($n = 10$, black dots) and caffeine-insensitive ($n = 9$, blue diamonds) and -sensitive subjects ($n = 11$, red squares) young men. Samples were collected 5 min before and 30 and 60 min after caffeine intake, and at 3-h intervals following the first dose of caffeine. The data of 1 caffeine-insensitive and 1 caffeine-sensitive individual could not be analyzed because of insufficient saliva volumes. Values represent means ± SEM. Mixed-model ANOVA with the factors "*group*" (aged, insensitive, sensitive) and "*time*" (14 measurements) revealed no significant difference among the groups ("*group*" × "*time*" interaction: $F_{2,26} = 1.2$, $p > 0.2$).

sustained attention reflected different caffeine levels in saliva. One hour after the second dose of caffeine, the concentration in saliva equaled roughly 16–20 µmol/l (aged: 19.8 ± 1.1 µmol/l; insensitive: 15.7 ± 2.7 µmol/l; sensitive: 16.4 ± 2.5 µmol/l). Afterward, the drug levels declined at a similar rate in all groups and reached almost zero at the end of sleep deprivation (**Figure 6**).

WHICH MECHANISMS MAY UNDERLIE REDUCED AGE-RELATED SENSITIVITY OF THE ADENOSINERGIC SYSTEM?

The competitive A_1 and A_{2A} receptor antagonist, caffeine, "replaces" endogenous adenosine in dose-dependent manner (Fredholm, 1995). Microdialysis studies in rats provided inconsistent results to the question whether extra-cellular adenosine in basal forebrain is differently affected by sleep deprivation in old and young animals (Murillo-Rodriguez et al., 2004; Rytkönen et al., 2010). In humans, the half-life time of caffeine varies widely and differences in habitual caffeine intake may induce physiological adaptations to different cerebral caffeine exposure. The data from carefully controlled studies demonstrate that a fixed dose of caffeine leads to similar saliva concentrations in aged and young individuals who have modest habitual caffeine consumption (**Figure 6**; see also Carrier et al., 2009). Thus, reduced absorption by the organism is unlikely to underlie the attenuated effects of caffeine on waking EEG and

neurobehavioral functions after sleep loss. Non-invasive, multimodal imaging techniques may be developed in the future, to simultaneously investigate cerebral adenosine concentrations and distinct adenosine receptor dynamics as a function of exogenous ligand exposure. Such an approach could help to further clarify the exact roles for adenosine and adenosine receptors in age-related changes in individual vulnerability to sleep deprivation.

Pharmaco-genetics provides another powerful avenue in humans to identify molecular mechanisms underlying individual responses to sleep loss. This strategy was successfully employed in young adults to elucidate adenosinergic and dopaminergic mechanisms of sleep–wake regulation (Rétey et al., 2007; Bodenmann and Landolt, 2010; Bodenmann et al., 2012). As a molecular basis contributing to individual caffeine sensitivity, it was found that the distribution of distinct c.1976T > C genotypes (single nucleotide polymorphism rs5751876) of the adenosine A_{2A} receptor gene (*ADORA2A*) differed between self-rated caffeine-insensitive and -sensitive people (Rétey et al., 2007). Subsequent, more sophisticated genetic and laboratory studies in selected individuals showed that common variants of *ADORA2A* are important determinants of psychomotor vigilance in rested and sleep deprived state (Bodenmann et al., 2012). The same gene variants also modulate the neurobehavioral response to caffeine after sleep loss. More specifically, 2 × 200 mg caffeine were ineffective to improve sustained attention in carriers of HT4 alleles, while the same dose efficiently improved performance in non-HT4 allele carriers (**Figure 7**). These findings demonstrate that genetic variation of *ADORA2A* alters the efficacy of pharmacological blockade of A_{2A} receptors on neurobehavioral performance in young individuals. Although secondary effects of caffeine cannot be excluded (Yang et al., 2010), we suggest that age-related differences in A_{2A} receptor function contribute to the observed age-related changes in neurobehavioral performance after sleep loss.

CONCLUSION

Large inter-individual differences characterize the changes induced by prolonged wakefulness on rhythmic brain activity and neurobehavioral performance in young and older healthy individuals, yet the underlying neurobiological mechanisms are not well understood. Advanced age was recently recognized to importantly modulate individual vulnerability to sleep deprivation. Consistent evidence demonstrated that the consequences of sleep loss on sleep and waking EEG, subjective sleepiness, and different aspect of waking state and performance are attenuated in healthy older individuals. To receive first insights into possible neurobiological underpinnings of these age-related changes in humans, the combined effects of sleep deprivation and caffeine on frontal EEG theta activity and sustained attention were evaluated in healthy older men. The response in this cohort to both challenges of the sleep–wake cycle was similar to that in young individuals who are caffeine-insensitive, and significantly less pronounced than in young caffeine-sensitive individuals. Moreover, the effects of sleep deprivation and caffeine were inversely related. These data provide the first experimental evidence in humans that impaired sensitivity of the adenosinergic system contributes to reduced neurobehavioral consequences of sleep deprivation in older age. Provided that genetic variation of *ADORA2A* in young adults modulates subjective and objective effects of caffeine in wakefulness and sleep, it should be investigated whether cerebral A_{2A} receptors undergo functional changes in normal aging. Future research will also have to establish whether similar age-related changes also exist in higher cognitive processing such as working memory and other executive functions (Van Dongen

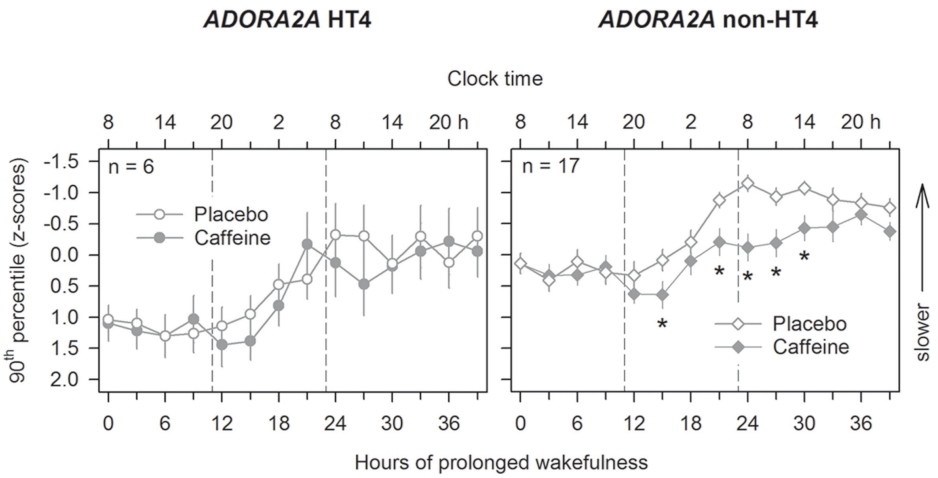

FIGURE 7 | Genetic variation of *ADORA2A* modulates the effects of caffeine on psychomotor vigilance after sleep loss. The psychomotor vigilance task (PVT) was administered at 3-h intervals throughout prolonged wakefulness, beginning 30 min after wake-up from the baseline nights. Mean values (±SEM) of the 10th percentile of reaction times (expressed as speed, 1/reaction time) in young carriers of HT4 (left panels) and non-HT4 haplotype (right panels) alleles of *ADORA2A* are plotted. Ticks on the *x*-axes were rounded to the previous hour. Compared to placebo (open symbols), 2 × 200 mg caffeine (filled symbols) improved optimal PVT speed after sleep loss in non-HT4 haplotype carriers only (ANOVA: "haplotype": $F_{1,21.2} = 7.91$, $p < 0.02$; "session": $F_{13,205} = 13.43$, $p < 0.0001$, "treatment": $F_{1,68} = 8.45$, $p < 0.005$; "haplotype" × "treatment" × "session": $F_{26,219} = 2.1$, $p < 0.003$). *$p < 0.05$ (caffeine vs. placebo; two-tailed, paired *t*-tests).

et al., 2004), as well as in performance in ecological situations such as nocturnal driving (Sagaspe et al., 2007). Given the large demographic changes currently occurring in the Western World, this research is of high scientific interest because it will reveal new insights into the normal age-related changes in physiological sleep–wake regulation. In addition, it is also of clinical importance, because it may identify predictors and biomarkers of behavioral and health consequences of shift work, jet lag, and voluntary sleep restriction, which are highly prevalent in the modern "24/7" society. Finally, it may lead to the rational development of novel, effective, and safe countermeasures to reduce sleepiness and behavioral and cognitive impairments as a consequence of insufficient sleep.

ACKNOWLEDGMENTS

We thank Dr. R. Khatami, MD, for the medical examination of the aged study participants. The authors' research was supported by the Swiss National Science Foundation grants # 31-67060.01, 3100A0-107874, and 310000-120377, and the EU Marie Curie grant MCRTN-CT-2004-512362.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 January 2012; paper pending published: 19 February 2012; accepted: 02 April 2012; published online: 27 April 2012.

Citation: Landolt H-P, Rétey JV and Adam M (2012) Reduced neurobehavioral impairment from sleep deprivation in older adults: contribution of adenosinergic mechanisms. Front. Neur. ***3****:62. doi: 10.3389/fneur.2012.00062*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in
NEUROLOGY

ORIGINAL RESEARCH ARTICLE
published: 11 July 2012
doi: 10.3389/fneur.2012.00109

The effects of pre-sleep learning on sleep continuity, stability, and organization in elderly individuals

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Several studies have consistently shown that pre-sleep learning is associated to changes of sleep structure. Whereas previous research has mainly focused on sleep states, namely REM and NREM amount, very little attention has been paid to the hypothesis that pre-sleep learning might improve sleep continuity, stability, and cyclic organization, which are often impaired in aging. Thus, aim of this research was to assess, in a sample of 18 healthy elderly subjects, whether a memory task administered at bedtime would determine changes in any sleep parameter, with special regard to sleep continuity, stability, and organization. To this purpose, a baseline sleep (BL), i.e., a normal sleep with 9-h time in bed (TIB), was compared to a post-training sleep (TR), with the same TIB but preceded by an intensive training session. For the latter, a verbal declarative task was used, consisting in learning paired-word lists, rehearsed, and recalled for three times in a row. To control for individual learning abilities, subjects were administered several sets of lists with increasing difficulty, until they reached an error rate ≥20% at third recall. Relative to BL, TR shows a significant reduction in the frequency of brief awakenings, arousals, state transitions, "functional uncertainty" (FU) periods, and in the percentage of time in FU over total sleep time (TST). A significant increase in the number of complete cycles, total cycle time (TCT), and TCT/TST proportion was also found. All these changes are evenly distributed over the sleep episode. No sleep stage measure display significant changes, apart from a slight reduction in the percentage of Stage 1. Scores at retest are negatively correlated with both the frequency of arousals and of state transitions. Our data suggest that pre-sleep learning can yield a beneficial re-organizing effect on elderlies' sleep quality. The inverse correlation between recall scores and the measures of sleep continuity and stability provides further support to the role of these features in memory processes.

Keywords: aging, arousals, learning, memory consolidation, NREM-REM cycles, sleep continuity, sleep organization, sleep stability

INTRODUCTION

As many as 50% of older individuals complain about sleep problems, often reporting disturbed or "light" sleep, frequent night awakenings, early morning awakenings, and undesired daytime sleepiness (Foley et al., 1999; Vitiello et al., 2004). Though one relevant cause of these impairments is the presence of illness or the use of sleep-disturbing drugs, even carefully screened older adults who do not complain of sleep disturbances and with minimal medical burden show similar changes when compared to young adults (Vitiello, 2006).

Among the major objectively measured sleep changes associated to the aging process (for exhaustive reviews, see Bliwise, 1996; Ancoli-Israel et al., 2008), there are significant impairments of: (a) sleep continuity, with increased number and duration of intra-sleep awakenings (Åkerstedt et al., 2002); (b) sleep organization, expressed by a reduction of cycles' number and a decrease of time spent in cycles over total sleep time (Salzarulo et al., 1998).

In light of the classical two-process model of sleep regulation (Borbély, 1982), the main age-related sleep changes have been explained with either a disruption of the circadian pacemaker (Dijk et al., 1999), or with age-dependent intrinsic lightening of sleep homeostatic processes (Wauquier and van Sweden, 1992). Also, it has been sometimes pointed out (Vitiello, 2006) that sleep-wake rhythms in elderly people could be altered by a number of dramatic changes in lifestyle (i.e., retirement, bereavement, and institutionalization); these, on their turn, could act via a reduction of cognitive activity, whose effects on sleep features appear to have been largely underestimated.

The idea that sleep is modulated not only by the duration of wakefulness but also by its "intensity," resulting from physical and cognitive activity and measured through cerebral metabolic rate, was originally put forward by Feinberg (1974) to explain the "restorative role" of SWS.

In line with this suggestion, we have recently proposed (Conte and Ficca, 2012) that a specific aspect of waking activity, i.e., the learning processes, should be considered as a major additional factor in sleep regulation. In fact, a fecund line of research has consistently shown that post-training sleep (TR) displays relevant changes, both in animals and humans (see Peigneux et al., 2001 for a thorough review). These changes have usually been

explained with the assumption that, following intensive learning, the sleep episode will tend to express all those components necessary for sleep-dependent memory consolidation. However, most studies have focused on post-training rebounds of quantitative sleep parameters (e.g., NREM and REM amounts, spindle density). Their controversial results, and the quite complicated picture deriving from them, have been described and commented in previous reviews of ours (Ficca and Salzarulo, 2004; Conte and Ficca, 2012). Instead, the possibility that pre-sleep learning could benefit sleep quality, in terms of a higher degree of sleep continuity, stability, and organization, has been almost totally neglected. This is somehow surprising, since there is growing evidence on the role of these parameters for the effectiveness of sleep-dependent consolidation processes.

Animal studies suggest that sleep fragmentation might disrupt memory consolidation by interrupting the natural development of biological mechanisms required for learning. Tartar et al. (2006), showed, in rats, that experimental interruptions of sleep impair spatial learning by inhibiting hippocampal long term potentiation. In mice, after the learning phase of an object recognition task, Rolls et al. (2011) used optogenetics to activate hypocretin/orexin neurons, which play a key role in arousal processes, in order to fragment sleep without affecting sleep overall amount or sleep depth. The authors found a significant decrease of performance on the subsequent day, concluding that, regardless of the total amount of sleep, a minimal unit of uninterrupted sleep is crucial for memory consolidation.

As for humans, in a sample of patients with post-traumatic stress disorder (PTSD), who often complain of sleep disturbances and memory deficits, the number of night awakenings, together with GH secretion, turned out to be an independent predictor of post-sleep recall at a word lists task (van Liempt et al., 2011).

Relatively close to the notion of "sleep continuity" is the one of "sleep stability." If sleep-dependent memory consolidation unfolds over a continuous time course, its disruption might result not only from full behavioral awakenings, but also from any event reversing the natural build up of the sleep episode (supposed to be made by gradual deepenings periodically punctuated by transitions to REM sleep).

To our knowledge, the only attempts to provide an operational definition of sleep stability come from the bulk of studies on the cyclic alternating pattern (CAP) (Terzano et al., 2001; Parrino et al., 2011). CAP is a periodic EEG activity of NREM sleep characterized by repeated spontaneous sequences of transient events (phase A) which clearly stand out from the background rhythm (phase B) of the ongoing sleep stage, with an abrupt frequency/amplitude variation. Parrino et al. (2011) propose that specific configurations of this pattern could represent a marker of sleep instability. For instance, the prevalence in pre-school children (Bruni et al., 2005) and elderly subjects (Parrino et al., 1998) of desynchronized CAP phases (A2 subtype) over synchronized patterns (A1 subtype) would suggest a greater sleep instability in these age groups. Interestingly, A1 pattern displayed a significant increase in a post-training night, compared to baseline (Ferri et al., 2008), as well as a positive correlation with morning retest performance (Ferri et al., 2008; Aricò et al., 2010). These results provide interesting evidence on the role of slow-wave activity for learning and suggest the importance of sleep stability in memory processing.

Besides CAP as a crucial microstructural facet, here we would like to extend the definition of "stability" by considering sleep phenomena with a wider temporal resolution and not limited to patterns of NREM sleep. In fact, in our view, instability indexes should also include arousals and state transitions, which refer to a notion conceptualized by Salzarulo et al. (1997) as "functional uncertainty," and defined as "the inability of the Central Nervous System to sustain a stable condition." In other terms, unstable sleep phases are those in which the characteristics of one well-defined state occur only for short intervals, so that the individual appears to oscillate continuously between different states, being unable to "decide" for one or another. This kind of sleep pattern would be particularly evident in extreme age groups (children and elderly individuals), as well as in those subjects affected by fragmenting sleep disorders.

Finally, the hypothesis of a role of sleep cycles for learning processes has been underlined, together with the behavioral, biological, neurophysiological, and neuroanatomical evidence supporting it, in the frame of what we call "sleep organization" (Ficca and Salzarulo, 2004). Experimentally, this hypothesis was confirmed by a few findings. In a sample of healthy elderly individuals, Mazzoni et al. (1999) found that post-sleep recall of word pairs was significantly correlated with average duration of NREM REM cycles and with the proportion of time spent in cycles total cycle time (TCT) over total sleep time (TST), whereas it was not related to any other sleep measure. One year later, it was shown that the experimental disruption of sleep cycles determined significantly worse recall of word pairs, relative both to undisturbed sleep and to fragmented sleep with sleep cycle preservation (Ficca et al., 2000). Finally, the number of sleep cycles was significantly correlated with performance at a visuo-spatial task in a group of patients with chronic non-restorative sleep (Göder et al., 2007).

Due to the aforementioned traits of discontinuity, instability, and disorganization of elderlies' sleep, a "re-compacting" and "re-organizing" effect of pre-sleep training would be particularly beneficial for this population.

Therefore, the aim of this study is to assess whether a learning task administered before sleep onset determines changes in any sleep parameter of the subsequent sleep episode, with special regard to sleep continuity, stability, and organization, in a sample of healthy elderly subjects.

MATERIALS AND METHODS

SUBJECTS

Prior to subjects' recruitment, the design of the study was submitted to the Ethical Committee of the School of Psychology, University of Naples II, that approved the research and certified that the use of human subjects was performed according to acceptable standards.

Eighteen elderly volunteers ($F = 10$, $M = 8$; age range: 65–85 years, mean age: 72.5 ± 5 years), all home-dwelling, were recruited from the general population.

Participants were screened through: (a) a brief *ad hoc* interview to collect general demographic data and information on medical condition and health habits; (b) the Mini Mental State

Examination (MMSE), a brief 30-point questionnaire test, commonly used in the clinical context to screen for cognitive impairment (Folstein et al., 1975); (c) the Pittsburgh Sleep Quality Index (PSQI), a questionnaire on sleep habits and quality (Buysse et al., 1989).

Inclusion criteria were the following: age ≥65 years; absence of any relevant somatic disease, either acute or chronic; no evidence of current or past psychiatric illness; absence of cognitive decline (MMSE score ≥25); no symptoms of sleep apnea or other respiratory disorders; no complaints of insomnia or daytime sleepiness; absence of relevant sleep-wake rhythm disruptions; no history of drug or alcohol abuse; being a non-smoker; limited caffeine and alcohol consumption (no more than three cups of coffee and a glass of alcohol a day).

PROCEDURE

Each subject underwent three nights of sleep recording at home, separated by an interval of 3 days to 1 week. An adaptation night was followed, in balanced order, by two experimental conditions: (a) baseline sleep (BL), i.e., a normal night's sleep with 9-h time in bed (TIB) allotted, (b) Post-TR, with the same maximum TIB but preceded by a training session.

For the 3 days preceding each sleep recording session, subjects were requested to maintain regular bed- and rise-times and regular napping habits. Specifically, in order to assure the maintenance of *habitual* sleep-wake rhythms, subjects were allowed to take naps only if these represented a daily habit. In that case, naps should not differ from the subject's usual naps neither in length nor in circadian placement. To control for these variables, participants were asked to complete a sleep log for a week preceding each sleep recording night and to wear an actimeter from 9 a.m. of each recording session day until 9 a.m. of the following morning. Furthermore, during the days scheduled for recording, participants were requested to avoid cognitively engaging activities (such as reading, solving crossword puzzles, playing cards, etc.).

On TR day, the experimenter arrived at the subject's house approximately 1 h before usual bedtime and proceeded to electrode montage. The subject was then administered the training session and was instructed to go to bed immediately after that. In the BL condition, instead, the subjects went to bed immediately after electrode montage. The following morning, subjects completed the sleep diary and, in the TR condition, retest was performed 30 min after awakening.

To control for mood and sleepiness levels, a Visual Analog Scale for mood (VAS-mood, McCormack et al., 1988) and the Karolinska Sleepiness Scale (KSS, Akerstedt and Gillberg, 1990) were administered immediately before bedtime on the recording night and at awakening the following morning. In addition, in the TR condition, the two scales were also completed in the evening before training administration and immediately before retest in the morning.

POLYGRAPHIC AND ACTIGRAPHIC RECORDINGS

Polysomnographic (PSG) recording was performed in accordance with standardized techniques (Rechtschaffen and Kales, 1968), using digital EEG, EMG, and EOG signals acquired through a multi-channel ambulatory recorder (XLTEK Trex™ HD Home Sleep).

For actigraphic monitoring, a Micromini Motionlogger Actimeter was used. The actimeter was worn on the wrist of the non-dominant hand.

LEARNING TASK

For the training session, a verbal declarative task, consisting in learning paired-word lists, was developed *ad hoc* for the experiment. Lists were made up of bysillabic concrete nouns, and they were balanced for number of semantically associated pairs and mean frequency of use of words (Bortolini et al., 1971). The total number of word pairs was 168, divided as follows: 3 lists of 8 word pairs, 3 lists of 12, 3 lists of 16, and 3 lists of 20.

At the beginning of the training session, each subject was informed that a recall test would be administered the following morning. During list presentation, the experimenter read each word pair out loud, with an interval of 1 s between each pair. Immediately after list presentation, the experimenter read only the first member of each pair and the subject was asked to recall the second one. In order for learning to take place, this procedure was repeated three times for each list.

To control for individual learning abilities and amount of cognitive effort, each subject was presented several sets of lists with increasing length, until they reached an error rate of 20% at third recall (see **Figure 1** for scheme and explanation).

At retest in the morning, subjects were presented only the first members of the pairs belonging to the lists administered to that subject the night before. For data analysis, scores at retest were calculated as percentage of words recalled in the morning over the total number of words recalled by the subject in the training session.

SLEEP MEASURES

Sleep recordings were scored through visual inspection, according to standard criteria (Iber et al., 2007). However, as in Mazzoni et al. (1999), SWS was scored without considering the amplitude criterion, following Webb and Dreblow's (1982) criteria.

Sleep scoring was performed by an expert technician who was blind to the condition to which the recording belonged. To verify the reliability of scoring, randomly selected sleep recordings were also scored by another expert technician. Inter-rater agreement was 95.2%.

Classical sleep quantitative variables considered in our study were: TIB, TST (total amount of time, expressed in minutes, from the first appearance of Stage 1 sleep to morning final awakening), actual sleep time (AST, i.e., total amount of time spent in sleep, expressed in minutes), sleep latency, sleep efficiency, sleep stage proportions, percentage of wake after sleep onset (WASO) over TST.

An additional set of parameters was used to specifically address sleep continuity, stability, and organization.

As for sleep continuity: (a) number of awakenings <2 min per hour of AST; (b) number of awakenings ≥2 min per hour of AST; (c) number of awakenings from Stage 1, Stage 2, SWS, REM sleep per minute of that stage; (d) mean duration of awakenings; (e)

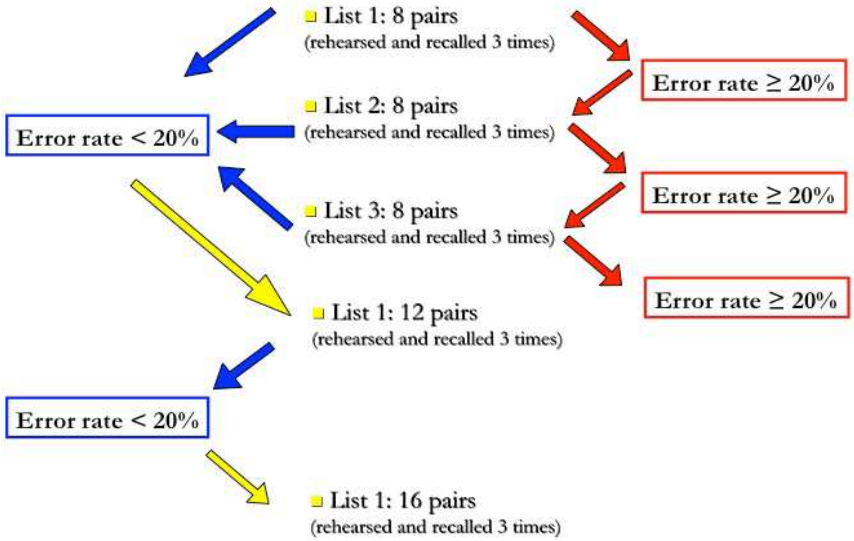

FIGURE 1 | Task administration procedure. The trial starts with the administration of a 8-pairs list; if, at third recall, the number of errors is lower than 20%, the subject will proceed to the next difficulty level, i.e., a 12-pairs list, otherwise he will continue with another list of the same length. The trial is terminated when the subject does not succeed in decreasing his error rate below 20% at third recall; otherwise, this same procedure is repeated with longer (12-, 16-, and 20-pairs) lists.

number of arousals per hour of AST (arousals were defined as all transitions to shallower NREM sleep stages and from REM sleep to stage 1); (f) number of arousals from stage 2, SWS, REM sleep per minute of that stage.

Concerning sleep stability: (a) number of "state transitions" per hour of TST ("state transitions" were defined as all transitions from one state to another, including all those to and from wake, and all those from one stage to another); (b) number of "functional uncertainty periods" (FU periods) per hour of TST (FU periods were defined as periods in which a minimum of three state transitions follow one another with no longer than 1 min and a half intervals); (c) mean duration of FU periods; (d) percentage of total time spent in FU (TFU) over TST.

Finally, with respect to sleep organization: (a) number of complete sleep cycles, defined as sequences of NREM and REM sleep (each lasting at least 10 min), not interrupted by periods of wake and/or stage 1 longer than 2 min; (b) TCT, i.e., total time spent in cycles (minutes); (c) percentage of TCT over AST; (d) cycle mean duration.

STATISTICAL ANALYSIS

Due to non-normal distribution of variables, non-parametric statistics was chosen for data analysis. BL and TR variables were compared by means of Wilcoxon's signed rank test (for directed hypothesis).

Spearman's analysis of correlation was carried to assess the association between TR sleep parameters and recall scores at morning awakening.

Finally, TST was divided in quarters for each sleep episode and a two-way analysis of variance (ANOVA), with "condition" and "quarter" as factors, was carried to explore the time course of the effects of training on sleep continuity and stability variables across the sleep episode.

RESULTS

Two subjects had to be excluded from analyses due to the absence of fragmentation in their BL sleep (0 awakenings in both subjects). Thus the final sample for data analysis included 16 participants (F = 9, M = 7; age range: 65–85 years, mean age: 70.1 ± 6.6 years).

QUANTITATIVE SLEEP VARIABLES

A significant increase of AST emerged at TR, compared to BL. Reduced WASO was also found in TR vs. BL, paralleled by a significant increase of sleep efficiency. No significant differences were observed between the two conditions in stage amount percentages, with the only exception of a slight reduction of Stage 1 in TR (**Table 1**).

No other quantitative sleep variable showed significant differences between BL and TR in (**Table 1**).

SLEEP CONTINUITY

We have summarized the comparisons of continuity variables between BL and TR in **Figure 2**. Though no modifications were found in the frequency of long – i.e., lasting 2 min or more – awakenings (BL: 1.73 ± 1.53 vs. TR: 1.21 ± 0.54, Wilcoxon's $z = 1.245$, ns), we detected a significant decrease at TR in the frequency of both short – i.e., less than 2 min – awakenings (BL: 1.68 ± 1.01 vs. TR: 0.72 ± 0.74, Wilcoxon's $z = 2.223$, $p = 0.01$) and arousals (BL: 5.47 ± 2.18 vs. TR: 4.29 ± 0.92, Wilcoxon's $z = 1.689$, $p = 0.04$). Mean awakenings duration, not displayed in the Figure, was not modified by training (Wilcoxon's $z = 0.140$; ns).

Table 2 shows the distribution of fragmenting events in the different sleep stages.

No awakening measure displayed significant changes at TR relative to BL.

Table 1 | Quantitative sleep variables.

	Baseline	Training	Wilcoxon's *z*	*p*-Value
Time in bed (min)	406.2 ± 88.7	410.8 ± 44.9	0.099	ns
Total sleep time (min)	391.4 ± 88.6	398.2 ± 51.9	0.356	ns
Actual sleep time (min)	326.7 ± 99.9	360.5 ± 58.6	1.689	**0.04**
Latency (min)	14.7 ± 13.9	12.6 ± 11.8	0.296	ns
Stage 1 (%)	21.2 ± 8.8	15.7 ± 9.5	1.689	**0.04**
Stage 2 (%)	44.5 ± 15.2	39.9 ± 8.4	1.334	ns
SWS (%)	12.9 ± 9.6	17.8 ± 10.2	1.423	ns
REM (%)	16.4 ± 10	20.4 ± 5.7	1.511	ns
WASO (%)	17.3 ± 13.8	10.8 ± 5.6	2.223	**0.01**
Sleep efficiency	79.9 ± 15.1	86.7 ± 7.6	2.312	**0.01**

Bold represents the significant p-values.

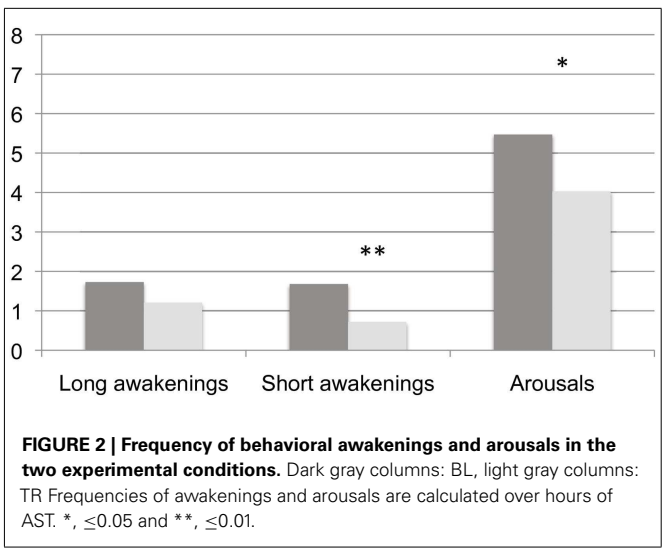

FIGURE 2 | Frequency of behavioral awakenings and arousals in the two experimental conditions. Dark gray columns: BL, light gray columns: TR Frequencies of awakenings and arousals are calculated over hours of AST. *, ≤0.05 and **, ≤0.01.

As for arousals, a significant reduction in the frequency of arousals from Stage 2 to Stage 1, from SWS to Stage 2 and from SWS to Stage 1 was found at TR, whereas those from REM sleep to Stage 1 were unmodified.

SLEEP STABILITY

A highly significant reduction emerged at TR for the frequency of FU periods per hour of TST, and for percentage of total time spent in FU over TST. The frequency of state transitions also displayed a significant decrease at TR, while the mean duration of FU periods did not show any changes (**Table 3**).

SLEEP ORGANIZATION

All sleep cycles measures (number of cycles and TCT, both absolute and relative to AST), except for cycle mean duration, showed significant increases from BL to TR (**Table 4**).

ANALYSIS OF CORRELATION

Significant negative correlations between morning recall performances and TR sleep variables emerged for total arousal frequency

Table 2 | Sleep fragmentation in different sleep stages.

	Baseline	Training	Wilcoxon's *z*	*p*-Value
AWAKENINGS FREQUENCY*				
from Stage 1	0.13 ± 0.09	0.08 ± 0.05	1.067	ns
from Stage 2	0.05 ± 0.07	0.03 ± 0.02	0.089	ns
from SWS	0.04 ± 0.06	0.03 ± 0.05	0.889	ns
from REM	0.05 ± 0.05	0.03 ± 0.05	1.423	ns
AROUSALS FREQUENCY*				
Stage 2 to Stage 1	0.13 ± 0.07	0.08 ± 0.04	1.689	**0.04**
SWS to Stage 2	0.39 ± 0.23	0.27 ± 0.22	1.956	**0.02**
SWS to Stage 1	0.03 ± 0.05	0.01 ± 0.01	1.820	**0.03**
REM to Stage 1	0.02 ± 0.01	0.02 ± 0.03	0.178	ns

**Awakenings and arousals from a certain stage are calculated as frequencies over the total time spent in that stage (minutes).*
Bold represents the significant p-values.

Table 3 | Sleep stability.

	Baseline	Training	Wilcoxon's *z*	*p*-Value
State transitions TST (h)	15.5 ± 5.6	11.8 ± 4.0	1.956	**0.02**
FU periods TST (h)	1.2 ± 0.6	0.7 ± 0.3	1.867	**0.03**
TFU TST (%)	9.7 ± 5.6	5.5 ± 2.2	2.223	**0.01**
FU periods mean duration (min)	4.3 ± 1.5	4.4 ± 0.8	0.089	ns

Bold represents the significant p-values.

Table 4 | Sleep organization.

	Baseline	Training	Wilcoxon's *z*	*p*-Value
N cycles	0.9 ± 1	2.1 ± 1.7	2.200	**0.01**
TCT (min)	48.14 ± 56.6	113.9 ± 102.5	2.073	**0.02**
TCT AST (%)	13.1 ± 14.4	30.8 ± 24.8	1.955	**0.02**
Cycle mean duration (min)	30 ± 32.6	43.6 ± 26.1	1.007	ns

Bold represents the significant p-values.

(Spearman's $\rho = -0.67$, $p = 0.01$) and state transition frequency (Spearman's $\rho = -0.62$, $p = 0.02$; see **Figure 3**).

TIME DISTRIBUTION OF SLEEP CONTINUITY AND STABILITY MEASURES

Analysis of variance did not show a significant main effect of the factor "quarter" for any of the sleep continuity and stability measures, nor any significant interaction "condition × quarter" (**Table 5**).

DISCUSSION

The presence in the baseline nights of a notable degree of sleep fragmentation and disorganization, expressed by the high number of awakenings and arousals and by the low sleep efficiency, as well by a low TCT/TST, proves that sleep features in our sample are consistent with what is known on elderlies' sleep (Dijk et al., 2001;

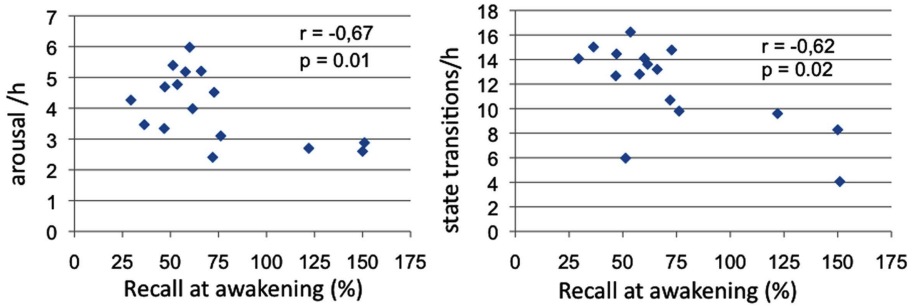

FIGURE 3 | Sleep measures correlated with memory recall at awakening. Panel 1: Correlations of arousal frequency with recall at awakening (% over pre-sleep recall); Panel 2: Correlations of state transitions frequency with recall at awakening (% over pre-sleep recall).

Table 5 | Time distribution of sleep fragmentation.

	Quarter *F*	Condition *F*	Quarter × condition *F*
Short awakenings AST (h)	2.154	4.717**	1.272
Long awakenings AST (h)	1.657	1.584	0.570
Arousals AST (h)	1.894	7.596*	0.336
State transitions TST (h)	0.769	4.601*	1.347
FU periods TST (h)	0.484	5.274**	0.709
TFU TST (%)	0.510	9.655**	0.354

** < 0.05 and ** < 0.01.*

Vitiello, 2006; Ancoli-Israel et al., 2008). In fact, only 2 of the 18 recruited subjects showed no behavioral awakenings at baseline and were excluded for aberrant values, whereas, for the remainder subjects, the mean absolute number and the frequency of awakenings were even higher than those reported in most literature on aging (for a review, see Åkerstedt et al., 2002).

This evidence supports our preliminary hypothesis that the chosen sample was adequate to explore a possible re-organizing effect of the cognitive manipulation.

The main result of the present study is the significant impact of the verbal learning task administered before bedtime on the subsequent sleep episode, both in terms of sleep continuity and stability, and in terms of sleep cyclic organization.

As for the observed reduction of arousals and awakenings, the protective effect of pre-sleep training against fragmentation appears to be effective mainly on weaker arousing events, i.e., those which determine shifts to lighter sleep stages or very brief awakenings; instead, it does not seem able to prevent stronger arousing drives (those leading to full, and often very long, behavioral awakenings) which are probably the result of a sum of different factors (internal and or external).

Our analysis of the time course of sleep fragmentation proves it to be quite different in the elderly than in young subjects. While the latter are characterized by a tendency to spontaneously wake up from REM sleep, therefore with a higher degree of sleep fragmentation in the last part of the sleep episode (Langford et al., 1972; Murphy et al., 2000), and longer wake in late than in early sleep cycles (Merica and Gaillard, 1986), the former seem vulnerable to fragmentation all over the sleep episode. In the present study, this is actually true not only for behavioral awakenings, but also for arousals and state transitions. This set of data apparently gives support to what proposed some years ago: "either sleep is shallow and fragile in elderly patients, thus diminishing differences in arousability between sleep stages, or sleep is less shielded against the intrusion of external disturbances which may lead to arousals and awakening independent of the ongoing sequence of sleep stages" (Åkerstedt et al., 2002). Very interestingly, also the effect of training in reducing this high arousability seems to be evenly exerted across the whole night.

It must be acknowledged that a limitation in our study is the use of only one among the many different operational definitions of the term "arousal" (Ficca, 2002), which is aimed to detect macrostructural superficializations of sleep in the frame of the epoch-by-epoch visual EEG scoring. It would be important to replicate these findings with other definitions, such as the one adopted by American Sleep Disorder Association (1992), which refers to "EEG changes whose duration may be very short, even not longer than 3 s."

Also the signals of sleep instability, namely the state transitions and the FU periods, that are conspicuously present in baseline nights, undergo a significant decrease in post-TR.

Our results on sleep stability variables, together with recent data from clinical studies on fibromyalgia (Kishi et al., 2010) and sleep-disordered breathing (Swihart et al., 2008), suggest the possible utility of including these measures in standard sleep assessments on both normal and clinical populations as further indexes of sleep quality. These parameters could usefully complement the evaluations of the CAP (Terzano et al., 2001), which, although limited to NREM sleep, was shown to represent a reliable marker of sleep instability (Parrino et al., 2011).

Results on sleep organization suggest that bedtime training has a positive impact also on sleep cycling, since the number of cycles and TCT, both absolute and relative to TST, were significantly increased in the TR condition. Instead, cycles mean duration was unmodified. However, this result could be explained by the very "conservative" definition of cycle adopted (see Materials and Methods), in analogy with previous studies (Mazzoni et al., 1999; Ficca et al., 2000). Rather than on already long uninterrupted cycles, it is well possible that training would have exerted its lengthening

effect on those short NREM-REM sequences, which have not been included as actual sleep cycles in the analysis, since not fulfilling the required criterion of a minimum duration for both sleep states.

Overall, these findings represent encouraging evidence on the possibility to exploit planned pre-sleep training sessions to improve sleep and subsequent wake quality in all those conditions affected by fragmented and disturbed sleep.

Of course it might be argued that the changes we have observed in post-TR are specific for the aged population. However, a similar pattern of results has already been obtained, by means of the same experimental paradigm, on a sample of nine young subjects complaining of frequent awakenings and disturbed sleep (Conte et al., 2010).

Some remarks can also be made with regard to the debate on the mechanisms underlying the effect of sleep on memory consolidation.

The significant increase in sleep cycles variables is consistent with our working hypothesis, assuming, in the frame of the "sleep cycles model" (Mazzoni et al., 1999; Ficca et al., 2000), a central role of sleep organization for memory processing during sleep.

On the other hand, further exploration of this issue is required in light of the absence, in our study, of significant correlations between cycles measures and memory recall, at variance with previous data (Mazzoni et al., 1999; Göder et al., 2007).

As for sleep continuity and stability, the reduction at TR of brief awakenings, arousals, state transitions, and FU measures induces us to confirm the hypothesis that these features also play a role in sleep-dependent consolidation, in agreement with a few other studies (Tartar et al., 2006; Rolls et al., 2011; van Liempt et al., 2011). Obviously, a necessary assumption is that the observed post-TR changes are specifically dependent on the triggering of consolidation processes. The significant correlations between recall performances and continuity and stability variables, seems to us encouraging supports to this assumption.

However, the elderly population poses a specific problem to the interpretation of these results, concerning the age-related modifications of slow-wave activity. Despite some authors' proposal (Webb and Dreblow, 1982; Lombardo et al., 1998) that the reduced delta power in the elderly depends solely on reduced amplitude of delta waves, rather than on an inability to produce them, other authors (e.g., Feinberg, 1989) claim that the elderly individuals' brain becomes less capable to produce a visually detectable slow-wave rebound. If this is the case, then the characteristics of the sample studied do not allow us to fully exclude: (a) that the contribution of an unspecific effect (more generally dependent on cognitive "effort" and fatigue), which could determine a homeostatic SWS rebound, is at work; (b) that a shift toward more slow-wave element production, that has been connected to synaptic potentiation and memory consolidation in previous articles (e.g., Tononi and Cirelli, 2003; Huber et al., 2004), would have been detectable even in this elderly population with more fine-grained techniques of SWA analysis, as it was shown in a previous paper by Ferri et al. (2008) through measurement of CAP parameters. For these reasons, future studies could add important information by adding a non-learning performance task control condition, as well as more sensitive measures of slow-wave changes.

A final remark concerns the implications of our findings in the understanding of sleep quality disruption in aging.

It has been shown that the worsening of elderlies' sleep quality is partly determined by changes in lifestyles and daily activities intervening with aging and particularly with retirement, such as social isolation (Ohayon et al., 2001; National Sleep Foundation Poll, 2003), or reduction of physical activities (Foley et al., 1999).

However, while this evidence has so far been attributed only to the disruption of the "zeitgebers" system, either photic (light-based) or non-photic (e.g., exercise activities, scheduled meals, or social cues; Vaz Fragoso and Gill, 2007), we propose that the impoverished socio-relational network of the elderly negatively affect his sleep quality through the consequent reduction of cognitive activity.

The analysis of our results opens the way to a series of interesting theoretical speculations to be explored in future studies:

(a) It is possible that post-TR is characterized, along with the sleep variables we have considered, by some microstructural correlates supporting its greater stability and continuity, that is a lower tendency to awakenings and superficializations. For instance, in a very recent study aimed at investigating sleep maintenance ability in young subjects, Dang-Vu et al. (2010) found that the subjects displaying higher arousal thresholds in the face of environmental sounds showed higher spindle densities. The authors concluded that, in addition to perhaps actively contributing to memory consolidation, spindles may shield sleep from disruption, allowing consolidating processes to operate unhindered.
(b) In our opinion, although we currently have experimental evidence concerning only declarative tasks, i.e., recall of paired words lists (Mazzoni et al., 1999; Ficca et al., 2000), and delayed recall of the Rey–Osterreith Complex Figure task (Göder et al., 2007), there is no particular reason to rule out a contribution of "good sleep quality" (in terms of adequate cycling, continuity, and stability), to the consolidation of different types of tasks usually grouped under procedural learning.

In conclusion, the findings of our study support the hypothesis that administration of learning tasks may improve subsequent sleep quality in the elderly individuals, in terms of continuity, stability, and organization. The promising applicative implication is the possibility to plan specific training sessions in populations affected by disturbed sleep, both in natural (aged individuals) and clinical settings (pathologies fragmenting sleep).

Furthermore, our results encourage to conceive further studies on the role of sleep continuity, stability, and organization for sleep-dependent memory consolidation.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 03 March 2012; accepted: 16 June 2012; published online: 11 July 2012.

Citation: Conte F, Carobbi G, Errico BM and Ficca G (2012) The effects of pre-sleep learning on sleep continuity, stability, and organization in elderly individuals. Front. Neur. ***3****:109. doi: 10.3389/fneur.2012.00109*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in
NEUROLOGY

REVIEW ARTICLE
published: 14 December 2012
doi: 10.3389/fneur.2012.00176

NREM sleep oscillations and brain plasticity in aging

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The human electroencephalogram (EEG) during non-rapid eye movement sleep (NREM) is characterized mainly by high-amplitude (>75 μV), slow-frequency (<4 Hz) waves (slow waves), and sleep spindles (~11–15 Hz; >0.25 s). These NREM oscillations play a crucial role in brain plasticity, and importantly, NREM sleep oscillations change considerably with aging. This review discusses the association between NREM sleep oscillations and cerebral plasticity as well as the functional impact of age-related changes on NREM sleep oscillations. We propose that age-related reduction in sleep-dependent memory consolidation may be due in part to changes in NREM sleep oscillations.

Keywords: aging, sleep, NREM, declarative memory, procedural memory, cognition, slow waves, sleep spindles

SLOW-WAVE NREM SLEEP OSCILLATIONS

Non-rapid eye movement (NREM) sleep is characterized by different degrees of cortical synchronization, from lower in lighter sleep stages (1 and 2) to higher in deeper slow-wave sleep (SWS) stages. In mammals, more time spent awake results in higher cortical synchronization in NREM sleep, whereas synchronization dissipates as sleep progresses (Achermann et al., 1993). Cortical synchronization during NREM sleep is characterized by slow waves (SW). At the cellular level, SW have two phases: hyperpolarization [surface electroencephalogram (EEG) negative], during which cortical neurons are mostly silent (OFF period); and depolarization (surface EEG positive), during which most cortical neurons fire intensively (ON period; Steriade, 2006; Csercsa et al., 2010). Animal studies have demonstrated that, under high homeostatic sleep pressure, short periods of intense cortical activity (ON periods) alternate frequently with relatively long periods of neuronal silence (OFF periods). Conversely, under low homeostatic sleep pressure, long ON periods are interrupted by sporadic, short OFF periods (Vyazovskiy et al., 2009). Greater homeostatic sleep pressure is associated with higher SW density and amplitude, faster SW frequency (Hz), and steeper slope between negative and positive phases (Esser et al., 2007; Riedner et al., 2007; Bersagliere and Achermann, 2010; Carrier et al., 2011; Mongrain et al., 2011).

Electroencephalogram SW originate more frequently in prefrontal–orbitofrontal regions and travel in an anteroposterior direction (Massimini et al., 2004). Source modeling has shown that SW are more likely to originate in the insula and the cingulate gyrus, but often involve frontal areas and the precuneus (Murphy et al., 2009). Recent fMRI studies have confirmed that SW are associated with activation of the brainstem, inferior frontal gyrus, posterior cingulate cortex, and precuneus, which are important for sleep maintenance and cerebral plasticity (Dang-Vu et al., 2008).

SLOW WAVES AND CEREBRAL PLASTICITY

Increasing evidence suggests that specific brain areas that are recruited for a particular task may require more slow-wave activity (SWA) than other brain areas (Kattler et al., 1994; Huber et al., 2004). According to the synaptic homeostasis hypothesis, cerebral plastic processes during wakefulness produce a net increase in synaptic strength, reducing the capacity for further potentiation. SWA during NREM sleep is associated with the downscaling of synaptic strength, which then allows for further synaptic potentiation and learning to occur following sleep (Tononi and Cirelli, 2006). Accordingly, waking behaviors associated with synaptic potentiation would be expected to increase SW, whereas waking behaviors associated with synaptic depression would be expected to reduce SW (Hanlon et al., 2009). In support of this hypothesis, somatosensory stimulation (Kattler et al., 1994) and training on a motor adaptation task (Huber et al., 2004) increased SWA the following night. Additional support for the synaptic homeostasis hypothesis in humans is supported by studies that applied TMS to manipulate neural excitability immediately prior to sleep (Huber et al., 2007, 2008; Massimini et al., 2009). Results showed that TMS-evoked increases in cortical responsiveness (potentiation) prior to sleep enhanced local SWA at central derivations, whereas TMS-evoked decreases in cortical responsiveness (depression) reduced SWA locally during subsequent sleep. These findings provide compelling evidence in support of the synaptic homeostasis hypothesis (Huber et al., 2007, 2008) and the potential role of SW in brain plasticity (Tononi and Cirelli, 2006).

CHARACTERISTICS OF SLEEP SPINDLE OSCILLATIONS

Sleep spindles appear on the EEG as transient waxing and waning oscillations recurring approximately once every 3–10 s (Steriade, 2005). Two types of spindles have been described, distinguished by their frequency, scalp topography, and associated neural correlates identified using fMRI (Schabus et al., 2007). Slow

spindles (∼11–13 Hz) predominate frontal derivations, whereas fast spindles (∼13–15 Hz) are more prominent at centro-parietal derivations (De Gennaro and Ferrara, 2003). Spindles reflect oscillatory activity in thalamocortical (TC) networks during NREM sleep, and may be associated with loss of perceptual awareness and consolidation of memory traces (Steriade, 2006). On the one hand, spindle oscillations have the intrinsic property to hyperpolarize TC cells through recurrent inhibition of reticular thalamic activity. This inhibitory spindle activity prevents afferent signals from being transmitted to the cortex, thus reducing cortical responsiveness to external stimulation during sleep (Steriade, 1994; Dang-Vu et al., 2011). On the other hand, post-inhibitory rebound firing of TC cells causes the depolarization of cortical pyramidal neurons through rhythmic excitatory spike bursts. Cortical involvement is crucial in mediating spindle duration, as recently observed by intracellular recordings and computational models (Bonjean et al., 2011). Corticothalamic (CT) feedback can not only trigger spike bursts in reticular thalamic neurons to initiate a spindle oscillation, but it also can terminate the spindle by desynchronizing the thalamic network through depolarization of TC cells. Thus, spindle duration can be maintained by a synchronized spiking activity of the TC system, but is interrupted when thalamic and cortical firing fall out of phase.

SLEEP SPINDLES AND SYNAPTIC PLASTICITY

The highly recurrent and coherent firing pattern associated with sleep spindles may promote plastic changes underlying learning and memory consolidation (Steriade and Timofeev, 2003). Indeed, spindle activity creates the ideal conditions for massive Ca^{2+} entry into depolarized dendrites of cortical neurons, a molecular event involved in synaptic plasticity and long-term potentiation (LTP; Sejnowski and Destexhe, 2000). In fact, LTP was successfully induced by trains of spindle activity in the rat somatosensory cortex (Rosanova and Ulrich, 2005), and the induction of LTP by tetanization of the rat corpus callosum increased the reliability of evoked spindle oscillations (Werk et al., 2005). Human neuroimaging studies have revealed that both fast and slow spindles are associated with increased hemodynamic responses in the thalamic nuclei and paralimbic areas (Schabus et al., 2007). Slow spindles are associated with greater cerebral activation in the superior frontal gyrus, whereas fast spindles recruit several cortical regions usually involved in sensorimotor processing as well as the hippocampus and mediofrontal areas. In addition, evidence from rodents has shown that prefrontal cortical spindles are temporally coordinated with high-frequency ripples in the hippocampus (Sirota et al., 2003). Since sleep spindles have been implicated in memory consolidation for hippocampal-dependent memory (see Fogel and Smith, 2011, for review), it is tempting to speculate that the temporal relationship between spindles and ripples may be a reflection the hippocampal-neocortical dialog thought to be required for memory consolidation (Siapas and Wilson, 1998). Taken together, these findings suggest that sleep spindles are associated with neurophysiological processes underlying brain plasticity.

AGE-RELATED CHANGES IN NREM SLEEP OSCILLATIONS

Non-rapid eye movement sleep synchronization changes considerably with age, with a substantial reduction in SWS, an increase in lighter NREM sleep stages, and significant decreases in SWA (spectral power between 0.5 and 4 Hz) and sigma (13–14 Hz) activity during NREM sleep, beginning as early as middle age (Carrier et al., 2001; Landolt and Borbély, 2001; Darchia et al., 2007). Previous studies have shown the greatest age-related decreases in the spectral power of delta frequencies in frontal derivations (Munch et al., 2004; Robillard et al., 2010). Recently, we evaluated cortical mechanisms of NREM synchronization by characterizing changes in automatically detected SW in a large sample of young and middle-aged subjects (Carrier et al., 2011). Compared to young adults, older individuals had both lower SW amplitude and lower SW density, especially in prefrontal/frontal brain areas, where they most frequently originate (Massimini et al., 2004). In addition, older subjects had lower SW slope and longer SW positive and negative phases compared to young subjects. These age-related differences suggest that cortical neurons take more time to synchronously enter SW hyperpolarization and depolarization phases. This age-related reduction in slow activity during NREM sleep may have a negative impact on brain plasticity and sleep-dependent memory consolidation.

In addition to reduced SW during NREM sleep, spindle density, amplitude, and duration are reduced in older compared to young subjects (Guazzelli et al., 1986; Wei et al., 1999; Crowley et al., 2002), and this decline has been shown to be progressive with age (Principe and Smith, 1982; Nicolas et al., 2001). Yet spindle frequency shows a slight increase with age (Principe and Smith, 1982; Wei et al., 1999; Nicolas et al., 2001; Crowley et al., 2002). Spindle dynamics over the course of the night also change with age. While young subjects typically show increased sigma activity and spindle density from the beginning to the end of the night (Jankel and Niedermeyer, 1985; Aeschbach and Borbély, 1993), older subjects do not show this trend, or show it to a lesser extent (Guazzelli et al., 1986; Landolt et al., 1996; Wei et al., 1999).

Most studies exploring the effects of age on sleep spindles have restricted their analysis to a single EEG scalp derivation. Yet spindles are known to be topographically heterogeneous (Zeitlhofer et al., 1997). In fact, Nir et al. (2011) recently demonstrated that the majority of spindles occur independently across brain regions: most spindles appeared simultaneously in only a minority of brain areas, suggesting local rather than global modulation. Consistent with Nir et al. (2011), we reported that age effects differed across scalp location (Martin et al., 2013). Age-related decreases in spindle density and amplitude were most prominent at anterior derivations, whereas shorter duration was maximal at posterior derivations. Surprisingly, there were no age-related differences in spindle frequency at any derivations. It remains to be tested whether an age-related reduction in sleep spindle activity may have a negative impact on sleep stability (Dang-Vu et al., 2010), and whether this may underlie reduced age-related sleep-dependent memory consolidation.

ROLE OF NREM SLEEP OSCILLATIONS IN DECLARATIVE LEARNING

The contributions of sleep to learning, memory, and brain plasticity have been studied for over 30 years (Smith et al., 1974; for a review, see Smith, 1985, 1996; Maquet, 2001; Walker, 2005; Stickgold and Walker, 2007; Diekelmann and Born, 2010). However, it remains a contentious topic (Stickgold and Walker, 2005). Indeed, it is unclear which sleep stages support the enhancement and/or consolidation of different memory systems.

Numerous recent studies propose the role of NREM sleep oscillations in declarative learning. It has been hypothesized that SW-dependent downscaling benefits memory by eliminating weak synapses (i.e., noise), thereby improving the signal-to-noise ratio in the synapses that were strongly potentiated during prior wakefulness (Tononi and Cirelli, 2006). According to another dominant hypothesis, declarative memory consolidation during sleep would occur during SWS via repeated reactivations (replay; see Bergmann et al., 2012; Diekelmann and Born, 2010, for recent reviews). This replay would benefit memory by transferring new memories from the hippocampus to the neocortex via hippocampal–neocortical dialog. In addition, Buzsáki (1989, 1998) has provided an alternative, but complementary viewpoint largely based on work done in rats. He suggests that during SWS, potentiated neurons of the hippocampus communicate with the neocortex via sharp-wave bursts. This communication is thought to underlie the hippocampal-neocortical transfer of information during sleep, leading to memory consolidation.

Studies suggest the key role of hippocampal/neocortical reactivation during early NREM in the consolidation of hippocampal-dependent memories, such as declarative memory (Peigneux et al., 2004; Rasch et al., 2007). Compared to an equivalent period of wake, post-learning sleep has been shown to enhance declarative memory task retention (e.g., word pair retention; Tucker et al., 2006; Gais et al., 2007) and increase hippocampal activation during recall (Gais et al., 2007). In rats, the pattern of hippocampal place cell firing observed during spatial learning is reproduced during subsequent periods of SWS (Wilson and McNaughton, 1994), suggesting that memory reactivation may occur during SWS. In humans, Peigneux et al. (2004) observed that brain regions (including the hippocampus) that are active during virtual maze navigation are also active during SWS, suggesting that SWS may play a similar role for spatial memory reactivation in humans. Furthermore, declarative memory benefits mainly from sleep periods rich in SWS rather than rapid eye movement (REM) sleep (Plihal and Born, 1999; Gais and Born, 2004; Drosopoulos et al., 2005). A recent study (Rasch et al., 2007) has shown that spatial declarative memory can be enhanced when a contextual odor cue during learning is presented again during SWS. No enhancement was observed in the vehicle-only control condition or when the odor was re-presented during REM sleep. They concluded that the cue served to reactivate the memory trace during SWS, inducing enhanced SWS-dependent memory consolidation. Moreover, several studies have reported positive associations between the characteristics of NREM sleep including SWA, SW, and spindle oscillations and greater declarative memory retention after sleep (Clemens et al., 2005; Tucker and Fishbein, 2008; Tamminen et al., 2010; Van Der Werf et al., 2011; Wilhelm et al., 2011). However, several of these studies lacked a control night to distinguish state-like associations (spindle enhancement after learning and memory performance) from trait-like associations (inter-individual differences in cognitive abilities related to individual differences in spindles). It is necessary to consider inter-individual differences in spindle activity when investigating their night-to-night changes in response to learning, since spindles are associated with rather stable cognitive traits such as intellectual ability (Schabus et al., 2006; Fogel et al., 2007a). Nonetheless, several studies have clearly demonstrated that declarative learning prior to sleep increases SW and spindle oscillations, which are associated with overnight memory retention (Gais et al., 2002; Schabus et al., 2004, 2008; Schmidt et al., 2006; Molle et al., 2009). Moreover, boosting SW with transcranial direct current stimulation (TDCS) during sleep enhances verbal declarative memory retention (e.g., learning word pair associations; Marshall et al., 2006), and reducing SWA and slow sigma power during NREM sleep with TDCS reduces verbal declarative memory retention (Marshall et al., 2011), suggesting a causal relationship between SW and declarative memory. Thus, taken together, these results suggest that NREM sleep plays an important, if not a crucial role for declarative memory consolidation. Moreover, specific aspects of NREM sleep such as SW and spindles are correlated with memory consolidation and increase in a learning-dependent manner following declarative learning. Thus, suggesting that these events may play an active role in memory consolidation processes.

THE IMPACT OF AGE-RELATED CHANGES IN SLEEP ON DECLARATIVE MEMORY

Currently, there is no clear consensus on the impact of aging on sleep-dependent declarative memory consolidation. One study identified reduced sleep-related consolidation of verbal memory in older subjects, associated with an age-related decrease in early-night SWS (Backhaus et al., 2007). Other studies found no age-related differences in sleep-dependent consolidation of verbal declarative memory (Aly and Moscovitch, 2010; Wilson et al., 2012). Discrepancies between these results may be attributable to statistical power issues and confounding factors, such as circadian effects on initial encoding and retrieval, and importantly, their interaction with age. Future studies should also use objective sleep measurements.

To our knowledge, only three studies have assessed whether NREM sleep oscillations are associated with declarative overnight memory retention in older participants. Higher SWA was linked with better overnight declarative memory retention in both healthy elderly adults and patients with mild cognitive impairment (Westerberg et al., 2012), whereas higher sleep spindle density was associated with better overnight visuospatial memory retention in older women (Seeck-Hirschner et al., 2012). A study in Alzheimer patients found no association between spindles and overnight memory retention, but instead found a positive relationship between memory performance prior to sleep and spindle intensity in subsequent sleep (Rauchs et al., 2008). However, these studies did not control for baseline sleep to distinguish between state-like associations versus trait-like associations. Nevertheless, another study has assessed a clear state-like association between

SWA and memory performance in healthy elderly patients, by experimentally reducing SWA using acoustic neurofeedback. This procedure was found to decrease the encoding of novel declarative information in older subjects (Van Der Werf et al., 2011). Taken together, these results suggest that NREM sleep spindles and SWA are related to declarative memory encoding and retention in older adults. The impact of age-related changes in sleep, and specifically the changes in NREM sleep oscillations on sleep-dependent declarative memory consolidation remains to be clarified.

NREM SLEEP OSCILLATIONS AND PROCEDURAL LEARNING

Consolidation of various procedural skills (e.g., finger movements, gross movements involving target tracking, dexterity, tracing, and fine motor skills) has been shown to benefit from a period of sleep, whether a daytime nap (Fischer et al., 2002; Korman et al., 2003, 2007; Backhaus and Junghanns, 2006; Milner et al., 2006; Nishida and Walker, 2007; Doyon et al., 2009) or overnight sleep (Fischer et al., 2002; Walker et al., 2002; Korman et al., 2003; Peters et al., 2007). Among the most consistent findings in support of the role of sleep in memory consolidation is a series of studies demonstrating a link between procedural memory and stage 2 (Smith and MacNeill, 1994; Fischer et al., 2002; Walker et al., 2003; Fogel and Smith, 2006; Fogel et al., 2007b) and SWS sleep (Huber et al., 2004; Fogel et al., 2007b). Even a short amount of stage 2 sleep from daytime nap was found to be correlated with the delayed gains in performance on a procedural task (Korman et al., 2007). Given that procedural learning is a broadly defined and heterogeneous category, it is important to first distinguish between the types of task demands, in order to understand the link between procedural learning and sleep states. On the one hand, there is evidence that task performance depends more on REM sleep when the task involves the acquisition of entirely new skills or rules, or when individuals are not very proficient during acquisition (Smith and Weeden, 1990; Buchegger et al., 1991; Smith, 1993; Plihal and Born, 1997; Smith and Smith, 2003). On the other hand, procedural learning appears to depend more on stage 2 sleep when the task is cognitively simple and involves the refinement of skills that individuals may have already acquired to some extent (Fischer et al., 2002; Walker et al., 2002; Fogel and Smith, 2006; Fogel et al., 2007b). A number of studies support this hypothesis, originally proposed by Smith et al. (2004). The first direct evidence for this dissociation (Peters et al., 2007) revealed that when subjects were trained on a rotary pursuit procedural task and then subdivided into "high-skill" and "low-skill" groups, post-training spindle density was correlated with performance in the high-skill but not the low-skill group. Conversely, post-training changes in REM density were correlated with performance in the low-skill but not the high-skill group. Although correlational, this dissociation suggests that the type of sleep involved in memory consolidation depends on not only task type or task demands, but perhaps the individual's proficiency on the task.

Further support for this hypothesis comes from deprivation studies showing that stage 2 sleep disruption, but not REM deprivation in the last half of a night's sleep, leads to impaired performance on the pursuit rotor, a simple procedural task (Smith and MacNeill, 1994). In addition, studies investigating the impact of procedural learning on subsequent sleep found increased stage 2 sleep duration following simple procedural learning (Fogel and Smith, 2006; Fogel et al., 2007b). Moreover, sleep spindles in stage 2 sleep increased following simple procedural learning involving gross motor skills (Fogel and Smith, 2006; Fogel et al., 2007b) and motor sequence learning (MSL; Walker et al., 2002). Not only does sleep spindle density increase after performing a simple procedural task, but the morphology of the spindle also changes: sleep spindle amplitude and duration were shown to increase, and the increase in spindle density persisted into SWS (Fogel et al., 2007b). Taken together, these results suggest that the brain responds to simple procedural learning by increasing sleep spindles in a variety of ways, collectively leading to massively increased spindle activity over the course of a night's sleep. These changes are thought to reflect memory consolidation processes during sleep.

Initially, MSL relies on a variety of brain structures, including the cerebellar-cortical and striatal-cortical networks (for a review, see Doyon et al., 2003), and in some cases the hippocampus was found to be involved (Albouy et al., 2008). Once consolidated, procedural memory generally relies on a network of striatal-cortical structures (Doyon et al., 2003, 2009; Doyon and Benali, 2005). It was proposed that sleep spindles play a role in the transfer (or transformation) of information from brain structures involved in learning and in early consolidation of MSL (Walker et al., 2005). A recent study (Barakat et al., 2012) showed that spindle amplitude at frontal regions was correlated with offline gains in performance and changes in activity in the putamen over a sleep interval. These results provide some of the first direct evidence of the neural substrates involved in sleep-dependent MSL consolidation that is specifically related to spindle activity.

The role of sleep in motor adaptation tasks is less clear. While we showed that procedural consolidation was not sleep-dependent (Doyon et al., 2009), Huber et al. (2004) observed increased SWA during sleep after subjects were trained on a more complex motor adaptation task. The increased SWA was circumscribed to a region of the posterior parietal cortex known to be activated by this task (Ghilardi et al., 2000). Motor adaptation task complexity may also explain discrepancies between studies.

THE IMPACT OF AGE-RELATED CHANGES IN SLEEP ON PROCEDURAL MEMORY

Age-related changes in sleep may have a negative impact on sleep-dependent procedural memory consolidation. In support of this hypothesis, Spencer et al. (2007) investigated the effect of a retention period filled with either sleep (or wake) on the performance of implicit and explicit versions of a MSL task in young and older subjects. They found that sleep-dependent gains in performance were observed in young but not in older subjects for both the implicit and explicit task versions of the task. In addition, Brown et al. (2009) has shown that sleep does not provide the same benefit to procedural memory consolidation in older adults as compared to young subjects. More specifically, they used an implicitly learned, cued version of the serial reaction time task to assess MSL for both sequence and random-order versions of

the task. Surprisingly, increased learning was observed in older subjects during the training session as compared to young subjects. However, only young subjects showed gains in performance over an intervening retention sleep period. It is important to note that this result was not attributable to age-related differences in speed or baseline performance. While these two studies suggest that sleep provides a benefit to procedural memory consolidation in young but not in older individuals, the characteristics of sleep were not investigated. A related study by Peters et al. (2008) suggested that age-related changes in sleep spindles were correlated with sleep-dependent procedural memory consolidation in young but not older adults. They found that learning a pursuit rotor task increased sleep spindles in young subjects but not in older subjects. Furthermore, whereas both young and older subjects improved with practice on the pursuit rotor task, the magnitude of the improvement was greater for young subjects when tested 1 week after initial learning, suggesting that young subjects performance was consolidated to a greater extent than older individuals. Better performance in young subjects at acquisition was associated with larger increases in spindle density, but not in older individuals. These results suggest that the age-related reduction in sleep spindles may underlie age-related deficits in procedural memory consolidation, however this hypothesis remains to be directly tested.

CONCLUSION

One of the most marked changes in sleep in elderly populations is a reduction of SW and sleep spindles. NREM sleep oscillations are related to the reactivation of recently learned material, cerebral plasticity, and synaptic homeostasis. We propose that an age-related reduction in sleep-dependent memory consolidation may be due in part to changes in NREM sleep oscillations. Further research is required where NREM sleep oscillations are causally manipulated, to better disentangle the role that sleep spindles and SW have for memory consolidation in older subjects. Spindles and SW are generated by the neural oscillation between hyperpolarized and depolarized phases, believed to play a crucial role in brain plasticity (Steriade, 2006). At present, there is ample evidence to suggest that spindles and SW are involved in the consolidation of both declarative and procedural learning. Thus, it is difficult to conclude whether they serve dissociable roles for different memory systems, or not. Future research should evaluate whether age-related changes in spindles and SW interfere differently with declarative and procedural learning.

ACKNOWLEDGMENTS

Our review is supported by fellowships and salary supports from the Canadian Institutes of Health Research (CIHR) and the Fonds de recherche en Santé du Québec (FRSQ).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 August 2012; accepted: 29 November 2012; published online: 14 December 2012.

Citation: Fogel S, Martin N, Lafortune M, Barakat M, Debas K, Laventure S, Latreille V, Gagnon J-F, Doyon J and Carrier J (2012) NREM sleep oscillations and brain plasticity in aging. Front. Neur. ***3****:176. doi: 10.3389/fneur.2012.00176*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in
NEUROLOGY

MINI REVIEW ARTICLE
published: 02 February 2012
doi: 10.3389/fneur.2012.00008

How aging affects sleep-dependent memory consolidation?

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Memories are not stored as they were initially encoded but rather undergo a gradual reorganization process, termed memory consolidation. Numerous data indicate that sleep plays a major role in this process, notably due to the specific neurochemical environment and the electrophysiological activity observed during the night. Two putative, probably not exclusive, models ("hippocampo-neocortical dialogue" and "synaptic homeostasis hypothesis") have been proposed to explain the beneficial effect of sleep on memory processes. However, all data gathered until now emerged from studies conducted in young subjects. The investigation of the relationships between sleep and memory in older adults has sparked off little interest until recently. Though, aging is characterized by memory impairment, changes in sleep architecture, as well as brain and neurochemical alterations. All these elements suggest that sleep-dependent memory consolidation may be impaired or occurs differently in older adults. This review outlines the mechanisms governing sleep-dependent memory consolidation, and the crucial points of this complex process that may dysfunction and result in impaired memory consolidation in aging.

Keywords: sleep, memory consolidation, aging, episodic memory, procedural memory, slow wave sleep, hippocampus

In humans, sleep is characterized by the cyclic occurrence of two main physiological stages, namely non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. The former is usually subdivided in stage 1, stage 2, and slow wave sleep (SWS, stages 3 and 4) according to sleep depth. A sleep cycle lasts about 90–100 min, but SWS is most abundant during the first half of the night (up to 80% of sleep time), whereas REM sleep prevails in the second half of the night, alternating with stage 2.

Likewise, memory is not a unitary phenomenon but is composed of multiple systems. In this review, we will focus on episodic and procedural memory, the two memory systems that were most investigated in this field. Episodic memory, a subcomponent of declarative memory, supports the encoding, storage, and retrieval of life events set in a specific spatiotemporal context. It relies upon the hippocampus and surrounding cortices, as well as the frontal and parietal cortices (Dickerson and Eichenbaum, 2010 for review). In contrast, procedural memory enables the gradual acquisition of skills through training and is not necessarily accessed consciously (non-declarative memory). This memory system mainly relies on striato-cortical networks (Doyon et al., 2003).

Ample evidence indicates that sleep is a physiological state favoring memory consolidation, the process by which recently acquired and labile memory traces are progressively strengthened into more permanent and/or enhanced forms. We will first see how sleep-dependent memory consolidation occurs in young healthy subjects and then examine the changes that may compromise this process in older adults.

SLEEP-DEPENDENT MEMORY CONSOLIDATION IN YOUNG ADULTS

Over the past two decades, numerous studies have provided evidence that sleep enhances memory consolidation. It has been initially shown that consolidation of declarative/episodic memories is enhanced by early SWS-rich periods of sleep whereas procedural memory rather benefits from late sleep during which REM sleep prevails (e.g., Plihal and Born, 1997). Other authors have pointed out the relevance of the succession of NREM–REM sleep cycles for memory consolidation regardless of the memory system the trace belongs to (Giuditta et al., 1995), potentially reflecting different processes operating on memory traces. Thus, Gais et al. (2000) showed that performance on a procedural visual discrimination task requires REM sleep but also a certain amount of preceding SWS. We also showed a complementary role of REM sleep and SWS in the consolidation of truly episodic memories. Whereas early SWS favors consolidation of the temporal aspects of episodic memories, REM sleep rather supports the consolidation of the spatial characteristics of these memories (i.e., location of words on a paper sheet) and the richness of contextual details (Rauchs et al., 2004). Consolidation of

emotionally laden material also depends on REM sleep (Wagner et al., 2001).

More recently, studies have tried to unravel the electrophysiological substrates that mediate the beneficial effect of sleep on memory consolidation. Three main mechanisms may participate in this complex process of reorganization of memory traces during sleep: hippocampal reactivations, neocortical slow oscillations, and thalamo-cortical sleep spindles.

Using hippocampus-dependent spatial learning tasks in rodents, studies have reported that hippocampal place cells, activated during training, were reactivated in the same sequential order during subsequent periods of sleep (Wilson and McNaughton, 1994). Such neuronal reactivations were mainly observed during SWS (Skaggs and McNaughton, 1996; Kudrimoti et al., 1999) and more rarely during REM sleep (Louie and Wilson, 2001). These re-expressions are not limited to the hippocampus but also occur in the striatum and thalamus (Ribeiro et al., 2004) and in various neocortical areas (Qin et al., 1997; Ji and Wilson, 2007; Peyrache et al., 2009). This phenomenon was also observed in humans. Thus, Peigneux et al. (2004) showed that the hippocampus, activated during a spatial learning task, was reactivated during post-learning SWS. Interestingly, the amount of hippocampal activity during SWS was positively correlated with the overnight improvement of memory performance. More recently, Rasch et al. (2007) showed that reinstating during SWS an odor that was used as a contextual cue during learning, significantly enhanced episodic memory performance. This improvement was mediated by the hippocampus as odor re-exposure during SWS induced hippocampal activation that was even greater than during wakefulness.

Brain oscillations also participate actively in memory consolidation. Spindle density, spindle activity (index reflecting the activity or intensity of the spindle process), and the frequency of hippocampal ripples are increased during post-learning sleep (Fogel and Smith, 2011; Girardeau and Zugaro, 2011 for reviews). Learning experience increases the amplitude and slope of slow oscillations as well as slow wave activity during subsequent sleep (Diekelmann and Born, 2010 for review). These increases are associated to enhanced memory performance (e.g., Huber et al., 2004). In addition, inducing slow oscillation-like potential fields during post-learning sleep with transcranial direct current stimulation increases time spent in SWS, enhances EEG power in the slow oscillation frequency band and in the slow spindle band, and improves retention on an episodic memory task (Marshall et al., 2006).

THE HIPPOCAMPAL–NEOCORTICAL DIALOGUE: A MODEL OF SLEEP-DEPENDENT MEMORY CONSOLIDATION

The different findings cited above are summarized in a model of sleep-dependent consolidation of declarative/episodic memories termed the *hippocampo-neocortical dialogue* (Buzsáki, 1996; **Figure 1A**). Briefly, during wakefulness, freshly learned information is temporarily encoded into neocortical and hippocampal networks. During SWS, memory traces are repeatedly reactivated within hippocampal networks. Reactivations are associated with sharp wave-ripple activity in the hippocampus. They are driven by slow oscillations which synchronize reactivations with the occurrence of thalamo-cortical spindles to drive the transfer of memory traces toward neocortical sites where they will be stored durably. Low levels of cortisol and acetylcholine are required to allow the replay and transfer of information (Diekelmann and Born, 2010). The existence of this process has been demonstrated in rodents (Bontempi et al., 1999) and in humans using fMRI (Takashima et al., 2006). It occurs more so in subjects who slept after learning than in subjects who were sleep-deprived (Gais et al., 2007). With time, the ventromedial prefrontal cortex plays an important role in the retrieval of consolidated memories.

For procedural memories, the mechanism could be very similar, involving however different brain areas such as the striatum and cortico-cerebellar networks (Doyon and Benali, 2005).

Besides this active system consolidation hypothesis, an alternative mechanism has been proposed as the "*synaptic homeostasis hypothesis*" (Tononi and Cirelli, 2006). During wakefulness, encoding of new information leads to an increase in synaptic strength in the brain. Such a state is not sustainable in terms of energy and tissue volume demands, and saturates the capacity of synapses for

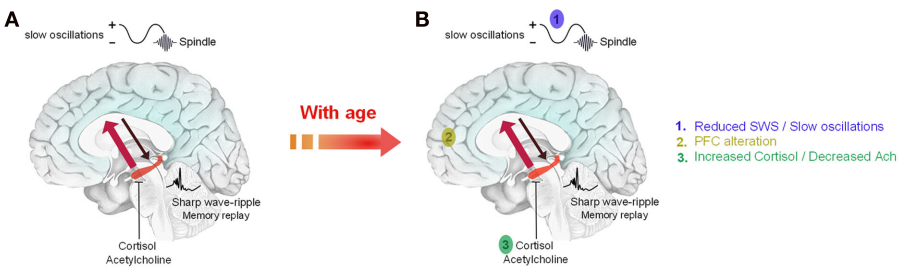

FIGURE 1 | Schematic representation of the possible alteration of sleep-dependent consolidation of declarative memories in older adults. (A) During wakefulness, information is encoded in neocortical and hippocampal networks (black arrow). During SWS, recently acquired information is repeatedly reactivated within hippocampal networks. Reactivations are associated with sharp waves-ripples and are driven by slow oscillations which also synchronize hippocampal memory reactivations with the occurrence of sleep spindles. These reactivations stimulate the transfer of memory traces toward neocortical sites for long term storage (red arrow). This transfer is allowed by low levels of acetylcholine and cortisol during early sleep. **(B)** With age, the decrease in SWS and slow oscillations combined with anatomical and functional changes in memory-related brain areas and neurochemical changes (acetylcholine, cortisol) are likely to explain that sleep-dependent memory consolidation is impaired in older adults. Adapted from Born et al. (2006).

new learning. Sleep, and more precisely slow oscillations, would serve to downscale synaptic strength to a baseline level, keeping nevertheless a difference between synapses that were potentiated during prior waking and those that were not. This hypothesis has found experimental support in animals (Vyazovskiy et al., 2008; Bushey et al., 2011) and in humans (Huber et al., 2004; Van Der Werf et al., 2009).

AGE-RELATED CHANGES IN SLEEP

Sleep is substantially modified with increasing age. Older adults complain of early awakening in the morning and of difficulties to maintain continuous sleep. These difficulties are attested by an increase in the number of arousals during the night leading to sleep fragmentation. Total sleep time decreases, whereas time spent awake during the night or wake after sleep onset increase, thereby decreasing sleep efficiency (i.e., proportion of sleep time compared to time spent in bed). Sleep efficiency declines progressively with age, from approximately 86% at ages 37–54 to 79% over age 70 (Bliwise, 2005). In contrast, the frequency of daytime naps increases with age (Humm, 2001), potentially worsening the disruption of nocturnal sleep.

The most striking change in sleep architecture is the dramatic decrease in time spent in SWS across the adult lifespan. This decline is further accompanied by a reduction in the number and amplitude of slow oscillations (Petit et al., 2004). To a lesser extent, changes of phasic events in stage 2, such as K-complexes and sleep spindles are also observed (Crowley et al., 2002). Changes concerning REM sleep tend to become significant only after age 50. Thus, while the duration of REM sleep episodes increases through the night, it remains constant in older adults (Van Cauter et al., 2000), and the density of REMs is reduced (Darchia et al., 2003). Aging is further characterized by alterations of circadian rhythms (Bliwise, 2005) and reduced melatonin secretion (Pandi-Perumal et al., 2005). These two points may also have an impact on sleep-dependent memory consolidation. Indeed, there is a circadian control of REM, but not of NREM sleep (Dijk and Czeisler, 1995; Dijk et al., 2000). Alterations of circadian rhythms may therefore result in changes in REM sleep. Melatonin is also intimately connected to memory consolidation as melatonin secretion is low during REM sleep (Birkeland, 1982) and high levels of this neurohormone inhibit memory formation during night (Rawashdeh et al., 2007).

SLEEP-DEPENDENT CONSOLIDATION OF MEMORIES IN OLDER ADULTS

Several elements suggest that sleep-dependent memory consolidation is altered with aging. First, older adults complain of memory impairment concerning mainly episodic memory. As mentioned above, consolidation of episodic memories relies upon SWS, which is also significantly reduced in older adults. Furthermore, with age some memory-related areas such as the frontal cortex undergo substantial structural and functional alterations (Kalpouzos et al., 2009). In contrast, the alteration of the hippocampus is more debated. This may be explained by the fact that the effects of age are not homogeneous within the hippocampus but rather concern its posterior part (Kalpouzos et al., 2009). More precisely, Mueller and Weiner (2009) reported a significant volume loss of CA3 (Mueller and Weiner, 2009). Albeit not consistently found (e.g., La Joie et al. (2010) who reported a strong effect of age on the volume of the subiculum only), this point is of particular interest since during SWS, freshly encoded memories are reactivated in the CA3 subfield and then spread back into CA1 and cortical areas for effective consolidation (Hasselmo, 1999). Evidence of impaired hippocampal reactivations after spatial learning has been provided in aged rats compared to young animals (Gerrard et al., 2008). In addition, frontal white-matter tracts are also affected by age and may lead to impaired interactions between the prefrontal cortex and the hippocampus (Salat et al., 2005).

Age-related changes in some neuroendocrine and neuromodulatory systems may likewise have an impact on sleep quality and architecture, and therefore on memory consolidation. Thus, aging is accompanied by a cholinergic hypofunction (Schliebs and Arendt, 2006). Classically, acetylcholine levels are high at the waking state – allowing encoding of new information – and reach a minimum during SWS. The nadir of acetylcholine during early sleep allows the reactivation of memory traces within hippocampal networks and their transfer toward neocortical areas (Hasselmo, 1999; Gais and Born, 2004). Age-related cholinergic hypofunction may not have consequences on SWS-dependent consolidation of declarative memories but could have repercussions on consolidation of procedural memories during REM sleep, during which acetylcholine levels are high. Indeed, cholinergic activation during REM sleep appears to be a critical factor mediating the beneficial effect of sleep on procedural memories (Rasch et al., 2009). Finally, aging is also accompanied by changes in the hypothalamo-pituitary–adrenal axis schematically leading to increases in evening cortisol levels (Buckley and Schatzberg, 2005). As memory consolidation requires low cortisol levels during early sleep (Plihal and Born, 1999) and since the hippocampus contains a high density of cortisol receptors (Roozendaal et al., 2009), elevated glucocorticoid levels may impair hippocampal functioning and impede the hippocampo-neocortical transfer.

All the points mentioned above seem closely interlinked and underline the complexity to assess sleep-dependent memory consolidation in older adults (**Figure 1B**). A handful of studies have been conducted in recent years and have provided mixed results (see also Pace-Schott and Spencer, 2011 for review).

The first studies conducted in healthy older adults (without depressive disorder or dementia) have mainly focused on REM sleep, due to the potential pharmacological modulations by cholinergic agents. Thus, Schredl et al. (2001) revealed positive correlations between overnight improvements on a word-pair recall task and REM sleep augmentation following administration of the cholinesterase inhibitor donepezil before bedtime during six consecutive nights. More recently, Hornung et al. (2007) assessed the effect of various REM sleep manipulations (increase or decrease in time spent in REM sleep) on episodic and procedural memory consolidation. REM sleep suppression was achieved by selective deprivation of this sleep stage. REM sleep augmentation was performed either physiologically through REM sleep rebound after a selective REM sleep deprivation or pharmacologically by administration of donepezil. All these manipulations had no effect on episodic memory. In contrast, only pharmacological REM

sleep augmentation had positive effects on procedural memory consolidation, suggesting that cholinergic activation, more than REM sleep *per se*, is a crucial component of REM sleep memory consolidation in elderly people.

Other studies tried to relate memory performance with sleep stages in healthy older adults, without administration of cholinergic medication. Thus, Mazzoni et al. (1999) reported correlations between recall performance on a word-pair learning task and the mean duration of NREM/REM sleep cycles and the proportion of time spent in cycles, indicating that sleep structure and the cyclic succession of NREM–REM sleep are important for sleep-dependent memory consolidation in older adults. More recently, Backhaus et al. (2007) reported a decline of sleep-dependent consolidation of semantically related word-pairs, associated with a decrease of early nocturnal SWS in 50 years old subjects. Retention of word-pairs after sleep was also positively correlated with the amount of SWS. These results were not replicated with lists of unrelated word-pairs (Wilson et al., in press). Finally, Aly and Moscovitch (2010) showed that memory of stories and personal events in older adults benefited from a night of sleep as much as in young adults. In addition, the number of hours slept was positively correlated with recall performance. The personal relevance of the material is therefore a crucial factor favoring sleep-dependent memory consolidation.

Concerning procedural memory, Spencer et al. (2007) have proposed to young and older adults a serial reaction time task. Performance was assessed after a 12-h interval filled with sleep or wakefulness. Older and young adults showed similar degrees of initial learning. However, performance of older adults did not improve following sleep, indicating that sleep-dependent consolidation is impaired with age. These results were replicated and extended to middle-aged subjects who showed, compared to young adults, a reduced sleep-dependent change in performance (Wilson et al., in press).

In another study, Peters et al. (2008) compared young and older healthy participants on a simple pursuit rotor task. Both age groups exhibited significant improvements after a 1-week delay but the magnitude of this improvement was lower in the older group. Interestingly, spindle density significantly increased after learning in young but not in old subjects. Finally, Tucker et al. (2011) were the only ones to observe, using a motor sequence task (finger-tapping), similar improvements after sleep in young and older adults, although full expression of these improvements was seen later during the retest session in older participants. As reported by Peters et al. (2008), no correlation between overnight improvement and sleep architecture or spindle density was observed in the elderly group.

Overall, studies conducted in older adults have provided mixed results, especially for declarative memory. While one may logically expect an impaired consolidation of declarative memories during early sleep, due to the dramatic decrease in SWS, this result was not consistently found. Qualitative differences between tasks may influence sleep's effect on memory processing. Further studies are needed to better understand the effects of age. As for procedural memory, studies report that sleep-dependent consolidation is impaired, or that the magnitude of overnight changes in performance is reduced or that the behavioral expression of consolidation is delayed compared to young adults. The reduction of cholinergic activation during REM sleep during aging is one of the mechanisms likely to account for these quantitative or qualitative changes in memory performance.

CONCLUSION AND FUTURE DIRECTIONS

Over the past 20 years, a plethora of studies have shown that sleep benefits memory consolidation in young healthy subjects. In older adults, several factors closely interlinked (decrease in SWS and slow oscillations, hypofunctioning and atrophy of frontal areas, reduction of the cholinergic tone, etc.) appear to hamper memory consolidation during sleep. Even if this field of research has sparked renewed interest during the last 5 years, some questions remain unanswered. In particular, studies combining sleep recordings, memory consolidation assessment, and functional neuroimaging acquisitions are needed to determine which brain areas will subserve the reorganization of memory traces during sleep and compensate for the frontal dysfunction. Studies in healthy older adults are also a prerequisite to understand how sleep-dependent memory consolidation is disrupted in neurological diseases such as Alzheimer's disease. Indeed, we observed in patients with mild Alzheimer's disease a specific decrease in the number and intensity of fast spindles (Rauchs et al., 2008) as well as a faster mean theta frequency during SWS (Hot et al., 2011). Both parameters were positively correlated with episodic memory performance confirming the deleterious impact of sleep changes on memory function and the existence of compensatory mechanisms in the early stages of the disease to maintain, albeit inefficiently, memory performance.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 07 November 2011; accepted: 10 January 2012; published online: 02 February 2012.

Citation: Harand C, Bertran F, Doidy F, Guénolé F, Desgranges B, Eustache F and Rauchs G (2012) How aging affects sleep-dependent memory consolidation? Front. Neur. ***3****:8. doi: 10.3389/fneur.2012.00008 This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.*

frontiers in
NEUROLOGY

MINI REVIEW ARTICLE
published: 29 May 2012
doi: 10.3389/fneur.2012.00087

Sleep apnea syndrome and cognition

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Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive episodes of airflow cessation resulting in brief arousals and intermittent hypoxemia. Several studies have documented significant daytime cognitive and behavioral dysfunction that seems to extend beyond that associated with simple sleepiness and that persists in some patients after therapeutic intervention. A still unanswered question is whether cognitive symptoms in OSA are primarily a consequence of sleep fragmentation and hypoxemia, or whether they coexist independently from OSA. Moreover, very little is known about OSA effects on cognitive performances in the elderly in whom an increased prevalence of OSA is present. In this review we will consider recent reports in the association between sleep apnea and cognition, with specific interest in elderly subjects, in whom sleep disturbances and age-related cognitive decline naturally occur. This will allow us to elucidate the behavioral and cognitive functions in OSA patients and to gain insight into age differences in the cognitive impairment. Clinically, these outcomes will aid clinicians in the evaluation of diurnal consequences of OSA and the need to propose early treatment.

Keywords: obstructive sleep apnea, hypoxemia, sleep fragmentation, sleepiness, cognitive functions, elderly

INTRODUCTION

Previous studies investigating the effects of obstructive sleep apnea (OSA) on alertness and cognitive functions have demonstrated that apnea recurrence, sleep fragmentation, and nocturnal hypoxemia may affect diurnal behavior, cognitive function, and well-being in these patients. A wide range of cognitive impairment has been identified in OSA patients, from attention and vigilance to memory and executive functions (Jackson et al., 2011). A still controversial point is which factor is mainly responsible for the cognitive impairment, given that up to now all considered factors, i.e., sleep fragmentation, sleepiness, apnea + hypopnea index (AHI), and hypoxemia, showed weak correlation with cognitive scores. Moreover, standard measures used in the clinical setting do not provide a reliable assessment of cognitive dysfunction, particularly in elderly subjects in whom it is difficult to differentiate between the age-related cognitive decline and the OSA-related impairment.

In this review, current knowledge about the type of cognitive dysfunction and the mechanisms underlying cognitive impairment are reviewed. Then we summarize what is know about cognitive dysfunction in the elderly in whom conflicting results are reported in the literature. These controversial data open discussion on the effect of therapy on cognitive dysfunction.

INCIDENCE OF SLEEP APNEA SYNDROME

Previous studies on sleep-related breathing disorders have focused on OSA to indicate a clinical entity characterized by repetitive episodes of complete or partial upper airway obstruction during sleep, inducing falls in oxygen saturation, and hypercapnia. To restore pharyngeal patency, patients have recurrent arousals from sleep, inducing sleep fragmentation and sleep discontinuity. The nocturnal hypoxemia and the recurrent arousals contribute to the development of sleepiness, hypertension, and cognitive impairment. Several factors increase the OSA risk such as genetic predisposition, obesity, upper airways shape (Pillar et al., 2000), craniofacial morphology (Schellenberg et al., 2000), hormonal influences (Bixler et al., 2001), and APOE4 phenotype. (Gottlieb et al., 2004)

Prevalence studies conducted over the past decades (Young et al., 1993; Quan et al., 1997; Bixler et al., 2001) have demonstrated that up to 5% of adults in Western countries are likely to have undiagnosed OSA. When we consider the severity of the disease stratified according to an AHI ≥ 5 and an AHI ≥ 15, the prevalence is from 3 to 28% for mildly severe cases (AHI > 5) and from 1 to 14% for moderately severe cases (AHI > 15). Results of cohorts in Wisconsin (1490 subjects; Young et al., 1993), Pennsylvania (932 subjects; Bixler et al., 1998, 2001), Spain (455 subjects; Duran et al., 2001), and from the Sleep Heart Health Study (6642 subjects; Quan et al., 1997) have demonstrated that 1 in every five adults has at least an AHI > 5 and 1 in every 15 has at least an AHI > 15. In community-dwelling older adults (age 65–95 years), 81% of participants had an AHI > 5, with prevalence rates of 62% for an AHI > 10, 44% for an AHI > 20, and 24% for an AHI > 40 (Ancoli-Israel et al., 1991). Furthermore, in about 6000 older adults aged 63.5 years examined in the Sleep Heart Health study (Young et al., 2002) the authors found that in subjects aged 60–69 years, 32% had an AHI between 5 and 14, and 19% an AHI > 15. The rising trend in elderly subjects may be explained by changes in the anatomy or function of the upper airway (Eikermann et al., 2007) or by the coexistence of other medical disorders, i.e., diabetes, hypertension, and cardiovascular disease. However, recent data suggest that in the elderly, the cut-off point of an AHI of 5 or 10 (Ancoli-Israel and Coy, 1994) is a less sensitive marker in distinguishing subjects with or without OSA, an

AHI ≤ 15 being present in the majority of healthy elderly subjects (Pavlova et al., 2008). This would support the hypothesis (Bliwise, 1994; Bixler et al., 1998; Pavlova et al., 2008; Lavie and Lavie, 2009) that the presence of a greater AHI in the older population may reflect either an age-related or an age-dependent disease, the first inducing the typical OSA symptoms, and the second having fewer clinical consequences.

COGNITIVE PERFORMANCE AND OSA

Despite differences in the definition of OSA syndrome, several studies suggest that apnea recurrence, sleep fragmentation, daytime sleepiness, and nocturnal hypoxemia may induce an impaired cognitive function in OSA patients (Kim et al., 1997; Engleman and Joffe, 1999; Engleman et al., 2000; Adams et al., 2001) affecting attention, vigilance, memory, psychomotor performance, and executive function (Beebe et al., 2003; Aloia et al., 2004; Jackson et al., 2011). However, the presence and the extent of the cognitive changes in OSA subjects is still a matter of debate, the cognitive impairment worsening with disease severity but not linearly (Bedard et al., 1991; Boland et al., 2002). One study stresses that although sleepiness and hypoxemia might cause the neuropsychological deficits in OSA patients, the co-morbidities usually observed in these patients, i.e., cardiovascular diseases, obesity, physical inactivity, are more important than sleep apnea *per se* in affecting neurocognitive functions (Lim and Veasey, 2010). Finally, we have to consider that there is a large heterogeneity in the neuropsychological tests used in OSA patients making it difficult to compare the results (Décary et al., 2000).

Bearing in mind these limitations, in recent years special interest has focused on impairments of executive function that refer to the ability to develop and sustain an organized goal-directed and flexible approach to problem situations and to allow individuals to use adaptively their basic skills in a complex and changing external environment. This domain could be examined by tests demanding working memory, mental flexibility, planning, organization, and problem solving (Fulda and Schulz, 2001; Saunamaki and Jehkonen, 2007), tasks related to prefrontal cortex activity (Beebe and Gozal, 2002). Results of studies on cognitive function in OSA are heterogeneous, some studies suggesting an executive dysfunction (Bedard et al., 1991; Naëgele et al., 1995; Boland et al., 2002; Ferini-Strambi et al., 2003; Lis et al., 2008; Torelli et al., 2011), and others an attentional impairment (Redline et al., 1997; Lee et al., 1999; Salorio et al., 2002; Verstraeten and Cludydts, 2004; Gosselin et al., 2006; Yaouhi et al., 2009; Quan et al., 2011). The controversial results may be partially explained by the severity of the disease, a minor cognitive impairment present in mild cases (Redline et al., 1997; Gosselin et al., 2006; Lis et al., 2008) and a greater deficit particularly in terms of executive function (Naëgele et al., 1995; Ferini-Strambi et al., 2003; Aloia et al., 2004) in severe cases (AHI circa 50).

In some studies supporting an executive dysfunction, performance deficits are not only reported in executive tests but in all examined cognitive abilities, (Naëgele et al., 1995; Feuerstein et al., 1997; Boland et al., 2002) suggesting a global cognitive impairment. As suggested by Verstraeten and Cludydts (2004), a methodological bias in the assessment of executive function is the lack of control of attention performances during the task, OSA patients showing a decline in the ability to sustain attention (Dinges and Kribbs, 1991) and having alertness instability (Doran et al., 2001). These two factors influence their performance. To overcome this limitation, two studies (Naëgelé et al., 2006; Lis et al., 2008) performed a combined evaluation of the executive function and alertness, measuring both n-back task and reaction time performances. Naëgelé et al. (2006) found that the untreated OSA group did not differ from the control group on dual tasks, e.g., combined auditory and visual digit span, that measure attentional resources. In contrast, they differ in the maintenance and processing components of working memory, suggesting that OSA subjects have difficulties in the processing of new information without attention deficit. In contrast, Lis and coworkers (Lis et al., 2008) performing a combined evaluation of executive function (i.e., repeated working memory), and alertness (i.e., repeated reaction time and subjective and objective sleepiness assessment), found a decline in reaction time on all tasks and a lowered accuracy only in the n-back test, suggesting a deficit in attention and more basic cognitive processes.

In terms of memory, studies in middle-aged patients (Salorio et al., 2002; Naëgelé et al., 2006; Yaouhi et al., 2009) found a minor impairment in word list learning and slightly decreased recall in a visual episodic memory task. Naëgelé et al. (2006) observed a free recall deficit in episodic memory but normal maintenance and recognition, confirming that the memory impairment in OSA is mild (Fulda and Schulz, 2001) and does not affect all memory processes (Naëgele et al., 1995; Salorio et al., 2002; Naëgelé et al., 2006).

EFFECTS OF TREATMENT

The current treatment of choice in OSA patients is the continuous positive airway pressure (CPAP) inducing a significant improvement in daytime sleepiness (Engleman et al., 1996), a reduction in occupational, work, and road accidents (Cassel et al., 1996) as well as an improvement in general health (Reimer and Flemons, 1999; Sanner et al., 2000; Barbé et al., 2001; McFadyen et al., 2001). When we consider the effect of CPAP on the cognitive function, we can see that while some deficits can be improved by therapy, other domains such as executive function remain unchanged (Matthews and Aloia, 2011). To exclude the effect of an insufficient treatment, Weaver et al. (2007) examined patients before and after CPAP therapy considering the objective adherence to treatment. They found that, even among patients using CPAP for more than 7 h per night, only 30% of these patients had a normalization of objective sleepiness and only 50% had normal results on the Functional Outcome of Sleep questionnaire. Zimmermann et al. (1996) studied verbal memory changes in 58 memory-impaired OSA patients after 3 months of CPAP therapy. They found a dose-response relationship between the level of CPAP adherence and the extent of improvement in verbal memory with, however, a third of the patients with 6 h adherence not showing any improvement. Similar data were reported by Antic et al. (2011) and Lau et al. (2010) confirming that even the most optimally treated OSA patients may not experience a complete reversal in attention and executive function, probably due to a permanent brain alteration in severe cases (Bedard et al., 1993; Naëgele et al., 1995; Feuerstein et al., 1997; Ferini-Strambi et al., 2003).

PATHOGENESIS OF COGNITIVE IMPAIRMENT

In large epidemiological studies (Kim et al., 1997; Boland et al., 2002) analyzing memory and cognitive and psychomotor functions, some authors found that OSA severity, as indicated by the AHI, was significantly related to diminished psychomotor efficiency with, however, a weak correlation. Similar findings were described in the Danish MONICA study cohort comprising of 848 participants (Jennum and Sjol, 1994) in that an AHI > 5 was associated with self-assessed concentration problems but not with memory impairment. Today there is general agreement that not apnea recurrence in itself, but the associated sleep fragmentation and nocturnal hypoxemia, are the key factors affecting cognitive function in patients with OSA (Bedard et al., 1991; Redline et al., 1997; Engleman and Joffe, 1999; Daurat et al., 2008). This hypothesis has been confirmed by animal studies showing that both intermittent hypoxia (Kalaria et al., 2004; Xu et al., 2004) and sleep fragmentation (Tung et al., 2005; Nair et al., 2011), two essential features of the OSA syndrome, can independently lead to neuronal loss in the hippocampus and prefrontal cortex, areas closely associated with memory processes and executive functions.

According to Beebe and Gozal (2002), the prefrontal cortex is selectively susceptible to both sleep deprivation and hypoxemia. The prefrontal cortex may exert modulatory influences on lower-level processes sub-served by posterior cortical regions (Knight et al., 1999) that have biological vulnerability to sleep loss and sleep fragmentation (Horne, 1993, 1998; Thomas et al., 2000). Moreover, attention control is believed to rely on the prefrontal cortex and its interaction with the thalamus that we know is implicated in alertness, vigilance and selective and sustained attention (Portas et al., 1998; Jones and Harrison, 2001). If so, a combined deficit in executive and attention skills is to be expected in OSA patients. It might be suggested that at the beginning of the disease when patients are asymptomatic or showing minimal cognitive impairment, a chemical and dysfunctional brain injury could occur, reflected in increased compensatory frontal activation during executive tasks. During the progression of the disease, the chronic recurrence of apneas and the progressive worsening of the hypoxemic stimulus will induce structural brain lesions, explaining the greater cognitive alteration, the impairment of executive tasks, and the lack of cognitive normalization after treatment.

ROLE OF SLEEPINESS AND SLEEP FRAGMENTATION

Experimental reports (Dinges and Kribbs, 1991; Dinges et al., 1997; McCoy and Strecher, 2011) in healthy subjects assumed that cognition varies in parallel with changes in alertness, supporting the hypothesis that sleepiness is the major factor underlying performance impairment. However, when we consider OSA patients, there is no linear relationship between the degree of sleepiness and cognitive impairment, suggesting that in these patients cognitive impairment is related more to an instability state (Doran et al., 2001) acting on vigilance and attention than on executive dysfunction (Verstraeten and Cludydts, 2004). Moreover, OSA patients without notable cognitive impairment have been found in approximately half of a non-clinical population (Quan et al., 2006) as well as in an elderly community population (Bixler et al., 1998; Sforza et al., 2010), suggesting that there are some factors protecting OSA patients from substantial cognitive deficits (Beebe et al., 2003). These factors include sleep deprivation tolerance (Mu et al., 2005) and cognitive reserve that allow sleep-deprived subjects (Drummond et al., 2005) or patients (Stern, 2002; Alchanatis et al., 2005) to maintain intact performances. The hypothesis of a reserve brain activation has been confirmed by functional imaging studies (fMRI) using cognitive tasks (Thomas et al., 2005; Ayalon et al., 2006a, 2009a,b; Castronovo et al., 2009; Yaouhi et al., 2009; Zhang et al., 2011) showing a decrease in frontal cortex metabolism in the resting condition and an increase in neural activation in frontal lobe, cingulate, thalamus, and hippocampus during task activation.

ROLE OF HYPOXEMIA

From large population studies (Telakivi et al., 1988; Jennum and Sjol, 1994; Kim et al., 1997; Redline et al., 1997; Horne, 1998; Engleman and Joffe, 1999; Adams et al., 2001; Beebe and Gozal, 2002) it would seem that, while the excessive daytime sleepiness and sleep fragmentation influences attention, the hypoxemia contributes to frontal impairment, and executive dysfunction. Using an experimental model of OSA (Gozal et al., 2001) in rats exposed for 2 weeks to intermittent hypoxia, the authors found a neuronal loss or apoptosis indicating a greater vulnerability of the frontal lobe to hypoxemia. Moreover, Mc Coy et al. (2010) recently showed an impaired allocation of attentional resources in rats exposed one week to intermittent hypoxia. Since frontal lobes have dense connections to other cortical areas (Fulda and Schulz, 2001; Beebe and Gozal, 2002) the primary frontal dysfunction will progressively affect other brain regions, inducing more complex cognitive dysfunction. If so, the persistence of a neuropsychological deficit after CPAP (Bedard et al., 1993; Zimmermann et al., 1996; Lau et al., 2010; Antic et al., 2011; Matthews and Aloia, 2011) may be explained. However, if hypoxemia alone may explain the cognitive dysfunction in severe cases, in mildly affected patients (Redline et al., 1997; Lim and Veasey, 2010) the interacting effect of cognitive reserve (McCoy and Strecher, 2011), intelligence level (Quan et al., 2006), and depression (Sachs-Ericsson et al., 2005; Cross et al., 2008) needs to be considered.

NEUROIMAGING DATA

Within the past decade, the growing prevalence of functional neuroimaging studies has induced an increased interest in the association between OSA and cognition and has opened a new window on the role of cerebral metabolic and circulatory impairment in neuropsychological dysfunction. Routine neuroimaging studies (MRI) in OSA patients have reported inconsistent findings (Davies et al., 2001) or silent vascular lesions (O'Donoghue et al., 2005; Nishibayashi et al., 2008) suggesting a general brain impairment. Voxel-based morphometry (Macey et al., 2002, 2008) have demonstrated a gray matter reduction in brain regions that regulate memory and executive functions, i.e., cingulum, frontal, parietal and temporal areas, and hippocampus. More sensitive techniques (Zimmermann and Aloia, 2006) such as spectroscopy (Kamba et al., 1997; O'Donoghue et al., 2012), functional MRI (Canessa et al., 2011), or positron emission tomography (PET; Morrell et al., 2003) have revealed functional alterations in specific brain areas implicated in cognitive function and affecting the prefrontal and the parieto-occipital cortex (Yaouhi et al., 2009) and

the hippocampus (Torelli et al., 2011), the latter critical for memory. Interestingly, in the Yaouhi et al. (2009) study, the authors found that gray matter density and metabolic levels were altered even in patients without cognitive disturbances, suggesting that cerebral changes precede the onset of neuropsychological deficits. Canessa et al. (2011) performed a neuropsychological testing and voxel-based morphometry in 17 severely affected patients before and after 3-months of CPAP treatment. Prior to treatment the patients had poorer performances in some cognitive tests and a reduction of gray matter volume in the hippocampus, parietal cortex and frontal areas. After treatment there was an improvement in memory, attention and executive functions that paralleled the gray matter increase in the hippocampus and frontal areas, without, however, a complete normalization both in cognitive function and gray matter density. In contrast, a recent study using magnetic resonance spectroscopy (O'Donoghue et al., 2012) shows that OSA patients had decreased metabolic activity in the frontal lobe and hippocampus that did not correlate with cognitive scores and did not change after 6 months of CPAP therapy.

To date, any significant relationship between cognitive scores and brain morphological alteration has been reported, except for a slight association between hippocampal gray matter decrease, and memory dysfunction (Yaouhi et al., 2009) and the gray matter increase in the left entorhinal cortex in patients showing a reduction of errors at the Stroop test (Canessa et al., 2011). The lack of significant relationship between morphological changes and neuropsychological scores may be explained by the interplay of compensatory mechanisms reflected by the increased activation of frontal areas and hippocampus in fMRI and PET studies (Castronovo et al., 2009; Yaouhi et al., 2009).

COGNITIVE FUNCTION IN ELDERLY OSA SUBJECTS

Although several studies have shown that the prevalence of OSA increases with age (Bixler et al., 1998, 2001; Young et al., 2002) there is debate as to whether OSA phenotype in older adults is equal to that in middle-aged patients (Ancoli-Israel et al., 1991; Phillips et al., 1992; Bliwise, 1994; Young, 1996) and whether the aging *per se* increases the susceptibility to cognitive dysfunction (Alchanatis et al., 2008; Mathieu et al., 2008). A first epidemiological survey (Boland et al., 2002) has not revealed any evidence of a dose-response relationship between the respiratory disturbance index and cognitive function score in a cohort of 837 men and 923 women over 60 years old. Studies performed on sleep clinic patients have given conflicting results, some authors reporting a relationship between cognitive impairment and OSA (Kim et al., 1997; Cohen-Zion et al., 2001) in older patients, while others do not (Phillips et al., 1992). Severity of the disease seems to play a key role in cognitive deficit, older patients being more likely to have a cognitive deficit in attention and executive function when the AHI is greater than 30 (Aloia et al., 2004). In a prospective study conducted on 289 women aged 82 with mild cognitive impairment and dementia (Yaffe et al., 2011) the authors demonstrated that older OSA women had an increased risk of developing mild cognitive impairment or dementia after 5 years, stressing the key role of OSA in the increased cognitive risk. When treated, patients without (Aloia et al., 2003) or with mild dementia (Ancoli-Israel and Coy, 1994; Ayalon et al., 2006b; Ancoli-Israel et al., 2008; Cooke et al., 2009) have a slower cognitive deterioration and sometimes even an improvement thus stressing the link between cognitive decline and OSA.

To explain the link between cognitive decline and OSA in the elderly, an emerging hypothesis is that the chronic intermittent hypoxemia observed in OSA patients might be seen as a factor which expedites the effects of other conditions, particularly aging, that are known to cause brain atrophy or damage in the prefrontal cortex and hippocampus. Ayalon et al. (2010) demonstrate that the presence of OSA accelerates the age-related decline in cognitive performances in middle-aged patients (>45 years) showing a decreased activation of the frontal gyrus, hippocampus, and parietal lobe during a sustained attention and a verbal encoding task. These results are supported by a morphological study (Torelli et al., 2011) showing a correlation between age and volumes of the total and left hippocampus, amygdale, and brain parenchyma in OSA patients. If the presence of OSA can be seen as a factor which accelerates the process of brain aging, an early treatment should be proposed (Pack and Maislin, 2001; Ancoli-Israel, 2007) to prevent or to slow the cognitive deterioration (Cohen-Zion et al., 2001).

In summary, the connection between OSA and cognition, the increase of OSA risk in general population and the increasing aging population underline the need of further studies on the risk of development of a cognitive impairment in OSA patients and on the long-term effect of therapy on the age-related cognitive decline.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 19 November 2011; paper pending published: 15 March 2012; accepted: 07 May 2012; published online: 29 May 2012.

Citation: Sforza E and Roche F (2012) Sleep apnea syndrome and cognition. Front. Neur. ***3****:87. doi: 10.3389/fneur.2012.00087*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in
NEUROLOGY

MINI REVIEW ARTICLE
published: 17 May 2012
doi: 10.3389/fneur.2012.00082

Cognition in rapid eye movement sleep behavior disorder

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Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by excessive muscle activity and undesirable motor events during REM sleep. RBD occurs in approximately 0.5% of the general population, with a higher prevalence in older men. RBD is a frequent feature of dementia with Lewy bodies (DLB), but is only rarely reported in Alzheimer's disease. RBD is also a risk factor for α-synuclein-related diseases, such as DLB, Parkinson's disease (PD), and multiple system atrophy. Therefore, RBD has major implications for the diagnosis and treatment of neurodegenerative disorders and for understanding specific neurodegeneration patterns. Several markers of neurodegeneration have been identified in RBD, including cognitive impairments such as deficits in attention, executive functions, learning capacities, and visuospatial abilities. Approximately 50% of RBD patients present mild cognitive impairment. Moreover, RBD is also associated with cognitive decline in PD.

Keywords: sleep, cognition, elderly, REM sleep behavior disorder, mild cognitive impairment, Parkinson's disease, dementia with Lewy bodies

DESCRIPTION OF RBD

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by the presence of undesirable and often violent motor manifestations during REM sleep, such as laughing, shouting, reaching, gesturing, arm flailing, punching, kicking, sitting up, or leaping out of bed (Schenck et al., 1986). These behaviors are generally associated with dream contents: individuals appear to act out their dreams. The violent nature of some dream-enactment behaviors may cause severe injury to individuals with RBD or their bed partners (Schenck et al., 2009). RBD generally affects adults aged 50 years and over, with an estimated prevalence of about 0.5% in the general population (Ohayon et al., 1997). This rate may increase to about 7% in people aged 70 and over (Boot et al., 2012). RBD is predominantly reported in men, at a proportion of around 85% (Bodkin and Schenck, 2009). The reasons for this gender disproportion remain unclear (selection bias or a biological effect).

In normal individuals, muscular activity during REM sleep is suppressed (atonia). In RBD, the mechanisms responsible for atonia are altered, causing abnormally excessive chin or limb electromyographic activity during REM sleep (Montplaisir et al., 2010). This leads to the vigorous behavioral manifestations reported by patients and relatives, which can also be seen on infrared videotape in a sleep laboratory. The RBD diagnosis is confirmed by polysomnographic recording, including analyses of electromyographic activity during REM sleep (American Academy of Sleep Medicine, 2005). Polysomnographic recording has the additional advantage of eliminating other sleep disorders that are confused with RBD, such as somnambulism or moderate to severe sleep apneas. Questionnaires are also available for assessing clinical RBD (Li et al., 2010; Boeve et al., 2011). For treatment of RBD symptoms, clonazepam and melatonin are the two most commonly used pharmacological agents (Gagnon et al., 2006a; Aurora et al., 2010). Changing the sleep environment is also recommended to prevent injuries to the patient and the bed partner. Although the pathophysiology of RBD in humans is still debated, anomalies in the pontomedullary brainstem neural networks responsible for the suppression of muscle tone during REM sleep (i.e., the sublaterodorsal nucleus or coeruleus/subcoeruleus complex) are strongly suspected (Boeve et al., 2007; Luppi et al., 2011).

RBD SUBTYPES

There are different forms of RBD. The acute form is triggered by certain psychotropic drugs (pharmacology-induced RBD), such as antidepressants (Gagnon et al., 2006a). RBD is also strongly associated with certain neurological disorders (symptomatic RBD), including narcolepsy, Machado–Joseph disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, and Guillain–Barre syndrome (Gagnon et al., 2006b; Iranzo et al., 2009). Symptomatic RBD can also be induced by focal lesions (vascular or inflammatory), tumors, or neurodegenerative processes in brainstem regions responsible for normal REM sleep muscle atonia (Gagnon et al., 2006b; Iranzo et al., 2009; Limousin et al., 2009). In fact, RBD is very frequent in synucleinopathies, a class of neurodegenerative diseases characterized by abnormal deposition of α-synuclein proteins. For instance, RBD affects about 33–46% of patients with Parkinson's disease (PD; Gagnon et al., 2002; Sixel-Döring et al., 2011), 75% of patients with dementia with Lewy bodies (DLB; Ferman et al., 2011), and almost 100% of patients with multiple system atrophy (MSA; Vetrugno et al., 2004). Synucleinopathies share a common brainstem neurodegeneration with RBD, which may explain their strong association. On the other hand, RBD is rare in tau-related diseases such as Alzheimer's disease (AD), progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia (Gagnon et al., 2006b; Iranzo et al., 2009). RBD is therefore a useful feature to consider for differential diagnosis between DLB and AD. In fact, inclusion of RBD as a core clinical feature improves the DLB diagnosis accuracy (Ferman

et al., 2011). Finally, RBD can appear alone ("idiopathic" RBD or iRBD) without any associated condition (Gagnon et al., 2006b; Iranzo et al., 2009). However, the term "idiopathic" is subject to challenge because iRBD may be a risk factor for synucleinopathies (Fantini et al., 2005; Ferini-Strambi, 2011).

"IDIOPATHIC" RBD AS A RISK FACTOR FOR SYNUCLEINOPATHIES

Three longitudinal studies performed in a sleep disorders center found that RBD is a significant risk factor for developing synucleinopathies. Schenck et al. (1996) reported in 29 iRBD patients that 38% had parkinsonism 3.7 years after RBD diagnosis. Another study in 44 iRBD patients found that 36% developed a synucleinopathy 5.1 years following RBD diagnosis (Iranzo et al., 2006). Of the converted patients, 56% developed PD, 38% DLB, and one patient developed MSA. Four additional patients with iRBD met the criteria for mild cognitive impairment (MCI) at follow-up. In 2009, our group published the follow-up results on a large cohort of 93 patients with iRBD: 28% developed a neurodegenerative disease 4.8 years following RBD diagnosis (Postuma et al., 2009a). Of the diseased patients, 54% developed PD, 42% DLB, and one patient developed MSA. Using a life table (survival) analysis, the risk for developing a synucleinopathy in iRBD patients was estimated at 18% after 5 years, 41% after 10 years, and 52% after 12 years (Postuma et al., 2009a).

In the only population-based study to date, Boot et al. (2012) followed 651 cognitively intact participants, including 44 individuals with baseline clinical iRBD. After a median of 3.8 years, only 2% of iRBD patients developed PD, whereas 32% met MCI criteria. Although the conversion rate was far lower than in previous clinical studies, the iRBD patients had a 2.2-fold increased risk of developing MCI or PD over non-RBD patients. A potential explanation for the link between RBD symptoms and the development of synucleinopathies comes from studies on the pathological progression of synucleinopathies (Braak et al., 2003; Halliday et al., 2011). In the first stages, before clinical motor symptoms appear, Lewy bodies and Lewy neuritis can be found in brainstem areas involved in RBD pathophysiology. The gradual progression of the neurodegeneration to more rostral brain structures would subsequently cause symptoms characteristic of synucleinopathies. This may explain why RBD is an early symptom in certain patients with synucleinopathies. These results show the importance of performing neurological and neuropsychological assessments to detect early signs of a synucleinopathy or MCI in iRBD patients, particularly for those referred to a sleep disorders center.

MARKERS OF NEURODEGENERATION IN "IDIOPATHIC" RBD

Several markers of synucleinopathies have been identified in iRBD. Recent studies have reported that the severity of the loss of REM sleep muscle atonia (Postuma et al., 2010), olfaction and color vision impairments (Postuma et al., 2011a), substantia nigra hyperechogenicity, and decreased striatal dopamine transporters uptake (Iranzo et al., 2010a) can predict the development of synucleinopathies in iRBD (Postuma et al., 2011b). Other studies have found cognitive (Ferini-Strambi et al., 2004; Gagnon et al., 2009), subtle motor (Postuma et al., 2009b), waking EEG (Fantini et al., 2003), autonomic (Miyamoto et al., 2006; Postuma et al., 2009b), and functional and structural neuroimaging (Unger et al., 2010; Hanyu et al., 2011; Scherfler et al., 2011; Vendette et al., 2011) anomalies in iRBD, similar to those reported in synucleinopathies (Gagnon et al., 2006b; Postuma et al., 2011b).

COGNITIVE DECLINE IN RBD

POOR COGNITIVE PERFORMANCE IN "IDIOPATHIC" RBD

Increasing evidence shows that iRBD patients perform poorly on neuropsychological tests (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009; Marques et al., 2010; Fantini et al., 2011). However, results vary across studies depending on which cognitive domain is impaired (**Table 1**). Population heterogeneity, small sample size, and the use of different cognitive tasks with variable sensitivity to detect deficits and variable specificity to a cognitive domain may explain these discrepancies. In general, attention, executive functions, episodic verbal memory (mainly free recall capacities), and non-verbal learning are the most affected domains in iRBD (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009; Marques et al., 2010; Fantini et al., 2011). Additionally, some studies reported in iRBD anomalies in visuospatial/visuoperceptive abilities (Ferini-Strambi et al., 2004; Iranzo et al., 2010b; Marques et al., 2010; Fantini et al., 2011), but this remains controversial (Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009). In fact, the presence of visuospatial (or non-verbal learning) impairment appears to be related to the extent of cognitive decline in iRBD patients (Iranzo et al., 2006; Molano et al., 2010; Fantini et al., 2011), as reported in RBD-associated neurodegenerative diseases such as PD or DLB (Ferman et al., 2002; Gagnon et al., 2009). On the other hand, language and praxis appear to be well preserved in iRBD, although these functions have received little research attention.

Table 1 | Controlled studies on cognitive performance in "idiopathic" rapid eye movement sleep behavior disorder.

Cognitive domains	Terzaghi et al. (2008)	Massicotte-Marquez et al. (2008)[a]	Gagnon et al. (2009)[a]	Marques et al. (2010)	Ferini-Strambi et al. (2004)[b]	Fantini et al. (2011)[b]
Attention/executive functions	Yes	Yes	Yes	Yes	Yes	No
Verbal episodic memory	Yes	Yes	Yes	Yes	Yes	Yes
Non-verbal memory	Yes	–	–	–	Yes	Yes
Visuospatial abilities	No	No	No	Yes	Yes	Yes

[a,b] *Share common participants; Yes = patients show poorer performance than controls ($p < 0.05$); No = similar performance between patients and controls.*

Box 1 | Case report.

Mister X is a 62-year-old man referred to a memory clinic for cognitive assessment. He complains about his reduced abilities to concentrate and recall information. The scan is normal. No vascular risk factors or major psychiatric symptoms are found. The neuropsychological exam shows mild deficits in cognitive tests assessing attention and episodic verbal memory (affected free recall capacities with preserved recognition). Daily life activities are reported as satisfactorily accomplished. Based on this clinical profile, Mister X meets the criteria for mild cognitive impairment. When questioned about his sleep, he reports the presence of violent behaviors associated with vivid dreams. His wife confirms this and reports that she sleeps in a separate bed to avoid potential injury. Mister X is referred to a sleep disorders center to confirm a diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD). The polysomnographic recording shows excessive chin muscle tone during REM sleep with no other anomalies. When these results are combined with the reports of dream-enactment behaviors, Mister X meets the RBD diagnosis criteria. Unfortunately, subsequent assessments at the memory clinic reveal cognitive decline, particularly in executive functions and visuospatial abilities. In addition, at the last visit, the patient reports a significant impact of the cognitive impairment on his daily life activities and shows signs of parkinsonism. The diagnosis of probable dementia with Lewy bodies is confirmed.

MCI IN "IDIOPATHIC" RBD

Mild cognitive impairment is known to be an intermediate state between normal cognitive functioning and dementia (Gauthier et al., 2006). MCI can be diagnosed according to the following criteria: (1) subjective cognitive complaint by the patient or a relative, (2) cognitive decline on neuropsychological testing compared to age- and education-equivalent individuals, and (3) preserved daily life activities (Gagnon et al., 2009; Albert et al., 2011). MCI can be subdivided into different subtypes according to the number (single-domain vs. multiple-domain) and nature (amnestic vs. non-amnestic) of the cognitive domains impaired (Petersen and Morris, 2005). MCI is a risk factor for dementia such as AD, DLB, or vascular dementia (Gauthier et al., 2006). However, the progression of MCI is also highly variable. Some MCI patients remain with mild cognitive deficits for many years whereas a substantial proportion return to normal cognitive functioning (Ganguli et al., 2004; Gauthier et al., 2006; Fischer et al., 2007). Moreover, several factors may disrupt cognition in elderly individuals, including psychiatric symptoms, medication side effects, respiratory conditions (sleep apneas, chronic obstructive pulmonary disease), and vascular diseases. Consequently, clinicians and researchers should be careful not to directly link MCI to the future development of a neurodegenerative disease or to consider MCI as part of a neurodegenerative disease.

Mild cognitive impairment is a frequent feature of iRBD (Iranzo et al., 2006; Gagnon et al., 2009; Molano et al., 2010). In iRBD patients referred to a sleep disorders center, MCI frequency was estimated at up to 50% compared to 8% in healthy subjects (Gagnon et al., 2009). The main MCI subtype reported was non-amnestic MCI single-domain with predominant attention and executive dysfunctions. No study to date has systematically followed a large cohort of iRBD patients with MCI to determine the risk of developing dementia. However, Molano et al. (2010) followed seven iRBD patients for many years. All patients met MCI criteria and subsequently developed Lewy body disease, which was confirmed by autopsy. This suggests that iRBD patients with MCI are at higher risk for developing DLB.

COGNITIVE DECLINE IN PD ASSOCIATED WITH RBD

A substantial proportion of PD patients have cognitive impairment, and more than 50% will develop dementia during the course of PD (Aarsland and Kurz, 2010). As mentioned above, RBD is also a frequent feature of PD (Gagnon et al., 2002; Sixel-Döring et al., 2011). RBD in PD patients has been associated with cognitive impairment (Sinforiani et al., 2006; Vendette et al., 2007; Gagnon et al., 2009; Naismith et al., 2011), waking EEG slowing (Gagnon et al., 2004), a predominance of akinetic-rigid signs (Postuma et al., 2008), symmetric disease (Bliwise et al., 2010), visual hallucinations (Pacchetti et al., 2005), and autonomic dysfunction (Postuma et al., 2009b, 2011c). Our team found a higher risk of having MCI in PD with concomitant RBD: MCI was present in 73% of PD patients with RBD compared to 11% of PD patients without RBD and 8% of healthy controls (Gagnon et al., 2009). Moreover, we recently conducted a prospective follow-up study in a cohort of PD patients to assess whether the presence of polysomnographic-confirmed RBD at baseline predicted the future development of dementia according to neurological and neuropsychological assessments (Postuma et al., 2012). The sample comprised 42 PD patients without dementia, including 27 with RBD and 15 without RBD. Over a mean 4-year follow-up, 48% of PD patients with RBD developed dementia, whereas none of PD patients without RBD converted to dementia. Although these results remain to be confirmed in a larger cohort of PD patients, they suggest that the presence of RBD in PD could indicate a more devastating and wide-spread neurodegenerative disease compared to PD patients without RBD symptoms (Postuma et al., 2012).

CONCLUSION

Box 1 summarizes a case report of an individual referred to a memory clinic for cognitive decline and subsequently diagnosed with RBD. This case shows the importance of identifying RBD in patients with cognitive impairment. A better understanding of this sleep disorder would enable a deeper grasp of the underlying pathophysiology and diagnosis of synucleinopathies, and would contribute to the development of neuroprotective treatments.

ACKNOWLEDGMENTS

The authors thank Dr. Jacques Montplaisir and Dr. Ronald Postuma for their contribution to the research program on cognition in REM sleep behavior disorder and Parkinson's disease. Our research is supported by the Canadian Institutes of Health Research and the Fonds de recherche du Québec – Santé.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 19 January 2012; accepted: 25 April 2012; published online: 17 May 2012.

Citation: Gagnon JF, Bertrand JA and Génier Marchand D (2012) Cognition in rapid eye movement sleep behavior disorder. Front. Neur. ***3****:82. doi: 10.3389/fneur.2012.00082*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in
NEUROLOGY

ORIGINAL RESEARCH ARTICLE
published: 28 June 2012
doi: 10.3389/fneur.2012.00105

Orbitofrontal gray matter relates to early morning awakening: a neural correlate of insomnia complaints?

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Sleep complaints increase profoundly with age; prevalence estimates of insomnia in the elderly reach up to 37%. The three major types of nocturnal complaints are difficulties initiating (DIS) and maintaining (DMS) sleep and early morning awakening (EMA), of which the latter appears most characteristic for aging. The neural correlates associated with these complaints have hardly been investigated, hampering the development of rational treatment and prevention. A recent study on structural brain correlates of insomnia showed that overall severity, but not duration, of insomnia complaints is associated with lower gray matter (GM) density in part of the left orbitofrontal cortex (OFC). Following up on this, we investigated, in an independent sample of people not diagnosed with insomnia, whether individual differences in GM density are associated with differences in DIS, DMS, and EMA. Sixty five healthy participants (mean age = 41 years, range 18–56) filled out questionnaires and underwent structural magnetic resonance imaging. Three compound Z-scores were computed for questionnaire items relating to DIS, DMS, and EMA. Whole-brain voxel-based morphometry was used to investigate their association with GM density. Results show that participants with lower GM density in a region where the left inferior OFC borders the insula report more EMA, but not DIS or DMS. This is the first study to investigate structural brain correlates of specific sleep characteristics that can translate into complaints in insomniacs. The selective association of EMA with orbitofrontal GM density makes our findings particularly relevant to elderly people, where EMA represents the most characteristic complaint. It is hypothesized that low GM density in aforementioned orbitofrontal area affects its role in sensing comfort. An intact ability to evaluate comfort may be crucial to maintain sleep, especially at the end of the night when sleep is vulnerable because homeostatic sleep propensity has dissipated.

Keywords: insomnia, aging, early morning awakening, orbitofrontal cortex, voxel-based morphometry, structural magnetic resonance imaging

INTRODUCTION

With prevalence estimates of 4–11%, chronic insomnia belongs to the most common disorders. The most important risk factor for insomnia is age; estimates of the prevalence in elderly people reach up to about 40% (Foley et al., 1995; Morphy et al., 2007). Individual sleep complaints are much more frequent, with an estimated one third of the population experiencing at least one DSM-IV insomnia symptom (Ohayon, 2002). Three relatively independent major sleep complaints can be discriminated, which can be present with variable severity; difficulties initiating sleep (DIS), difficulties maintaining sleep (DMS), and early morning awakening (EMA; American Psychiatric Association, 1994; American Academy of Sleep Medicine, 2005). Of these three, complaints of EMA most clearly increase with age, while DIS may actually decrease with age; both in clinically diagnosed insomniacs and in the general population of elderly people (Abe and Suzuki, 1985; National Sleep Foundation, 2003a,b). Additional daytime complaints of insomniacs concern non-restorative sleep and problems with daytime functioning.

In spite of the high prevalence and strong impact on well-being, quality of life and society (Leger and Bayon, 2010), the brain

Abbreviations: DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; EMA, early morning awakening; GM, gray matter; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; ROI, region of interest; VBM, voxel-based morphometry.

mechanisms underlying insomnia have hardly been explored. Several psychological models have been proposed, mostly addressing three factors; predisposing personality traits like the tendency to worry, precipitating events like stress, and perpetuating attitudes and practices like misconceptions about required sleep (Spielman, 1986; Perlis et al., 1997). Physiological observations have identified a "hyperaroused" central and autonomic nervous system profile; not only in insomniacs (Bonnet and Arand, 1997; Riemann et al., 2010), but also in individuals that are at risk of developing insomnia (Fernandez-Mendoza et al., 2010). Nevertheless, the brain mechanisms that underlie predisposing traits and a hyperaroused profile have hardly been explored.

Behavioral genetics studies in cohorts of twins and families indicate a considerable heritability of insomnia (Beaulieu-Bonneau et al., 2007) as well as sleep complaints in general (Boomsma et al., 2008). Heritable structural brain characteristics that might be associated with insomnia complaints are thus of particular interest. One of the most heritable structural brain characteristics is the topography of cerebral cortical gray matter (GM) density, particularly so for prefrontal GM where heritability estimates reach up to 95% (Thompson et al., 2001). A recent study demonstrated that elderly insomniacs have a significantly reduced GM density in part of the left orbitofrontal cortex (OFC; Altena et al., 2010). The reduction was found in a region compatible with the border of Brodmann areas 47/12M and 13L of the "orbital network" (Ongur et al., 2003), which is proposed to be essential for the hedonic evaluation of somatosensory input (Kringelbach, 2005), including the evaluation of thermal comfort (Dunn et al., 2010). The observation of compromised thermal comfort-evaluation abilities in elderly insomniacs (Raymann and Van Someren, 2008) supports the possible functional relevance of a reduction in GM density in this relatively small orbitofrontal area. Furthermore, individual differences in GM density in the aforementioned region were strongly correlated with differences in the overall severity of complaints, rendering it the first candidate for a structural brain correlate of insomnia (Altena et al., 2010). In striking contrast, individual differences in GM density were not associated with differences in the duration of insomnia. This dissociation suggests that a low GM density in a region at the border of areas 47/12M and 13L of the OFC is more likely to represent a pre-existing vulnerability to insomnia complaints, rather than a consequence of having experienced a period of insomnia.

The present study aimed to follow up on the promising suggestion of a neural correlate of insomnia by Altena et al. (2010), by investigating, in an independent sample of participants not diagnosed with insomnia, whether individual differences in GM density in aforementioned orbitofrontal region of interest (ROI) are associated with individual differences in the three major types of sleep characteristics: DIS, DMS, and EMA.

MATERIALS AND METHODS

PARTICIPANTS AND PROCEDURES

Good quality magnetic resonance imaging (MRI) scans and completed questionnaires could be obtained from 65 self-declared healthy controls participating in the Netherlands Study of Depression and Anxiety (NESDA) neuroimaging study, which is part of a large-scale multisite, longitudinal, observational cohort study on the development and course of anxiety and depression (Penninx et al., 2008). Participants were between 18 and 57 years of age and had never been diagnosed with any of the DSM-IV disorders (American Psychiatric Association, 1994). Further exclusion criteria were the presence or history of major internal or neurological disorder, dependence on or recent abuse (past year) of alcohol and/or drugs, hypertension, any suspicion of current subclinical depression (see van Tol et al., 2010), and contraindications for participating in an MRI study. Diagnoses according to DSM-IV criteria were established using the structured Composite International Diagnostic Interview, lifetime version 2.1 (Robins et al., 1988), assessed by a trained interviewer. **Table 1** provides an overview of participant characteristics, including data on circadian preference (mid-sleep time on free days corrected for sleep debt, computed as described in the supplemental data of; Roenneberg et al., 2004) and overall severity of insomnia complaints (total score on the Women's Health Initiative Insomnia Rating Scale; WHIIRS, see below). The ethical review boards of each center approved this study and all participants provided consent after receiving written information.

ASSESSMENT OF SLEEP COMPLAINTS

Participants filled out a range of self-rating questionnaires, which included the WHIIRS (Levine et al., 2003a,b) and an early version of the Munich Chronotype Questionnaire (MCTQ, Zavada et al., 2005). Although the WHIIRS has only been validated in women, it contains clearly defined items pertaining to all the core symptoms of insomnia and can thus readily be used to investigate structural brain correlates of specific sleep characteristics in both women and men. Compound Z-scores were computed for questionnaire items relating to the three main sleep characteristics: DIS, DMS, and EMA. An estimate of DIS was obtained by calculating the average of standardized ratings on an item of the WHIIRS that asked about trouble falling asleep, and three items of the MCTQ, which ask for the time needed to fall asleep on workdays, on days off, and in general, respectively. An estimate of DMS was obtained by calculating the average of standardized ratings on three items of the WHIIRS that ask about waking up several times at night, about having trouble getting back to sleep, and about restlessness of one's typical night's sleep. An estimate of EMA was obtained by calculating the average of standardized ratings on an item of the WHIIRS asking about waking up earlier than planned, and two items of the MCTQ (Zavada et al., 2005) that ask for the time in the morning one is wide awake on workdays and days off.

Table 1 | Participant characteristics [numbers, ratios, and mean ± standard deviation (range)].

Cases (#)	65
Sex (male/female)	24/41
Age (years)	40.5 ± 9.71 (21, 56)
Scan site (AMC/LUMC/UMCG)	27/26/12
Total gray matter volume (cc)	725.5 ± 76.6 (565, 924)
Mid-sleep time on free days, corrected (time, $N = 54$)	4:04 ± 30 min (2:53, 5:55)
WHIIRS score ($N = 62$)	4.97 ± 3.47 (0, 15)

MAGNETIC RESONANCE IMAGING ACQUISITION

Imaging data were acquired using a Philips 3T MRI system (Best, The Netherlands) located at the Leiden University Medical Center (LUMC), Amsterdam Medical Center (AMC) of the University of Amsterdam or the University Medical Center Groningen (UMCG), equipped with a SENSE-8 (LUMC and UMCG) or SENSE-6 (AMC) channel head coil. For each subject, anatomical images were obtained using a sagittal three-dimensional gradient-echo T_1-weighted sequence (repetition time = 9 ms; echo time = 3.5 ms; matrix = 256 × 256; voxel size = 1 mm isotropic; 170 slices).

VOXEL-BASED MORPHOMETRY-PROCESSING

Imaging data were analyzed using voxel-based morphometry (VBM: Ashburner and Friston, 2000) with Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL: Ashburner, 2007) in the Statistical Parametric Mapping (SPM version 5; http://www.fil.ion.ucl.ac.uk/spm) suite of tools. DARTEL is a fully deformable registration and normalization method that is effectively unconstrained by number of degrees of freedom. It has proven good registration accuracy and has been recommended in favor of standard SPM normalization or the SPM unified segmentation approaches for whole-brain and regional analysis without segmenting regions of interest (Yassa and Stark, 2009). Pre-processing of the images has been described in detail previously (van Tol et al., 2010) and included (1) manual reorientation; (2) segmentation; (3) registration, normalization, and modulation (leaving the images in DARTEL template space at a resolution of 1.5 mm isotropic); and (4) smoothing at 8 mm full-width at half-maximum. Total (native) GM volume for each participant was computed by summing all the voxels in their GM image resulting from segmentation (step 2).

VOXEL-BASED MORPHOMETRY ANALYSIS

Using the peak voxel from the voxel-wise regression analysis against severity of insomnia as reported in Altena et al. (2010), we created a spherical ROI with a 16 mm radius in aforementioned DARTEL template space. First, a matrix describing registration from Montreal Neurological Institute (MNI) space to DARTEL template space was computed using fully affine registration. Next, the obtained transformation matrix was used to transform MNI coordinates ($x, y, z = -20, 22, -14$) to the present DARTEL template space. Finally, a sphere with a 16 mm radius was centered on these coordinates using the WFU Pickatlas tools (Maldjian et al., 2003, 2004). Visual inspection showed that the resulting ROI predominantly contained parts of the left OFC as well as smaller parts of the left medial frontal, anterior insular and subcallosal cortex, and left caudate. All voxel-wise analyses were performed using the general linear model framework of SPM (Friston et al., 1995). To test for associations with DIS, DMS, and EMA, a whole-brain voxel-wise regression analysis was performed. Age, sex, total GM volume, and imaging site (by means of two dummy variables) were entered as covariates in each analysis. To achieve maximal sensitivity, optimize voxel residual smoothness estimation, and exclude false positives outside GM tissue, voxel-wise analyses were masked using a explicit optimal threshold GM mask created using the Masking toolbox (Ridgway et al., 2009). To preserve optimal normalization accuracy, we left the normalized, modulated, and smoothed images in DARTEL space. Therefore, coordinates are not equivalent to MNI coordinates. Regions are identified using the detailed brain atlas of Talairach and Tournoux (1988). Additionally, we registered the DARTEL template to MNI space and applied the resulting transformation matrix to the coordinates of the peak voxel in DARTEL space, resulting in an approximation of the location in standard space.

Statistical thresholding was performed roughly analogous to the original publication by van Tol et al. (2010); i.e., when performing whole-brain voxel-wise analyses we applied different statistical thresholds for analysis *within* and analysis *outside* a ROI. For analyses within the 16 mm radius spherical ROI centered on the peak voxel reported by Altena et al. (2010), we used a two-step approach to reduce the likelihood of Type I errors. Initially, a whole-brain voxel-wise height-threshold of $Z > 3.09$ ($P < 0.001$) and cluster size threshold of 50 contiguous voxels was set. If this initial analysis showed a significant cluster within our ROI, it was followed by a conclusive analysis within our ROI at a threshold of $P < 0.05$, family wise error voxel-corrected. For analysis outside our ROI, a whole-brain threshold of $P < 0.05$ family wise error cluster-corrected was set.

To gain more insight into effect size as well as for illustrative purposes, we computed mean GM density within significant clusters by averaging of the GM probabilities for each voxel in a cluster. To investigate the amount of explained variance in mean GM density within a significant cluster by DIS, DMS, and EMA, multiple regression analysis was performed twice; once with and once without DIS, DMS, or EMA, using age, sex, total GM volume, and imaging site (by means of two dummy variables) as predictors of no interest in each analysis.

ANALYSIS OF SLEEP MEASURES

The general linear model framework of Statistical Package for the Social Sciences (SPSS version 17.0, Chicago, IL, USA) was used for the analyses of compound Z-scores. Reliability (internal consistency) of the DIS, DMS, and EMA measures was evaluated by calculating Cronbach's alpha.

MISSING DATA

In case of missing values on any of the questionnaire items in a participant, compound Z-scores were computed over the remaining items for that specific sleep complaint. For DMS, compound Z-scores could not be computed in three participants because scores were not available for any of the three items that make up DMS, leaving 62 participants for the analysis of the association of GM density and DMS.

RESULTS

VOXEL-BASED MORPHOMETRY ANALYSIS

Voxel-wise analysis showed that the EMA compound Z-score significantly predicted GM density in a 66 voxel, 0.223 cc cluster at $P < 0.001$ uncorrected. The complete cluster was located within our 16 mm radius spherical ROI and the peak voxel (approximate MNI coordinates = −30, 13, −13) survived correction for multiple comparisons ($P = 0.029$, family wise error voxel-corrected). An auxiliary analysis, using mid-sleep time on free days (corrected

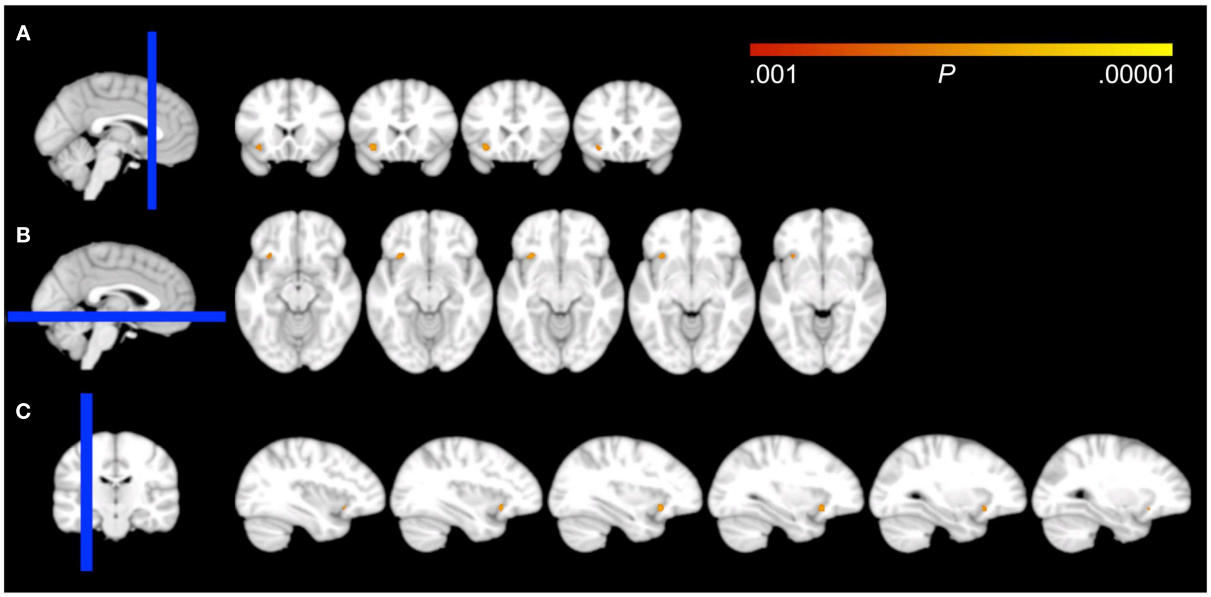

FIGURE 1 | Effects of voxel-based regressions. A cluster of voxels is shown in which GM probability was a significant predictor for the early morning awakening compound *Z*-score, overlaid on all coronal **(A)**, axial **(B)**, and sagittal **(C)** 1.5 mm slices that contain the cluster from the DARTEL template, according to neurological convention (left = left). The blue bar in the localizer on the left side of the panels represents the slab of which slices are shown on the right. Note that the cluster overlaps the border of the inferior part of the orbitofrontal cortex and the most anterior aspect of the insular cortex.

for sleep debt) instead of EMA to predict GM density, showed no significant voxels within our ROI at $P < 0.001$ uncorrected. The cluster for EMA encompassed the region where the left inferior OFC borders with the most anterior aspect of the insular cortex (**Figure 1**). The association of EMA with the average GM density within this cluster (i.e., an average of the GM probabilities for each voxel in the cluster) is visualized in the scatterplot of **Figure 2**; EMA explained an additional 6% of variance on top of the other predictors age, sex, total GM volume, and imaging site. Voxel-wise analysis at $P < 0.001$ uncorrected within our ROI showed no significant association of GM density with either DIS or DMS.

No effects were observed when testing at the conservative threshold of $P < 0.05$ family wise error cluster-corrected. At the liberal threshold of $P < 0.001$ uncorrected, only a single cluster was found outside our ROI for EMA (in the posterior division of the right superior temporal gyrus), which speaks to the specificity of the observed effect in our voxel-wise ROI analysis.

SLEEP COMPLAINTS

Although Cronbach's alpha underestimates reliability when computed for a limited number of items, it demonstrated at least a minimally acceptable to even good internal consistency for the compound *Z*-scores when compared to commonly used standards for larger item pools (Cronbach's alpha DIS: $\alpha = 0.85$, DMS: $\alpha = 0.69$, and EMA: $\alpha = 0.59$). As to independence of the three compound scores, correlation analysis demonstrated that DIS was relatively independent of both DMS [$r(62) = 0.20$, $P = 0.12$] and EMA [$r(65) = 0.06$, $P = 0.66$], while DMS and EMA showed a significant correlation [$r(62) = 0.52$, $P < 0.001$].

DISCUSSION

We aimed to investigate whether individual differences in GM density in a ROI compatible with the border of Brodmann areas 13L and 47/12M of the left OFC are associated with individual differences in the self-reported degree by which they experienced DIS, DMS, and EMA. This ROI was chosen because previous work from our group showed a strong correlation between GM density in this area and the severity of complaints in people diagnosed with chronic primary insomnia (Altena et al., 2010), thus indicating it to be a neural correlate of insomnia severity. The present study also supports an involvement of this area in sleep characteristics of people that have not been diagnosed with insomnia. Moreover, findings indicate that the association is specific for EMA; it was absent for difficulties initiating and maintaining sleep. This selectivity makes our findings particularly relevant to elderly people; EMA represents the complaint that most characteristically increases with age (Abe and Suzuki, 1985) and prefrontal GM volume is especially vulnerable to age-related decline (Raz et al., 1997, 2005; Good et al., 2001).

The present study has a considerable limitation with respect to the quantification of DIS, DMS, and EMA. We calculated summary *Z*-scores over relevant items derived from different self-rating questionnaires designed for different purposes, for which data was available in the NESDA study. DIS was computed over four items, while DMS and EMA were both calculated over three items. With very few items, it is unlikely to obtain high alphas unless the items are nearly identical to one another. Considering the small number of items used and their inevitable heterogeneity, even reliabilities above four are often considered reasonable. We can at present only conclude that orbitofrontal GM density shows a significant

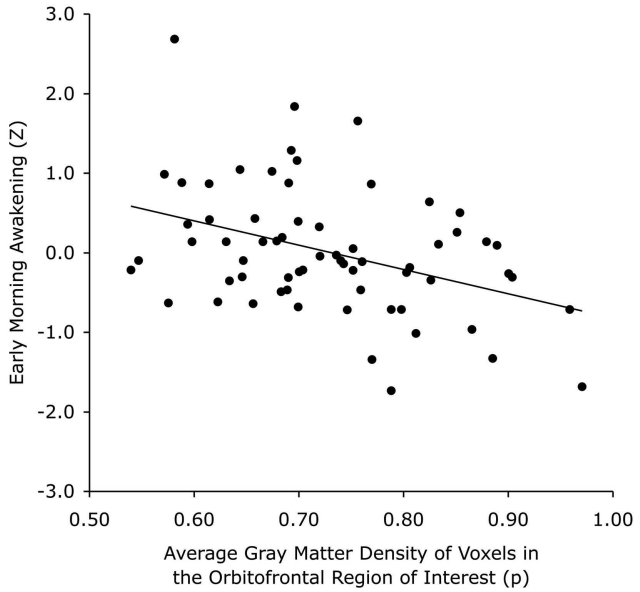

FIGURE 2 | Scatterplot showing that individuals (represented by a dot) with less GM in a cluster compatible with the border of areas 13L and 47/12M of the left orbitofrontal cortex are more likely to experience earlier morning awakening. The solid line represents the linear regression fit.

negative association with earlier awakening in the morning, which may or may not result from different underlying causes and may not be independent of DMS. It would be interesting to investigate, using large item pools, whether DIS, DMS, and EMA are each unidimensional, or rather multidimensional, constructs. Presently, we are not aware of sleep questionnaires that evaluated and validated unidimensional multi-item subscales for DIS, DMS, and EMA.

For the current study, imaging and questionnaire data was available for a sample of individuals spanning a wide age range (18–56 years). As both sleep complaints and brain atrophy increase with age, the observed correlations could in theory merely be due to common age affects. However, both native total GM volume and age were included as confound regressors in all our analyses, thus correcting for intra-individual differences in global brain atrophy as well as age-related changes in local GM volume. Consequently, we are confident that common aging effects cannot explain the observed relation between GM density and EMA.

The orbitofrontal area we focused on in the present study may represent a "hot-spot" for the hedonic evaluation of somatosensory input since it activates with pleasant stimuli (Kringelbach, 2005). It is important to note that there does not appear to be a unidimensional monotonic deactivation of this area from pleasure to aversion; the latter activating a more lateral orbitofrontal area instead (O'Doherty et al., 2001). A recent human brain imaging study elegantly showed that an orbitofrontal region compatible with the border of areas 13L and 47/12M is key to the evaluation of thermal comfort, irrespective of the evaluation of warmth or coolness itself (Dunn et al., 2010). This finding is of interest, because insomniacs have a compromised ability to judge thermal comfort (Raymann and Van Someren, 2008) and even small deviations from comfortable temperature have a strong impact on sleep (Van Someren, 2004, 2006; Raymann et al., 2008). It is tempting to suggest that a low GM volume in the orbitofrontal region at the border of areas 13L and 47/12M could predispose people to suboptimal sensing of comfort. An intact ability to evaluate comfort may be crucial to maintain sleep especially at the end of the night, when sleep is vulnerable because homeostatic sleep propensity has dissipated.

The cluster where the present study found EMA to account for 6% of the interindividual variability in GM density is not limited to the OFC, but extends toward the border of the insula. The insula is an interesting area with respect to the slow oscillations that characterize deep non-REM sleep. High-density sleep-EEG studies have demonstrated that slow oscillations tend to travel over the cortex mostly in an anteroposterior direction (Massimini et al., 2004). Although they can emerge at any part of the cortex, source estimates showed they are most likely to first appear in the insula and then propagate along the anteroposterior axis through the brain midline (Murphy et al., 2009). It is tempting to speculate that a relatively low GM volume in part of the insula may predispose people to a less firm generation of slow oscillations. Slight interindividual differences in ability to ignite slow oscillations may become noticeable only at the end of the night, when sleep is vulnerable because homeostatic sleep propensity has dissipated.

From the perspective of present-day models on sleep regulation, involvement of the OFC and comfort sensing in sleep EMA may be surprising at first glance. The consensus model of sleep-wake regulation consists of a circadian process and a homeostatic process and is aptly referred to as the two-process model of sleep regulation (Borbely, 1982; Daan et al., 1984; Dijk and Czeisler, 1995). The circadian process refers to the timing of sleep and wakefulness driven by the clock of the brain, located in the hypothalamic suprachiasmatic nucleus (Mistlberger, 2005). The homeostatic component refers to the hourglass of the brain, that keeps track of the time we are awake and gradually increases the pressure for sleep. This pressure dissipates as soon as sleep sets in. The decrease follows an exponential trajectory, so that most of the sleep pressure is dissipated within a few hours of sleep (Achermann et al., 1993; Leemburg et al., 2010; Van Someren, 2010). The neurobiological mechanisms underlying this hourglass mechanism are not as well characterized as the mechanisms of the clock, but are likely to involve adenosine (Porkka-Heiskanen et al., 1997), cytokines (Krueger et al., 2011), and an increase in synaptic density during wakefulness (Tononi and Cirelli, 2006).

Recently, it has been argued that the two-process model of sleep regulation falls short of recognizing that the ability to sleep also crucially depends on whether sleep-permissive conditions are met (Romeijn et al., 2012). Trivial as it may seem, one is unlikely to sleep without feeling comfortable – one of the sleep-permissive conditions – unless the circadian and homeostatic sleep drives are so high that they overrule the obstacle of being uncomfortable. Along this line of reasoning, a hypothesis can be forwarded on why a low GM density in an area that is essential for comfort sensing would be associated with EMA, but not with difficulties initiating or maintaining sleep. The circadian and homeostatic sleep processes concertedly provide a very strong drive to sleep during the initial part of the night, enforcing sleep even if sleep-permissive conditions,

like comfort, are suboptimal. During the final part of the night, however, the homeostatic sleep pressure has dissipated virtually completely and the circadian clock is ready to switch to the promotion of wakefulness. It is in this final part of the night that one can presume suboptimal comfort signaling to interfere most strongly with the continuation of sleep. Whatever the experienced impact and reason of EMA – and subjects could well differ here –, it may require optimal comfort sensing and signaling by the OFC to continue sleep after the arousals that normally occur more frequently in the morning. This situation may be compared to someone being able to sleep in an uncomfortable upright sitting position when exhausted, while it would require the comfort of lying supine on a bed to catch any sleep if sleep propensity is low. Although admittedly highly speculative, this line of reasoning is amenable to hypothesis-driven experimental studies, into the possible involvement of OFC, insula, comfort sensing, and slow wave generation in sleep complaints. Innovative hypothesis-driven studies are direly needed to advance our understanding and treatment of insomnia; still one of the least understood disorders that chronically impacts the lives of so many, especially in the elderly population.

ACKNOWLEDGMENTS

The authors thank Prof. Dr. André Aleman for kindly providing MRI data from controls scanned at the UMCG. This work was supported by the Netherlands Organization for Scientific Research (NWO), The Hague, The Netherlands (VICI innovation grant number 453-07-001) and by the FP7-PEOPLE-ITN-2008 Marie Curie Actions Networks for Initial Training (ITN) funding scheme, grant number 238665, project Neuroendocrine Immune Networks in Ageing (NINA). The infrastructure for the Netherlands Study of Depression and Anxiety study (http://www.nesda.nl/nl/) was supported by the Geestkracht program of the Netherlands Organization for Health Research and Development (Health Care Research the Netherlands, Medical Science, grant No. 10-000-1002), VU University Medical Center, Geestelijke GezondheidsZorg (GGS) in Geest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare, Netherlands Institute for Health Services Research and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 08 March 2012; paper pending published: 13 April 2012; accepted: 12 June 2012; published online: 28 June 2012.

Citation: Stoffers D, Moens S, Benjamins J, van Tol M-J, Penninx BWJH, Veltman DJ, Van der Wee NJA and Van Someren EJW (2012) Orbitofrontal gray matter relates to early morning awakening: a neural correlate of insomnia complaints? Front. Neur. ***3****:105. doi: 10.3389/fneur.2012.00105*

This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

frontiers in NEUROLOGY

ORIGINAL RESEARCH ARTICLE
published: 04 July 2012
doi: 10.3389/fneur.2012.00106

Variations in dream recall frequency and dream theme diversity by age and sex

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We assessed dream recall frequency (DRF) and dream theme diversity (DTD) with an internet questionnaire among a cohort of 28,888 male and female participants aged 10–79 years in a cross-sectional design. DRF increased from adolescence (ages 10–19) to early adulthood (20–29) and then decreased again for the next 20 years. The nature of this decrease differed for males and females. For males, it began earlier (30–39), proceeded more gradually, and reached a nadir earlier (40–49) than it did for females. For females, it began later (40–49), dropped more abruptly, and reached nadir later (50–59). Marked sex differences were observed for age strata 10–19 through 40–49 and year-by-year analyses estimated the window for these differences to be more precisely from 14 to 44 years. DTD decreased linearly with age for both sexes up to 50–59 and then dropped even more sharply for 60–79. There was a sex difference favoring males on this measure but only for ages 10–19. Findings replicate, in a single sample, those from several previous studies showing an increase in DRF from adolescence to early adulthood, a subsequent decrease primarily in early and middle adulthood, and different patterns of age-related decrease in the two sexes. Age-related changes in sleep structure, such as decreasing %REM sleep which parallel the observed dream recall changes, might help explain these findings, but these sleep changes are much smaller and more gradual in nature. Changes in the phase and amplitude of circadian rhythms of REM propensity and generational differences in life experiences may also account for some part of the findings. That decreases in DTD parallel known age-related decreases in episodic and autobiographical memory may signify that this new diversity measure indexes an aspect of autobiographical memory that also influences dream recall.

Keywords: dreaming, dream recall, dream diversity, sleep, aging, sex differences, epidemiology

INTRODUCTION

The recallability, content, and organization of dreaming reflect influences from underlying circadian and ultradian fluctuations in cognitive activity (Wamsley et al., 2007; Nielsen, 2011). Age-related changes in dreaming might thus be expected to parallel changes seen in other domains of cognitive functioning, such as episodic or autobiographical memory (St-Laurent et al., 2011), or even to reveal age-related changes in cognitive activity that are unique to sleep (Pace-Schott and Spencer, 2011).

There is a relatively broad consensus, based on results from both survey and laboratory studies, that the capacity to recall dreams decreases with age (for reviews see Funkhouser et al., 1999; Guenole et al., 2010). One early study of 17- to 70-year-old college-educated participants ($n = 295$) found that dream recall frequency (DRF) was at its highest level (9.8 dreams/month) in the late teens, progressively lower at ages 30–39 (6.1/month), 40–49 (4.2/month), and 50–59 (3.7/month) and then somewhat higher again at ages 60–69 (4.5/month; Herman and Shows, 1983). A second measure of dream recall in this study, the number of separate dreams recallable in 5 min, produced a clear linear decrease with age. A subsequent, much larger, cross-sectional study of participants aged 17–92 years ($n = 2328$) found progressively lower DRF with increasing age, but only up to the age of 56, when no further decrease was apparent (Giambra et al., 1996). In contrast to these findings, however, a home diary study (Waterman, 1991) found no difference in dream recall or dream report length between middle-aged (45–60 years) and older (61–75 years) participants. This may be attributable to the lack of a younger comparison group in this study (see later section).

Findings from laboratory studies have been largely consistent with those of surveys. The first laboratory study of this question (Kahn et al., 1969) found a relatively low proportion of dream recall after awakenings from REM sleep among a 66- to 87-year-old group (45%) compared with that of a younger, 18–33 year old, group (87%) reported in a previous study (Kahn et al., 1962). A subsequent study (Fein et al., 1985) also reported lower dream recall from REM sleep awakenings for a 69- to 75-year-old group of women (71.4%) than for a younger comparison group of unspecified age (90.2%), as well as a trend for lower recall from Stage 2 sleep awakenings (47.2 vs. 60.3%). The length of reports did not differentiate the old and young groups however. A third study (Grenier et al., 2005) reported lower REM sleep dream recall in a group of 60- to 77-year-old women (81%) than in a comparison group of 18- to 35-year-old women (98%); the mean word

count of the older women's dreams was also lower than that of the younger women.

Several studies suggest that this reliable age-related decrease in DRF occurs abruptly at a young age rather than progressively over the lifespan. First, the survey study cited earlier (Herman and Shows, 1983) reported a sudden decrease in DRF between 17–20 year-olds and those aged 30–69. Similarly, Kahn et al. (1969) found that the biggest decrease in DRF occurred between 25 and 35 years of age, while Giambra et al. (1996) found the decrease to occur between ages 20 and 38.

Some studies have also reported a sex difference in DRF, with women reporting higher recall frequencies than men (Giambra et al., 1996). A meta-analysis (Schredl and Reinhard, 2008) confirms the presence of such a difference, indicating that it is small in magnitude, and especially small in children. Moreover, our previous longitudinal study of nightmares in adolescents (Nielsen et al., 2000) showing a sex difference in both DRF and nightmare recall frequency between ages 13 and 16 suggests that age-related changes in DRF manifest differently for the two sexes.

The goal of the present study was thus to examine age and sex differences in DRF in a large cohort of participants who had completed an online questionnaire about their dreams. Two different measures were available; one, a retrospective estimate of the number of dreams recalled in a typical month; the other, a dream theme diversity (DTD) score presumably assessing the lifetime prevalence of a number of different typical dream themes (Nielsen et al., 2003). As a relatively new measure, the DTD has no known correlates and its interpretation remains an open question. However, since it assesses degree of recall for all of the themes on the Typical Dreams Questionnaire (TDQ), the DTD is thought to reflect the breadth of an individual's recall of various typical dream themes, i.e., their ability to recall a wide variety of their most common lifetime dream experiences. In this respect, the DTD can be viewed as assessing a form of episodic or autobiographical memory.

Based on the literature reviewed above, we expected to see DRF scores decrease with advancing age but especially in early adulthood. In contrast, we expected to see scores on the DTD measure increase with age, since this is a lifetime prevalence index that should increase as older participants accumulate more opportunities for recalling typical dream themes. Finally, we expected to see: age-related changes for both sexes on the DRF and DTD measures, sex differences (favoring women) on both measures, and different patterns of age-related change for the two sexes.

MATERIALS AND METHODS

PARTICIPANT SAMPLE

Records were taken from participants who had completed a 56-item version of the TDQ (Nielsen et al., 2003) and demographic items available on the "participate" portion of the *Dream & Nightmare Laboratory* website (http://dreamscience.ca/virtualdreamlab/) between January 1997 and June 2008. Participants were first informed that results from the study would be used in research and published in group form at a later date.

The data set was initially screened by an assistant who used server-logged dates, times, and IP addresses to identify and remove duplicate and spoiled records. This resulted in an initial data set containing 33,015 records. From these, 2305 records were dropped because either age was not reported ($n = 2186$) or was indicated to be <10 ($n = 77$) or >79 ($n = 21$), or excessively high estimates of dream recall (>124/month) or nightmare recall (>94/month) were given ($n = 21$). An additional 1822 records that did not contain valid scores for the retrospective monthly dream recall measure (although they did have valid DTD scores) were dropped because these subjects did not complete the entire questionnaire correctly. Thus, the sample for final analysis consisted of 28,888 participants (5884 male, 23,004 female) who possessed valid scores for the age, sex, DRF, and DTD measures. A breakdown of the cohort by Sex and Age stratum appears in **Table 1**. Native language was specified by 99.0% (28,608) of the sample. Of these, 82.9% (23,724) indicated their native language to be English, 13.6% indicated French (3898), and 3.4% indicated other (986). A total of 97.6% of the participants (28,198) specified an occupation; of these 50.7% indicated student (14,299), 42.5% indicated non-student (11,998), 0.9% indicated unemployed (245), and the remainder indicated specific types of employment (5.9% or 1656).

Although the mean ages of males ($M = 25.5 \pm 10.6$) and females (25.0 ± 10.1) differed only by 6 months, this difference was significant for such a large sample ($t_{30489} = 2.95$, $p = 0.005$). However, there were no significant age differences between the two sexes for any of the six 10-year age strata (10–19, 20–29, 30–39, 40–49, 50–59, 60–79) considered separately (all $p > 0.185$). Age (in years) was used as a covariate for some analyses.

DREAM THEME DIVERSITY MEASURE

Participants were instructed to complete the TDQ, which consists of a list of 56 themes judged in previous research to be relatively

Table 1 | Dream recall frequency (DRF) scores by sex and age stratum.

Sex	Age	Mean	SD	*N*
Females	10–19	1.024	0.349	8742
	20–29	1.062	0.350	7958
	30–39	1.058	0.368	3576
	40–49	1.023	0.388	1992
	50–59	0.960	0.397	612
	60–79	1.000	0.469	124
	Total	1.040	0.359	23,004
Males	10–19	0.944	0.377	2173
	20–29	0.970	0.381	2014
	30–39	0.953	0.397	894
	40–49	0.928	0.413	501
	50–59	0.973	0.453	238
	60–79	0.921	0.414	64
	Total	0.953	0.389	5884
Combined	10–19	1.008	0.356	10,915
	20–29	1.044	0.358	9972
	30–39	1.037	0.377	4470
	40–49	1.004	0.395	2493
	50–59	0.964	0.413	850
	60–79	0.973	0.451	188
	Total	1.023	0.367	28,888

typical in the dream content of the general population (Griffith et al., 1958; Nielsen et al., 2003). The first online version of the TDQ, accounting for 84.7% of the current sample, prompted participants as follows: *For the following items, please check all of the boxes [] that apply. Have you ever dreamed of. . .?* followed by a list of 56 themes with check boxes. Each endorsed item was scored 1, otherwise 0. The second online version (see Typical Dreams Questionnaire in Appendix), accounting for 15.3% of the current sample, was modified to assess the frequency of each theme. The prompt read *Please rate how often in your life you have dreamed about each of the following themes; for each theme please circle a number from 0 to 4 as defined by this scale: 0: never; 1 = 1 time; 2 = 2–3 times; 3 = 4–10 times; 4 = 11+ times.* To combine the two sets of results, responses to the second version of the TDQ were recoded into a dichotomous scale equivalent to that of the first (i.e., *0 = never; 1 = 1 to 11+ times).* The DTD total score was calculated as the number of items (out of 56) with a score of 1; the range of the scale was thus 0–56.

The TDQ, which contains the DTD themes, has been translated into several languages and the rank order of the themes found to be highly similar across cultures (Schredl et al., 2004; e.g., Yu, 2008). The DTD measure is identical to the *Divers 55* subscale of our previous study of Canadian university students (Nielsen et al., 2003), but with the addition of a single item (*56. encountering a kind of evil force or demon*). The *Divers 55* measure was found to have a mean score of 16.4 ± 8.2 (mode: 13; median: 15), to not differ by sex or geographic regions, and to be relatively normally distributed (Nielsen et al., 2003). A reduced, 55-item, version of the DTD was calculated in the present study for comparison with the *Divers 55* score.

DREAM RECALL FREQUENCY MEASURE

Following completion of the TDQ, participants were asked to retrospectively estimate their monthly dream recall with the following question: *How many dreams of any kind do you recall in a typical month?* followed by a free response box. These responses were initially screened by a human scorer to remove all unusable responses (e.g., "lots," "not very many," etc.). The raw per month estimates were subsequently log-transformed [log(raw + 1)] to minimize the effect of extreme scores. This transformed variable constituted the DRF measure for final analysis.

The item on dream recall was followed by the question: *How many nightmares do you recall in a typical month?* These results have been reported elsewhere (Nielsen et al., 2006; Nielsen, 2010) and the log nightmare measure was used in the present analysis only as a covariate. The dream and nightmare recall items were followed by additional questions that varied in nature for the first and second online versions of the questionnaire and that are not assessed further here.

RESULTS

DREAM RECALL FREQUENCY

A 2 × 6 ANOVA with Sex and Age (10–19, 20–29, 30–39, 40–49, 50–59, 60–79) as independent variables and DRF as dependent variable revealed a significant Sex main effect ($F_{1,28876} = 41.95$, $p < 0.0000001$): females recalled more dreams per month than did males (**Table 1**). It also revealed an Age effect ($F_{5,28876} = 8.09$, $p < 0.0000001$) and a Sex × Age interaction ($F_{5,28876} = 3.20$, $p = 0.007$) such that the Sex difference obtained for Ages 10–19, 20–29, 30–39, and 40–49 (all $p < 0.000001$) but not for Ages 50–59 and 60–79 (**Figure 1**).

For females, contrasts revealed differences between Ages 20–29, 30–39, and all others (all $p < 0.006$) with the exception of a smaller difference between 20–29 and 60–79 ($p = 0.05$) and a marginal difference between 30–39 and 60–79 ($p = 0.076$). Age 50–59 was lower than all other ages ($p < 0.05$) except 60–79, from which it did not differ. *T*-tests conducted year-by-year for the two youngest Age strata revealed that the increase in DRF occurred at two points; first, a gradual increase from age 10 to 15 ($p < 0.023$) and, second, a relatively abrupt increase from age 18 to 20 ($p < 0.019$).

For males, contrasts revealed a significant differences between Ages 10–19 and 20–29 ($p = 0.03$) and between Ages 20–29 and 40–49 ($p = 0.03$). Year-by-year *t*-tests revealed an abrupt DRF increase between 17 and 20 ($p < 0.023$) similar to that for females.

To control for the effect of Age on the Sex difference, a univariate ANOVA with Sex as independent variable and age (in years) as a covariate was calculated. The Sex effect was still obtained ($F_{2,28887}$) = 133.36, $p < 0.0000001$.

To further control for significant Sex and Age effects for nightmares found in our previous study using this cohort (Nielsen et al., 2006), the previous 2 × 6 ANOVA was repeated with an ANCOVA design using log (nightmares/month + 1) as a covariate. All three effects were still observed: Sex main effect ($F_{1,28045} = 17.95$, $p < 0.00003$), Age main effect ($F_{1,28045} = 6.35$, $p < 0.000008$), and Sex × Age interaction ($F_{5,28045} = 2.81$, $p = 0.015$).

T-tests conducted year-by-year on the 10–19 Age stratum revealed that the Sex effect first appeared at age 14 ($t_{885} = -2.41$, $p = 0.017$); all comparisons for prior years were not significant (all $p > 0.20$). Year-by-year *t*-tests for the 40–49 Age stratum revealed that the Sex effect disappeared definitively at age 45 ($t_{254} = -0.44$, $p = 0.649$); prior years in that stratum revealed either significant differences (all $p < 0.02$) or trends (all $p < 0.08$). Thus, a more

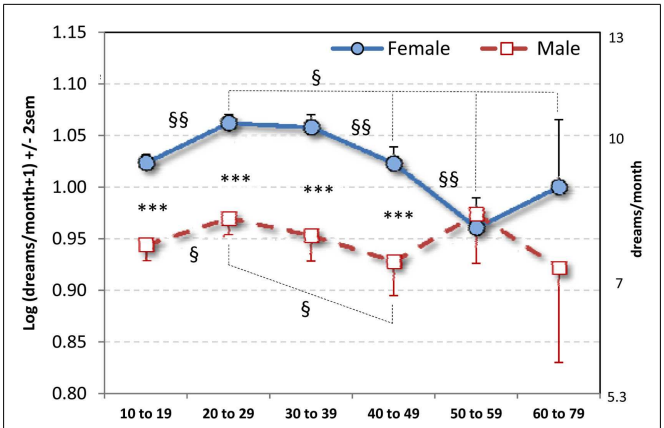

FIGURE 1 | Mean log dream recall per month (±2 SEM) for six age strata. Equivalent number of dreams per month raw values appear on right vertical axis. *** $p < 0.000001$: comparisons between sexes; §§ $p < 0.006$, § $p < 0.05$: comparisons between Age strata within Sex. By year, the Sex difference is apparent only for ages 14–44 (see text).

precise estimate of the duration of the Sex difference in this sample is from ages 14–44.

There were no significant Pearson correlations between age (in years) and DRF for the entire sample ($r_{28888} = -0.010$, $p = 0.103$) or for either males ($r_{5884} = -0.006$, $p = 0.654$) or females ($r_{23004} = -0.008$, $p = 0.246$). There were also no significant Pearson correlations between age (in years) and DRF at any Age stratum for either males (all $r > -0.052$ or <0.110) or females (all $r > -0.038$ or <0.007).

DREAM THEME DIVERSITY

A 2 × 6 ANOVA with Sex and Age (10–19, 20–29, 30–39, 40–49, 50–59, 60–79) as independent variables and DTD as dependent variable revealed a significant main effect for Age ($F_{5,28876} = 22.62$, $p < 0.0000001$) but no Sex main effect or Sex × Age interaction (**Figure 2**). The Age main effect was described best by a linear polynomial ($p < 0.0000001$) and to a lesser extent by quadratic ($p = 0.008$) and cubic ($p = 0.011$) trends.

For females, the Age main effect ($F_{5,23003} = 16.17, p < 0.0000001$) and linear ($p < 0.0000001$) and quadratic ($p = 017$) trends were observed. The decrease by Age stratum was significant for 10–19 to 20–29 ($p = 0.010$), 20–29 to 30–39 ($p = 0.013$), 40–49 to 50–59 ($p = 0.014$) and 50–59 to 60–79 ($p = 0.030$) but not for 30–39 to 40–49 ($p = 0.221$). The youngest and oldest strata differed substantially ($p < 0.0000001$).

For males, the Age effect ($F_{5,5883} = 9.22$, $p < 0.0000001$) and linear ($p = 0.000002$) and cubic ($p = 0.042$) trends were observed. For adjacent Age strata, the decrease was significant only for 10–19 to 20–29 ($p = 0.001$) and 50–59 to 60–79 ($p = 0.021$). The youngest and oldest strata differed substantially ($p < 0.0000001$).

Sex differences in DTD were found only at Age 10–19 ($t_{10913} = -9.401$, $p = 0.003$; all other $p > 0.441$), with males scoring higher than females. This effect was even stronger when age (in years) within the stratum was controlled as a covariate ($p < 0.000001$).

To control for the possible confounding effect of nightmares, the previous 2 × 6 ANOVA was reproduced in an ANCOVA using log (nightmares/month + 1) as a covariate. The Age main effect was still observed ($F_{5,28045} = 11.14$, $p < 0.0000001$) as was the absence of a Sex × Age interaction; moreover, the Sex main effect was now significant ($F_{1,28045} = 4.50$, $p = 0.034$). The Age main effect was again described best by a linear polynomial ($p < 0.0000001$) and to a lesser extent by quadratic ($p = 0.023$) and cubic ($p = 0.002$) trends.

Pearson correlations between age and DTD calculated separately by Sex and Age stratum revealed uniformly low coefficients. For females, the coefficients were uniformly negative and significant for 10–19 ($r = -0.035$, $p = 0.001$), 20–29 ($r = -0.024$, $p = 0.028$), and 30–39 ($r = -0.041$, $p = 0.012$), but not for 40–49 ($r = -0.025$, $p = 0.249$), 50–59 ($r = -0.013$, $p = 0.730$) or 60–79 ($r = -0.156$, $p = 0.070$). For males, the coefficients were significant for 10–19 ($r = -0.062$, $p = 0.022$), but no others ($r = -0.036$ to 0.048, all ns).

Pearson correlations revealed low, but highly significant, positive correlations between DRF and DTD for the entire sample ($r_{28888} = 0.282$; $p < 0.0000001$) and for males ($r_{5884} = 0.276$; $p < 0.0000001$) and females ($r_{23004} = 0.287$; $p < 0.0000001$) considered separately. For females, positive correlations between DRF and DTD of the same magnitude were found for every age stratum (all $p < 0.0000001$ except 60–79: $p < 0.001$); for males, positive correlations of the same magnitude were also found for every age stratum (all $p < 0.00004$) except 50–59 ($r = 0.097$, $p = 0.134$).

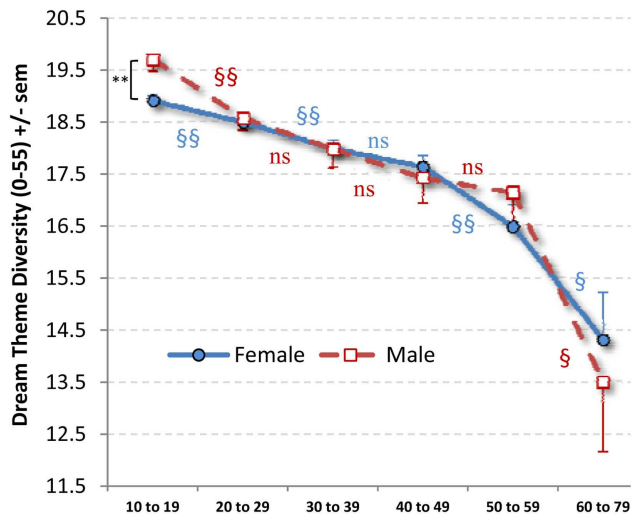

FIGURE 2 | Mean (SEM) dream theme diversity scores by Age stratum and sex. A Sex difference was observed only for 10–19 (** $p = 0.003$). Age differences between adjacent strata within Sex ($^{§}p < 0.05$; $^{§§}p < 0.02$) are indicated with red markers for males and blue markers for females.

PARTICIPANT SELF-SELECTION BIAS

To determine if participants visiting our (dream-themed) website were more likely than the general population to possess a higher level of dream recall, mean scores for the 55-item version of the DTD were compared with those from the identical *Divers 55* scale from our previous study of 1181 first-year Canadian University students (Nielsen et al., 2003). The latter were given the opportunity to participate in the research protocol for course credit but were nonetheless not required to do so. Participants in the previous study were aged 19.8 ± 3.9 years (males: 20.1 ± 3.60; females: 19.7 ± 3.97) and were thus compared with participants in the 10–19 and 20–29 age strata of the present study. Overall, the mean DTD score of the University student sample (16.4 ± 8.14) was about 2 points lower than that of the 10–19 age stratum (18.5 ± 10.46) and 1.5 points lower than that of the 20–29 age stratum (17.9 ± 10.02) of the present sample. For females, this value (16.4 ± 7.77) was 2.0 and 1.6 points lower for the two age strata (18.4 ± 10.23 and 18.0 ± 9.88 respectively) while for males, this value (16.3 ± 8.99) was 2.5 and 1.5 points lower (18.8 ± 11.33 and 17.8 ± 10.56). Thus, there was evidence of only a slight selection bias among both the male and female visitors to our website.

POSSIBLE "CHECKLIST FATIGUE" EXPLANATION FOR DTD FINDINGS

A specific pattern of results might be expected if the observed decrease in DTD scores was due to a tendency for older participants to prematurely grow weary of filling out the 56-item TDQ,

i.e., progressively fewer responses with increasing age for late, relative to early, parts of the questionnaire. If not, we would expect similar age-related decreases on all parts of the questionnaire. To test this possibility, the DTD score was divided into four quarters: Q1 (items 1–14), Q2 (items 15–28), Q3 (items 29–42), and Q4 (items 43–56). The relative frequencies of these scores were then compared over age strata. A 4 × 6 ANOVA with DTD quarter (Q1, Q2, Q3, Q4) as a repeated measure and Age as an independent measure revealed a main effect for DTD quarter ($F_{3,30484} = 7887.7$, $p < 0.0000001$) such that fewer responses were given for all of the quarters with increasing age (**Figure 3**). Further, the highest scores were given for Q1, followed by Q3, followed by Q2 then Q4. Considered separately, each quarter showed a linear decrease with age; however, these were more robust for Q1, Q2, and Q3 (all $p < 0.0000001$) than for Q4 ($p = 0.002$) which was, in fact, better described by a cubic trend ($p = 0.005$). *Post hoc t*-tests for Q4 indicated an abrupt drop-off after age 10–19 (all contrasts $p < 0.005$; all strata from 20–29 to 50–59 did not differ from each other). By contrast, Q1, Q2, and Q3 all showed relatively smooth linear decreases.

DISCUSSION

DECREASE IN DREAM RECALL FREQUENCY

Our results replicate findings from several previous cross-sectional studies showing decreased DRF with advancing age (for reviews see Funkhouser et al., 1999; Guenole et al., 2010). They are especially consistent with the finding that this DRF decrease occurs in early-to-middle adulthood rather than in later years (e.g., Herman and Shows, 1983; Giambra et al., 1996). We also demonstrate that this DRF decrease is preceded by a significant *increase* during adolescence, i.e., during the transition from ages 10–19 to 20–29. This increase replicates our previous findings in a longitudinal cohort of a DRF increase between ages 13 and 16 among both girls and boys (Nielsen et al., 2000). It also replicates findings from several other home and laboratory studies (Kales et al., 1968; Foulkes, 1982; Schredl, 2009). On the other hand, the year-by-year analyses of our youngest age groups confirmed an early DRF increase (from 10 to 15 years) among girls but not boys and a later increase (from 17 to 18 up to age 20) for both sexes. In the present study, the 10–19 and 20–29 age strata were the two largest cohorts ($N = 10{,}915$ and 9972) so the increases observed for these time periods are likely robust.

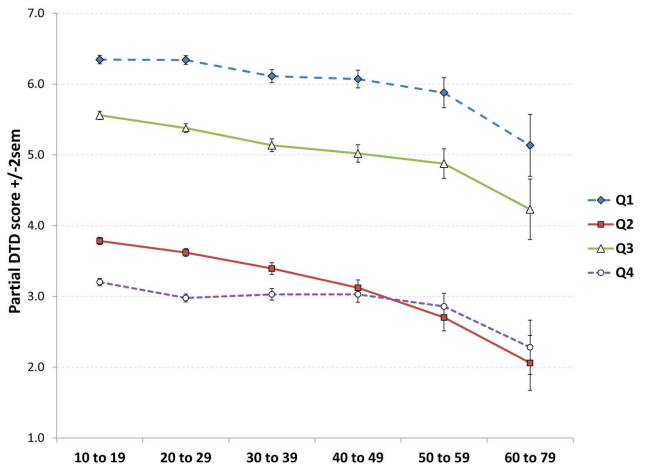

FIGURE 3 | Test of the "checklist fatigue" explanation of decreasing DTD scores with increasing age. Scores decrease with age for all four quarters of the questionnaire, but especially Q1 to Q3, observations not consistent with the fatigue hypothesis. Similarly, the consistent occurrence of higher scores for Q3 than Q2 suggests that participants did not grow weary of filling out the checklist by Q3.

The increase and subsequent decrease in DRF with age were observed for both male and female participants, but sex differences in the specific patterns of change suggest that females increase access to their dreams at a younger age, maintain it at a higher level, and decrease it later in the lifespan than do males. First, both sexes show the DRF increase from 10–19 to 20–29 but, considered year-by-year, girls increase gradually between ages 10 and 15, whereas boys do not. Second, DRF for both sexes increases in the late teens (males starting at 17, females at 18) to the age of 20. Third, females maintain a DRF advantage over boys until age 44. Fourth, males start their age-related DRF decrease earlier (30–39) than do females (40–49) and also reach their DRF nadir earlier (40–49) than do females (50–59). In this respect, the findings are remarkably consistent with those of Giambra et al. (1996, see Figure 1) who found that males show an abrupt DRF decrease starting in their 30s and reaching a nadir in their 40s; women begin a slower decrease in their 30s that continues to their 50s. Our results differ slightly from these in that females in the Giambra study showed a more gradual decrease than did the males whereas the reverse was true for our findings.

In sum, different age-related patterns of DRF for the two sexes suggest an overall greater access to dreaming during much of the lifespan for females than for males. The frequency of dream recall increases for females earlier (ages 10–15), remains elevated longer (14–44), decreases more abruptly, and reaches a nadir later (50–59) than it does for males (ages 17–20, 20–29, 40–49 respectively).

Mechanisms responsible for the age-related decline in DRF observed here and elsewhere remain uncertain. An obvious possibility is the decrease in amount of REM sleep that occurs with age (see meta-analyses in Ohayon et al., 2004; Floyd et al., 2007). The most vivid dreaming is reliably recalled from REM sleep and a decrease in the latter might be expected to result in less dream recall overall. However, the age-related decline in %REM sleep is small at best, estimated to be only 0.6% per decade (2.9% total from age 19 to 75); the correlation between age and %REM is only $r = -0.168$ (Floyd et al., 2007).

Physiological features of REM sleep have also been evoked to explain the age-related decrease in dream recall. Changes in specific EEG frequencies and topographic distributions of the EEG have been linked to age-related differences in DRF (Chellappa et al., 2012), but these associations are much more apparent for NREM than for REM sleep. The phase advance and decrease in amplitude of endogenous circadian rhythms (e.g., temperature, melatonin, cortisol) with advancing age have also been proposed to influence DRF; changes in the circadian rhythm of REM sleep propensity are especially pertinent (Chellappa et al., 2009). The latter group's use of a 40-h 75/150 min multiple nap schedule revealed that older subjects' deficit in dream recall relative to that

of young controls occurred during the subjective day, close to the peak of REM sleep propensity – the amplitude of which was also diminished in the older group. Cortisol has also been discussed as a potential marker of dream content due to its circadian patterning (Nielsen, 2004; Payne and Nadel, 2004) and its relationship to memory consolidation (Payne, 2010); changes in cortisol rhythmicity with age (increased nadir, curve flattening; Ferrari et al., 2001) may well negatively affect dream recall. Such changes are, in fact, associated with other cognitive deficits (Ferrari et al., 2001).

Other possible modulators of an age-related decrease in DRF include a diminished interest in dreams or a relative lack of current concerns that might influence dreams (Strunz, 1993), or a progressive deterioration of memory or cognitive skills such as those related to both spatial perception and dreaming (Zanasi et al., 2005). One possible cognitive mechanism, an age-related decrease in episodic and autobiographical memory, will be discussed later relative to DTD.

In sum, there is some evidence that the age-related decrease in dream recall may be influenced by a parallel decrease in %REM sleep, by changes in sleep physiology such as an advance or diminishment of the circadian rhythm of REM sleep propensity, by changes in the circadian pattern of cortisol production, or by progressive deficits in other memory and cognitive mechanisms. None of this evidence is conclusive, however, and none readily explains our observation that DRF decreases in two distinct age-related patterns for males and females.

SEX DIFFERENCE

The present findings replicate a sex difference in DRF favoring females that has been observed in children, adolescents, and adults (see meta-analysis in Schredl and Reinhard, 2008). Because of our large sample, we were able to determine with some confidence that this sex difference appears in early adolescence (age 14) and (with less confidence) that it disappears in middle adulthood (age 44). The precision of these findings may help explain why some previous studies have identified a sex difference in DRF for children, i.e., because they grouped participants who were both younger and older than age 14.

Although there is no definitive explanation for the sex difference reported here, the cognitive processes of women are known to differ from those of men in a number of basic ways that might be related to superior recall of dream content. These include enhanced processing of novel visual stimuli (Yuan et al., 2012) and facial expressions (McClure, 2000), superior performance on several social cognition tasks (Gur et al., 2012), and better memory for emotional stimuli (Canli et al., 2002), episodic stimuli (Herlitz and Rehmann, 2008), and autobiographical episodes (Seidlitz and Diener, 1998; Fivush, 2011; Zucco et al., 2012), whether such episodes are positive, negative, or neutral in affective tone (Seidlitz and Diener, 1998). The neurophysiological differences contributing to sex differences in emotional processing are well-known (Cahill et al., 2004; Andreano and Cahill, 2009), including those underlying sex differences in autobiographical memory (Piefke and Fink, 2005). As there is good evidence that episodic and autobiographical memory processes also diminish with age, this may be the most appropriate explanation for the observed sex difference. In short, superior dream recall may be but one expression of an underlying advantage that women enjoy in the processing and remembering of novel, emotional, social imagery.

DREAM THEME DIVERSITY FINDINGS

Findings for the DTD measure contradicted our expectation that the prevalence of typical dream themes would accumulate with increasing age. Rather, DTD scores decreased monotonically with age for both sexes. This unexpected finding forces us to reconsider our initial interpretation of the DTD measure in light of several alternatives. A first possibility that we examined in our analyses considered that DTD scores may have decreased with age because of "checklist fatigue" or the possible tendency for a subject's motivation to complete the entire 56-item questionnaire to wane with age. We found evidence that this was likely not the case in that linear decreases with age were seen for all four quarters of the questionnaire when considered separately and that such a decrease was *least* evident for the fourth quarter of the questionnaire where the steepest decrease would have been expected. A related consideration is that instructions for completing the questionnaire may not have been properly understood to refer to dreams recalled over the *entire* lifespan and participants therefore only reported dreams they could recall from recent memory. While it seems unlikely that all participants would misconstrue the instructions in this manner, the possibility would imply that the DTD findings are due to an age-related decline in recall for recent typical dreams.

A second possible explanation of the DTD findings is that the typical dreams comprising this measure are sensitive to generational differences in life experiences. Older participants may have had fewer of the life experiences that are thought by some (e.g., Freud, 1900) to trigger typical themes such as those on the questionnaire. By this reasoning, for example, fewer experiences with airplane flight by older individuals might be reflected in a lower likelihood of having flying dreams, or less witnessing of violence might lead to a lower likelihood of having attack dreams, and so forth. While this possibility could not be addressed directly with the present measures, evidence for such an effect was found to partially explain a progressive age-related decrease in color dreams (Schwitzgebel, 2003; Murzyn, 2008), specifically, older subjects had both fewer color dreams and more past exposure to black and white televisions (Okada et al., 2011). Notwithstanding this finding, the latter authors also found that the effect size of the generational influence on color dreams was only one twentieth of the effect size observed for aging *per se*. The generational explanation is also not consistent with the fact that Griffith et al.'s (1958) early cohorts of American and Japanese participants had a mean diversity proportion of 44% (calculated out of a total of 34 typical dream items) which was much higher (not lower) than those in the present study for any Age stratum, which were (from youngest to oldest) 35, 33, 32, 31, 31, and 24% (calculated out of 56 items). Future studies could further assess this hypothesis by examining age-related changes in individual DTD items for which associated life experiences have either remained constant over generations (e.g., losing teeth, falling down) or have become less, not more, accessible to more recent generations (e.g., seeing snakes, seeing violent wild beasts).

A third possible explanation is that the DTD decrease observed here reflects a parallel age-related decrease in nightmare frequency

reported elsewhere. For a participant cohort largely overlapping with the present one we previously showed a decrease for the nightmare frequency measure, log (nightmares + 1), that had Sex, Age, and Sex × Age interactions that were similar to the ones for DRF found in the present study (see Figure 1 in Nielsen et al., 2006). However, this possibility is not supported by the fact that, when the log nightmare measure was controlled as a covariate in the present analyses, the main effects and interactions for both DRF and DTD measures were maintained.

A final possibility – and one favored here – is that the DTD is effectively a measure of one form of episodic or voluntary autobiographical memory; accordingly, its age-related decrease may be an expression of similar decreases that have been demonstrated for these latter memory systems (Piolino et al., 2002). Many studies indicate that both episodic memory and autobiographical memory (i.e., memory for episodes that are personally significant and emotional in nature) are reduced with age whereas semantic memory is preserved (Kensinger, 2009; St-Laurent et al., 2011). In fact, older adults, relative to younger adults, show a decrease in the episodic richness of autobiographical memories, i.e., in the proportion of specific episodic details relative to semantic information (Levine et al., 2002; Piolino et al., 2002; St Jacques and Levine, 2007). This decrement is apparent for autobiographical memories that are voluntarily evoked in response to cues (such as for the items of the TDQ), but not for autobiographical memories that occur involuntarily (Schlagman et al., 2009).

To illustrate these findings, one study (Levine et al., 2002) using a standardized *Autobiographical Interview* method, demonstrated that younger adults who were asked to recall memories from five distinct life periods reported mainly episodic details reflecting happenings, locations, perceptions, and thoughts whereas older adults reported primarily semantic details not connected to a particular time and place. This group difference persisted even when subjects were specifically probed to report contextual details. Thus, the DTD in the present study may be a type of cued-recall autobiographical memory measure analogous to the *Autobiographical Interview* in that it probes for the simple recognition of 56 high-probability dream themes also occurring in different life periods. And, like other cued-recall measures, the DTD may be sensitive to age-related memory declines.

An exception to the conclusion that the richness of autobiographical memories is attenuated with age is the fact that many such memories tend to date from adolescence/early adulthood, a phenomenon referred to as the "reminiscence bump" (Schlagman et al., 2009). Memory associations to dreams have, in fact, been found to conform to this curvilinear reminiscence pattern for older but not younger subjects (Grenier et al., 2005). The existence of the reminiscence bump is consistent with the notion that recall for some long-past autobiographical material remains as good as, or even better than, it is for more recent material. Such a disproportionate memory for remote material is referred to by some as a "temporal gradient" and has been found repeatedly in pathological amnesias such as Korsakov's syndrome but also less severely in normal aging using past media-related events as probes (Bizzozero et al., 2008). Thus, to the extent that typical dream themes originate in adolescence/early adulthood, evidence of an age-related autobiographical memory decline may not be a sufficient explanation for the observed DTD results. Rather, the results may reflect some other type of cognitive or affective deficit, such as memory reconsolidation. On the other hand, it is not known whether most TDQ themes in fact do date from the adolescence/early adulthood time period. Moreover, that the reminiscence bump occurs for important and positive memories but not sad, traumatic, or negative memories (Berntsen and Rubin, 2002; Thomsen et al., 2011) suggests that positive DTD items would be less likely than negative items to suffer age-related decreases. Given that many of the DTD items are highly emotional in nature in either a positive (e.g., flying, sexual experiences, finding money) or a negative (e.g., being chased, being attacked, being tied up, dying) sense, they may well be differentially sensitive to the autobiographical reminiscence bump. This alternative explanation of the DTD findings could be tested further by determining if age-related decreases occur for individual DTD items whose emotions are highly positive vs. negative in nature.

To summarize, a number of alternatives may be considered in explaining the unexpected age-related decrease in dream diversity observed here. Some of these, such as age-related changes in REM sleep physiology and circadian regulation or generational differences in opportunities for life experience, are supported by only a limited number of studies whose effects are small. A more parsimonious explanation may be that the DTD measure reflects age-related changes in episodic and autobiographical memory that have been demonstrated in a number of other contexts. If so, this interpretation raises questions about how participants come to forget typical dreams that they may once have experienced and remembered, which types of typical dreams are more likely to be forgotten in this manner, and whether the reliable age-related decreases in DRF may, too, be partly explained by such changes in episodic and autobiographical memory.

VALIDITY OF INTERNET SAMPLES

It is now widely accepted that Internet samples constitute a valid source of information about self-reported human behavior; such samples may even be superior to other sampling methodologies in several respects. The use of Internet surveys has increased markedly in many areas, including sleep medicine (Mindell et al., 2010; e.g., Saxvig et al., 2012) and dreaming (e.g., Cheyne et al., 1999; Brand et al., 2011) as well as in other areas that concern sensitive personal information. Surveys of sexual health (e.g., Foster et al., 2010) and the use of illicit drugs (e.g., Noack et al., 2011) are but two of many examples. Advantages of Internet surveys include the sharing of information and experiences that might not be disclosed by other means, reduction of social desirability and yea-saying biases, reduction of error, and access to hidden and hard-to-reach populations (for review see Rhodes et al., 2003). Online surveys have been validated against paper-and-pencil tests (Knapp et al., 2004), mail surveys (McCabe, 2004), and national population studies (Ross et al., 2005), with high concordances between methods having been reported (Mindell et al., 2010; e.g., Saxvig et al., 2012).

In contrast, health-oriented web sites such as our own may attract more individuals who suffer from health difficulties; our site is particularly likely to attract individuals with an interest in sleep, dreaming, and nightmares. Since females are more likely than males to seek help, especially for emotional problems (Moller-Leimkuhler, 2002), a self-selection gender bias may have influenced the composition of our sample. There may also be self-selection biases toward younger, more educated and more affluent respondents, such as those who can afford Internet access (Ross et al., 2005; Mindell et al., 2010). Additionally, the sample of the present study may have been biased in that responses by participants who did not respond to DRF items with quantifiable numbers were excluded.

ACKNOWLEDGMENTS

Research was supported by grants from the Social Sciences and Humanities Research Council of Canada, the Natural Sciences and Engineering Research Council of Canada, and the Canadian Institutes of Health Research.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 19 March 2012; accepted: 12 June 2012; published online: 04 July 2012. Citation: Nielsen T (2012) Variations in dream recall frequency and dream theme diversity by age and sex. Front. Neur. **3**:106. doi: 10.3389/fneur.2012.00106*
This article was submitted to Frontiers in Sleep and Chronobiology, a specialty of Frontiers in Neurology.

APPENDIX

TYPICAL DREAMS QUESTIONNAIRE

Please rate how often in your life you have dreamed about each of the following themes; for each theme please circle a number from 0 to 4 as defined by this scale:

0, never; 1, 1 time; 2, 2–3 times; 3, 4–10 times; 4, 11+ times.

1	Being chased or pursued, but not physically injured	0	1	2	3	4
2	Being physically attacked (beaten, stabbed, raped, etc.)	0	1	2	3	4
3	Trying again and again to do something	0	1	2	3	4
4	Being frozen with fright	0	1	2	3	4
5	Eating delicious foods	0	1	2	3	4
6	Arriving too late, e.g., missing a train	0	1	2	3	4
7	Swimming	0	1	2	3	4
8	Being locked up	0	1	2	3	4
9	Snakes	0	1	2	3	4
10	Finding money	0	1	2	3	4
11	Flying or soaring through the air	0	1	2	3	4
12	Falling	0	1	2	3	4
13	Being inappropriately dressed	0	1	2	3	4
14	Being nude	0	1	2	3	4
15	Being tied, unable to move	0	1	2	3	4
16	Having superior knowledge or mental ability	0	1	2	3	4
17	Creatures, part animal, part human	0	1	2	3	4
18	Your teeth falling out/losing your teeth	0	1	2	3	4
19	Seeing yourself in a mirror	0	1	2	3	4
20	Having magical powers (other than flying or floating through the air)	0	1	2	3	4
21	Floods or tidal waves	0	1	2	3	4
22	Tornadoes or strong winds	0	1	2	3	4
23	Earthquakes	0	1	2	3	4
24	Insects or spiders	0	1	2	3	4
25	Being a member of the opposite sex	0	1	2	3	4
26	Being an object (e.g., tree or rock)	0	1	2	3	4
27	Being killed	0	1	2	3	4
28	Seeing yourself as dead	0	1	2	3	4
29	Vividly sensing, but not necessarily seeing or hearing, a presence in the room	0	1	2	3	4
30	Being unable to find, or embarrassed about using, a toilette	0	1	2	3	4
31	School, teachers, studying	0	1	2	3	4
32	Sexual experiences	0	1	2	3	4
33	Losing control of a vehicle	0	1	2	3	4
34	Fire	0	1	2	3	4
35	A person now dead as alive	0	1	2	3	4
36	A person now alive as dead	0	1	2	3	4
37	Being on the verge of falling	0	1	2	3	4
38	Failing an examination	0	1	2	3	4
39	Being smothered, unable to breathe	0	1	2	3	4
40	Wild, violent beasts	0	1	2	3	4
41	Being at a movie	0	1	2	3	4
42	Killing someone	0	1	2	3	4
43	Lunatics or insane people	0	1	2	3	4
44	Being half awake and paralyzed in bed	0	1	2	3	4
45	Seeing a face very close to you	0	1	2	3	4
46	Seeing a UFO	0	1	2	3	4
47	Seeing extra-terrestrials	0	1	2	3	4

(Continued)

Continued

0, never; 1, 1 time; 2, 2–3 times; 3, 4–10 times; 4, 11+ times.						
48	Traveling to another planet or visiting a different part of the universe	0	1	2	3	4
49	Being an animal	0	1	2	3	4
50	Being a child again	0	1	2	3	4
51	Seeing an angel	0	1	2	3	4
52	Encountering God in some form	0	1	2	3	4
53	Discovering a new room at home	0	1	2	3	4
54	Seeing a flying object crash (e.g., airplane)	0	1	2	3	4
55	Someone having an abortion	0	1	2	3	4
56	Encountering a kind of evil force or demon	0	1	2	3	4

Other (please describe)
Which theme occurred *most often* in your life (please specify number from 1 to 56)? _____.
Which theme occurred *earliest* in your life (please specify number from 1 to 56)? _____ At what age?_____years.
How many *dreams* of any kind do you recall *in an average month (circle one)*? 0, 1–2, 3–5, 6–10, 11–15, 16–20, 21–25, 26–30, 31+.
How many *nightmares* do you recall *in an average month (circle one)*? 0, 1–2, 3–5, 6–10, 11–15, 16–20, 21–25, 26–30, 31+.