Thomas Penzel • Roberto Hornero
Editors

Advances in the Diagnosis and Treatment of Sleep Apnea

Filling the Gap Between Physicians and Engineers

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Editors
Thomas Penzel
Sleep Medicine Center
Charite Universitätsmedizin Berlin
Berlin, Berlin, Germany

Roberto Hornero
Biomedical Engineering Group
University of Valladolid
Valladolid, Spain

Centro de Investigación Biomédica en
Red Bioingeniería
Biomateriales y Nanomedicina
(CIBER-BBN)
Valladolid, Spain

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Preface

Sleep apnea is a sleep disorder with a very high prevalence and many health consequences. As such it is a major health burden (Benjafield et al., 2019). Sleep apnea has been systematically explored only a little more than 40 years now (Guilleminault & Dement, 1978). Major impacts of sleep apnea are sleepiness and associated risks for accidents (Bonsignore et al., 2021). Major health impacts are cardiovascular risk and pathophysiological traits, even if this is currently much debated when focusing on the apnea-hypopnea index as the measure for sleep apnea severity (Arnaud et al., 2020). Sleep apnea is a disorder which is a chronic condition and can be treated successfully.

The disorders of sleep-disordered breathing have largely supported the growth of sleep medicine in general from a small specialty field to a major spectrum of disorders in the arena of medical specialties. This activity helped to convert the niche field of sleep research into sleep medicine, a clinical discipline with its own departments, its own center certification, physician certification, dedicated conferences, journals, and research activities. The recognition and importance have grown so much that the new International Classification of Disorders by WHO in its 11th version, being launched in 2022, has added a new section on sleep and wake disorders with its own range of codes. This worldwide recognition will enable the growth of medical education on sleep physiology, sleep pathology, and specific sleep disorders.

The diagnostic field for sleep disorders, and for sleep apnea specifically, is strongly linked to the development of new and recent methods, which allow long-term recording and analysis of physiological functions during sleep. Sleep and sleep apnea are not just identified by taking a single blood sample or by a single measurement by a physician at a visit, but sleep recording requires the continuous recording of biosignals. This is comparable to monitoring of vital functions during anesthesia or intensive care. Because of this methodological challenge, biomedical engineering as well as new sensor and analysis technologies are closely linked to the development of sleep apnea diagnosis. New technologies helped to a large extent develop new diagnostic and treatment modalities for sleep-disordered breathing. Sleep apnea diagnostic research is now linked to the development of new wearables, nearables, and smartphone apps, and profits much from the ubiquitous development of photoplethysmography recording everywhere.

Artificial intelligence is playing a very important role in analyzing sleep recordings and, particularly, in automatizing several of the stages of sleep apnea diagnosis. Since the generalization of computerized analysis in the 1990s, automated processing of cardiorespiratory and neuromuscular signals from polysomnographic studies provided a number of indices able to assist sleep experts in the characterization of the disease (Shokoueinejad et al., 2017). Parameterization of the influence of apneic events on biological system dynamics has relied on widely known techniques from the engineering field, such as spectral and nonlinear analysis. Currently, there is a demand for novel alternative metrics able to overcome the limitations of the standard apnea-hypopnea index concerning its low association with patient symptoms and outcomes (Malhotra et al., 2021). In this regard, signal processing and pattern recognition are going to play a key role. In addition, machine learning has also shown its usefulness in the last decades (Uddin et al., 2018) and, like many other areas in our society, sleep apnea diagnosis is rapidly entering the deep learning era (Mostafa et al., 2019) and big data. These new analytical techniques, along with the advances in health device development, are the main hope for reaching a reliable diagnostic paradigm shift. One that finally could cope with the disease prevalence, personalized interventions, and runaway spending.

Beyond the widespread application of machine learning methods to automate polysomnography scoring and to provide sleep experts with tools for automated diagnosis, artificial intelligence has also the potential to significantly improve the management of sleep apnea treatment. Recent advances in the framework of big data together with remote monitoring capability of novel treatment devices are able to promote conventional sleep medicine towards a real personalized medicine. Identification of refined clinical phenotypes of patients will allow the development of precision interventions, enabling the quick identification of the treatment option that best fits the particular characteristics of a patient (Watson & Fernández., 2021). Similarly, machine learning is able to accurately model patient's adherence from usage data (pressure setting, residual respiratory events, mask leaks) derived from portable treatment devices, improving the efficacy of available therapies (Goldstein et al., 2020). Thus, artificial intelligence is going to significantly change the management of sleep apnea treatment in the short term.

This volume gives a basis of current knowledge on sleep research, sleep medicine, and sleep apnea, with a strong focus on new challenges and new research directions in the diagnosis of sleep apnea and its treatment. The volume contains three sections: the first one is on physiology and pathophysiology, the second one is on diagnostic advances, and the third one is on treatment advances. Each chapter author was asked to not only describe the state of the art but also develop visions for future research as seen from their special angle and viewpoint.

As editors, we think that the volume can serve as an introduction to the field of sleep-disordered breathing, can serve as a basis for educating in sleep-disordered breathing, and can immediately stimulate and trigger new research in physiology, clinical trials, and biomedical engineering for sensors and analysis methodologies.

Berlin, Berlin, Germany — Thomas Penzel
Valladolid, Spain — Roberto Hornero

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Contents

2 Covering the Gap Between Sleep and Cognition – Mechanisms and Clinical Examples

Javier Gomez-Pilar, Gonzalo C. Gutiérrez-Tobal, and Roberto Hornero

Abstract

A growing number of studies have shown the strong relationship between sleep and different cognitive processes, especially those that involve memory consolidation. Traditionally, these processes were attributed to mechanisms related to the macroarchitecture of sleep, as sleep cycles or the duration of specific stages, such as the REM stage. More recently, the relationship between different cognitive traits and specific waves (sleep spindles or slow oscillations) has been studied. We here present the most important physiological processes induced by sleep, with particular focus on brain electrophysiology. In addition, recent and classical literature were reviewed to cover the gap between sleep and cognition, while illustrating this relationship by means of clinical examples. Finally, we propose that future studies may focus not only on analyzing specific waves, but also on the relationship between their characteristics as potential biomarkers for multiple diseases.

Keywords

Sleep · Cognition · Sleep spindles · Slow oscillations · Slow waves

2.1 Why We Need to Sleep?

Surprisingly, after decades of research, there is still no consensus or a clear answer to this question. This is probably not due to a lack of knowledge of the sleep functions, but to the number of functions it performs both for the brain and for the whole body. Finally, after multiple studies, we are now able to understand some of them.

J. Gomez-Pilar (✉) · G. C. Gutiérrez-Tobal
Biomedical Engineering Group, University of Valladolid, Valladolid, Spain

Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Valladolid, Spain
e-mail: javier.gomez@gib.tel.uva.es

R. Hornero
Biomedical Engineering Group, University of Valladolid, Valladolid, Spain

Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Valladolid, Spain

Mathematics Research Institute of the University of Valladolid (IMUVa), Valladolid, Spain

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More than 40 years ago, the famous researcher Allan Rechtschaffen, accepted that sleep functions should be of unquestionable utility, since "if sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made". Although Rechtschaffen's intuition was correct, he probably did not imagine the number of functions of sleep, which include the elimination of toxins (Xie et al., 2013), regulation of glucose level (Van Cauter et al., 2008) and endocrine functions (van Cauter et al., 2007), stimulation of immune function (Ganz, 2012), modulation of emotional brain processes (Walker, 2009), or reinforcement of learning and memory mechanisms (Antony et al., 2019; Fang et al., 2019; Fernandez & Lüthi, 2020; Schabus et al., 2004), among others (see the review from Assefa and colleagues (ZAssefa et al., 2015) for different theories of the sleep functions).

In this chapter, we are interested in addressing one of these sleep functions, in particular delving into the proven relationship between sleep and cognition across the lifespan (Murawski et al., 2018; Ohayon et al., 2004; Reynaud et al., 2018; Yaffe et al., 2014), as well as its link with a large number of diverse pathologies (Ferrarelli & Tononi, 2017; Gutiérrez-Tobal et al., 2021; Vgontzas & Pavlović, 2018; Weng et al., 2020). Accordingly, it is essential to mention sleep spindles as a mechanism that plays a central role in cognitive processes, such as memory consolidation (Fogel, Albouy, et al., 2017; Fogel & Smith, 2011; Fogel, Vien, et al., 2017). Therefore, our main aim is to provide a synthesis of the role of sleep, with special focus on sleep spindles, and the relationship between sleep abnormalities and diverse pathologies.

2.2 Sleep Electrophysiology

2.2.1 Acquisition of the Electroencephalogram

The usual way to acquire the neuronal electrical signal is the use of the electroencephalogram (EEG). The equipment usually used is between 8 and 64 channels, although there are already systems with more than 1000 electrodes (ref). The sampling frequency depends on the equipment but is usually not less than 128 Hz or more than 1000 Hz. Although these are the usual characteristics, the acquisition of the EEG during sleep is usually performed in specialized Sleep Units, where many other signs are usually acquired, such as those from a polysomnography (PSG) (Jafari & Mohsenin, 2010).

Given the great variability of acquisition characteristics, the American Academy of Sleep Medicine (AASM) suggests minimum characteristics for EEG acquisition during sleep (Iber et al., 2007). Among them, they recommend a desirable sampling rate of 500 Hz, establishing the minimum into 200 Hz. In this way, according to Nyquist's theorem, it is possible to analyze frequencies up to 100 Hz. However, for clinical utility a high-frequency filter of 35 Hz is also recommended. Additionally, electrode impedance must keep under 5 KΩ and the minimum resolution should be 12 bits per sample.

2.2.2 Sleep Stages and the Cyclical Sleep

Sleep is far from uniform. Conversely, it is essentially cyclical, with cycles lasting about 90 minutes on average. However, the duration of each cycle is highly variable, increasing its duration throughout the night (Březinová, 1974). During a typical 8-hour restful sleep, there are usually between four to six cycles chained in a row (Keenan, 1999). Within these cycles, there are different stages of sleep that, according to the latest version of the AASM guide (Iber et al., 2007), are divided into two main periods: rapid eye movement (REM) and non-rapid eye movement (NREM). While REM stage is not divided into other subphases, NREM, in turn, consists of three different stages: N1, N2, and N3.

It is known that the duration of these sleep stages is not constant with age. In particular, as we get older, there is an increasing percentage of sleep in N1 and N2 stages, while the percentage of time in N3 and REM is decreased, resulting in

less restful sleep and, sometimes, increased age-related cognitive decline (Feinsilver, 2003; Ohayon et al., 2004). It seems, therefore, that each stage of sleep has a specific function and that small percentual alterations in their duration have a great influence in both the short and the long term.

If we take a closer look at what happens in each of the stages of sleep, we can see that each one has well-differentiated characteristics:

N1) Stage 1 is essentially a transition stage from "wake" to "sleep" states, and it usually lasts just one to five minutes (Březinová, 1974). During N1 sleep, the body starts to slow down, giving rise to periods of brief and sudden movements (hypnogogic jerks) (Vetrugno & Montagna, 2011). Brain activity slows down too, and the alpha frequencies (in adults) are no longer the most dominant (Iber et al., 2007). As sleep cycles occur, phase N1 serves as a reset to restart a new cycle, but an uninterrupted sleep may not spend much more time in N1 throughout the night.

N2) During N2, the body reduces its temperature, relaxes the muscles, and slows the heart and breathing rates. At the same time, eye movement stops, and brain waves lower their dominant frequency relative to N1 (Schönauer & Pöhlchen, 2018). At this time, brief bursts of activity, characteristic of this stage, begin to emerge: the *sleep spindles* (Schönauer & Pöhlchen, 2018). Among the various functions of spindles (some of them are addressed in the next subsection), it is known that they help resist being woken up by external stimuli (Walker, 2009). Although the N2 stage can last from 10 to 25 minutes during the first sleep cycle, it lengthens as the night progresses, reaching approximately half of the total sleep time (Březinová, 1974).

N3) Stage 3 is also known as deep sleep. During this stage it is more difficult to wake someone up. Muscle tone, pulse, and respiratory rate decrease further (Diekelmann & Born, 2010). Something similar occurs with brain activity: thalamocortical neurons fall into a hyperpolarized state, resulting in slow waves (SW) between 0.5 and 4.5 Hz (i.e., delta activity) (Bernardi et al., 2018). During the first few sleep cycles, the N3 stages typically last between 20 and 40 minutes. As one goes through the cycles, this stage gets shorter, and more time is spent in REM sleep instead.

REM) Paradoxically, during REM sleep, brain activity increases, reaching levels of complexity that resemble activity during wakefulness, or at least N1 (Zilio et al., 2021). The body experiences atony except for the eyes that move rapidly, reason why this stage receives its name. Although dreams can occur at any stage of sleep, they are more common and intense in REM sleep, which is believed to be related to certain cognitive functions such as memory, learning, and creativity (Cai et al., 2009). REM stages are lengthened, especially in the second half of the night, lasting up to an hour.

The cyclical repetitions of the sleep phases described above are chained in a repeating pattern, which is usually represented by a hypnogram (see Fig. 2.1). Although with certain limitations, there are various automatic methods to identify the sleep phases from the EEG signal (Boostani et al., 2017), so it is common in clinical practice that this identification is not carried out manually (Aboalayon et al., 2016).

2.2.3 The Nested Hierarchy of Electrophysiological Waves during Sleep

In each of the sleep stages, there is a dominant oscillation activity easily measurable by means of the EEG signal. This dominant signal is fundamentally slower than the EEG during wakefulness. Nonetheless, there is a complex microarchitecture, comprising both slow and fast non-stationary burst events (Gorgoni et al., 2020). Thus, while some networks such as visual, auditory, somatomotor, and the default mode remain almost unchanged during sleep relative to wakefulness (Larson-Prior et al., 2009), different brain waves, such as slow oscillations (SOs), spindles

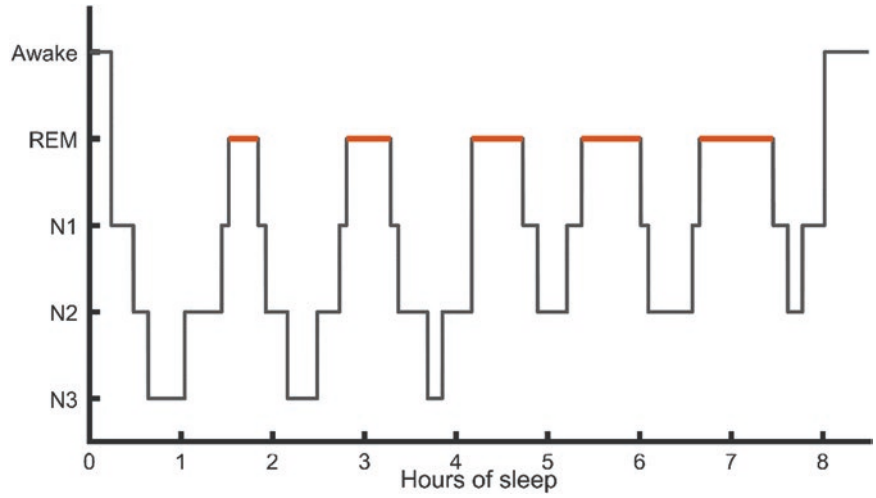

Fig. 2.1 Hypnogram. Representation of sleep stages as a function of time. This hypnogram shows typical sleep architecture with the majority of slow-wave sleep (N3) in the first half of the night, while REM sleep majority is in the last half, with progressive longer durations

and ripples, are generated through activation of rhythmic neuronal thalamocortical connections. These waves do not occur in isolation, but are elicited within a well-defined nested hierarchy, where SOs are thought to have a relevant role in their organization (Gomez-Pilar et al., 2021; Staresina et al., 2015).

SOs are oscillations around 0.75 Hz that, during their up-state, facilitate the production of spindles (Ngo et al., 2019; Staresina et al., 2015), which are easily recognized as burst between 11 and 16 Hz (Antony et al., 2019), i.e., signa band (see Fig. 2.2 for an example of the nesting between SOs and spindles). In turn, sleep spindles facilitate the firing of ripples in the hippocampus, high frequency bursts around 100 Hz (Axmacher et al., 2008; Staresina et al., 2015).

Although the function of these neuronal triggering chain reactions is still not fully understood, the dynamic interaction of these waves is believed to be closely related to the exchange of information between distributed cortical regions, promoting various cognitive functions (Axmacher et al., 2008; Ngo et al., 2019; Staresina et al., 2015).

2.3 Memory Consolidation – The Role of Sleep Spindles

Memory processes begin with the neural encoding of experiences, which results in storage "within" the brain (Harrison & Horne, 2000; Poh & Chee, 2017; Stickgold & Walker, 2005). However, without post-encoding memory processes, this initial encoding does not persist over time. Therefore, the so-called memory consolidation is necessary for long-term storage.

Thanks to sleep deprivation studies, it is known that sleep plays an important role in the encoding processes during wakefulness (Drummond et al., 2000). Even more interesting are some recent studies that have shown that sleep strongly influences memory consolidation (Fogel, Albouy, et al., 2017; Hahn et al., 2019). Although the precise underlying processes are still unknown, we have gained valuable clues about them.

Traditionally, a link between REM and memory has been stablished both in human (Siegel, 2001) and animal studies (Pearlman, 1979). More recently, NREM sleep has been associated with

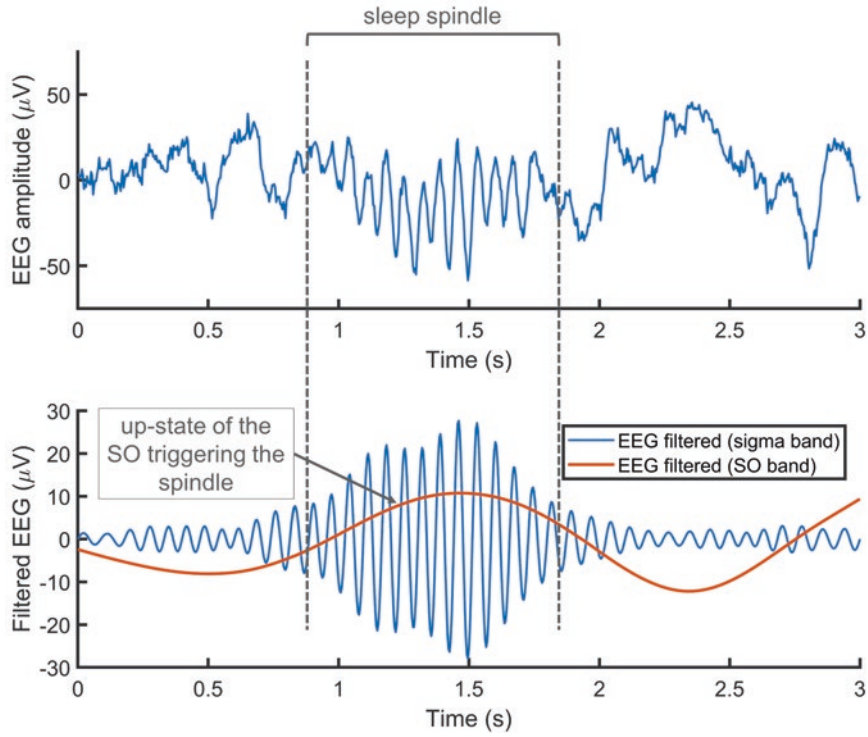

Fig. 2.2 Oscillatory hierarchy nested during sleep. The upper panel shows the EEG signal at the Cz electrode during a spindle event (during N2). The lower panel represents the signal filtered to show the slow oscillation (low pass filtering between 0 and 1 Hz) and show the sleep spindle (bandpass filtering between 11 and 16 Hz). It can be seen how, just after the up-state of the slow oscillation, the spindle is elicited

memory consolidation, especially the stages related to the appearance of sleep spindles (Cairney et al., 2018). These memory consolidation processes during NREM stages are based on the strengthening of particular memory pathways through the delivery of auditory cues (Cairney et al., 2017), a procedure known as targeted memory reactivation (TMR) (Cairney et al., 2018). Interestingly, the time window that coincides with spindle activity overlaps with the TMR process (Cairney et al., 2018). This fact, together with the positive correlation between spindle density and cognitive performance (Fogel & Smith, 2011), procedural memory (Fogel & Smith, 2006), or IQ (Fang et al., 2017), highlights the role of sleep spindles in the service of memory consolidation.

2.4 Is There Room for Slow Oscillations?

As previously stated, sleep spindles are not isolated events. Changes in electrophysiological activity are often mediated by an external stimulus, varying from ongoing activity to task-related activity elicited by external stimulus. However, this transition between states can also be mediated by "internal stimulus", eliciting what is known as internally evoked activity (i.e., internally-guided cognition) (Nakao et al., 2012). Sleep spindles could be considered an example of this internal evoked activity triggered by SOs and elicited during their up-state.

This relationship was evidenced in a recent study in which pre-spindle and spindle activity

strong correlations were reported (Gomez-Pilar et al., 2021). Curiously, these correlations were stronger than wake-related evoked activity (Wolff et al., 2019). In other words, this suggests that the brain dynamics associated with SOs determine with great fidelity the characteristics of the following spindle. Whether SOs and the posterior spindle interact with the sleep spindles following an additive (Arieli et al., 1996) or non-additive (Huang et al., 2017) model remains unclear. Non-additive models are based on the assumption that there is a nonlinear superposition between the different waves of the brain activity, which is between SOs and sleep spindles. It would be associated with higher uniformity of the activity, which facilitates the information processing in the cortex (Monier et al., 2003; White et al., 2012). This increased stability would lead to a more structured dynamics enhancing the data predictability (Gershenson & Fernández, 2012). Being aware of the repetitive and uniform patterns in closed loop between the thalamus, reticular nucleus, and the neocortex during SOs and spindle generation (Schönauer & Pöhlchen, 2018), this stability would play a fundamental role for sending information units to distributed neocortical sites for long-term storage. Therefore, a non-additive model in which SOs have a fundamental role is, in principle, presented as a more likely model during sleep for memory consolidation. This is supported by a previous study focused on boosting SOs through transcranial stimulation (Marshall et al., 2006), instead of stimulating the generation of spindles (Berner et al., 2006; Ladenbauer et al., 2017). However, future work is required to support this hypothesis.

2.5 Consequences of Poor Sleep Quality – Illustrative Examples

At this point, we can be confident of the relevant role that sleep has not only in a number of cognitive processes, especially those related to encoding and memory consolidation processes, but also in metabolic processes (van Cauter et al., 2007; Van Cauter et al., 2008). Then, it is worth asking what effects may arise related to pathologies that cause a reduction in the quality of sleep. Or, in the opposite direction, a poor quality of sleep can increase the probability of developing (or worsening) certain diseases?

The number of diseases in which a close relationship with sleep has been found is far from negligible, and it seems to be constantly increasing, such as sleep apnea, migraine, Alzheimer's disease, schizophrenia (all the above are explained below in this section), schizoaffective disorders (Castelnovo et al., 2018), Parkinson (Latreille et al., 2015), or Asperger's syndrome (Godbout et al., 2000), among others. We here present some illustrative examples about the importance of sleep quality and health. Although in some cases the consequences of poor sleep quality that are not related to cognition are mentioned, the main focus is cognition from a neurophysiological point of view.

2.5.1 Non-pathological or Quasi-Pathological Consequences

The effects of a poor sleep quality on behavior and cognition have been fundamentally assessed by sleep deprivation studies. These cognitive – and metabolic – deficits are accentuated if the poor quality of sleep is prolonged in time, without the affected individual being fully aware of it (Goel et al., 2009).

The causes for sleep deprivation, or at least a reduction in its quality, that are not directly related to any pathology are very diverse and range from individual lifestyle to specific shifting in sleep period in relation to the circadian cycle (e.g., due to shift work) (Orzeł-Gryglewska, 2010). If sleep deprivation is total, the consequences depend largely on the number of sleepless nights (Orzeł-Gryglewska, 2010). However, there is great interindividual variability that suggests the influence of genetic alleles associated with differential cognitive vulnerability to sleep loss (Goel et al., 2009). The consequences range from tremor and increased muscle tone (when sleep deprivation is for a single night) to disturbances in reasoning and orientation, visual and

tactile hallucinations, fatigue, irritability, and delusions, when sleep deprivation is for 4 or 5 days (Orzeł-Gryglewska, 2010).

Although sustained total sleep deprivation is not common in healthy individuals, sleep problems constitute a global epidemic that threatens the health and quality of life of around 40% of the adult population (Ohayon & Partinen, 2002). This prevalence is similar in children (Fricke-Oerkermann et al., 2007) and is even increased in the elderly (Foley et al., 1995). These problems often do not have a direct tangible effect, but the long-term consequences are of paramount importance, highlighting obesity, diabetes mellitus, hypertension, and decreased cognitive performance, among others (Calhoun & Harding, 2010; Van Cauter & Knutson, 2008).

2.5.2 Sleep Apnea and Cognitive Consequences

Obstructive sleep apnea (OSA) is probably one of the pathologies that most obviously affects healthy and restorative sleep. OSA is mainly characterized by repetitive pharyngeal collapse during sleep, leading to intermittent interruptions of breathing (apnea) (Malhotra & White, 2002). This usually leads to arousals that disrupt the cyclical architecture of sleep (Ferreira et al., 2020; Korkalainen et al., 2021).

Interestingly, recent studies have reported that OSA also has effects on specific oscillations, such as the progressive slowdown of SOs directly related to the severity of the disease (Gutiérrez-Tobal et al., 2021). It has been suggested that this deceleration could be due to an inhibitory effect on thalamus produced by OSA (Gutiérrez-Tobal et al., 2021). Previous studies in rats have shown that suppression of the role of the thalamus leads to a deceleration of the typical frequency of SO, leading to cortical attempts to substitute the role of the thalamus (David et al., 2013). Together, although speculative, we hypothesize that OSA directly influences the neural underpinning involved in the SOs generation (Gutiérrez-Tobal et al., 2021).

As previously stated, SOs are precursors and facilitators of the generation of spindles. Therefore, if SOs are affected, it seems reasonable to think that there would be alterations in the density of spindles beyond the interruptions of the sleep cycle. This is supported by previous studies that show alterations in the spindles in patients with OSA, both in the pediatric population (Brockmann et al., 2018; Weichard et al., 2016), as well as in adults (Ahuja et al., 2018).

The effects on different cognitive processes (especially those related to memory consolidation) that patients with OSA may develop due to hypoxia and sleep fragmentation are still not entirely understood. What is clear, however, is that the fastest intellectual changes happen during school-age (Fry & Hale, 2000), which explains the focus of the increasing number of OSA studies and its related changes in micro and macro sleep architecture in this population (Brockmann et al., 2018; Gruber et al., 2013; Gutiérrez-Tobal et al., 2021).

2.5.3 Migraine and Sleep – A Bidirectional Relationship?

The relationship between sleep and migraine can be interpreted as a bidirectional relationship. In fact, insomnia can be seen as both a cause and a consequence of migraine (Vgontzas & Pavlović, 2018). This leads researchers to think that migraine and sleep problems are "two sides of the same coin", that is, that they both have a common underlying pathophysiology (Vgontzas & Pavlović, 2018). In the outstanding review of Vgontzas and Pavlović (2018), the glymphatic system was proposed as a possible common mechanism. This system is responsible for macroscopic waste removal, primarily active during sleep (Iliff et al., 2012). On the other hand, cortical spreading depression – a wave of excitation followed by inhibition in cortical neurons that may be a direct cause of aura phase that precedes migraine headache – has been shown to cause impaired glymphatic flow (Schain et al., 2017). Therefore, a deterioration in this system could produce an accumulation of waste products that would contribute to later migraine attacks.

2.5.4 The Role of Glymphatic System and Sleep Spindles in Alzheimer's Disease

The accumulation of amyloid-β peptide in the brain appears to be the trigger for a series of events that lead to Alzheimer's disease (Ju et al., 2014). Given that sleep deprivation increases the amyloid-β peptide concentrations, glymphatic system – in charge of removing this toxic substance (Iliff et al., 2012) – seems to be the link between sleep Alzheimer's disease (AD).

Nonetheless, this does not appear to be the only link between AD and sleep. It is well-known that AD is a disease characterized by memory impairments. On the other hand, we have previously shown a number of studies that link sleep spindles functions and memory consolidation. With these precedents, previous studies have searched for a direct relationship between spindles and AD (see (Weng et al., 2020) for a recent review). As might be expected, it is observed that a higher density of spindles is inversely related to the evolution of AD (Gorgoni et al., 2016; Liu et al., 2019). Even more noticeable, a recent positron emission tomography (PET) study showed that the nesting hierarchy between SOs and spindles was altered and predicted accumulated tau levels in the medial frontal cortex (Winer et al., 2019), which is significantly more hyperphosphorylated in AD than in the normal adult brain (Iqbal et al., 2010). Therefore, albeit speculative, the alterations in SOs and spindles produced by OSA could be a potential underlying mechanism for the well-known relationship between OSA and AD (Kheirandish-Gozal et al., 2016). These findings in AD support our previous hypothesis about the importance of the relationship between SOs and spindles (and not spindles alone) for memory consolidation processes.

2.5.4.1 Sleep Spindles as Biomarker of Schizophrenia

Sleep disorders have been associated with the onset of psychosis (Benson, 2015; Zhang et al., 2020). These disorders are unrelated to pharmacological treatment since this association has been reproduced in patients with schizophrenia without antipsychotic medication (Chouinard et al., 2004). Sleep disturbances in schizophrenia patients do not only correspond to alterations in its macroarchitecture (Poulin et al., 2003; Yang & Winkelman, 2006) (i.e., the distribution of time spent in different sleep stages), but also in its microarchitecture (Ferrarelli et al., 2007; Göder et al., 2015) (i.e., characteristics of the waves associated with each stage of sleep). This concordance could have a genetic origin, since both sleep fingerprints, such as spindles (Goldschmied et al., 2021), and schizophrenia (Cao et al., 2019) appear to be highly heritable and share common aspects. For example, the risk gene in schizophrenia that encodes a calcium channel (Lubeiro et al., 2020), CACNA1I, plays a critical role in the generation of spindles in the thalamus (Steullet et al., 2018).

Among the abnormalities found in the sleep microarchitecture in schizophrenia, the reduction in the density of spindles stands out (Ferrarelli et al., 2007). The production of spindles begins with the inhibition of the thalamocortical neurons mediated by the gabaergic inhibition of the reticular nucleus (Berry et al., 2012; Steriade, 2003). This process is followed by glutamatergic rebound peaks that cause cortical neurons to oscillate at the typical spindle frequency (Contreras & Steriade, 1996). Therefore, spindle production depends entirely on the inhibitory onset of the reticular nucleus, which is known to show structural and biochemical abnormalities in schizophrenia (Court et al., 2002; Smith et al., 2001; Steullet et al., 2018). Furthermore, spindle production is governed by an orchestrated organization of inhibitory (gabaergic) and excitatory (glutamatergic) neurons. This excitatory-inhibitory balance is altered in schizophrenia (Kehrer, 2008; Northoff & Gomez-Pilar, 2021), especially affecting the thalamus, as has recently been discovered (Quiñones et al., 2021).

Together, these findings show that the spindle generation process in schizophrenia is disrupted, reducing the density of spindles and likely producing other changes in sleep architecture. Therefore, spindles are postulated as a noticeable biomarker of increasing importance in schizophrenia.

2.6 Conclusion

As new studies appear, the relationship between restful sleep and health is increasingly evident. In this relationship, the role of spindles has gained much relevance due to its proven importance with memory consolidation processes. However, recent studies have shown that SOs are at least equally important in many of these processes. Future studies should be directed to analyze whether the relationship between SOs and spindles is altered in different sleep-related pathologies – and not just the spindles themselves. If so, changes in their relationship could shed new light on the pathophysiological mechanisms involved.

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