

Evolutionary significance of sleeping

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SUMMARY

We have evolved to sleep a third of our lives, eight hours each night. However, when we sleep, we are unable to gather food, reproduce, fulfill our social needs, and we are more vulnerable to predation. Therefore, from an evolutionary perspective, we would not have been selected by nature to sleep this much if sleep was not absolutely vital to our survival. In this literature review, we attempt to explore the vital roles of sleeping at a physiological level. This study explains the effects of sufficient sleep on mental processes of memory and learning, emotion regulation, creativity and problem solving. Moreover, we discuss how lack of sleep and extended wakefulness are highly correlated with the impairment of the mentioned processes and the pathology associated with them. This study identifies sleep as the main pillar of well-being and health. The implications of this are becoming more and more relevant as humans are the only species that intentionally deprive themselves of sleep, resulting in one of the major troubling problems of the 21st century.

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INTRODUCTION

From an evolutionary standpoint, sleeping seems to be an unfit behaviour for our survival. Sleeping prevents us from gathering food, looking for mates to reproduce, protecting ourselves and our families, and interacting with our environment to fulfill our other needs. Yet, sleeping seems to be a dominant behaviour across humans' lifespans. We sleep approximately one third of our lives, during which we are less sensitive to external stimuli and adopt a recognisable posture as our antigravitational muscles are relaxed, we are lying down, and our eyes are closed (Peigneux et al., 2001). During this time we pass through different stages of sleep, with the main two stages being non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Box 1). The REM cycle encompasses 20-25% of our sleep cycles and during this time, we dream (Carskadon and Dement, 2011). Based on the approximate amount of time spent sleeping in our lives and the

20-25% of that time spent dreaming, we spend one-twelfth of our lives dreaming. During that time, we expend energy to produce this seemingly useless and psychotic experience, which we usually forget most or all of. Thus, it does not seem that sleeping and dreaming are the most efficient or fit choice for natural selection, unless these behaviours are absolutely vital to our survival.

This review will investigate the evolutionary benefits of sleeping by stating the vital roles it has on our fundamental mental processes such as memory and learning, emotion regulation, problem solving, and creativity. For a better understanding of the evolutionary significance of sleeping, we expand on the impairments of these mental processes and the pathologies associated with them as a result of sleep deprivation (SD). These include Alzheimer's disease (AD) and psychological disorders. Furthermore, this study explores the negative effects of SD on other major

BOX 1 | STAGES OF SLEEP

Sleep is comprised of two main states, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These are characterised based on physiological parameters, among which the main is the presence/absence of rapid eye movements. Wakefulness, NREM, and REM are distinguished by their distinct patterns on an electroencephalogram (EEG), electromyograms (EMG), and electrooculograms (EOG), which are the most common devices in the objective study of sleep in laboratory settings (Carskadon and Dement, 2011).

NREM sleep is subdivided to stages 1, 2, 3, and 4 (N1, N2, N3, and N4) based on the appearance of particular wave patterns on the EEG; the emergence of waveforms such as sleep spindles, K-complexes, and high voltage slow waves (Moorcroft, 2013). The number of each stage is associated with the depth of that sleep stage or its arousal threshold. With N1 having the lowest arousal threshold and N4 having the highest. Subjectively, NREM sleep is characterised by minimal brain activity in a moveable body which is prevalent in the beginning third of the night (Carskadon and Dement, 2011).

On the other hand, REM sleep is categorised into two less significant stages: phasic stage and tonic stage. The former being the state of high rapid eye movement activity and the latter being the calmer episodes between those bursts. Dreaming is the key component of REM sleep which co-occurs with this state and produces high brain activity (Carskadon and Dement, 2011). To prevent the motor activity triggered by the internal stimuli in a dreaming brain, the skeletal muscles are paralysed inhibitory activity of motoneurons (Brooks and Peever, 2012). Therefore, REM sleep is characterised by intense brain activity in a paralysed body, as it is shown in EEG, EMG, and EOG (Moorcroft, 2013).

systems, as we discuss the relationship between SD and cardiovascular diseases (CVD), and immunopathology and cancer.

VITAL ROLES OF SLEEPING

SLEEPING IN LEARNING AND MEMORY

Whenever the brain engages in an action, thought, or experience, the synaptic activity profile in the respective neural pathway will change (Walker, 2009b). Consequently, the formation or “encoding” of memories that contain information about those events takes place (Walker, 2009b). Encoding is the result of changes in the synaptic efficacy and strength in different neural pathways. These changes which are known as long term potentiation (LTP), will form a memory trace in a specific neural pathway (Shors and Matzel, 1997; Rasch and Born, 2013). The result is the short-term storage of this learned information. This fragile memory then needs “consolidation”, which involves further stabilisation of the synaptic strength in that memory trace and its integration with the pre-existing knowledge networks (Rasch and Born, 2013). Once the memories are

consolidated, they are accessed and recalled through a process called “retrieval”. Therefore, memory function consists of three main subprocesses: encoding, consolidation, and retrieval (Rasch and Born, 2013). Sleep plays important roles in all three processes for both types of memory: 1) declarative memory which consists of episodic and semantic memories; 2) non-declarative memory involving procedural and perceptual learning and memories, as well as conditioning and implicit learning (Rasch and Born, 2013).

Sleep and declarative memory

Declarative memories are our episodic and semantic memories. The former is concerned with the continuity and the spatiotemporal context of the past experiences. Whereas the latter involves fact-based knowledge that is independent from the context of the experiences (Winocur, Moscovitch and Bontempi, 2010). Declarative memories can be encoded intentionally or unintentionally, but they are recalled and accessed with awareness (Rasch and Born, 2013). These memories are thought to be hippocampus-dependent and their

BOX 2 | ALTERNATING STAGES OF SLEEP: NREM-REM CYCLES

NREM and REM sleeps alternate throughout the night in a cyclic manner. The onset of sleep starts after a few minutes of N1 with a very low arousal threshold; a soft touch or noise might result in awakening (Carskadon and Dement, 2011). The sleep then transitions into N2 where arousal threshold increases and the same stimuli as N1 will not result in arousal, but information of K-complexes—large slow peaks on EEG that last for 0.5 s. This stage is rich in rhythmic oscillatory waveforms that are moderately intense and fast (12-14 Hz), called sleep spindles (Moorcroft, 2013). In 10-25 minutes, N2 progresses into N3 and N4 as high-voltage slow waves start to appear. Hence, N3 and N4 are called slow-wave sleep (SWS), or delta sleep. This stage lasts for 20-40 minutes in the first few cycles and is followed by a brief stage two transition to REM sleep. REM sleep has variable arousal threshold as the external stimuli can be incorporated into dreams' content; thus, REM arousal threshold is the highest across the night (Carskadon and Dement, 2011).

NREM-REM cycles throughout the night are not the same and the length of each component varies. SWS is abundant in the first cycles and disappears in the later cycles, where N2 dominates NREM sleep. REM sleep periods take over these cycles, in particular towards the last third of the night. On average NREM-REM cycles last between 90 to 110 minutes across the night (Carskadon and Dement, 2011).

encoding and consolidation are thought to be highly associated with sleeping (Walker, 2009b). Consolidation of declarative memory during sleep can be explained by the hippocampal-neocortical dialogue model. This model states that during wakefulness, newly acquired information gets stored in terms of changes in synaptic plasticity in specific neural pathways in the hippocampus (a neural representation of the information). These neural representations are fragmented, fragile and prone to interference and decay (forgetting). However, during slow-wave sleep (SWS), the abundance of synchronous bursts of hippocampal neurons that are propagated towards the network of neocortical structures will reactivate and transfer these representations to the neocortex (Buzsáki, 1996; Buzsáki, 1998; Born, Rasch and Gais, 2006) (Box 2). Consequently, getting sufficient sleep in consecutive days will lead to the transfer of acquired information to the neocortex (long-term memory storage space). Thus consolidation and integration of memories into the pre-existing knowledge networks takes place. The consolidated memories are then independent of the hippocampus for retrieval (Born, Rasch and Gais, 2006) (Figure 1).

The occurrence of hippocampal-neocortical consolidation during NREM sleep has two consequences: 1) the hippocampus-independent storage and retrieval of learned memories (Born, Rasch and Gais, 2006); 2) refreshed encoding

capacity of the hippocampus for post-sleep learning (Walker, 2009b). Therefore, sleep, and in particular NREM sleep, is critical to all declarative memory subprocesses. When we sleep, we transfer the newly formed short-term memories to our long-term memory storage space (consolidation). We can then recall those memories in future attempts (retrieval) and our hippocampi encoding capacity is refreshed to acquire new information in subsequent experiences.

Sleep and non-declarative memory

Non-declarative memories are memories that are encoded, learned, and recalled implicitly (without awareness). These memories are acquired independent from the medial temporal lobe structures, specifically the hippocampus. They are associated with different memory systems such as motor areas, striatum, and cerebellum for procedural memories as well as sensory cortices for perceptual learning (Peigneux et al., 2001; Rasch and Born, 2013). Sleep is shown to be associated with the consolidation of different types of non-declarative memories such as procedural motor learning, perceptual learning, and different types of priming or conditioning (Rasch and Born, 2013).

Many studies have used finger sequence tapping and visual texture discrimination to test for

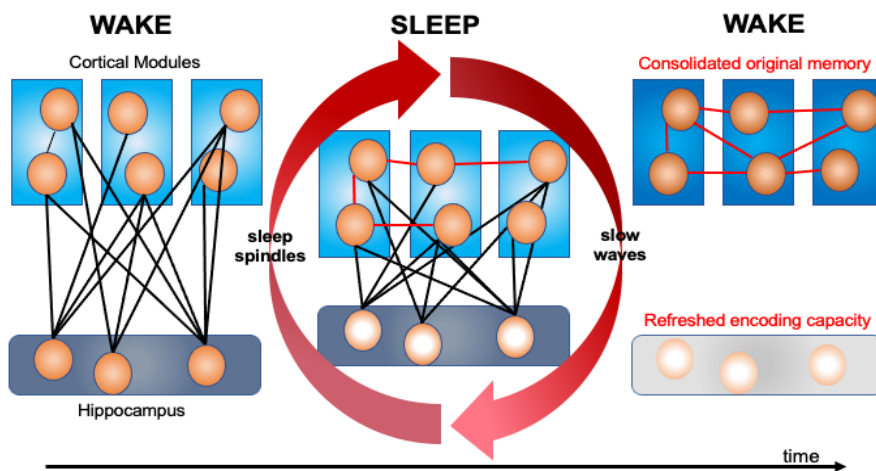


Figure 1: The process of hippocampal-dependent memory consolidation as explained by the hippocampal-neocortical model. Synchronous neural potentiation across NREM sleep produced by sleep spindles and slow-wave activity leads to the consolidation and integration of hippocampal short-term memory to neocortical long-term memory. This leaves a refreshed encoding capacity for the hippocampus (adapted from Walker, 2009b).

procedural and perceptual learning improvement due to sleep (Born, Rasch and Gais, 2006). Across all these studies, the results predominantly showed significant improvements in perceptual and procedural skills due to sleep with no further training (Walker et al., 2002a; Fischer et al., 2005; Kami et al., 1995; Karni et al., 1994). These results illustrated that the neural representations of the learned skills are constantly being reactivated and formed in different synaptic circuitry while asleep (Fischer et al., 2005). Throughout most studies, it was found that non-declarative memory was enhanced particularly by REM sleep (Born, Rasch and Gais, 2006; Fischer et al., 2005; Kami et al., 1995; Karni et al., 1994). However, in a study by Walker et al. in 2002, a significant improvement in accuracy and speed in a finger sequence tapping was associated with stage two NREM sleep (Walker et al., 2002a). This finding, along with similar findings such as a study by Smith and MacNeil in 1994, suggest that the procedural learning enhancement occurs in the late nocturnal sleep when REM and stage two sleep is abundant (Smith and MacNeil, 1994, p.2; Smith, 2001). However, it is worth mentioning that other findings point to the REM-dependent improvements of non-declarative skill learning and SWS improvement of declarative memories (Stickgold et al., 2000; Rauchs et al., 2004). These findings as a whole suggest that sleep-dependent

learning by the two memory systems are not generally mutually exclusive. Instead, they are complementary in each specific task, such as learning a new language (Peigneux et al., 2001).

Sleep is a key component in both declarative and non-declarative memory functioning in all three subprocesses: encoding, consolidation, and retrieval. SWS (early sleep cycles) is majorly

associated with declarative memory enhancement whereas stage two and REM sleep (late sleep cycles) are shown to be beneficial to non-declarative learning and memory. However, in reality tasks engage both memory systems, making them complementary. As different studies have discovered, task-specific impairments have been seen in both memory systems, using REM, SWS, and NREM stage 2 controlled deprivations (Walker et al., 2002a; Stickgold et al., 2000; Rauchs et al., 2004). Therefore, sufficient sleep is an evolutionary advantage due to its vital role on our memory and learning. Furthermore, this vital role in learning and memory can be clinically relevant to different types of diseases and disorders. Alzheimer's disease (AD) is an example that will be discussed in future sections (Mander et al., 2016).

SLEEP IN EMOTION REGULATION

Emotion generation and regulation is the result of the connectivity of subcortical emotion centres of

the brain, and their interactions with the regulatory cortical centres. More specifically, connectivity of the limbic structures such as the amygdala and striatum with the medial prefrontal cortex (mPFC) (Goldstein and Walker, 2014). Sleep is vital to emotion stabilisation and regulation as neuroimaging of the sleeping brain illustrates high activity and connectivity of the amygdala and mPFC, distinctly in the REM state (Nofzinger, 2005). REM sleep is characterised with very unique neuroanatomical, neurophysiological, and neurochemical properties, which are particularly adaptive to emotional stability and regulation in a sleeping brain and body. In terms of neuroanatomy, REM involves the increased activity of limbic and paralimbic structures where the acquired pre-sleep emotional memories are being revisited and processed (Nofzinger, 2005; Pace-Schott and Hobson, 2002). Neurophysiological properties of REM enables efficient integration and connectivity of cortical and subcortical structures. This is due to the prevalent propagation of theta (sawtooth) oscillations through the connective neural nodes (Pace-Schott and Hobson, 2002; Nishida et al., 2009). Finally, REM has a neurochemical advantage compared to wakefulness and NREM, as it suppresses noradrenergic activity of the locus coeruleus (LC) (Pace-Schott and Hobson, 2002). These unique biological traits grant REM with two major roles in emotion regulation: de-potentialisation of the arousing affective weight of memories to better retain the informational core of the experiences associated with them and recalibration of emotional sensitivity and reactivity for the post-sleep affective experiences (Goldstein and Walker, 2014).

REM in affective de-potentialisation of memories

During exposure to an affectively charged experience, the encoding of memory in the hippocampus co-occurs with the emotional value attachments via the amygdala. These emotional attachments to memories are due to the orchestrated, synchronous bursts of adrenergic neurons facilitated by LC (Walker, 2009a). These characteristics give affective memories an advantage in encoding and retention over the affective-neutral memories. However, the future retrieval of these salient memories is accompanied

by diminished affective tone compared to the original experience, while the information core of the experience remains intact (Pace-Schott and Hobson, 2002). In a study done by van der Helm et al. in 2011, the neural mechanism of this REM-dependent decoupling was investigated (van der Helm et al., 2011). During the study, they found that low central adrenergic activity in the brain—correlated with REM gamma activity—leads to increased connectivity of the ventromedial prefrontal cortex (vmPFC). This connectivity ensures a top-down regulation of the recently acquired salient emotional memories as well as decreasing the affective salience of the acquired neural representations (Figure 2).

Consequently, suppressed adrenergic concentrations during REM silences the emotional

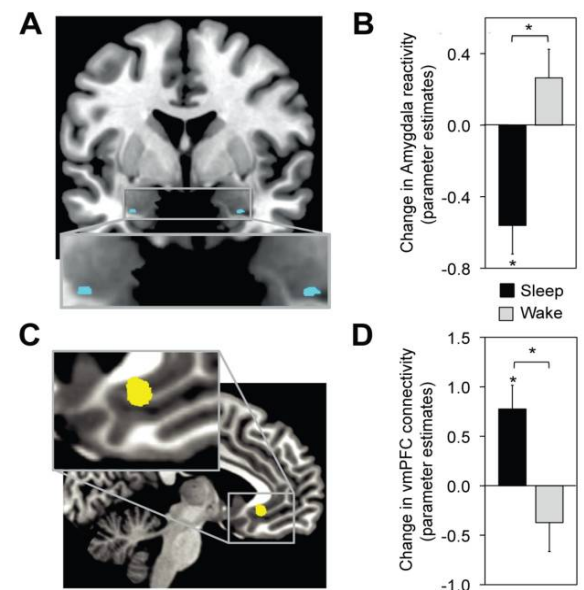


Figure 2: (A, B) This shows the relative difference in amygdala reactivity to affective stimuli between the first encounter and the second encounter in sleep group versus wake group. Sleep group shows a significant decrease in amygdala reactivity whereas the wake group shows an increase. (C, D) This shows the change in connectivity of the amygdala and vmPFC in sleep versus wake group. Sleep group shows a significant increase in connectivity whereas there is a decrease in connectivity in the wake group (van der Helm et al., 2011).

responsivity to the recent affective experiences in an overnight sleep, both in neural (determined by brain imaging) and subjective levels (van der Helm et al., 2011). Therefore, revisiting the memories of the previously encountered affective stimuli will show a softer affective tone.

REM in emotional recalibration

As mentioned, unique biological features of REM sleep provides emotional recalibration. Emotional recalibration refers to the overnight preparation of the brain and body for novel post-sleep emotional experiences (Goldstein and Walker, 2014). The brain needs to establish a homeostatic level for emotional centres so that during next-day affective encounters, these centres distinguish between salient and non-salient (important and non-important) experiences and respond with appropriate sensitivity and specificity (Goldstein and Walker, 2014). REM gamma activity plays an important role in determining noradrenaline concentrations throughout the night. Noradrenergic activity is crucial to optimal emotional behaviour and attention during wakefulness; hence the "housekeeping" role of REM in the noradrenergic activity of the LC is key to emotional recalibration for the next-day wakefulness (Sara, 2009; Siegel and Rogawski, 1988). The LC modulates the function of the amygdala and mPFC through noradrenergic interactions, but via different receptors. This modulation during REM with low adrenergic activities decreases the amygdala responsiveness to only salient stimuli and enhances mPFC activity. This further enhances the amygdala specificity by regulation. Thus, the specificity of the amygdala gets restored during sleep for next-day experiences (Goldstein and Walker, 2014; Ramos and Arnsten, 2007). Overall, REM prepares the body for post-sleep affective experiences by increasing connectivity between emotion regulators and generators, decreasing the affective tone of past emotional memories, and providing proper sensitivity and specificity (calibre) for our emotional centres.

Therefore, REM sleep is necessary to our emotional function, homeostasis, and health. This is a determining factor in our behaviour and decision-making abilities. Whereas, insufficient amounts of REM sleep would break this stability

and produce affective imbalance that will be discussed in later sections

SLEEP IN PROBLEM SOLVING AND CREATIVITY

One of the defining evolutionary advantages of our species is its ability to integrate pieces of knowledge and memory, to connect the existing knowns in new ways. This provides a greater understanding of the unknown solution to a problem (Walker, 2017). This ability to create new from old is called creativity. Studies conducted in recent decades have provided us with supportive data for the benefits of sleep, specifically REM sleep, to creativity and problem-solving (Stickgold and Walker, 2004).

In a study done by Sio et al. in 2013, they used remote-associate tests (RATs) to see the effects of sleep on problem-solving abilities of 27 male and 34 female healthy participants. RAT is an assessment in which the participant is given three seemingly unrelated words (e.g. "home", "sea", "bed") and asked to find a word that is associated with all three (e.g. the answer is "sick"). In this study, they divided their subjects into three main groups: control groups, incubation group, and sleep groups. The experiment consisted of two tests, and the second test consisted of unsolved questions from the first test and 12 additional random questions. The control groups (a.m. and p.m. control groups) were assigned to take the second test right after the first test without any breaks in between. The incubation group took the first test in the a.m. session and the second test in the p.m. session with a resting period in between, but no sleep. The first sleep subgroup wrote the first test in the p.m. session and the second test in the following a.m. session, while the other subgroup did both in different p.m. sessions to account for the bias of the circadian effect on the results. This study found that sleep groups showed significant sleep-dependent improvements in the second test compared to the first one. This significant difference did not appear in the other groups. This difference was also more apparent in difficult questions since it is believed that simpler problems have a narrower associated word network. The study hypothesised that this sleep-dependent enhancement in problem-solving is due to REM sleep as this state provides higher cognitive activity compared to NREM sleep (Sio,

Monaghan and Ormerod, 2013). This hypothesis had been tested in 2009 by Cai and coworkers. In their study, they used RATs to look at the effects of incubation (quiet resting without sleep), NREM sleep, and REM sleep in a nap paradigm on creative problem-solving improvements. They used nap paradigm to control for the circadian influence on problem-solving. In this study, in addition to RAT, they gave the participants a set of analogies after their a.m. test (e.g. chips: salty, candy: s_; the answer is sweet), where the answers to them were also the answers to some of the p.m. RAT questions (e.g. "sixteen", "heart", "cookies"). This added a priming effect which was hypothesised to trigger associative nodes in the answer word's network pathway, resulting in a better opportunity to test the effects of quiet resting, REM, and NREM on creating associations. Cai et al. found that incubation has a sleep-independent adaptive effect in problem-solving. However, after priming, the REM group showed significantly better creative problem-solving abilities than NREM and quiet resting groups (Cai et al., 2009). These results were also in agreement with an older study on REM-enhanced problem solving, conducted by Walker et al. in 2002 (Walker et al., 2002b). A study by Wagner and coworkers in 2004 suggested that not only does sleep improve problem solving, but it also inspires insight and deeper understanding of the problem. This results in exploring more efficient solutions or "short-cuts" in more complex problems, such as mathematical tasks (Wagner et al., 2004).

As data and studies suggest, sleep provides the brain with opportunities to revisit pre-sleep problems and its associated activated nodes in neural pathways. This reactivation leads to the expansion of the activity to memories, facts, and information associated with the problem (Cai et al., 2009). This expansion is suggested to be significant in REM sleep, as low noradrenergic activities within the brain will increase neocortical connectivity (Hasselmo, 1999). In conclusion, sleep simply provides a better understanding of a problem and enhances our capabilities in seeking solutions to it. This has been an influential evolutionary advantage in human development.

LACK OF SLEEP EFFECTS AND PATHOLOGY

By a joint consensus statement by the American Academy of Sleep Medicine and Sleep Research Society in 2015, eight hours of sleep per night was reported as sufficient amount of sleep for adults. This consensus statement also recognised sleeping for less than seven hours or more than nine hours per night as unhealthy behaviours if done on a regular basis (Watson et al., 2015).

Until this point, we have been discussing the benefits of the presence of sleep and how sufficient sleep, i.e. eight hours, is a significant evolutionary advantage. However, to appreciate the true value of sleep in our survival, we need to understand the deleterious impacts of sleep deprivation (SD) to our mental processes and physiology as well as the pathology associated with it. Moreover, we have to keep in mind that the effects of SD are not merely due to the absence of sleep, but also due to the resulting extended periods of wakefulness.

SLEEP DEPRIVATION AND IMPAIRED LEARNING AND MEMORY

As mentioned previously, all stages of sleep are fundamentally important to different types of memory functions. Thus, the detrimental effects of SD on learning capacity and memory formation and processing are not unexpected. SD is especially disruptive in hippocampal-dependent memory functioning.

SD has been shown to decrease hippocampal LTP induction as the result of adenosine build-up in neuronal extracellular space. Excessive adenosine concentrations in synaptic regions suppresses cAMP signaling, leading to disrupted NMDA and AMPA activity which is crucial for LTP induction. As a result, the hippocampal encoding capacity is negatively impacted as the neural representations of the memories are not stably maintained (Abel et al., 2013). According to neuroimaging studies, SD decreases hippocampal connectivity with cortical regions, such as neocortex structures (Yoo et al., 2007b). Thus, not only does encoding suffer detrimental effects, but also based on the

hippocampal-neocortical model, consolidation of memories are interrupted. Additionally, extended periods of wakefulness provides more encoded memories to the hippocampus, reducing its ability to form more memories. This is due to the lack of slow-wave activity that prevents the hippocampus from transferring information to the neocortex and getting refreshed to acquire new information (Born, Rasch and Gais, 2006; Krause et al., 2017). Given the disruptive effects of SD in memory functioning, this condition can be clinically relevant as many disorders are directly impacted by sleep, learning, and memory interruptions. Two substantially relevant conditions are aging and dementia (Krause et al., 2017); the two combined are one of the major health challenges of the 21st century, as globally, one in ten seniors above the age of 65 suffers from Alzheimer's disease (AD) (Sperling, Jack and Aisen, 2011). As recent studies have found, sleep, and more specifically, NREM sleep deprivation (NSD), is highly correlated with dementia and AD (Mander et al., 2016). The following section will investigate this correlation.

Sleep deprivation and its relationship with Alzheimer's Disease

Alzheimer's disease is the most common cause of senile dementia. It is caused by the accumulation of β -amyloid ($A\beta$) in the form of plaque in the brain's parenchyma or blood vessels (Wang, Dickson and Malter, 2006). This accumulation is typically due to the high production and/or low degradation and clearance from the extracellular fluid in the central nervous system. $A\beta$ deposition causes progressive memory loss due to the destruction of synapses and neurons in cortical and limbic structures, including the hippocampus and amygdala (Wang, Dickson and Malter, 2006). A high correlation between NREM sleep deprivation and $A\beta$ accumulation has come to light in recent years. NREM sleep has been found to have a distinct role in $A\beta$ clearance (Mander et al., 2016). During NREM sleep, glial cells show a significant reduction in volume, producing a hypertonic environment in the brain. This situation attracts the cerebrospinal fluid (CSF) flow via the interstitial space. This phenomenon clears many toxic metabolites and chemicals, $A\beta$ in particular, from the extracellular space. This clearance is twice

as efficient as the clearance occurring in the waking state (Xie et al., 2013). In addition, $A\beta$ production is highly correlated with the oxidative and metabolic neuroactivity in the brain (Misonou, Morishima-Kawashima and Ihara, 2000). The brain consumes a substantial amount of oxygen and ATP as the neurons are actively responding to external and internal stimuli during wakefulness (Dworak et al., 2010). Conversely, in NREM sleep, the low cognitive activity in the brain requires less oxygen and also restores ATP, resulting in a lower toxin-producing oxidative and metabolic activity (Misonou, Morishima-Kawashima and Ihara, 2000; Yatin et al., 1999). Therefore, NSD promotes $A\beta$ accumulation in two ways: 1) producing higher levels of $A\beta$ by longer periods of wakefulness. 2) less $A\beta$ clearance due to lower amounts of NREM sleep.

On the other hand, AD has shown to be characterised by NREM and SWS disruptions, sleep apnea, and insomnia. This is thought to be due to the $A\beta$ deposition in NREM slow-wave generator regions of the brain, such as the medial and lateral prefrontal structures (Murphy et al., 2009; Buckner et al., 2005). This loss of NREM in AD further increases the progress of the disease as it provides a vicious cycle where NREM loss leads to $A\beta$ aggregation and $A\beta$ aggregation results in NREM loss.

Based on these findings, NREM and SWS are suggested to be a novel biomarker for AD diagnosis in the onset of the disease (Mander et al., 2016). Moreover, preventative and therapeutic benefits of enhanced NREM sleep have been suggested. An increase in NREM sleep quality and quantity is suggested to provide a reduced risk for AD in mid- to late-life. Additionally, NREM sleep enhancement in people who already suffer from $A\beta$ aggregation pathology can minimize the cognitive decline rates as a therapeutic factor (Mander et al., 2016) (Figure 3). There are currently active areas of research in finding non-pharmacological methods for NREM SWS enhancement and induction of hygienic sleep patterns (Morin, 2015; Bayer et al., 2011; Marshall et al., 2006; Ngo et al., 2013). In addition, pharmacological studies in this area are being done; however, the results are reported to be less promising (Mander et al., 2016).

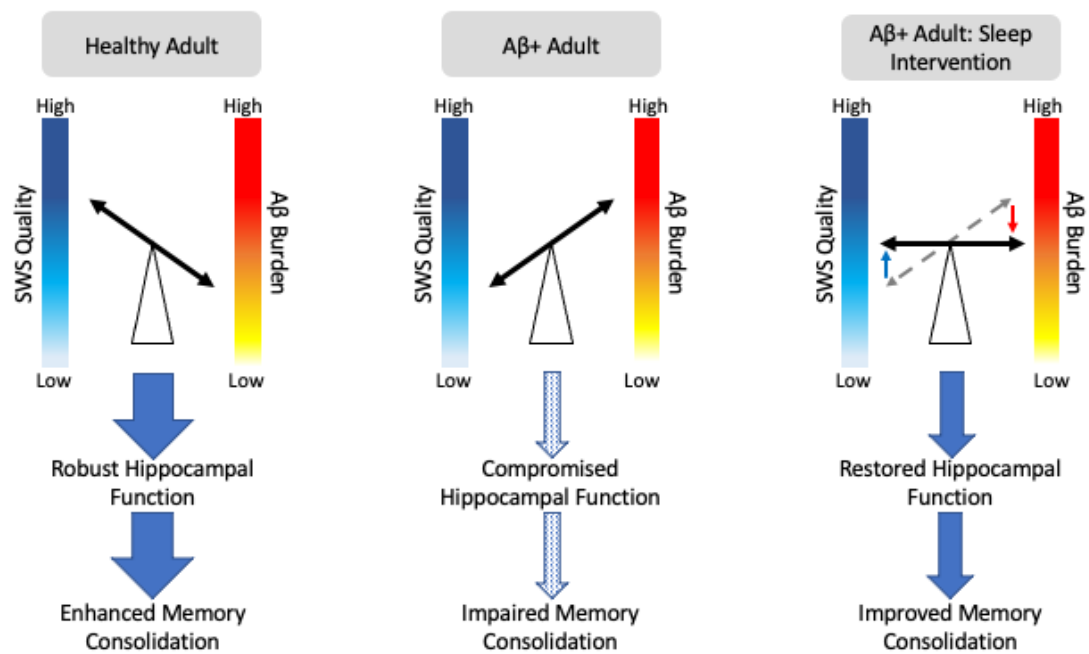


Figure 3: The relationship between NREM SWS quality and Aβ concentrations in the brain and the ability of sleep treatments and interventions to reverse these effects (adapted from Mander et al., 2016).

SLEEP DEPRIVATION, EMOTIONAL IMBALANCE AND PHYSIOLOGICAL DISORDERS

In the earlier sections, the vital role of sleep in emotion regulation was discussed. In particular, REM sleep is shown to be pertinent to optimal emotional behaviour due to its role in the emotional recalibration of the brain (Goldstein and Walker, 2014). For a better insight into this crucial role of sleep, it is important to study the sleep-deprived human brain and behaviour. In this section, the negative impacts of SD on emotional balance and regulation, as well as its clinical relevance will be investigated.

In various studies, it was found that a sleep-deprived brain is more sensitive to negative emotions. This is associated with the hyperactivity of emotion generators, the amygdala and striatum, and the decreased activity and connectivity of regulatory cortical regions, especially mPFC (Goldstein and Walker, 2014; Yoo et al., 2007a). The sensitivity to affectively negative stimuli is directly correlated with the emergence of stress, anxiety, anger, and increased impulsivity (Anderson and Platten, 2011; Minkel et al., 2012). Interestingly, this emotional dysregulation impacts

sensitivity to positive emotions related to reward stimuli as well. SD produces increased sensitivity in mesolimbic dopaminergic areas which causes overestimations for reward stimuli. Further, it causes a blunted connectivity in the medial and orbital prefrontal cortex which decreases emotion regulation (Gujar et al., 2011). The outcome is that a sleep-deprived person develops a greater tendency to do pleasure-evoking tasks while undermining the associated risks of those behaviours (Venkatraman et al., 2007). These behaviours include primary and higher order needs. For instance, increased appetite causing overeating and additionally, monetary risk-taking which includes gambling (Mckenna et al., 2007; Libedinsky et al., 2011; Greer, Goldstein and Walker, 2013). Therefore SD produces a bidirectional affective imbalance by increasing sensitivity of subcortical limbic and striatal structures to stimuli and decreasing the connectivity of these structures with mPFC—hence, blunted top-down emotion regulation (Goldstein and Walker, 2014). This is clinically significant since in many psychopathologies, same brain activity patterns are observed and sleep impairment is often a co-occurring symptom. Some of these effective psychiatric disorders include addiction disorders, major depression,

bipolar disorder, anxiety disorders, and post-traumatic stress disorder (PTSD) (Goldstein and Walker, 2014; Brower and Perron, 2010; Rauch et al., 2000; Etkin and Wager, 2007; Babson et al., 2010; Soehner et al., 2018). For a better understanding of this clinical relevance, the role of SD in addiction and PTSD will be discussed in more details in the following section.

Sleep deprivation and addiction

The increased sensitivity of dopaminergic mesolimbic areas is shown to have a causal effect on addiction disorders (Brower and Perron, 2010). High dopaminergic sensitivity is posed to be a common pathway through which SD increases responsiveness and acquired addiction potential to reward-stimulating substances. Sleep loss is also correlated with the maintenance of substance abuse and higher relapse rates in withdrawal attempts in different studies (Brower and Perron, 2010; Volkow et al., 2009). Therefore, sleep disturbance and deprivation is a recognised hallmark of addiction (Goldstein and Walker, 2014; Brower and Perron, 2010).

Sleep deprivation and Post-Traumatic Sleep Disorder (PTSD)

As an outcome of a traumatic event, sleep disturbances are observed in patients with, or susceptible to, PTSD. PTSD patients have shown decreased REM sleep time and quality (Germain, 2013; Mellman et al., 2002). As previously mentioned, LC activity and the adrenergic profile of the brain are regulated by REM sleep and this regulation is vital to emotion recalibration. Disruptions in this key sleep component are shown to be a predictive measure and early symptom of PTSD. For instance, the presence of insomnia in war veterans was used as a predictive factor in PTSD symptom developments (Wright et al., 2011). This is expected since both functions of REM sleep in emotion regulation are tightly connected with PTSD. First, loss of REM sleep will decrease the ability of affective de-potentialisation of the traumatic experiences in the following nights. Thus, the next day external cues related to the trauma will lead to intense emotional reactivity (Mellman et al., 1995). Secondly, disturbances during REM sleep causes adrenergic dysregulation and results in disrupted emotional recalibration. Consequently, amygdala sensitivity to the negative

emotions caused by the external cues in next-day experiences will significantly increase. Therefore, REM sleep loss can easily be correlated to the development of PTSD in people exposed to traumas.

LACK OF SLEEP AND OTHER MAJOR HEALTH ISSUES

The role of sleep robustly exceeds beyond mental processes and is critical to all the major organs and systems in our body. Therefore, the destructive effects SD expand across a wide variety of health problems (Walker, 2017). Chronic and acute SD can be correlated to serious health problems such as cardiovascular diseases (CVD) and cancer to name a few (Walker, 2017).

Sleep deprivation and cardiovascular diseases

Sleep deprivation is associated with many CVDs such as coronary artery diseases, congestive heart failure, metabolic disorders, and hypertension (Kent et al., 2014; Tasali et al., 2008; Cappuccio et al., 2010). This is due to the sympathetic bias produced by SD in the autonomous nervous system (Tobaldini et al., 2017). This bias results in higher blood pressure, increased inflammatory response, altered hormonal profile, and overall it provides conditions that are recognised for the development of atherosclerosis and CVD (Tobaldini et al., 2017; Mullington et al., 2009).

Sleep deprivation and cancer

Lack of sleep results in many dysregulations in the neuroendocrine system, and as the immune system is heavily dependent on the neuroendocrine pathways, SD has a substantial effect in cell proliferation and immune defence (Haus and Smolensky, 2013). Due to the cancer-stimulatory cytokine production, as the result of SD, cell proliferation and tumour initiation occur (Blask, 2009). Additionally, SD causes a decline in natural killer cell counts due to the sleep-dependent immune regulation (Irwin et al., 1996). These detrimental effects result in higher tumour initiation and lower tumour destruction. Therefore, chronic SD can be recognised as a risk factor for cancer (Haus and Smolensky, 2013; (Blask, 2009); Irwin et al., 1996).

FUTURE RESEARCH

Considering the fact that sleep is vital to a vast variety of mental and physiological processes, sleep research is a very active and viable area of science. There are still numerous underexplored avenues in this area that require scientific attention. As there is an unquestionable relevance to increasing levels of sleep deprivation in modern societies, the scientific community should take actions in developing sleep enhancement techniques. Currently, non-pharmacological techniques are being developed by researchers to serve as a preventative and therapeutic sleep prescription. For instance, transcranial direct current stimulation, auditory closed-loop stimulation, and kinesthetic stimulation are newly implemented techniques with very promising results across many sleep studies. Although they are promising they still require more improvement to be a practical sleep prescription (Morin, 2015; Bayer et al., 2011; Marshall et al., 2006, 2004). Furthermore, pharmacological studies on sleep enhancement have not shown to be significantly effective and thus, more studies should be conducted to develop effective drugs with low adverse effects (Mander et al., 2016).

CONCLUSION

We have evolved to sleep one-third of our lives and any less results in destructive consequences. The answer to “why we sleep?” is infinitely vast and complex. There is no major organ that does not function better in the presence of sufficient sleep and become deteriorated by its deprivation. Sleep is closely related to our physiology, behaviour, and mental processes. Its profound role in our survival suggests that despite all the discoveries and studies in this area, we still have to learn about the significance of sleeping to our existence. As SD is one of the alarmingly increasing health challenges in modern societies, an increase in public awareness on the importance of sufficient sleep is a necessity. Especially, when the core of our health-care system—doctors and nurses—are trained under extreme sleep-depriving conditions. Natural selection has selected those of us who slept eight hours per day because of the countless benefits it provides to our memory and learning, emotional balance, creativity, and general physical health. On the other hand, the modern lifestyle is leading us to the opposite direction, causing one of the major

health challenges of the 21st century. Therefore, we are eight hours of sleep away from solving one of the main global troubling problems and its consequences.

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