Chapter 1

Sleep and Cognition

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http://dx.doi.org/10.5772/58735

1. Introduction

Sleep is an ancestral and primitive behaviour, an important part of life thought to be essential for restoration of body and mind. As adults, we spend approximately a third of our lives asleep and as we progress through life there are certain shifts in sleep architecture, most notably in sleep quantity. These biological or physiological age-dependent changes in sleep are well documented [1], and alongside the shifts in sleep architecture there is an increased susceptibility to certain sleep disorders.

Sleep disturbances and sleep deprivation are common in modern society. Most studies show that since the beginning of the century, populations have been subjected to a steady constant decline in the number of hours devoted to sleep. This is due to changes in a variety of environmental and social conditions (e.g. less dependence on daylight for most activities, extended shift work and 24/7 round-the-clock activities) [2].

Developments in the fields of molecular genetics, behavioural neuroscience, sleep neurobiology, and the cognitive neurosciences have produced converging evidence of a fundamental role for sleep in cognition. Sleep is required for good mental health, and insufficient sleep has negative effects on mood, cognitive performance and motor function [3]. Cognition is a broad term, which encompasses a variety of mental processes including memory, problem solving, language, forward planning and attention, which can all, be differentially affected by inadequate sleep. This can have serious real-life consequences, where many industries including airlines, long-distance truck driving, manufacturing and emergency services have recognised that sleep deprivation has major effects on performance.

Epidemiologists and clinical neuroscientists have also documented significant links between degree of sleep disturbance and severity of impairment on selective cognitive functions in a variety of clinical populations, including persons at risk for various dementing illnesses [4, 5].

Sleep disorder, in fact, may be one of the earliest signs of neurodegenerative disorders, including early Alzheimer's disease (AD) [6].

This chapter will briefly examine the relationship between sleep (quantity and quality) and cognition throughout the life course, and will consider the evidence which suggests that sleep deprivation and sleep disorders are associated with poor cognitive function. More specifically, it will examine the effects that sleep deprivation and sleep disorders have on both amnestic (memory function) and non-amnestic (non-memory function) cognitive processes.

2. Sleep quantity and cognition

Numerous studies have shown that short sleep, long sleep and sleep problems are associated with poorer cognitive function [7-9]. Self-reported short sleep, tiredness and fatigue are more strongly associated with subjective measures of cognitive function than with objective measures [7]. Findings from the Whitehall II study show that adverse changes in sleep over time (decrease from 6, 7 or 8 hours, or increase from 7 or 8 hours) are associated with lower scores on a variety of cognitive function tests, but not memory function [10]. Similarly, a Spanish study found that people who sleep for 11 hours or more per night have significantly lower global cognition scores than those who sleep for 7 hours [11]. A unique study has also reported on the effects of a post-lunch nap on subjective alertness and performance following partial sleep loss. A short nap has been found to improve alertness, sleepiness, short-term memory and accuracy, but does not affect reaction times [12].

Interestingly, there is little research into the effects of subtle changes in circadian phase on cognition, such as those that commonly occur in the general population after daylight saving time or returning to work after later weekend sleep. One study has revealed that performance on memory and verbal fluency tasks is significantly reduced on Monday morning following delayed weekend sleep [13]. Overall, proper alignment between sleep-wakefulness and internal circadian time may be crucial for cognitive performance, and humans may be very sensitive to small shifts in circadian timing.

The first recorded experiments on sleep deprivation began in the late 19th century [14], and research into the association between sleep and performance began around 50 years ago [15]. There is now clear evidence that deficits in daytime performance due to sleep loss are associated with a significant social, financial and human cost [3].

There are two types of sleep loss: acute sleep loss consisting of one continuous extended wake episode, and chronic sleep loss consisting of insufficient sleep over multiple days. A substantial amount of research has been conducted to understand the impact of short-term total sleep deprivation (<48h) on various cognitive domains. A recent meta-analysis examined the effect of sleep deprivation on six cognitive categories (simple attention, complex attention, working memory, processing speed, short-term memory and reasoning) for both speed and accuracy. Generally, effect sizes for each cognitive domain fall along a continuum, with tasks of greater complexity being less susceptible to the effects of total sleep deprivation. Simple attention, or

vigilance, is most strongly affected by short-term sleep deprivation, emphasising that this deficit is the one for which compensation is least available. This has implications for tests of work fitness, where deficits in sustained attention could act as an early warning for subsequent cognitive failure in more complex situations [16].

Therefore, sleep debt can be expressed as an additional wakefulness that has a 'cost' (i.e. cognitive impairment), which accumulates over time [17]. Homeostatic physiological processes that occur during sleep can replenish this capacity, but how much sleep is required for satisfactory alertness and performance continues to be debated [18].

3. Sleep quality and cognition

Whereas sleep quantity is concerned with the amount of time we spend asleep, sleep quality is measured by how well we actually sleep during the night. This is usually assessed via self-reported frequency of nocturnal awakenings; difficulty initiating sleep; waking up early; or waking up feeling tired, using validated tools such as the PSQI [19]. Research has suggested that as well as sleep quantity, sleep quality may also play an important role in cognition. One such study in elderly women has found that disturbed sleep is associated with an increased risk of developing a cognitive impairment, but not with accelerated cognitive decline [20]. However, self-reported poor sleep is not independently related to cognitive function in community-dwelling older men, suggesting that there may be an interplay between sleep quantity and quality which accounts for the detrimental effects on cognitive function [21]. The Maastricht Ageing Study (MAAS) aimed to determine whether subjective sleep complaints (i.e. difficulty falling asleep, waking up too early, and restless or disturbed sleep) in middle aged and older adults predict global cognitive decline over a period of 3 years. The study found that subjective sleep complaints are negatively associated with cognitive performance at follow-up, where waking up too early has the strongest association with cognitive decline of the three sleep quality assessment questions [22]. However, the association between sleep complaints and cognitive decline disappears once depression is controlled for, raising the question of whether poor quality of sleep leads directly to poor cognitive function, or whether poor sleep causes an increase in depressive symptoms which then results in cognitive decline [22]. This finding highlights the importance of accounting for the effects of other variables, such as depression, on sleep and cognitive function when interpreting various study results and potentially contradictory conclusions.

4. Sleep and cognition: A life course perspective

The amount of time we spend asleep fluctuates across the lifespan according to changes associated with age, health and life events. Newborn infants need between 10.5 and 18 hours sleep per day, and this gradually reduces to between 9 and 12 hours by the end of the first year of life [23], before we settle into a pattern of around 7 to 8 hours sleep per night as adults [2].

Studies indicate that as we age, total sleep quantity, sleep efficiency and deep sleep tend to decline, whereas the incidence of waking after sleep onset tends to increase [24]. More specifically in terms of sleep architecture, the time spent in deep, slow wave sleep (SWS) diminishes, along with a decrease in rapid eye movement (REM) sleep, and the time spent in lighter, stage 1 and stage 2 sleep increases. As a consequence, older people often find it takes longer to fall asleep, have more fragmented sleep, and wake up earlier [1]. Furthermore, ageing is also associated with increased daytime sleep via napping and dozing. Gender and socioeconomic dynamics also play an important role during the life course in determining sleep patterns and their potential effect on health [25]. For example, in women, sleep is affected by life events such as pregnancy and the menopause. In the following sections, we consider the possible effects that these changes in sleeping patterns may have on cognitive function.

4.1. Sleep and cognition in childhood and adolescence

It is well established that sleep plays a vital role in brain maturation and in the development of important cognitive functions, such as memory consolidation and learning [26]. With modern advances in technology, many environmental factors and social activities potentially restrict the time spent sleeping once children and adolescents retire to the bedroom. For example, televisions, mobile phones and computers or video games are becoming common bedroom fixtures [27].

A typical child spends more time asleep than engaged in any other activity during the 24 hour cycle. As a rule of thumb, the optimal amount of sleep for children is more than 12 hours per night for pre-schoolers, about 12 hours per night for primary school children, and about 9 hours per night thereafter [26]. Between the ages of 3 and 5 years, there is a shift in sleep architecture, with a significant reduction in total sleep time and a decrease in the amount of time spent in 'deep' sleep, SWS and REM stages [28]. Further, sleep is distributed across the day until around the age of 5 years, when children shift from a polyphasic to a monophasic sleep pattern, usually due to the changes in daytime schedule associated with attending school [29]. It is commonplace for toddlers and pre-schoolers to engage in midday naps but, until recently, relatively little was known about the function and structure of this sleep period in children. Research has now shown that classroom naps consolidate learning in preschool children, and that the memory loss associated with nap-deprivation is not reversible with overnight sleep [30]. When children are allowed to nap during the day, they recall around 10% more learned material on waking than when tested after an equivalent period of being kept awake. Sleep spindle density in particular is strongly implicated in this memory consolidation process in children, highlighting that the nap does not merely protect the memory from wakeful interference, but that consolidation of learned material is a process unique to sleep [30]. This finding has implications for educational strategies, where scheduled classroom naps could enhance interventions designed to help children achieve academic goals and acquire necessary cognitive skills, with particular relevance to children with a learning delay [30].

There have been few longitudinal studies of sleep-wake patterns in children [31, 32], and only a small number of studies have investigated sleep behaviours [33, 34]. Therefore, what constitutes normal sleep patterns and normal sleep behaviour during childhood is still

debatable. The lack of available data undoubtedly reflects the challenges to studying sleep in children and adolescents, which include reluctance of parents to leave children in the care of unfamiliar adults in laboratory studies, children's sleep becoming further disrupted in unfamiliar environments, and the potential for increased risk (e.g. fall in school performance, vehicle accidents in young drivers) following sleep restriction studies [35]. However, data from available studies has shown that sleep deprivation has a significant impact on cognitive abilities in children. Children aged between 10 to 14 years who are restricted to only 5 hours sleep show impaired cognitive performance on verbal creativity and the Wisconsin Card Sorting task, in comparison to those allowed to sleep for 11 hours [36]. Similarly, in a further study, children who are allowed to sleep for one hour longer perform significantly better in continuous performance and simple reaction time tests than those who sleep for one hour less, or those who receive no intervention [37]. Longitudinal research has shown that over the course of 3 years, children who experience an increase in sleepiness also show slower improvement in verbal comprehension than children who report lower levels of sleepiness at baseline [38]. The authors highlight the need for interventions to remedy sleep disorders and reduce the deleterious effect on cognition before the transition to puberty [38].

Circadian rhythms shift developmentally and sleep physiology changes considerably during adolescence (particularly SWS), which may alter the response to sleep restriction [39]. During the weekends, bed times and waking times can change extensively and persistently in children and in adolescents. These shifts are much more likely in adolescence, when the sleep phase rhythm can be seriously disrupted during weekends, and sleep debt is common [40]. Furthermore, the effects of delayed sleep phase in adolescents (characterised by problems with falling asleep and rising at appropriate times) extend into the week, where associations with lower average school grades, and greater incidence of anxiety and depression have been reported [41]. However, the effects of sleep duration on cognition can be different for males and females during the adolescent period. Whilst male adolescents who sleep for 8 hours or more demonstrate higher overall cognitive performance than those sleeping less than 8 hours, there is no association between sleep and cognition for adolescent females [42]. This supports previous findings that cognition is more susceptible to the effects of sleep deprivation in males than in females [43], and the authors propose that this is also consistent with the evolutionary demands of the female role in child rearing and nurturing [42].

4.2. Sleep and the elderly

Cognitive ageing is a heterogeneous process, in that not everyone experiences the same rate of decline. Indeed, many neuronal changes associated with cognitive decline begin to appear during middle-age [44]. Biological or physiological age-dependent changes in sleep have been well documented, and include shifts in sleep architecture as well as increased susceptibility to certain sleep disorders [1]. In addition to changes in SWS and REM, electroencephalography (EEG) studies have shown specific changes to delta waves, sleep spindles and K complexes during sleep in the elderly. It has been hypothesized that some of these changes might be early biological markers of the gradual deterioration of the central nervous system with age [45].

Furthermore, chronic ill-health, disability, and pain and discomfort at night may also contribute to poor sleep quality in an ageing population [46].

Ageing is associated with increased daytime sleep via napping and dozing, due to excessive daytime sleepiness (EDS) or feeling not rested upon awakening [47, 48]. The Medical Research Council Cognitive Function and Ageing Study (CFAS) looked at the association between self-reported sleep measures and cognition in over 2, 000 cognitively unimpaired individuals over the age of 65 years. The authors found that daytime napping at baseline is associated with a lower risk of cognitive decline at 2 and 10 year follow-ups, and that reports of both EDS and obtaining less than 6.5 hours of night-time sleep at baseline are associated with an increased risk of cognitive decline at 10 year follow-up [49]. Sleep structure is also important in aged adults, where the duration of sleep cycles, but not the amount of REM, non-REM or SWS or total sleep time, is positively associated with morning memory performance [50].

Sleep problems are a common occurrence in those with mild cognitive impairment (MCI) [51] and dementia [52]. Those with dementia experience highly fragmented sleep, with frequent daytime napping and night-time periods of wakefulness. Furthermore, sleep disorders have been associated with, and are predictive of, cognitive decline [5], and severity of cognitive impairment in diseases such as dementia and AD [53, 54]. A study has shown that non-demented, Japanese-American men who report EDS at baseline are twice as likely to be diagnosed with incident dementia at 3 year follow-up examination than those without EDS [55]. These findings were replicated in a sample of elderly French men and women [56], with the cross-cultural validation adding weight to the association between EDS and incident dementia.

Studies have also reported on sleep disturbances in specific types of dementia. In AD, for instance, which is characterized by episodic memory impairment, there are changes in global sleep architecture [57]. Modifications in the stages of sleep, including increased stage 1 sleep and reduced SWS, as well as decreases in sleep spindles, are well documented in dementia and AD [58, 59]. Less time in bed is associated with better cognitive function in AD [60], whereas EDS is strongly predictive of vascular dementia [61]. Changes in sleep architecture and sleep disturbances are found in a range of other neurodegenerative disorders such as progressive supranuclear palsy, Huntington's disease (HD), Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB) and Creutzfeldt–Jakob disease (CJD) [57]. Only a few studies, however, have investigated the prospective association between sleep architecture and later neurodegenerative disorder. Furthermore, the available results are inconsistent, which may be due to population selection, duration of follow-up, age of participants or type of cognitive impairment [57].

4.3. Partum

Pregnant women experience prolonged sleep latency, frequent awakenings, fewer hours of night sleep, and reduced sleep efficiency, which begins in the second trimester of pregnancy and extends through at least the first 2-3 months after delivery [62, 63]. Sleep quality diminishes progressively throughout pregnancy, is most affected immediately after delivery, and then subsequently improves steadily [64]. Whilst many new mothers report feelings of confusion

and forgetfulness during the early postpartum period, objective investigations thus far have not provided equivocal results. In some studies, women have significantly lower scores on tasks of immediate memory, complex mental functions (e.g. problem solving) and overall daytime function during the immediate postpartum period, with suggestions that this is influenced by sleep disturbance (e.g. fragmentation, deprivation) [62, 65, 66]. Indeed, although overall cognitive scores may not always differ between new mothers and controls, performance on memory and concentration tasks in postpartum women is significantly predicted by the amount of sleep they had the night before [63].

4.4. Menopause

Sleep complaints during or after menopause are a common medical problem. Whereas some studies have shown an association between sleepiness, sleep complaints and cognitive performance during and after menopause [67], other studies have not shown this association [68]. For example, one study showed that both self-reported and objectively-measured disturbed sleep are associated with diminished cognitive function during and after menopause. However, another study has showed that there is a higher association between self-reported poor sleep quality, rather than objectively measured poor sleep quality, and decreased cognitive test performance [69]. Weber et al found that memory complaints in particular are associated with increased sleep disturbance in perimenopausal women [70]. However, it has been suggested that it is age, rather than the menopause *per se*, which contributes to the decrease in cognitive performance [68].

5. Sleep disruption and work

Modern society depends on the continuous operation of a diverse array of crucial services. Thus the 24-hour culture-with shift work, night work, and longer, irregular working hours, and the associated shorter quantity of sleep-is becoming a frequent occurrence throughout the world [71, 72]. Sleep deprivation and consequent disruption of the circadian rhythm is a common situation experienced by individuals in many different professions, such as medical staff. After 8 hours of work, an individual's performance and ability to concentrate decreases, whilst the risk of fatigue [73] and cognitive errors increases [74]. Consequently, working at night and working excessive hours that restrict sleep opportunity are implicated in compromised health and safety at work [75]. A combination of factors are involved in this process including age, shift pattern, changes in sleep quality and quantity, sleep disruption and shorter daytime sleep (as compared to the usual night-time sleep), sleepiness and fatigue, and repeated stress induced by desynchronization of the circadian system [76, 77].

Sleepiness in the medical profession is a common occurrence due to the extensive hours worked and disturbed sleep [78]. During a typical shift, physicians perform complex problem solving whilst undertaking a multitude of different tasks. There is extensive research into the effects of sleep deprivation on specific tasks (such as endotracheal intubation and catheterization) [79], and in many different specialties such as anaesthetics [80], emergency medicine

[81], surgery or intensive care [82]. A landmark study of medical residents working in an adult intensive care unit shows that residents make more medical errors when they work frequent shifts of at least 24 hours, than when they work shorter shifts [83]. Thus, the effect of sleep deprivation on physicians could have a direct impact on quality of health care.

Subjectively, medical residents report disturbances of sleep, alertness and mood during the night float rotation [84]. Studies have also shown that residents are more likely to have a motor vehicle crash or 'near miss' after a night of on-call duty [85], or after a shift lasting 24 hours or longer [86]. Sleep-deprived residents also have more attention lapses, experience more adverse events and make more diagnostic errors while on duty overnight [86, 87]. From a training perspective, sleep deprivation may affect residents' skill acquisition and retention.

Aviators and aviation crews are also at a profound risk of sleep deprivation and disturbance given the nature and requirements of their work. Military pilots are required to synthesize vast amounts of information and subsequently make critical decisions. Thus, factors, which may impair cognitive performance, such as fatigue and sleep disruption, must be identified and alleviated wherever possible. A survey of US Army aircrew found that almost 62% of respondents did not feel that they received adequate daytime sleep while on shift [88]. A further study showed that there is a significant positive association between level of effectiveness (as determined by sleep–wake patterns) and neurocognitive functioning before flight operations [89]. In addition, the influence of chronic jet lag on cognitive efficiency in cabin crew has been investigated. Prolonged cortisol elevations (over 8 hours jet lag per week, for more than 3 years) results in a reduced temporal lobe volume within the brain, as well as deficits in spatial learning and memory, which become apparent after just five years of exposure to high cortisol levels [90].

Alongside studies into the effects of shift work and subsequent sleep disruptions on cognitive function, there has been on-going research into performance enhancers for shift and night workers. Various studies have found that improvements in alertness and performance during night shifts are associated with the use of stimulants such as caffeine [91] and modafinil [92, 93], and even exposure to bright light [94]. Laboratory and field studies corroborate that scheduled exposure to bright light (for work) and darkness (for sleep) shifts the circadian clock to align completely with a night work/day sleep schedule [95, 96]. As mentioned previously regarding post-lunch naps [12], short naps may also be useful for improving alertness during night shifts [91]. However, these countermeasures do not address the underlying cause of the problem, which is misalignment between circadian rhythms and the sleep and work schedule.

Few studies have assessed the *long-term* consequences of chronic sleep deprivation and repeated disruption of circadian rhythms on cognitive function. Findings from the Whitehall II study show that working more than 55 hours per week is associated with short sleep and lower scores in many cognitive performance tests, including vocabulary and reasoning, at both baseline and 5 year follow-up [97]. Another key study has found that male shift workers have lower cognitive scores and slower cognitive processing than those who have never been exposed to shift work, and that memory performance decreases with increasing shift-work duration [98]. Interestingly, individuals who ceased shift work more than 4 years earlier

demonstrated no cognitive impairments, which suggest that the effect of shift work on cognitive function may be reversible [98]. Overall, these results imply that long term exposure to shift work, resulting in insufficient sleep due to a disrupted circadian rhythm, leads to the deterioration of cognitive function (at least in men).

6. Sleep and amnestic and non-amnestic cognition

The term 'cognition' refers to various higher mental processes, which allow us to think, perceive, remember, imagine and plan ahead in everyday life. These specific processes can be grouped into two broader categories of 'amnestic' (memory) and non-amnestic (not involving memory) cognitive function. This is a useful dichotomy when considering age-related cognitive decline and the conversion from normal cognitive ageing to MCI, since MCI is typically diagnosed as amnestic (aMCI) or non-amnestic (naMCI) type [99]. These two types of MCI have different trajectories, with aMCI potentially developing into AD, and naMCI possibly developing into various forms of dementia (e.g. vascular dementia, DLB, frontotemporal dementia) [100].

Despite the advance in knowledge of MCI subtypes, to date, most studies into the effects of sleep on cognitive function have reported results from tests of 'global' cognitive function, such as the Mini-Mental State Exam (MMSE) [101]. Nevertheless, it is possible to distinguish between amnestic and non-amnestic function using the MMSE, as reported recently in a study on sleep characteristics and subsequent cognitive impairment at one-year follow up [102]. In this study, amnestic cognitive impairment is distinguished from non-amnestic impairment by scores on the delayed recall task in the MMSE. That is, if participants cannot recall any of the three items in the memory task, or can only recall one of the items, this is categorised as a failure and thus the participant is attributed with an amnestic cognitive impairment. With regards to sleep quantity, amnestic cognitive impairments at one-year follow up are significantly predicted by long sleep durations (≥ 9 hours) in women, and by short sleep durations (≤ 5 hours) in men. It is possible that women are more resilient to the effects of short sleep due to environmental demands [42], or that men are more susceptible than women to cognitive impairment following sleep deprivation [43], although the authors urge that sex differences in these results should in interpreted with caution [102]. That is, males made up a smaller proportion of the sample and so some effects may not be detected due to a lack of statistical power. In addition, there was no association between sleep quantity and non-amnestic function in this sample of community-dwelling older adults.

Gaining knowledge of different predictors of amnestic and non-amnestic cognitive impairment is important, now more than ever, owing to the advances in MCI and dementia research which will eventually allow earlier, and more accurate, diagnoses of cognitive impairments and dementia. Although Potvin et al. (2012) have shown that the MMSE can be used to extract amnestic and non-amnestic cognitive scores; the findings should be interpreted with caution [102]. Relying on the results of one item from a test of global cognition is not a robust method of diagnosing memory impairment, not merely because there are so many more tests, which

comprise the non-amnestic score on the MMSE. Further research is now needed to validate and standardise specific tests of amnestic and non-amnestic cognitive function, which will allow more accurate and specific diagnoses of MCI subtypes, thus giving way to earlier detection and diagnoses of dementia and AD, which in turn will improve the level of support provided to patients and their families.

7. Sleep disordered breathing, sleep disorders and cognitive function

The term sleep-disordered breathing (SDB) refers to conditions, which are characterised by intermittent reduction (hypopnoea) or cessation (apnoea) of breathing due to narrowing of the upper airways. These apnoeas and hypopnoeas occur during sleep, causing recurrent arousals from sleep and subsequent EDS. The condition is very common in the elderly, with reports of prevalence rates between 24 and 42% [103]. Each of the two consequences of SDB (sleep fragmentation and hypoxia) is associated with the risk of developing neurocognitive impairments in various domains [5, 104, 105].

7.1. Sleep apnoea

The most common form of sleep apnoea is obstructive sleep apnoea (OSA) or obstructive sleep apnoea syndrome (OSAS). OSAS is associated with frontal lobe and subcortical damage, which in turn is associated with diminished attention span, memory, delayed recall, impaired language and executive functions [106]. Research suggests that the specific brain damage associated with OSAS could therefore increase the risk of developing dementia [107]. Furthermore, a significant positive correlation between the apnoea index (the number of apnoeas occurring per hour) and severity of dementia has also been reported in AD patients [108]. Indeed, SDB may exacerbate cognitive dysfunction in patients with dementia and AD [109].

The EDS associated with OSAS usually becomes worse as AD progresses. Several studies have suggested a relationship of EDS with the occurrence of dementia [55, 56, 61], but it remains unclear as to whether SDB precedes cognitive impairment or vice versa. It is imperative that the causal associations are established as SDB has a high rate of associated morbidity, and utilisation of established and effective treatments (such as continuous positive airways pressure (CPAP)) might prevent or slow future cognitive decline. For instance, research has shown that treatment of OSA via CPAP improves some aspects of cognitive function in dementia patients as well as in non-demented elderly patients with OSA [109, 110]. However some neurobehavioural deficits, such as impairments in driving performance, may not be reversed by CPAP treatment in patients with severe OSA, and so further research is needed to assess the causes of such impairments [111].

7.2. Rapid eye movement sleep behaviour disorder (RBD)

RBD is a parasomnia, which is characterized by recurrent dream enactment and loss of normal voluntary muscle atonia during REM sleep, causing excessive motor activity [112]. These movements can cause excessive limb or body jerking leading to complex violent behaviours.

RBD is now recognized to be a symptom or prodrome of the group of diseases, which include PD, MSA and DLB [113]. The first study to document this relationship reported that 38% of patients diagnosed with isolated, idiopathic RBD later went on to develop a Parkinsonian disorder after a mean of 12.7 years from RBD onset [114]. Subsequent studies have confirmed similar findings, with typical mean intervals from RBD to PD, DLB, or MSA of around a decade [115-117]. This lengthy preclinical phase has important implications for interventions, which are designed to slow or halt the neurodegenerative process [4], and could therefore potentially slow the rate of associated cognitive decline.

7.3. Insomnia

Insomnia is a commonly reported sleep disorder in Western European countries. It is estimated that between 10% and 35% of the population of Western Europe have varying degrees of insomnia symptoms [118]. Insomnia has been defined in a variety of different ways in epidemiological research, from the presence of any difficulty initiating or maintaining sleep through to validated diagnostic criteria provided by the Diagnostic and Statistical Manual of Mental Disorders [119], with prevalence rates varying with each definition [120].

There is a growing amount of literature showing that insomniacs are at increased risk of cognitive decline (see [121] for a review). One study has shown that insomniacs have decreased memory ability compared to normal sleepers, where the detrimental performance is not attributable to sleepiness [122]. Furthermore, performance deficits in reaction times and vigilance tests often found in insomniacs may be related to specific SWS deficiencies [123].

8. Mechanisms

The underlying mechanisms regarding the association between sleep and cognition are still relatively poorly understood. However, specific brain regions involved with certain neurocognitive domains, including executive attention, working memory and higher cognitive functions, are known to be particularly vulnerable to sleep deprivation [3]. Furthermore, it has been suggested [124] that fragmented daytime sleep (following a night shift) is associated with large reductions in activity in the corticothalamic network, which mediates alertness, attention and higher-order cognitive processes. Performing higher-order cognitive tasks, such as decision-making, at night may be reliant on prefrontal brain areas, which suggests either the recruitment of a focused attentional strategy, cortical compensation for sleep deprivation, or both [125].

Despite decades of research, the significance and functions of sleep and its various stages, in particular REM sleep, are still not fully understood. A close association with cognitive functions was assumed shortly after the discovery of REM sleep and its relationship to dreaming [126] and there is now considerable evidence showing that newly learned material and skills are consolidated during REM sleep [127]. Furthermore, studies show a link between brain cholinergic activity, timing and density of REM sleep and cognitive functioning [128]. Thus, deficiencies of REM sleep might correlate with or predict cognitive deficits in the elderly.

Research linking SWS to mental restorative processes has been somewhat limited and less convincing. Only a few studies have attempted to examine the relationship between nocturnal SWS and subsequent daytime performance. In one study of healthy young male subjects, those who had slower reaction times on a daytime vigilance test also had lower amounts of nocturnal SWS than did age-and gender-matched individuals who had relatively faster reaction times [129]. Further to findings of the importance of SWS to daytime performance in younger people, Spiegel et al. report both confirmatory and contradictory results concerning the associations between loss of SWS and cognitive decline in adult life. They speculate that the role or functional significance of SWS may change over the course of the life span, which could account for their inconsistent findings, where SWS plays a restorative role in the cognitive functioning of older adults [130]. It is however possible that these studies are measuring different aspects of SWS and that the observed differences may reflect a lack of resolution in the available measurements.

The formation of long-term memories requires a process of consolidation, which is facilitated by sleep. The formation of declarative (consciously recalled) memories, which are hippocampus-dependent, appears to benefit mainly from SWS [131]. Recently, the focus has also been placed on stage 2 sleep and more precisely on sleep spindles, where research shows that overnight verbal memory retention is highly correlated with an increase in the number of sleep spindles [132].

Substantial inter-individual differences in vulnerability to the effects of sleep loss have been demonstrated by various studies [133]. These differences are partly due to tolerance of disturbances in circadian and social rhythm, which varies considerably between individuals [134]. There is also substantial individual variability in the magnitude of age-related cognitive decline [135]. Suggested sources for this variability focus on individual differences in the amount of age associated brain dysfunction, such as cortical [136], white matter pathology [137], and reductions in neurotransmitter receptor binding [138].

Sleep deprivation, mental fatigue, depression, or sleep disorders such as narcolepsy may result in an individual experiencing a transient loss of perception of external stimuli. This is known as a microsleep, and may last up to 30 seconds [139]. Microsleeps can occur at any time without warning, and the sufferer is usually unaware of the occurrence. As such, microsleeps are extremely dangerous in situations that require constant attention or vigilance, such as driving or operating heavy machinery [140]. Through a combination of EEG and neuroimaging techniques, research has shown that there are distinct and localised increases in activity in the fronto-parietal cortex which accompany microsleeps [141]. This activity may be part of a mechanism to restore responsiveness during the transient loss of arousal. Positron Emission Tomography (PET) studies have also confirmed that the 'resting brain' is surprisingly active. Raichle and Mintun (2006) report that, not only are there specific areas of the brain associated with higher regional cerebral blood flow (rCBF) during rest than during attention-demanding tasks, but that attention-demanding tasks are associated with just a 10% increase in global brain metabolism compared to periods of rest [142]. The Default Mode Network (DMN) is responsible for the default state of 'resting' brain activity, which is vital for brain functioning and possibly consciousness [143]. The DMN comprises the posterior and anterior cingulate cortex,

and the temporo-parietal cortex [144], where activity decreases during attention-demanding tasks and increases when no such tasks are preformed (i.e. during rest) [145]. Interestingly, Picchioni et al. (2008) also found a transient increase in activity within the DMN during early stage 1 sleep [146].

Closely related to the DMN is the process of 'mind wandering' (or daydreaming), which is described as the default mode of operation of the brain [144]. It has been argued that rather than being a passive process, mind wandering is vital to healthy cognition, for example by integrating past and present experiences to facilitate future planning and personal goal resolution [147]. There has been speculation regarding the similarity between thought processes involved in mind wandering during wakeful periods and dream mentation during sleep [148], encouraging a more scientific enquiry into whether daydreaming and dreaming are mediated by the same neural networks. Indeed, meta-analyses of neuroimaging data show overlaps in activation of areas of the DMN during mind wandering, and dreaming during REM sleep [148].

9. Public health importance

There is no doubt that sleep is an integral part of life, and many studies have suggested that it should not be overlooked by clinicians, especially in older adults. Studies have shown that poor sleep quality can be an early sign of amnestic cognitive decline [102] and that EDS may be an early marker and potentially reversible risk factor of cognitive decline and onset of dementia [56].

Cognitive failures associated with total sleep deprivation are of great interest and importance, as their real-world consequences are often catastrophic [149, 150]. Night work is associated with safety risks for both the individual worker as well as society [149, 151]. Deficits in many aspects of cognition such as decision-making, memory processes and importantly in sustained attention are implicated in errors and accidents [16]. Diminished alertness during night shifts has been linked to ability to drive a motor vehicle, which can result in accidents [80, 85, 152]. There is also evidence that air traffic controller (ATC) performance declines and error rates increase on the night-shift, and that ATCs may be falling asleep while on-duty [153]. This, together with the evidence that flying performance decrements occur due to fatigue [154], poses a real worry. Considerable controversy exists regarding optimal work hours for physicians and surgeons, especially those in training [86]. There is a trade-off between providing a continuity of care; educational opportunities; and traditionally defined professionalism vs. clinicians' fatigue and health; erroneous decision-making and performance; patient care and safety; and overall cost of health care [152, 155].

The implementation of the European Working Time Directive (EWTD) has dramatically shortened doctors' working hours in an effort to reduce resident fatigue, with the anticipated result of decreasing fatigue-related medical errors and improving residents' well-being

[156]. Following the implementation of these regulations, increasing attention has been focused on the role of resident physicians' fatigue and the occurrence of medical errors, percutaneous needle sticks, laceration injuries and post-call motor vehicle crashes [157]. Although certain aspects remain controversial, there seems to be a positive effect on residents' fatigue levels, quality of life and job satisfaction, which may positively influence patient safety [158, 159]. Despite these changes, long working hours remain a common feature in health care worldwide [160]. An evidence-based approach is needed to minimize the risk that current work hour practices bestow while optimizing education and continuity of care [86].

Research shows that the effect of sleep deprivation on cognition is an important public health issue. Results of these studies have important implications in many areas of society, from new policies in medical education [87] to flight psychologists, improving overall sleep patterns and enhancing the war-fighting efforts of aviators in combat [89]. Understanding the fundamental properties and mechanisms through which sleep disruption and sleep disorders are related to cognition, and how sleep regulates alertness and performance in humans, also has therapeutic implications for the development of treatment and prevention strategies, as well as novel wake-promoting therapies [18].

10. Conclusions

Studies to date suggest that sufficient quantity and quality of sleep are required for many aspects of amnestic and non-amnestic cognition, most notably executive attention, working memory and higher cognitive functions. The amount of sleep required continues to be debated, but it is generally agreed that people at the extremes of the sleep distribution, i.e. short (<5hr) and long (>9hr) sleepers [20], are subject to cognitive deficits and accelerated cognitive ageing. Proper alignment between sleep-wakefulness and internal circadian time is crucial for optimal cognitive performance.

A vast amount of research has been conducted into the effect of sleep on cognition in specific scenarios as highlighted in this review. Shift workers who may have shortened sleep patterns have been implicated in compromised health and safety at work due to cognitive deficits. Furthermore, during pregnancy, postpartum and the menopause, women are vulnerable to sleep disturbances, which can have profound effects on different areas of cognition, most notably memory. Age-dependent changes in sleep have been well documented, and research has been conducted into the association between these changes and effects on normal and pathological cognitive decline. Sleep disorders have also been shown to negatively affect cognitive function across the lifespan.

Further research is required to understand the associations and mechanisms involved in more detail, where the findings could have huge impacts in many areas of medicine, from normal ageing to neurocognitive disorders and public health.

Acknowledgements

The study is part of the *Sleep, Health & Society* Programme of The University of Warwick. This project was supported by a small grant from the University of Warwick Undergraduate Research Scholarship Scheme (URSS). We thank Patricia McCabe for help with the preparation of the manuscript.

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