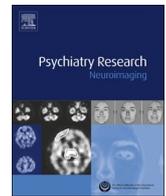




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Opinion

The role of slow wave sleep in the development of dementia and its potential for preventative interventions

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ABSTRACT

The increasing incidence rate of dementia underlines the necessity to identify early biomarkers of imminent cognitive decline. Recent findings suggest that cognitive decline and the pathophysiology of Alzheimer's disease are closely linked to disruptions in slow wave sleep (SWS) – the deepest sleep stage. SWS is essential for memory functions and displays a potentially causal and bidirectional link to the accumulation of amyloid beta deposition. Accordingly, improving SWS in older adults – especially when at risk for dementia – might slow down the rate of cognitive decline. Recent work suggests that SWS can be improved by specifically targeting the electrophysiological peaks of the slow waves with acoustic stimulation. In older adults, this approach is still fairly new and accompanied by challenges posed by the specific complexity of their sleep physiology, like lower amplitude slow waves and fragmented sleep architecture. We suggest an approach that tackles these issues and attempts to re-instate a sleep physiology that resembles a younger, healthier brain. With enough SWS of high quality, metabolic clearance and memory functions could benefit and help slowing the process of cognitive aging. Ultimately, acoustic stimulation to enhance SWS could serve as a cost-effective, non-invasive tool to combat cognitive decline.

1. Introduction

Alzheimer's disease (AD) and other forms of dementia represent one of the most pressing public health issues of the 21st century. The World Health Organization states that in 2015, 47 million people worldwide suffered from dementia and this number is believed to be multiplied by one and a half in 2030 and tripled by 2050 (Prince et al., 2015). In order to fight against an increasing incidence rate of dementia, it is of utmost importance to target early and readily modifiable risk factors. Research suggests that - next to non-modifiable risk factors such as age and genetic predisposition - there are several modifiable risk factors that contribute to the pathogenesis of dementia. Evidence is strongest for factors such as diabetes, smoking, mid-life hypertension, mid-life obesity, hyperlipidemia, physical inactivity, as well as depression (Deckers et al., 2015). These factors are at the basis of vascular biomarkers which are further explored by Badji et al. (2020). Recently, light has been shed on a new and largely overlooked biomarker: sleep quality. Although the health benefits of a good night's sleep have long been known, it is only recently that its connection to cognitive decline was uncovered. Specifically, the deepest sleep stage commonly referred

to as slow wave sleep (SWS) has been highlighted (Mander et al., 2016). In this article, we first report accumulated evidence on age-related changes in sleep quality, particularly in electrophysiological sleep microstructures such as sleep slow waves and sleep spindles. We underline the importance of these oscillatory events in the electroencephalogram (EEG) for memory functioning and their connection to mild cognitive impairment (MCI) and AD. Additionally, potential mechanisms linking impaired SWS to cognitive decline, such as structural degradation and metabolic clearance are discussed. Concerning the latter, we highlight a potentially bidirectional and causal relationship between decreased slow wave activity (SWA) and amyloid-beta deposition. Finally, we outline the potential for a therapeutic tool to target and improve impaired sleep slow waves. This goes one step further than Koenig et al. (2020) who discuss how to employ information on diagnostic purposes. A therapeutic tool improving sleep slow waves may have the potential to counteract age-related as well as pathophysiological cognitive decline.

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2. Sleep quality impairments in aging

Sleep changes considerably as we grow older, both on its macro- and micro-level. Electrophysiological changes on the micro-level involve changes in the abundance and magnitude of oscillations such as slow wave activity (SWA) as well as oscillatory events such as sleep spindles. Among the changes on the macro-level are alterations in sleep architecture, namely a relative decrease in SWS and rapid eye movement (REM) sleep as well as an increase in the lighter sleep stages N1 and N2 (Ohayon et al., 2004). Furthermore, increases in the sleep latency (the time needed to fall asleep), the time spent awake during the night as well as a fragmentation of sleep stages are observed (Conte et al., 2014; Ohayon et al., 2004). Increased fragmentation of sleep means that the orderly fashion with which the different sleep stages alternate becomes more haphazard, and the intervals of transitions of sleep stages shorter. On the micro-level, one of the most drastic and arguably most relevant changes occurs in the low-frequency, high amplitude slow waves that are characteristic for SWS. SWS entails SWA, further divided into delta activity (1–4 Hz) and slow oscillations (SOs, <1 Hz; Rasch and Born, 2013). These electrophysiological measures reflect global synchronous neural activity alternating between phases of depolarization (up-state), associated with the positive half-wave of the slow wave, and phases of hyperpolarization (down-state), associated with the negative half-wave of the slow wave. Up- and down-states mirror increased and decreased neuronal excitability, respectively (Steriade, 2006; Steriade et al., 1993). SWA naturally starts to diminish in middle-aged adults, and this trend gets progressively more pronounced with aging (Dijk et al., 1989, 2010). More specifically, the density and frequency of slow waves is altered which is mirrored in fewer SOs with lower amplitudes (Feinberg and Campbell, 2003; Landolt and Borbely, 2001). Changes in the morphology of slow waves, namely the shallower slopes and the longer duration of up- and down-states indicate prolonged synchronization, meaning lengthier depolarization and hyperpolarization processes (Carrier et al., 2011). Another oscillatory event that is affected by age is the sleep spindle, an oscillatory burst of 9 to 16 Hz that often occurs in SWS. Compared to younger adults, there is a reduction in the density of spindles as well as in their duration and amplitude (Mander et al., 2014; Martin et al., 2013).

3. Consequences of impaired sleep slow waves for memory related processes

SWA and, to some extent, sleep spindles serve vital functions, hence, their age-related impairments should not be dismissed as a mere by-product of aging. SWS has been connected to processes of hormone and cellular energy regulation, clearance of metabolic waste products, functions of the immune and autonomic nervous system, cardio-vascular and mental health, as well as memory (Baglioni et al., 2016; Habas-Rubio et al., 2015; Leger et al., 2018).

One reason why age-related changes in SWA and sleep spindles are of particular interest is their connection to episodic memory consolidation. The episodic memory system entails memories of personally experienced events in the context of time and space (Tulving, 2002). Acquiring such associative, hippocampus-dependent memories is one of the most prominent cognitive functions to steadily decline with aging (Nilsson, 2003; Nyberg et al., 1996). Sleep has a crucial function in the consolidation of memory traces. It has been shown that episodic memory retention of contents learned before sleep is markedly improved following sleep and, critically, this improvement can be attributed to early night sleep that is particularly rich in SWS (Gais and Born, 2004; Plihal and Born, 1997). After a memory encoding task the spindle density is elevated, and this increase is correlated with post sleep memory recall (Clemens et al., 2005; Gais et al., 2002). One influential theory offering an account for the benefits of SWA and spindles on episodic memory performance is the active system consolidation

theory. This approach suggests that memory traces of encoded information are repeatedly reactivated during sleep slow waves (Diekelmann and Born, 2010; Rasch and Born, 2013). Through a co-ordinated dialog between the hippocampus and the neocortex, memory traces are repeatedly strengthened and eventually stored into long-term memory. This dialog is believed to be mediated by a temporal coupling between SWA, sleep spindles and short, high-frequency bursts of activity originating in the hippocampus, so-called hippocampal ripples. This coupled interaction between SWA and spindles is impaired in older adults when compared to younger adults, which traces back to the age-related reduction of SWS (Helfrich et al., 2018; Muehlroth et al., 2019). Furthermore, the quality of SWA-spindle coupling predicted overnight memory retention.

More evidence for a role of SWA in memory functioning is highlighted in the synaptic homeostasis hypothesis (Tononi and Cirelli, 2006). This theory suggests that SWA regulates the synaptic connectivity of the brain by modifying the weights of synapses and, therefore, the communication between specific neurons. While encoding new information, relevant synapses are strengthened. As these processes consume a large amount of energy, sleep is needed to bring the system back to its original state by renormalization of synapses previously involved in memory processes, with renormalization being achieved through SWA. In line with this notion, selectively depriving subjects of SWS while leaving total sleep time intact impairs post sleep encoding performance compared to undisturbed sleep, arguably because subjects did not have renormalized synapses allowing new learning at their disposal (Van Der Werf et al., 2009). Supporting this claim, the capacity to encode new information after waking is positively linked to the amount of SWA (Antonenko et al., 2013).

4. Sleep slow waves and neurodegeneration

Regarding pathological aging, it is well established that deficits in episodic memory functions are accelerated in MCI and AD (Dubois et al., 2007; Sperling et al., 2003). While disruptions of SWA and spindles are present in healthy aging, they are more pronounced in older adults suffering from cognitive decline. Both AD and MCI patients show a decrease in spindle density and SWS when compared to age-matched healthy controls (Gorgoni et al., 2016; Rauchs et al., 2008; Westerberg et al., 2012). This decrease was positively correlated with Mini-Mental State Examination scores, suggesting a gradual deterioration in line with the severity of cognitive decline (Gorgoni et al., 2016).

The most well-known pathophysiological markers of AD, beta-amyloid (A β) plaques and neurofibrillary tangles (Ballatore et al., 2007; Hardy and Selkoe, 2002), have been found to be more prominent in subjects with diminished SWS. In a study with AD patients, cerebrospinal fluid (CSF) t-tau protein levels were associated with decreased SWS (Liguori et al., 2014). Even in cognitively normal older adults, both cortical A β pathology (Mander et al., 2015) and cerebrospinal fluid A β levels (Varga et al., 2016) were elevated as a function of impaired SWA. While not yet fully unraveled, there are two major mechanisms linking disrupted SWA and AD pathology, namely structural degradation and disrupted metabolic clearance.

Structural degeneration of brain regions is linked to impairments in the generation and propagation of SWA. Source modeling approaches suggest that sleep slow waves predominantly originate in the insula and the cingulate gyrus, travel along the anterior-posterior axis, and involve several cortical areas in the frontal gyrus (Murphy et al., 2009). Dube et al. (2015) found that in older adults, cortical thinning in regions involved in the generation or propagation of slow waves (SWs) is correlated with the decrease in SW density and amplitude. Age-related effects on SW-characteristics are most strongly found for frontal derivations (Carrier et al., 2011; Dube et al., 2015; Landolt and Borbely, 2001). Accordingly, atrophy in a specific frontal region, the medial prefrontal cortex, was linked to a decrease in SWA (Mander et al., 2013), and an impairment in SWA-spindle coupling

(Helfrich et al., 2018). Notably, while age-related atrophy was present in other structures, including the hippocampus, it did not mediate the age-related changes in SWA (Mander et al., 2013). This is particularly noteworthy as the hippocampus plays a crucial role in sleep-dependent memory consolidation (Diekelmann and Born, 2010). Consequently, hippocampal atrophy might not directly reduce SWA, but influence slow waves indirectly through its functional connection with medial prefrontal areas.

Disrupted SWA has been linked to AD pathology via disturbed clearance of metabolic byproducts. Depriving mice of sleep increased A β deposition (Roh et al., 2014) and augmented soluble A β (Kang et al., 2009). Following sleep deprivation, all mice showed a period of recovery sleep which immediately reduced soluble A β levels. Conversely, exposing mice to cortical A β debris markedly shortened NREM sleep duration and increased wakefulness (Roh et al., 2012). After A β deposits had been eliminated, sleep-wake cycles normalized, suggesting a bidirectional relationship.

In humans, reduced SWA was linked to both CSF and cortical A β levels (Mander et al., 2015; Varga et al., 2016) and selectively depriving subjects of SWS was correlated with an acute increase in CSF A β (Ju et al., 2017). How fast CSF A β levels renormalized again was not assessed. It is noteworthy that A β deposition seems to be selectively connected to SOs, the slowest waves of SWA (<1 Hz) whereas the decline in a broader SWA range (1–4 Hz) is more likely linked to gray matter atrophy (Mander et al., 2015, 2013, 2016). Also, disrupted SOs, but not general SWS, was positively correlated to A β deposition in the medial prefrontal cortex (Mander et al., 2015), one of the first cortical sites to aggregate A β (Mander et al., 2016; Sepulcre et al., 2013). Furthermore, the proportion of SOs positively predicted hippocampus-dependent memory retention. Consequently, A β seems to impair hippocampus-dependent memories indirectly via impaired <1 Hz SWA (Mander et al., 2015, 2016).

In animal models, A β accumulates during wakefulness while its glymphatic clearance is high during sleep (Xie et al., 2013). Therefore, the restorative function of sleep might be attributable to the removal of waste products accumulated during the day. It is suggested that SWA mainly contributes to metabolic clearance, both in murine and human models (Fultz et al., 2019; Hablitz et al., 2019; Ju et al., 2014). Recently, it has been shown in humans that during SWA cerebral blood flow is lowered, which leads to a compensatory increase in CSF inflow potentially enabling clearance of waste products (Fultz et al., 2019).

Mander et al. (2016) suggested a theoretical framework where A β burden is reciprocally linked to wakefulness and SWS. A β accumulates naturally during wakefulness through mechanisms such as high oxidative stress (Villafuerte et al., 2015) and low glymphatic clearance (Xie et al., 2013). To balance this, SWS serves as a compensatory factor by lowering A β -burden through contrasting mechanisms such as high glymphatic clearance (Fultz et al., 2019; Xie et al., 2013). This process works best in healthy, young adults. However, since SWA decreases with aging and even more in MCI and AD, the restorative function of SWA becomes less and less abundant and, as a consequence, A β clearance is hindered. Additionally, preexisting amyloid burden negatively impacts oxidative stress (Yatin et al., 1999) and glymphatic clearance (Weller et al., 2009) and, therefore, accelerates its own accumulation. Furthermore, A β -burden negatively impacts SWA (Mander et al., 2015; Varga et al., 2016). Consequently, this imbalance may lead to a vicious cycle where – in a self-accelerating process – more A β means less SWS and less SWS means more A β (Ju et al., 2014; Mander et al., 2016).

5. A chance for intervention

Based on these results, impaired SWS/SWA can be seen as an early biomarker of AD risk, which in turn opens up possibilities for intervention. There are several pathways through which SWS can be increased (Wilckens et al., 2018). One promising way of enhancing SWA

is by means of closed-loop (CL) acoustic stimulation during SWS. In such protocols short tones or click sounds are repeatedly presented in phase with the peaks of SOs thereby increasing amplitudes and boosting spindle activity (Ngo et al., 2013). Additionally, such protocols have been shown to improve overnight memory retention, likely due to increased consolidation brought about by the increased SWA (Leminen et al., 2017; Ngo et al., 2013, 2015; Ong et al., 2016). However, this effect is not consistently found which underlines the importance of the right protocol (Weigenand et al., 2016). CL stimulation has also been shown to affect encoding capacity (Antonenko et al., 2013), endocrine and immune (Besedovsky et al., 2017), as well as autonomic functions (Grimaldi et al., 2019) in young populations. Recently, CL stimulation has been applied to healthy older adults (Navarrete et al., 2020; Papalambros et al., 2017; Schneider et al., 2020) as well as MCI patients (Papalambros et al., 2019) with mixed results concerning beneficial effects on memory performance. There was a positive effect on overnight memory consolidation in one group of healthy elderly (Papalambros et al., 2017), but not in MCI patients (Papalambros et al., 2019). Using a different stimulation procedure, one study did not find any beneficial effects on memory performance (Schneider et al., 2020). Taken together, these mixed results indicate first, that in older adults, responsiveness to acoustic stimulation might not be as readily achieved as in younger adults. Secondly, it underlines the importance of a fine-tuned algorithm that is able to cope with the complexity of older adults' sleep physiology.

6. How to apply acoustic closed loop (CL) stimulation to boost SWS in older adults

To tackle the issue of older adults' complex sleep physiology, we suggest using a CL algorithm that addresses specific challenges with sleep architecture and neurophysiology in older adults. Notably, such an algorithm should aim to detect sleep slow waves of low amplitude. This is particularly important as age negatively impacts the amplitude of slow waves more than the frequency of their occurrence (Colrain et al., 2010). Therefore, if only high-amplitude slow waves were targeted in older adults, many potential targets for slow wave boosting might be missed.

Further, we suggest slow wave boosting over multiple consecutive nights. This way, the assumed positive influence of SWA on memory performance can be studied as it unfolds over time. We hypothesize stronger, more systemic effects that might be reflected in sustained memory performance as compared to an isolated intervention session.

Lastly, A β should be assessed before and after the intervention to test for effects of intervention on A β clearance. Such an assessment also allows the comparison of an at-risk population of amyloid-positive older adults to a low-risk group of amyloid-negative older adults.

Extensive testing is needed in order to find the right protocols that can be widely applied to older adults with a range of SWA quality. Long-term studies incorporating ambulatory stimulation protocols and indicators of metabolic clearance are desirable in order to determine the scope of CL acoustic stimulation benefits. In the long run, such approaches might serve as a preventative and therapeutic tool that helps stabilizing SWA and delaying the onset or slowing down cognitive decline. Importantly, currently deployed pharmacological approaches to ameliorate sleep deficits can lead to issues of tolerance and dependency and have daytime side effects (Leger et al., 2018). It has even been suggested that the use of zolpidem, a popular hypnotic, might increase the risk of developing AD (Shih et al., 2015). While tolerance and side effects have yet to be fully investigated, acoustic stimulation during sleep bears potential to be developed into a non-invasive and inexpensive tool to battle cognitive decline.

Author Contribution

All of the authors conceptualized the manuscript. M.W. drafted the outline and a first version of the manuscript. M.A.Z. provided critical revision of both outline and manuscript as well as final approval. K.D.F., C.N. and S.K. provided critical revision of the manuscript and final approval.

Declaration of Competing Interest

The authors declare no conflict of interest.

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