Universidade do Minho
Escola de Medicina

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Putting the focus on sleep quality: subjective sleep measures, actigraphy and brain correlates in ageing

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e do
Professor Doutor Nuno Jorge Carvalho Sousa

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"To go far you must begin near, and the nearest step is the most important one." (Jiddu Krishnamurti)

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

Putting the focus on sleep quality: subjective sleep measures, actigraphy and brain correlates in ageing

Abstract

Sleep is a multidimensional phenomenon with a relevant role in the maintenance of organism homeostasis, overall well-being and optimal cognitive function. Throughout the lifespan, changes in sleep dimensions occur, namely on its timing, duration, architecture and quality. In what concerns to sleep quality, studies are highly heterogeneous; not only the tools used are extremely variable, but also the way this concept is defined. Thus, the present thesis aims at providing a thorough analysis on the meaning of sleep quality, contributing to the clarification of its definition. It also aims to determine the sleep patterns, routines and quality of Portuguese community-dwellers across the adult lifespan and determine the main predictors of self-reported sleep. It is also an aim to explore the association between a composite measure of sleep quality and brain correlates. For these purposes, a systematic review of the literature on sleep quality meaning was performed and three original studies developed considering a cross-sectional and/or a longitudinal approach. Portuguese community-dwellers within the adult lifespan (18 and more years) were recruited and self-reported sleep quality and psychological variables were assessed in the first two studies and in the third, neuroimaging information was also collected. Results show that sleep quality is a multidimensional concept that should integrate information from different settings (e.g. clinical measures such as the Pittsburgh Sleep Quality Index, and parameters that reflect the interpretation of lay individuals of it). Lay people interpretation of sleep quality seems to be stable across the adult lifespan and no differences between men and women are observed regarding the parameters reported. Poor subjective sleep quality is associated with decreases in functional and structural connectivity of specific brain networks, with an overlapping node in the middle left temporal region. Overall, the present work contributes for the clarification of sleep quality concept, enabling a better comparison between study results. Despite the contributions of this doctoral work to the body of literature, there are still avenues to be explored so that individuals can benefit from personalized sleep care, and physicians can better act on the subjective informations reported by their patients, feasibly taking advantages of the new technologies to better monitor sleep in ecological settings.

Key Words: Actigraphy; MRI; PSQI; Psychological Variables; Subjective sleep quality.

Colocando o foco na qualidade de sono: medidas subjetivas de sono, actigrafia e correlatos cerebrais no envelhecimento

Resumo

O sono é um fenómeno multidimensional, com um papel relevante na manutenção da homeostasia do organismo, no seu bem-estar geral e no bom funcionamento da sua função cognitiva. Ao longo da vida ocorrem alterações nas suas diferentes dimensões, nomeadamente nos seus horários, duração, arquitetura e qualidade. No que respeita à qualidade de sono, os estudos são altamente heterogéneos; não só os instrumentos utilizados são muito variáveis, mas também a forma como o conceito é definido. Assim, a presente tese tem como objetivos realizar uma análise aprofundada do conceito "qualidade de sono" e contribuir para a clarificação da sua definição; determinar os padrões, rotinas e a qualidade de sono de uma amostra de indivíduos potugueses adultos, bem como os principais preditores das variáveis de sono reportadas; e determinar a associação entre uma medida compósita de qualidade de sono e correlatos cerebrais. Para este propósito, realizaram-se uma revisão sistemática da literatura sobre a definição de qualidade de sono e três estudos empíricos com uma abordagem transversal e/ou longitudinal, onde se recrutaram indivíduos de 18 e mais anos, e se avaliaram a qualidade de sono e algumas variáveis psicológicas nos dois primeiros estudos, e se realizou ainda uma ressonância magnética cerebral no terceiro. Os resultados indicam que a qualidade de sono é um conceito multidimensional, que deve integrar informação de de diferentes contextos (ex. medidas clínicas como a do Índice de Qualidade de Sono de Pittsburgh, mas também parâmetros que decorrem da interpretação do conceito pelo indivíduo). A interpretação deste conceito pelos indivíduos da comunidade parece ser estável ao longo da vida adulta, não se observando diferenças entre homens e mulheres nos parâmetros reportados. Uma má qualidade de sono correlaciona-se com uma diminuição da conectividade funcional e estrutural em redes cerebrais que se sobrepõem na região temporal média esquerda. O presente trabalho contribui para a clarificação da definição de qualidade de sono, promovendo comparações mais adequadas entre resultados de estudos. No entanto, apesar das contribuições, existem ainda caminhos a serem explorados, para que os indivíduos possam beneficiar de cuidados de sono personalizados e para que os seus médicos possam agir melhor sobre as informações subjetivas relatadas, aproveitando as vantagens das novas tecnologias para melhor monitorizar a qualidade de sono em ambientes ecológicos.

Palavras-chave: Actigrafia; MRI; PSQI; Qualidade Subjetiva de Sono; Variáveis psicológicas.

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LIST OF ABBREVIATIONS

A

AAL – Anatomical Automatic Labeling

AD – Axial Diffusivity

ANOVA – Analysis of Variance

AC – Anticorrelational network

B

BOLD – Blood Oxygen Level Dependent

BMI – Body Mass Index

BCT – Brain Connectivity Toolbox

C

CPAP – Continuous Positive Airway Pressure

CSF – Cerebrospinal Fluid

CNS – Central Nervous System

D

DMN – Default Mode Network

DTI – Diffusion Tensor Imaging

DWI – Diffusion Weighted Imaging

E

EEG – Electroencephalogram

EMG – Electromyogram

EOG – Electrooculogram

ECG – Electrocardiogram

ESS – Epworth Sleepiness Scale

EPI – Echo-Planar Imaging

F

FA – Fractional Anisotropy

FC – Functional Connectivity

fMRI – Functional Magnetic Resonance Imaging

G

GDS – Geriatric Depression Scale

GM – Gray Matter

GMV – Gray Matter Volume

H

H - Hours

I

ICV – Intracranial Volume

IQR – Interquartile Range

M

MD – Mean Diffusivity

MNI – Montreal Neurological Institute

MRI – Magnetic Resonance Imaging

N

NREM – Non rapid eye movement

NBS – Network Based Statistics

O

OSA – Obstructive Sleep Apnea

P

Process S – Sleep Homeostatic process

Process C – Circadian process

PSG - Polysomnography

PSQI – Pittsburgh Sleep Quality Index

PRISMA – preferred reporting items for systematic reviews and meta-analyses

R

RSN – Resting State Network

REM – Rapid eye movement

RLS – Restless Legs Syndrome

ROC – Receiver Operator Characteristic

rs-fMRI – Resting-State Functional Magnetic Resonance Imaging

RD – Radial Diffusivity

ROI – Regions of Interest

S

SCN – Suprachiasmatic Nucleus

SpO2 - Oxygen saturation

SC – Structural Connectivity

SE-EPI – Spin-Echo, Echo-Planar Imaging

SDB - Sleep-disordered breathing

T

TTB – Total Time in Bed

TST – Total Sleep Time

W

WASO – Wake After Sleep Onset

WM – White Matter

WMSA – White Matter Hypointensities Volume

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CHAPTER I

The state of the art

1.1. Introduction

Sleep is a ubiquitous phenomenon, critical for the organism homeostasis and overall well-being. Across the lifespan, alterations in sleep habits, routines and architecture occur and often, there is an increase in sleep complaints, especially in middle-aged and older individuals. Notwithstanding, it is still unclear whether these changes are biologically programed or a consequence of external conditions (e.g. societal burdens or/and chronic sleep restriction throughout the years). Indeed, while some studies have shown that it is not the ageing process *per se* that deteriorates (at least some) sleep processes (e.g. the ability to fall asleep), it is still to be determined how many sleep complaints and of what type should be expected in normative ageing. Thus, and because there is an important behavioral-related component associated to sleep, it is crucial to determine how individuals integrate and provide meaning to these sleep changes. In fact, determining the specificities of sleep complaints can be a relevant contribute to better understand and overcome some sleep disturbances and to promote overall health, quality of life and the maintenance of a proper neuropsychological status. Thus, the aims of the present thesis are twofold. First, to clarify the subjective sleep quality concept by providing a critical view on this construct. Second, to present an integrative view on sleep patterns and subjective quality across the lifespan, exploring for associations between subjective sleep quality, psychological factors and brain correlates. This information is provided across five chapters. In the present chapter, **Chapter I**, a frame of the topic of the thesis provides the necessary theoretical background. **Chapter II** concerns a systematic literature review on sleep quality construct, focusing on subjective sleep quality and addressing needed clarifications on its meaning. **Chapter III** delivers a characterization of the rest patterns of community-dwellers from 18 to 87 years of age and addresses some of the limitations identified in the literature review presented in Chapter II. Associations between what is reported by the individual in terms of sleep quality, and the results from a standard self-reported measure of sleep quality (obtained from the Pittsburgh Sleep Quality Index), are also determined. In **Chapter IV**, differences between week and weekend days regarding sleep patterns, routines and quality are addressed, as well as age and sex differences in these patterns. **Chapter V** explores the association between the composite measure of sleep quality derived from the Pittsburgh Sleep Quality Index and structural and functional brain correlates. **Chapter VI** provides a summary of the findings of the thesis and discusses ongoing work and future prospects.

1.2. Historical perspective [1]

Sleep is a recurrent and reversible neurobehavioral state characterized by behavioral quiescence, perceptual disengagement from the environment and decreased consciousness (Carskadon & Dement, 2011; Siegel, 2009). Unlike other behaviors which are directed towards a clear goal (e.g. getting food, mating, catching or running from something), sleep does not readily indicate any 'intent' of engaging in a clear action. Furthermore, what seems to remain upon a sleep episode is a subjective experience of loss of consciousness and not a proper remembrance of the occurrence. Consequently, different individuals, throughout time and societies, can adopt different patterns and interpretations of sleep. In fact, for a long time, the lack of memory of mental activity during the sleep episode seemed to foster the notion of sleep as a state of reduced or non-existent brain activity (Scott & Sherrington, 2009) and, thus, not compatible with behaviors that nourish and/or propagate species. This conception was challenged with the discoveries of the regular cyclic alteration of rapid eye movement (REM) and non-REM (NREM) sleep (Aserinsky & Kleitman, 1953), and the strong association between REM sleep and vivid hallucinatory dreaming (Dement & Kleitman, 1957). Indeed, these served as evidence against this belief that sleep was caused by/or associated with a cessation of brain activity (Hobson, 2005).

Beyond its biological component, sleep is also a social, cultural and historically variable phenomenon (Ohayon, 2004; Williams, Meadows, & Arber, 2010). Hence, changes in each of these domains can relate to changes in sleep patterns. A prime example of this occurred during the Industrial Age, when sleep went from being regarded as 'the honey-heavy dew of slumber' (Shakespeare), or 'the golden chain that ties health and our bodies together' (Thomas Dekker), to the 'criminal waste of time and a heritage from our cave days' (Thomas Edison). In fact, while before the Industrial Age it was customary to receive visitors in bed, thereafter the bedroom was regarded as private and sleeping for seven or eight hours *per* night as laziness[1]. Interestingly, even nowadays, after the importance of sleep for health and well-being has been demonstrated, there are still certain sayings, such as 'don't get caught napping', 'if you snooze you lose' or 'time is money', that promote this view of sleep as either optional, a luxury, or unimportant (Colten et al., 2006). More so, the advent and widespread use of artificial light also changed human behavior.

[1]Most information from this section was obtained from the site http://healthysleep.med.harvard.edu/interactive/timeline

Not only work and leisure hours were extended past natural sunset, but also a significant segment of the daytime workforce was moved indoors, limiting the exposure to natural light (Sharkey & Van Reen, 2014). This extension of work and leisure hours past natural sunset has been shown to associate with poorer mental health and more sleep disturbances in individuals working longer hours (Afonso, Fonseca, & Pires, 2017; Virtanen et al., 2009). Similarly, "day-to-day" social factors also seem to affect sleep across the lifespan, including marriage/co-habitation (Troxel et al., 2010), parenthood (Medina et al., 2009; Smedje et al., 1998), caregiving (Castro et al., 2009; McCurry et al., 2007; Rittman et al., 2009; Simpson & Carter, 2010; Song et al., 2018; von Känel et al., 2012) or widowhood (Monk et al., 2008). Thus, sleep disruption appears to be on the rise in our 24-h society, albeit its important for a large set of biological and psychological processes (Cirelli & Tononi, 2008; Diekelmann & Born, 2010; Irwin, 2015; Irwin & Opp, 2017; Maquet, 1995; Meerlo et al., 2009; Payne et al., 2009; Pilcher, Ginter, & Sadowsky, 1997; Shokri-Kojori et al., 2018; Stickgold, 2006; Tononi & Cirelli, 2006; Walker & Stickgold, 2004; Wulff et al., 2010; Xie et al., 2013). Therefore, considering the different features of sleep, namely duration, timing and quality, understanding and determining the conceptions and expectations of the individual towards sleep is crucial to demystify myths and choose the most effective approach to promote a good sleep and of quality. In Figure 1, a *chronological frieze* of some of the most relevant milestones regarding sleep and its research is presented.

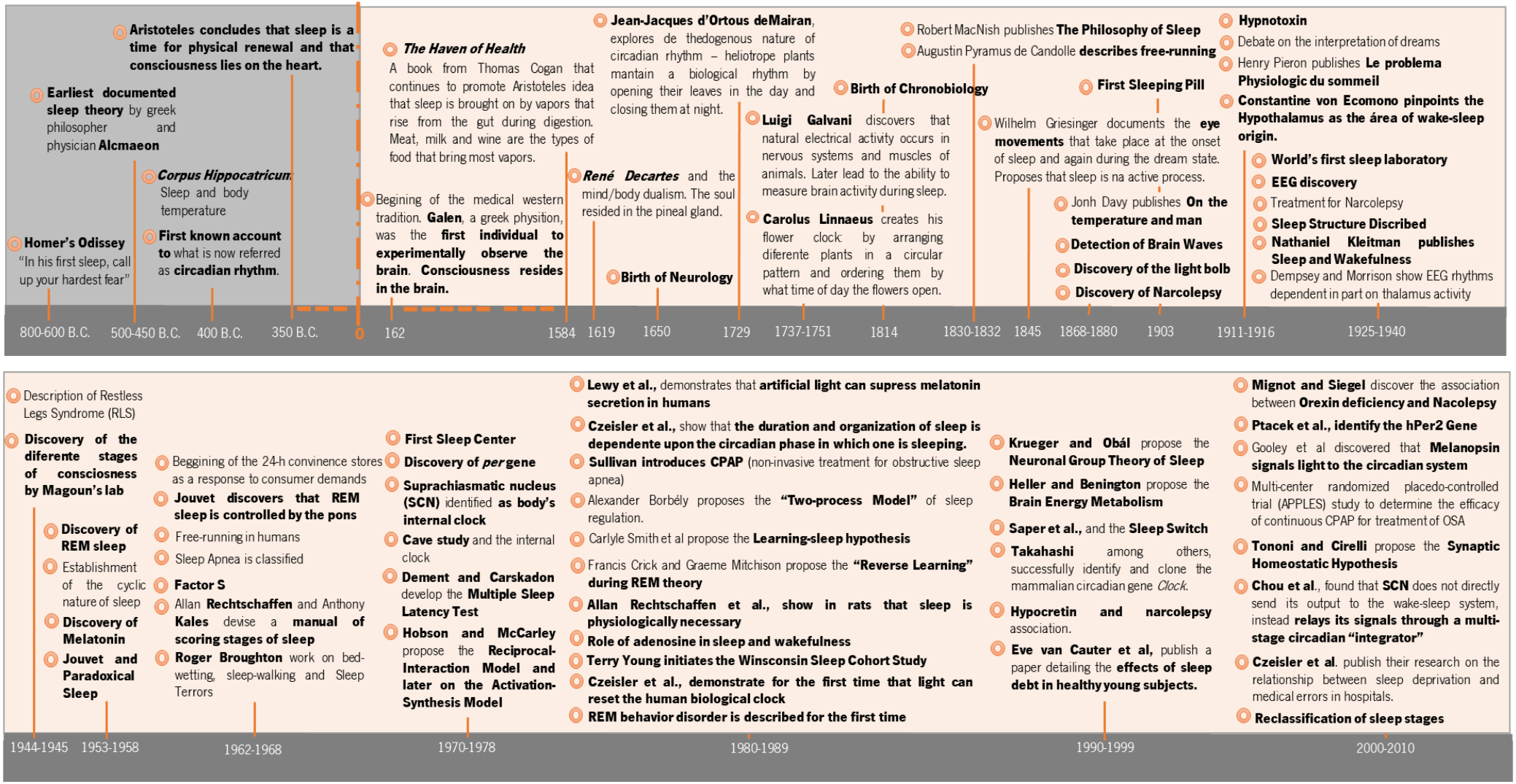

Figure 1. Chronological frieze of sleep research milestones across time (based and adapted from: http://healthysleep.med.harvard.edu/interactive/timeline).

1.3. Sleep architecture

To access the basic structural organization of sleep, the standard method used is Polysomnography (PSG), which allows for sleep characterization in its discrete stages through a minimum of eleven channels, including electroencephalogram (EEG), electromyogram (EMG), electrooculogram (EOG), oxygen saturation (SpO2), and electrocardiogram (ECG). The quantitative electroencephalogram (EEG) mapping has shown that during the different sleep phases there are brain regional differences in electrical activity (Achermann & Borbély, 1997, 1998) and sleep has been classified as either rapid-eye-movement (REM) or non-REM sleep based on these changes in EEG, EOG and EMG (Figure 2).

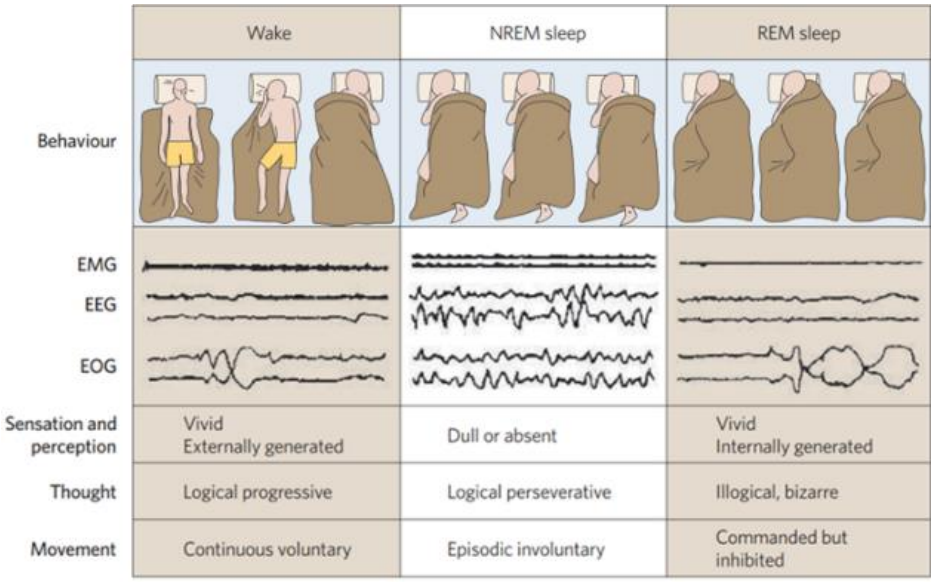

Figure 2. Features of wake-sleep behavior states (adapted from Hobson, 2005 with permission; license number: 4553100288346).

In 1968, Rechtschaffen and Kales provided the first frame for sleep scoring. Although these guidelines were meant just as a reference, they rapidly became gold standard (Himanen & Hasan, 2000). The reappraisal of the scoring occurred only in 2007, with not only the alteration of the standard guidelines for sleep classification, but also the development of guidelines for terminology, recording method, and scoring rules for sleep-related phenomena by the American Academy of Sleep Medicine (AASM) (Iber, Ancoli-Israel, Chesson, & Quan, 2007). Currently, sleep is divided into wake, NREM stage 1 (N1), NREM stage 2 (N2), NREM stage 3 (also denominated 'deep sleep', N3 reflects slow wave sleep and stages S3 + S4 in the previous scoring from 1968) and REM sleep (Figure 3). NREM sleep is characterized by an electrical activity progressively more synchronous

and with slower waves of bigger amplitude; while REM sleep is characterized by rapid eye movements, asynchronous cortical electric activity with low amplitude waves of high frequency, muscular hypotony (except for diaphragmatic muscles and muscles from middle ear and erectile tissues) and dreamlike activity (Paiva & Penzel, 2011; Stickgold & Walker, 2010). Furthermore, within NREM sleep, N1 is considered a transition period from wake to sleep, N2 is characterized by typical sleep elements (such as sleep spindles and K-complexes), and N3 is described as a deep sleep with slow electric waves of high amplitude (Paiva & Penzel, 2011) (Figure 3). REM sleep, due to its low-amplitude, high mixed-frequency waves, has been termed 'desynchronized' sleep (Stickgold & Walker, 2010).

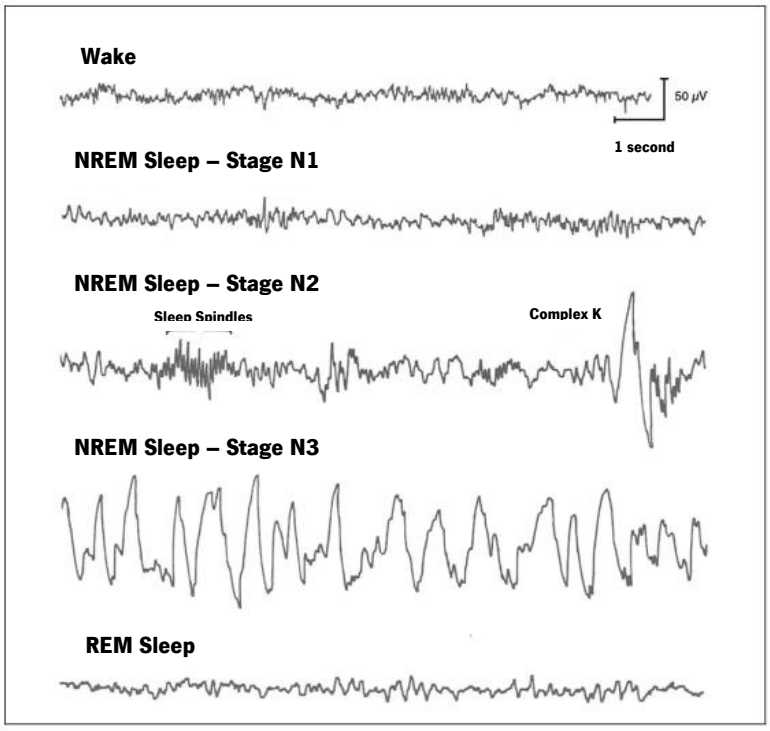

Figure 3. EEG trace for the different stages of sleep.

Overall, it is expected that an adult without any sleep disturbance should be able to have a night of about 8 hours of sleep (Hirshkowitz et al., 2015), which can represent 4 or 5 sleep cycles, each of 90 to 120 minutes (Stickgold & Walker, 2010). The way REM, NREM and wake are distributed within each of these cycles, varies with the part of the night in which it occurs and with the previous sleep episode (Dement & Kleitman, 1957; Stickgold & Walker, 2010). For example, in an individual sleeping within the appropriate quality and range of time, NREM sleep has a longer duration in the first half of the night, while, in the second half of the night, REM sleep is predominant (Figure 4).

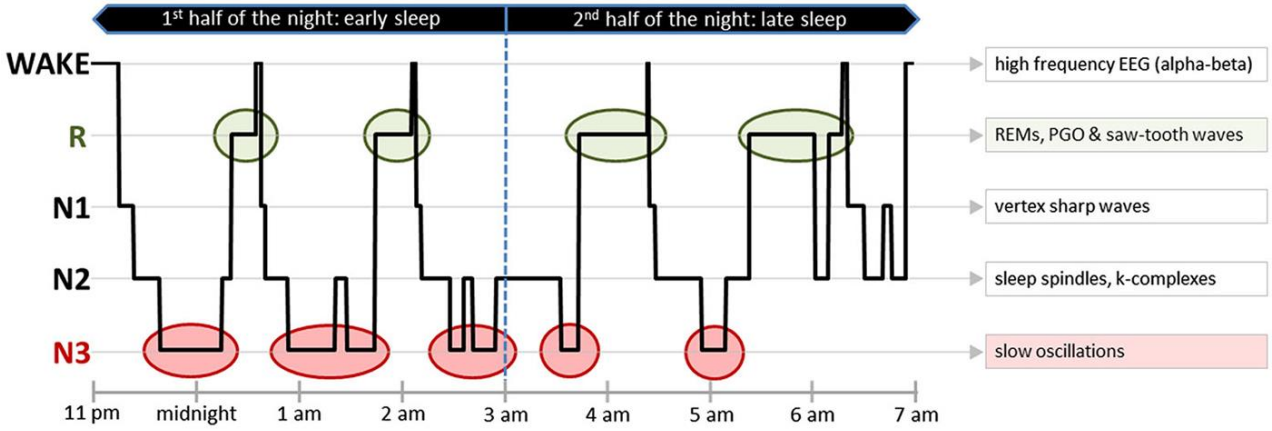

Figure 4. Hypnogram depicting the different sleep stages of a healthy individual, over 8-h nocturnal sleep (image from Blume, del Giudice, Wislowska, Lechinger, & Schabus, 2015).

1.4. Neurobiology of sleep

As already mentioned, the behavioral hallmarks of sleep are diverse (ranging from reduced responsiveness to external stimuli and rapid reversibility, to homeostatic rebound after sleep loss). While early animal studies shed light on the importance of the reticular brainstem region for sustained wakefulness (Magoun, 1952), later studies have shown that the majority of sleep-regulating stimuli are integrated in the ascending reticular activating system (ARAS) originated in the brainstem (Saper, Scammell, & Lu, 2005). Despite the exact wake-sleep mechanisms are still not completely understood or defined, it is consensual that a sleep control system has to be able to fulfill a multitude of functions, among which blocking locomotor activity, gating sensory pathways, inhibiting arousal systems and relieving sleep pressure (Donlea et al., 2018).

The first hypothesis on wake-sleep mechanisms and its neuro-circuitry appeared around 1930's. Based on the observation of patients with the viral illness *encephalitis lethargica,* Baron Constantin von Economo proposed a wake-promoting influence from the brainstem that would keep the forebrain awake, and a sleep-promoting influence from the anterior hypothalamus that would contradict the waking drive during sleep. In the later decades of the 20th century, it was found that the wake-promoting influence innervated the thalamus and passed through the more ventrally situated hypothalamus and the basal forebrain, to project to the entire cerebral cortex (Saper et al., 2005). Specifically, neurons from monoaminergic cell groups project to the intralaminar and midline thalamic nuclei and innervate the lateral hypothalamus, basal forebrain, and cerebral

cortex (Saper et al., 2005). These neurons fire faster during wakefulness compared to non-REM (NREM) sleep, and most stop firing altogether during rapid eye movement (REM) sleep (Aston-Jones and Bloom, 1981; Fornal et al., 1985; Steininger et al., 1999). At this time, it was considered that the wake-promoting influence arised mainly from monoaminergic and cholinergic neurons in the upper brainstem (Saper et al., 2005). However, later on, a sleep-promoting cell group was identified in the ventrolateral preoptic (VLPO) and median preoptic nuclei (Saper et al., 2010; Suntsova et al., 2002). This group of cells were shown to provide GABAergic innervation of the entire wake-promoting system, thus allowing the inhibition of arousal during sleep (Saper et al., 2010; Suntsova et al., 2002). Furthermore, evidence from lesion and opto- and chemogenetic excitation and inhibition studies showed that monoaminergic and cholinergic systems played mainly a modulatory role on wake–sleep control. In fact, the backbone of the wake–sleep regulatory system seems to depend upon fast neurotransmitters, such as glutamate and GABA (gamma-aminobutyric acid) (Saper et al., 2010; Saper et al., 2005) (Figure 5).

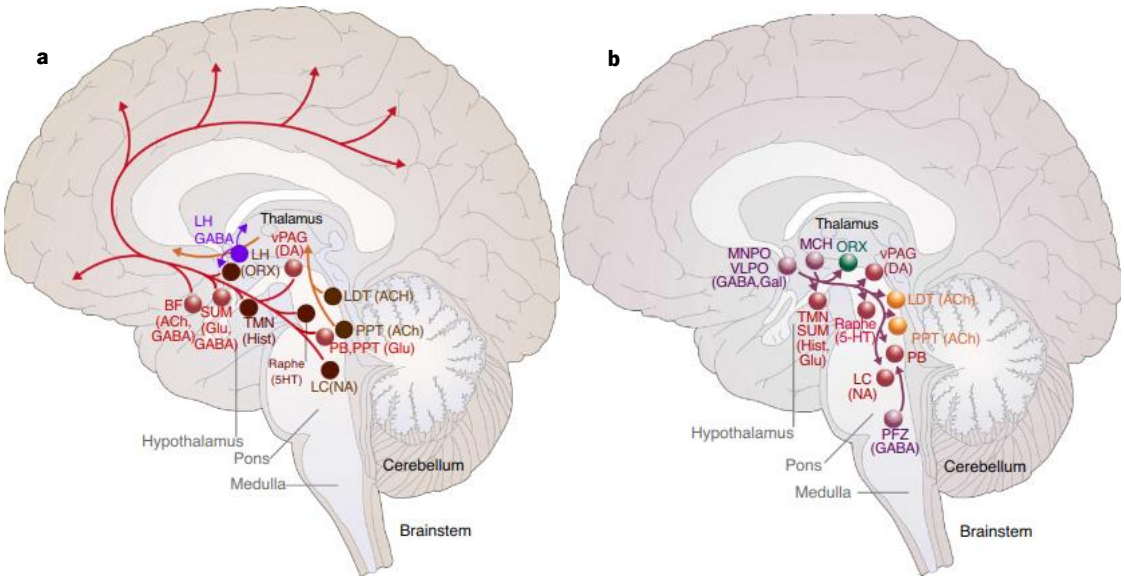

Figure 5. Wake-sleep regulating systems.
(adapted from Saper & Fuller, 2017 with permission. License number: 4540261429584).

(a) In red, the fast neurotransmitter system that appear to play the largest role in promoting wakefulness; in brown, the monoaminergic, cholinergic, and peptidergic neurons in the brainstem and hypothalamus that have a modulatory role; in violet, two populations of GABAergic neurons in the lateral hypothalamus (LH).
(b) In purple, the fast neurotransmitter systems that contribute to sleep promotion. The ventrolateral preoptic (VLPO) and median preoptic (MnPO) GABAergic neurons send axons to most components of the arousal system (in red, orange, and green), and are thought to inhibit them in a coordinated fashion.
Abbreviations: 5HT, serotonin; Ach, acetylcholine; Hist, histamine; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus NA, noradrenlaine; ORX, orexin; TMN, tuberomammillary nucleus.

Overall, at sleep onset, neurons from VLPO become active and inhibit the ascending arousal systems of the brainstem, posterior hypothalamus and basal forebrain, which allows the transition from the waking state to NREM sleep (Stickgold & Walker, 2010). Once NREM sleep is initiated, delta and slow oscillatory rhythms, with its spindles and k-complex wave forms, are generated by thalamic and cortical neural circuits (Stickgold & Walker, 2010). These interconnected circuits shift into an oscillatory mode after the sleep onset, when the influence of subcortical ascending arousal systems decreases. During this time, the transmission of sensory information to the cortex is blocked (Stickgold & Walker, 2010). During REM sleep, the intrinsic rhythms of NREM are prevented mainly by influence on the thalamus and basal forebrain, from the cholinergic (acetylcholine) subcomponent of these systems, originating in the mesopontine brain stem, including the laterodorsal tegmental and pedunculo-pontine nuclei. In contrast, during waking, NREM oscillatory rhythms are prevented due to the neuromodulation of thalamocortical circuits and cortex, by ascending projections from arousal-promoting systems of the brain stem, hypothalamus, and basal forebrain (Figure 5). Recently, a theoretical review proposed a complementary approach to this "bottom-up" regulation of arousal and sleep (Krone et al., 2017). The authors suggest the existence of a "top-down" mechanism in wake-sleep regulation, generated from neocortex to the thalamus (Krone et al., 2017). More studies are needed on this topic, but this hypothesis not only contributes to a re-interpretation of sleep-wake mechanisms, but also raises important new avenues in the treatment of sleep disturbances.

1.5. A Sleep Regulation Model

In the last three decades, the regulation of wake-sleep cycles has been mainly explained by the two-process model of sleep regulation (Figure 6), which has served as a major conceptual framework in sleep research (Borbély, 1982; Borbély, 2009; Borbély & Achermann, 1992; Borbély et al., 2016). This model addresses questions such as "*how do we know we are tired and that it is time to sleep?*", "*why, when excited, we can go without sleep*", "*why, after a sleepless night, we feel the need to take a nap or go to bed earlier the next night?"*. According to it, sleep is modulated by two distinct and independent mechanisms: (1) the sleep homeostat (Process S) that controls how much we sleep; and (2) the circadian clock (Process C) that dictates when we sleep (Figure 6).

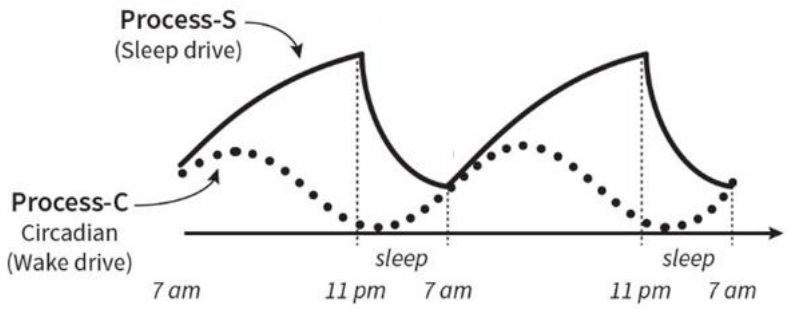

Figure 6. The Two-Processes Model of Sleep Regulation (adapted from Walker, 2017).

The homeostatic component arises from the preoptic area and increases with time spent awake (Borbély, 1982; Borbély et al., 2016; Dijk & von Schantz, 2005; Hodkinson et al., 2014). This homeostatic sleep-promoting process continuously increases during the time spent awake and is concomitant with both a decrease in waking performance and alertness and an increase in sleepiness/fatigue (Borbély, 1982). During sleep, this process continuously decreases, given the dissipation of sleep pressure. Process C, on the other hand, is characterized by a nearly 24-hr endogenous oscillatory variation for sleep propensity and a synchronized clock-like action, independent of whether the person is asleep or awake (Borbély, 1982). Thus, circadian-based sleep propensity is at its lowest level during the early evening hours, when homeostatic sleep pressure is high, and reaches its maximum during the early morning, when homeostatic sleep pressure is low (Borbély, 1982) (Figure 6).

In humans, the sleep-wake cycle is the most overt manifestation of this circadian rhythmicity, being possible to observe patterns of brain wave activity, hormone production, cell regeneration and other biological activities, linked to this 24-hour cycle (Hodkinson et al., 2014). These rhythms are promoted by biological clocks (i.e. autonomous anticipatory oscillators) that play a critical role in the organization and information processing from genome to the whole organism (Bass & Lazar, 2016). These clocks, which seem to have evolved in parallel with the geological history of the Earth, can be central or peripheral and run in an approximately 24h rhythm (Paranjpe & Sharma, 2005; Sharma, 2003). The central circadian clock (i.e. '*master clock*') is located within the suprachiasmatic nucleus (SCN) of the hypothalamus and accounts for approximately 20,000 neurons (Manfredini et al., 2018). Under normal conditions, it is synchronized with the external environment *via* light-dark cues and routines, allowing the organism to anticipate and prepare for external changes (e.g. seasonal changes) (Hodkinson et al., 2014; Meijer, Michel, Vanderleest, &

Rohling, 2010; Paranjpe & Sharma, 2005; Pevet & Challet, 2011) (Figure 7). Notwithstanding, external factors (e.g. light, mealtime, social activities and work) can also contribute to the disruption of internal clocks, enabling internal desynchronization (Knutson et al., 2007) and ultimately disturbing phase relation of circadian fluctuations in behavioral, hormonal, and metabolic variables (Haus & Smolensky, 2006).

Overall, endogenous circadian 'clocks' and homeostatic processes regulate cycles of rest and activity (or sleep and wakefulness), with homeostatic processes reflecting both the increased propensity to sleep associated to longer wakefulness and the recuperative benefits of sleep itself (Gillin, 2001). However, this model seems to neglect a variety of other social, emotional and environmental factors. Indeed, results from a recent study (Geissmann et al., 2019) show that circadian drive, rather than the homeostatic regulation, is the main contributor to sleep pressure in flies, indicating that sleep occurs due to a combination of various biological and evolutionary drives. For example, it has been shown that mixed-sex groups of flies tend to sleep less than single-sex groups, presumably to engage in sexual activity (Liu et al., 2015), and that female flies appear to sleep less after mating, possible to lay eggs (Elwyn et al., 2010). Moreover, a study has also shown that starved flies sleep less than well-fed flies, presumably to forage for food (Keene et al., 2010). In the extreme, the evolutionary vital function of sleep might even be questioned, as some wild-type fruit flies not only are virtually sleepless at baseline conditions, but also seem not to be affected by complete forced sleep restriction (usually a lethal treatment) (Geissmann et al., 2019). As circadian rhythms have the potential to be biomarkers of health and disease (e.g. Lévi et al., 2014) and, as mentioned above, sleep is an adjustable behavior that takes into account the different needs of the organism (Griffith, 2013), it could be worthy to explore more this dynamic hierarchy.

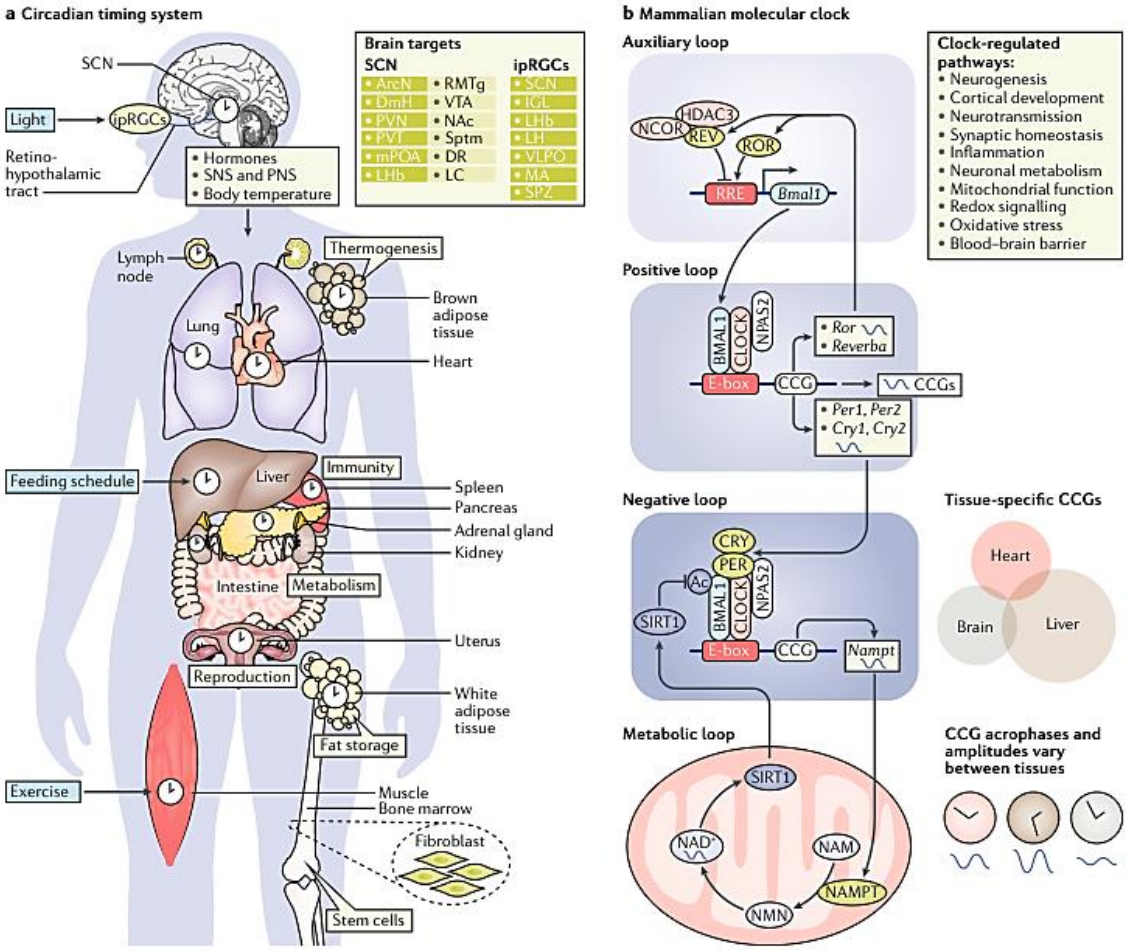

Figure 7. The circadian timing system (adapted from Logan & McClung, 2018 with permission; license number: 4540250804271).

1.6. Sleep and neuroimaging

In the past decade, the descriptive study of sleep has been complemented by the use of brain imaging techniques that have been regarded with enthusiasm. Not only these techniques present better temporal and spacial resolution, but also have the potential to overcome some PSG limitations, namely its poor association with subjective perception of sleep (Stevner et al., 2019; Edinger et al., 2013). Studies using brain imaging techniques, have shown a variation in brain regional activity in relation to sleep stage, sleep physiological events and previous waking activity (Dang-Vu et al., 2007; Czisch et al., 2004; Maquet et al., 1996). Thus, when compared to wakefulness, it has been shown that while NREM sleep presents decreased brain regional activity, during REM sleep it seems that a sustained level of brain function occurs (Schabus et al., 2007; Dang-Vu et al., 2007; Dang-Vu et al., 2010; Maquet, 2000; Maquet & Phillips, 1998).

PET studies have shown that, compared to wake, during NREM sleep it is possible to observe a reduction in brain activity of subcortical (brainstem, thalamus, basal ganglia, basal forebrain) and cortical (prefrontral cortex, anterior cingulate cortex and precuneus) regions (Dang-Vu et al., 2010; Maquet, 2000; Maquet et al., 1997). On the other hand, during REM sleep it seems simultaneously observed an enhancement in the activity of brain regions, such as the pontine tegmentum, thalamus, basal forebrain, amygdala, hippocampus, anterior cingulate cortex and temporo-occipital areas, but also a decrease in activity of regions such as the dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus, and inferior parietal cortex (Braun et al.,1997; Maquet et al., 2000; Maquet et al., 1996; Maquet et al., 2005). Following this line, and by providing better information on temporal and spacial features, MRI has enabled the association between event-based assessment of brain responses and the occurrence of phasic sleep activities (Dang-Vu et al., 2010). For example, in a study from Schabus and colleagues (2007) using EEG-fMRI, it was possible to observe that the sleep spindles detected were associated with an increase in brain responses in the lateral and posterior regions of the thalamus, as well as in paralimbic (anterior cingulate cortex, insula) and neocortical (superior temporal gyrus) areas (Schabus et al., 2007).

Neuroimaging studies have also been used to study sleep deprivation. However, the brain processes that mediate the cumulative deficits of sleep deprivation are still largely uncharacterized. Nonetheless, there is a consensus regarding the fact that subcortical thalamic and basal ganglia brain regions are more affected by circadian processes, and association cortices (especially in the frontoparietal attention network), are particularly sensitive to sleep pressure (Muto et al., 2016).

Currently, new fMRI approaches are being used, enabling the questioning of traditional views of sleep staging. In fact, in a recent study, this traditional sleep staging was projected onto probabilistic maps of transitions between whole-brain network states (Stevner et al., 2019). Results showed that not only brain activity prior to sleep was significantly different from the one just after sleep, but also that increased activity in the DMN can potentially serve as a gate-function for the entry into NREM sleep. Apart from this, the neurobiological significance and consequences of FC dynamics during rest is still not fully established or understood (Haimovici et al., 2017), which might be partly explained by the generalized use of specific experimental conditions (e.g. laboratory-controlled environment) or populations (e.g. sleep deprived individuals), providing for a 'limited vision' of the mechanisms and processes.

1.7. Sleep and ageing

The ageing process is accompanied by multifactorial alterations that range from social and familial, to psychological and biological. On the socio and familial level, changes can include marital status, having children, or children leaving the family home, getting or losing a job, retirement, or the death of a spouse, relative or friends (Ohayon, 2004). In terms of biological alterations, changes on immune (Zeleznik, 2003), respiratory (Janssens et al., 1999) or cardiovascular systems (Rehman, 1999), but also on sleep architecture, can also occur (Mander, Winer, & Walker, 2017) (Figure 8). In fact, all of these changes are recognized to occur with age and often to be associated to an increase in sleep complaints. However, at this point, it is not yet known whether these changes are within the normative ageing process and, thus, to be expected, or if it is something that can be avoided. If all this is to be expected, why do not all individuals exhibit this trend? For example, studies have shown that sleep latency (i.e. the time needed to fall asleep) increases with age; however, this age-related difference is very small, i.e., between the ages of 20 to 80 years, the length of sleep latency increases is less than ten minutes on average. Furthermore, it has also been shown that older adults report sleeping around seven hours a night, which was closed to what was reported by younger adults (Ancoli-Israel, 2009) and within the considered good quality standards (Hirshkowitz et al., 2015).

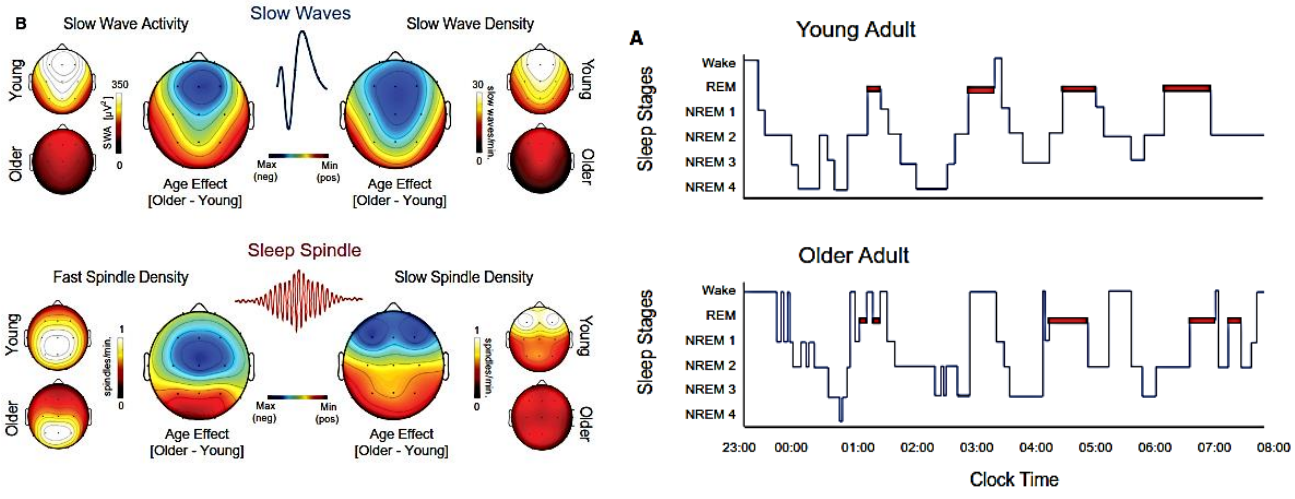

Figure 8. Schematic of Age-Related Changes in Sleep Architecture and NREM Sleep Oscillations (image from Mander et al., 2017).

Sleep disruption often leads older individuals to report symptoms of disturbed sleep to their physicians in an attempt to alleviate the disturbance. With the rapid increase in the older

population, it should be clear for the practicing physician, what changes to expect in sleep–wake patterns in normative ageing. On this, studies have reported that advancing into the fifth decade of life can lead to: (1) earlier bedtimes and rise times (i.e. advanced sleep timing); (2) longer time taken to fall asleep (i.e. longer sleep-onset latency); (3) shorter overall sleep duration; (4) increased sleep fragmentation (i.e. less consolidated sleep with more awakenings, arousals, or transitions to lighter sleep stages); (5) more fragile sleep (i.e., higher likelihood of being woken by external sensory stimuli); (6) reduced amount of deeper NREM sleep known as slow wave sleep (SWS); (7) increased time spent in lighter NREM stages 1 and 2; (8) shorter and fewer NREM-REM sleep cycles; and (9) increased time spent awake throughout the night (Mander et al., 2017) (Figure 8). An increase in the frequency of diurnal naps, particularly unplanned naps, is also observed in later life, given excessive sleepiness (Foley et al., 2007). However, as Mander and colleagues reported, excessive daytime sleepiness and daytime napping are not a universal feature of old(er) age. For a portion of older adults, daytime sleep propensity and daytime ratings of subjective sleepiness diminish with the transition from midlife into older adulthood (Mander et al., 2017; Dijk et al., 2010). On this, a factor that appears to be determinant is the presence of comorbid conditions, such as chronic pain, depression and sleep disorders, or frequent nighttime urination breaks (Mander et al., 2017; Foley et al., 2007; Vitiello, 2009). These changes can be interpreted in light of the reported functional deterioration of different systems, among which is the one involving the circadian clock. Thus, early intervention is critical and sleep-wake patterns might have an important role as a marker of disease onset or progression. For example, considering Alzheimer's disease (AD), and the work from Lucey and colleagues (2019), where sleep patterns were analyzed in normal cognitive ageing (subjects without cognitive-related pathology), results showed that NREM sleep negatively correlated with tau pathology and Aβ deposition in several brain areas. Such suggests that alterations in NREM sleep may be an early indicator of AD pathology, and that noninvasive sleep analysis might be useful for monitoring patients at risk for developing AD (Lucey et al., 2019).

Overall, there are several reasons for the difficulty of studying sleep in ageing. For instance, the high prevalence of comorbidities in older individuals raises questions about what should be considered within normal ageing. In fact, if on the one hand, individuals with comorbidities should be excluded, on the other, how representative or generalizable would be a sample composed only by "super-healthy" individuals? This debate is still ongoing and what should be considered "healthy

ageing" is still an open question. Nonetheless, studies of community-dwellers, within the normative ageing process, are needed in order to better understand sleep process and its mechanisms. This is even more important when considering some sleep research protocols that not only are time-consuming, but also make it difficult to assess vulnerable populations. Furthermore, clinical samples can reflect referral biases that are complicated to overcome in order for the results to be generalized to the overall population. Thus, there is a posing need to start earlier the study of sleep in ageing in order to understand the different profiles and trajectories.

1.8. Epidemiology of Sleep

In 1998, a representative cohort of Portuguese individuals with 18 and more years was interviewed by telephone about their sleep habits and disturbances (Ohayon, 2004; Ohayon & Paiva, 2005). Results showed that while approximately 12% of the sample (more females than males) reported difficulties in initiating sleep, 21% had difficulties in maintaining their sleep (again, more females compared to males). This trend increased with age; but, interestingly, for difficulty in initiating sleep, age evolution was in a U shape - higher for younger individuals (18–24 years), lower between the ages of 25 and 44, increasing again for the other age groups (Ohayon & Paiva, 2005). Results also showed that 9.8% indicated having non-restorative sleep, 28.1% reported having at least 1 insomnia symptom and 10.1% being globally dissatisfied with their sleep (Ohayon & Paiva, 2005). In what concerns sleep patterns, analysis were performed only for individuals with ages $\geq$ 55 years (Ohayon, 2004). Data indicated that the median sleep duration for individuals between 55 and 74 years old was 7h, and this value increased with age (7,5h for individuals between 75 and 84 years, and 8h for individuals with 85 or more years) (Ohayon, 2004). It was also observed that sleep latency remained the same across age groups (median=15 minutes) and that bedtime decreased with age (Ohayon, 2004). Specifically, individuals between 55 and 64 years went to bed in median at 23:30; while, individuals with ages comprised between 65 and 84 years, and with 85 years or more, went to bed in median at 23:00 and 22:45, respectively (Ohayon, 2004). In terms of waking time, the median wake time was 7:00 between 55 to 74 years, 7:30 in individuals with ages comprised between 75 and 84 years and 8:00 for individuals with 85 and more years (Ohayon, 2004).

In 2006, Paixão and colleagues showed the evolution of sleep parameters in the adult Portuguese population (18 and more years of age) through a longitudinal study, with data collected in 1999

and 2004. In terms of amount of hours slept in weeknights, results showed that 87% of respondents in 1999 and 85% in 2004 usually slept six or more hours of nocturnal sleep in weekdays. Interestingly, the individuals reporting sleeping more hours during the week were most frequently men (88.4%, in 2004), from younger age groups and with higher educational levels. It was also observed that from 1999 to 2004, there was a decrease in the percentage of individuals sleeping six or more hours in Lisboa and Vale do Ave region but not in other regions. More so, this decrease trend was also observed with age. Results also show that most individuals did not have a nap routine (82% in 1999 and 86% 2004), and such habit was a more frequent behavior in older age groups. Furthermore, while in 1999, 45% of the individuals usually woke up during the night more than once a week, in 2004 that percentage raised to 71%. In terms of difficulties in falling asleep, percentages remained stable (19%) (Paixão, Branco, & Contreiras, 2006). Regarding the consequences of a poor sleep, 15% of the inquired in 1999 and 16% in 2004 complained of tiredness when waking up and 14% in 1999 and 12% in 2004 complained of diurnal sleepiness. In this line, approximately 11% of the participants in 1999 and 14% in 2004 reported the use of medication (Paixão et al., 2006), which follows the global trend of increase in sleep medication consumption (Bertisch, Herzig, Winkelman, & Buettner, 2014; Marom, Rennert, Stein, Landsman, & Pillar, 2016). Moreover, it was interesting to observe differences between the different country regions, with Algarve having the least percentage of individuals reporting the use of medication to sleep. A statistically significant increase was observed from 1999 to 2004 in the Northern region of Portugal, which went from being a region with a lower percentage of medication use to the highest. A statistical significant association was also found between waking up tired/diurnal somnolence all the time or most of the time and consumption of sleep medication (Paixão et al., 2006).

Several factors can contribute for the disruption of the organism homeostatic balance and it seems that young adults, particularly college students, and older individuals, are particularly vulnerable groups to circadian rhythm/sleep disruptions. In fact, studies have shown that anywhere between 20 to 60% of college students are poor sleepers (Ahrberg et al., 2012; Bahammam et al., 2012; Lund et al., 2010; Preišegolavičiūtė et al., 2010) and that many older adults present sleep disturbances, with most having irregular sleep-wake patterns (Lund et al., 2010). In both cases, individual performance throughout the day seems to be affected (Schmidt et al., 2009). Obtaining sufficient sleep, and of adequate quality, is rapidly becoming a major public health concern (Colten

et al., 2006). The environmental and social conditions of our 24-hour societies appear to have enabled the steady and constant decline in the number of hours devoted to sleep, increasing not only deprivation, but also sleep disturbances (Cappuccio et al., 2010). The detrimental effects of this reality were first acknowledged by the industry (e.g. airlines, long-distance driving, shift-work manufacturing industry, emergency services), and later by the population at-large. This lack of rhythmicity in modern societies hinders the adaptive mechanism provided by regularity in lifestyle. The rhythmicity in lifestyle seems to aid in the maintenance of good health and well-being.

Nonetheless, few studies provide solid epidemiological data on sleep-wake patterns and its evolution through the time (Youngstedt et al., 2016). Epidemiological studies on sleep are also scarce for the Portuguese population, especially for community-dwellers. Thus, it is important to work on this, so that we are able to determine the trend of evolution of sleep parameters throughout time and across ages, and understand how these correlates associate with other aspects of the individual life.

1.9. Sleep quality and its measurement

There are several different methods of assessing sleep. As mentioned, the gold standard is polysomnography (PSG). However, sleep can also be estimated using diaries and wrist actigraphy. Regarding the latter, it involves wearing a wristwatch-like device that counts wrist movements (no movement counts equals sleep) and simply identifies movement *versus* no movement that is then converted into sleep *versus* wake. Compared to PSG, actigraphy has the advantage of being easily used to monitor not only for 24-hours, but also for multiple days, providing a measure of habitual behavior (Landry, Best, & Liu-Ambrose, 2015; A. Sadeh, Sharkey, & Carskadon, 1994; Avi Sadeh, 2011; Avi Sadeh & Acebo, 2002). A large set of devices is available and the choice of what to wear depends on the study purposes. On this, Table 1 provides an overview of the most used devices in research and some of their most important features. The amount of time participants wear the monitor varies across studies, but usually it is accepted that a minimum of 7-days is enough to provide a representative sample (e.g. Rowe et al., 2008). It is also common practice to ask participants to wear the device in the non-dominant wrist in order to reduce noise. Total time in bed, total sleep time, sleep latency, sleep efficiency, wake after sleep onset, number of awakenings and time of each awakening are some of the possible measures that the device can provide. It is

important to be aware of a number of pitfalls of actigraphy. Specifically, validity has neither been established for all scoring algorithms or devices, nor for all clinical groups, albeit it exists for some. Furthermore, actigraphy is not sufficient for the diagnosis of sleep disorders in individuals with motor disorders, or high motility during sleep and the use of computer scoring algorithms without controlling for potential artifacts can lead to inaccurate and misleading results (Sadeh and Acebo, 2002). Of note, for our studies, it was used ActiSleep+, firmware2.2.1 (ActiGraph, LLC, Pensacola, Florida, USA), a small (4.6×3.3 ×1.5 cm), electronic, light weight (19 grams), water proof, tri-axial wrist-worn device, which measure activity "counts" and are initialized at a sample rate of 30 Hz to record activities for free-living conditions. The obtained information is downloadable using ActiLife 6 software (v 6.9.0; ActiGraph, LLC, Pensacola, FL, USA) and integrated into 60-s epochs for posterior analysis using Cole-Kripke algorithm (Cole et al., 1992).

While for sleep parameters, such as sleep quantity or latency, it is easy to extract information, for sleep quality the same does not occur. In fact, a clear definition of what is sleep quality has not yet been provided, which consequently lead to different studies conceiving it differently. For example, while in some studies, sleep quality is a multidimensional concept (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), in others it can either represent the adequate values of each of the different dimensions or be a global score that represents how satisfied the individual is with his/her sleep (e.g. Sun et al., 2018; Takeuchi et al., 2018). This high variability in the approach used makes it difficult to compare studies' results. Thus, the first step should be to properly define sleep quality, so that it can be easier to compare results across studies. It is also important to state that, with a proper definition, the comparability across studies can be potentially attained not only via an objective/quantitative method, such as actigraphy or polysomnography, but also subjectively through self-report. As long as the concept measured is the same, all these methods provide for complementary information. In the Chapters II and III, this issue will be addressed in more detail.

Table 1. Actigraphy monitors comparison[2].

Company	**Actigraph**					**Phillips Respironics**		**CamNtech Inc**		**SOMNOmedics America Inc**		**Ambulatory Monitoring Inc**	
Monitor	 CentrePoint Insight Watch	 ActiGraph GT9X Link	 ActiGraph wGT3X-BT	 wActiSleep-BT Monitor[3]	 ActiSleep+ Monitor[4]	 Actiwatch Spectrum PRO	 Actiwatch Spectrum	 Motionwatch-8	 PRO-Diary	 SOMNOwatch plus	 SOMNOwatch	 Micro Motionlogger Watch	 Motionlogger Watch
Website	**www.actigraphcorp.com**					**www.actigraphy.com**		**www.camntech.com**		**www.somnomedics.com**		**www.ambulatory-monitoring. com**	
Peer Reviewed Validation Articles	www.actigraphcorp.com/category/research-database/sleep	Cellini N, Buman MP, McDevitt EA, Ricker AA, Mednick SC. Direct comparison of two actigraphy devices with polysomnographically recorded naps in healthy young adults. Chronobiol Int. 2013;30(5):691-8.	https://onlinelibrary.wiley.com/doi/abs/10.1111/sbr.12103 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172535 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5779275/	——	——	www.actigraphy.respironics.com/webliography https://academic.oup.com/sleep/article/39/6/1219/2453957		Stevens A, et al. The effect of sleep disturbance during pregnancy and perinatal period on postpartum psychopathology in women with bipolar disorder. J Women's Health Care. 2014;3(6):196.	Rumbold PL, Dodd-reynolds CJ, Stevenson E. Agreement between paper and pen visual analogue scales and a wristwatch-based electronic appetite rating system (PRODiary©), for continuous monitoring of freeliving subjective appetite sensations in 7-10 year old children. Appetite. 2013; 69:180-5.	——	——	Five peer-reviewed articles validate this actigraph. Example: Cole R, et al. Automatic sleep/wake identification from wrist activity. Sleep. 1992;15(5):461-9. https://www.ncbi.nlm.nih.gov/pubmed/25687438	Rupp TL, Balkin TJ. Comparison of Motionlogger Watch and Actiwatch actigraphs to polysomnography for sleep/wake estimation in healthy young adults. Behav Res Methods. 2011 Dec; 43(4):1152-60.
Dimensions (cm)	4.83x3.43x1.04	3.5x3.5x1.5	4.6x3.3x1.5	4.6x3.3x1.9	4.5x3.4x1.9	4.8x3.7x1.5	4.8x3.7x1.4	3.81x2.54x1.016	5.1x3.4x0.8	4.5x4.5x1.6	4.5x4.5x1.6	3.6x3.6x1.2	5.5x4.5x1.8
Weight (g)	35	38	19	22	22	31	30	16.8	16	30	30	30	65
Time/Date Display	Yes	Yes	No	No	No	Yes	Yes	No	Not reported	No	No	Yes	Yes
Event Marker Button	Yes	No	No	No	No	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes
Sleep Efficiency Calculation	Yes	No	Yes	Yes	Yes	Not found	Not found	Yes	Not reported	Yes	Yes	Yes	Unkown

[2] Adapted from http://www.sleepreviewmag.com/2018/12/actigraphy-guide/. The website of each company was also consulted.
[3] Descontinued.
[4] Descontinued.

Sleep Latency Calculation	Yes	No	Yes	Yes	Yes	Not found	Not found	Yes	Not reported	Yes	Yes	Yes	Unkown
Temperature	No	No	No	No	No	Not found	Not found	No	No	No	No	Yes	Yes
Other	Total sleep time (TST), wake after sleep onset (WASO), daytime activity (energy expenditure, steps taken, activity intensity, sedentary time), raw acceleration data Real-time data uploads to cloudbased CentrePoint software platform via home data hub and mobile application. Slim and compact design, interchangeable wrist bands.	Gyroscope and magnetometer sensors for advanced positional data capture; integrated wear time sensor for off-wrist detection; support for heart rate (wireless HR sensor required); automatic bedtime detection; daytime activity profile. Compatible mobile app supports real-time data uploads and subject feedback.	——	Integrated wear time sensor for off wrist detection, support for heart rate (wireless HR sensor required), PLM scoring, automatic bedtime detection, body position, and daytime activity profile. Compatible mobile app for iPhone, iPad, and Android platforms supports real time device communicatio n and data reports.	——	The Actiwatch Spectrum PRO incorporates all of the features of the Actiwatch Spectrum Plus and provides subjective scoring capabilities and audible and vibrational alarms. The alarms remind subjects to enter subjective scores on a pre-programmed schedule or on a manual basis. This capability adds another dimension to data collection when studying parameters such as pain and fatigue.	——	It is possible to collect information on circadian rhythm and 40 sleep parameters	Paperless diary with OLED screen interface and touch sensitive slider. Uses the Motionware software for sleep analysis and has additional software for user designed questionnaires with 8 different question types. FDA approved and validated against paper diaries in clinical work with timed, random, or user activated prompts. Allows up to 250 questions. Questionnaires can be designed using the PRO-Diary software and then loaded via USB. Questions can be asked at given times, random times or can be user initiated with flexible scheduling of up to 30 days. Full visibility of when your subject is answering questions and how long it takes them to do so.	PLMS scoring; programmable start and stop periods for several recording periods	PLM scoring, 1 external channel possible (2nd Actisensor, ECG, EEG, respiratory), programmable start and stop periods for several recording periods, linking of several SOMNOwatch recordings thanks to high synchronizatio n rate.	Ambient light, visual status indicator, multimode data collection, off-wrist detection.	Off-wrist detection channel, PVT test, user rating scale entry, alarms (1 user and up to 10 fixable), stopwatch, countdown timer
Battery Life *	30 days	14 days (wireless & gyro disabled, 30 Hz sample rate)	25 days (Wireless disabled, 30 Hz sample rate)	30 days	30 days	50 days	8 months with continuous use	90 (light sensor on), 120 (without light sensor)	14 days, assuming 10 minutes of questionnaire interface time per day. If motion logging is not selected, the PRO-Diary can record for up to 28 days,	30 days	+26 days	+ 30 days	+ 30 days

									assuming 10 minutes of interface time per day.				
Battery Options	Rechargeable lithium polymer	Rechargeable lithium polymer	Rechargeable lithium polymer	Rechargeable lithium polymer	Rechargeable lithium polymer	CLB 2032 lithium ion rechargeable (factory replaced)	CR 2430 Lithium Coin Cell (factory replaced)	Common watch CR2032	Lithium-ion rechargeable through a USB port or independent USB charger	Up to 25 day study duration (depending on number of sensors attached)	Lithium-ion-Accu, inbuilt, rechargeable	Lithium battery	1 DL2450 disposable coin cell
Memory Size	4 GB	180 days/4 GB	4 GB	4 GB	4 GB	32MB	Non-volatile 1 Mbits	4MB	4 MB	64MB	8 MB internal storage card	2 MB	2 MB
Sample Rate	32-256 Hertz	30-100 Hertz	30-100 Hertz	30-100 Hertz	30-100 Hertz	Not reported	32 Hertz	1, 2, 5, 10, 15, 30, 60 Hertz	Not reported	256/32 Hertz	1 per second up to 256 per second	16 Herzt	Not reported
Accelerometer Technology	Primary accelerometer (±8G)	3-axis solid state accelerometer with digital filtering	3-axis solid state accelerometer with digital filtering	3-axis solid state accelerometer with digital filtering	3-axis solid state accelerometer with digital filtering	MEMS type accelerometer	Solid-state "Piezo-electric" accelerometer	triaxial accelerometer	tri-axial accelerometer	3 activity sensors (x, y, z-axis, magnitude), ambient light, patient marker with acoustic tone	3 activity sensors (x, y, z-axis, magnitude), ambient light, patient marker with acoustic tone	Zero Crossing (ZC) or Proportional Integrating Measure (PIM, selectable high or low sensitivity	Solid state triaxial
Water Resistance	water resistant, IP57 I meter, 30 min	Yes	Yes	Yes	Yes	Waterproof at 1m for 30 min per IP27 IEC 60529	Waterproof 1 m for 30 min per IPX7 IEC 60529	waterproof to 3 bar; acceptable for swimming	No	Not reported	Not reported	Yes	50 m water-resistant
Light Sensor Wavelength Range (nm)	n/a	Yes	Yes	Yes	Yes	Yes	400 - 700 nm Three color light sensors that provide irradiance and luminous flux recordings in three color bands of the visible spectrum: red, green, and blue.	wide spectrum visible	Not reported	n/a	n/a	Yes	Photodiode, 400 ton 700 (520 peak)

*days, during regular use

Objectives

Sleep is a multidimensional concept that is influenced by the environment and the diversity of activities, (social) roles and contexts of the individual. Beyond the social, cultural and psychological influences, studies have shown that throughout the lifespan sleep changes are also due to biological transformations. Among these alterations are changes in both sleep patterns and routines, and in the amount of complaints reported by the individual, which seems to increase in middle-agers and older adults. Despite the marked progress in answering the fundamental questions – what is sleep, what are its mechanisms and functions –, subjective measures of sleep are still not fully understood and sleep diagnostic and monitoring tools and instruments are still evolving. Thus, herein, we propose to first dissect the meaning of a "good sleep quality" across the adult lifespan, and, then, explore associations between subjective sleep quality and neuropsychological and neuroimaging correlates. For this purpose, individuals with ages comprised between 18 and 87 years were recruited from family- and community-based health care centers, following a cross-sectional and a longitudinal design. We hypothesized that the way individuals conceive their sleep is associated to personal and psychological traits, which further associates with their rating of subjective sleep quality. Furthermore, it is suggested that functional and structural brain connectivity information might help explain, and be explained, by subjective sleep quality parameters. The results of the present work are expected to contribute to a future development of individual profiles that will allow better anticipating, predicting and acting on different health and cognitive outcomes across the lifespan.

Specifically, the research questions of the present thesis are:

1. Across the adult lifespan, how do community-dwellers regard the meaning of "good sleep quality"?
2. Across the adult lifespan, are there age or sex differences in the way individuals define good sleep quality?
3. What is the association between self-rating quality of sleep and the standard measure PSQI (Pittsburgh Sleep Quality Scale)?
4. What are the determinants of "good" and "poor" sleep quality?
5. What is the association between subjective sleep quality measured by PSQI and brain functional and structural connectivity as assessed by MRI?

We hypothesized that:

1. Individuals conceive sleep quality as a multidimensional concept and the parameters reported as important for a good sleep quality might change with age and sex;
2. There is an association between self-rating scales and the standard PSQI. However, considering that different people might define a good sleep quality differently, we expect this association to be moderate. We also speculate that the type of scale used to determine sleep quality influences the amount of bias on its scoring;
3. Social, personal and psychological variables are known to influence sleep. Thus, variables such as age, sex, marital status, psychological morbidity, and certain personality traits, associate with subjective sleep quality;
4. Functional connectivity (FC) decreases with poor sleep quality. Given that previous studies have shown that decreases in synchrony occur with sleep loss and fragmentation, we expect that this can also be observed with a subjective measure of sleep quality. Furthermore, because this measure reports to the previous month, it is also expected that it will be sufficient to allow to observe changes in structural connectivity (SC).

As such we propose to: 1) review the construct of sleep quality (Chapter II); 2) study how adult community-dwellers across the lifespan conceive "good sleep quality" (Chapter III); 3) characterize sleep patterns and routines (Chapter III and Chapter IV); and 4) determine the associations between subjective sleep quality and psychological variables and brain correlates (Chapter III and Chapter V). Ultimately, the work is expected to lay a foundation for raising awareness about misadjusted sleep/rest behaviors and/or patterns, and develop and promote strategies that empower the individual to make better and healthier decisions.

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CHAPTER II

The importance of defining what we are measuring: a systematic review on sleep quality meaning

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(Submitted)

The importance of defining what we are measuring: a systematic review on sleep quality meaning

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Abstract

To date (December 2018), there are approximately 18 000 articles on PubMed addressing sleep quality. Of these, 2256 just in the last one-year period. However, the vague use of terminology may be contributing to the variability of study results. Here, to understand the state of the art, and clarify the meaning of the concept 'sleep quality', we performed a systematic review on what is sleep quality and how can it be operationalized. Studies considering for a definition of sleep quality, subjective sleep or perceived sleep, were included. Results show that few studies indicate which elements should be considered in defining sleep quality, with none providing a definition, albeit, some indicating parameters that contribute for it. More so, studies are not uniform as to the measures used, resulting in different interpretations of the sleep quality construct among the general population. Older studies, combining subjective and objective measures, and promoting variability within the study design, considered sleep continuity variables as the most important element contributing for subjective sleep quality construct. However, more recent studies focusing only on qualitative data seem to indicate that the main feature when reporting a good sleep quality relates to next day performance and the memory of the previous night sleep. Given the importance of 'sleep quality' construct not only for research, but also for clinical practice, namely in its monitoring and in diagnosis and treatment of sleep-related disorders, it is of crucial importance to clarify its meaning and definition.

Key-words: sleep quality; definition; meaning; construct; subjective sleep quality; systematic review

Introduction

Sleep is a multidimensional construct, often referred to as in terms of its quality (Ohayon et al., 2017). Indeed, sleep quality has been a well-recognized predictor of physical and mental health, cognitive status, wellness and overall vitality (Alhola & Polo-Kantola, 2007; Asif, Iqbal, & Nazir, 2017; Besedovsky, Lange, & Born, 2012; Freeman et al., 2017; Lim & Dinges, 2010; Ohayon et al., 2017; Simon & Walker, 2018; L. Xie et al., 2013). However, among the results of population-based studies, there is a concerning heterogeneity which might be associated to different conceptualizations of 'sleep quality'.

Efforts to define sleep quality have been mainly driven by clinical considerations and may not necessarily reflect the general population understanding of it (Goelema et al., 2018). This is particularly relevant because often, it is the perception of poor sleep quality that takes the individuals to seek their doctor (Akerstedt, Hume, Minors, & Waterhouse, 1997). Furthermore, physicians frequently rely on objective measures of sleep to diagnose sleep disturbances, which has been shown in the literature not to correlate to self-reports of poor sleep quality. For instance, studies indicate that objective sleep parameters, driven from polysomnographic (PSG) or EEG measurements, often do not translate self-reported measures of poor sleep quality or a history of chronic insomnia (Moul et al., 2002; Rosa & Bonnet, 2000). Adding to this, there is a lack of operationalization of the concept 'sleep quality' or, at least, an heterogeneity in the parameters that are being used to refer to it (e.g. Kwok et al., 2018). For example, while some studies use 'sleep satisfaction' (e.g. Delaney et al., 2018) or 'depth of sleep' (e.g. Takeuchi et al., 2018) when addressing 'sleep quality', others use self-ratings of the previous night (e.g. Vitale et al., 2018) or the Pittsburgh Sleep Quality Index (PSQI) (e.g. Li et al., 2017). Indeed, this is an issue already identified by other authors (e.g. Harvey et al., 2008) that also suggest that the vague use of terminology might be a possible reason for the variability among study results. To understand the state of the art on this topic, and to determine what should be the future steps for providing an objective and adequate definition of Sleep Quality, we performed a systematic review on what is 'sleep quality' and how it can be operationalized.

Methods

Literature search on the measures used for sleep quality assessment

The first step was to perform a PubMed search with the expression ‘sleep quality‘. The purpose of this was to determine the tools that are being used for ‘sleep quality‘ assessment and, consequently, to understand how this concept is been conceptualized, i.e., the choice of the instrument used has implicit a particular definition of the construct. The search was conducted on December 4th (2018) and reviewed on December 13rd. Due to the expected high number of articles, results were restricted to the first 100 articles and to last one-year publications. Articles were then screened regarding the measure/tools used for sleep quality assessment.

Systematic review of the subjective meaning of a good sleep quality/a good night of sleep

Next, a systematic review addressing the question of how the general adult population (18 years and more) conceived the meaning of a good sleep quality was conducted. Different search engines were considered and the search expression was adjusted to its specificities. The expression used for the search on PubMed was *("subjective sleep"[All Fields] OR "perceived sleep"[All Fields] OR "sleep quality"[All Fields]) AND (meaning[All Fields] OR definition[All Fields])*, sorted by Best Mach. The search was performed on December 4th (2018) and reviewed on January 10th (2019), in order to guarantee that no new results would be left out of the analysis. No date, language or article type restrictions were imposed to the search. To guarantee that all literature of interest was considered, a search in EBSCO (through Psychology and Behavioral Sciences Collection) was also performed. The search expression used was ("subjective sleep quality meaning" OR "sleep quality definition" OR ("perceived sleep" AND "meaning")). A search was also performed in Google Scholar with the search expression ("subjective sleep quality meaning" OR "sleep quality definition"), to guarantee that no potential articles of interest were left without consideration. A cross-ref was also executed. All articles that aimed to clarify or contribute to the meaning/definition of a ‘good sleep quality‘ were considered, including reviews or works that used objective measures of sleep quality, as long as it was in association to the meaning of this concept. All articles that filled the inclusion criteria were considered for the literature analysis (Figure 1).

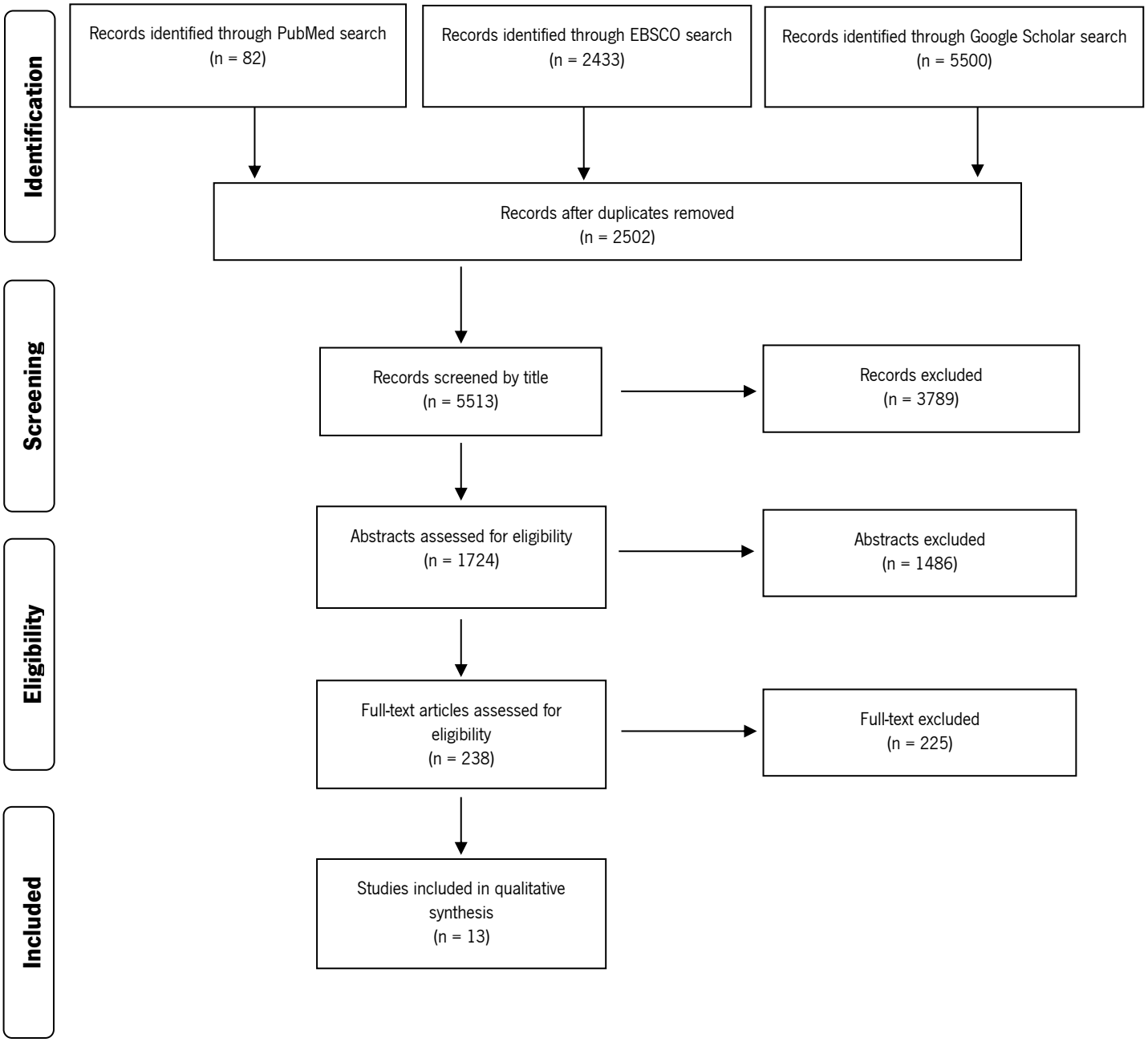

Figure 1. Flow diagram of the systematic review process.

Results

Heterogeneity of the measures used to assess sleep quality

From the first part of the work (the PubMed search on the expression 'sleep quality' for the determination of the tools being used for sleep quality assessment), a total of 17674 results were obtained. When restricting the results to last one-year (January to December 2018), 2253 articles remained. From these, in order to determine the measures being used to assess sleep quality, and how it was being defined, the first 100 articles were included for further analysis (Table 1). Of

these, 66% used the Pittsburgh Sleep Quality Index (PSQI), a composite measure of subjective sleep quality; and, among these, two also used the Insomnia Severity Index (ISI), but both measures were considered independently as sleep quality. The remaining studies considered objective measures such as actigraphy, EEG or polysomnography (PSG), using one or more indices individually. Importantly, some studies employed adapted questions from PSQI, or used other questionnaires that not PSQI, or even asked participants one particular question (such as "How would you rate the depth of your usual sleep", 'How would you evaluate your most recent night's sleep?', "How do you evaluate the quality of your sleep?", "How did you evaluate your sleep situation last month?", "How deep was your sleep?") providing them with answer options that varied from analogic and visual scales, to scales like "use of sleeping pills or drugs, difficult to fall asleep, dreamy sleep, can fall asleep but easily awaken, and sleep well". The options to answer could also be presented in a dichotomized format; for example, "Sleep well" (for those who rated their sleep quality as "good", "very good" and "excellent") or "Do not sleep well" (for those who rated it as "bad" or "regular")". Sleep quality inference also ranged from the deepness of sleep to its duration. As an example, in one of the reviews considered (Kwok et al., 2018), this heterogeneity was particularly visible. Sleep quality was an outcome variable, but the methods being used by the different studies were so different that it was difficult to compare the studies and draw conclusions.

Table 1. Results from the analysis of the first 100 papers on PubMed under the scope of "sleep quality".

Year	Journal	Author	Measure of Sleep Quality
2018	Int J Environ Res Public Health	(Gao et al., 2018)	Pittsburgh Sleep Quality Index
2018	Int J Environ Res Public Health	(Wu et al., 2018)	Pittsburgh Sleep Quality Index
2018	Front Psychol	(van Eerde & Venus, 2018)	Pittsburgh Sleep Quality Index
2018	Ind Health	(Musa, Moy & Wong, 2018)	Pittsburgh Sleep Quality Index
2018	J Headache Pain	(Song et al., 2018)	Pittsburgh Sleep Quality Index
2018	Sleep Disord	(Berhanu et al., 2018)	Pittsburgh Sleep Quality Index
2017	BMJ Open	(Li et al., 2017)	Pittsburgh Sleep Quality Index
2018	Int J Environ Res Public Health	(Kong et al., 2018)	Pittsburgh Sleep Quality Index
2018	Diabetes Metab Syndr Obes	(Darraj et al., 2018)	Pittsburgh Sleep Quality Index
2018	Epidemiol Health	(Thichumpa et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Cardiovasc Nurs	(Risom et al., 2018)	Pittsburgh Sleep Quality Index
2018	Front Psychol	(Rönnlund & Carelli, 2018)	Karolinska Sleep Questionnaire (KSQ)

2018	Front Ageing Neurosci	(Amorim et al., 2018)	Pittsburgh Sleep Quality Index
2018	North Clin Istanb	(Teker & Luleci, 2018)	Pittsburgh Sleep Quality Index
2018	J Behav Addict	(Simor et al., 2018)	Pittsburgh Sleep Quality Index
2018	BMC Neurol	(Kotterba et al., 2018)	Pittsburgh Sleep Quality Index
2018	Int J Environ Res Public Health	(Chirwa et al., 2018)	Pittsburgh Sleep Quality Index
2018	Medicina (Kaunas)	(Jurado-Fasoli et al., 2018)	Pittsburgh Sleep Quality Index
2018	PLoS One	(Benito-González et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Pain Res	(Liu et al., 2018)	Visual analog scale (VAS)
2018	PLoS One	(Kim, Kim, Jeon, & Hong, 2018)	Pittsburgh Sleep Quality Index
2017	Turk J Obstet Gynecol	(İlhan et al., 2017)	Pittsburgh Sleep Quality Index
2018	Sports Med Open	(Hoshikawa, Uchida, & Hirano, 2018)	Pittsburgh Sleep Quality Index
2018	J Korean Med Sci	(Kim et al., 2018)	Pittsburgh Sleep Quality Index
2018	Int J Environ Res Public Health	(Krističević, Štefan, & Sporiš, 2018)	Pittsburgh Sleep Quality Index
2018	Health Qual Life Outcomes	(Manzar et al., 2018)	Pittsburgh Sleep Quality Index
2017	Evid Based Complement Alternat Med	(Cho, Lee, & Hur, 2017)	Verran & Snyder-Halpern Sleep Scale
2018	Front Psychol	(Li, Kee, & Lam, 2018)	Pittsburgh Sleep Quality Index
2018	BMJ Open	(Štefan, Sporiš, Krističević, & Knjaz, 2018)	Pittsburgh Sleep Quality Index
2018	Ann Gastroenterol	(Michalopoulos, Vrakas, Makris, & Tzathas, 2018)	Pittsburgh Sleep Quality Index
2018	Front Neurol	(Raikes et al., 2018)	Pittsburgh Sleep Quality Index
2018	Cancer Manag Res	(Rafie et al., 2018)	Pittsburgh Sleep Quality Index
2018	Int J Environ Res Public Health	(Gombert, Konze, Rivkin, & Schmidt, 2018)	"How do you evaluate this night's sleep?" (1 = very poor; 4 = excellent)
2018	Front Psychiatr	(Klumpp, Hosseini, & Phan, 2018)	Pittsburgh Sleep Quality Index
2018	Sci Rep	(Montesinos, Castaldo, Cappuccio, & Pecchia, 2018)	Sleep quality variations were assessed using sleep diary (Consensus Sleep Diary), actigraphy and heart rate variability (HRV). Sleep was monitored at home, using an unobtrusive wearable device. The PSQI global score was used to compare baseline sleep quality over the past month between groups.
2018	Sci Rep	(Takeuchi et al., 2018)	"How would you rate the depth of your usual sleep" (1= can have a sound sleep; 2= can relatively have a sound sleep; 3= neither; 4= relatively bad; 5= very bad) (sound sleep represents sleep depth, continuity and good quality and the response to this question was used as a continuous variable.)
2018	J Physiol Anthropol	(Ko & Lee, 2018)	10-question index: questions 1 to 7 (part 1) derived from Verran and Snyder-Halpern Sleep Scale) related to degree of fragmentation and depth of the previous sleep, and questions 8 to 10 (part 2) providing a subjective evaluation of the bedroom

			environment (temperature, humidity, and thermal comfort).
2018	BMJ Open	(Zhang et al., 2018)	'How would you evaluate your most recent night's sleep?' (from very bad (1) to very good (4))
2018	Biomedicine (Taipei)	(Moudi et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Clin Res Pediatr Endocrinol	(Baran, Atar, Pirgon, Filiz, & Filiz, 2018)	Pittsburgh Sleep Quality Index
2018	Crit Care	(Simons et al., 2018)	Richards Campbell sleep questionnaire (RCSQ)
2018	J Behav Addict	(Xie, Dong, & Wang, 2018)	8 items adapted from the Pittsburgh Sleep Quality Index
2018	BMJ Open	(Rogers, Morrison, Rorie, Mackenzie, & MacDonald, 2018)	Pittsburgh Sleep Quality Index
2018	Int J Environ Res Public Health	(Zou, Yeung, Quan, Boyden, & Wang, 2018)	Review of literature. Included studies on sleep quality: only one study adopted the Parkinson's disease Sleep Scale, six studies adopted the Pittsburgh Sleep Quality Index.
2018	Nat Sci Sleep	(Denis, 2018)	Sleep quality as a multifaceted construct that can encompass many different factors such as sleep duration, sleep latency, as well as more subjective aspects such as the "restfulness" of sleep. Several measures were considered. Some examples are: "How would you assess the quality of your sleep during the previous month?"; Pittsburgh Sleep Quality Index Insomnia Symptoms Questionnaire Sleep Condition Indicator (SCI) Use of sleep measures that are not referred within the concept of sleep quality.
2018	Cureus	(Gangwar et al., 2018)	Pittsburgh Sleep Quality Index
2018	Rev Paul Pediatr	(de Oliveira, da Silva, dos Santos, Ritti-Dias, & Diniz, 2018)	Sleep quality perception was measured by: "How do you evaluate the quality of your sleep?" ("positive" for those who rated their sleep quality as "good", "very good" or "excellent", and "negative" for those who rated it as "poor" or "fair")
2018	Trials	(Falck et al., 2018)	The outcome sleep quality is given by sleep efficiency measured by MotionWatch8©. Good and poor sleepers in the beginning of the study are assessed through the Pittsburgh Sleep Quality Index. The authors consider that each of the parameters derived from actigraphy can be identified as objective sleep quality and they used PSQI for subjective sleep quality assessment.
2018	Ochsner J	(Lee et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Clin Sleep Med	(Gupta, Ulfberg, Allen, & Goel, 2018)	Pittsburgh Sleep Quality Index
2018	Healthcare (Basel)	(Zwart, Smits, Egberts, Rademaker, & van Geijlswijk, 2018)	Pittsburgh Sleep Quality Index; Insomnia Severity Index (ISI)
2018	J Thorac Dis	(Gu et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Am Heart Assoc	(Kwok et al., 2018)	Review. Authors considered studies recurring to different questionnaires or direct questioning to ascertain information about different aspects of sleep that are considered sleep quality. See Table

			S4 in the supplementary material of the article for more details.
2018	Ann Occup Environ Med	(Kim et al., 2018)	Pittsburgh Sleep Quality Index
2018	BMJ Open	(Min et al., 2018)	Participants were asked about their recovery from fatigue after sleeping for the seven most recent days (sleep quality) Possible answers: very good, good, moderate, poor and very poor. Answers were regrouped into three groups of sleep quality to simplify the categories: good (very good and good), moderate and poor (poor and very poor).
2018	NPJ Breast Cancer	(Beverly et al., 2018)	Woman's Health Initiative Insomnia Rating Scale (WHIIRS)
2018	Behav Neurol	(Mantua, Helms, Weymann, Capaldi, & Lim, 2018)	Insomnia Severity Index (ISI); FOSQ-10
2018	J Clin Sleep Med	(Lao et al., 2018)l	"How did you evaluate your sleep situation last month?" (answer options: use of sleeping pills or drugs, difficult to fall asleep, dreamy sleep, can fall asleep but easily awaken, and sleep well).
2018	PLoS One	(Sakamoto et al., 2018)	Pittsburgh Sleep Quality Index
2018	Ci Ji Yi Xue Za Zhi	(Rebello, Kallingappa, & Hegde, 2018)	Pittsburgh Sleep Quality Index
2018	Brain Behav	(Chen et al., 2018)	Pittsburgh Sleep Quality Index
2018	PeerJ.	(Banno et al., 2018)	Pittsburgh Sleep Quality Index; Insomnia Severity Index (ISI)
2018	J Clin Med	(Grabovac et al., 2018)	Medical Outcome Study Sleep Scale (MOS-SS)
2018	Prev Nutr Food Sci	(Kang et al., 2018)	Pittsburgh Sleep Quality Index
2018	Rev Paul Pediatr	(Batista et al., 2018)	Self-perception of sleep quality was measured by: "How do you rate the quality of your sleep?" (answers dichotomized into: "Sleep well" (for those who rated their sleep quality as "good", "very good" and "excellent") and "Do not sleep well" (for those who rated it as "bad" or "regular"))
2018	Biomed Res Int	(Zhao et al., 2018)	Pittsburgh Sleep Quality Index
2018	Evid Based Complement Alternat Med	(Greeson et al., 2018)	Pittsburgh Sleep Quality Index
2018	Front Physiol	(Vitale, Banfi, La Torre, & Bonato, 2018)	Actigraphy and subjective value of sleep quality in a scale from 0 = very poor sleep quality, to 10 = optimal sleep quality
2018	Multidiscip Respir Med	(Brandão, 2018)	Pittsburgh Sleep Quality Index
2018	Front Psychiatry	(della Monica, Johnsen, Atzori, Groeger, & Dijk, 2018)	Polysomnography and Quality of Sleep Last Night (sQoS) and How Refreshed they felt upon Awakening (sRuA), using a Visual Analogue Scale (VAS)
2018	Int J Clin Health Psychol	(Brandolim Becker et al., 2018)	Pittsburgh Sleep Quality Index
2018	Iran J Pharm Res	(Mousavi et al., 2018)	Pittsburgh Sleep Quality Index
2018	Health Psychol.	(Stephan, Sutin, Bayard, Križan, & Terracciano, 2018)	WLS group - participants were asked whether or not they had trouble sleeping in the past six months. If participants reported that they had trouble, they answered two additional items: "How often have

			you had trouble sleeping?" with scores ranging from 1 (monthly or less) to 3 (daily or more often) and "How much discomfort has trouble sleeping caused you in the last six months?" with scores ranging from 0 (none) to 3 (a lot). Participants were coded zero if they answered no to the first question, and the two additional items were summed if participants responded yes to the first question. The scores ranged from 0 to 6 with higher scores representing worse sleep quality. HRS participants answered four questions: "How often do you have trouble falling asleep?", "How often do you have trouble with waking up during the night?", "How often do you have trouble with waking up too early and not being able to fall asleep again?", and "How often do you feel really rested when you wake up in the morning?". The responses of "most of the time" or "sometimes" to the first three questions and "sometimes" or "rarely or never" to the fourth question were coded as indicators of sleep difficulties. These four items were then summed as an index of sleep quality, with scores ranging from 0 to 4 (higher scores indicating worse sleep quality). MIDUS participants were asked to indicate how often they experienced each of the following: "Have trouble falling asleep", "Wake up during the night and have difficulty going back to sleep", "Wake up too early in the morning and are unable to get back to sleep", and "Feel unrested during the day, no matter how many hours of sleep you had". Response items were"almost always", "often", or "sometimes", coded as indicators of poor sleep quality. These four items were summed as an index that ranged from 0 to 4; higher scores representing worse sleep quality. In the MIDJA, participants were asked a single question: "During the past 30 days, how often have you experienced...trouble getting to sleep or staying asleep?". Answer from 1 (not at all) to 6 (almost every day).
2018	Curr Dev Nutr	(Gwin & Leidy, 2018)	Perceived sleep quality
2018	BMJ Open	(Angelhoff et al., 2018)	Sleep quality is subjective and described as the duration of sleep followed by spontaneous awakening and alertness throughout the day. A study-specific sleep diary for four consecutive days will be used to provide data on perceived sleep quality on a five-point scale (1=bad, 5=good). Actigraphy was also considered.
2018	J Neurosci Rural Pract	(Aliyu et al., 2018)	Pittsburgh Sleep Quality Index
2018	Obstet Gynecol	(Warsi et al., 2018)	Pittsburgh Sleep Quality Index
2018	Innov Ageing	(Brush et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Inv Violence Res	(Tabrizi et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Ophthalmol	(Ji et al., 2018)	Pittsburgh Sleep Quality Index

2018	Innov Aging	(Zeng et al., 2018)	Sleep quality was evaluated as self-rated reports.
2018	PLoS One	(Kim, Yim, & Park, 2018)	Pittsburgh Sleep Quality Index
2018	BMC Cancer	(Duivon et al., 2018)	Pittsburgh Sleep Quality Index
2018	Int J Environ Res Public Health	(Ropponen et al., 2018)	Pittsburgh Sleep Quality Index
2018	PLoS One	(Li et al., 2018)	Numeric Rating Scale (NRS, an 11-point scale where 0 indicates the worst sleep and 10 the best)
2018	Sleep Sci	(Forner-Cordero, Umemura, Furtado, & Gonçalves, 2018)	Pittsburgh Sleep Quality Index Actigraphy
2018	BMJ Open	(Delaney et al., 2018)	Self-reports of sleep quality will be assessed during the 24-hour period using: the Richards-Campbell Sleep Questionnaire, subjective sleepiness evaluated via the Karolinska Sleepiness Scale, along with a prehospital discharge survey regarding patients' perception of sleep quality and disturbing factors using the Little Sleep Questionnaire
2018	J Atr Fibrillation	(Kwon, 2018)	Objective sleep quality through Polysomnography
2018	BMJ Open	(Tse, Lee, Zhang, & Lai, 2018)	Actigraphy. Parent reports'
2018	Saudi Med J	(Turk et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Diabetes Investig	(Hirota et al., 2018)	EEG measurements
2018	BMJ Open	(Sun et al., 2017)	'How would you evaluate this night's sleep?', the response format for which ranged from very bad (1) to very good (4)
2018	J Clin Sleep Med	(Lappharat et al., 2018)	Pittsburgh Sleep Quality Index
2018	Parkinsons Dis	(Fabregues et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Ophthalmol	(Swaminathan et al., 2018)	Pittsburgh Sleep Quality Index
2018	Adv Med Educ Pract	(Hangouche et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Occup Health	(Ikeda et al., 2018)	Pittsburgh Sleep Quality Index
2018	J Lifestyle Med	(Kim et al., 2018)	Pittsburgh Sleep Quality Index
2018	Innov Aging	(Kim & Yoon, 2018)	Self-reported questionnaire – abstract only (from Poster session – do not mention what was the measure)
2018	Sci Rep	(Tsou, Huang, Wu, Hung, & Chang, 2018)	Polysomnography analysis for sleep quality
2018	Schizophr Bull	(Villa et al., 2018)	Pittsburgh Sleep Quality Index

For the purpose of this systematic review, the question addressed in each study is not of note. Rather, only the sleep quality instrument used in the assessment is of consideration. / *Visual analog scale (VAS) - 10-cm straight line with bilateral limits that indicated the worst sleep quality on one end, and the best on the other. The participant selected the place best representing the overall condition of his/her sleep quality from 0 (the worst sleep quality) to 10 (the best sleep quality) in the preceding 4 weeks. / *Verran & Snyder-Halpern Sleep Scale (measured sleep quality over the course of 2 days at 8 a.m. when patients awoke) - the scale comprises 9 questions including the number of times one wakes up during the night, how much one tosses and turns, total hours spent sleeping, the depth of sleep, how long it takes to fall asleep, how one feels when waking up, how one awakes from sleep, and level of satisfaction with sleep. The final question is a short-answer question. Excluding the short-answer question, the remaining 8 questions ranged from 0 to 10 points with a lowest possible score of 0 points and highest possible score of 80 points. Higher scores indicated higher quality of sleep. / *Richards Campbell sleep questionnaire (RCSQ) - 5-item questionnaire, evaluates different aspects of sleep, namely perceived sleep depth, sleep latency, number of awakenings, efficiency and time awake. Each item is rated on a visual analog scale (VAS) (0–100 mm), whereby higher scores indicate better sleep. The mean of the scores on these 5 items represents the overall RCSQ score. Usually, one item, regarding whether the noise level is disturbing for sleep is also part of the questionnaire and therefore this item was added to the questionnaire. / Sleep Condition Indicator (SCI) - assess insomnia symptoms. / WHI Insomnia Rating Scale (WHIIRS) - a measure of perceived insomnia symptoms from the past 4 weeks.

Back to basics: a literature review on sleep quality meaning and definitions

Regarding the systematic review addressing the meaning and/or definition of sleep quality, a total of 238 articles were considered for full text analysis (Figure 1). Of these, 13 were included in the systematic review, based on the defined criteria. Table 2 presents a simple characterization of the included studies regarding the country where it was performed, the parameter(s) or definition of sleep quality used in the study and the most relevant limitations. In Table 3, a detailed characterization of the main aspects of each of these studies is provided in order to better elucidate the reader.

Table 2. Summary table of the principal limitations of the studies considered for the systematic review and indication of the country in which the information was collected.

Reference	Data Collection Place	Sleep quality definition	Study limitations
(Goelema et al., 2018)	The Netherlands	Daytime functioning as the more important parameter	Results from literature review are not shown. Small sample size for the age range considered.
(Ramlee et al., 2017)	England	Mostly influenced by memories of what happened during sleep and their experience upon waking	Small sample size. Only young individuals were considered.
(Ramlee et al., 2018)	England	Is not solely determined by nighttime parameters but also by daytime processes through retrospective judgment	Small sample size. Only young individuals were considered.
(Rosipal et al., 2013)	European	Objective and subjective sleep parameters and its association witht daytime quality variables	(n.a. – review)
(Krystal & Edinger, 2008)	USA	Likert-style rating of the previous night's sleep quality.	Sleep quality is only considered as a score from a rating of the previous nigh;
(Harvey et al., 2008)	UK	Subjective feelings regarding the day following sleep appeared to be the most important basis for judging sleep quality	Small sample size. Young individuals only.
(Yi et al., 2006)	South Korea	Sleep quality was defined considering the answers to the questions: How is your sleep these days? What do you think a good sleep is? What do you think of a poor sleep?	Small sample size for all the groups considered; The same population was used to develop and test a new instrument to assess sleep quality.
(Keklund & Akerstedt, 1997)	Sweden	Subjective sleep quality is related to perceptions of ease of initiation and maintenance of sleep. From a physiological point of view, subjective sleep quality seems to be a matter of SWS and sleep continuity (i.e. as indicated by sleep efficiency).	Small sample size. Only young individuals were considered.
(Akerstedt et al., 1994)	Sweden	Mainly involved variables of sleep continuity, in particular, perceived calmness of sleep and sleep efficiency.	The same sample is used in both studies. Small sample size. Mostly young individuals. In one of the studies only females were considered.
(Åkerstedt et al., 1994)	Sweden	Mainly related to sleep efficiency but also to the closeness of the awakening to the circadian acrophase	
(Buysse et al., 1989)	USA	Composite measure of different parameters, namely sleep duration, latency, disturbance, medication, day dysfunction, perceived quality. Developed PSQI	Index was defined only considering clinical implications.

(Snyder-Halpern & Verran, 1987)	USA	Described in terms of sleep fragmentation (i.e., midsleep awakenings and movement during sleep); sleep length (i.e. the total sleep period); delay (i.e. sleep latency) and depth (i.e. soundness of sleep, rest upon awakening; method of awakening; subjective quality of sleep.	It was only considered a clinical population; There is no comparison of this measure with other standard methods.
(Johns et al., 1971)	Australia	Definition derived from two questions: at what time do you usually go to bed at night on weekdays? how would you describe your usual sleep?	Small sample size Only young individuals and students are being considered,

Overall, few studies (5.56%) addressed the meaning of "sleep quality" in the general population. Despite in most studies authors mentioned that a review of the literature was performed, none of them presented the results of such review nor its implications for their approach to the problematic. Studies were comprised of small samples (ranging in sample size from n= 16 to n= 64), two employed the same sample (Åkerstedt et al., 1994; Akerstedt et al., 1994), and most (61.5%) recurred to young college students. A comparison between "normal sleepers" (defined as individuals without sleep complaints or reported poor sleep quality) and "problematic populations" (such as individuals with chronic pain or sleep disturbances) was also addressed in some of the studies (Ramlee et al., 2018). In terms of findings, it was possible to observe an association between sleep quality and the (reported) delay to sleep, total time awake, duration of night sleep, and nightmares (Akerstedt et al., 1994; Goelema et al., 2018; Ramlee et al., 2018, 2017). A "good sleep quality" was mainly reported as a question of sleep continuity variables (Åkerstedt et al., 1994; Akerstedt et al., 1994). However, in the most recent studies (Goelema et al., 2018; Ramlee et al., 2018, 2017), this is no longer the case as sleep quality judgment seems to depend more on matters of performance in the next day, which is aligned to the memory that the individual has of the previous sleep time. Briefly, we observe that: (1) studies developed to understand how sleep quality is interpreted by the general population are few; (2) except for one study (Goelema et al., 2018), all studies considered only samples with young individuals, including those that explored for comparisons between insomniacs *vs* good/normal sleepers; (3) at no moment it is used an approach in which is the participant had to think and present the parameters that he/she uses to define a good sleep quality or a good night of sleep; (4) there was no attempt to determine the association between the reported parameters of subjective sleep quality and existing standard measures, such as PSQI; 5) no determination of the association of the profiling of answers and other psychological parameters, or even sleep routines, was performed.

Table 3. Summary table of the information from the studies that also explored the meaning of "sleep quality".

Year	Journal	Author	Country	Title	Aims	Methods	Results	Conclusions
2018	BMC Research Notes	(Goelema et al., 2018)	Netherlands	Conceptions of sleep experience: a layman perspective	To understand the essence of the sleep experience and the concepts held by lay people without sleep disorders	Cross-sectional study. n=64 respondents 32 females; age range: 18-79yrs Young (≤ 49 years)/Old (≥ 50 years) Study conducted online. 4 participants per group of sex, age (young and old), education (high, ≥ bachelor; low, < bachelor) and PSQI (good, ≤ 5; poor, > 5). Sample of healthy individuals – not actively screened for signs of undiagnosed-sleep disorders. Sleep Sentence Completion Questionnaire (SSCQ) (projective data collection technique) was used to survey participants' conceptions of sleep experience. This measure was obtained after a pilot study in which 10 participants answer to a sample of a 62-item stem completion questionnaire that was then analyzed in terms of word frequency. Demographic information, educational level and the Dutch version of the Pittsburgh Sleep Quality Index (PSQI) were also applied. Objective sleep measurements not performed. A phenomenological data analysis approach was adopted. Two coders performed independently a direct content analysis to ensure the validity of the clustering. The two coders achieved a consistency of 0.81 Cohen's kappa.	PSQI range: 1-16 Bed time_ 23:38:59 (1:13:42) Wake up time_ 7:31:41 (1:11:35) 9 themes resulted from data analysis: next day state; interruptions during the night; before bed state; sleep characteristics; bedroom environment; thoughts about sleep; routine; alarm clock; other. The largest category in the analysis was 'next day state', followed by 'interruptions during the night' and 'before bed state'. In the category 'other' were statements concerning dreams/nightmares, regular bedtimes, bad food and some few single statements. This category also involved statements about sleeping posture, sleep rhythm and sleeping on time.	The experienced sleep quality is not depending solely on the progress of the night. Daytime functioning seems more important for people to judge their sleep experience than the actual night itself. Sleep quality definition, from a subjective point of view, should involve factors, such as stress/well-being levels, rest feeling and functioning during the day. This implies that the experienced sleep quality is not only depending on the progress of the night. These results can guide future research to provide suitable psychometric measures for normal sleepers, as well as the design of sleep data visualization applications in the context of health self-monitoring.
2017	Sleep	(Ramlee et al., 2017)	England	What Sways People's Judgment of Sleep Quality? A Quantitative Choice-	To examine the relative weight that specific factors carry in the sleep quality judging process.	Cross-sectional study. Sample characteristics n=111, age range: 18 and 30 years Recruited from a university-wide subject panel	The parameters that occurred during the day before sleep did not have a significant impact on the participants' choices (amount of activity: p = .38; day went well?: p = .93; mood: p = .19).	Participants were asked to make choices between 2 concrete scenarios and indicate with their choice which scenario represents a better (or worse) night's sleep. By conceptualizing the sleep quality judgement as a decision-making process,

	Making Study With Good and Poor Sleepers	To determine the possible interaction between the parameters of sleep quality extracted from different periods, between different types of sleeper, and between different types of judgment.	Excluded individuals: - n=11, because they did not show for the experimental session; - n=7 for noncompliance to the task instruction. - n=6 due to the methodological issues. Groups: - "good sleeper": scored 7 or below on the Insomnia Severity Index (ISI) n=44, male/female ratio: 20/24 - "poor sleeper": scored 8 or above on the ISI and experienced 1 or more of the following symptoms for at least 3 nights a week, during at least 3 months, despite having an adequate opportunity to sleep: (1) difficulty initiating sleep (taking longer than 30 minutes to fall asleep), (2) difficulty staying asleep (frequent midnight awakenings), (3) early morning awakening with an inability to return to sleep, (4) daytime functioning impairment (e.g., poor concentration, excessive sleepiness). n=43, male/female ratio: 28/15 Questionnaires for characterization: - information about participant's demographics - typical sleep pattern - insomnia severity in the past 3 months Experimental session - Self-report sleep quality was conceptualize as a decision-making process. - Placed in small groups of 3 to 4 participants in a lab with multiple computers partitioned into stations. The lab was sound attenuated with central air conditioning and lighting control. Each participant was assigned to a computer at some distance from the others to minimize distraction and response contamination. - The participants were asked to read and imagine themselves being the person experiencing 48 pairs of scenarios. They read a pair of scenarios in each trial and were asked to choose one scenario from	Of the pre-sleep parameters, only physiological arousal ($p < .001$) had a significant impact on the participants' choices (readiness to sleep: $p = .06$; cognitive arousal: $p = .09$). Of the sleep parameters, SOL ($p < .001$), WASO ($p < .001$) and TST ($p < .001$) had a significant impact, whereas memory of dream ($p = .08$) did not have a significant effect on the participants' choices. Both of the upon waking parameters had a significant impact (feeling refreshed: $p < .001$; motivated to get up: $p < .001$). All of the day after parameters had a significant impact (alertness: $p = .01$; thinking: $p < .001$; mood: $p < .001$; sociability: $p < .001$; physical activity: $p < .001$). The most important individual parameter of sleep quality, was TST, followed by feeling refreshed (upon waking), then mood (day after) and then motivated to get up (day after). The most important time period was during sleep, followed by upon waking, then day after, then pre-sleep, and finally the parameters that occurred day before sleep were least important. The "best-preferred scenario" for a better night's sleep was as follows, with words in bold/italic indicating the adjustable option of the 11 significant parameters: "I felt ***very comfortable*** lying in bed. It took me ***no time*** to fall asleep. I ***slept through the night***. I think I slept for ***9.5 hours***. This morning, I ***felt somewhat refreshed*** on waking. I felt ***motivated*** to get out of bed. During the day, I felt ***alert***	the authors managed to quantitatively identify and estimate the relative importance of different sleep and non-sleep parameters in influencing their judgement of sleep quality. 11 out of 17 identified sleep quality parameters were found to have a significant effect on the participants' sleep quality judgment. - participants relied most heavily on TST, feeling refreshed (upon waking) and mood (day after) to make their judgment of sleep quality. - participants' judgment of sleep quality was most influenced by their memories of what happened during sleep and their experience upon waking, followed by their feelings and functioning during the day after, then pre-sleep experience of the night before, and lastly their experience the day before. Synergetic effects were found between: - WASO and feeling refreshed (upon waking); - feeling refreshed (upon waking) and types of question. However, whether the participant was a good or poor sleeper did not appear to make a difference in the way in which the sleep quality judgment was made..

					each pair that represents a night of better (or worse) sleep quality, depending on the question that they were presented. To avoid misunderstanding what was being expected from the tasks, in addition to verbal explanations the participants were given detailed written instructions on the computer screen. Each scenario described a self-reported experience of sleep, in the first person narrative, stringing together 17 possible determinants of sleep quality that we had identified from our literature review. The data from these trials were used to evaluate the relative importance of each determinant (sleep quality parameter). Data were analysed using the statistical software R (http://www.r-project.org/). Descriptive statistics were used to describe participants' characteristics. Means and standard deviations were presented to describe continuous variables, whilst frequencies and percentages were reported for categorical variables. Independent sample t-test and chi-square statistics were used to describe the differences in characteristics between the good and poor sleeper groups.	and my head was ***reasonably clear***. My mood was ***good***. I was ***somewhat sociable*** and physically I was ***reasonably active*** today". Only WASO and feeling refreshed had a significant interaction ($p < .001$). This interaction judged a night with both WASO and feeling unrefreshed to be a particularly poor night's sleep. However, if participants either felt at least somewhat refreshed or if they slept through the night, then they judged it to be a reasonably good night's sleep. There was no significant interaction between parameters and types of sleeper. The interaction between parameters and types of question allowed to statistically test whether participants used the same parameters to define a good and a bad night's sleep. Only one significant interaction was found between feeling refreshed and types of question ($p = .003$), suggesting that feeling refreshed was more important to the participants when judging a good night's sleep than when judging a poor night's sleep.	
2016	Behavioral Sleep Medicine	(Ramlee et al., 2018)	England	Do People With Chronic Pain Judge Their Sleep Differently? A Qualitative Study	To extend the investigation of sleep quality and its definition to people with chronic pain. .	Cross-sectional study. Qualitative study. Inductive qualitative approach to explore the mental representations of sleep quality in the patients' mind. In-depth one-to-one interviews were carried out to provide the data and context for the researchers to interpret and extract meanings. Sample: n=17 Characteristics - Sex ratio: 9 male, 8 female - Mean age 42.1 ±15.5 (age range: 19 to 64 years)	Four themes resulted from the thematic analysis. Specifically: - Theme 1: Memories of nighttime sleep disruptions Clear consensus that the participants judged their sleep quality based on their remembered ability to "switch off" and stay asleep. Awakenings in the middle of the nights were cited as indicators of poor sleep quality; the more memories of wakefulness, the stronger the feeling of having had a bad night's sleep. A good	Sleep quality is not solely determined by nighttime parameters but also by daytime processes through retrospective judgment. Particularly, people with chronic pain view pain experience and sleep quality as two linked entities that influence their ability to engage in daytime activities as planned. To the sleepers, using indirect indicators to infer sleep quality is only natural as they do not have access to sleep assessment technology and the experience of sleep is marked by darkness, loss of

	- Mean BMI 27.9±5.89 - Work status: 7 were in full-time employment, 7 were on sick leave, medically retired, retired or not working, and the remaining 3 were studying full-time. Groups: - Chronic widespread musculoskeletal pain (fibromyalgia)_ n=6 - Chronic localized musculoskeletal pain (back pain)_ n=5 - Absence of chronic pain_ n=6 healthy individuals Recruitment Participants were recruited through advertisements circulated within local pain patient support groups and flyers displayed across the university campus and the local community. All participants in the fibromyalgia and back pain groups confirmed that they had received a formal diagnosis of fibromyalgia or back pain from a physician. Inclusion criteria (a) aged between 18 and 65 years (b) English-speaking (c) for participants in the fibromyalgia or back pain group: the presence of pain for at least six months Exclusion criteria (a) physical disabilities or neurological disorders that prevent them from completing the questionnaire or attending the interview (e.g., visual impairment, dementia); (b) severe psychiatric illnesses (e.g., psychosis); (c) sleep disorders that might explain sleep disturbance (e.g., sleep apnea, narcolepsy). Questionnaires - a blank body manikin to assess the spread of pain (Lacey, Lewis, Jordan, Jinks, & Sim, 2005),	night's sleep was typically characterized by the general absence of interruptions to sleep and absence of memory of noise or any non-sleep activities. - Theme 2: Feelings on waking and cognitive functioning during the day Feeling refreshed on waking emerged as a key criterion of good quality sleep; when they felt refreshed by sleep they would be motivated to get up and be ready to start the day without any hesitation. In contrast, a poor night's sleep was generally associated with a struggle to get up in the morning, tiredness on waking, and the desire to stay in bed and get some more sleep. The feeling of being refreshed by sleep appeared to be linked to the ability to overcome the sleep inertia upon transitioning from sleep to wakefulness. The participants also retrospectively judged their sleep quality based on their daytime task performance. They noted that a night of poor sleep was typically followed by a day of forgetfulness and mind-wandering. Theme 3: Ability to engage in daytime physical and social activity Following a poor night's sleep, they tended to find themselves avoiding social engagements. Lacking energy, they would cancel appointments to give themselves an opportunity to catch up on sleep. Daytime fatigue and social withdrawal during the day were perceived to be indicators of poor quality sleep. Theme 4: Changes in physical symptoms and pain intensity The participants paid attention to their bodily sensations when they made	consciousness, and amnesia. The current findings highlight the potential benefits of targeting daytime symptoms in attempts to improve sleep quality.

		- the Brief Pain Inventory to examine pain severity and interference (BPI; Cleeland & Ryan, 1994), - Insomnia Severity Index to assess sleep problems (ISI; Bastien, Vallieres, & Morin, 2001), - Epworth Sleepiness Scale to measure daytime sleepiness (ESS; Johns, 1991), - Multidimensional Fatigue Inventory to assess fatigue (MFI; Smets, Garssen, Bonke, & Haes, 1995), - Hospital Anxiety and Depression Scale to assess symptoms of anxiety and depression (HADS; Zigmond & Snaith, 1983), - Dysfunctional Beliefs and Attitudes About Sleep Scale (DBAS; Morin, Vallieres, & Ivers, 2007) - several standard questions about the participants' demographics such as age, sex, body mass index (BMI), and employment status. Semistructured interview - approximately 40 minutes long - participants were invited to talk in depth about their current sleep patterns and how they make judgments about their sleep quality - five open-ended questions were presented to ensure coverage of these topics All interviews were audio-recorded and transcribed verbatim by an independent professional transcriber. The transcripts were then reviewed by the interviewer (FR) and another member of the research team (EA) for accuracy. Data analysis A thematic analysis was carried out on all transcripts in accordance with the Braun and Clarke (2006) guidelines. Steps in data analysis: - the lead author (FR) familiarized herself with the data by reading and rereading the transcripts. Initial ideas and impressions related to the	judgment of their sleep quality. Physical symptoms (e.g., headache, migraine and sore eyes) and unexpected loss of appetite were used to infer poor sleep quality. For participants with fibromyalgia or back pain, they factored in their current pain when judging sleep quality. These participants perceived an increase in pain as an indicator of poor night's sleep and showed appreciation of the self-perpetuating cycle of pain and poor sleep. They believed that a poor night's sleep would aggravate pain and fuel the risk of re-injury.

research questions were noted and highlighted. This step allowed the researcher to develop a thorough understanding of the data.

- initial codes (i.e., brief description of the concepts identified from the data) were constructed as transcripts were being read again. All the coded data were then collated and semantically arranged.
- potential themes were extracted from the coded data.
- potential themes were carefully reviewed and, at this stage, the researcher consulted and discussed with a senior researcher with clinical and research experience in pain and sleep (NT) regarding the precision of the themes and the relevance of the coded data. Differences in opinions were resolved by discussion.
- to ensure our interpretation did not deviate from original meaning of the data, the extracted themes and codes were sent to a subsample of the participants (n = 7) for validation. Feedbacks from the participants were

incorporated into the final stage of analysis, which led to the naming of each theme. The coded data were arranged into a table in accordance with the themes they supported. When generating the themes, the researchers not only paid attention to words used by the participants, but also the context in which the participants articulated themselves.

- the researchers compared and contrasted the themes across fibromyalgia, back pain, and the healthy groups, which allowed the researchers to examine whether people with chronic pain judged their sleep quality differently from those without chronic pain, and whether people with fibromyalgia evaluated their sleep quality differently from people with back pain.

2013	Biological Psychology	(Rosipal et al., 2013)	Europe	In search of objective components for sleep quality indexing in normal sleep	To investigate to what extent polysomnographic (PSG) recordings of nocturnal human sleep can provide information about sleep quality in terms of correlation with a set of daytime measures.	Cross-sectional, multi-centric study.	
2008	Sleep Medicine	(Krystal & Edinger, 2008)	USA	Measuring sleep quality	To consider objective measures of the subjective "sleep quality" experience.	Review. A Likert-style rating of (the previous night's) sleep quality was used as the core sleep quality indicator. Employed simple Likert-style rating of (the previous night's) sleep quality, commonly included as an item on sleep diaries and used here as the core sleep quality indicator. Potential objective measures discussed include polysomnography, cyclic alternating pattern and actigraph	The major factor limiting research on sleep quality is the lack of a standard definition.

2008	SLEEP	(Harvey et al., 2008)	UK	The Subjective Meaning of Sleep Quality: A Comparison of Individuals with and without Insomnia	To conduct a detailed and systematic investigation of the subjective meaning of sleep quality among individuals who meet diagnostic criteria for insomnia compared with a group of normal sleepers.
					
					To determine which sleep quality variables are judged as most important.
					
					To use a qualitative approach to determine whether there are important variables influencing perception of
						Cross-sectional.
						Comparisons between groups: insomniac (n = 25) and normal sleepers (n = 28).
						Participants' recruitment:
						- from January to July, 2004;
						- *via* flyers posted around the city and referrals from primary care physicians.
						- the sample was a non–treatment seeking sample that was drawn from a university city and included university students.
						Inicial sample: n = 208; Final Sample: n = 53
						Exclusions:
						Total_ n = 152
						n = 30 due to falling outside the inclusion criteria;
						n = 6 currently taking sleep medication;
						n = 4 difficulty with the English language;
						n = 48 insufficient time;
						n = 7 presented sleep disturbances attributable to a medical or psychological problem;
							Compared to normative sleepers, insomniacs reported longer SOL and WASO and less TST. They also reported lower sleep satisfaction. On the Sleep Quality Index, they had a lower total score (i.e. poorer sleep quality) and scored lower on the questions "how well you slept", "difficulty falling asleep" and "early waking and not being able to go back to sleep". The insomnia group also scored lower on the overall sleep quality rating.
							Overall, the experimenter administered significantly more prompts when participants were describing a good night than a bad night of sleep. There was no effect of group and no interaction.
								The meaning of sleep quality among individuals with insomnia and normal sleepers was broadly similar; subjective feelings regarding the day following sleep appeared to be the most important basis for judging sleep quality.
								All three used procedures implicated tiredness on waking and throughout the day as most consistently associated with sleep quality judgements and two out of the three methods implicated feeling rested, restored, refreshed, replenished on waking and awakenings in the night.
								A comprehensive assessment of a patient's appraisal of their sleep quality may require an assessment of waking and daytime variables.

	sleep quality not covered in the existing research literature To compare the insomnia and normal sleeper groups on the meaning of sleep quality.	n = 57 not able to be contacted (n = 57). n = 3 completed the first session but did not return to the second session Inclusion in insomnia group: - met criteria for primary insomnia on the Insomnia Diagnostic Interview (IDI) - the problem must been present at least three nights per week for at least one month. Inclusion in normative sleepers group: - not meeting criteria on the IDI - score of ≤7 on the Insomnia Severity Index Characterization of insomnia group: - 18 females, 7 males - 9 participants (17% of the total sample) met criteria for one or more current DSM-IV-TR Axis 1 diagnoses (specific phobia = 4, major depression = 2, generalized anxiety disorder = 1, anorexia = 1, and alcohol abuse = 1). Characterization of normative sleepers group: - 25 females, 7 males - 2 participants (4% of the total sample) met criteria for specific phobia. Procedures (1) "Speak Freely" in which participants described good and poor sleep quality nights; (2) "Sleep Quality Interview" in which participants judged the relative importance of variables included in previous research on sleep quality (applied to 4 normal sleepers and 4 insomnia patients); (3) Sleep quality diary completed over seven consecutive nights. Other measures applied: the Structured Clinical Interview for DSM-IV (SCID); the Insomnia Severity Index (ISI); Beck Depression Inventory (BDI), State	The greatest number of people mentioned 5 categories, 4 of which were the same for both groups: - "Motivation to get up or sleep in the morning" - "Tiredness on waking and throughout the day" - "Sleep onset latency" - "Awakenings in the night" And 1 was different: - insomniacs: "Anxiety, worry, and mood on waking and throughout the day" - normative sleepers: "Alertness, clear-headedness, concentration on waking and throughout the day". Insomniacs were more likely to mention "monitoring" and "body sensations on waking and throughout the day" compared to the normative sleepers and the latter were more likely to mention "memory of sleep" comparatively to insomniacs. For insomniacs, the most important items for judging sleep quality were: - "how well you slept" (Sleep Quality Index item), - "how tired you feel" when you wake up - "how tired you feel" during the day, - "how rested you feel" when you wake up - "how restored you feel" when you wake up. For normative sleepers, the most important items for judging sleep quality were: - "whether you get enough sleep" - "how rested you feel" - "how restored you feel" when you wake up - "how tired you feel" when you wake up - "how alert you feel" throughout the day.	

		Trait Anxiety Inventory (STAI), the Sleep over the past week questionnaire. Statistical Analysis - Independent sample t-tests or chi-square tests used for participant characteristics' and basic sleep variables. - "Speak freely" information was reported as the percentage of participants who mentioned each category. - Chi-square tests were used to analyze differences between the 2 groups. Fisher's exact test was conducted when the cell size was <5. - "Sleep Quality Interview" data was analyzed through the use of a multivariate analysis for each domain was followed by independent sample t-tests to investigate significant main effects. Wherever variables were skewed even after transformation, nonparametric tests were conducted. Wherever the equal variance assumption was not upheld, the Levene correction was employed. Weighing the possibility that multiple comparisons increase the chance of a type I error with the view that adopting more conservative error rates increases the chance of type II errors, compromise was achieved by using $P < 0.01$ as the cutoff for statistical significance. Qualitative analysis was performed in the data from "speak freely" and from the item asking participants to describe the basis on which they made their sleep quality judgment, in the 7-day sleep diary assessment. All descriptions were carefully transcribed in full. They were then divided into utterance units which were defined as a clause containing only one thought, action, or idea. Utterance units were coded using the N6 version of the Non-numerical Unstructured Data Indexing Searching and Theorizing System. 78% interrater	Insomniacs and normative sleepers presented significant results in what concern waking variables. Regarding the sleep diaries, the five categories mentioned by the greatest number of people were: - in the insomnia group: "awakenings in the night", level of "tiredness on waking and throughout the day", "total sleep time", "feeling rested, restored, refreshed, replenished on waking" and "time of waking in the morning." - in the normal sleep group: "awakenings in the night" "sleeping well or badly" level of "tiredness on waking and throughout the day", "total sleep time", and "feeling rested, restored, refreshed, replenished on waking". A significantly greater percentage of the normal sleepers mentioned "sleeping well/badly" and a nonspecific feeling of "good" or "bad" (e.g., "I don't feel too bad this morning"; and "I woke up feeling quite good") than the insomnia group. A significantly greater percentage of the insomnia group mentioned "time of waking in the morning" and "body sensations on waking and during the day" relative to the normal sleeper group.

					agreement was achieved in the qualitative analysis.		
2006	Journal of Sleep Research	(Yi et al., 2006)	Korea	Development of the Sleep Quality Scale	To develop an instrument for measuring sleep quality (SQS) and to study its validity and reliability.	Sleep quality was defined through a literature review and then their contents were confirmed by an in-depth interview. The subjects (32 males, 18 females) were 50 adults aged 21–59 years. They comprised 17 subjects with insomnia symptoms, 17 with obstructive sleep apnea, six with snoring, two with narcolepsy, and eight good sleepers. The main interview questions were: - How is your sleep these days? - What do you think a good sleep is? - What do you think of a poor sleep? The interview took about 30–60 min for each subject. The subjects underwent one or two interviews which were recorded and later transcribed. Content analysis of the interview data was conducted line-by-line and the results were confirmed by two nursing college professors with considerable experience of qualitative research.	SQS, composed of 28 items and six factors, accounted for 62.6% of the total variance. The difference of SQS score between insomniacs and normal subject confirmed the construct validity. Concurrent validity was identified by the significant correlation of SQS with the Pittsburgh Sleep Quality Index. The Cronbach's alpha coefficient was 0.92 for internal consistency and the correlation coefficient was 0.81 for test–retest reliability at a 2-week interval.	
1997	Journal of Sleep Research	(Keklund & Akerstedt, 1997)	Sweden	Objective components of individual differences in subjective sleep quality	To investigate the item structure of the Karolinska Sleep Diary (KSD) and the covariation between KSD and sleep-stage variables.	Observational, cross-sectional and inter-individual design. Natural conditions. n=37 (14 males; 23 females; age range: 24-58 yrs). Participants followed their normal habits during the evening, at bedtime, and during the following workday. They were told to avoid hard physical work and refrain from alcohol during the day before the sleep recording. Electrodes - EEG (C3-A2), EOG (oblique derivation) and EMG (submental) - were attached aprox. 9 0 min before bedtime. A reference electrode was attached to the left mastoid. The recordings were made on four-channel Medilog tape recorders. After the final awakening, subjects completed the	The factor analysis of the KSD yielded two factors with an eigenvalue > 1. 'Ease falling asleep', 'sleep quality' and 'calm sleep' showed high loadings in the first factor. The items: 'slept throughout', 'well-rested', 'ease awakening' and 'sufficient sleep', showed their highest loadings in the second factor. The item 'slept throughout' had a low communality (0.30), being poorly reflected in the obtained factors. Authors decided to move this item to the first factor. The first factor formed a SQI calculated as a mean score of the items 'ease falling asleep', 'sleep quality', 'calm sleep' and 'slept throughout'.	In the present study, maybe a sufficient variation of sleep quality (including also poor sleep) was generated providing the variance needed for a correlation between subjective and objective measures. The present study suggests that there is a good agreement between laboratory and field situations with respect to how the subjective items are inter-related, and to the covariation between subjective and objective measures of sleep. Subjective sleep quality is related to perceptions of ease of initiation and maintenance of sleep but is unrelated to the perception of the ease of awakening. From a physiological point of view,

	Karolinska Sleep Diary (KSD; Akerstedt et al. 1994b) in the morning. The electrophysiological recordings were visually scored in 30-s epochs according to the rules of Rechtschaffen and Kales (1968). Brief EEG arousals, characterized by abrupt changes in EEG frequency (suggesting an awake state) and increases in EMG amplitude, were scored as micro-arousals according to the rules of the American Sleep Disorders Association (1 992). Reliability checks were made between scorers and the epoch-by-epoch correspondence was >85u/0. Study 1: early morning work n=22, all females early group_start time: 506.30 hours late group_ start time 209.00 hours (Kecklund el al. 1997). Participants were cabin crew. In the morning work study sleep was recorded in the subjects' homes. Study 2: sleep in a truck-berth (Volvo F H 16, 1994 version) (Kecklund and Akerstedt, 1997). n=15 subjects, 14 males and 1 female Participants were truck drivers (n=6) or students at Karolinska (n =9). The truck was parked outside our institute where the exposure to noise and vibration was low. The data set includes a sample of sleep episodes ranging from very good sleep to rather disturbed sleep. KSD was factor analyzed through principal components with varimax transformation, for examination of the item structure. The factors were presented after orthogonal rotation and with an eigenvalue >1. The internal consistency of the factors was tested by computing the alpha coefficient (Cronbach 1951).	The items of the second factor were also correlated with the SQI (ease awakening, r=0.32, P=0.05; well-rested, r=0.49, P<0.01; sufficient sleep, r=0.50, P<0.001). Thus, the items were not clearly conceptually homogenous enough to form an index. The alpha coefficient of the SQI was 0.74. The SQI was correlated with the traditional sleep-stage variables and showed (positive) significant correlation coefficients with SWS, sleep efficiency, TST, and a negative one with stage 0. In a stepwise multiple regression analysis, these variables were used as predictors of the SQI. The variables 'study' and age were retained as predictors to control for possible confounding between the two studies or age. SWS and sleep efficiency became the significant predictors, accounting for 33% of the total variance (F=8.5, PCO.01, DF=2/34). The regression analyses showed that subjectively good sleep, as indicated by the SQI. was (equally) related to the continuity (sleep efficiency) and depth (SWS) of sleep, whereas the sleep timing variables and age were of no importance.	subjective sleep quality seems to be a matter of SWS and sleep continuity (i.e. as indicated by sleep efficiency).

						The analysis of the covariation between the subjective ratings and polysomnography was based on correlations and stepwise multiple regression analysis. Variables with a skewness >±2.0 were log transformed.		
1994	Perceptual and Motor Skills	Akerstedt et al. (Akerstedt et al., 1994)	Sweden	The subjective meaning of good sleep, an intra-individual approach using the Karolinska Sleep Diary	To assess what is meant by a "good sleep" by relating subjective sleep quality to other subjective sleep measures in an intra-individual design. To construct an index of sleep quality for use in repeated-measures designs.	Cross-sectional, intra-individual design. Performed in a sleep Lab. n=16 (all female; age range: 18-34 years; healthy; free from substance abuse, including smoking). Subjects slept in an isolation unit according to variable schedules (15 sleeps) designed to provide variable quality of sleep. Measurements performed at all stages of the menstrual cycle. After four control days (three control nights) during which subjects lived a regular and conventional lifestyle (sleep 00.00-08.00 hr.), an irregular sleep-wake schedule lasting nine days was undertaken. This consisted of 12 6-hr. sleep periods, three starting at each of the times 03.00, 09.00, 15.00, and 21.00 hr. The total number of sleeps were 15. The time awake between sleeps was of 6, 12, or 18 hr duration. Whenever a waking period was due to last 12 hr or 18 hr, a 1-hr nap was scheduled after 5.5 hr of waking time. If the waking period lasted 18 hr, then a further 1-hr nap was scheduled after 11.5 hr of waking time. Naps were treated like full sleeps. No naps or sleeps were allowed at other times when the lights (300-500 lux) had to remain on. The subjects were required to stay in bed with lights extinguished and to try to sleep for the duration of the scheduled sleep period. Mealtimes were selected by each group, as was the composition of each meal. Subjects were allowed to wear their watches throughout the experiment.	Results showed significant variation across sleep conditions for all variables, except awakenings per hour. "Sleep quality" was significantly correlated with almost all variables except "ease of awakening" and "dreams". Most subjective sleep measures showed strong covariation across conditions. "Feeling refreshed" showed essentially the same pattern except that it had a significant correlation with the "ease of awakening". "Sleep quality," "calm sleep," "ease of falling asleep," sleep efficiency, sleep latency, and number of awakenings per hour are highly inter-correlated. "Sleep throughout" and "refreshed" also correlated with "ease of awakening". "Ease of awakening", did not correlate significantly with any other variable than "sleep throughout" (and "refreshed"). "Dreams" correlated significantly only with number of awakenings. The significant predictors of sleep quality were "calm sleep" and sleep efficiency, which together explained the large amount of variance. The significant predictors of being "refreshed" were "ease of awakening" and "sleep quality".	Subjective quality of sleep mainly involved variables of sleep continuity, in particular, perceived calmness of sleep and sleep efficiency. "Sleep quality", "calm sleep," "ease of falling asleep," and ability to "sleep throughout" the time allotted strongly covaried and formed an index of sleep quality. Self-rated ease of awakening deviated from the general pattern and was associated with poor sleep quality. So was reported dreaming (related to awakenings). It was concluded that subjectively good sleep mainly involved calmness and efficiency of sleep and that most subjective sleep parameters strongly covary across conditions. Overall, "good sleep" seemed mainly a question of sleep continuity.

						The Karolinska Sleep Diary (KSD) was administered upon awakening from each sleep. For a systematic variation across sleeps, the ratings were subjected to a repeated-measures analysis of variance, corrected for sphericity using the epsilon coefficient of Huyn-Feldt. Correlation between variables was computed within each individual and the resulting correlation coefficients were then averaged across individuals for each pair of variables and the result tested (by Student's t) against zero correlation, with df = 15 (after z-transformation of r). The major predictors of good sleep were determined by multiple regression analysis, while taking inter-correlations between predictors into account. Sleep measures were used as predictors, except ''sleep quality'' that was used as the dependent variable. The process was repeated with ''refreshed'' as the dependent variable. Regarding the Index, tests of internal consistency were not applicable given the type of data, intra-individual. The authors computed the mean intra-individual correlation of each item with the index (with the item itself excluded). To assess if there existed a quantitative meaning to the more quality-oriented items ''sleep quality,'' ''ease of falling asleep,'' and ''calm sleep,'' we also regressed the group means per sleep for these variables against their corresponding quantitative measures.	The index of sleep quality should include ''sleep quality'', ''calmness of sleep'', ''ease of falling asleep'' ''sleep throughout'' and ''refreshed after sleep''- Sleep efficiency, sleep latency, and number of awakenings should be used as separate quantitative variables. Ratings of ease of awakening and dreaming do not belong in an index of sleep quality because their correlations with sleep quality and related variables are absent or negative. The mean correlation for ''feeling refreshed'' was unsatisfactory and the item was excluded. Sleep efficiency increased by 5% (from 76% at a score of 1) for each unit of sleep quality. Sleep latency fell by 24 minutes (from 100 min. at a score of 1) for each unit increase of ''ease of falling asleep'' and the number of awakenings fell by 0.10 awakenings per hour for each unit of ''calm sleep'' (from 0.61 at a score of l).	
1994	Journal of Sleep Research	(Åkerstedt et al., 1994)	Sweden	The meaning of good sleep: a longitudinal study of polysomnography and subjective sleep quality.	To study, under controlled laboratory conditions, the longitudinal covariation between global sleep satisfaction and polysomnographic sleep parameters.	Longitudinal, intra-individual design. n=8 females, age range: 18 to 34 years; in good health and free from substance abuse (including smoking). Isolation Unit was used to performed the general protocols. After 3 control days during which the subjects lived a regular a conventional lifestyle (sleep: 00:00 to	Subjective sleep quality and sleep quality index were highly correlated with sleep efficiency, TST, Stage 2, final wake and REM. Subjective ease of awakening was significantly and negatively related to TST, Stage 2, sleep efficiency and final wake time (positively).	The analysis showed that subjective sleep quality was related to mainly sleep efficiency but also to the closeness of the awakening to the circadian acrophase. Most of the other sleep parameters (e.g. stage 2, REM, ...) correlated with rated quality but sleep efficiency accounted for most of the variance of these variables.

08:00), an irregular sleep/wake schedule lasting nine days was undertaken, which meant 12 6-h sleep periods, three starting at each of the times: 03:00, 09:00, 15:00, 21:00. The sleep periods were arranged randomly, as well as the wake periods between them that could have the duration of 6, 12 or 18h. Whenever the waking period was due to last 12h or 18h, a 1-hour nap was schedule after 5.5h of waking day. If the waking period lasted 18h then a further 1-hour nap was scheduled after 11.5h of waking time.

Naps were treated as full sleeps insofar as subjects were required to attempt sleep in their beds with no talking and with lights extinguished. No naps or sleep where allowed at other times. Subjects were allowed to decide meal time and to wear their watches throughout.

A total of 8 sleep episodes and eight naps were considered for the analysis. Sleep was recorded through Medilog recorders (Oxford Instruments Ltd). The EEG was obtained from a bipolar CzOz derivation and the EOG from a bipolar, oblique derivation from the left eye. The sleep records were scored in 20s intervals by standard methods (Rechtschaffen and Kales, 1968), but since the CzOZ derivation was used, the amplityde criteria for delta activity were adjusted to 100 μV. this adjustment yielded sleep stage data whithin a few percent of data obtained using the traditional derivation C4A1. The parameters extracted were: total sleep time (TST), sleep efficiency (TST/time in bed), sleep stages 0-4, rapid eye movement sleep (REM sleep), sleep latency (to stage 1), movement time, REM latency, Stage 3 latency (SWL), final time awake (time between final awakening and rising) and the number of awakenings. Stage 3 and 4 were combined to yield slow-wave sleep (SWS).

The physiological sleep variables Stage 1, wake and movement time and number of awakenings lacked significant correlations with the subjective variables.

The mean individual correlations between the objective and subjective measure of the same sleep characteristic were high and significant for sleep length, sleep latency and final time awake.

Number of awakenings and amount of REM sleep lacked significant correlations with their subjective counterparts.

Regarding the quantification of subjective sleep parameters, for sleep length, for every minute recorded the subjective length increased half a minute; for sleep latency, every minute of recorded sleep latency increase 0.3 minutes in subjective sleep latency. Concerning the interpretation of sleep quality quantitatively and in terms of sleep efficiency, results show that for every unit of subjective sleep quality, sleep efficiency increases 15%. Regarding subjective sleep latency, for every unit of ease of falling asleep, the recorded sleep latency fell by 15 minutes. For the ability to sleep throughout the allotted time, the number of minutes of final time awake fell by 20.8 minutes with each unit of subjective ability to sleep throughout the allotted time.

When comparing in absolute terms objective and subjective total sleep time and sleep latency, results show that subjective ratings overestimated total sleep time but not sleep latency. Regarding naps, results show that rating underestimated

Sleep efficiency is clearly more central to "good sleep" than continuity variables, like sleep latency, final wake time and time awake within sleep, which makes sense given that sleep efficiency represents the combination of these variables.

The content of sleep (SWS, REM) apparently lacked importance for subjective sleep quality, at least beyond that related to sleep length.

Maximum sleep quality was rated when sleep ended close to the acrophase, which might be due to the circadian variation of alertness which reaches an acrophase in the early evening. Thus, circadian phase needs to be considered when interpreting sleep quality ratings.

The sleep quality index showed the same results as the item "sleep quality". "Refreshed" also showed the same results but the amount of explained variance was much lower.

The subjective ease of awakening had a significant but weak relation to the objective variables, increasing not only with closeness to the circadian acrophase, but also with lower sleep efficiency, which might provide a reason why, within limits, poor sleep might have a positive effect on this particular aspect of sleep quality.

When sleeps had the duration of 6h, subjective sleep length was underestimated up to 260 minutes, thereafter sleep length was overestimated.

The intercept and regression weight of the regression functions may be used to help interpret the quantitative meaning of subjective sleep ratings. Thus, it appears

						Circadian rhythmicity was assessed by the single cosinor method, which was applied to successive 24h runs of data (real-time), starting at midnight real-time. An acrophase was considered only if the cosine curve fitted the data better than a straight line. Only data on phase is used and for days when no significant results were obtained the mean of the adjacent days was substituted. Sleep diary was administered upon awakening and contained 10 items of which most offered 5 response alternatives graded from 1 to 5. "Sleep quality" and "feeling refreshed" were used as global indicators of sleep. Four items formed a sleep quality index, based on their close covariation across time: sleep quality, calmness of sleep, ease of falling asleep and sleep throughout the allotted time. The relationship between subjective and objective sleep parameters was first analyzed through simple intra-individual regression. The resulting correlation coefficients were then averaged across individuals for each par of variables, and the result t-tested against zero correlation, with d.f. = 7 (after z-transformation). To identify the major physiological predictors of good sleep, while taking correlations between predictors into account, multiple regression was used with polysomnograpical variables as predictors and subjective sleep quality as the dependent variable (stepwise multiple regression for key predictors and multiple regression within each individual to test the obtained predictors and the same dependent variable).	total sleep time of naps (by 8 minutes) and overestimated nap latency (by 7 minutes). Rated sleep quality increased with increased sleep efficiency and with closeness to the acrophase. The four item sleep quality index showed essentially the same results. The subjective feeling of being refreshed from sleep was also predicted by higher sleep efficiency and less deviation from the acrophase, although less strongly. Rated wase of awakening was predicted by the deviation from the acrophase and by sleep efficiency. The ease increased with closeness to the acrophase but decreased with sleep efficiency.	that "rather good" sleep may refer to a sleep efficiency of 87% and above, whereas "rather poor" sleep is applied to an efficiency of 57% or lower. In the same vein, a "rather easy" sleep onset may take 13 minutes or less and a "rather difficult" one may take 43 minutes or more. Early awakenings may be rated "too early" when they leave 60minutes or more in bed before intended rise time.
1989	Psychiatry Research	(Buysse et al., 1989)	USA	The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric	To provide a reliable, valid, and standardized measure of sleep quality.	Longitudinal, prospective study. Measure *The PSQI is a self-rated scale composed by 19 questions to be answer by the individual and 5	Analysis of variance (ANOVA) indicated a significant difference in age between groups (F= 5.20, p< O.OOI), with post hoc differences between control subjects and DIMS and DOES patients.	- Individuals find PSQI easy to use. - The seven major components of the index, as well as the 19 individual questions, are internally consistent.

	Practice and Research	To discriminate between "good" and "poor" sleepers. To provide an index that is easy for subjects to use and for clinicians and researchers to interpret. To provide a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality.	questions rated by the bedpartner or roommate (these latter only used for clinical information). *These I9 items are grouped into 7 component scores, each weighted equally on a 0 to 3 scale. These 7 component scores are summed to yield a global PSQI score, which has a range from 0 to 21; higher scores indicate worse sleep quality. *The 7 components are standardized versions of areas routinely assessed in clinical interviews of patients with sleep/wake complaints, namely: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. *PSQI items were derived from three sources: - clinical intuition and experience with sleep disorder patients; - a review of previous sleep quality questionnaires reported in the literature; - clinical experience with the instrument during 18 months of field-testing. Study procedures Recruitment from the research studies: - sleep and aging (MH-37869) - nocturnal penile tumescence (MH-40023) - sleep in depression (MH-40023, MH-30915) Study period: 18 months Individuals were excluded if not in a 2-week medication-free interval and if they present some known central nervous system disease. No specific exclusion criteria were used for the clinic sample of sleep-disorder patients. Evaluation for all subjects included: - a complete medical history and physical examination. - a 2-week sleep/wake diary and a sleep habits questionnaire.	Male subjects had a lower mean age (46.5 years; SD = 16.7) than female subjects (55.4 years; SD = 18.9) (t = -3.01, p<0.005). Many of the male subjects were involved in studies of nocturnal penile tumescence in depression, while female subjects were participating mainly in studies of sleep, aging, and depression. Age was negatively correlated with the subjective sleep quality (r = -0.22, p < 0.05) and daytime dysfunction (r = -0.29, p < 0.02) component scores in the healthy controls. The PSQI global score and other component scores (sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and use of sleeping medications) were not significantly correlated with age. The seven component scores of the PSQI had an overall reliability coefficient (Cronbach's alpha) of 0.83, indicating a high degree of internal consistency. The largest component-total correlation coefficients were found for habitual sleep efficiency and subjective sleep quality (0.76 for each), and the smallest correlation coefficient was found for sleep disturbances (0.35). The mean component-total correlation coefficient was 0.58. Pearson product-moment correlations between component scores and the PSQI global score were also calculated for the entire group, as well as each group separately. Once again, the strongest	- The global scores, component scores, and individual question responses are stable across time. - The validity of the index is supported by its ability to discriminate patients from controls, and, to a more limited degree, by concurrent polysomnographic findings. PSQI was designed to assess clinical samples, while most previous questionnaires have been designed to assess normal sleep habits or entire populations. The PSQI is primarily intended to measure sleep quality and to identify good and bad sleepers, not to provide accurate clinical diagnoses. Nevertheless, responses to specific questions can point the clinician toward areas for further investigation. This is particularly true for the "sleep disturbances" component, which may guide clinical evaluations for specific patients, even though mean scores do not discriminate between groups. Furthermore, a PSQI global score > 5 indicates that a subject is having severe difficulties in at least two areas, or moderate difficulties in more than three areas. The global score is therefore "transparent," i.e., it conveys information about the severity of the subject's problem, and the number of problems present, through a single simple measure. PSQI responses were not found to correlate with polysomnographic measures. It is not surprising that subjects differed in subjective and polysomnographic variables, since the PSQI asks for a global

	- a routine polysomnography. The routine sleep montage included: electroencephalographic (C4, referenced to tied mastoids), electro-oculographic (EOG), and electromyographic (submental) leads. Most subjects had additional monitoring for sleep apnea, myoclonus, or nocturnal penile tumescence, dictated by clinical indications or research protocol involvement. All sleep records were scored in 1-min epochs according to standard criteria (Rechtschaffen and Kales, 1968) using Stage 2 sleep onset and standard convention for definition of sleep efficiency (time spent asleep/total recording period). All I48 subjects completed the PSQI on at least one occasion during the course of their clinical and research evaluation. For the majority of subjects (n = 107) the PSQI was completed before sleep studies. For some subjects with stable sleep/wake complaints (n= 41) the PSQI was completed after sleep studies. A subgroup of 91 subjects (43 controls, 22 depressives, and 26 sleep-disorder patients) completed the index a second time (an average of 28.2 days later, range: I-265 days). The second PSQI was completed before any pharmacological treatment began. *Group 1: "good" sleepers n=52, healthy controls without sleep complaints Mean age: 59.9 years (range: 24-83) Male/female ratio: 40/12 *Group 2: "poor" sleepers n=34, patients with major depressive disorder (24 outpatients and 10 inpatients at the Western Psychiatric Institute and Clinic) Mean age: 50.9 years (range: 21-80) Male/female ratio: 25/9	correlations were seen for habitual sleep efficiency and subjective sleep quality. Individual items were also strongly correlated with each other, indicated by a reliability coefficient (Cronbach's a) of 0.83. Item-total correlation Coefficients ranged from 0.66 for question #9 (enthusiasm to get things done) to 0.20 for item #8 (difficulty staying awake). Pearson product-moment correlations between individual items and the global score ranged from 0.83 (subjective sleep quality) to 0.07 (cough or snore during sleep). 91 patients completed the PSQI on two separate occasions. Paired t-tests for the global PSQI score, as well as the seven individual component scores, showed no significant differences between the two time points. Two differences were noted for depressed patients, who showed a reduction in sleep disturbances and daytime dysfunction. Pearson product-moment correlations again demonstrated stability in global and component scores. The correlation coefficient for global PSQI scores was 0.85 ($p < 0.001$). Component scores had coefficients ranging from 0.84 (sleep latency) to 0.65 (medication use) ($p < 0.001$ for each component score). Global PSQI scores for each diagnostic group were also significantly correlated between the two testing times, with $r's > 0.40$, $p < 0.005$) for each group. Component scores within each subject group showed more variability across time, but all of these scores were significantly correlated ($r's > 0.35$, $p <$	estimate spanning 1 month, and is not sensitive to daily variability. The PSQI's simplicity and its ability to identify different groups of patients suggest several clinical and research applications in psychiatry and general medical settings. Most fundamentally, it may be used as a simple screening measure to identify cases and controls, or "good" and "poor" sleepers. In a general clinical setting, the PSQI could be used to screen patients for the presence of significant sleep disturbance. In psychiatric settings, the PSQI may identify patients who are likely to have a sleep disturbance concomitant with their psychiatric symptoms. In addition, it may direct the clinician to specific areas of dysfunction that require further investigation. The PSQI could also be used in clinical research and epidemiological studies to identify groups that differ in the quality of their sleep. The PSQI may also have several longitudinal applications in clinical practice and research.

All depressed patients met criteria for definite or probable current major depressive disorder.

*Group 3: "poor" sleepers
n=62, physician-referred outpatients at the Sleep Evaluation Center (SEC) of the Western Psychiatric Institute and Clinic.
(Patients were referred to the SEC for assessment of a variety of sleep/wake complaints, but only patients with Disorder of Initiating and Maintaining Sleep (DIMS, n=45) or Disorders of Excessive Somnolence (DOES, n =17) (Association of Sleep Disorders Centers-ASDC, 1979) were included in this study).
Mean Age: DIMS_ 44.8 years (range: 20-80); DOES_ 42.2 years (range:
19-57).
Male/female ratio: DIMS_ I6/29; DOES_ 8/9
Sleep-disorder patients meeting criteria for DSM-III (American Psychiatric Association, 1980) major depression were excluded from the current study.

All depressed patients and healthy controls were assessed with:
- Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L).
- Research Diagnostic Criteria.
- Hamilton Rating Scale for Depression.
Sleep-disorder patients were evaluated as described elsewhere (Jacobs et al., 1988) and given preliminary diagnoses according to ASDC nosology.

Statistical procedures
- Descriptive statistics
- ANOVA.
- Internal homogeneity (Cronbach's Alpha, corrected component-total correlation coefficients and Pearson product-moment correlations)
- Test-retest reliability (consistency) (paired t-tests and Pearson product-moment correlations for

0.05). The single exception was medication use in control subjects, which showed no correlation between the two testing times.

Global PSQI scores differed significantly between subject groups, using an ANCOVA with age and sex as covariates. Control subjects differed from all patient groups (Student-Neuman-Keul's procedure).
Group differences resulted in distinctive component and global score profiles.

Age was a significant covariate only for the daytime dysfunction component; but contrary to expectations, these factors were inversely correlated, i.e., reported severity of daytime dysfunction tended to be greater in younger than in older subjects.
Sex was a significant covariate for use of sleeping medications and habitual sleep efficiency, with males showing higher scores for each of these components. Age and sex were both significant
covariates for the PSQI global score, but group differences were highly statistically significant even after covarying for these factors.

A post hoc cutoff score of 5 correctly identified 88.5% (131/148) of all patients and controls (kappa = 0.75, $p < 0.001$). This represents a sensitivity of 89.6% and a specificity of 86.5%. The same cutoff score correctly identified 84.4% (38/45) of DIMS patients, 88% (IS/ 17) of DOES patients, and 97% (33/34) of depressives.

Group differences in PSQI global scores were also substantiated by polysomnographic results, which showed significant group differences for sleep latency ($F= 4.53$, $p < 0.00I$), sleep

		PSQI global score, component scores, and individual items, at Time 1 versus Time 2. - Validity (the degree to which the index detected differences between groups recognized clinically as distinct. This assumes that the index measures differences between groups at the same time point as a clinical "gold standard". In this case, the relevant "gold standard" diagnoses were based on a combination of clinical interviews, structured interviews, and polysomnographic data. For this analysis, an analysis of covariance (ANCOVA) was used to compare patient groups for PSQI global and component scores, and the Student-Neuman-Keul's procedure was used for pairwise comparisons. Age and sex were used as covariates because of group differences in age and sex ratio. A multiple ANCOVA (MANCOVA) was performed for the PSQI global score, again using age and sex as covariates. A secondary analysis of validity, we compared PSQI scores with polysomnographic results, being cognizant of the fact that PSQI scores reflect the experience of sleep during the previous month, while polysomnographic data were limited to 2 or 3 nights. PSQI estimates of sleep latency, sleep duration, and sleep efficiency were compared to their homologous polysomnographic measures, using both t-tests and Pearson product-moment correlations. Global PSQI scores were also compared to polysomnographic variables selected a priori as being likely to correlate with overall sleep quality, again using Pearson correlations. The specific variables selected were REM Yc, Delta 70, sleep latency, sleep efficiency, and sleep duration. Finally, group differences for these polysomnographic variables were assessed using one-way ANOVAs.	efficiency ($F = 5.78$, $p < 0.00l$), sleep duration ($F= 4.82$, $p < 0.003$), and number of arousals ($F= 2.87$, $p < 0.04$). Significant group differences were not found for rapid eye movement (REM) % or delta sleep %. Validity of the PSQI was further examined by comparing PSQI estimates of sleep variables with those obtained by polysomnography. T tests showed no differences between PSQI estimates and laboratory findings for sleep latency, but PSQI estimates of the past month's usual sleep duration and efficiency were greater than those obtained during polysomnography ($t = 9.98$ and 4.50, respectively; both p's < 0.001). This pattern was true for the total subject pool as well as individual subject groups. Pearson correlations demonstrated no significant positive correlations between PSQI estimates and polysomnographic results, except in sleep latency for the total subject pool ($r = 0.33$, $p < 0.001$) and for the depressive subgroup ($r = 0.37$, $p < 0.02$). Similarly, the global PSQI score was compared with several polysomnographic measures which we selected a priori as being likely to correlate with perceived sleep quality. For all subjects, the global score was weakly correlated only with objective sleep latency ($r = 0.20$, $p < 0.01$). For individual subject groups, the global PSQI score correlated only with REM Yc in controls ($r = 0.34$, $p < 0.006$) and number of arousals in depressives ($r = 0.47$, $p < 0.002$).	

1987	Res Nurs Health	(Snyder-Halpern & Verran, 1987)	USA	Instrumentation to describe subjective sleep characteristics in healthy subjects	To develop and test the Verran and Snyder-Holpern (VSH) Sleep Scale, an instrument to subjectively measure sleep characteristics.	
1971	British Journal of Preventive and Social Medicine	(Johns et al., 1971)	Australia	Sleep Habits of healthy young adults: use of a sleep questionnaire	To describe the variations in, and the inter-correlations between, the answers given by students to questions relating to the quality and quantity of their usual sleep. Some of these students took part also in two additional studies on the relationship between levels of adrenocortical activity and sleep habits, and between personality and sleep habits, the results of which will be reported separately.	Sample: n=249 in a total of 286 medical students n=122 students in 1969 n=127 in 1970 Cohort characterization: Mean age= 21.5 ± 1.5 yrs; 213 males and 26 females; 230 unmarried, 17 married and 2 divorced. The questionnaire designed asked such questions as: - 'at what time do you usually go to bed at night on weekdays?' - 'how would you describe your usual sleep?' A range of possible answers was provided and the most appropriate were selected by each student. The questionnaire used in 1970 had 27 questions while that in 1969 had 31 questions, all of the important questions being the same. The total delay before falling asleep, duration of night awakenings and of sleep during the night and day, etc., were each calculated in hours per week rather than hours per 24 hours, thereby partially overcoming differences between weekdays and weekends.

Discussion

In our 24-h society, social pressures weaken and/or suppress biological drives, ultimately, affecting sleep habits and needs. The combination of different social roles, and the high demands inherent to this, often put the individual in the position of sacrificing personal rest and sleep time, increasing the vulnerability to health problems and sleep complaints. The decrease in sleep duration is frequently associated to decreases in sleep quality, a far more heterogeneous and less consensual concept. In fact, when performing a quick search on PubMed®, filtering for one-year results, it is possible to observe not only a high number of articles addressing sleep quality without a definition of what "sleep quality" actually is, but also a high heterogeneity in the assessment tools used. This not only leads to different sleep quality considerations, but consequently to a high variability across studies' results (Harvey et al., 2008).

For some authors sleep quality is a composite measure constituted by different sleep parameters (Amorim et al., 2018; Gupta, Ulfberg, Allen, & Goel, 2018; Kim et al., 2018; Klumpp, Hosseini, & Phan, 2018), as it happens when using the global PSQI score. For others, it concerns one particular parameter, such as the rating of sleep "depth" or of the quality of the sleep of the previous night or month (Gombert, Konze, Rivkin, & Schmidt, 2018; Liu et al., 2018; Takeuchi et al., 2018; Zhang et al., 2018). On this topic, it is also relevant to highlight that these ratings can also be an important source of bias. In fact, across studies, there is a wide range of options concerning the length and type of scales used. For example, while in some studies, visual analog scales are the ones used, in other studies, more qualitative options are considered. This can be within itself quite subjective and bias promoter. In fact, in one of the analyzed studies, individuals had to rate their "depth of sleep" using the following options: "1= can have a sound sleep; 2= can relatively have a sound sleep; 3= neither; 4= relatively bad; 5= very bad" (Takeuchi et al., 2018). However, not only the meaning of "sound sleep" is subjective, but also the value that this has to the participant is of care. In another study, the options used were not mutually exclusive, e.g.: "use of sleeping pills or drugs", "difficult to fall asleep", "dreamy sleep", "can fall asleep but easily awaken", and "sleep well" (Lao et al., 2018). Nonetheless, quantitative scales also present variability issues important to consider, namely, options ranging from 0 to 5, 0 to 10 or even 0 to 80, depending on the study (Angelhoff et al., 2018; Vitale, Banfi, La Torre, & Bonato, 2018; Zhang et al., 2018). This poses the question of how sure we are that they are all the same, especially because it is unclear how differently individuals interpret these ranges and how reliable they are to translate what the individual think.

Furthermore, in some studies an adaptation of existing questionnaires was used (6%) without indication for a proper validation study. For example, in the study of Ko & Lee (2018), a set of questions was considered from Verran and Snyder-Halpern Sleep Scale and in another study (Xie, Dong, & Wang, 2018) the same procedure was done regarding the PSQI, but none of them explored for the validity of this new measure they were considering. Furthermore, when considering the first 100 articles addressing "sleep quality", it was quite striking the amount of ways sleep quality was being addressed. If in one hand, there was a combination between subjective and objective measures (Montesinos, Castaldo, Cappuccio, & Pecchia, 2018), on the other, there was the use of measures of disturbance, such as insomnia, considered as a measure of sleep quality (or, at least, the lack of it) (Mantua, Helms, Weymann, Capaldi, & Lim, 2018). Thus, with so much variability, to what extent are these studies comparable? Does any of them reflect the actual interpretation that the general population has regarding sleep quality?

In a recent report from the National Sleep Foundation (Ohayon et al., 2017), a panel of experts systematically reviewed the literature in order to produce guidelines and recommendations regarding parameters of good sleep quality throughout the lifespan. However, a proper definition of good sleep quality remains elusive. It is still unclear what is the meaning of sleep quality, what constitutes it (i.e. different instruments consider different parameters), in what proportion, and whether it is immutable or not. In fact, sleep quality might be more than just sleep quantity, timing, simple stage structure or occurrence of pathologic events (Krystal & Edinger, 2008). While some authors argue that sleep quality perception often translates one's satisfaction with his/her sleep (Ohayon et al., 2017), others suggest that daytime functioning is more important for people to judge their own sleep experience when compared to the actual night itself (Goelema et al., 2018). In fact, the only proposed definition of sleep quality is the one from Yi and colleagues (2016) that used (and adapted) the definition from the Oxford English Reference Dictionary – sleep quality is the "degree of excellence in sleep". However, this is not a satisfying definition, because it still doesn't answer to the above stated questions and, as Yi and colleagues, stated, no measure can be developed until the nature of the concept has been delineated (Yi et al., 2006). Nevertheless, it should be noted that sleep quality has been measured on the basis of this definition (Freedman, Kotzer, & Schwab, 1999; Hawkins & Shaw, 1992; Shaver, Giblin, & Paulsen, 1991; Yi et al., 2006).To overcome this gap, a qualitative approach is of value . That is, the understanding of how lay people describe and conceptualize sleep holds a relevant role.

Here, results indicate that the experienced sleep quality might be more dependent on the daytime functioning than on the progress of the night (attained by retrospective judgment) (Goelema et al., 2018; Harvey et al., 2008; Ramlee et al., 2018). In fact, by conceptualizing sleep quality judgement as a decision-making process, it is possible to quantitatively identify and estimate the relative importance of different sleep and non-sleep parameters influencing this judgement (Ramlee et al., 2018). Among these parameters, participants mostly rely on total sleep time, feeling refreshed upon waking and the mood state in the following day (Ramlee et al., 2017). However, in older studies, results show that subjective sleep quality seems to be essentially associated to perceptions of ease of initiation and maintenance of sleep but unrelated to the perception of the ease of awakening (Keklund & Akerstedt, 1997). In other study of the same group, subjective quality of sleep mainly involved variables of sleep continuity, and "sleep quality", "calm sleep", "ease of falling asleep," and the ability to "sleep throughout" the time allotted, strongly co-varied and formed an index of sleep quality (Akerstedt et al., 1994). Interestingly, self-rated ease of awakening deviated from the general pattern, as well as reported dreaming (related to awakenings), both associating with poor sleep quality (Akerstedt et al., 1994). Another interesting point, concerns to the variability in the meaning of subjective sleep quality across (clinical) conditions. Not only people with chronic pain conceive pain experience and sleep quality as two linked entities, which influence their ability to engage in planned daytime activities (Ramlee et al., 2018), but also the meaning of sleep quality among individuals with insomnia and normal sleepers, or even between good or poor sleepers, may actually be broadly similar (Harvey et al., 2008; Ramlee et al., 2017). Thus, according to Goelema and colleagues, sleep quality definition, from a subjective point of view, should also consider factors such as stress/well-being levels, rest feeling and functioning during the day, guiding future research in what concerns suitable psychometric measures for normal sleepers, as well as the design of sleep data visualization applications in the context of health self-monitoring (Goelema et al., 2018). Furthermore, a comprehensive assessment of a patient's appraisal of their sleep quality may require an assessment of waking and daytime variables (Harvey et al., 2008). Importantly, in the study from Keklund & Akerstedt, it is argued that because they created a sufficient variation of sleep quality (including also poor sleep), the needed variance for a correlation between subjective and objective measures was achieved (Keklund & Akerstedt, 1997). In fact, a good agreement between laboratory and field situations with respect to how the subjective items are inter-related, and to the covariation between subjective and objective measures of sleep

was observed (Keklund & Akerstedt, 1997). Considering the association between objective sleep parameters in subjective sleep quality, it has been shown that subjective sleep quality was related mainly to sleep efficiency (accounted for most of the variance) but also to the closeness of the awakening to the circadian acrophase (Åkerstedt et al., 1994). In this particular study, sleep efficiency was more central to "good sleep" than continuity variables, like sleep latency, final wake time and time awake within sleep, which makes sense given that sleep efficiency represents the combination of these variables (Åkerstedt et al., 1994). Furthermore, sleep architecture (e.g. SWS and REM) apparently lacked relevance in subjective sleep quality, at least in what concerns sleep length (Åkerstedt et al., 1994). Interestingly, maximum sleep quality was rated when sleep ended close to the acrophase, which was suggested to be due to the circadian variation of alertness that reaches an acrophase in the early evening (Åkerstedt et al., 1994). The indication is that in future studies, circadian phase should be considered in the interpretation of sleep quality ratings (Åkerstedt et al., 1994).

The limitations associated to the small samples and restriction to mostly college students are obvious, as they leave out the population that frequently complaints about their sleep. What does a good sleep quality mean for the general population? What words do they use? Is it dependent on cultural issues? What is the association between this definitions and standard measures of sleep quality, such as the PSQI? What are the determinants of a subjective good sleep quality? These are still unanswered questions. Future studies should address for this in community-dwellers, across the adult lifespan, so to develop a new measure that can be used as standard, not only for research but also for clinicians, permitting for further associations with standard measures, such as the Pittsburgh Sleep Quality Index (PSQI), should also be determined.

Overall, sleep quality can be defined as a multidimensional concept constituted by a set of different dimensions, such as duration, efficiency and continuity. Despite using these different dimensions as proxies to good or poor sleep, it is not adequate to refer to any of these as "sleep quality" if only one dimension is being considered. The weight of each parameter in the overall measure of sleep quality is yet to be determined. Thus, studies must start to address the importance of each parameter in not only determining a final composite measure, but also in identifying for possible individual profiles (an adjusted measured).

Conclusions

Sleep quality has stirred a lot of interest, and has been refereed to in many studies, evidencing for its recognized role in health, cognition, immune function, among others. However, no consensus on what constitutes sleep quality has actually been reached. In fact, a high variability exists in the way the phenomenon is conceptualized and measured, making it difficult for researchers and clinicians to understand how sleep quality monitoring, measuring and treatment can be performed. This review sought to clarify the meaning of sleep quality, providing a state of the art of the studies that explored this dimension and an overall view of the next steps to be performed. We propose that "sleep quality" should be considered as a multidimensional phenomenon that can only be determined with measures that consider this multidimensionality and not the dimensions separately.

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.

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CHAPTER III

Sleep quality meaning and its association with the Pittsburgh Sleep Quality Index (PSQI): a population-based study across the adult lifespan

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Sleep quality meaning and its association with the Pittsburgh Sleep Quality Index (PSQI): a population-based study across the adult lifespan

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Abstract

Sleep is a complex, dynamic and multidimensional phenomenon, whose impact has been demonstrated in health and well-being. While the dimension 'sleep quantity' is clearly defined, such does not apply to the 'sleep quality' construct. In fact, different conceptualizations of it have led to a high variability in the methodologies used and, consequently, in the results obtained across studies. Likewise, authors still have not addressed the meaning of a good sleep quality across the adult lifespan, nor its stability over time. Here, to addresses these aspects, and explore the association of sleep quality self-ratings with the Pittsburgh Sleep Quality Index (PSQI), community-dwellers were invited to participate in the study (n=343, after inclusion and exclusion criteria; age range: 18-87 years). Participants were asked to provide their interpretation of a good sleep quality and a good night of sleep. Self-ratings of sleep quality, patterns and habits and information on psychological variables were also collected. Content analysis was performed with the qualitative data and the obtained parameters were considered as to their frequency. Associations between self-rated sleep quality and PSQI were determined, and the predictors of good/poor sleep quality explored. Results show that the distribution of the reported parameters used to describe a 'good night of sleep' and a 'good sleep quality' differs. While the most frequently reported parameters for 'good sleep quality' are 'sleep continuity', 'sleep characteristics' and a dyad involving these two, for a 'good night of sleep' the most reported information related to the dyad 'sleep duration-sleep continuity' and to 'sleep duration' and 'sleep continuity' individually. Results also indicate that self-rated sleep quality measures and the PSQI are highly correlated, and no differences were found across lifespan in the distribution of these parameters. One year later, 52% of the invited individuals who were re-evaluated maintained the definition provided in the first assessment moment. The results contribute to the clarification of the meaning of 'a good sleep quality', and provide a relevant framework for future studies addressing the complaints and sleep changes across lifespan.

Keywords: Sleep quality; definition; determinants; content analysis; lifespan; network analysis.

Introduction

Sleep is a ubiquitous phenomenon that has been shown to change as age progresses (Mander, Winer, & Walker, 2017). Within the normative ageing process, the ability to initiate and maintain sleep seems to decrease (Mander, Winer, & Walker, 2017), possibly as a consequence of sleep architecture alterations. While this can partially explain the increase in sleep complaints among the adult population, it does not justify why sometimes these complaints are not translated into objective measures of sleep disturbances (Moul et al., 2002; Rosa & Bonnet, 2000). In fact, different hypothesis have been raised. If, on one hand, subjective sleep complaints can be a misconception of what to expect of sleep; on the other hand, these complaints might actually reflect some physiologically relevant disturbances that are not captured by the traditional objective sleep measurement. Either way, a first important step should be to address this subjective sleep dimension, clarifying its meaning, in order to understand the variability of results and its potential in clinical practice.

When reviewing the literature, it is quite clear the vast heterogeneity of the measures used to address sleep quality. Most studies, when focusing on the subjective dimension of sleep quality, use the Pittsburgh Sleep Quality Scale (PSQI) (Buysse et al., 1989). This self-report index was developed under the assumption that sleep quality comprises not only quantitative aspects of sleep, such as sleep duration, sleep latency, or the number of arousals, but also purely subjective aspects, such as “depth” or “restfulness” of sleep (Buysse et al., 1989). The PSQI provides an overall score of sleep quality, but also individual scores for all the subdomains considered. Despite widely used, the items that compose this index were mainly derived from a review of previous sleep quality questionnaires and clinical intuition and experience with sleep disorder patients (Buysse et al., 1989). In fact, the exact elements of sleep quality, and their relative importance, are considered to vary between individuals (Buysse et al., 1989), providing arguments to study the meaning of a good sleep quality for “lay” (non-clinical) individuals. More so, previous studies addressing the meaning of a “good sleep quality” in community-dwellers have provided heterogeneous results (Akerstedt et al., 1994; Goelema et al., 2018). While, in some studies, a "good sleep quality" is mainly a question of sleep continuity (Akerstedt et al., 1994), others suggest that is more related to the “next day feelings of refreshment” (Harvey et al., 2008). Furthermore, these studies considered small samples, usually of young individuals (Akerstedt et al., 1994) or insomniacs vs

good sleepers (Harvey et al., 2008). Finally, most studies used a paradigm in which participants had to choose or complete sentences, thus impeding or limiting a self-definition.

On this, a possible approach is qualitative research. In fact, there has been an increased interest in this approach when exploring and describing complex phenomena (Erlingsson & Brysiewicz, 2017). By giving voice to the user, patients, and/or vulnerable populations, and providing textual versions of the individuals' view of the phenomenon, there is a significant contribution to its better understanding (Erlingsson & Brysiewicz, 2017). Here, to our knowledge, no study has explored the meaning of a "good sleep quality" across the adult lifespan or assessed for an association of this with the standard measure of subjective sleep quality, the Pittsburgh Sleep Quality Index (PSQI), or the determinants of a good/poor sleep quality, concurrently in the same study population. Nonetheless, to determine how lay people describe and understand sleep holds a high potential to not only improve health outcomes but, also, to contribute to the development of more appropriate and reliable tools that aid in sleep monitoring. Moreover, with the growing interest in sleep monitoring devices, such approach promotes a valuable opportunity to not only empower the individual to better understand and monitor his/her sleep, but also assist healthcare providers to better understand and intervene on sleep complaints.

In this context, herein we aimed to determine the meaning of a good sleep quality for community-dwellers across the adult lifespan, as well as its stability and the association between self-rated measures that represent this conception of a good sleep quality and PSQI. We expect stability in the parameters used to describe "good sleep quality" and an association between the different self-reported measures. The understanding of these complex dynamics will lead to new avenues for diagnosis, monitoring and treatment of sleep disorders.

Methods

Ethical Considerations

The study was conducted in accordance with the principles expressed in the Declaration of Helsinki (59th amendment) and its protocol received full ethical approval from the local and national ethics committees. All volunteers who agreed to participate provided written informed consent.

Participants

Potential participants were randomly and consecutively invited to enroll the study while attending their regular (weekday) annual GP appointment in, non-private, primary health care centers in the northern region of Portugal. All Portuguese adults aged 18 years and above were considered eligible if able to provide voluntary informed consent. Exclusion criteria included non-fluency in the Portuguese language, inability to read or write, working night shifts and choice to withdraw from the study.

A total of n=343 participants were recruited after inclusion and exclusion criteria. Of these, n=112 individuals were able to complete the full study protocol before being called-in to their GP appointment; the remaining completed as much as possible before the appointment. Specifically, n=308 participants answered the questions "what is a good night of sleep?" and "what is a good sleep quality?" and provided information on rest patterns and bedtime routines; and, n=227 completed the Pittsburgh Sleep Quality Index (PSQI), n=118 the Epworth Sleepiness Scale (ESS, sleepiness scale) (Johns, 1991), n=172 the Depression, Anxiety and Stress Scale of 21-items (DASS-21) (Lovibond & Lovibond, 1996; Pais-Ribeiro, Honrado, & Leal, 2004), n=116 the NEO-FFI scale on personality traits (Bertoquini & Pais-Ribeiro, 2004), and n=112 the Positive and Negative Affect Scale (PANAS) (Galinha e Pais-Ribeiro, 2005). Instruments were administered always in the same order and by the same accredited clinical psychologist. Because it was expected that the majority of individuals had occupational activities after their GP appointment, individuals were not approached after finishing their appointment (so to complete the study protocol) as this would create undue stress in arriving late to their professional obligations/work schedule (the justification slip for the work absence-related event only covers the duration of the GP appointment and the waiting room period), and be potentially condusive to bias in reporting due to rush.

Self-reported sleep parameters

Participants were asked to provide short written answers to the questions:

- What does it mean -to yourself- to have a good night of sleep?
- What does it mean -to yourself- to have good sleep quality?

They were also requested to "rate their sleep quality" by using two different scales. First, to rate the quality of their sleep in a qualitative manner. For this, the scale used mimics the item 6 of the Pittsburgh Sleep Quality Index (PSQI) and is composed of the rating options "very poor", "poor", "good" and "very good". The second scale, is a self-rated scale, that ranges from 0 to 100, and the user must attribute a numerical value to the quality of their sleep. Finally, participants completed the PSQI. In this instrument, the higher the score the poorer the sleep quality; while, in the self-rating scales, higher scores mean better reported sleep quality. Information about their usual sleep patterns and bedtime routines was also obtained, as well as a composite subjective measure of sleep quality derived from the PSQI (PSQI global score) (Buysse et al., 1989; Del Rio João, Becker, de Neves Jesus, & Isabel Santos Martins, 2017).

Psychological measures

Participants were asked to provide information on sleepiness via the ESS (Johns, 1991); with higher scores representing higher sleepiness level. Psychological morbidity was evaluated via the DASS-21 scale (Lovibond & Lovibond, 1996; Pais-Ribeiro et al., 2004), in which higher scores represent more stress, anxiety or depression symptomatology. Personality traits were assessed via the NEO-FFI-21 (Bertoquini & Pais-Ribeiro, 2004), and positive and negative affect via PANAS (Galinha & Pais-Ribeiro, 2005).

Qualitative analysis

The information obtained from the two questions was analyzed using content analysis. Answers to each question were considered separately and given the length of the statements (short), there was no need for a specific software to perform the analysis. A total of 616 sentences were obtained (two *per* participant who completed this part of the study protocol). The first analysis step was to read and re-read the obtained information multiple times in order to have a sense of the whole and to identify prominent themes. Then, the text was divided into smaller parts, i.e. meaning units. For example, from the sentence "It means to sleep well and have no difficulties falling asleep", the

following units were derived: “sleep well” and “no difficulties falling asleep”. From this, categories grouping the meaning units were created. For instance, from the example above, “sleep well” was put in the category “sleep characteristics” and “no difficulties falling asleep” into a category termed “sleep onset”. The information provided by the participants was analyzed until saturation was achieved. Then, a new reading of the complete sentences, meaning units and the complete sentences and categories was performed, so to guarantee that the meaning of the sentences had not been lost. Next, group categories that had the same underlying theme were grouped together. For example, “sleep all night” and “sleep 8 hours” were both categorized as “sleep duration” and “sleep all at once” and “only wake one time in the night” as “sleep continuity” (see Table 3 for more details).

Considering that the later step could provide some bias to the analysis, and to ensure the validity of the clustering, one independent researcher with expertise in qualitative analysis was asked to provide an independent analysis of randomly selected sentences and to allocate them into categories. All the meaning units that were dubious for the first researcher were discussed with the independent researcher. The results from both researchers were compared and discussed, to guarante that all answers were properly allocated to meaningful and not overlapping units. The final analysis step was to consider information from studies on the subject (Akerstedt et al., 1994; Goelema et al., 2018; Harvey et al., 2008; Krystal & Edinger, 2008), and label the categories considering their terminology/ labeling (if possible) allowing for comparisons between studies and result interpretation across studies.

Stability of the meaning of “good sleep quality” and a “good night of sleep”

In order to explore the stability of the distribution of the parameters to each question, 53 individuals were randomly selected to be re-evaluated one year later. The number of participants was calculated with G-Power for a statistical significance of 0.05 and a power of 0.80. Qualitative analysis was performed as before, but this time having already the categories to allocate the obtained meaning units.

Statistical analysis

JAMOVI (V0.9.5.12) was used for statistical analysis and GraphPad (Prism, V7.04) for graphic representations. Participants with missing values were only excluded from the analysis that involved

that particular variable(s). Normality and symmetry assumptions were tested and statistical tests choose accordingly. Descriptive analysis was performed and mean/median, standard deviation/IQR, and percentages (%) were used to characterize the sample.

A quantification of the results obtained from the qualitative analysis was performed (frequency of report) and a graphic representation was derived from it. Network analysis was performed with the items derived from the responses to the questions: "For you, what does it mean a good night of sleep?" and "For you, what does it mean a good sleep quality?" using JASP (V0.9.0.1). The answers to these questions were qualitatively analyzed, and data was grouped into categories that for the purpose of this network analysis were dichotomized: 0 if the parameter was not mentioned by the participant, 1 if it was. In the visualization of the network models, each parameter (or variable) - "sleep duration", "sleep continuity", "sleep onset", "sleep characteristics", "room environment", "final wake up" and "next day performance", for each question – is depicted as a circle denominated by "node". Nodes are connected through lines that are denominated "edges" and indicate some statistical relationship between the nodes. The edges can differ in strength of connection i.e. edge weight, indicating if a relationship is strong (visualized with thick edges) or weak (thin, less saturated edges) and positive (blue edges) or negative (red edges). The resultant network estimated shows the multivariate dependencies in the data. This same strategy was also used to explore the associations between PSQI and the self-rated measures provided by the participants, as well as for the possible association between variables that could be determinants in that rating. The estimator EBICglasso (Foygel & Drton, 2010; Friedman, Hastie, & Tibshirani, 2008; Friedman, Hastie, & Tibshirani, 2014) was used. The tool estimates the partial correlations between all variables, and shrinks the absolute weights to zero. Consequently, edge weights are slightly biased but small edge weights are shrunken to be exactly zero (avoid the risk of false positive interrelations). This allows to estimate the network in which each edge represents the relationship between two variables, controlling for all other relationships in the network. Furthermore, within the EBICglasso estimator, the correlation method "auto" was chosen, given that it automatically detects the correct measurement scale of the variable from the raw data (pearson for two continuous variables, polychoric for two dichotomous variables, and polyserial for one continuous and one dichotomous variable).

Network inference is based on the estimated network and the interrelatedness (or 'centrality') coefficients. Three coefficients were considered: node strength, which is the sum of the interrelation

values (e.g. regularized partial correlations) of a given sleep parameter with all directly related sleep parameters (i.e. the sum of the absolute values of the sleep interrelations). The expected influence is based on the formula of node strength, but takes negative relationships between sleep parameters into account (i.e. the sum of the relative values of the sleep interrelations). Node predictability is defined as the amount of variance of each sleep parameters that is explained by the directly related sleep parameters. Node predictability is an absolute metric ranging from zero to 100 percent explained variance. For dichotomous sleep parameters, we based the node predictability on the normalized accuracy, instead of on the variance explained. Accuracy can be scrutinized through calculating nonparametric bootstrap confidence intervals (CIs, 95%) for the sleep parameters interrelations. The widths of these CIs give an indication for accuracy. Stability can be analyzed through re-calculating interrelatedness coefficients such as the node strength for sample subsets. If the node strength remains similar in the subsets, this indicates that the sleep parameters network is stable. Accordingly, we bootstrapped the sleep parameters interrelations (i.e. accuracy) and applied a subset bootstrap on node strength and expected influence (i.e. stability), with 300 bootstraps each. As sensitivity analysis, we correlated the sleep parameters interrelations of the full-information networks with the sleep parameters interrelations of the complete-information networks, which are based on listwise case deletion. The stability of the parameters was determined by calculating the percentage of individuals that used different parameters to report the meaning of good sleep quality.

The association between the different measurements of sleep quality was addressed using the Spearman's correlation test.

In order to test the differences between individuals in good and poor sleep quality groups, qualitative and quantitative and PSQI measures were used to form the groups. The first step was to convert all scales in order for them to be in the same direction (PSQI – higher scores, lower sleep quality, self-reports used – higher scores, better sleep quality). For this, qualitative and quantitative self-reports were converted in a direct manner, i.e., scales were inverted. Then, for the qualitative self-report, the options "really bad" and "more or less bad" were converted in 1 and "very good" and "more or less good" were converted in 0. For the qualitative scale (range: 0 to 100), direct inversion of the scale first and then the ROC method was applied (PSQI as Standard Measure) and 27.5 was the cut-off value for good sleep quality (see Appendix 1 for more details). Thus, all values bellow 27.5 were considered 0 (good sleep quality) and all values above were

defined as 1 (poor sleep quality). For PSQI, it was considered the validated cut-off of 5 (Del Rio João et al., 2017) and the PSQI global score was considered in its dichotomous form. Differences between individuals with good and poor sleep quality were then tested for each method of group derivation – PSQI global score, qualitative self-report and quantitative self-report - using Man-Whitney test. After determining the differences between groups, the variables of interest were used as determinants of good sleep quality in logistic regression models. All tests were corrected for multiple comparisons.

Results

Socio demographic and psychological characterization of the cohort

A total of n=343 individuals agreed to participate in the study (63.7% female; median age 47 years (IQR=23); 66% married; 38% thirteen or more years of education; 67% employed). However, because of time constraints, only n=308 individuals constituted the qualitative study sample (the sample did not significantly differ from the original sample in the socio-demographic characteristics listed). From the participants able to provide information regarding their psychological status, the median value of subjective sleep quality is 6 (IQR=5) (all values above 5 indicates poor sleep quality according to validation studies) (Buysse et al., 1989; Del Rio João et al., 2017), and 46.3% had poor sleep quality. The median value of sleepiness was 7 (IQR=5) (equal or above 10 it is considered excessive sonmnolence), and stress was the dimension of psychological morbidity with the highest median (median=5; IQR=5). Socio-demographic characteristics, subjective sleep, personality and psychological parameters characterization are shown in Table 1.

Table 1. Sociodemographic and psychological characterization of the cohort.

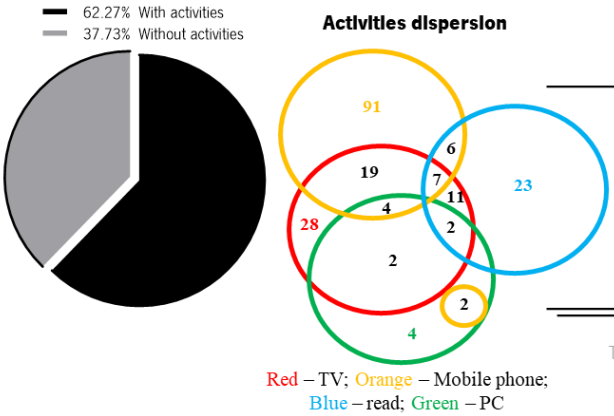
		n (%)	Median (IQR)
Age		–	47 (23)[¥]
Sex	Female	216 (63.7%)	
	Male	127 (36.3%)	
Education	No education	4 (1.2%)	
	0 to 4 yrs	39 (11.6%)	
	5 to 9 yrs	74 (22%)	
	10 to 12 yrs	92 (27.4%)	
	13 or more yrs	127 (37.8%)	
Marital Status	Single	85 (24.8%)	
	Married	228 (66.5%)	
	Divorced	22 (6.4%)	
	Widowed	8 (2.3%)	
Household	Alone	20 (5.9%)	
	Husband/Wife	133 (39.1%)	
	Family[#]	183 (53.8%)	
	Others[*]	4 (1.2%)	

Occupation	Retired	48 (14.1%)	
	Employed	230 (67.4%)	
	Unemployed	29 (8.5%)	
	Student	28 (8.2%)	
	House keeper	6 (1.8%)	
Living Place	City	193 (56.6%)	
	Rural	148 (43.4%)	
Children in School	Yes	134 (39.9%)	
Grandchildren in School	Yes	47 (14.3%)	
PSQI[£]	Good	105 (46.3%)	4 (2)[¥]
	Poor	122 (53.7%)	9 (4)[¥]
ESS		118 (–)	7.55 (±3.94)
DASS-21	Stress	172 (–)	5 (5)[¥]
	Anxiety		1 (3.25)[¥]
	Depression		1 (4)[¥]
PANAS	Positive Affect	112 (–)	33.3 (6.13)
	Negative Affect		17 (8)[¥]
NEO-FFI	Neuroticism	116 (–)	6.05 (2.78)
	Extroversion		9.91 (2.55)
	Openness to experience		9.95 (3.33)
	Agreeableness		10-6 (2.78)
	Consciousness		12 (2)[¥]

[¥]Normality and symmetry assumptions not filled, thus, values presented are for median and IQR. [#]Family - includes any family members, e.g. children, parents, grandparents; [*]Others – e.g. friends, boyfriend/girlfriend, professional residencies. PSQI – Pittsburgh Sleep Quality Index ([£]$PSQI_{Total\ population}$: median= 6; IQR=5); ESS – Epworth Sleepiness Scale; DASS-21 – Depression, Anxiety and Stress Scale 21 items; PANAS – Positive and Negative Affect Scale; NEO-FFI-21 – 5 Factors Personality Scale

Sleep patterns and bedtime routines characterization throughout adult lifespan

Regarding sleep schedules, results show that participants go to bed at 23:00 (median) (IQR=1), turn off the lights around the same time (IQR=1), take 15 minutes to fall asleep (IQR=25), wake up at 7:00 (IQR=3), rise 10 minutes (IQR=17) later and report having slept 7 hours (IQR=2). In terms of patterns of routines when going to bed, of the n=326 participants that provided information regarding these parameters, 62.3% indicate having some type of activity in bed, with the majority reporting the use of the mobile phone (Figure 1). The median time spent in activities after going to bed was of 40 minutes (IQR=17). In what concerns the use of alarm clock to wake up, 46.3% of the participants reported its use in every day of the week and at weekends, and 34.9% indicate it would depend on the circumstances and of the day (week or weekend days). No differences were found between men and women in what concerns bedtime routines ($\chi 2(7) = 7.88$, $p=0.344$). When exploring the effect of age, a small effect was observed on subjective sleep quality ($rho=0.188$, $p=0.005$) and on the reported amount of sleep ($rho=-0.297$, $p=0.001$), with no significant impact on sleep latency ($rho=0.079$, $p=0.189$). A moderate effect of age was observed regarding sleep ($rho=-0.331$, $p<0.001$) and wake times ($rho=-0.512$, $p<0.001$) (Figure 2).



Frequencies of bedtime routine activities

	n (%)	Mean time (min)
No bed time activity	123 (37.7%)	—
Watching TV	28 (8.6%)	34.2
Using the mobile phone	91(27.9%)	48.4
Reading	23 (7.1%)	31.4
Using the computer	4 (1.2%)	75.0
Listening to radio	1 (0,3%)	180
Embroiding	1 (0,3%)	180
More than one activity	54 (16.6%)	82.2
TV + Read	11	
TV +Read + Mobile Phone	7	
TV +Mobile Phone	19	
Read + Mobile Phone	6	
TV + Computer	2	
TV + Read + Computer	2	
TV + Mobile Phone + Computer	4	
Computer + Mobile Phone	2	
TV + Read + Cross-words	1	

Figure 1. Bedtime routines across lifespan.

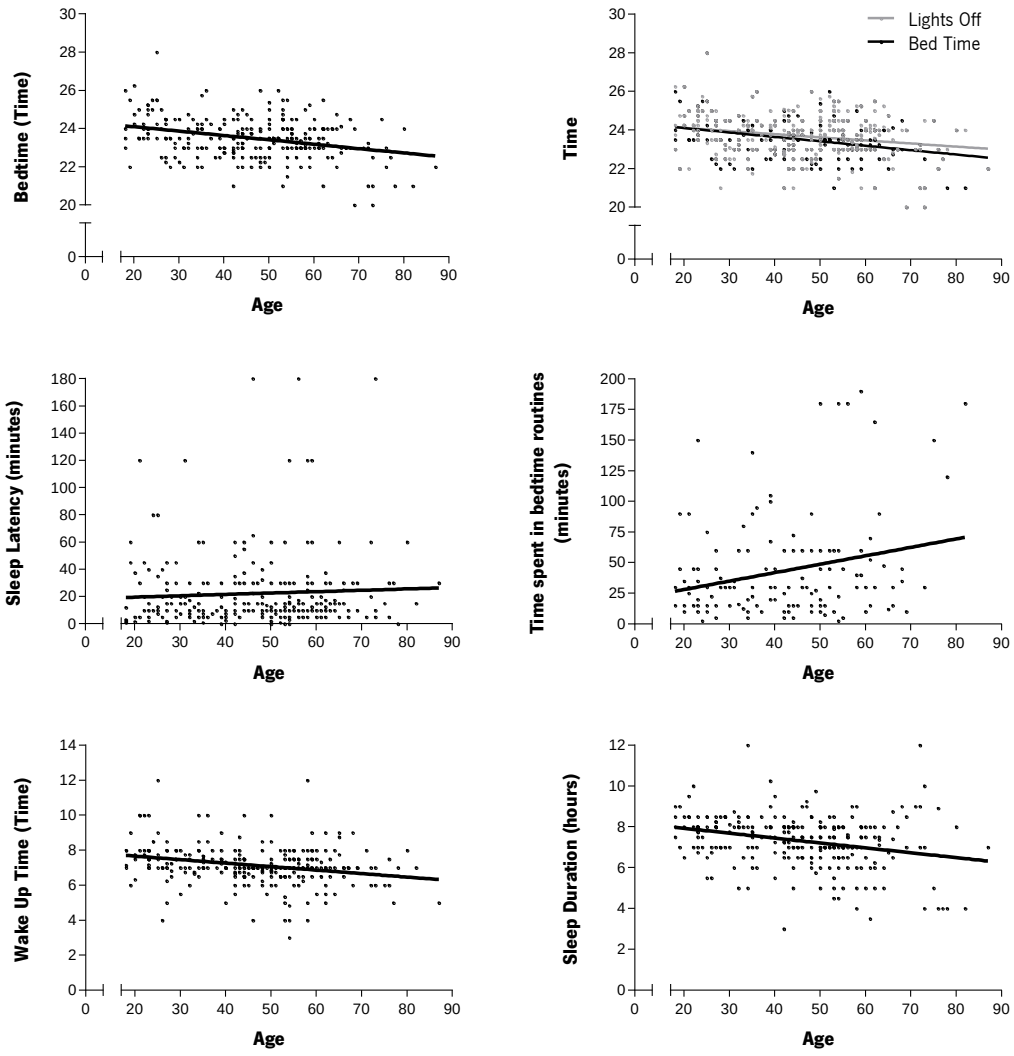


Figure 2. Sleep patterns across lifespan.

A good sleep quality for a lay individual – content analysis results

The content analysis resulted in seven units of analysis/categories: "sleep duration", "sleep continuity", "sleep onset", "sleep characteristics", "room environment", "final wake up" and "next day performance" (see Table 2 for more details). It was determined, for each unit of analysis, the percentage of individuals that referred it. The same was performed regarding dyads of units and units grouped in one response. A graphic representation of these results is presented in Figures 3 and 4. Answers varied according to the question being about a good night of sleep or a good sleep quality. Particularly, when asked about their night of sleep, participants more frequently reported the dyad "sleep duration"-"sleep continuity" and individually, the units "sleep duration" and "sleep continuity" (Figure 3). The distribution of the answers changed for the question related to a good sleep quality, where inquirers most frequently reported "sleep continuity" aspects alone (Figure 4). It was also common to observe answers related with the individual unit "sleep characteristics" and the dyad "sleep continuity"-"sleep characteristics" (Figure 4).

Table 2. Operationalization of the units of analyze resultant of the 604 statements regarding the meaning of "a good night of sleep" and "a good sleep quality".

Units of analyses	Description	Examples
Sleep duration	Contains all the information referring to the amount of time the subject sleep.	*"Sleeping at least 8h"; "Sleeping all night"; "Sleep the appropriate number of hours".*
Sleep continuity	Contains information about the continuity of sleep and interruptions throughout the night. Sleep fragmentation can be either by internal causes (e.g. need to go to the toilet) and external causes (e.g. children needing assistance or noise).	*"Sleep in a continuous way"; "Sleep 8-h without interruptions"; "Sleep without dreams/nightmares interruptions and awaking"; "Only wake up once through the night to go to the bathroom".*
Sleep onset	Contains information regarding sleep latency (i.e. the amount of time to fall asleep) and statements regarding factors that can relate to the amount of time to fall asleep, like pain, worries or the use of medication.	*"Fall asleep without difficulties"; "Fall asleep quickly"; "Fall asleep peacefully"; "Fall asleep without bad thoughts or worries"; "Fall asleep without pills"; "Go to bed and immediately fall asleep".*
Sleep characteristics	Contains the subjective perceptions regarding sleep as well as mentions to dreams and nightmares.	*"To be able to relax physically and mentally"; "A peaceful sleep"; "Sleep well"; "Have a refreshing and peaceful sleep"; "To be able to rest body and mind"; "Restful sleep"; "Sleep with dreams"; "Sleep without dreams or nightmares".*
Room environment	Contains statements about the physical elements in the bedroom, like the mattress, pillow, lights and temperature but also aspects like noise and the comfortableness of the individual in the bed.	*"Quiet room"; "Being in a comfortable position"; "Without noises, with a temperature of approximately 19°C and a dark bedroom, so that it is possible to sleep peacefully"; "Comfortable"; "In silence".*
Final wake up and rise	Contains statements that inform about the waking up. Specifically, how the participants feel waking up and whether the waking is with or without an alarm clock.	*"Wake up with rest body and mind"; "Wake up in the morning with felling of being well"; "Wake up naturally, without alarm clock"; Wake up with the alarm clock"; "Wake up with energy"; "Wake up refreshed"; "Wake up in a good mood".*
Next day performance	Contains information about daytime functioning and statements that mention broad consequences of a good sleep.	*"Enjoy the day in its fullness"; "Be ready for the day without feeling tired"; "Having quality of life"; "Not being sleepy throughout the day"; "Being calm throughout the day"; "Being productive during the day"; "Being in a good health"; "Don't feel tired through the day.*

A

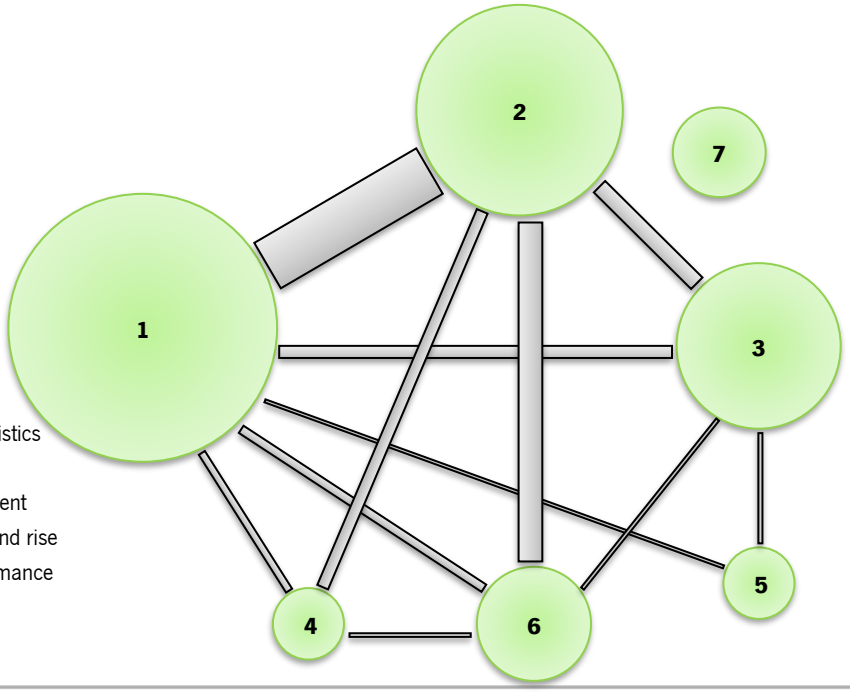


FIGURE LEGEND

1. Sleep duration
2. Sleep continuity
3. Sleep characteristics
4. Sleep onset
5. Room environment
6. Final wake up and rise
7. Next day performance

B

	Duration (n)	Continuity (n)	Onset (n)	Characteristics (n)	Room environment (n)	Final wake (n)	Next day performance (n)
Duration	49						
Continuity	75	42					
Onset	2	7	0				
Characteristics	7	11	0	20			
Room environment	1	0	0	1	0		
Final wake	5	21	1	1	0	12	
Next day performance	0	0	0	0	0	0	7

C

Duration	Continuity	SleepOnset	Sleep characteristics	Room environment	Final wake up	Next day performance	n
							1
							7
							5
							3
							1
							1
							7
							3

Figure 3. Graphical representation of the reported parameters for a good night of sleep.
1A is a schematic representation of parameters reported in the global analysis for the question: "For you, what is a good night of sleep?". Each node represents one unit of analysis and its size reflects the number of participants that have reported it. The connection between nodes represent the dyads of parameters that were simultaneously reported and its with reflects the amount of participants referring it. In **1B**, it is represented the number of individuals that report information in each categories and the dyads of observed units of analysis. This table is the raw data considered to develop 1A. In **1C**, it is observable the number of individuals that report more than two units of analysis when answering to the question.

A

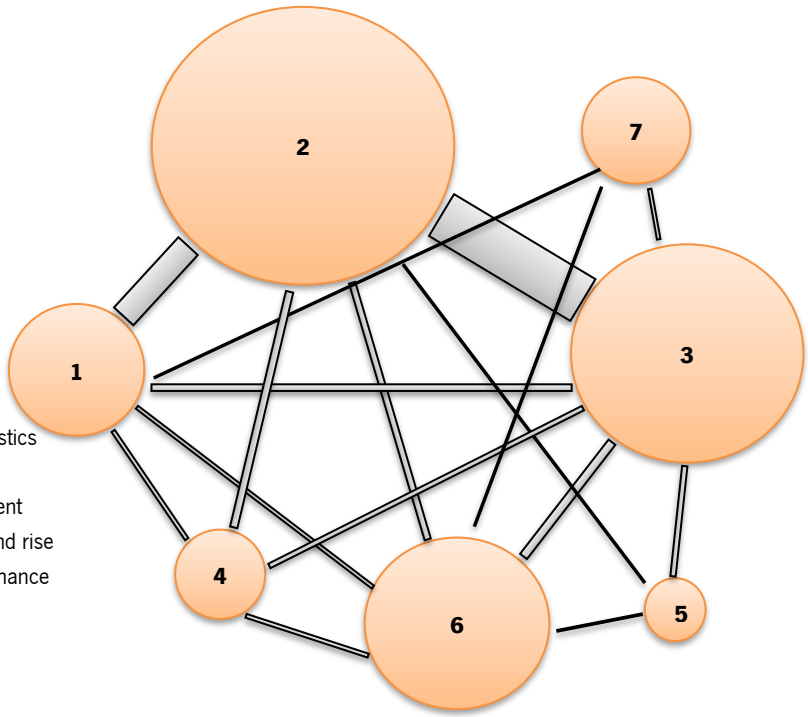


FIGURE LEGEND

1. Sleep duration
2. Sleep continuity
3. Sleep characteristics
4. Sleep onset
5. Room environment
6. Final wake up and rise
7. Next day performance

B

	Duration (n)	Continuity (n)	Onset (n)	Characteristics (n)	Room environment (n)	Final wake (n)	Next day performance (n)
Duration	16						
Continuity	25	58					
Onset	2	6	2				
Characteristics	6	36	3	45			
Room environment	0	1	0	2	0		
Final wake	2	6	2	8	1	33	
Next day performance	1	0	0	2	0	1	6

C

Duration	Continuity	SleepOnset	Sleep characte	Room environ	Final wake up	Next day perfe	n
							1
							3
							2
							1
							3
							1
							5
							1
							1
							1
							1

Figure 4. Graphical representation of the reported parameters for a good sleep quality.
2A is a schematic representation of parameters reported in the global analysis for the question: "For you, what is a good sleep quality?". Each node represents one unit of analysis and its size reflects the number of participants that have reported it. The connection between nodes represent the dyads of parameters that were simultaneously reported and its with reflects the amount of participants referring it. In **2B**, it is represented the number of individuals that report information in each categories and the dyads of observed units of analysis. This table is the raw data considered to develop 1A. In **2C**, it is observable the number of individuals that report more than two units of analysis when answering to the question.

Network analysis on statistical structure of the answers from content analysis – a descriptive approach

Network analysis (Fried et al., 2015; Schmittmann et al., 2013) was used to obtain relations between the variables and information about their clustering (Figure 5).

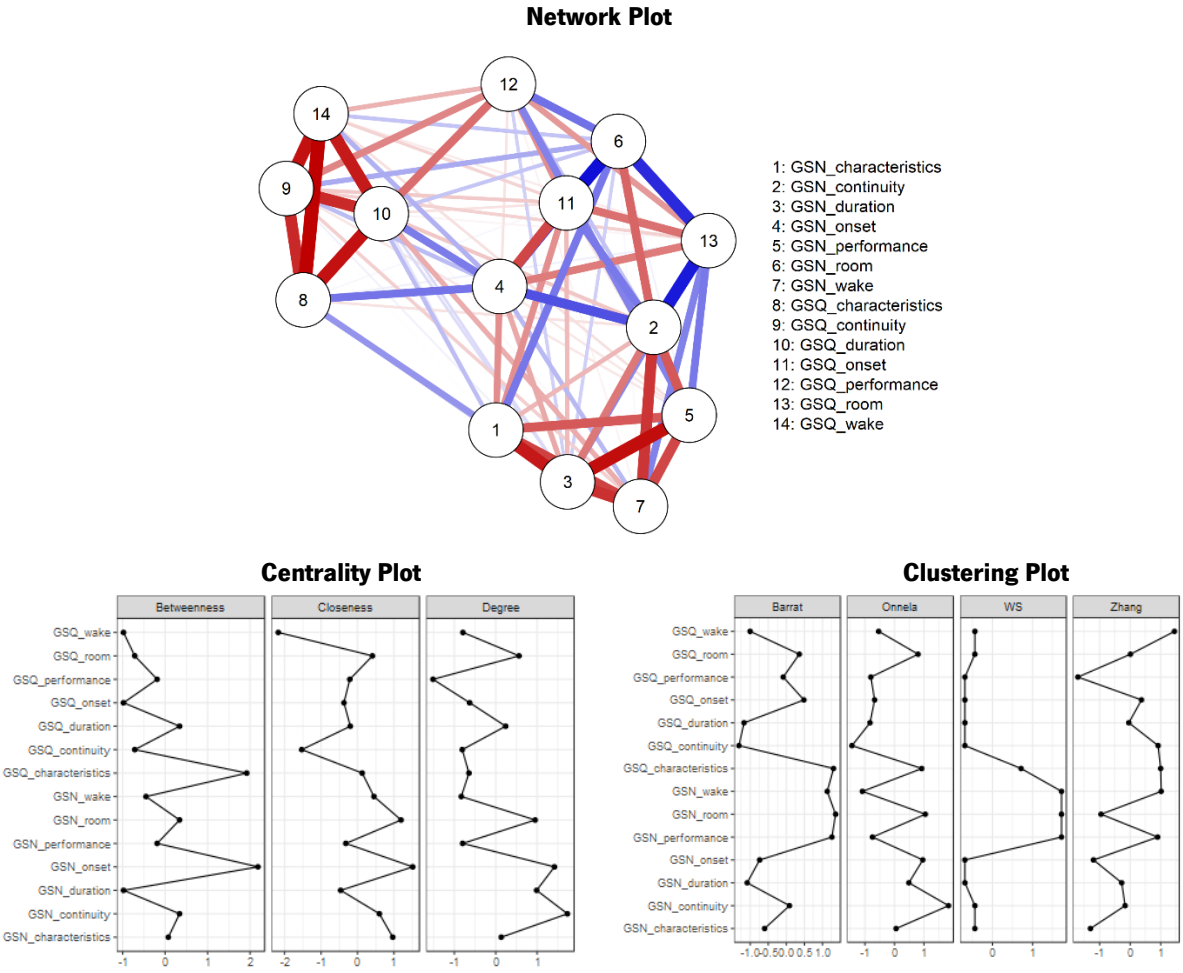


Figure 5. Network visualization of reported sleep aspects. Nodes represent categories obtained from the content analysis of the questions: "What is for you a good night of sleep?" and "What is for you a good sleep quality?" Network Plot is the result of the application of the estimator EBICglasso to the data, which cluster the variables according to the appropriate test. The Centrality and Clustering measures are also important. Regarding the centrality measures there is: betweness, which provides information related to the nodes that have the highest number of shortest paths; closeness corresponds to the inverse of the sum of all shortest paths from the node of interest to all other nodes; and the degree is the sum of the absolute input weights of that node.

From the network plot, it is possible to observe that the sleep quality (GSQ) parameters "characteristics", "continuity", "duration" and "final wake" are clustered together with a strong association between them. A cluster between sleep quality and sleep night (GSN) parameters is also observed: "GSQ_onset"-"GSN_room"-"GSQ_room"-"GSN_continuity". In terms of centrality measures, the betweeness of "GSQ_characteristics" and "GSN_onset" is relatively high when

compared to other nodes, which means that there are more shortest paths passing through these two nodes, than to any other node (i.e. it is easier to traverse from other nodes to "GSQ_characteristics" and "GSN_onset"). In general, a higher centrality measure indicates that the node is more central to the network. When exploring the network analysis only for the question regarding the meaning of good sleep quality, results indicate that the parameters "final wake" and "sleep continuity" seem to be the most central for the obtained network. In fact, in the formed cluster (see network plot) the parameters sleep "continuity" and "final wake" are the ones with the stronger association. The parameter sleep "characteristics" appeared also as important being clustered to "final wake" and sleep "duration" and, in a weaker association, to sleep "continuity" (Figure 6).

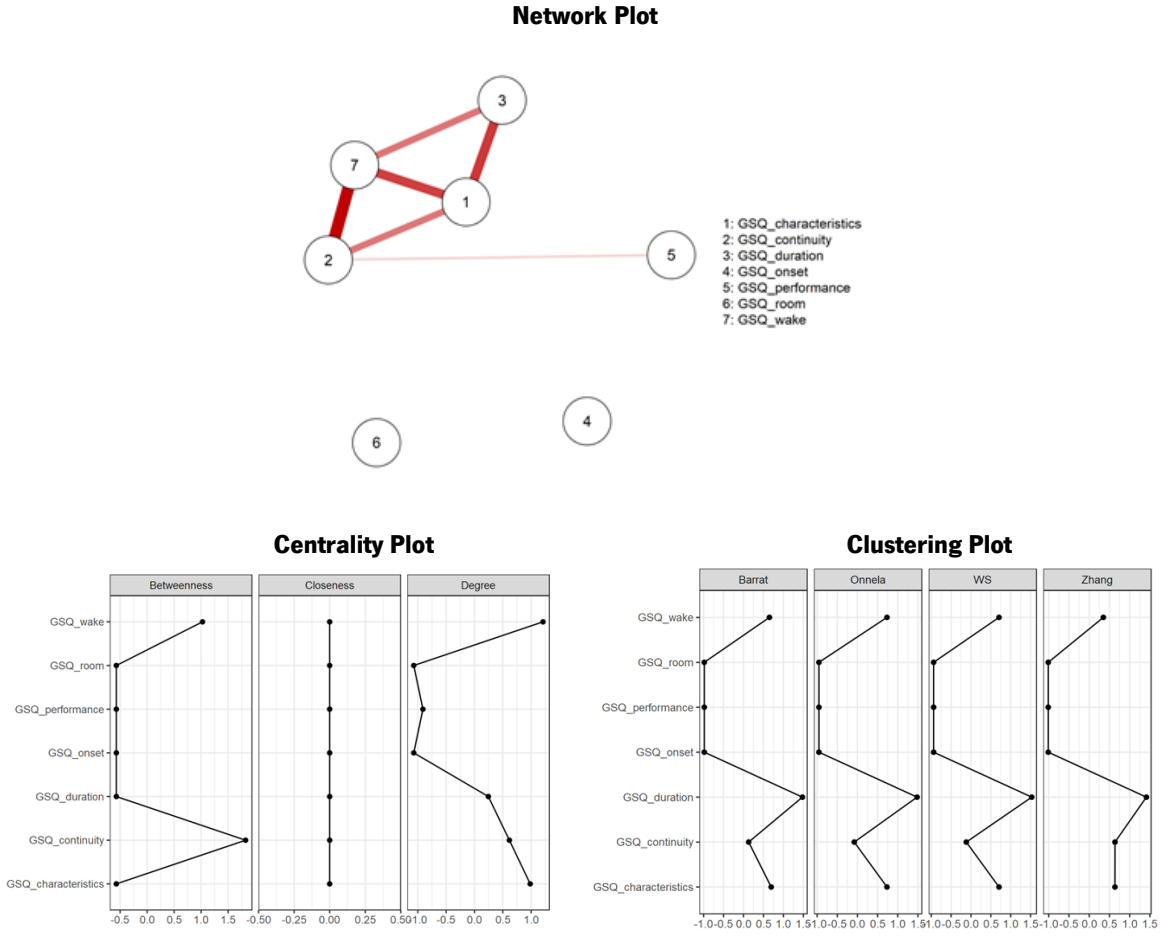


Figure 6. Network visualization of reported sleep aspects. Nodes represent categories obtained from the content analysis of the question: "What is for you a good sleep quality?"

Network Plot is the result of the application of the estimator EBICglasso to the data, which cluster the variables according to the appropriate test. The Centrality and Clustering measures are also important. Centrality measures: betweness, which provides information related to the nodes that have the highest number of shortest paths; closeness corresponds to the inverse of the sum of all shortest paths from the node of interest to all other nodes; and the degree is the sum of the absolute input weights of that node.

Stability of the definitions provided by the participants

To determine the stability of the "good sleep quality" concept, n=53 participants were re-evaluated one year later. Of these, 52% used the same parameters to describe a good sleep quality compared to the year before (Figure 7). Table 3 shows the changes that occurred from moment 1 to moment 2 in the parameters used to describe a good sleep quality.

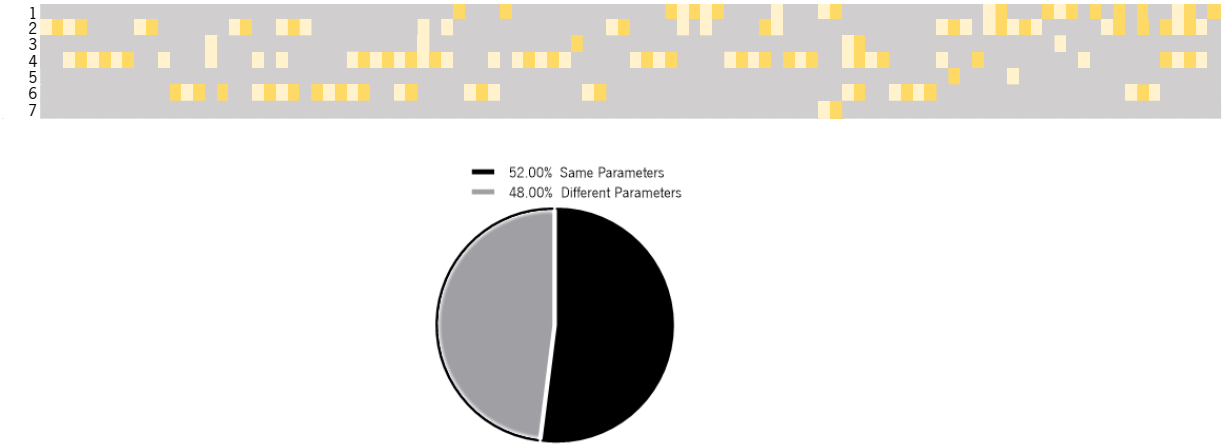


Figure 7. Graphic representation of the results from the longitudinal qualitative analysis to the meaning of "good sleep quality" and the frequency of individuals that use the same or different parameters in its description. The figure on top represent the results from the qualitative analysis, and the bottom plot the frequency in the response. The light yellow color concerns the first moment of evaluation and the dark yellow color represents the second moment of assessment, one year later. Numbers from 1 to 7 concern the units of analysis that resulted from the qualitative analysis: 1-Sleep duration; 2-Sleep continuity; 3-Sleep onset; 4-Sleep characteristics; 5-Room environment; 6-Final wake up and rise; 7-Next day performance. Each column represents one study participant.

Table 3. Observed changes in the parameters reported to define a good sleep quality from moment 1 to moment 2.

Moment 1	Moment 2
Sleep characteristics	Final Wake and Rise
Sleep onset; Sleep characteristics	Final wake and rise
Sleep characteristics; Final wake and rise	Final wake and rise
Sleep continuity; Sleep characteristics; Final wake and rise	Sleep continuity; Final wake and rise
Sleep continuity	Final wake and rise
Sleep continuity; Sleep onset; Sleep characteristics	Sleep characteristics
Sleep characteristics	Sleep onset
Sleep characteristics	Sleep duration; Sleep characteristics
Sleep duration; Sleep continuity	Sleep duration
Sleep characteristics	Sleep continuity; Sleep characteristics
Sleep duration; Sleep continuity	Sleep characteristics
Sleep continuity; Sleep characteristics	Sleep continuity; Room environment
Sleep continuity	Sleep characteristics
Sleep continuity; Room environment	Sleep continuity
Sleep continuity	Sleep duration
Sleep duration; Sleep onset	Sleep duration
Sleep characteristics	Sleep duration

Sleep continuity	Sleep duration; Sleep continuity
Final wake and rise	Sleep duration; Sleep continuity; Final wake and rise
Final wake and rise	Sleep continuity; Sleep characteristics
Sleep continuity; Seep characteristics	Sleep duration

Self-ratings of sleep quality and PSQI score

A moderate statistically significant association was found between self-ratings of sleep quality and PSQI global score ($r_{qualitative}$= -0.418, p<0.001; $r_{quantitative}$= -0.609, p<0.001), and between them and the sleep quality subdomain of PSQI ($r_{qualitative}$= -0.511, p<0.001; $r_{quantitative}$= -0.560, p<0.001). A strong and statistically significant association was found between self-ratings (R = -0.759, p<0.001) (Table 4). The percentage of poor sleepers identified by each of the assessment methods was also determined. Specifically, when using the PSQI global score (threshold of good sleep quality – 5; every score above 5 indicates poor quality sleep), 54.1% of the participants had poor sleep quality. If considering the qualitative self-report scale, 33.2% of participants presented poor sleep quality. Finally, 48.1% of the participants presented poor sleep quality if considering the self-report quantitative scale (see Appendix 1 for threshold determination).

Table 4. Association between different subjective measures scores

	PSQI_ global score	**PSQI_sbdn Sleep Quality**	**Qualitative report**	**Quantitative report**
PSQI_global score	___	___	___	___
PSQI_sbdn Sleep Quality	0.729	___	___	___
Qualitative report	- 0.418***	-0.511***	___	___
Quantitative report	-0.609***	-0.560***	0.759***	___

PSQI – Pittsburgh Sleep Quality Index; PSQI_sbdn Sleep Quality_ subdomain from the Pittsburgh Sleep Quality Index "Sleep Quality" – it is a self-report measure of sleep quality regarding the previous month; Spearman Test; *** significance level below 0.001.

Determinants of a good subjective sleep quality

Results regarding the differences between good and poor sleep quality groups that result from the different assessment modalities - PSQI global score, qualitative self-report and quantitative self-report – are presented in Table 5, Table 6 and Table 7. Briefly, good and poor sleep quality groups are different, no matter the assessment modality used to create them. However, the variables for which the differences exist vary. For PSQI-related groups, the differences exist for psychological morbidity (stress: U= 1905, p< .001; depression: U= 2315, p< .001; anxiety: U= 2448, p< .001) and neuroticism variables (U= 1096, p= .003) (Table 5).

Table 5. Mann-Whitney U Test results for PSQI global score.

	Statistic	p
Age	5537	0.038
Sex	6585	0.713
Work situation	6446	0.702
Marital Status	5834	0.035
ESS	1482	0.241
EADS_Stress	1905	**< .001***
EADS_Depression	2315	**< .001***
EADS_Anxiety	2448	**< .001***
Neuroticism	1096	**0.003***
Extroversion	1429	0.296
Openess to Experience	1380	0.184
Consciousness	1604	0.963
Positive Affect	1172	0.034
Negative Affect	1107	0.012
Time to rise after wake	2935	0.435
Bedtime routines/activities	5720	0.166

*p-value statistically significant at 0.003 (correction for multiple comparisons). Significant p's are represented in bold. Work situation: retired, employed, unemployed, student, domestic. ESS – Epworth Sleepiness Scale. EADS – Anxiety, Depression and Stress Scale. Personality traits neuroticism, extroversion, openness to experience and consciousness are derived from the NEO-FFI-21.

When the division of good and poor quality groups is performed based on the qualitative and quantitative self-reports, differences exist between good and poor sleep quality groups regarding age (U= 9195, p< .001) and marital status (U= 9348, p< .001) for the first method (Table 6), and age (U= 6692, p< .001), work situation (U= 7800, p= .003) and marital status (U= 6873, p< .001) for the latter (Table 7).

Table 6. Mann-Whitney U Test results for qualitative self-reports of sleep quality.

	Statistic	p
Age	9195	**< .001***
Sex	11544	0.261
Work situation	10282	0.008
Marital Status	9348	**< .001***
ESS	913	0.018
EADS_Stress	2241	0.016
EADS_Depression	2305	0.025
EADS_Anxiety	2383	0.052
Neuroticism	1246	0.923
Extroversion	961	0.054

	Statistic	p
Openess to Experience	1133	0.410
Consciousness	1167	0.540
Positive Affect	831	0.020
Negative Affect	1138	0.798
Time to rise after wake	5168	0.201
Bedtime routines/activities	10938	0.439

To an easier comparison between the different group creation methods, all are converted into: 0 – good sleep quality; 1 – poor sleep quality. *p-value statistically significant at 0.003 (correction for multiple comparisons). Significant p's are represented in bold. Work situation: retired, employed, unemployed, student, domestic. ESS – Epworth Sleepiness Scale. EADS – Anxiety, Depression and Stress Scale. Personality traits neuroticism, extroversion, openness to experience and consciousness are derived from the NEO-FFI-21.

Table 7. Mann-Whitney U Test results for quantitative self-report of sleep quality.

	Statistic	p
Age	6692	**< .001***
Sex	9333	0.742
Work situation	7800	**0.003***
Marital Status	6873	**< .001***
ESS	966	0.036
EADS_Stress	2074	0.010
EADS_Depression	2155	0.020
EADS_Anxiety	2422	0.201
Neuroticism	1064	0.345
Extroversion	998	0.156
Openess to Experience	1161	0.800
Consciousness	1191	0.968
Positive Affect	803	0.022
Negative Affect	1069	0.778
Time to rise after wake	4238	0.497
Bedtime routines/activities	8602	0.504

To an easier comparison between the different group creation methods, all are converted into: 0 – good sleep quality; 1 – poor sleep quality. *p-value statistically significant at 0.003 (correction for multiple comparisons). Significant p's are represented in bold. Work situation: retired, employed, unemployed, student, domestic. ESS – Epworth Sleepiness Scale. EADS – Anxiety, Depression and Stress Scale. Personality traits neuroticism, extroversion, openness to experience and consciousness are derived from the NEO-FFI-21.

After testing the differences, possible models for predictors of good and poor sleep quality were tested. Results indicate that individuals who have poor sleep quality (PSQI-derived groups) are more likely to present more depressive symptomatology (OR=1.34, p<.05) (Table 8). When considering the groups formation from qualitative or quantitative self-reports, individuals with poor sleep quality are most likely not married ($OR_{qualitative}$= 2.86, p<.001; $OR_{quantitative}$=2.21, p<.05) and, in the

qualitative-derivation of groups, are also more likely to spend more time in bed after waking up ($OR_{qualitative}$= 1.02, p<.005) (Table 9 and Table 10).

Table 8. Results from binomial logistic regression for predictors of good and poor sleep quality groups derived from PSQI global score

			Overall Model Test		
Deviance	**AIC**	**R^2N**	**χ^2**	**df**	**p**
63.9	75.9	0.491	32.3	5	< .001

Predictor	Estimate	SE	Z	p	Odds ratio
Intercept	-2.51689	1.0066	-2.500	0.012	0.0807
EADS_Stress	0.14010	0.1085	1.291	0.197	1.1504
EADS_Depression	0.29541	0.1488	1.986	**0.047**	1.3437
EADS_Anxiety	0.32626	0.1851	1.762	0.078	1.3858
Neuroticism	-0.01675	0.1654	-0.101	0.919	0.9834
Time to rise after wake	-0.00555	0.0266	-0.208	0.835	0.9945

Estimates represent the log odds of "PSQI_CLASS = poor sleep" vs. "PSQI_CLASS = good sleep". Reference group: "Good Sleep Quality". Statistically ignificant p's are represented in bold. EADS – Anxiety, Depression and Stress Scale. Personality trait neuroticism was derived from the NEO-FFI-21.

Table 9. Results from binomial logistic regression for predictors of good and poor sleep quality groups derived from qualitative self-report on sleep quality

			Overall Model Test		
Deviance	**AIC**	**R^2N**	**χ^2**	**df**	**p**
247	255	0.216	38.2	3	< .001

Predictor	Estimate	SE	Z	p	Odds ratio
Intercept	-2.7831	0.57787	-4.82	< .001	0.0618
Age	0.0145	0.01189	1.22	0.224	1.0146
Marital status	1.0497	0.31521	3.33	**< .001**	2.8569
Time to rise after wake	0.0159	0.00549	2.90	**0.004**	1.0160

Estimates represent the log odds of "Self-rated sleep quality_qualitative_transInv = 1" vs. "Self-rated sleep quality_qualitative_transInv = 0". Reference group: "Good Sleep Quality". Statistically significant p's are represented in bold.

Table 10. Results from binomial logistic regression for predictors of good and poor sleep quality groups derived from quantitative self-report on sleep quality

			Overall Model Test		
Deviance	**AIC**	**R^2N**	**χ^2**	**df**	**p**
230	240	0.183	27.6	4	< .001

Predictor	Estimate	SE	Z	p	Odds ratio
Intercept	-1.28969	0.79595	-1.62	0.105	0.275
Age	0.01548	0.01328	1.17	0.244	1.016
Work situation	-0.32097	0.20948	-1.53	0.125	0.725
Marital status	0.79259	0.31713	2.50	**0.012**	2.209
Time to rise after wake	0.00857	0.00506	1.69	0.090	1.009

Estimates represent the log odds of "Self-rated sleep quality_quantitative_transInv = 1" vs. "Self-rated sleep quality_quantitative_transInv = 0". Reference group: "Good Sleep Quality". Statistical significant p's are represented in bold.

Discussion

In the present work, we proposed to study the meaning of "good sleep quality" across the adult lifespan of community-dwellers, determining the most significant parameters and its stability throughout time. It was also of interest to determine the association between self-reports of sleep quality and the PSQI, as well as the predictors of good/poor subjective sleep quality. Individuals described "good sleep quality" and a "good nigh of sleep" using the same words, but the frequency of those differ according to the question. When addressing the stability of this definition, 52% of the individuals maintained their self-report (words) one year later. From the application of network analysis, the referred parameters for a "good sleep quality" and a "good night of sleep" tend to cluster separately, and when considering solely "good sleep quality" the most central nodes are "sleep continuity" and "final wake". There is a moderate association between the different measures of subjective sleep quality, with the predictors of this construct changing according to the type of measure used to form the groups.

The lack of consciousness about what happens during sleep, raise significant concerns towards the relevance of self-reports as a reliable tool. More so, when complaints of poor sleep are not translated into objective measures of sleep disturbances (Moul et al., 2002; Rosa & Bonnet, 2000; Unruh et al., 2008). However, self-reported measures are, in some cases, the best available tool for a proper sleep disturbance diagnosis. In fact, in many studies, self-reported tools are the only

that can be used to characterize a large number of individuals. Thus, how can we improve its quality and reliability?

One first step can be by clarifying the concepts addressed. For example, "sleep quality" has been differently conceptualized between studies (Akerstedt et al., 1994; Buysse et al., 1989; Goelema et al., 2018; Krystal & Edinger, 2008). Consequently, a high variability in results has been observed, as well as a prement difficulty in determining the real value of the construct. Adding to this, there are age-changes in sleep patterns and architecture (Mander et al., 2017) which increase the complexity towards the understanding of sleep complaints in middle-agers and older individuals. Age plays an important role in the variability of population-level sleep habits, despite not being a primary determinant of sleep timing (Rosipal, Lewandowski, & Dorffner, 2013). Here, in the present characterization of sleep patterns across the adult lifespan, it was interesting to observe that from middle age on, participants report turning off the lights later than bedtime, suggesting that they spent some time awake before laying to sleep. Another implication of this, concerns the time that it is registered as going to bed to sleep, and the effective/actual time when it happens. This has a real implication in the estimates of sleep onset and may suggested that the individual is taking longer to fall asleep than in reality. Other type of questions also emerge. Specifically, can these age-related changes contribute to the acceptance that complaints of poor sleep quality are within the normative spectrum, even when they are not? Can this be one of the factors contributing to the percentage of underdiagnosed individuals?

To determine the meaning of a good sleep quality across the adult lifespan, here we asked community-dwellers, ranging in ages from 18 to 87 years, to provide an answer to what they consider to be "a good night of sleep" and "a good sleep quality". Results showed that for a good night of sleep, "sleep duration" (e.g. sleep for a certain amount of hours) and "sleep continuity" (e.g. sleep all night without interruptions or with very few) were the most reported information. While, for a good sleep quality, the most stated information concerned "sleep continuity", "sleep characteristics" (e.g. having a good sleep or not having dreams or nightmares) and "final wake" (e.g. feeling rested or refreshed upon awaking). This distinction was quite interesting because it remained true one year later, suggesting a degree of stability in the distinction between concepts, and raising questions regarding the indiscriminant use of methods that seem to provide distinct information (or, at least, that are interpreted as distinct). In fact, this aspect might help explaining variability between studies' results. Still, it is also pertinent to highlight that some participants,

when assessed one year later, changed the parameters used to describe each of the questions, possibly suggesting that despite discriminating between questions, the distribution of the parameters might be flexible.

Interestingly, considering the meaning of a good sleep quality, the most reported parameters in our study ("sleep continuity", "sleep characteristics" and "final wake") are congruent to previous studies' results, even with those that used an inter-individual approach (Akerstedt et al., 1994; Domino, Blair, & Bridges, 1984; Webb, Bonnet, & Blume, 1976).

The use of network analysis to estimate the relation between all variables directly, instead of trying to reduce the structure of the variables to their shared information (latent variable modeling) is a relatively new and promising method for modeling interactions between large numbers of variables (Epskamp, Borsboom, & Fried, 2017). Interestingly, while in the first model all parameters were considered together (from the meaning of a good sleep quality but also from the meaning of a good night sleep), "sleep onset" was a central parameter of the model (also observed in Goelema and colleagues study (2018)). On the other hand, when considering only the parameters obtained in the sleep quality analysis, results showed not only that "sleep continuity" and "final wake" were central nodes to the obtained network, but that there was also a weak association between "final wake" and "next day performance". This suggests that it may be important a more broad approach to the sleep quality meaning in order to properly cover all the important aspects of it.

In a recent study from Goelema and colleagues, their results indicated "daytime functioning", "interruptions during the night" and "before bed state" as major aspects of sleep experience for lay people (Goelema et al., 2018). To a certain degree, our results are similar. Nonetheless, a direct comparison is not possible since they were less restrictive in what they consider for each category. For example, in the category "sleep characteristics", "other sleep parameters such as sleep onset latency, deep sleep and sleep duration" were considered; while, here we consider all the subjective aspects used to describe sleep (e.g. good sleep, restful sleep or components like with or without dreams or/and nightmares).

Overall, it appears that individuals judge their sleep quality retrospectively considering both their memory of nighttime sleep and their experience during the day (Ramlee et al., 2018; Ramlee, et al., 2017), specifically their feelings upon waking. Furthermore, when conceiving sleep quality judgement as a decision making progress, daytime functioning was more important for people to judge their sleep experience than the actual night of sleep itself (Ramlee et al., 2018; Ramlee et

al., 2017). These -feelings upon waking and the evaluation of their mood and daytime performance- resonate with previous work that suggest a significant role of daytime impairments in the genesis of insomnia complaints (Ramlee et al., 2017).

Considering that "sleep continuity" was the most mentioned category by our participants, here the progress of the night is of focus, which might also help explain feelings upon the final wake and its importance for our population. In fact, it was quite interesting to observe that often participants referred dreaming as indicator of poor sleep quality and that this trend has also been observed in other studies (Akerstedt et al., 1994; Goodenough, 1978). Those studies showed that the report of having no or few dreams was associated to fewer awakenings and, consequently, to the perception of dreaming as a proxy to sleep interruption and, consequently, as a signal of poor sleep. Furthermore, in the study from Goelema and colleagues (2008), participants indicated that their state of mind before bedtime was an import factor for the sleep experience, which has also been suggested by other studies (Åkerstedt et al., 2012; Eliasson et al., 2010). Interestingly, they pointed the link between categories, as stress before going to bed, which can promote longer sleep onset latency, more awakenings during the night and a shorter sleep duration (Akerstedt, 2006; Sadeh et al., 2004). Consequently, the individual may feel tired during the day.

With the present work, we extend on Goelema and colleagues (2018) and further explore differences in sleep quality conceptualization by determining the association between different measures of sleep quality and not only on PSQI subdomains, but also by exploring the determinants of sleep quality. Specifically, considering the association with PSQI subdomains, results showed that the categorization does not match with the questions of the PSQI. For example, PSQI questions relate more to the extremes of daytime functioning (e.g. 'During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?'), which does not always apply. For instance, while it is possible that people experience some degree of dysfunction during the day because of tiredness or not feeling refreshed, it is also possible that they do not experience problems with staying awake (Goelema et al., 2018). This point highlights the importance of a more comprehensive measure of sleep quality that can translate a continuous between health and disease. Following in the same line are the results concerning the association between self-reported measures of sleep quality (qualitative and quantitative) and PSQI (the standard measure for subjective sleep quality). A moderate association was observed, which made it clear for the need of a more comprehensive self-reported measure, because even though all

these measures assess the same construct, they are likely reflecting different aspects of sleep quality. Overall, it is clear that sleep quality has to be defined in a comprehensive manner. With this work it became clear that sleep quality is more than just sleep quantity, timing, simple stage structure, occurrence of pathologic events (Krystal & Edinger, 2008) or even one's satisfaction with his/her sleep (Ohayon et al., 2017). The need of a tool that can translate not only a little of each parameter used in the description of sleep quality, but that can also consider some of the known determinants of sleep is of great interest. Furthermore, with this work we also showed that the meaning of a good sleep quality does not differ with age. Nonetheless, further research is needed not only comparing different cultural groups with different sleep patterns and contexts, but exploring factors such as circadian rhythm, day-to-day variability, use of sleep medication, social conventions (e.g.,weekday/weekend distinction) or weather (e.g., availability of sunshine).

The understanding of the complex dynamic of perception and self-reported measures across the lifespan will cast some light in how we can obtain more reliable information in the clinic that can result in more efficient and adequate therapies. It was beyond the work scope to develop an index based in this qualitative definition of sleep quality. However, it should certainly be the next step and an approach similar to Akersted and colleagues (1994) can be followed. After their qualitative definition they asked individuals to rate each of the parameters and their overall sleep quality. Their results showed that sleep was rated "very good" if it contained 4% or less of waking, whereas "very poor" sleep corresponded to 24% or more of waking; it seemed that four minutes constituted a "very easy" sleep onset, in contrast, with "very difficult" that corresponded to a sleep latency of 100 min or more. Furthermore, "calmness of sleep" appeared maximal at 0.1 awakenings per hour or less and minimal at 0.5 awakenings per hour or more (Akerstedt et al., 1994) and they suggested that their results could be used as guidelines for qualitative interpretation of quantitative (but subjective) sleep parameters.

Some methodological aspects should be addressed. Given the heterogeneity in studies that focus on the subjective components of sleep quality, for the present study we aimed to focus on this subjective dimension without explore objective components of sleep quality.

To our knowledge, it is the first time that the same study determines the subjective meaning of sleep quality using not only a qualitative approach but also a network analysis of the data, exploring the association between different self-reported measures as well as the determinants of sleep quality considering the different measures. The choice to freely let the participants answer what

they consider to be the meaning of a good sleep quality was supported by the large number of participants, which confered some advantage to the approach given that having a large sample of individuals operationalizing the concept of a good sleep quality, provide less bias to the subjective interpretation of the phenomenon. Nonetheless, in future studies, it can be of interest to apply an automated analysis of free speech (Bedi et al., 2015) or even machine learning techniques.

With the present work we overcame some limitations of previous studies, namely the reduced number of participants and the lack of information about the stability of the definition of good sleep quality. These results can guide future research to provide suitable psychometric measures for normal sleepers, as well as the design of sleep data visualization applications in the context of health self-monitoring.

Conclusion

The present works contributes to the literature by providing information in a still highly debatable question: what is considered a "good sleep quality" for the general population. We were able to provide qualitative information that corroborates previous results with smaller sample sizes, but we also add the possibility of studying quantitatively some of the aspects that remained open from previous studies, namely what happens to the meaning of a good sleep quality with age and what are the weighs of mood and personality as determinants of the answer provided but also the self-rating of sleep quality.

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.

Contributions

LA, NS and NCS conceived the study. LA recruited the participants and collected the data with the help of Alexandra Sousa (a medical student). LA analyzed the data and wrote the first draft of the manuscript. All authors contributed to the final manuscript.

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Appendix 1

Quantitative self-report scale 0 to 100 threshold determination for a poor sleep quality

Methods

The first step was to invert (direct inversion) the scale in order to obtain the same direction as in PSQI – higher scores indicating poorer sleep quality. This step is crucial given that the standard measure considered for the receiver operating curve (ROC) method was PSQI, a standard measure of subjective sleep quality.

Results

The results from ROC are presented in Figure S1. Overall, the analysis demonstrated satisfactory discriminant validity with the area under the curve pointing for a threshold score of equal or below 27.5 for good sleep quality [75.8% (95% CI: 69–82.5%)].

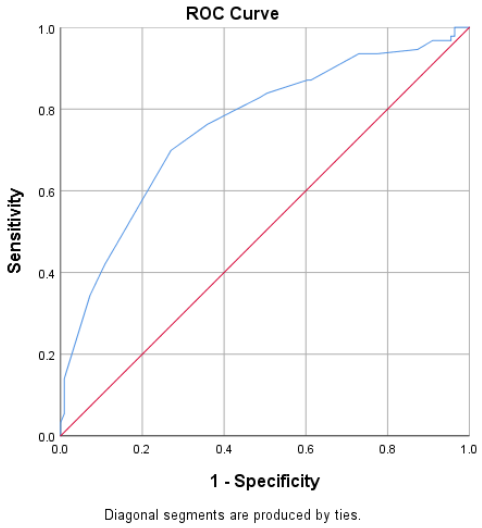

Figure S1. ROC curve of the quantitative (0-100) self-report scale. The area under the curve was 75.8% (95% CI: 69–82.5%).

CHAPTER IV

A short report on week-weekend variability of self-reported sleep patterns, routines and quality: preliminary results

Liliana Amorim, Nuno Sousa, Nadine Correia Santos

(In preparation)

A short report on week-weekend variability of self-reported sleep patterns, routines and quality: preliminary results

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Abstract

Sleep is a multidimensional phenomenon important for a vast set of biological and psychological processes. At its core, circadian and homeostatic processes regulate sleep, but external factors also interfere in these mechanisms. In fact, in our 24-h society, sleep schedules are often dependent on social schedules and personal routines. Thus, in this exploratory study, we propose to characterize the sleep patterns and quality of Portuguese community-dwellers across the adult lifespan (n=307; age range: 18-87 years, mean age: 46.6 ± 15), on week and weekend days. For this purpose, adult community-dwellers were recruited from health centers of the northern region of Portugal and asked about their sleep patterns and quality. Results show that throughout the adult lifespan, contrary to sleep latency that remains without change, sleep and wake times as well as sleep routines alter with time. These differences are more pronounced when observing weekend. As expected, reported sleep quality is better on weekends and, quite interestingly, Saturday was the day of the week most reported as the best for a good night of sleep. On the contrary, Sunday was the most reported day for a poor night of sleep. On this, the main reasons provided were related to work or school as for the worst night and being with family and having time for personal matters (e.g. exercise, going out, do not have to go to work) as reasons for a good night of sleep. Overall, these preliminary results highlight the importance of social and personal factors in sleep quality constrainings, providing new insights on possible factors that can be used to improve sleep health.

Key words: week-weekend variability; sleep routines; adulthood; subjective sleep quality.

Introduction

Sleep-wake behavior is one of the most overt manifestations of circadian rhythmicity in humans. This rhythmicity is relevant for the anticipation of events by the organism, both at micro- and macro-levels. In fact, it is now known that the circadian rhythm not simply regulates sleep-wake cycles, but also influences the molecular biology of individual cells and organ systems (Brainard, Gobel, Scott, Koeppen, & Eckle, 2015; Gilman, 2018). Its importance has been shown not only on biological processes such as cerebral clearance (Xie et al., 2013) or immunity (Asif, Iqbal, & Nazir, 2017), but also in neuropsychological processes such as social behavior (Simon & Walker, 2018) or cognition (Walker, 2008; Walker & Stickgold, 2004). However, in our 24-h society, disruptions are quite common, including on sleep patterns/habits. Sleep alterations also occur with age, with studies showing that there is a decrease in sleep efficiency, an increase in the time awake after sleep onset, a shift towards earlier bed and waking times and an increase in sleep complaints (Mander, Winer, & Walker, 2017; Ohayon, 2004; Ohayon & Paiva, 2005). Considering that subjective estimates of poor sleep quantity are not always predictive of sleep complaints (McCrae et al., 2003; Fichten et al., 1995), it is necessary to determine the factors associated. For this, it is not only relevant to determine the different sleep patterns throughout adulthood, but also the variation in sleep quality over this period. Week and weekend day's variations might aid in the understanding of this phenomenon. Hence, in the present work, it is aimed to characterize sleep patterns and routines of adult Portuguese community-dwellers on week and weekend days' and determine its association with self-reports of sleep quality.

Methods

Ethical Considerations

The study protocol received full ethical approval from the local and national ethics committees and was conducted in accordance with the principles expressed in the Declaration of Helsinki (59th amendment). Volunteers were explained the study protocol and those who agreed to participate provided written informed consent.

Study design

The design of the study is provided in Figure 1 and has also been described elsewhere (see chapter IV methods section). Briefly, potential participants were randomly and consecutively invited to enroll

the study, while awaiting for a regular medical appointment, in public primary health care centers, of the northern region of Portugal. Inclusion criteria was that all participants were Portuguese adults aged 18 years and above. The primary exclusion criteria included participants' choice to withdraw from the study, inability to understand informed consent and working night shifts. A total of 307 participants were considered for the cross-sectional analysis and from those, 53 were invited and agreed to be reassessed one year later.

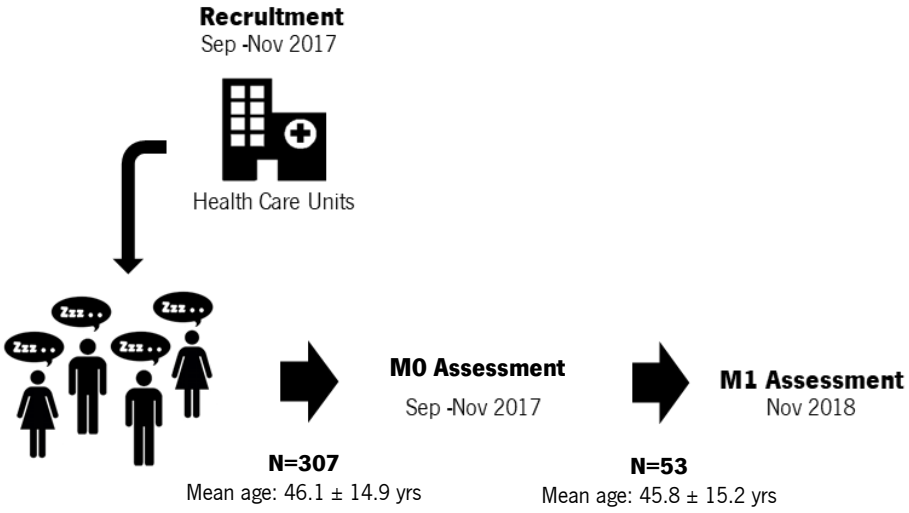

Figure 1. Study design.

Participants were asked about their sleep routines, schedules and sleep quality and sleepiness through the use of the questionnaires Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS).

Statistical analysis

GraphPad (Prism, V7.04) was used for graphic representations and JASP (V0.9.0.1) for statistical analysis. Descriptive analysis was performed and mean, standard deviation, and percentages (%) were used to characterize the sample. Participants with missing values were excluded from the analysis that involved that particular variable(s). Normality assumptions were tested and statistical tests chosen accordingly. Differences between week and weekend days were determined regarding sleep patterns, routines and quality. Subjective sleep quality regarding the previous month and overall sleepiness were also determined. The level of significance was set at 0.008 (correction for multiple comparisons).

Results

Participants' characterization

This cohort is constituted by 307 adult Portuguese community-dwellers, with a mean age (SD) of 45.8 ± 15.7 and of which, 63.7% are female. Most participants had 13 or more years of formal education (39.2%), were married (66.1%) and employed (67.9%). For more detail information on sociodemographic features see Table 1.

Table 1. Sociodemographic and psychological characterization of the cohort (n=340).

		Cohort		Sub-sample	
		n (%)	Mean ± SD	n (%)	Mean ± SD
Age		–	46.1 ± 14.9	–	45.8 ± 15.2
Sex	Female	195 (63.7%)		31 (58.7%)	
	Male	112 (36.3%)		22 (41.5%)	
Education	0 to 4 yrs	37 (12.0%)		2 (3.8%)	
	5 to 9 yrs	66 (21.6%)		11 (20.8%)	
	10 to 12 yrs	82 (27.2%)		19 (35.8%)	
	13 or more yrs	118 (39.2%)		21 (39.6%)	
Marital Status	Single	80 (26.1%)		14 (26.4%)	
	Married	203 (66.1%)		38 (71.7%)	
	Divorced	18 (5.9%)		1 (1.9%)	
	Widowed	6 (2.0%)		0	
Household	Alone	18 (5.9%)		0	
	Husband/Wife	112 (36.6%)		23 (43.4%)	
	Family[#]	171 (55.9%)		30 (56.6%)	
	Others[*]	6 (1.6%)		0	
Occupation	Retired	39 (12.8%)		3 (5.7%)	
	Employed	207 (67.9%)		47 (88.7%)	
	Unemployed	26 (8.5%)		1 (1.9%)	
	Student	28 (9.2%)		2 (3.8%)	
	House keeper	5 (1.6%)		0	
Living Place	City	167 (54.8%)		18 (34.0%)	
	Rural	140 (45.2%)		35 (66.0%)	

Cohort – n=307; Subsample= 53, however, some participants did not provide all information asked, so, it is possible that in the characterization of the variables there is a mismatch.
#Family - includes any family members, e.g. children, parents, grandparents; *Others – e.g. friends, boyfriend/girlfriend, professional residencies.

Sleep patterns, routines and quality

Regarding sleep patterns, results show statistically significant differences between week and weekend days in some parameters, namely, at the time at which participants went to bed ($Z=1202$, $p<0.001$), the time they turn off the lights ($Z=1163$, $p<0.001$), the time at which they woke up ($Z=367$, $p<0.001$), in the amount of time to rise after waking up ($Z=1411$, $p<0.001$) and on the amount of hours slept ($Z=285$, $p<0.001$). Specifically, the mean difference between weekend and week is: 1 hour for bedtime, 5 minutes for sleep latency, 1,75 hours for waking time and 1,5 hours for the amount you sleep (Table 2).

Table 2. Sleep patterns characterization (n=307).

	Week (median, IQR)	Weekend (median, IQR)	p*
Bedtime (time)	23.0 (1.30)	24.0 (1,50)	<.001
Light off (time)	23.5 (1.00)	24.0 (2.00)	<.001
Sleep latency (min)	15 (21.25)	10 (25.00)	.022
Time spent in routines after going to bed (min)	30 (45)	30 (45)	<.001
Wake up time (time)	7.0 (0.83)	8.0 (2.50)	<.001
Time to rise after waking up (min)	5 (13.00)	10 (25.00)	<.001
Sleep duration (hours)	7 (2.00)	8 (1.63)	<.001
Alarm clock use (yes)	172 (56.4%)#	56 (18.7%)#	<.001

IQR refers to interquartile range; p refers to *p*-value reflecting statistical significance; #considering that it is a dichotomous variable it is reported n (%). Furthermore, the statistical test used was McNemar Test. Test performed to assess week-weekend differences: Wilcoxon test. *p-value was adjusted for multiple comparisons; statistical significance is verified with values lower than 0.008.

The use of alarm clock during week and weekend days was also explored. Results show that in weekdays 52.3% of the participants used an alarm clock and that this percentage drastically decreased during the weekend to 17.6%.

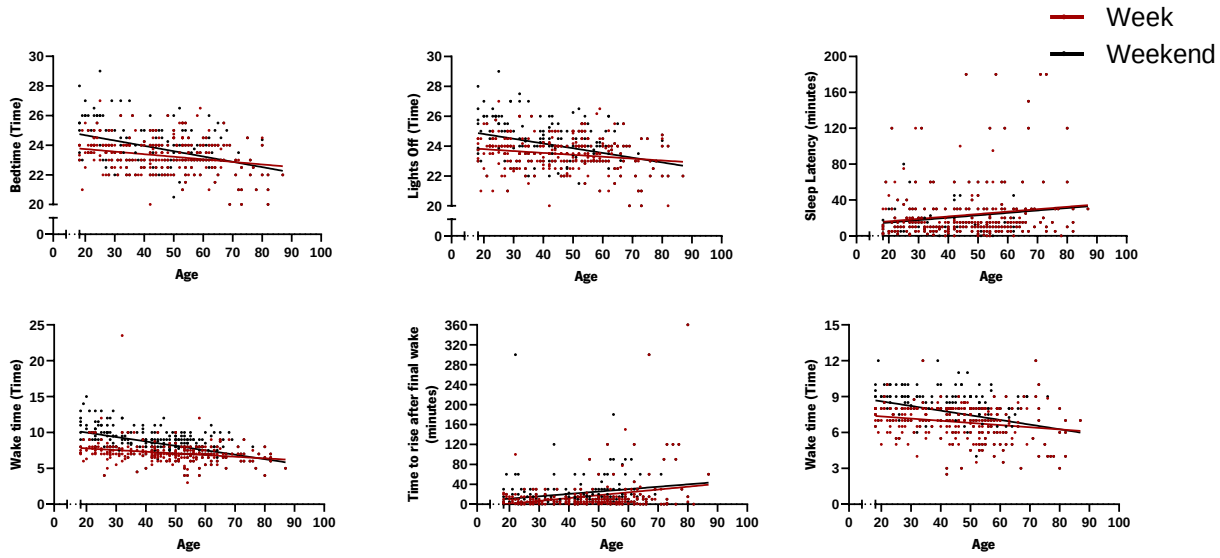

Figure 1. Characterization of the Rest Patterns of a sample of community-dwellers from 18 to 86 yrs on week and weekend days, by age and sex (n=307).

Age appears also as a relevant factor when analyzing sleep patterns. Specifically, an increase in age was associated, both on week and weekend days, to earlier sleep times (rhoweek= -0.194, p<0.001; rhoweekend= -0.343, p<0.001) and earlier wake up times (rhoweek= -0.302, p<0.001; rhoweekend= -0.531, p<0.001). With age, the reported hours of sleep also decreased (rhoweek= -0.197, p=0.001; rhoweekend= -0.371, p<0.001) (Figure 1). Figure 2 presents the distribution of sleep parameters in men and women, throughout the lifespan. A statistically significant association

is observed between sex, age and sleep latency (F(2, 290)Week=7.90, p<0.001, R2 adj=0.045; F(2, 290)weekend=8.52, p<0.001; R2 adj=0.049), both on week and weekend days.

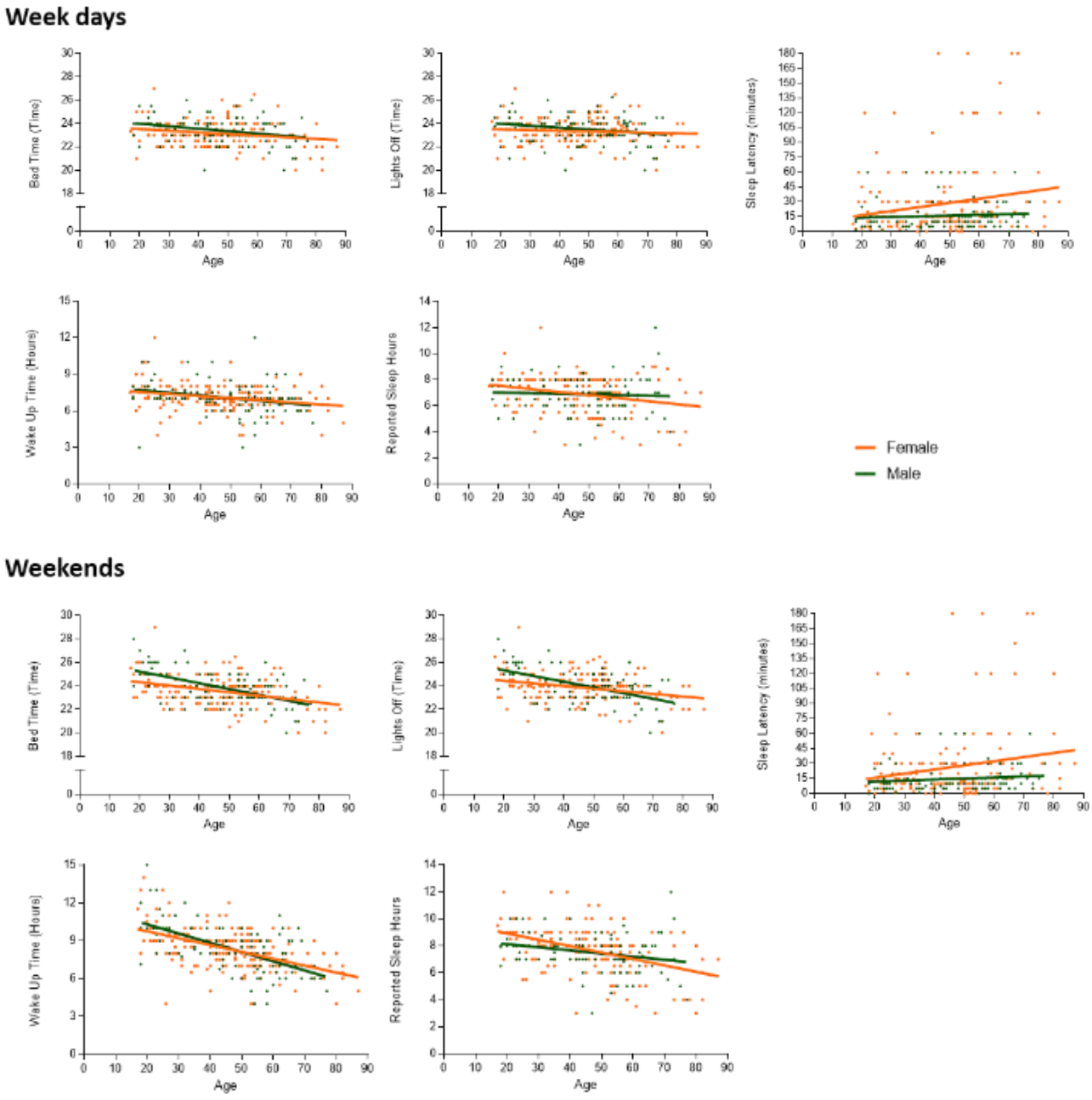

Figure 2. Characterization of the Rest Patterns of a sample of community-dwellers from 18 to 86 yrs on week and weekend days, by age and sex (n=307).

Sleep routines at bedtime where also explored. On this, results show that during weekdays, 52.6% of the participants reported some type of activity when going to bed. This percentage slightly increased during weekend days (54.67%) with individuals spending also a little more time in those (Figure 3). In fact, considering only the participants that reported spending time in, at least, one of

these routines, results indicate that the total amount of time ranged from 5 to 210 minutes. Participants were engaged for more time in bedtime activities during weekends ($Mean_{week}$= 46.68 minutes vs $Mean_{weekend}$= 54.38 minutes; $t_{(147)}$= 3.106, p=0.002, R^2=0.062).

Activities	Work/week days (n, %)	Time (min)	Off/weekend days (n, %)	Time (min)
Go to bed to sleep	137 (47,40%)	n.a.	131 (45,33%)	n.a.
TV in bed before sleep	102 (35,29%)	42,16	109 (37,72%)	48,36
Phone in bed before sleep	46 (15,92%)	25,98	49 (16,96%)	29,5
Read in bed before sleep	35 (12,11%%	28,07	35 (12,11%)	31,61
PC use in bed before sleep	10 (3,46%)	37,22	10 (3,46%)	48,33
Radio in bed before sleep	1 (0,35%)	180	1 (0,35%)	180
Embroide in bed before sleep	1 (0,35%)	180	1 (0,35%)	180
Cross-words in bed before sleep	1 (0,35%)	50	1 (0,35%)	50

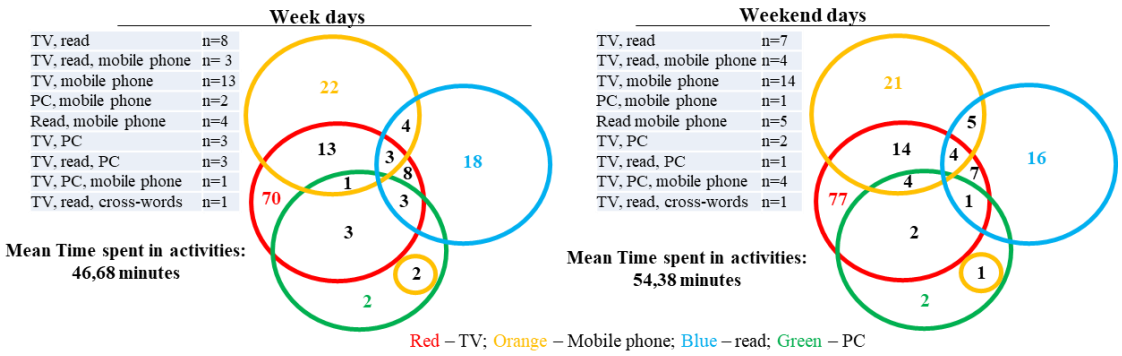

Figure 3. Characterization of the Rest Patterns of a sample of community-dwellers from 18 to 86 years on weekdays and weekend, by age (n=307).

When testing the influence of age and sex, results show that with age the time spent in bedtime activities increase both in week and weekend days (F_{week}= 17.56, p<0.001; $F_{weekend}$= 9.44, p=0.0025), and differences regarding men and women were only observed for weekdays, with men reporting more time in bedtime activities when at younger age, and women at higher ages.

Exploratory longitudinal study and determination of week-weekend subjective sleep quality

To determine how sleep patterns, routines and quality evolve throughout one year, an exploratory longitudinal study was developed. Results show only a statistically significant difference for bedtime between Moment 0 and Moment 1 (Z=199.5, p=0.003). Furthermore, the differences between week and weekend days were maintained in Moment 1, similarly to Moment 0 (Table 3).

Table 3. Longitudinal characterization of sleep patterns characterization of the subsampled cohort (n=53).

	Moment 0		Moment 1·	
	Week (median, IQR)	**Weekend (median, IQR)**	**Week (median, IQR)**	**Weekend (median, IQR)**
Bedtime	23.0 (1.20)	23.5 (1.60)	23.0 (1.60)	23.3 (1.6)
Light off	23.5 (1.20)	23.8 (1.50)	23.0 (1.50)	24.0 (2.0)
Sleep latency	10 (10)	10 (12.5)	15min (12.5)	10min (10.0)
Wake up time	7.0 (0.67)	8.5 (0.75)	07:00 (0.75)	8:00 (1.63)
Time to rise after waking up	8.75 (10.0)	15 (7.5)	10min (7.5)	15min (15.0)
Sleep duration	7 (1.50)	8 (2.0)	7h (2.0)	8h (2.0)
Alarm clock use#	35 (71.4%)	11 (22%)	31 (69.8%)	11 (23.4%)

·Moment 0 – occurred 12 months after Moment 0. #n (%)

Our participants were also asked about the variation of their sleep quality in week and weekend days. A statistically significant difference was found, with reported sleep quality being better in weekends (Figure 4).

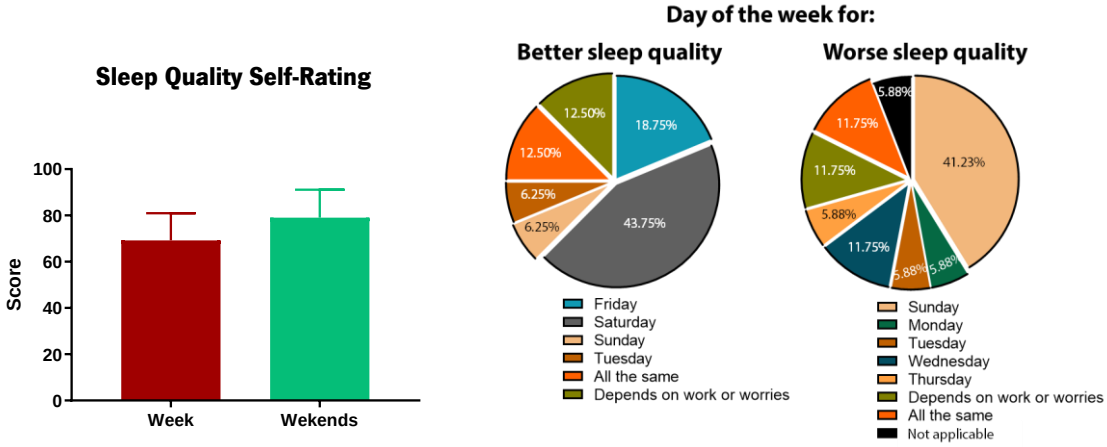

Figure 4. Subjective sleep quality on week and weekend days.

Interestingly, Saturday was the day of the week most reported has the better night sleep and Sunday the worse night in terms of sleep quality. Factors provided by participants as related to this was worrying about work for a worse night on Sunday as well as becoming alone (children return to rent home for university classes during the week) and exercise or off day as reason for the better sleep quality night (Figure 4).

Discussion

In our 24-h society, the demands of the different roles that each individual performs can promote unhealthy lifestyles, particularly in what concerns to sleep habits and routines, which can ultimately result in sleep disruption and deprivation. While sleep disturbances have been shown to affect a wide variety of biological systems and processes (Medic et al., 2017; Potter et al., 2016; Wickens et al., 2015; Finan et al., 2015), irregularities in sleep schedule have been mostly associated to poor subjective sleep quality (Monk et al., 2003). Interestingly, these irregularities in sleep scheduling can often be part of a coping strategy to deal with sleep loss. For instance, it is not uncommon for the the individual to engage in daytime napping or to extend nighttime sleep during weekends or other periods free from social or work obligation, with the purpose of obtaining a few extra hours of sleep. Thus, studying week and weekend variation of sleep can provide valuable information to develop new strategies and models to overcome some of the challenges that are still associated to sleep complaints and disturbances.

Differences between week and weekend days have been mostly addressed in adolescents and young adults (Hasler et al., 2012; Gradisar et al., 2008). However, as we can see with the present results, this variation also occurs across the adult lifespan, although less proeminently at older ages. In Portugal, very few epidemiological studies have focused on the sleep topic, and the last one dates from more than a decade ago. Thus, this work enabled a first characterization of sleep patterns and quality in a sample of adults within its normative ageing process. Overall, differences were found between sexes and across ages in what concerns sleep patterns and routines. Furthermore, the mean difference between weekend and weekdays was of 1 hour for bedtime, 5 minutes for sleep latency, 1,75 hours for waking time and 1,5 hours for the amount you sleep. In order to provide a better comprehension of how sleep habits and routines are in Portugal and what are the aspects that influence them, we should continuing exploring these data and how it evolves throughout time. Thus, it will be important to finish the follow-up assessments and to start building predictive models, but also, to expand the recruitment beyond the convinence sample, so that it will be possible to generalize the results to the adult Portuguese population.

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.

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Contributions

LA, NS and NCS designed the study. LA performed data collection and analysis. LA wrote the first draft. All authors wrote the final manuscript and gave input to the work.

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CHAPTER V

Poor sleep quality associates with decreased functional and structural brain connectivity in normative ageing: a MRI multimodal approach

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Poor sleep quality associates with decreased functional and structural brain connectivity in normative ageing: a MRI multimodal approach

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Abstract

Sleep is a ubiquitous phenomenon, essential to the organism homeostasis. Notwithstanding, there has been an increasing concern with its disruption, not only within the context of pathological conditions, such as neurologic and psychiatric diseases, but also in health. In fact, sleep complaints are becoming particularly common, especially in middle-aged and older adults, which may suggest an underlying susceptibility to sleep quality loss and/or its consequences. Thus, a whole-brain modeling approach to study the shifts in the system can cast broader light on sleep quality mechanisms and its associated morbidities. Following this line, we sought to determine the association between the standard self-reported measure of sleep quality, the Pittsburgh Sleep Quality Index (PSQI) and brain correlates in a normative ageing cohort. To this purpose, 86 participants (age range 52 to 87 years) provided information regarding sociodemographic parameters, subjective sleep quality and associated psychological variables. A multimodal magnetic resonance imaging (MRI) approach was used, with whole-brain functional and structural connectomes being derived from resting-state functional connectivity (FC) and probabilistic white matter tractography (structural connectivity, SC). Brain regional volumes and white matter properties associations were also explored. Results show that poor sleep quality was associated with a decrease in FC and SC of distinct networks, overlapping in right superior temporal pole, left middle temporal and left inferior occipital regions. Age displayed important associations with volumetric changes in the cerebellum cortex and white matter, thalamus, hippocampus, right putamen, left supramarginal and left lingual regions. Overall, results suggest that not only the PSQI global score may act as a proxy of changes in FC/SC in middle-aged and older individuals, but also that the age-related regional volumetric changes may be associated to an adjustment of brain connectivity. These findings may also represent a step further in the comprehension of the role of sleep disturbance in disease, since the networks found share regions that have been shown to be affected in pathologies such as depression and Alzheimer's disease.

Keywords: Pittsburgh Sleep Quality Index; PSQI; MRI; Whole-brain modeling; Brain Connectivity; resting-state.

Introduction

Sleep is a recurring and reversible neurobehavioral state that involves reduced responsiveness to external stimuli and is frequently accompanied by postural recumbence and behavioral quiescence (Carskadon and Dement, 2011). Propensity to sleep is determined by the interaction of the circadian rhythm ('process C'), controlled by the suprachiasmatic nucleus, and a sleep homeostatic process ("process S"), that increasingly drives the need for sleep as a function of the time spent awake (Borbély, 1982; Borbély et al., 2016). For the individual to thrive and efficiently cope with the waking day demands, guidelines advise a human adult to sleep seven to nine hours every day (Hirshkowitz et al., 2015) and to have sleep continuity parameters (i.e. sleep latency, awakenings >5 minutes, wake after sleep onset and sleep efficiency) within a specific range (see Ohayon et al., 2017 for details). In fact, having a 'good sleep' ensures metabolic homeostasis, cerebral clearance, adequate immune function and overall good cognitive and mental status (Cirelli and Tononi, 2008; Freeman et al., 2017; Irwin, 2015; Shokri-Kojori et al., 2018; Stickgold, 2006; Tononi and Cirelli, 2006; Xie et al., 2013). However, factors such as inappropriate exposure to light or food, lifestyle schedules, work, or psychological morbidity can interfere with the appropriate timing and duration of the sleep/wake cycle, leading to wide-range adverse effects on health (Archer and Oster, 2015; Schwartz et al., 1999; Stickgold, 2006; Wulff et al., 2010). More so, age also emerges as a critical modifier of sleep-wake patterns, being responsible for a shorter overall sleep duration and increase in sleep fragmentation and fragility, mostly after the fifth decade of age (Mander et al., 2017). In addition, in an increasingly older population (United Nations, Department of Economic and Social Affairs, Population Division, 2013), sleep dissatisfaction is one of the most common complaints in primary care (Aikens and Rouse, 2005) contributing not only for a growth vulnerability to disease, but also for a considerable economic burden, consequence of the costs of sleep aids and work absenteeism (Hillman et al., 2006). In addition, the dyad sleep-depression is of relevant weight since not only sleep problems may underlie an increased risk for the middle-aged or older individuals to be depressed (Almeida and Pfaff, 2005), but are also a robust predictor of incident depression (Livingston et al., 1993; Mallon et al., 2000).

In view of these associations and comorbidities, and because many neurological and psychiatric disorders share underlying brain network disturbances (Buckholtz and Meyer-Lindenberg, 2012; Deco and Kringelbach, 2014; Uhlhaas and Singer, 2012), it is vital to determine how one's sleep complaints and perceptions affect neural circuitries and overall biological systems. On this, the

Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989; Landry et al., 2015), a standard subjective measure of overall sleep quality, may provide important and clinically relevant insights. In fact, magnetic resonance imaging (MRI) studies using this composite measure have revealed an association between poor subjective sleep quality and reduced volume within the right superior frontal cortex in cross-sectional analyses, as well as a widespread increased rate of atrophy in frontal, temporal and parietal regions in longitudinal analyses (Sexton et al., 2014). Poor sleep has also been associated with alterations in functional connectivity (FC) of resting state (e.g. default mode network) and attentional networks (De Havas et al., 2012; Kaufmann et al., 2016; Sämann et al., 2010; Scullin, 2017), amygdalar circuits (Shao et al., 2014), as well as in the dorsal nexus-dorsolateral prefrontal cortex connection (Bosch et al., 2013). However, different measures of sleep quality are considered in different studies and most of them tend to evaluate how specific networks behave under strict experimental protocols (e.g. sleep deprivation protocols) or in target populations (e.g. mostly young adults or individuals with sleep pathologies), thus providing a limited view of the occurring mechanisms and processes.

A whole-brain multimodal MRI approach can, therefore, provide new insights into general principles of brain function from health to disease (Deco and Kringelbach, 2014). Hence, in the present study, we used this approach to explore the association between subjective sleep quality (PSQI global score) and FC and structural connectivity (SC). PSQI global score will provide an overall value of the previous month sleep quality. Specifically, we hypothesized that this measure will provide an important overall view of sleep disruption parameters that may affect FC of a network with nodes in frontal, temporal, parietal and occipital regions during restful wake, given the described behavior of these regions during sleep and in sleep pathologies. Furthermore, because PSQI evaluates sleep quality over a 1-month period, we also hypothesized that it will be possible to observe the impact of poor sleep quality in SC.

Methods

Ethics Statement

The present study was conducted in accordance with the principles expressed in the Declaration of Helsinki (59th amendment) and was approved by the local and national ethics committees. All participants gave informed written consent after the study aims were explained.

Participants

The participants included in the present study are part of a cohort recruited for the SWITCHBOX Consortium project (www.switchbox-online.eu/). They were randomly selected from Guimarães and Vizela local area health authority registries as representative of the general middle-aged and older Portuguese population for age, gender and education (Costa et al., 2013; Santos et al., 2014). Primary exclusion criteria included inability to understand the informed consent, participant choice to withdraw from the study, incapacity and/or inability to attend the MRI session, dementia and/or diagnosed neuropsychiatric and/or neurodegenerative disorder (medical records). A sample of 120 individuals was invited to the follow-up assessment based on neuropsychological scores. 86 individuals agreed to be re-evaluated (n=17 declined to participate; n=2 could not be reached; n=6 could not be reassessed due to multiple schedules incompatibilities) and from these, 77 were able to perform an MRI scanning session. All MRI acquisitions were obtained during the afternoon to avoid morning and night circadian fluctuations.

Questionnaires

All participants were asked, in a structured interview format given participants' age and educational status, about the following information: sociodemographic; subjective sleep quality (Pittsburgh Sleep Quality Index, PSQI) (Buysse et al., 1989; Del Rio João et al., 2017); depressive symptoms (Geriatric Depression Scale, GDS) (Yesavage et al., 1982); sleepiness (Epworth Sleepiness Scale, ESS) (Johns, 1991; Santos, 2001). In the questionnaires used, the higher the score, the poorer the outcome. Furthermore, in the present study, PSQI global score was considered as a continuum.

Actigraphy

Actigraphy is a valuable tool in the study of sleep and circadian rhythms given its ability to measure 24 over 24-h activity (Ancoli-Israel et al., 2003; Landry et al., 2015). ActiSleep+ (Firmware 2.2.1; ActiGraph, LLC, Pensacola, Florida, USA) is a small (4.6cm x 3.3cm x 1.5cm), electronic, light weight (19 grams), water proof, tri-axial wrist-worn device, that measures activity "counts" and was initialized at a sample rate of 30Hz to record activities for free-living conditions. The obtained information was then downloaded using ActiLife 6 software (v 6.9.0; ActiGraph, LLC, Pensacola, FL, USA) and integrated into 60-sec epochs for posterior analysis using Cole-Kripke algorithm (Cole et al., 1992). In the present study, 64 participants (of the 86 invited for the study) agreed to use

the monitor in the non-dominant wrist for a seven-day period. For each participant, the mean of the seven days for the following parameters were obtained: total time in bed, total sleep time, sleep latency, sleep efficiency, wake after sleep onset, number of awakenings and time of each awakening. Participants were instructed to never remove the monitor. However, in case of removal, they were instructed to register it in the sleep diary they had to fill for each of the seven days. Similarities between the period of assessment using ActiSleep+ and the month assessed by PSQI was addressed by asking the participants for that information. For the analysis of the actigraphy information, data from 31 participants was admissible. Exclusion criteria included differences between the actigraphic week and the month assessed by PSQI (n=8); less than 6 days of actigraphic data (n=3); sleep diaries not matching quality standards (e.g. not properly filled) (n=22).

MRI data acquisition

The imaging session was performed at the Hospital of Braga (Braga, Portugal) on a clinical approved Siemens Magnetom Avanto 1.5 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany), using a 12-channel receive-only head-coil. All acquisitions were performed between 2 p.m. and 6 p.m. to control for circadian fluctuations. The imaging protocol consisted of three types of acquisitions: structural, resting-state (rs) and diffusion weighted imaging (DWI). For the structural acquisition, a 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was used. The used parameters were: 176 sagittal slices, TR/TE=2,730/3.48 ms, flip angle=7°, slice thickness=1.0 mm, in-plane resolution=1.0×1.0 mm^2, FoV=256×256 mm. For the rs-fMRI acquisition, a blood oxygen level dependent (BOLD) sensitive echo-planar imaging (EPI) sequence was used and the following parameters were used: 30 axial slices, TR=2.0 s, TE=30 ms, flip angle=90°, slice thickness=3.5 mm, slice gap=0.48 mm, in-plane resolution=3.5×3.5 mm^2, FoV=224×224 mm and 190 volumes. During this resting state scan, participants were instructed to be awake, with their eyes closed, as motionless as possible and they should try not to think of anything in particular and let the mind wander. We choose this approach because our population are middle-aged and older individuals that usually tend to feel very uncomfortable inside the MRI machine, thus moving a lot. Therefore, to reduce the discomfort and movement inside the MRI machine, we choose to ask the participants to stay awake with their eyes closed. In the end of this session, all participants confirmed that they had not fallen asleep. For the Diffusion Weighted Imaging (DWI) scan, a spin-echo echo-planar imaging (SE-EPI) sequence with the following

parameters was used: TR=8800 ms, TE=99 ms, FoV=240×240 mm, acquisition matrix=120×120, 61 slices, slice thickness= 2 mm, 30 non-collinear gradient directions with b=1000 s/mm^2, one b=0 s/mm^2 acquisition and two as the total number of repetitions.

MRI data pre-processing

A certified neuro-radiologist visually inspected all acquisitions to confirm that they were not affected by critical head motion (certifying its quality) and that participants had no brain lesions/pathology. The structural scans of each subject were segmented using FreeSurfer toolkit version 5.1 (http://surfer.nmr.mgh.harvard.edu), which implements a semi-automated segmentation workflow and allows the segmentation of Gray Matter (GM), White Matter (WM) and subcortical regions. For a complete description of the stages of processing implemented in this pipeline see Desikan, Destrieux and Fischl works (Desikan et al., 2006; Destrieux et al., 2010; Fischl et al., 2002, 2004). Fischl and colleagues (Fischl et al., 2002) validated the procedures against manual segmentations, with robust results across sessions, scanner platforms, updates, and scanner field strengths (Jovicich et al., 2009). The quality of the segmentations was visually inspected and corrections conducted as indicated in Freesurfer guidelines. For the present study, values of intracranial volume (ICV), total gray matter volume (GMV), white matter hypointensities volume (WMSA) and regional brain volumes according to Desikan (Desikan et al., 2006) and Destrieux (Destrieux et al., 2010) segmentations were considered.

rs-fMRI data pre-processing was performed using FMRIB Software Library (FSL v5.07; http://fsl.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004) tools. The first five volumes of the rs-fMRI acquisition were removed to allow the habituation of the subjects to the EPI sequence noise and environment, as well as to avoid the spin history effects on the first volumes and the confounding effects over those (Friston et al., 1996). Furthermore, given that our population are middle-aged and older individuals, and likely extra sensitive to the MRI environment, we considered this step to be important. The remaining data was corrected for slice timing (for Siemens interleaved acquisition) followed by head motion correction using the mean image as reference. In order to reduce potential contamination of motion on functional connectivity, motion scrubbing (Power et al., 2012) was also performed, in order to identify and further exclude time-points where head motion could be critical. One subject was excluded for having more than 10 motion-contaminated time-points. Each subject functional dataset was then spatially normalized to the Montreal

Neurological Institute (MNI) standard space through an indirect procedure that included: (i) skull stripping of the mean image of the functional acquisition and of the structural acquisition allowing the isolation of brain signal; (ii) rigid-body registration of the mean functional image to the skull stripped structural scan; (iii) affine registration of the structural scan to the MNI T1 template; (iv) nonlinear registration of the structural scan to the MNI T1 template using the affine transformation previously estimated as the initial alignment; (v) nonlinear transformation of the functional acquisition to MNI standard space trough the concatenation and application of the rigid-body transformation and the nonlinear warp followed by resampling to 2 mm isotropic voxel size. Linear regression of motion parameters, mean WM and cerebrospinal fluid (CSF) (extracted using the FSL white matter and CSF tissue priors) signal and motion outliers was performed and the residuals of the regression were band-pass temporal filtered (0.01–0.08Hz) and used for the subsequent analysis.

Pre-processing of diffusion data was performed using the FSL toolbox FDT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT) (Behrens et al., 2003). The pre-processing consisted of: i) eddy current and movement correction and matching rotation of the diffusion directions; ii) isolation of brain signal by extraction of the skull; for the probabilistic tractography analysis this was followed by iii) calculation of the non-linear normalization from MNI space to the subjects native space by concatenating an affine registration from structural to the diffusion space to the inverse of the previously described warp map from native structural to MNI space; iv) the normalization was applied to the AAL atlas to bring all its ROIs to native diffusion space; v) local modeling of the diffusion parameters was done using bedpostx which runs Markov Chain Monte Carlo sampling to build voxel wise distributions of the diffusion parameters; for the voxel wise diffusion parameters analysis ii) was followed by vi) the diffusion tensor was fitted to the data and the scalar maps were computed. This was achieved using DTIFIT that is part of the FDT Toolbox. DTIFIT fits a diffusion tensor model at each voxel and generates the scalar maps of fractional anisotropy (FA) and mean diffusivity (MD), and eigenvector and eigenvalue maps. Axial Diffusivity (AD) scalar map was defined as the principal diffusion eigenvalue (L1) and radial diffusivity (RD) as the mean of the second and third eigenvalues ((L2+L3)/2).

MRI data analysis

A connectomics approach was used for resting state functional and diffusion structural connectivity analysis and the networks were built using the Anatomical Automatic Labeling (AAL) atlas. For the functional data analysis, the mean signal across time was extracted for each of the 116 ROIs and for each subject. Then, Pearson correlations between each possible pair of regions were computed and a symmetric adjacency matrix R, where each entry rij represents the Pearson correlation coefficient between the time series of region i and j, was obtained. These matrices were transformed into Z-score matrices by the application of Fisher's r-to-Z transformation to assure the normality of the correlation coefficients. To increase the statistical power of the analysis, the network-based statistic (NBS) procedure implemented in the NBS toolbox (https://sites.google.com/site/bctnet/comparison/nbs) was used [Zalesky et al., 2010]. NBS evaluates the null hypothesis at the level of interconnected edges (i.e., subnetworks) surviving a predefined primary threshold (instead of considering the null hypothesis at the single edge level). The null hypothesis assumes that a sub-network with similar number of edges, surpassing the primary threshold, occurs by chance. It is recommended the use of different primary thresholds in order to capture different effects. In the present study, three different primary thresholds were used ($P < 0.01$, $P < 0.005$, $P < 0.001$) to capture less pronounced but more extent effects (less stringent primary threshold— $P < 0.01$) as well as localized and pronounced effects (most stringent threshold— $P < 0.001$). Five thousand permutations were performed and networks were considered significant at a network size corrected level of $P < 0.05$. To simplify visualization of the results, when similar networks were found across the threshold levels, we favor the presentation of the network surviving the higher threshold. BrainNet viewer (http://www.nitrc.org/projects/bnv/) was used for visualization purposes.

For the diffusion data probtrackx from the FDT toolbox (Behrens et al., 2007) was used to estimate the structural connectivity by calculating the number of streamlines connecting each pair of ROIs from the atlas, through sampling the principle directions previously calculated at each voxel. A total of 5000 streamlines were attempted per-voxel. This resulted in a matrix representing the number of streamlines reaching from one ROI to the other. This matrix was normalized by first dividing each line by the number of voxels x number of streamlines and then the upper and lower triangles were averaged to give an undirected connectivity. To filter the connectivity matrix, keeping only connections significantly different from zero, a one-sample t-test was done at each connection. Only

connections with a *p* lower than 0.01 were considered. To test the structural networks the same procedures for NBS described for functional connectivity were applied. Voxel-wise statistical analysis of scalar maps was performed using tract-based spatial statistics (TBSS) procedures (Smith et al., 2006), also implemented in FSL, following thresholding option TFCE (Threshold-Free Cluster Enhancement). For TBSS, first, the FA maps of each participant were slightly eroded and the end slices were zeroed, so that potential outliers from diffusion tensor fitting could be removed. Then, a non-linear registration was applied to align all FA images to a 1x1x1 mm standard space. In order to perform this, the FA image from each subject was nonlinearly registered to each other in order to find the most representative one (i.e., the one that requires the least warping to align all images) that served as the study specific template. This template image was then affine transformed into Montreal Neurological Institute (MNI) 152 standard space and each FA map was transformed into standard space by combining the nonlinear transformation to the FA target with the affine transformation into MNI space. Then, all FA images were averaged and the resulting image was skeletonized. The resultant skeleton image was thresholded at 0.3 so that skeleton regions including multiple tissue types could be removed. Finally, all scalar maps (FA, MD, AD and RD) were projected onto the mean FA skeleton using the transformations applied to the FA images.

Statistical analysis

Statistical analysis using SPSS version 22 (IBM, SPSS, Chicago, IL, USA) was used to determine the association between psychological, actigraphic, clinical and sociodemographic variables. The normality assumption for each variable was tested and non-parametric tests used when the assumption was not met. Bonferroni correction was used for multiple comparison testing and the significance level was set at $p<0.003$.

For the statistical testing of FC and SC it were considered: a Network Based Statistics (NBS, https://sites.google.com/site/bctnet/comparison/nbs) (Zalesky et al., 2010) approach, corrected for the size of the network, and a model that included GDS total score, PSQI global score, the interactions "PSQI x GDS", "PSQI x Age" and "PSQI x Sex" (as independent variables), age, sex and years of education (as covariates). NBS tests the hypothesis in two stages: first, at each possible individual network connection by applying a user defined significance threshold; second, by identifying sub-networks composed of connections whose significance surpasses the threshold and determining its significance according to the network size. The sub-networks significance was

calculated by comparing their sizes to the distribution of the size of sub-networks obtained through 5000 random permutations of the original hypothesis. Because different thresholds can yield topologically different networks, three thresholds were tested at $p<0.01$, $p<0.005$ and $p<0.001$. If the networks found at different thresholds are found to be equivalent, only the most significant one will be presented and discussed. The statistical analysis of the skeletonized maps of FA, MD, AD and RD was performed using permutation-based cross-subject statistics implemented in randomize, distributed with FSL. The model created was then used to test the main effect of PSQI variable and the PSQI by age, sex, years of formal education and GDS interactions. Ten thousand permutations were performed in the inference of each contrast of interest.

Volumetric data statistical analysis was performed ROI-wise using Matlab R2009b software (www.mathworks.com). A mix of Desikan (Desikan et al., 2006) and Destrieux (Destrieux et al., 2010) areas were considered for the subdivision of brain regions to be analyzed and a regression model considering sex, age, education, GDS total score, PSQI global score, ICV, the interactions "PSQI x Age" and "PSQI x sex" (independent variables) and the ROI volume of each area (dependent variable) was used. The choice of this regional brain areas was performed considering the most relevant areas regarding sleep that have been considered in different studies. White matter hypointensities and non-white matter hypointensities were also analyzed under this model. Bonferroni correction was used for multiple comparisons testing.

Results

Cohort characterization

The study sample was composed by 46 males and 40 females, with a mean age of 67.40 (±8.155) years and a median of 4 (IQR=3) years of education. More than half of the participants were married (77.9%), retired (75.6%) and presented a body mass index (BMI) above the considered normal range (93% with BMI above 25). 20% of the participants were on benzodiazepines use. See Table 1 for more details.

Table 1. Cohort characterization in terms of socio-demographic factors and clinical and psychological parameters.

		n (%)	Mean (±SD)
Socio-demographic parameters			
Age			67.4 (±8.155)
Sex	Male	46 (53.5%)	
	Female	40 (46.5%)	
Education			4 (3)[#]
Marital status	Single	1 (1.2%)	
	Married	67 (77.9%)	
	Divorced	3 (3.5%)	
	Widowed	15 (17.4%)	
Household	Alone	9 (10.5%)	
	Partner	38 (44.2%)	
	Family	39 (45.3%)	
Occupational status	Retired	65 (75.6%)	
	Employed	15 (17.4%)	
	Unemployed	6 (7.0%)	
Clinical parameters			
Weight (kg)			74.15 (±11.175)
Height (cm)			1.581 (±0.091)
BMI			29.40 (±3.539)
BP Systolic			133.50 (±39.827)
BP Diastolic			71.34 (±31.610)
Medication[¥]			
Insulin	Yes	1 (1.2%)	
Anti-diabetic	Yes	16 (18.6%)	
Anti-hypertensive	Yes	46 (53.5%)	
Aspirin	Yes	13 (15.1%)	
Anti-Inflamatory non-histeroid	Yes	11 (12.8%)	
Colestherol	Yes	39 (45.3%)	
Psychopharmacological	Yes	21 (24.4%)	
Benzodiazepines_CNS suppressors	Yes	20 (23.3%)	
Proton Pump Inibitors	Yes	28 (32.6%)	
Anti-Acids_H2 inibitors	Yes	4 (4.7%)	
Psychological parameters			
PSQI			7 (7.25)[#]
GDS			8 (10)[#]
ESS			7 (7.75)[#]

[¥]5.8% of participants do not present information regarding medication intake. [#]Median (IQR); BP Systolic= Systolic Blood Pressure; BP Diastolic; Diastolic Blood Pressure; CNS suppressors= Central Nervous System Suppressors; PSQI= Pittsburgh Sleep Quality Index global score; GDS= Geriatric Depression Scale; ESS= Epworth Sleepiness Scale.

Subjective sleep quality associates with sociodemographic and clinical variables

Almost half (49%) of the participants had poor sleep quality (PSQI global score higher than 5). No statistically significant differences were found for PSQI global score and sex (U=766.00, p=0.180). No statistically significant association was found between PSQI global score and depressive symptomatology (GDS; rho=0.279, p=0.011) but depressive symptoms and PSQI subdomains "Day Dysfunction" (rho=0.342, p=0.002), "Sleep Disturbance" (rho=0.377, p<0.001) and "Medication" (rho=0.421, p<0.001) were found to be associated. Furthermore, education was negatively correlated with the frequency of sleep medication intake (rho=-0.337, p=0.002) and with depressive symptoms (rho=-0.474, p<0.001). Results are presented in detail in Table 2.

Table 2. Correlation between subjective sleep quality and demographic, clinical and psychological parameters.

	Age	Education	Weight	BMI	BP Systolic	BP Diastolic	GDS	Epworth	PSQI Tota	PSQI Quality	PSQI Latency	PSQI Duration	PSQI Efficienc	PSQI Disturbanc	PSQI Medicatio
Education	**-.341****														
Weight	-.209	.190													
BMI	.090	**-.213***	.666**												
BP Systolic	**.227***	-.059	.053	**.217***											
BP Diastolic	**-.451****	**.248***	**.278****	.082	.321**										
GDS	.007	**-.474*****	.016	**.350****	.063	-.015									
Epworth	-.085	.009	**.273***	**.314****	-.157	-.006	**.254***								
$PSQI_{Total}$	-.075	-.167	.014	.127	.179	**.234***	**.279***	-.060							
$PSQI_{Quality}$	-.107	-.031	.139	.190	.108	**.246***	.213	.038	.690**						
$PSQI_{Latency}$	-.021	-.135	-.070	.021	.192	**.223***	**.248***	-.141	.788**	.533**					
$PSQI_{Duration}$	**-.224***	.069	-.031	-.115	-.088	.131	-.051	-.122	.604**	.398**	.358**				
$PSQI_{Efficiency}$	.021	-.111	.106	.195	.050	.110	.091	-.041	.679**	.320**	.531**	.578**			
$PSQI_{Disturbance}$	-.133	-.105	.140	.203	.047	.140	**.377*****	**.322****	.589**	.393**	.398**	.215*	.256*		
$PSQI_{Medication}$	.038	**-.337*****	-.115	.096	.149	.053	**.421*****	-.002	.595**	.340**	.386**	.127	.150	.430**	
$PSQI_{Day\ Disfunction}$	-.131	-.188	.139	**.322****	.123	.105	**.342*****	.048	.498**	.291**	.268*	.226*	.215*	.381**	.387**

Statistic test used: Spearman's rho; *Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed); ***Correlation is significant at the 0.003 level (Bonferroni correction). Significant results are highlighted in bold. BMI – Body Mass Index; BD Systolic – Systolic Blood Pressure; BP Diastolic – Diastolic Blood Pressure; PSQI – Pittsburgh Sleep Quality Index; GDS – Geriatric Depression Scale; ESS= Epworth Sleepiness Scale.

Subjective sleep quality associates with actigraphic parameters

To complement subjective sleep quality information, we asked a random sub-sample of participants to wear an actigraphic device concomitantly to the fill of a sleep diary for a 7-day period. No differences were found regarding age, depressive symptomatology and subjective sleep quality between this sub-sample and the total cohort (Table 3).

Table 3. Differences regarding age, PSQI global score, GDS and ESS between the original cohort and the subsample that used actigraphy.

	All cohort		Sub-sample		
	Mean (±SD)	Min-Max	Mean (±SD)	Min-Max	P
Age	67.4 (±8.16)	52-84	65.48 (±8.46)	52-84	0.26
$PSQI_{total\ score}$	7 (7.25)$^{\#}$	0-20	7 (10)$^{\#}$	0-20	0.1
GDS	8 (10)$^{\#}$	1–28	8 (11)$^{\#}$	0-28	0.88
EPW	7 (7.75)$^{\#}$	0–20	6.5 (7)$^{\#}$	0-18	0.92

$^{\#}$Median (IQR)

A description of the obtained actigraphy variables is presented in Table 4. Overall, this subsample went to bed in median at 23:06h and got up in the morning in median at 8:17h. Took aproximatly 6minutes to fall asleep and sleep for approximately 8h.

Table 4. Cohort characterization in terms of actigraphy variables.

Actigraphy derived parameters	Median (IQR)
Bed time	23:06 (1.94)
Out of bed	08:17 (1.98)
Sleep latency	6.17 (10.43)
Sleep efficiency	85.81 (8.46)
Total Time in Bed	550.71 (162.43)
Total Sleep Time	483.86 (126.33)
Wake After Sleep Onset	74 (42.86)
# awakenings	15.20 (8.86)
Avg time awakenings	4.33 (2.50)

"Bed time" respects the time participant went to bed; "Out of bed" concerns the hour of the day people get out of bed; "Sleep Latency" corresponds to the amount of minutes participants take to fall asleep; "Sleep Efficiency" is calculated automatically by ActiLife program; Total Time in Bed (TTB) and Total Sleep Time (TST) are presented in number of minutes, as well as WASO (Wake after sleep onset); # awakenings corresponds to the number of awakenings; Avg is the average of time of the awakenings.

PSQI domain associates with actigraphy-derived parameters

Results concerning the correlation between PSQI dimensions and actigraphy-derived sleep parameters revealed an association between the actigraphy-derived measures "Total Time in Bed" (TTB) and "Total Sleep Time" (TST) and the PSQI subdomain "Efficiency" (rho_{TTB}=0.583, p=0.001; rho_{TST}=0.597, p<0.001). Results also showed that sleepiness and the actigraphy-derived "Wake After Sleep Onset" were correlated (WASO, rho= 0.550, p=0.002) (Table 5).

Table 5. Correlation between subjective sleep quality, sleepiness, depressive symptoms and actigraphic parameters.

	PSQI total	PSQI Quality	PSQI Latency	PSQI Duration	PSQI Efficiency	PSQI Disturbance	PSQI Medication	PSQI DayDisfunction	Epworth	GDS	Actigraphy Bed Time	Actigraphy Wake Time	Actigraphy Latency	Actigraphy Efficiency	Actigraphy TTB	Actigraphy TST	Actigraphy WASO	Actigraphy #Awkenings
$PSQI_{total}$																		
$PSQI_{Quality}$	.811**																	
$PSQI_{Latency}$	.827**	.712**																
$PSQI_{Duration}$	.624**	.499**	.401*															
$PSQI_{Efficiency}$	.686**	.573**	.700**	.513**														
$PSQI_{Disturbance}$	.582**	.485**	.549**	.217	.277													
$PSQI_{Medication}$	.550**	.388*	.264	.275	.393*	.297												
$PSQI_{DayDisfunction}$	.580**	.294	.294	.292	.117	.473**	.529**											
Epworth	-.065	-.051	-.090	-.118	-.034	.278	.063	.248										
GDS	**.477****	**.391***	**.356***	.201	**.480****	.267	**.675****	**.357***	.142									
$Actigraphy_{BedTime}$	-.117	.126	-.272	.160	-.281	-.211	-.175	-.126	-.046	**-.408***								
$Actigraphy_{WakeTime}$	.238	.321	.276	-.060	**.387***	.115	.094	.105	.282	.127	.097							
$Actigraphy_{Latency}$	-.075	-.095	-.110	-.166	-.039	.064	.025	.013	.232	.188	-.249	.190						
$Actigraphy_{Efficiency}$	.123	.105	.117	.098	.043	.125	.175	.035	**-.483****	.064	.004	-.252	-.589**					
$Actigraphy_{TTB}$	**.382***	.202	**.495****	-.129	**.583*****	.289	.324	.202	.220	**.466****	-.688**	.574**	.307	-.204				
$Actigraphy_{TST}$	**.432***	.241	**.498****	-.070	**.597*****	.347	**.456****	.277	.150	**.589****	-.688**	.462**	.081	.142	.912**			
$Actigraphy_{WASO}$	.105	.065	.142	-.063	.275	.053	.003	.092	**.550*****	.152	-.219	.535**	.547**	-.886**	.572**	.269		
$Actigraphy_{\#Awkenings}$	.230	.236	.188	.199	.319	.077	.082	.100	.277	.122	-.161	.395*	.508**	-.638**	.455*	.194	.721**	
$Actigraphy_{AvgTAwkenings}$	-.068	-.177	.034	-.243	.055	-.065	-.068	-.064	.352	.096	-.312	.097	.029	-.458**	.323	.236	.500**	-.133

Statistic used: Spearman's rho; *Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); ***Correlation is significant at the 0.003 level (Bonferroni correction). In bold, statistically significant results are highlighted. PSQI – Pittsburgh Sleep Quality Index; Epworth – Epworth Sleepiness Scale; GDS – Geriatric Depression Scale. Actigraphy: Bed Time – time participant went to bed; Wake Time – time participant got up; TTB (Total Time in Bed) – total amount of time spent in bed; TST (Total Sleep Time) – number of minutes scored as sleep during time-in-bed; Latency – number of minutes from lights out until the first epoch of recorded sleep; Efficiency – calculated as (TST/TTB)×100; WASO (Wake After Sleep Onset) - number of minutes scored as wake after sleep onset; # Awakenings – total number of transitions to wake from sleep; Avg T Awakenings – average time of each transitions to wake from sleep.

Brain connectivity is associated with subjective sleep quality

The association of subjective sleep quality with brain connectivity was then assessed using a whole-brain multimodal approach with a restrict connection threshold of $p<0.001$ and correcting for the size of the network. Graph properties are presented in table 6.

Results revealed that individuals with poor sleep quality (i.e. higher PSQI global score) had decreased FC in a network with its principal nodes in bilateral inferior parietal regions (nodes 61 and 62) projecting to frontal (nodes 5, 9 and 15), temporal (nodes 81, 82, 84 and 85) and supramarginal (node 64) regions, as well as to the insula (node 30) and Rolandic Operculum (node 18) (network p=0.034, 13 connections; Figure 1A; Table 7). A statistically significant negative association was also found between "Age x PSQI" interaction and FC of a network with its principal nodes in the left inferior occipital (node 53) and left inferior parietal regions (node 61), as well as with the precuneus (nodes 67 and 68) (network p=0.0042, 13 connections; Figure 1B; Table 7). This network also comprised nodes in the right hippocampus (node 38), left middle temporal region (node 85), right inferior parietal region (node 62) and right rectus (node 28). Further analysis of "Age x PSQI" interaction revealed an inflection point at 67 years of age (Figure 1B), after which variations in PSQI global scores produced higher FC alterations when compared to the younger individuals of the cohort. In addition, the association between the amount of fibers connecting different brain areas and the PSQI global score revealed that the most altered connections involved left lingual (node 47), left caudate (node 71), right orbital medial frontal (node 26) and left rectus (node 27) nodes (network p=0.0344; Figure 1C; Table 7). We next explored the structural connection patterns within the patterns of functional interactions. Data showed that there was no overlapping network of the SC and FC associated to subjective sleep quality, but only specific nodes, namely, the right superior temporal pole, left middle temporal and left inferior occipital regions (Figure 2). The left middle temporal region was an overlapping node for the three networks found.

White matter properties and subjective sleep quality

No statistically significant results were found regarding the association of white matter properties and sleep quality.

Volumetric changes and subjective sleep quality

Age and depressive symptomatology, but not PSQI global score, were significantly correlated with regional brain volumes (Table 8). Specifically, an increase in age was associated to a decrease in the volumes of cerebellum white matter (left: r2=0.742, p<0.001; right: r2=0.674, p<0.001), cerebellum cortex (left: r2=0.643; p=0.01; right: r2=0.632, p=0.013), thalamus (left: r2=0.531; p=0.009; right: r2=0.543; p=0.001), hippocampus (left: r2=0.463; p=0.011; right: r2=0.421; p=0.004), right putamen (r2=0.414; p=0.033), left lingual (r2=0.341; p=0.014) and left supramarginal (r2=0.472; p=0.032). Furthermore, while increases in white matter hypointensities (r2=0.427; p=0.003) were associated to increased age, a negative association is observed between the depressive symptomatology measured by GDS and lower left putamen volumes (r2=0.415; p=0,046).

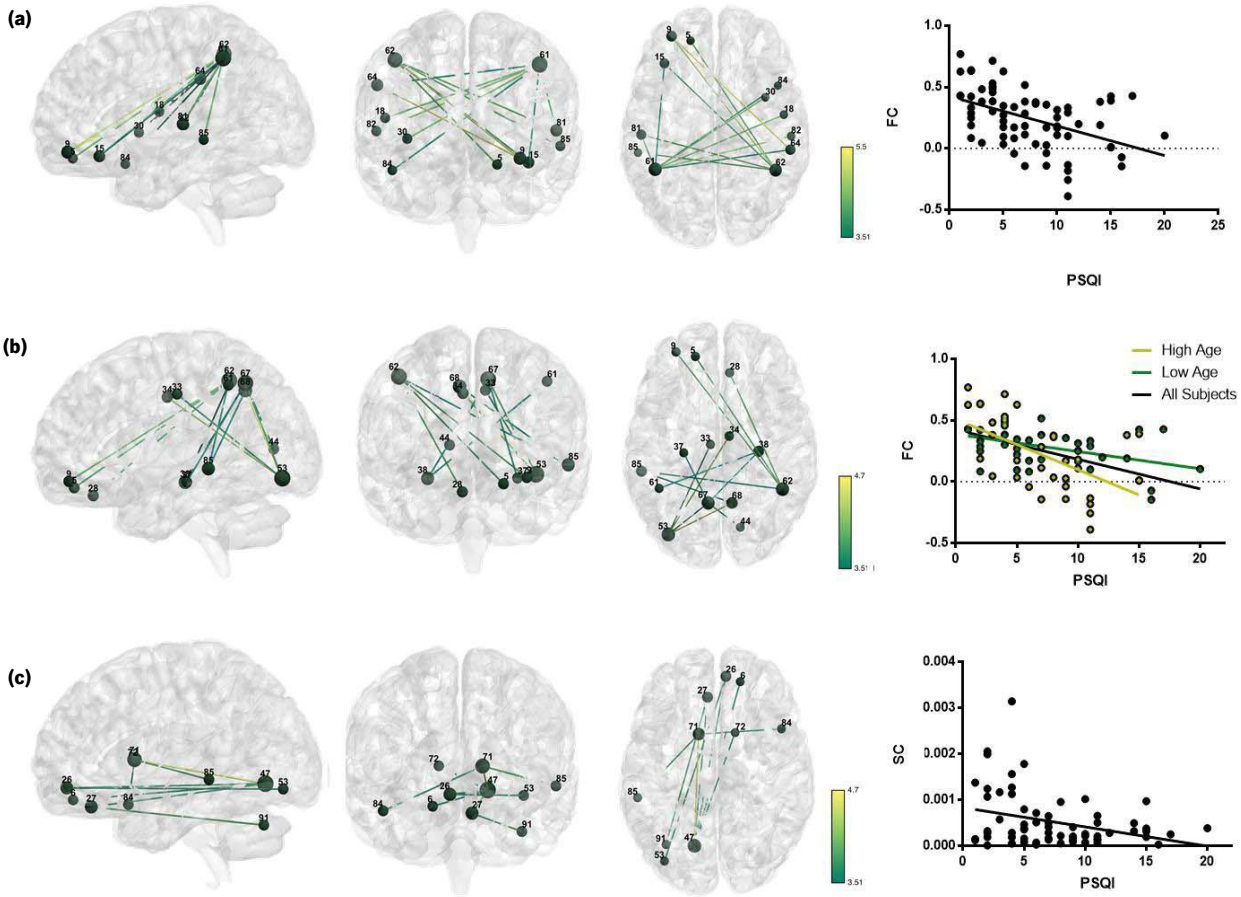

Figure 1. Whole-brain networks with altered functional and structural connectivity (FC and SC) in association with subjective sleep quality using p=0.0001 as primary threshold. **Color scheme:** higher connectivity from green to yellow; Nodes: Larger nodes, higher structural connectivity. **(a)** FC in association with PSQI (controlled for age, sex and GDS); **(b)** FC in association with "Age x PSQI interaction" (controlled for sex and GDS); **(c)** SC in association with PSQI (controlled for age, sex and GDS). **Numbers' legend:** (5) Frontal_Sup_Orb_L; (6) Frontal_Sup_Orb_R; (9)

Frontal_Mid_Orb_L; (15) Frontal_Inf_Orb_L; (18) Rolandic_Oper_R; (26) Frontal_Med_Orb_R; (27) Rectus_L; (28) Rectus_R; (30) Insula_R; (33) Cingulum_Mid_L; (34) Cingulum_Mid_R; (37) Hippocampus_L; (38) Hippocampus_R; (44) Calcarine_R; (47) Lingual_L; (53) Occipital_Inf_L; (61) Parietal_Inf_L; (62) Parietal_Inf_R; (64) SupraMarginal_R; (67) Precuneus_L; (68) Precuneus_R; (71) Caudate_L; (72) Caudate_R; (81) Temporal_Sup_L; (82) Temporal_Sup_R; (84) Temporal_Pole_Sup_R; (85) Temporal_Mid_L; (91) Cerebelum_Crus1_L.

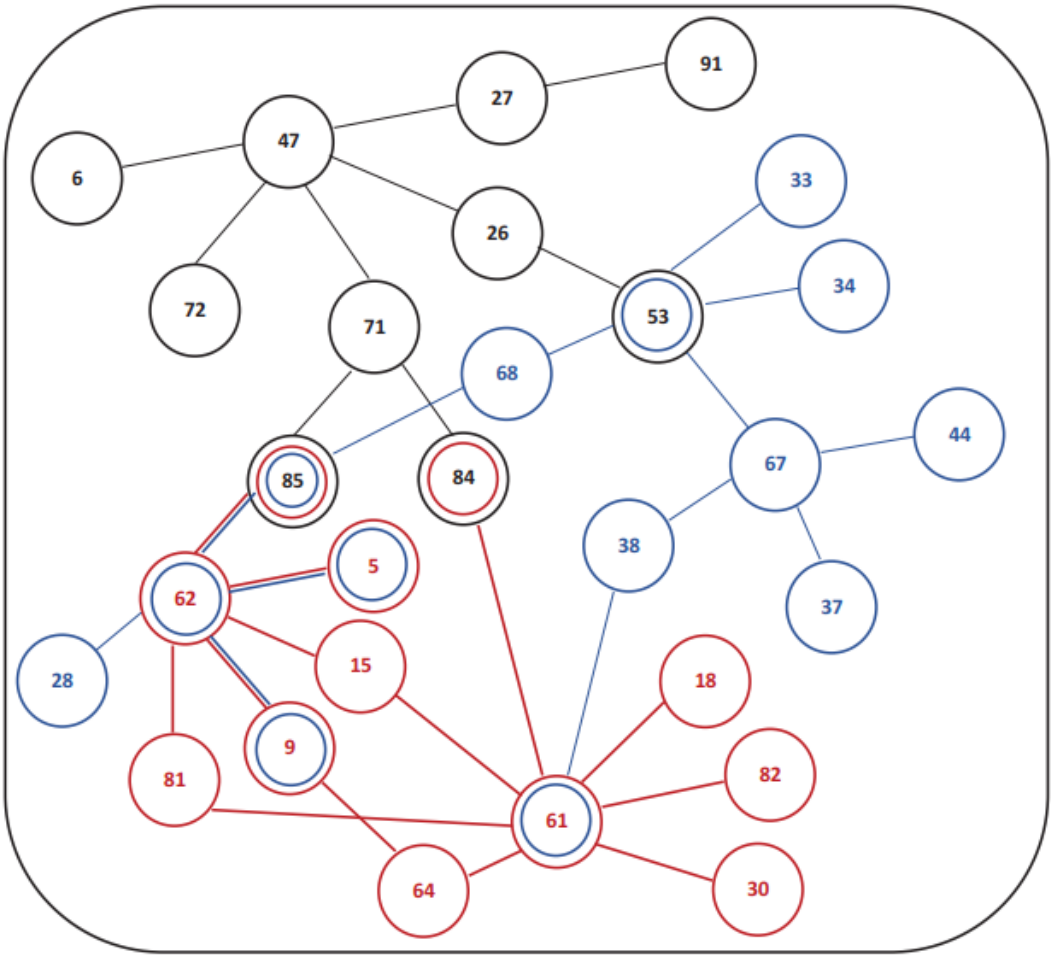

Figure 2. Schematic design or functional and structural connectivity in association with subjective sleep quality. (Red) Association PSQI and FC; (Blue) Association FC and "Age *x* PSQI" interaction; (Black) Association PSQI and SC. **Number legends**: (5) Frontal_Sup_Orb_L; (6) Frontal_Sup_Orb_R; (9) Frontal_Mid_Orb_L; (15) Frontal_Inf_Orb_L; (18) Rolandic_Oper_R; (26) Frontal_Med_Orb_R; (27) Rectus_L; (28) Rectus_R; (30) Insula_R; (33) Cingulum_Mid_L; (34) Cingulum_Mid_R; (37) Hippocampus_L; (38) Hippocampus_R; (44) Calcarine_R; (47) Lingual_L; (53) Occipital_Inf_L; (61) Parietal_Inf_L; (62) Parietal_Inf_R; (64) SupraMarginal_R; (67) Precuneus_L; (68) Precuneus_R; (71) Caudate_L; (72) Caudate_R; (81) Temporal_Sup_L; (82) Temporal_Sup_R; (84) Temporal_Pole_Sup_R; (85) Temporal_Mid_L; (91) Cerebelum_Crus1_L.

Table 6. Description of graph properties.

	Functional	Diffusion
Mean Global Clustering	0.1453	0.0061
Mean Efficiency	0.1410	0.014
Mean Transtivity	0.1595	0.005
Mean Nodal Strength	7.063	0.36
Mean Small Work	1.73	3.67

Average integrated graph properties calculated using the Brain Connectivity toolbox for the rs-fMRI FC network and the probabilistic tractography derived SC network. Integrated measure calculated for densities between 0.1 and 0.4 in steps of 0.025.

Table 7. Functional and Structural Connectivity results for the tested thresholds.

		FC						SC		
		PSQI negative			PSQI*Age negative			PSQI negative		
	Area	0.01 (p=0.046)	0.005 (p=0.071)	0.001 (p=0.034)	0.01 (p=0.006)	0.005 (p=0.011)	0.001 (p=0.042)	0.01 (p=0.049)	0.005 (p=0.077)	0.001 (p=0.0344)
5	Frontal_Sup_Orb_L	13.2	7.5649	4.2085	3.7706	3.7706	3.7706			
6	Frontal_Sup_Orb_R							0	3.5448	3.5448
9	Frontal_Mid_Orb_L	15.987	10.334	10.334	36.922	25.928	3.8624			
15	Frontal_Inf_Orb_L	16.827	14.078	7.5094						
18	Rolandic_Oper_R	10.647	10.647	4.2953						
26	Frontal_Med_Orb_R							7.3588	22.983	7.3588
27	Rectus_L							7.4671	7.4671	7.4671
28	Rectus_R				33.515	19.731	3.8328			
30	Insula_R	13.502	13.502	4.3353						
33	Cingulum_Mid_L				21.283	13.053	3.7055			
34	Cingulum_Mid_R				26.715	4.2642	4.2642			
37	Hippocampus_L				21.283	13.053	3.7055			
38	Hippocampus_R				26.715	4.2642	4.2642			
44	Calcarine_R				14.522	6.451	3.5345			
47	Lingual_L							11.965	22.11	18.981
53	Occipital_Inf_L				31.134	25.598	16.426	3.6763	13.409	3.6763
61	Parietal_Inf_L	63.511	52.564	27.808	39.472	19.801	3.4924			
62	Parietal_Inf_R	57.321	49.056	21.498	43.491	24.347	14.958			
64	SupraMarginal_R	38.545	27.308	8.876						
67	Precuneus_L				69.115	36.177	14.232			
68	Precuneus_R				55.128	44.089	8.1211			
71	Caudate_L							8.3909	15.375	12.011
72	Caudate_R							0	9.6374	3.4716
81	Temporal_Sup_L	28.369	17.374	8.2434						
82	Temporal_Sup_R	10.601	7.9123	4.5051						
84	Temporal_Pole_Sup_R	9.0372	3.5454	3.5454				0	6.5682	3.6199
85	Temporal_Mid_L	12.841	7.3347	4.1847	18.335	12.931	6.9458	3.807	3.807	3.807
91	Cerebelum_Crus1_L							3.7688	3.7688	3.7688

FC= Functional Connectivity; SC= Structural Connectivity. Underlined are the highest node values for each network in the considered significance threshold.

Table 8. Regional brain volumes association with age, sex, subjective sleep quality and depressive symptoms.

	r^2	B							p-value							p-value adjusted						
		PSQI	Age	Sex	GDS	Education	PSQI*Age	PSQI*Sex	PSQI	Age	Sex	GDS	Education	PSQI*Age	PSQI*Sex	PSQI	Age	Sex	GDS	Education	PSQI*Age	PSQI*Sex
Left-Cerebellum-White-Matter	0.742	-29.51	-148.96	-345.58	-71.84	-27.68	8.61	67.47	0.516	**0.000**	0.363	**0.004**	0.612	**0.043**	0.268	14.792	**0.000**	9.899	0.240	14.065	2.289	11.789
Left-Cerebellum-Cortex	0.643	-30.95	-208.06	-2787.04	-190.36	-85.24	7.81	71.24	0.810	**0.000**	**0.012**	**0.007**	0.582	0.512	0.679	10.752	**0.011**	0.664	0.411	15.005	7.817	12.160
Left-Thalamus-Proper	0.531	47.12	-36.25	-34.31	-20.73	42.12	2.43	-54.05	**0.037**	**0.000**	0.853	0.084	0.118	0.237	0.072	2.109	**0.009**	4.933	3.445	6.464	8.534	3.968
Left-Caudate	0.357	28.52	14.42	74.35	8.29	29.42	2.07	-45.71	**0.041**	**0.013**	0.518	0.259	0.077	0.114	**0.014**	2.268	0.516	11.181	7.725	4.541	5.260	0.882
Left-Putamen	0.415	57.47	-24.81	-62.18	-40.38	-0.13	2.56	-43.91	**0.009**	**0.006**	0.728	**0.001**	0.996	0.197	0.128	0.542	0.256	7.948	**0.046**	2.945	8.097	6.664
Brain-Stem	0.676	7.30	-54.59	-1891.21	-72.86	-122.26	13.32	70.85	0.914	**0.050**	**0.001**	**0.046**	0.133	**0.035**	0.431	6.261	1.612	0.078	2.333	7.074	1.949	15.531
Left-Hippocampus	0.463	27.40	-21.41	-245.12	-19.05	14.25	1.61	-20.37	**0.043**	**0.000**	**0.033**	**0.010**	0.396	0.199	0.254	2.324	**0.011**	1.739	0.549	15.446	8.097	11.418
Left-Amygdala	0.364	9.77	-6.24	-159.78	-6.09	3.14	1.04	-12.64	0.156	**0.028**	**0.007**	0.103	0.714	0.106	0.168	7.102	0.989	0.426	3.813	12.484	4.991	8.411
CSF	0.234	9.38	13.10	-0.32	8.70	-0.04	-1.01	-13.43	0.446	**0.012**	0.998	0.180	0.998	0.378	0.414	14.722	0.482	1.980	6.289	1.992	8.244	15.304
Left-Accumbens-area	0.355	2.15	-4.41	-46.63	-3.72	5.24	0.07	2.04	0.555	**0.004**	0.128	0.059	0.233	0.842	0.674	14.438	0.193	6.158	2.838	10.707	6.679	12.811
Left-choroid-plexus	0.381	-0.87	9.30	67.24	1.44	5.75	-0.34	-2.01	0.920	**0.010**	0.350	0.753	0.577	0.664	0.861	4.576	0.415	10.438	5.107	15.540	8.573	7.632
Right-Cerebellum-White-Matter	0.674	-60.02	-144.31	-475.94	-54.93	-39.11	5.46	92.32	0.256	**0.000**	0.281	**0.054**	0.536	0.263	0.192	9.996	**0.000**	10.395	2.647	16.549	8.431	9.232
Right-Cerebellum-Cortex	0.632	-42.01	-211.84	-3111.87	-238.33	-96.27	13.34	92.53	0.753	**0.000**	**0.007**	**0.001**	0.548	0.281	0.604	12.559	**0.013**	0.407	0.081	16.090	8.707	14.883
Right-Thalamus-Proper	0.543	41.27	-40.45	-107.93	-20.36	44.22	3.69	-30.80	0.061	**0.000**	0.551	0.082	0.093	0.069	0.290	3.138	**0.001**	10.245	3.458	5.206	3.370	12.458
Right-Caudate	0.317	34.67	12.11	124.09	0.48	31.06	3.33	-37.78	**0.019**	**0.046**	0.308	0.951	0.077	**0.018**	0.053	1.136	1.512	10.486	2.754	4.541	1.033	2.977
Right-Putamen	0.414	59.76	-30.02	-241.62	-29.33	-13.46	4.74	-35.91	**0.005**	**0.001**	0.161	**0.009**	0.582	**0.017**	0.188	0.282	**0.033**	7.560	0.495	14.545	0.980	9.220
Right-Hippocampus	0.421	28.65	-23.86	-245.99	-14.05	6.00	1.53	-22.60	**0.040**	**0.000**	**0.037**	0.063	0.728	0.237	0.220	2.268	**0.004**	1.907	2.945	11.640	8.534	10.125
Right-Amygdala	0.281	10.98	-4.66	-157.86	0.08	8.67	0.57	-18.83	0.202	0.185	**0.032**	0.986	0.421	0.479	0.103	8.693	4.632	1.739	1.902	15.339	8.163	5.546
Right-Accumbens-area	0.265	4.03	-3.83	-32.21	-1.11	0.10	0.56	-2.14	0.213	**0.005**	0.233	0.517	0.980	0.064	0.618	8.933	0.217	9.545	8.908	4.894	3.193	14.498
Right-choroid-plexus	0.400	-5.46	19.26	116.42	4.87	13.92	-0.96	-0.96	0.610	**0.000**	0.192	0.389	0.278	0.338	0.946	14.041	**0.003**	8.622	8.168	12.514	8.795	2.835
WM-hypointensities	0.427	-65.80	75.55	221.39	38.98	-46.87	-9.25	12.96	0.113	**0.000**	0.508	0.069	0.343	**0.020**	0.809	5.414	**0.003**	11.181	3.171	14.396	1.113	8.377
non-WM-hypointensities	0.112	-1.31	2.02	-0.58	0.93	1.77	-0.13	-1.12	0.407	**0.003**	0.965	0.290	0.351	0.375	0.595	14.655	0.124	3.614	7.593	14.396	8.533	15.437
Optic-Chiasm	0.280	0.58	-0.78	-46.81	-0.77	-3.70	0.23	1.97	0.812	0.421	**0.021**	0.544	0.196	0.299	0.546	10.530	4.530	1.169	8.790	9.427	8.439	15.811
lh_caudalanteriorcingulate_volume	0.103	4.83	-3.29	98.64	-14.70	-18.15	1.65	-19.30	0.756	0.605	0.449	0.080	0.333	0.252	0.355	12.045	2.835	10.770	3.534	14.325	8.463	14.201
lh_caudalmiddlefrontal_volume	0.273	77.30	13.55	-298.37	13.84	22.29	0.03	-119.28	**0.045**	0.383	0.348	0.495	0.625	0.994	**0.021**	2.390	4.983	10.438	8.908	14.065	1.977	1.264
lh_fusiform_volume	0.333	6.80	-25.60	85.92	19.77	64.05	4.20	-36.09	0.842	0.071	0.764	0.281	0.123	0.186	0.431	8.986	2.191	7.278	7.593	6.635	7.832	15.531
lh_inferiorparietal_volume	0.264	-28.99	-47.45	674.17	-18.66	66.68	9.30	91.99	0.663	0.084	0.227	0.599	0.404	0.133	0.302	13.914	2.352	9.527	7.956	15.429	5.835	12.684
lh_inferiortemporal_volume	0.384	70.59	-49.98	-113.59	-52.01	-38.86	7.48	-34.33	0.179	**0.022**	0.796	0.069	0.553	0.128	0.621	7.859	0.823	6.874	3.171	15.901	5.779	14.212
lh_lateraloccipital_volume	0.225	30.88	-24.99	-453.17	2.68	-1.34	3.13	-133.48	0.528	0.213	0.269	0.918	0.982	0.489	**0.044**	14.442	4.473	10.214	3.231	3.920	8.136	2.528
lh_lateralorbitofrontal_volume	0.418	-2.09	-11.53	-67.25	-20.50	11.12	2.71	-5.81	0.926	0.216	0.723	0.094	0.683	0.199	0.848	2.774	4.473	8.313	3.571	13.853	7.947	8.089
lh_lingual_volume	0.341	40.62	-53.23	-211.91	-48.23	-50.26	0.32	-73.16	0.234	**0.000**	0.456	**0.010**	0.220	0.919	0.110	9.589	**0.015**	10.770	0.530	10.348	4.547	5.854
lh_medialorbitofrontal_volume	0.420	2.20	0.73	-467.09	-13.57	-43.70	2.36	4.31	0.915	0.931	**0.009**	0.221	0.082	0.219	0.876	5.481	1.992	0.496	7.069	4.663	8.095	5.233
lh_middletemporal_volume	0.376	10.27	-53.61	-424.25	-26.94	-73.92	4.34	-51.70	0.817	**0.004**	0.255	0.258	0.169	0.291	0.385	9.746	0.197	10.094	7.725	8.430	8.479	14.884
lh_parahippocampal_volume	0.080	10.67	-3.39	-53.91	-2.49	1.32	2.15	-5.27	0.336	0.449	0.567	0.674	0.925	**0.038**	0.718	12.771	4.215	9.924	6.700	7.794	2.049	10.449
lh_precuneus_volume	0.225	15.32	-20.30	71.10	-15.18	-12.36	-0.73	-30.66	0.686	0.192	0.822	0.453	0.786	0.835	0.545	13.914	4.460	5.653	9.067	10.954	6.970	15.877
lh_superiorfrontal_volume	0.560	-16.84	-18.52	-393.05	-51.52	-49.45	4.87	40.91	0.768	0.406	0.397	0.091	0.461	0.341	0.594	11.345	4.983	10.314	3.568	16.152	8.490	15.437

lh_superiorparietal_volume	0.342	18.12	-13.63	626.43	-11.53	59.18	-3.44	-24.08	0.695	0.471	0.108	0.640	0.288	0.421	0.697	13.717	3.596	5.302	7.593	12.682	8.329	10.961
lh_superiortemporal_volume	0.377	80.50	-15.27	-892.17	-27.02	-51.48	4.36	-97.60	0.106	0.450	**0.034**	0.307	0.386	0.340	0.142	5.216	4.042	1.748	7.538	15.446	8.795	7.261
lh_supramarginal_volume	0.472	27.49	-55.79	141.18	-62.02	-85.06	-1.88	-29.43	0.471	**0.001**	0.657	**0.003**	0.067	0.593	0.564	15.081	**0.032**	8.679	0.193	3.999	8.297	15.283
lh_frontalpole_volume	0.046	-4.94	2.47	-26.05	-3.47	-1.43	0.08	-2.68	0.394	0.298	0.589	0.263	0.837	0.888	0.729	14.565	5.066	9.117	7.520	9.057	5.894	10.055
lh_temporalpole_volume	0.006	6.37	2.62	-92.36	-1.99	-10.54	2.09	-9.56	0.570	0.567	0.317	0.730	0.415	0.046	0.510	13.887	3.170	10.395	5.441	15.361	2.386	15.815
lh_insula_volume	0.451	-12.30	-0.81	-208.68	-20.12	-8.21	-0.04	33.76	0.620	0.936	0.315	0.132	0.782	0.986	0.310	14.041	1.863	10.486	4.736	10.954	3.675	12.703
rh_fusiform_volume	0.427	-29.07	-19.45	-408.09	-9.13	-9.65	-1.03	3.36	0.429	0.186	0.174	0.633	0.823	0.757	0.945	14.945	4.632	8.014	7.783	9.871	7.635	3.761
rh_inferiorparietal_volume	0.277	9.65	-66.57	-267.13	-14.18	31.49	5.34	-36.07	0.881	**0.014**	0.620	0.680	0.684	0.371	0.676	7.851	0.535	8.841	6.064	13.660	8.533	12.811
rh_inferiortemporal_volume	0.381	30.53	-19.13	-44.24	-24.16	-18.30	4.45	-9.74	0.489	0.303	0.904	0.302	0.728	0.283	0.868	15.164	5.066	4.265	7.549	12.146	8.707	6.888
rh_lateraloccipital_volume	0.260	7.94	-36.99	-100.51	-6.41	13.30	0.07	-26.80	0.872	0.071	0.808	0.808	0.823	0.988	0.685	8.425	2.191	6.370	4.038	10.214	2.959	11.544
rh_lateralorbitofrontal_volume	0.374	39.85	-12.16	2.86	-19.15	12.85	4.90	-25.26	0.146	0.275	0.990	0.189	0.694	0.054	0.487	6.852	4.956	2.895	6.440	12.999	2.760	15.594
rh_lingual_volume	0.250	57.60	-29.74	-361.29	-48.92	1.28	4.29	-33.78	0.154	0.073	0.283	**0.025**	0.979	0.249	0.529	7.102	2.128	10.395	1.336	5.789	8.463	15.877
rh_medialorbitofrontal_volume	0.454	-13.21	-2.94	-341.46	-11.35	-43.33	1.15	-1.66	0.427	0.664	**0.016**	0.203	0.033	0.453	0.940	14.945	2.420	0.906	6.688	2.004	8.163	4.379
rh_middletemporal_volume	0.393	-15.29	-52.10	-145.15	-40.84	-74.32	5.17	0.07	0.739	**0.005**	0.693	0.088	0.162	0.212	0.999	12.892	0.228	8.545	3.516	8.255	8.056	1.891
rh_parahippocampal_volume	0.258	6.86	-6.57	110.86	-3.18	17.50	1.62	-2.16	0.497	0.115	0.196	0.561	0.171	0.091	0.872	15.164	3.096	8.567	8.703	8.430	4.351	6.073
rh_paracentral_volume	0.288	13.75	-9.70	-99.02	-6.35	14.02	0.55	-24.44	0.510	0.257	0.570	0.568	0.576	0.774	0.382	14.905	4.883	9.647	8.412	15.540	7.573	14.884
rh_posteriorcingulate_volume	0.376	28.58	-14.37	-80.07	-5.89	25.99	2.98	-25.48	0.060	**0.022**	0.523	0.463	0.152	0.035	0.207	3.138	0.823	10.883	9.067	7.922	1.949	9.710
rh_precuneus_volume	0.332	-3.79	-24.52	269.03	-9.12	4.30	3.85	-26.42	0.925	0.138	0.423	0.670	0.929	0.300	0.622	3.678	3.579	10.565	7.042	7.398	8.365	13.671
rh_superiorfrontal_volume	0.423	-4.84	-29.03	-605.22	-39.49	-38.52	5.47	-29.53	0.947	0.331	0.321	0.311	0.660	0.416	0.762	1.853	4.628	10.144	7.357	13.853	8.329	8.761
rh_superiorparietal_volume	0.342	53.41	-39.94	397.73	-28.64	37.72	-6.31	-46.65	0.242	**0.034**	0.296	0.239	0.489	0.136	0.443	9.662	1.169	10.356	7.419	16.640	5.836	15.102
rh_superiortemporal_volume	0.401	86.53	-19.30	-404.29	-35.14	-28.70	8.52	-121.91	**0.021**	0.200	0.195	0.080	0.534	**0.015**	**0.015**	1.220	4.425	8.622	3.534	16.549	0.937	0.903
rh_supramarginal_volume	0.524	12.93	-33.93	182.60	-38.20	-27.98	8.11	-23.31	0.716	**0.022**	0.539	**0.048**	0.513	**0.016**	0.624	13.204	0.805	10.463	2.382	16.415	0.960	13.065
rh_frontalpole_volume	-0.024	0.91	2.92	-53.87	-3.42	-0.36	0.29	-6.64	0.894	0.306	0.354	0.354	0.965	0.659	0.470	7.047	4.856	10.138	7.795	6.501	8.573	15.510
rh_temporalpole_volume	-0.048	8.36	-4.76	-136.25	-1.84	11.66	-0.15	-6.54	0.555	0.412	0.252	0.808	0.494	0.909	0.730	14.438	4.867	10.094	4.519	16.640	5.326	9.475
rh_insula_volume	0.523	-41.52	5.97	-328.63	-27.90	-4.68	-0.84	66.88	0.077	0.528	0.093	**0.027**	0.866	0.694	**0.034**	3.825	3.296	4.639	1.394	8.367	7.973	1.963

The Intra-cranial volume was considered in the model in order to normalize the brain volumes of all participants. Each variable was controlled for all other variables; R^2= effect size (adjusted); **β**= Beta; Values of $p<0.05$ are considered significant and highlighted in bold.

Discussion

Herein, we applied a multimodal whole-brain MRI approach to determine, in a normative ageing cohort, the association between subjective sleep quality measured by PSQI global score, and brain connectivity. Results showed that poor sleep quality was associated with decreased FC and SC of two distinct networks, with overlapping nodes in the right superior temporal pole and in the left middle temporal region. The obtained data also showed that for older individuals, smaller increases in PSQI global score are sufficient to decrease FC in a network that has some overlapping nodes with the above-mentioned SC and FC networks. The left middle temporal region was significantly affected in all the found networks. Overall, the results indicate that network connectivity is adjustable in face of subjective sleep quality alterations and that a 1-month measure of sleep quality allows the observation of SC changes. In addition, the impacted networks, which are relevant for language, environment perception and assessment and self-awareness, seem to also permit inferences about a subjects' quality of sleep.

Across ageing a concomitant increase in sleep complaints and individuals' vulnerability to psychological distress and medical conditions occurs (Bliwise, 1993; Bliwise et al., 1993; Foley et al., 2004; Maggi et al., 1998; Mander et al., 2017; Scullin and Bliwise, 2015; Stranges et al., 2012). However, prevalent as they are, it is still debatable whether these sleep complaints are a product of age itself, a consequence of age-related medical and psychiatric conditions, or a mix of both (Mander et al., 2017). Here, 49% of the participants had poor sleep quality over the previous month and of those, 34% were on benzodiazepines use and 28% used other type of psychopharmacological medication. In line with this result is the found association between PSQI subdomains "Day Dysfunction", "Sleep Disturbance" and "Medication" and depressive symptoms. In addition, participants with lower education levels had higher scores not only in PSQI subdomain "Medication", which was also found in previous studies (e.g. Sivertsen et al., 2015), but also in GDS (depressive symptoms). In fact, more attention should be given to the weight of socio-demographic factors, given its association to health vulnerabilities, such as access to care or comprehension of health information. This is also relevant because it supports the concern about participants' cognitive and mental status and its influence in their ability to properly recall information. Herein, to address this limitation, PSQI information was combined with actigraphic measurement. A possible bias was addressed by the confirmation that no differences existed between the initial cohort and the subsample that used the ActiSleep+ units. The association

between PSQI global score, its subdomains and actigraphic parameters was also tested. Important correlations between PSQI subdomain "sleep efficiency" and actigraphic TTB and TST were observed, as well as between sleepiness and WASO (actigraphy derived). No association was found between PSQI global score and actigraphy, which we speculate to be due to the combination of the small sample size and the number of variables tested. This limitation should be addressed in future studies by increasing the number of participants wearing actigraphy units. Additionally, because changes in body composition (e.g. increase of body fat mass and decrease of muscle mass) are common in ageing (St-Onge, 2005), we also determined the distribution of BMI in our cohort and its association with sleep quality. Results showed that 56% of participants were overweight and 37.2% obese. These numbers are in line with the EuroStat information (Database - Eurostat) that shows a high prevalence of overweight individuals from middle to older age. However, despite common, high BMI promotes an increased vulnerability to chronic diseases such as sleep apnea, diabetes or cardiovascular diseases, which can further affect sleep quality (Hoevenaar-Blom et al., 2011; St-Onge, 2005). In our study, we were not able to perform polysomnography to exclude non-diagnosed sleep conditions; we just relied on clinical information from their clinical processes. It is, therefore, important to state this as a limitation of the study. However, given that the purpose was to characterize a normative ageing cohort, and since it is common to have underdiagnosed sleep disturbances in the general population, we did not consider that this limitation would invalidate our study or its results.

The ageing process also carries alterations to the neuronal system. In the present cohort, age-related changes in regional brain volumes occurred in areas involving cognitive function, motor behavior and emotional processing, which goes in line with other studies (Bernard and Seidler, 2014; Ritchie et al., 2015). Of note, we found a volumetric decrease of the putamen, which can be related not only to the ageing process but also to the presence of depressive symptoms. Interestingly, the decrease of the volume of the left putamen was significantly associated with global cognitive decline in older individuals with memory complaints and Alzheimer's disease, exceeding the strength of the left hippocampal correlation to cognitive performance (de Jong et al., 2008). This is particularly relevant because our results show the association between the volume of left putamen and depressive symptoms and, in a previous work from our team (Santos et al., 2013) these depressive symptoms were a determinant factor for poor cognitive performance. Furthermore, despite no associations between regional brain volumes and PSQI global score were

observed, some of the age-affected areas are relevant nodes in the FC and SC networks that in our study were found to be associated with subjective sleep quality. Thus, it is plausible to consider that age-related changes in brain regional volumes may be modulating not only SC, but also the FC of the networks associated to sleep quality. While it is easier to correlate brain volumetric changes with SC, the same does not apply to FC, given its plasticity, flexibility, and reorganization capabilities (Bullmore and Sporns, 2009; Fjell et al., 2017; Meier et al., 2016; Tewarie et al., 2014; van den Heuvel et al., 2009). We speculate that the age-related changes in brain regional volumes can modulate the number of connections between regions, which, in turn, will enable changes in regions that are working synchronously. We also cogitate that these can be a bidirectional relation, which means that it is possible that, at this point, we are also seeing the cumulative effect of disrupted (poor) sleep throughout lifetime and how much resilience people still have to it. Previous studies exploring the association between subjective sleep quality and brain parameters have used a single functional imaging modality. Here, we address the question with a multimodal approach, thus providing for a more comprehensive view of the phenomenon and casting some light in the still highly debated relationship between structural and functional brain connectivity. By complementing FC and SC we provide not only a measure of synchrony between regions (FC), but also evidence regarding the fiber connections and their integrity state (SC). Our results showed that three different networks were impacted by subjective sleep quality – two affected only by PSQI and the other by the interaction "PSQI x Age" – and that the left middle temporal region was the only node overlapping the three. When reflecting about the meaning of this result, two recent studies have to be considered: one from Van Someren and colleagues, in which results showed that medial temporal lobe atrophy was strongly associated to sleep-wake rhythm fragmentation (Van Someren et al., 2018); and another from Lauriola and colleagues, showing that despite the association between sleep disruptions and subjective cognitive decline, there was no correlation between sleep changes and the medial temporal lobe (Lauriola et al., 2017). Beyond the obvious methodological differences that can justify what seems to be contradictory results between these studies, another argument arises: maybe sleep changes precede medial temporal lobe atrophy (Liguori et al., 2017). In our results, the middle temporal region also presents a decrease of volume with age, so, maybe we are not only observing the effect of general age-related adjustments, but also age-related adjustments concerning chronic or cumulative effects of intermittent sleep disruption throughout lifetime. Furthermore, this region has been suggested to contribute to our ability to understand

action and non-dominant semantic association, allowing semantic retrieval to be shaped to suit a task or context (Davey et al., 2016). Having this in mind, and despite that the real value of the finding is still uncertain, we hypothesize that the left middle temporal region, when connected to specific nodes of each of the found networks, may be shaping our sense of self and our sense of the world, by selectively retrieving information relevant for our action and context. In fact, these changes are observed in individuals with depression, schizophrenia or Alzheimer's disease, possibly supporting the bidirectional link between sleep and these pathologies. Furthermore, this could partially explain why improving sleep may help managing or even improving depressive, schizophrenic or Alzheimer's disease symptoms (Greicius et al., 2004; Li et al., 2016, 2018; Onitsuka et al., 2004; Shokri-Kojori et al., 2018; Son et al., 2018; Veer et al., 2010; Yun et al., 2017). Thus, the potential of these results for clinical practice is of relevance, as it opens new perspectives to intervene timely in face of sleep disturbances.

On the association between subjective sleep quality and FC, our results, indicate that poor sleep quality is correlated with a decrease in the synchronized activity of a network with important nodes the inferior parietal regions and left orbital middle frontal region. The FC of these areas was also found to be altered in other studies using sleep deprivation protocols or addressing good sleepers against poor sleepers or insomniacs (Chen et al., 2014; Dai et al., 2014; Krause et al., 2017; Nie et al., 2015; Sämann et al., 2010; Yeo et al., 2015), suggesting that these regions may have the potential to be markers of sleep disturbances. For example, it has been described that insomniac patients present an overall cortical hyperarousal during sleep, which is thought to reflect persistent sensory processing and subsequent shallower sleep (Desseilles et al., 2008). As a consequence, during wakefulness, these individuals present a decreased metabolism in subcortical (thalamus, hypothalamus and brainstem reticular formation) as well as in cortical regions (bilateral prefrontal cortex, left superior temporal, parietal, and occipital cortices) (Desseilles et al., 2008). Our normative aged community-dwellers, in a restful wake MRI condition, also had a decreased connectivity in some of these regions, supporting the idea of a possible continuum from health to disease in sleep. A connection involving the inferior parietal region and the insula was also observed. The relevance of this finding is in the fact that the insula has a role in temporal and bodily states (Chen et al., 2014) integration, which in arousal networks may underlie the misperception of sleep quality and subjective distress in insomnia (Chen et al., 2014). In addition, the consistently impaired inferior parietal region has led to the hypothesis that this region may also

be used as an early marker for the effects of 24-hour sleep deprivation, serving as an indicator of unexplored behavioral impairments (De Havas et al., 2012). Some of the nodes of the networks associated to the PSQI global score are also relevant nodes for known networks, such as the default mode network, the attentional network and networks involved in reward, stress and social interaction. The structural connection patterns within the patterns of dynamic ('functional') interactions (Sporns, 2003) showed that subjective sleep quality was also correlated to alterations in the SC of a network with nodes in the left lingual region, left caudate, left rectus and right medial orbitofrontal regions. These regions have also been previously described to be implicated in sleep disturbances (Kay et al., 2016; Kay and Buysse, 2017). Remarkably, in all the results that we had none seem to suggest that compensatory mechanisms exist in what concerns to poor sleep quality. There are, however, some limitations that should be addressed, namely the ones imposed by the study design and sample size. While we have established novel associations between subjective sleep and brain properties, the cause-effect relation is still uncertain at this point. A longitudinal approach should be considered in further work. A larger sample size is also of need in order to incorporate other relevant variables that influence the sleep process, such as presence of relevant pathologies and use of medication and to promote a trait stratification analysis. The blood oxygenation level-dependent (BOLD) signal in functional MRI has been an increasingly used tool, but because it depends on hemodynamic parameters, like blood pressure, it is sensitive to medical conditions affecting the cardiovascular system. In our results, a weak but statistically significant association between diastolic blood pressure and PSQI global score was found. Since poor sleep quality is associated with increased vulnerability to cardiovascular diseases (Lao et al., 2018), we explored in our statistical model, whether diastolic blood pressure could be acting as a confounding effect. The results remained the same: the same networks were found and they were all statistically significant. On the other hand, the methodology employed in this study provides a novel perspective on the biology of sleep quality under normative conditions. Not only we considered a standard measure of sleep quality already in use in the clinical practice, but we also imaged whole-brain changes in MRI, thus allowing pinpointing the most relevant changes in the complex and dynamic brain networks. Moreover, by using a normative ageing cohort, we managed to capture the associations of sleep quality with biological processes under daily-life conditions, which could provide a much more realistic view and understanding of sleep with all of its environmental interactions and thus, be of more utility in the design of possible future clinical interventions.

To sum up, the present study shows that middle-aged and older individuals in their normal ageing process, display alterations in brain FC and SC of complex brain networks in association with subjective sleep complaints. This may be of relevance in the future, not only to design interventions that are effective in improving sleep quality but also to delineate studies that allow a better understanding of the mechanisms involving subjective sleep quality and its associated comorbidities.

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.

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Contributions

NS and NCS conceived the study and LA contributed to the study design. LA, TCC and CPN performed participants' recruitment. LA and TCC performed the psychological assessments. RM, PSM and PM performed the MRI acquisitions. RM, PSM and PM did the MRI data pre-processing. LA, RM and AC perform the data analysis. LA wrote the first draft of the manuscript and all authors contributed for the following and final versions of the manuscript.

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CHAPTER VI

General discussion, future perspectives and conclusion

General Discussion and Future Perspectives

Sleep is a complex and multidimensional concept of paramount importance for a balanced physical and mental health. Through its different dimensions (e.g. quantity, continuity, timing and quality), sleep has been shown to have a relevant role in the organism homeostasis (Tononi & Cirelli, 2006), immune function (Asif, Iqbal, & Nazir, 2017; Besedovsky, Lange, & Born, 2012), cognitive performance (Alhola & Polo-Kantola, 2007), cerebral clearance (Xie et al., 2013) and psychological status (Freeman et al., 2017). Sleep deprivation and disruption seem to be rapidly becoming a major public health concern (Colten, Altevogt, & Research, 2006a; Grandner & Pack, 2011), despite it being among the most readily treatable health problems. Among the factors contributing to this, is the low awareness among the general population, and the health care professionals and policy makers, regarding the sleep phenomenon (Colten, Altevogt, & Research, 2006b), with a concominant paired increase in the economic and health burden associated to chronic sleep loss and sleep disorders (Colten et al., 2006b). Thus, it is with no surprise that obtaining a sufficient and quality sleep has been designated a health priority within Healthy People 2020.

With the present thesis we aimed to clarify the meaning of "good sleep quality" in community-dwellers, across the adult lifespan, and determine not only sleep patterns across the adult lifespan, but also its association with variables such as psychological status and brain correlates. Results showed that the meaning of "a good sleep quality" does not seem to be influenced by age or sex, and it is relatively stable across time. But, sleep patterns and routines in the recruited sample were not only influenced by age, but also by sex. Interestingly, different subjective sleep quality measures were predicted by different sociodemographic and psychological variables. Moreover, when using the PSQI composite score, as a measure of subjective sleep quality, it was possible to find that it was significantly associated with brain correlates. Specifically, poor subjective sleep quality was associated to a decrease in functional and structural connectivity of specific networks, with age presenting an interaction effect on the association between subjective sleep quality and functional connectivity.

When studying sleep, several questions arise, but two are frequently posed: 'how much is "sufficient" sleep' and 'what we can understand from "quality" sleep'. Regarding sleep quantity, the National Sleep Foundation recently updated its' recommendations on the amount of sleep needed across the lifespan (Hirshkowitz et al., 2015a; Hirshkowitz et al., 2015b). Overall, it was

suggested 14 to 17 hours of sleep for newborns, 12-15 hours for infants, 11-14 hours for toddlers, 10-13 hours for preschoolers, 9-11 hours for school-aged children, 8-10 hours for teenagers, 7-9 hours for young adults and adults, and 7-8 hours of sleep for older adults (Hirshkowitz et al., 2015a; Hirshkowitz et al., 2015b). Concerning sleep quality, however, information is not so straightforward. In a recent report, Ohayon and colleagues (2017) reviewed the indicators of a good sleep quality across the lifespan and found evidence and consensus for the sleep continuity variables, sleep latency, number of awakenings >5 minutes, wake after sleep onset, and sleep efficiency. There were, however, not enough studies to conclude on/or to acquire consensus regarding sleep architecture or nap-related variables (Ohayon et al., 2017). Although of undisputed pertinence, this approach is insufficient to provide any information about the subjective dimension of "sleep quality". Since subjective complaints of poor sleep are often the main drivers for individuals to seek clinical aid, it becomes of utmost importance to clarify and study it.

Thus, in the present thesis, we not only reviewed the concept of "sleep quality" and its' subjective dimension, but also explored its meaning and how it correlates with psychological and brain parameters. Indeed, in Chapter II, a systematic review is presented so to understand how sleep quality as a concept is being defined and operationalized. The results were striking - not only a high heterogeneity in the tools being used was observed, but also an extraordinay variability in the way the concept is considered. Indeed, with a universal definition still to be found, researchers have to opt from a great diversity of tools and meanings, enabling not only the observed high variability in results, but also the increasing difficulty in studies comparison and applicability of the findings in improving sleep health and knowledge. 'Picking-up' on Buysse and colleagues (1989) work, we proposed that "sleep quality" should be treated as multidimensional concept, and when addressing it, it should be considered a composite measure and not individual parameters in its representation. As such, the relevant parameters for this concept should be determined, as their respective weights, in a global measure. This is especially relevant because the frequency of complaints related to sleep quality is frequently a symptom of sleep disruption or other medical disorders (Buysse et al., 1989). Following this line, an original study was conducted (Chapter III), in which Portuguese adults (lay people), across the lifespan, were asked to qualitatively and quantitatively provide information about their sleep quality, namely, regarding their interpretation about what is "good sleep quality" and a "good night of sleep". The results corroborated the idea that sleep

quality is a multidimensional concept and that the distribution of the reported dimensions of sleep varied within the individuals, but, curiously, not across the lifespan. Importantly, this opens the provocative question on whether this stability could be used to profile the sleep populations, make predictions on their evolutions and take preventive measures accordingly. Nonetheless, there is still a need to further analyze, at the individual level, the specificities of the content provided for each of given parameters. In fact, the idea that we are able to adapt and readjust our expectations on sleep, according to our previous experience of it, can take our work to the next level. In fact, results from Ramlee and colleagues' study, where sleep quality judgement was conceived as a decision making process, showed that sleep quality judgments appear to be determined by not only what occurs during sleep, but also what takes place after the sleep period (Ramlee et al., 2017). Bearing in mind results from our study, for example, the dimension "continuity" of sleep was reported as "sleeping all night without waking up" or "waking one or two times" or even "wake up frequently", which imply different thresholds of acceptability for different people. Considering the recent advances in techniques for semantic content analysis, we expect such tools to provide some useful insights in this topic and aid in creating profiles to better understand these nuances and predict health outcomes (Bedi et al., 2015; Mota et al., 2014; Mota et al., 2018). Thus, from this, the door to interventions whas been 'opened' - that is, by improving mood and functioning during the day, this may, even if inadvertently so, also improve people's self-reported evaluation of sleep quality (Ramlee et al., 2017).

Sleep complaints increase with age (Almeida & Pfaff, 2005; Maggi et al., 1998; Mander, Winer, & Walker, 2017). Still, it is unclear whether it is a biologically programed age-related aspect, or a consequence of cumulative unadjusted behaviors throughout lifespan. Across Chapter III and IV it was possible to observe that sleep patterns change with age, not only in terms of schedule, but also in terms of routines and, despite not so obvious, changes in reported sleep quality was also observed throughout ageing. This result raises the question of at what time in ageing is this effect observed. Having this in consideration, we asked 53 participants to be re-evaluated one year later. Results indicate that many sleep complaints are related to daytime worries (such as work), and that there is a difference between week and weekend days, not only in schedules and routines, but also in terms of sleep quality. Interestingly, most participants considered to have a worse sleep quality on Sunday nights. This appeared to be because the next day is a workday, and people had

either slept more during the weekend or started to worry about the week of work. On the other hand, Fridays and Saturdays were reported as nights that frequently were the better ones regarding sleep quality. The results are not unexpected. Several factors can interfere with a proper night of sleep. From external aspects like environmental features, passing through internal aspects of the individuals to the 24/7 society in which we live in, it is not easy to sleep in the XXI Century. In fact, emerging evidence has demonstrated that environmental factors alter healthy sleep (Johnson et al., 2018; Obradovich et al., 2017) and, in an exploratory study, we have also explored PSQI values variation with seasons (data not shown). Furthermore, considering the described variability week-weekend days in terms of sleep schedule, patterns and duration, it is also important to determine whether self-reported sleep quality also varies and what are the reported reasons for that. Thus, in Chapter IV, these variations across weekdays have been explored. Results showed that individuals reported an overall better sleep quality during the weekend than the week. Specifically, most individuals reported Saturday night has the night when they have sleep of better quality and Sunday night as the worse night in terms of sleep quality. In terms of reasons for these patterns, it seems that "worrying about work" or "being without the kids during the week" are the most frequent reasons for a poor sleep quality night and "having family and friends close by" the most reported reason for a better sleep quality on Saturdays nights. Because these are very preliminary data, it is aimed to increase the sample size and further explore the reasons reported for a better or worse sleep quality, but also, to determine the implications of these variations and its associated factors. This will provide relevant insights for more effective strategies to overcome poor sleep quality. Following this line, we are also analyzing data regarding seasonality and subjective sleep quality. It has been shown a variation not only on sleep patterns but also on sleep complaints with temperature derived from different seasons (Honma, Honma, Kohsaka, & Fukuda, 1992; Obradovich, Migliorini, Mednick, & Fowler, 2017), reason why we started exploring the data on our cohorts. Our preliminary results seem to go in line with results from other groups that show that high temperatures associate with poor sleep quality (Honma et al., 1992). It will be interesting to determine how chronotype influences these variations and whether melatonin and cortisol levels play a role in this association.

Considering that we did not have yet the opportunity to develop a comprehensive measure of sleep quality and have it validated, we used the standard measure Pittsburgh Sleep Quality Index (PSQI)

(Buysse et al., 1989) to study the effects of subjective sleep quality on brain parameters (brain regional volume, FC and SC) (Chapter V). This questionnaire was developed considering not only quantitative aspects of sleep, such as duration, latency, or number of arousals, but also subjective features, such as "depth" or "restfulness" (Buysse et al., 1989). Interestingly, results also corroborated this perspective of combining quantitative and more subjective aspects of sleep. We observed that, when controlling for depressive symptoms (measured by GDS), we still had a functional and structural connectivity network that was reflecting sleep impairments. Poor sleep quality measured by PSQI was associated to decreases in FC of a network with its most important nodes the inferior parietal regions and left orbital middle frontal region (Amorim et al., 2018). These areas were also found to be altered in studies addressing sleep disturbances like insomnia or sleep deprivation against individuals with proper sleep quality (Chen et al., 2014; Dai et al., 2014; Krause et al., 2017; Nie et al., 2015; Sämann et al., 2010; Yeo, Tandi, & Chee, 2015). Frequently, complaints of daytime fatigue and excessive sleepiness are associated to sleep-disordered breathing (SDB), a chronic condition characterized by partial or complete collapse of the upper airway during sleep that often results in apneas and hypopneas that lead to a reduction in oxyhemoglobin saturation and recurrent arousals from sleep (Punjabi & Aurora, 2009). An exclusion criteria for our cohorts was the presence of sleep pathology, still, for some of the participants, PSQI is higher than the minimum threshold to be consider sleep of poor quality. Therefore, as a next step, we should assess our cohorts for (undiagnosed) sleep disorders. SDB is one of the most frequent amongst middle-agers and older individuals, and it is known to be associated to impairments in cognitive function, poor work performance, increased risk for motor vehicle accidents and problems in daily living that diminish quality of life (Punjabi & Aurora, 2009). Thus, a future study direction is to better understand the implications of sleep disorders diagnosis in the general population that do not present specific complaints and did not recur to their physician. More so, during the time of this PhD, it was no possible to perform polysomnography to the participants. So, this will be an important step in order to screen for possible non-diagnosed sleep disturbances, but also to further explore the questions that we have here addressed. It would be of further interest to determine the association of subjective measures with not only a polysomnographic assessment (that will allow for sleep architecture characterization), but also with actigraphy and hormonal aspects (that will allow for a more broad reading of the phenomenon of

sleep). We already have some ongoing work derived from the obtained results, namely, an exploratory study where we address whether subjective sleep quality can also affect functional and structural connectivity in younger participants. A longitudinal assessment in the middle-aged and older participant's cohort has also been performed and data is ready for analysis. We also had the opportunity to collect data in a sample of pregnant women in order to try to understand how sleep quality and actigraphic variable vary with pregnancy. Particularly, concerning the association between the PSQI standard measure for sleep quality and its associations with brain correlates, two studies are already ongoing. First, the same analysis has been performed in young adults (age range 22-30 years) in order to determine whether the same patterns in network connectivity are obtained. While older individuals present more stable routines that allow for some consistency across months, in younger participants this is not so frequent. The period of time in which the assessment is performed can elucidate whether sleep will be more or less affected. For instance, it is hypothesized that if the assessment is performed in a time when they have to study for exams, sleep will be more affected than in regular school activities (or on non-academic periods). Another approach, following the FC and SC results in the aged cohort, is two-fold. First, we are analyzing the longitudinal data to determine whether these associations are maintained or if they change, and in what direction. Second, as above mentioned, to continue following this cohort of individuals and include a polysomnography study in order to determine sleep architecture and be able to assess possible sleep disturbances, like sleep apnea, that is frequently underdiagnosed, particularly in women. Furthermore, it will also be of interest to further explore the already obtained data, namely using dynamics approaches and longitudinal actigraphy data. The use of network analysis is an approach of note to the data organization in terms of meaningful connection patterns. Here, it is considered that optimal sleep is both an issue of sleep quantity or of sleep quality. Sleep quantity is discussed in terms of duration, timing, variability and dose-response relationships. Sleep quality is explored in relation to continuity, sleepiness, sleep architecture and daytime behavior (Blunden & Galland, 2014). More so, insufficient sleep may not only be impacted upon by age, but also driven by socio-cultural patterns and sleep-wake habits. In fact, for some individuals, the drive for insufficient sleep can be viewed in terms of a cost-benefit relationship, curtailing sleep in order to perform better while awake (Blunden & Galland, 2014). We conclude that defining optimal sleep is complex. The only method of capturing this elusive concept may be by somnotypology and taking

into account duration, quality, age, gender, culture, the task at hand, and an individual's position in both sleep-alert and morningness-eveningness continuums. At the experimental level, a unified approach to establish standardized protocols to evaluate optimal sleep across paediatric age groups is required (Blunden & Galland, 2014). Although sleep architecture changes with age, one study reported that sleep disturbances in older adults were more dependent on physical, environmental, and health factors than on age-dependent sleep changes (Martin, Sforza, Barthélémy, Thomas-Anterion, & Roche, 2014), and nearly all age-related changes in architecture occur in early and middle age. Research has also showed that subjective sleep assessment also seems to depend on the variability of the biological functions during the 24-h period. Of central importance is the development of a measure that somewhat can translate what is being considered here into some objective parameters able to be measured. Interestingly, results showed that it seems that people tend to focus in different parameters depending on the questions asked, bringing to live the discussion about the measures that are being used and how the results might be so variable giving the differences of the methods per se, and not because of other aspects. Krystal & Edinger reviewed the strengths and weaknesses of the existing measures and discussed the challenges of the developing an objective correlate of "sleep quality" ratings (Krystal & Edinger, 2008). As previously mentioned, they reflected about the fact that such ratings may reflect non-sleep phenomena such as mood or health status and the possibility that "sleep quality" may reflect different aspects of sleep among people (Krystal & Edinger, 2008). They also discuss new approaches intended to address these challenges, namely combining different types of measures, sub-grouping individuals based on clinical or physiological characteristics and developing different measures in these subgroups; and sub-grouping based on the association of potential measures and quality ratings over nigh (Krystal & Edinger, 2008).

There is much to be learned of the mechanisms for sleep disturbances in patients with depression and sleep disorders and, in these patients, relating sleep outcomes measures to the underlying neurobiology would appear to be a valid and productive approach (Roth, 2008). Some studies have showed that sleep discrepancy in patients with insomnia might be associated with altered brain activity during non-rapid eye movement sleep (Kay et al., 2017). Specifically, brain activity in the right anterior insula, left anterior cingulate cortex, and middle/posterior cingulate cortex seems to be involved in the perception and retrospective diary reports of sleep onset latency (Kay et al.,

2017). More so, Chen and colleagues (2014), in a study with young females with and without insomnia, observed that insomniacs had greater involvement of the anterior insula with salience networks, and higher insula BOLD correlation with EEG gamma frequency power during rest. This increased involvement of the anterior insula was associated with negative affect in insomniacs, which was speculated to underlie the misperception of sleep quality and subjective distress in insomnia, given insula's role on the integration of temporal and bodily states (Chen et al., 2014). Nonetheless, one of the largest groups of patients suffering from (reported) insomnia are the elderly. Not only do they have a greater prevalence of insomnia, but they also experience more negative consequences associated with insomnia and are at greater risk for falls, possibly due both to the sleep disorder and to the medication prescribed (Roth, 2008). Notwithstanding, subjective reports of quantitative variables have been shown biased (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008). For instance, Lauderdale and colleagues (2008) observed that individuals sleeping 5 and 7 hours over-reported, on average, by 1.3 and 0.3 hours, respectively, and that the overall correlation between reported and measured sleep duration was of 0.45 (Lauderdale et al., 2008). Interestingly, the extent of overestimation, calibration and correlation varied according to personal and sleep characteristics, which raised concerns about the bias that asking about sleep could bring (Lauderdale et al., 2008). Indeed, Buysse and colleagues (1989) have also pointed out the fact that the exact elements that compose sleep quality, and their relative importance, might vary between individuals.

As such, in an era of personalized medicine, all these factors can (and should) be taken into account. Thus, it is urgent to develop a measure that translate more than the clinical aspect of sleep quality and that can aid in predicting health outcomes. In this line, the development of more valid measures of sleep quality to improve and evaluate the management of sleep and sleep disordered patients has been attempted since 2008 (Roth, 2008). Ten years later, no major progress has been achieved, likely due to a lack of a comprehensive approach to "sleep quality" that allows to obtain valid sleep quality models, especially in patients with comorbidities that can confound a proper sleep quality assessment, such as depression (Roth, 2008a). Furthermore, while sleep laboratory measures may correlate with perceived sleep quality, they lack the ability to define it (Buysse et al., 1989). Therefore, in the future, it will be important to determine if the lack of correlation between objective and subjective measures of sleep can be given to unadjusted sleep

expectations or derived from other psychological traits. Identification of the source of the subjective–objective sleep discrepancy might lead to interventions capable of treating sleep disturbances, like insomnia, that cannot be determined by objective measures or have a high rate of treatment failure (Kay et al., 2017).

Conclusions

Studies have shown that sleep is key for proper development, performance and well-being. However, in our 24-h society, it is still difficult to obtain the adequate amount and quality of sleep. Consequently, sleep disruption leads to an increase vulnerability to disease conditions. From the present thesis, important clarifications regarding sleep's subjective quality components were provided, becoming clear that results variability have a strong methodologic component that frequently derived from posing different questions under the umbrella of sleep quality concept, as if they were the same, despite referring to different dimensions within the same phenomenon. In the present work, it was concluded that sleep quality should be regarded as a multidimensional concept and assessed as such. Each feature that is comprised within this construct should be attributed a specific weight that accounts for the variability between individuals and contexts. Thus, despite PSQI being a good measure of sleep quality, it is necessary to develop a new tool that considers the above-mentioned information. Nonetheless, our results also show that PSQI provides relevant information in an older population, regarding brain functional and structural connectivity. Overall, in an ageing world thriving to maintain good health and independence for as long as possible, sleep can be regarded as a key enabling factor for such purpose. Thus, beyond the body of literature and the contributions of this doctoral work, there are still avenues to be explored, so that individuals can benefit from a personalized sleep care.

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