REVIEW ARTICLE

The promise of portable remote auditory stimulation tools to enhance slow-wave sleep and prevent cognitive decline

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Summary

Dementia is the seventh leading cause of mortality, and a major source of disability and dependency in older individuals globally. Cognitive decline (and, to a lesser extent, normal ageing) are associated with sleep fragmentation and loss of slow-wave sleep. Evidence suggests a bidirectional causal link between these losses. Phase-locked auditory stimulation has emerged as a promising non-invasive tool to enhance slow-wave sleep, potentially ameliorating cognitive decline. In laboratory settings, auditory stimulation is usually supervised by trained experts. Different algorithms (simple amplitude thresholds, topographic correlation, sine-wave fitting, phase-locked loop, and phase vocoder) are used to precisely target auditory stimulation to a desired phase of the slow wave. While all algorithms work well in younger adults, the altered sleep physiology of older adults and particularly those with neurodegenerative disorders requires a tailored approach that can adapt to older adults' fragmented sleep and reduced amplitudes of slow waves. Moreover, older adults might require a continuous intervention that is not feasible in laboratory settings. Recently, several auditory stimulation-capable portable devices ('Dreem®', 'SmartSleep®' and 'SleepLoop®') have been developed. We discuss these three devices regarding their potential as tools for science, and as clinical remote-intervention tools to combat cognitive decline. Currently, SleepLoop® shows the most promise for scientific research in older adults due to high transparency and customizability but is not commercially available. Studies evaluating down-stream effects on cognitive abilities, especially in patient populations, are required before a portable auditory stimulation device can be recommended as a clinical preventative remote-intervention tool.

KEYWORDS
closed-loop, treatment, Alzheimer's disease, memory, slow-wave sleep (SWS), home-use devices

1 | INTRODUCTION

The prevalence of dementia and its impact on the individual and societal level continue to increase. The World Health Organization (WHO) classifies dementia as public health priority and estimates that, worldwide, >50 million people have dementia, with an estimated 10 million additional cases per year (Gauthier et al., 2021). This number is thought to double every 20 years (Qiu et al., 2009). In recent years, disturbed sleep has been identified as a potential early, modifiable risk factor for dementia (Mander et al., 2016; Wunderlin et al., 2020). As we age, sleep becomes more fragmented, and the amount of slow-wave sleep (SWS) reduces. Older adults have shorter total sleep time, spend less time asleep while in bed (low sleep efficiency), take more time to fall asleep (increased sleep latency), and are awake more often during the night (increased wake after sleep onset) (Wennberg et al., 2017). Although unfavourable, these changes do not necessarily reflect a pathological process per se. However, in individuals with mild cognitive impairment (MCI) and dementia, sleep disturbance is exacerbated (Westerberg et al., 2012), where the loss of SWS is a hallmark (Mander et al., 2017).

During SWS, the brain is highly active and performs crucial functions for its own recuperation. The brain sorts through memories, strengthening/consolidating important ones, while weakening less important ones to make room for new learning the next day (Diekelmann & Born, 2010; Rasch & Born, 2013; Tononi & Cirelli, 2012). Furthermore, amyloid beta (Aβ), a strong biomarker for Alzheimer's disease (AD) is cleared from the brain during SWS (Fultz et al., 2019). Consequently, poor sleep can impact fundamental neurobiological processes: a single night of sleep deprivation in healthy adults leads to diminished Aβ clearance from the brain (Falter & Van Den Bossche, 2021; Ooms et al., 2014; Shokri-Kojori et al., 2018). Mice exposed to Aβ before sleep showed impairment and fragmentation of SWS (Kang et al., 2009; Roh et al., 2014). This leads to the hypothesis that impaired sleep and impaired clearance of Aβ are bidirectionally linked in a vicious circle where each promotes the others detrimental development in a self-accelerating process (Mander et al., 2016) leading to a gradual cognitive decline.

When looking at the electrophysiological correlate of sleep, the detrimental effect of changed sleep physiology in old age on brain functions can be resolved on a more fine-grained level. Two key electrophysiological features of SWS in the electroencephalogram (EEG), i.e., slow waves and sleep spindles, support memory consolidation through an orchestration of their co-occurrence (Rasch & Born, 2013). Sleep spindles preferentially occur during the positive peaks of slow waves, exhibiting phase-amplitude coupling, allowing for cross-talk between cortico-thalamic loops and hippocampal neurones (Staresina et al., 2015). This dynamic coupling is impaired in older adults, and the degree of de-coupling correlates with overnight memory consolidation and brain atrophy (Helfrich et al., 2018).

In recent years, sleep has become a prominent intervention target (Mander et al., 2016; Wunderlin et al., 2020). Improving sleep could break the vicious cycle between Aβ and SWS by providing a much-needed opportunity for the brain to recuperate, which might slow or prevent the progression of cognitive decline. Optimally, preventative measures should be taken before the disease manifests, or during its early, pre-clinical stages, i.e., at the MCI-stage (Blackman et al., 2021). Direct SWS manipulation provides a powerful tool given the relationship between sleep and memory, to improve memory consolidation and prevent or ameliorate cognitive decline (Steinhubl et al., 2015). Although pharmacological methods to augment SWS exist (Walsh et al., 2006), they fail to provide benefits for memory performance (Feld et al., 2013). The use of hypnotics should be avoided on principle due to issues of tolerance, dependency, and side-effects (Léger et al., 2018). Although the hypnotic zolpidem may convey beneficial effects like improved slow wave-spindle coupling and memory (Kersanté et al., 2022; Niknazar et al., 2015; Simon et al., 2022; Zhang et al., 2020), it is associated with increased risk for dementia, rendering its potential long-term benefit questionable (Lee et al., 2018; Shih et al., 2015).

One of the most widely discussed non-invasive, non-pharmacological methods to boost SWS is phase-locked auditory stimulation (PLAS). Technical advances with this method in recent years has led to promising applications for home-use. Modern applications of PLAS allow for it to be used during a whole night of sleep after minimal manual setup and without direct expert supervision (Debellemaniere et al., 2018; Ferster et al., 2019; Garcia-Molina et al., 2018; Whitmore et al., 2022). Here, we will focus on PLAS as a potential intervention method to boost SWS to prevent cognitive decline. We first examine its application in a controlled laboratory setting and give an overview of available stimulation algorithms including their advantages and disadvantages. Many promising but rather small, cross-sectional laboratory-based studies exist (Wunderlin et al., 2021), and the consensus in the field is that larger, longitudinal studies are required. However, as laboratory settings provide limited feasibility for such large-scale, longitudinal studies, our focus is to evaluate if available portable home-use devices are suitable as research tools (verdict: yes, but not all devices are equally promising). Additionally, based on the limited available evidence, we explore whether such devices can already be recommended for routine clinical use (verdict: not yet).

2 | PHASE-LOCKED AUDITORY STIMULATION IN LABORATORY SETTINGS

Sleep research employing PLAS in humans is typically conducted in controlled sleep laboratory settings, supervised by trained experts, utilizing high-end EEG systems. Briefly, when boosting slow-wave activity using PLAS, non-intrusive tones are applied in sync with the intrinsic rhythmic occurrence of slow waves in the EEG (Ngo, Martinetz, et al., 2013). A computer algorithm monitors the online EEG and administers short acoustic stimuli, e.g., 50 ms of pink noise, to sleeping participants when a target phase, usually a slow-wave peak, is detected. The system typically monitors brain states (semi-) automatically under the supervision of a trained experimenter, but some implementations include online sleep scoring subroutines that aim to minimise off-target stimulations without the need for the constant supervision of an expert technician (Santostasi et al., 2016).

Multiple slow-wave prediction and stimulation algorithms exist that conceptually differ substantially. The first published algorithm that is still widely used detects slow-wave activity based on a simple amplitude threshold in one frontal channel (Ngo, Martinetz, et al., 2013). This highly accessible method is easy to replicate regarding both hardware and software. However, its simplicity is also its biggest shortcoming: due to the hard amplitude threshold, it is not an ideal solution when attempting PLAS in older adults that exhibit reduced slow-wave amplitudes. Many slow waves may be missed, but more importantly, we recently showed that in older adults, amplitude-based algorithms detect physiological states with spatiotemporal dynamics that differ significantly from the canonical slow wave they are supposed to detect (Wunderlin et al., 2022).

A novel approach, 'TOPOSO', works on the multidimensional topographic correlation of the online signal with a topographic template of the target slow-wave phase (Ruch et al., 2022). This approach is amplitude independent and more suited for older adults (Wunderlin et al., 2022), as the topographic representation of slow waves does not change with age (Muehlroth & Werkle-Bergner, 2020). TOPOSO is more sensitive, reliable, precise, and valid than amplitude-based prediction (Wunderlin et al., 2022). However, the algorithm's complexity is its biggest drawback: a sufficiently high-density EEG system (typically 64 channels or more) is needed to accurately determine the topographic distribution of the EEG signal. Many sleep laboratories are equipped with low-density EEG systems, and performance of TOPOSO with these systems is currently not known. Moreover, as the field continues to explore portable home-use devices with low electrode numbers at very selective positions, the applicability of TOPOSO in these settings is questionable.

Other widely used approaches seek to combine the low hardware requirements of the amplitude-based approaches (i.e., based on single electrodes) with the more complex, amplitude-independent algorithms that are better equipped to handle the sleep physiology of older adults. One such approach uses continuously updating sine-wave fitting to predict the target phase of slow-wave activity using general linear models (Cox et al., 2014). It continuously finds the sine-wave frequency that best fits the slow-wave filtered empirical signal and has no prerequisites regarding signal amplitudes. Another approach implements a phase-locked loop (PLL), which uses an intrinsic oscillator that continuously adjusts to match the frequency and phase of the empirical signal by reducing the phase error between intrinsic oscillation and empirical signal (Santostasi et al., 2016). PLL is more accurate and precise than both amplitude-based algorithms and sine-fitting (Santostasi et al., 2016). The newest addition to this family of slow-wave prediction algorithms uses a phase vocoder (PV) to 'auto-tune' a sine and cosine wave to the empirical signal by minimising phase error. This new approach performed similarly well as a PLL in high-amplitude data (as seen in younger adults), but notably was able to detect and stimulate more slow waves in low-amplitude data (as seen in older adults) and was more capable of adapting to individual sleep physiology (Ferster et al., 2022). Notably, it is important that algorithms are optimised towards a specific frequency, optimally targeting the lower part of the slow-wave spectrum, slow oscillations (SO, <1 Hz), while avoiding the delta frequency band of 1–4 Hz. Recent studies reported that SO and delta activity can have opposite functions. For instance, SO (especially in concert with coupled spindles) support memory consolidation and Aβ clearance, while delta waves rather promote forgetting and are associated with increased Aβ deposition (Kim et al., 2019; Mander et al., 2015; Winer et al., 2020). Theoretically, phase-targeting algorithms like the PLL are designed to match a specific phase and frequency. However, in studies utilising PLL targeting SO, entrainment seems to extend into the delta band (Papalambros et al., 2017; Santostasi et al., 2016). While it is not known if such delta-entrainment impacts Aβ clearance, the potential inability to specifically enhance SO may compromise the pursued benefits.

While all of these algorithms have been shown to produce physiological effects like entrainment of slow waves, increased slow-wave amplitudes and delta power (Ferster et al., 2022; Wunderlin et al., 2021), an important question is whether these induced physiological changes lead to down-stream behavioural effects, like improved memory performance. PLAS targeted to the up-phase of SWS improved word pair recall in young adults (Ngo, Claussen, et al., 2013; Ong et al., 2016) and in healthy older adults (Papalambros et al., 2017). There is limited but promising evidence from one study including a small sample of nine older adults with MCI (Papalambros et al., 2019). In this study, PLAS-induced physiological responses (i.e., slow-wave activity, as well as SO and spindle power) were associated with better word pair recall, but the study was too small to find robust main effects of stimulation on memory. Several studies from different laboratories replicated the beneficial effect of phase-targeted acoustic stimuli to boost slow waves in different age groups across the human life-span (Lustenberger et al., 2022; Wunderlin et al., 2021). However, in older adults, studies are sparse, and results more mixed. One study found that PLAS improved memory consolidation in older adults (Papalambros et al., 2017), while others did not (Diep et al., 2020; Schneider et al., 2020). We previously argued that key differences in these studies entail different stimulation algorithms and different stimulation dosages (Wunderlin et al., 2021). For instance, Papalambros et al. (2017) used a PLL algorithm across an entire night, while Schneider et al. (2020) used an amplitude-based algorithm only during the first half of a night. As a PLL should be more flexible and suitable for older adults than an amplitude-based algorithm (Ferster et al., 2022), it is not entirely surprising that PLL-based stimulation induces memory effects in older adults, while an amplitude-based approach fails to do so. However, the additional factor of stimulation dosage may play just as important a role regarding effectiveness of PLAS in older adults. As older adults' sleep worsens, several nights of repeated slow-wave boosting might be necessary to compensate for the physiological changes (i.e., sleep fragmentation and decreased slow-wave amplitudes). As costs of repeatedly testing older individuals over an extended period become a limiting factor, laboratory-based studies might not be the best way of approaching the question of stimulation dosage. Fortunately, recent developments in the field of home-use devices now allow for studies to employ PLAS in the comfort of one's home.

TABLE 1 Overview of home-use devices.

Device	Information	Advantages	Disadvantages
Dreem®	**Channels:** • 4 EEG (fixed; Fpz-O1, Fpz-O2, Fpz-F7, F8-F7) • 1 pulse oximeter • 1 accelerometer • 1 bone conductance speaker **Algorithm:** • Sine-fitting **Performance indices:** • Auto sleep staging comparable to manual scoring (Cohen's κ: 0.75 ± 0.10) • 45° ± 52° stimulation phase precision (mean ± SD) • +43% delta power in 4 s after stimulation	Commercially available. User-friendly. Amplitude-independent algorithm.	Limited transparency and flexibility (system configuration and data availability). Auditory stimulation no longer available in newest iteration of device (Dreem 3), but a limited supply of PLAS-capable Dreem 2 devices exists for study purposes.
SmartSleep®	**Channels:** • 1 EEG (fixed; Fpz-A2) • 2 EOG • 2 over-ear speakers **Algorithm:** • Amplitude threshold (first stimulation only, then 'driving' stimulation at fixed interval for short bursts) **Performance indices:** • N3 detection comparable to manual scoring (74% sensitivity, 97% specificity) • 96% of stimulations in N3 • Increased SWA in younger population, but not older	Commercially available. User-friendly.	Limited transparency and flexibility (system configuration and data availability). Suboptimal algorithm for low-amplitude populations (e.g., older adults). No longer available in Europe.
SleepLoop®	**Channels:** • 8 flexible-use electrophysiology (flexible positions) • 3.5-mm audio jack • General purpose input/output connectors **Algorithms:** • Amplitude threshold • PLL • PV **Performance indices:** • High phase precision for all algorithms (circular mean absolute error of 0.2–14°) • Targets 32%/44%/47% (amp/PLL/PV) of all slow waves in low-amplitude data, and 75%/82%/81% (amp/PLL/PV) in high-amplitude data • Increased SWA (dose–response) even in older population	Designed for research. Multiple amplitude-independent algorithms selectable. Full methodological transparency, high configurability, and full availability of raw data.	Complex setup. Limited availability (only through scientific collaboration, but commercial development planned).

Abbreviations: EEG, electroencephalography; EOG, electro-oculography; PLL, phase-locked loop; PV, phase vocoder; SWA, slow-wave activity.

3 | PHASE-LOCKED AUDITORY STIMULATION IN PORTABLE HOME-USE DEVICES

Laboratory-based approaches are expensive, time-consuming and require complex setups, partially explaining the low number of participants and study sessions per participant in existing studies. This limits the translation of laboratory-based findings to the real world. Furthermore, the low number of samples limits the identification of inter-individual differences (Ferster et al., 2019). From a hardware, software, and algorithmic perspective, analysing EEG in real-time and determining the optimal time for auditory stimulations

without human supervision is not trivial (Debellemaniere et al., 2018). Fortunately, this field has advanced considerably in recent years. With the advancement of increasingly sophisticated measurement and prediction algorithms, implemented in suitably high-quality portable EEG devices, PLAS studies at home have become a feasible option enabling repeated and individually tailored interventions (Sterr et al., 2018). Because sleep could be a key factor to promote brain and body health into old age, translating in-laboratory methods into a home-use setting shows enticing potential for the prevention of cognitive decline (Gulia & Kumar, 2018; Irwin & Vitiello, 2019).

Here, we compare three currently available home-used devices (Table 1) and evaluate their potential for slow wave boosting in older adults.

3.1 | 'Dreem®' wireless dry-EEG device (WDD)

The 'Dreem®' wireless dry-EEG device (WDD; www.dreem.com) is a commercial consumer-targeted product. It aims to provide clinicians, researchers, and other healthcare institutions with a remote patient monitoring solution. It measures four EEG derivations (Fpz-O1, Fpz-O2, Fpz-F7, F8-F7) and is additionally equipped with a pulse oximeter and an accelerometer. Using machine learning, it evaluates data quality and automatically scores sleep stages in real time. If the device detects SWS in sufficiently high quality data, it applies PLAS using an amplitude-independent sine-fitting algorithm (Cox et al., 2014). Stimuli are delivered over two bone-conductance transducers. Reports show that only 4.72% of data had to be rejected due to bad signal quality (Debellemaniere et al., 2018), and online sleep staging was comparable to standard laboratory-based polysomnography with a Cohen's kappa of 0.75 ± 0.10 (Arnal et al., 2020). Auditory stimulation showed a high degree of phase-precision (mean [SD] 45 [52]° for a target phase angle of 45°, i.e., the ascending phase prior to the peak, where 90° = slow-wave peak) and led to an increase in delta power of 43.9% in the 4 s after the onset of two stimulation trains (Debellemaniere et al., 2018). As of this report, no effects on global sleep architecture, frequency distributions, or down-stream effects on memory or other cognitive functions have been reported. No studies specifically testing feasibility of the Dreem® WDD for home-use in older adults have been reported.

The advantages of the Dreem® WDD are broad commercial availability, user-friendliness, and the usage of an amplitude-independent algorithm (albeit arguably not the best available option). However, the device offers limited transparency in data processing and management, limited flexibility regarding system configuration, and limited availability of data (raw data is available, but not sleep staging data), all of which are important for research applications. Furthermore, the newest iteration of the device (Dreem 3) does not include PLAS capability anymore, but a limited supply of the older Dreem 2 exists for study purposes, obtainable through direct contact with the manufacturer.

3.2 | Philips 'SmartSleep®'

Another consumer-targeted device, 'SmartSleep®' (www.usa.philips.com/c-e/smartsleep/deep-sleep-headband/smartsleep-professional-advocacy.html), is developed by Philips Respironics, Murrysville, PA, USA. It measures EEG from a single prefrontal sensor (Fpz), referenced against the right mastoid, and is equipped with two additional electro-oculogram sensors and earphones. Like the Dreem® WDD, SmartSleep® is capable of online monitoring of sleep EEG for arousal-free SWS. SmartSleep® utilises pre-defined frequency-band power thresholds to classify sleep stages. The PLAS algorithm is engaged if SWS is continuously detected for a minimum of 1.5 min, which is achieved with 97% specificity and 74% sensitivity (Garcia-Molina et al., 2018). PLAS is implemented using a custom algorithm that detects slow waves using an adaptable amplitude threshold (with an initial value of −40 μV), but then applies a non-phase locked 'driving' stimulation of multiple 50 ms tones at a fixed 1-s inter-tone interval. Sound volume is automatically adjusted to scale with detected sleep depth (range: 20–65 dB sound pressure level), with deeper sleep leading to louder stimulations. Results show significant slow-wave activity enhancement in younger adults, but no effect in older adults (Garcia-Molina et al., 2018). Importantly, older adults received only 57% of stimulations compared to younger adults, which arguably owed to the fact that an amplitude-dependent slow-wave detection algorithm was used that is not ideal for older adults (Wunderlin et al., 2022). In addition, using a constant driving stimulation, where only the first stimulus is synchronised with a slow-wave peak, will likely not provide the same level of precision as other, truly phase-locked methods. Indeed, the available phase histogram (Garcia-Molina et al., 2018) indicates a much broader distribution of tones across the slow wave as compared to the 'SleepLoop®' headband or the Dreem® WDD (Debellemaniere et al., 2018; Ferster et al., 2022). No reports for possible effects on global sleep parameters or down-stream effects on memory or other cognitive functions exist.

As with the Dreem® WDD, the SmartSleep® is readily available and offers a user-friendly design, but due to the methodological limitations described above, it seems suboptimal for use in older adults. Being a commercial device, it offers limited transparency in data processing and management, limited availability of raw data, and limited flexibility regarding system configuration. As a further caveat, the SmartSleep headband can no longer be ordered in Europe.

3.3 | 'SleepLoop®'

SleepLoop® (Mobile Health Systems Lab Sleep Band (MHSL-SB); http://www.sleeploop.ch/) is a portable home-use system designed for sleep-biosignals monitoring and PLAS developed and evaluated in a collaboration of ETH Zurich, University of Zurich, University Hospitals of Zurich, and University of Ulm (https://www.hochschulmedizin.uzh.ch/de/projekte/sleeploop/Konsortium.html). SleepLoop® is a customisable, modular system with integrated speakers and a capacity for

eight electrophysiology channels that allows electrode placement at any location on the scalp. Typically, a combination of EEG, electro-oculography, and electromyography is used (Ferster et al., 2019). Several algorithms for PLAS are implemented in SleepLoop®, including a simple amplitude threshold, a PLL, and a phase vocoder. Researchers may choose which algorithm to use. Like the other portable devices, SleepLoop® monitors sleep EEG (typically in frontal electrodes) and online classifies arousal-free SWS. For this purpose, SleepLoop® uses pre-defined frequency-band power thresholds. PLAS is engaged as soon SWS is detected based on a delta-power threshold. In a recent benchmarking report, phase precision was high for all used algorithms with a circular mean absolute error of 0.2–14° around a target phase of 45° (where 90° = peak), depending on application (including individuals with Parkinson's disease [PD]) (Ferster et al., 2022). Phase histograms were comparable to the Dreem® WDD (Debellemaniere et al., 2018) even in individuals with PD.

SleepLoop® is suitable to study older adults (Ferster et al., 2019; Lustenberger et al., 2022). In low-amplitude data, the novel phase vocoder algorithm was able to target 47.2% of slow waves, which was a significantly higher proportion compared to the PLL (43.5%) and the amplitude-based algorithm (32.3%). Notably, these values were higher in high-amplitude data (amplitude-based: 74.5%, PLL: 81.6%, phase-vocoder: 81.1%). In addition, the phase vocoder was more capable of adapting to individual sleep characteristics in older adults compared to the other algorithms, indicated by a stable phase-error rate compared to increased error rates for the other algorithms. In a recent study in older individuals, slow-wave activity was enhanced in a dose-dependent way. Neither subjective sleep quality, daytime sleepiness, nor psychomotor vigilance were consistently affected using SleepLoop®, but mood was lowered after real versus sham PLAS, both the following morning and across the whole following day. Mood reduction correlated with a tendency for reduced rapid eye movement (REM) sleep under stimulation (Lustenberger et al., 2022). No reports of down-stream effects on memory exist.

SleepLoop® is currently the only portable PLAS-capable home-use device explicitly designed for research purposes. Its biggest advantages are full methodological transparency, high configurability, and full availability of raw data. With multiple selectable amplitude-independent algorithms and detailed reports of their performance, including in low-amplitude data, SleepLoop® is suitable to apply PLAS in older adults, both healthy and experiencing PD (Ferster et al., 2022). Studies specifically testing feasibility in people with MCI do not exist, but a sample of individuals with PD was chosen in the benchmarking report to investigate robustness and flexibility of the device and its PLAS algorithms under challenging conditions and high inter-individual variability regarding sleep patterns (Ferster et al., 2022).

One disadvantage of SleepLoop® compared to the other devices is a more complex setup. Users need to manually connect cables and can potentially wear the device incorrectly if not supervised. It is therefore recommended that participants document (e.g., using photographs) how they setup the device before use. Another disadvantage is its currently limited availability. A commercial spin-off, 'Tosoo®' (http://www.tosoo.ch/) is planned but has not launched yet, and no further details are available as of this report. If Tosoo® maintains SleepLoop®'s transparency, configurability, and access to raw data, one of the biggest shortcomings of SleepLoop®, i.e., its low availability, could be resolved without sacrificing its value for research.

4 | DISCUSSION AND FUTURE DIRECTIONS

Cognitive decline and dementia are research topics of increasing relevance in our ageing society. Warning signs of a potential future affliction with AD do exist quite early on in a person's life. For instance, Aβ starts to accumulate up to 15 years, and changes in brain function can be observed up to 10 years, before the onset of symptoms (Beason-Held et al., 2013; Palmqvist et al., 2017). At the same time, the prevalence of sleep disorders is alarmingly high. About 30% of adults report some insomnia problems in any given year, and this number is thought to increase with the emergence of a '24/7' society (Ferrie et al., 2011). Decreased SWS is bi-directionally connected with lower Aβ clearance and impairment of memory performance (Mander et al., 2016), leading to a gradual cognitive decline. Therefore, improving sleep as an early preventative tool against cognitive decline would fill two needs with one deed.

A first step could be an early focus on good sleep hygiene. A combination of aerobic exercise and sleep hygiene education has led to improved sleep quality, mood, and quality of life in older individuals with insomnia (Reid et al., 2010). However, sleep hygiene education may not be enough: A systematic review determined that the evidence is insufficient to conclude that such an intervention alone is effective (Dietrich et al., 2016). Non-invasive brain stimulation, in particular PLAS, could serve as the next step in preventing cognitive decline, provided there are accessible, convenient options available to use at home.

The availability of portable devices and technologies with the aim of promoting health has increased substantially over recent years. These devices found their way into the consumer market and into people's homes, and the promise of strengthened SWS to improve memory is alluring. Using PLAS in portable home-use devices could also become a boon to memory clinics. Devices could be prescribed through memory clinics, where they could be individually setup and remotely supported by trained technicians. This would help shift the clinical burden of MCI to a preventative stage that does not require frequent visits at a clinic.

However, clinical validations are sparse. The lack of studies demonstrating effectiveness and efficacy prevents clinical recommendations for any portable, PLAS-capable device as a preventative remote intervention tool to combat dementia. Currently, there is no certified medical portable auditory sleep stimulation technology. Regarding possible future implementations of such devices in healthcare, it is important to evaluate their safety, costs, and clinical impact. Another

consideration for the feasibility of PLAS-capable devices is their comfort. Currently, there is no systematic evaluation of tolerability of these devices, but comfort is an explicit design consideration (Debellemaniere et al., 2018; Ferster et al., 2019). Notably, almost one-third of participants experienced discomfort using the Dreem WDD during sleep in a recent study (Zambelli et al., 2022). However, this rather small sample of 21 participants consisted of individuals with chronic pain who might be sensitive to discomfort. Still, comfort must be a consideration, especially if moving from a few nights in-laboratory to prolonged studies at home. Promisingly, Lustenberger et al. (2022) used the SleepLoop® device in older adults across 2 weeks, twice, and reported no issues with discomfort.

A novel portable PLAS-capable system has recently been introduced, utilising in-ear electrodes (Henao et al., 2022). These authors argue that classical scalp setups may lead to discomfort over extended applications and suggest an in-ear solution might be more tolerable. They report successful targeting and stimulation of slow waves recorded from in-ear sites. However, slow waves detected in-ear exhibit strongly attenuated signals at more canonical frontal detection sites. The waveform of in-ear detected slow waves aligned with frontally detected slow waves in only ∼30% of cases, leading to auditory stimuli being phase-misaligned with slow waves, questioning the validity of the approach. Although this in-ear system shows promise, particularly due to its ease of usage, more research should optimise and compare its performance to established approaches before it can be suggested as a direct alternative.

Even if it is too early for a recommendation for their use in a clinical standard of care or personal 'self-improvement' setting, PLAS-capable home-use devices can become a valuable tool for research, which is the only way to ultimately determine if such devices should be recommended for routine clinical and personal use. Next steps should include studies investigating potential down-stream effects of PLAS in portable devices on memory and other cognitive abilities, and clinical studies in individuals with MCI or individuals with a higher risk of developing dementia. From a basic science perspective, home-use studies should go beyond investigating effects of PLAS on sleep physiology and tackle underlying mechanisms in its chain of action. For instance, PLAS-induced improvements in slow wave-spindle coupling could be a mediator between enhanced sleep physiology and down-stream effects on cognition. Such analyses are technically feasible with the devices discussed here, as long as researchers have full access to raw data.

Shifting towards clinical trials, longitudinal studies in populations that might profit most from PLAS interventions are needed. Such populations include, e.g., individuals with an elevated risk of developing dementia due to genetic predisposition or due to subjective cognitive decline, or individuals with MCI. Accordingly, accessibility is an important consideration when designing home-use devices. Instructions should be easily understandable, and individuals should be able to setup the device by themselves.

Importantly, potential side-effects, like decreased mood and loss of REM sleep, must be carefully studied and evaluated. It is currently unclear if PLAS at home is suitable for everybody, or whether individual idiosyncrasies exist that might render treatment ineffective in certain individuals. In addition, many technical aspects that impact efficacy of PLAS in a home-use setting are not definitively settled. On the one hand, the optimal intervention period (days, weeks, or months) is not clearly established, and it is not clear if one can 'overdose' on PLAS. On the other hand, the type of PLAS algorithm used has a sensitive impact on the validity of the intervention. The reduced amplitudes and density of slow waves render simple, amplitude-based algorithms suboptimal in older individuals. As a matter of fact, new conceptual approaches posit that using amplitude criteria to classify SWS might be flawed in general (Decat et al., 2022; Guo et al., 2022). A recent study found that if sleep is classified based on the bi-modal distribution of individual slow-wave amplitudes rather than based on slow-wave amplitudes, older individuals do not exhibit a loss in the amount of SWS, just lower amplitudes (Guo et al., 2022). As an additional consideration, stimulation should be specific in enhancing SO (<1 Hz) supporting consolidation and Aβ clearance, while avoiding delta waves (1–4 Hz) associated with forgetting and Aβ deposition (Kim et al., 2019; Mander et al., 2015; Winer et al., 2020). All these aspects require further studies, carried out with methodological transparency, full configurability, and full data availability. Currently, SleepLoop® scores highest in these measures among PLAS-capable home-use devices, and thus we recommend SleepLoop® for research purposes in a remote setting.

AUTHOR CONTRIBUTIONS

Céline J. Zeller and Marc A. Züst conceptualised the present work and drafted the first version of the manuscript. All authors discussed and provided critical revision of the manuscript and gave final approval.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Arnal, P. J., Thorey, V., Debellemaniere, E., Ballard, M. E., Bou Hernandez, A., Guillot, A., Jourde, H., Harris, M., Guillard, M., Van Beers, P., Chennaoui, M., & Sauvet, F. (2020). The Dreem headband compared to polysomnography for electroencephalographic signal

acquisition and sleep staging. *Sleep*, *43*(11), zsaa097. https://doi.org/10.1093/sleep/zsaa097

Beason-Held, L. L., Goh, J. O., An, Y., Kraut, M. A., O'Brien, R. J., Ferrucci, L., & Resnick, S. M. (2013). Changes in brain function occur years before the onset of cognitive impairment. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *33*(46), 18008–18014. https://doi.org/10.1523/JNEUROSCI.1402-13.2013

Blackman, J., Swirski, M., Clynes, J., Harding, S., Leng, Y., & Coulthard, E. (2021). Pharmacological and non-pharmacological interventions to enhance sleep in mild cognitive impairment and mild Alzheimer's disease: A systematic review. *Journal of Sleep Research*, *30*(4), e13229. https://doi.org/10.1111/jsr.13229

Cox, R., Korjoukov, I., Boer, M., & Talamini, L. (2014). Sound asleep: Processing and retention of slow oscillation phase-targeted stimuli. *PLoS One*, *9*, e101567. https://doi.org/10.1371/journal.pone.0101567

Debellemaniere, E., Chambon, S., Pinaud, C., Thorey, V., Dehaene, D., Léger, D., Chennaoui, M., Arnal, P. J., & Galtier, M. N. (2018). Performance of an ambulatory dry-EEG device for auditory closed-loop stimulation of sleep slow oscillations in the home environment. *Frontiers in Human Neuroscience*, *12*, 88. https://doi.org/10.3389/fnhum.2018.00088

Decat, N., Walter, J., Koh, Z. H., Sribanditmongkol, P., Fulcher, B. D., Windt, J. M., Andrillon, T., & Tsuchiya, N. (2022). Beyond traditional sleep scoring: Massive feature extraction and data-driven clustering of sleep time series. *Sleep Medicine*, *98*, 39–52. https://doi.org/10.1016/j.sleep.2022.06.013

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience*, *11*(2), 114–126. https://doi.org/10.1038/nrn2762

Diep, C., Ftouni, S., Manousakis, J. E., Nicholas, C. L., Drummond, S. P. A., & Anderson, C. (2020). Acoustic slow wave sleep enhancement via a novel, automated device improves executive function in middle-aged men. *Sleep*, *43*(1), zsz197. https://doi.org/10.1093/sleep/zsz197

Dietrich, S. K., Francis-Jimenez, C. M., Knibbs, M. D., Umali, I. L., & Truglio-Londrigan, M. (2016). Effectiveness of sleep education programs to improve sleep hygiene and/or sleep quality in college students: A systematic review. *JBI Database of Systematic Reviews and Implementation Reports*, *14*(9), 108–134. https://doi.org/10.11124/JBISRIR-2016-003088

Falter, A., & Van Den Bossche, M. J. A. (2021). How non-rapid eye movement sleep and Alzheimer pathology are linked. *World Journal of Psychiatry*, *11*(11), 1027–1038. https://doi.org/10.5498/wjp.v11.i11.1027

Feld, G. B., Wilhelm, I., Ma, Y., Groch, S., Binkofski, F., Mölle, M., & Born, J. (2013). Slow wave sleep induced by GABA agonist tiagabine fails to benefit memory consolidation. *Sleep*, *36*(9), 1317–1326. https://doi.org/10.5665/sleep.2954

Ferrie, J. E., Kumari, M., Salo, P., Singh-Manoux, A., & Kivimäki, M. (2011). Sleep epidemiology—A rapidly growing field. *International Journal of Epidemiology*, *40*(6), 1431–1437. https://doi.org/10.1093/ije/dyr203

Ferster, M. L., Da Poian, G., Menachery, K., Schreiner, S., Lustenberger, C., Maric, A., Huber, R., Baumann, C., & Karlen, W. (2022). Benchmarking real-time algorithms for in-phase auditory stimulation of low amplitude slow waves with wearable EEG devices during sleep. *IEEE Transactions on Bio-Medical Engineering*, *69*, 2916–2925. https://doi.org/10.1109/TBME.2022.3157468

Ferster, M. L., Lustenberger, C., & Karlen, W. (2019). Configurable Mobile system for autonomous high-quality sleep monitoring and closed-loop acoustic stimulation. *IEEE Sensors Letters*, *3*(5), 1–4. https://doi.org/10.1109/LSENS.2019.2914425

Fultz, N. E., Bonmassar, G., Setsompop, K., Stickgold, R. A., Rosen, B. R., Polimeni, J. R., & Lewis, L. D. (2019). Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science*, *366*(6465), 628–631. https://doi.org/10.1126/science.aax5440

Garcia-Molina, G., Tsoneva, T., Jasko, J., Steele, B., Aquino, A., Baher, K., Pastoor, S., Pfundtner, S., Ostrowski, L., Miller, B., Papas, N., Riedner, B., Tononi, G., & White, D. P. (2018). Closed-loop system to enhance slow-wave activity. *Journal of Neural Engineering*, *15*(6), 066018. https://doi.org/10.1088/1741-2552/aae18f

Gauthier, S., Rosa-Neto, P., Morais, J. A., & Webster, C. (2021). *World Alzheimer Report 2021: Journey through the diagnosis of dementia*. Alzheimer's Disease International. https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf

Gulia, K. K., & Kumar, V. M. (2018). Sleep disorders in the elderly: A growing challenge. *Psychogeriatrics: The Official Journal of the Japanese Psychogeriatric Society*, *18*(3), 155–165. https://doi.org/10.1111/psyg.12319

Guo, D., Thomas, R. J., Liu, Y., Shea, S. A., Lu, J., & Peng, C.-K. (2022). Slow wave synchronization and sleep state transitions. *Scientific Reports*, *12*(1), 1–11. https://doi.org/10.1038/s41598-022-11513-0

Helfrich, R. F., Mander, B. A., Jagust, W. J., Knight, R. T., & Walker, M. P. (2018). Old brains come uncoupled in sleep: Slow wave-spindle synchrony, brain atrophy, and forgetting. *Neuron*, *97*(1), 221–230.e4. https://doi.org/10.1016/j.neuron.2017.11.020

Henao, D., Navarrete, M., Juez, J. Y., Dinh, H., Gómez, R., Valderrama, M., & Le Van Quyen, M. (2022). Auditory closed-loop stimulation on sleep slow oscillations using in-ear EEG sensors. *Journal of Sleep Research*, *31*(6), e13555. https://doi.org/10.1111/jsr.13555

Irwin, M. R., & Vitiello, M. V. (2019). Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *The Lancet. Neurology*, *18*(3), 296–306. https://doi.org/10.1016/S1474-4422(18)30450-2

Kang, J.-E., Lim, M. M., Bateman, R. J., Lee, J. J., Smyth, L. P., Cirrito, J. R., Fujiki, N., Nishino, S., & Holtzman, D. M. (2009). Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science*, *326*(5955), 1005–1007. https://doi.org/10.1126/science.1180962

Kersanté, F., Purple, R. J., & Jones, M. W. (2022). The GABAA receptor modulator zolpidem augments hippocampal-prefrontal coupling during non-REM sleep. *Neuropsychopharmacology*, 1–11. https://doi.org/10.1038/s41386-022-01355-9

Kim, J., Gulati, T., & Ganguly, K. (2019). Competing roles of slow oscillations and Delta waves in memory consolidation versus forgetting. *Cell*, *179*(2), 514–526.e13. https://doi.org/10.1016/j.cell.2019.08.040

Lee, J., Jung, S. J., Choi, J., Shin, A., & Lee, Y. J. (2018). Use of sedative-hypnotics and the risk of Alzheimer's dementia: A retrospective cohort study. *PLoS One*, *13*(9), e0204413. https://doi.org/10.1371/journal.pone.0204413

Léger, D., Debellemaniere, E., Rabat, A., Bayon, V., Benchenane, K., & Chennaoui, M. (2018). Slow-wave sleep: From the cell to the clinic. *Sleep Medicine Reviews*, *41*, 113–132. https://doi.org/10.1016/j.smrv.2018.01.008

Lustenberger, C., Ferster, M. L., Huwiler, S., Brogli, L., Werth, E., Huber, R., & Karlen, W. (2022). Auditory deep sleep stimulation in older adults at home: A randomized crossover trial. *Communications Medicine*, *2*(1), 1. https://doi.org/10.1038/s43856-022-00096-6

Mander, B. A., Marks, S. M., Vogel, J. W., Rao, V., Lu, B., Saletin, J. M., Ancoli-Israel, S., Jagust, W. J., & Walker, M. P. (2015). β-Amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nature Neuroscience*, *18*(7), 1051–1057. https://doi.org/10.1038/nn.4035

Mander, B. A., Winer, J. R., Jagust, W. J., & Walker, M. P. (2016). Sleep: A novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease? *Trends in Neurosciences*, *39*(8), 552–566. https://doi.org/10.1016/j.tins.2016.05.002

Mander, B. A., Winer, J. R., & Walker, M. P. (2017). Sleep and Human Aging. *Neuron*, *94*(1), 19–36. https://doi.org/10.1016/j.neuron.2017.02.004

Muehlroth, B. E., & Werkle-Bergner, M. (2020). Understanding the interplay of sleep and aging: Methodological challenges. *Psychophysiology*, *57*(3), e13523. https://doi.org/10.1111/psyp.13523

Ngo, H.-V. V., Claussen, J. C., Born, J., & Mölle, M. (2013). Induction of slow oscillations by rhythmic acoustic stimulation. *Journal of Sleep Research*, *22*(1), 22–31. https://doi.org/10.1111/j.1365-2869.2012.01039.x

Ngo, H.-V. V., Martinetz, T., Born, J., & Mölle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron*, *78*(3), 545–553. https://doi.org/10.1016/j.neuron.2013.03.006

Niknazar, M., Krishnan, G. P., Bazhenov, M., & Mednick, S. C. (2015). Coupling of Thalamocortical sleep oscillations are important for memory consolidation in humans. *PLoS One*, *10*(12), e0144720. https://doi.org/10.1371/journal.pone.0144720

Ong, J. L., Lo, J. C., Chee, N. I. Y. N., Santostasi, G., Paller, K. A., Zee, P. C., & Chee, M. W. L. (2016). Effects of phase-locked acoustic stimulation during a nap on EEG spectra and declarative memory consolidation. *Sleep Medicine*, *20*, 88–97. https://doi.org/10.1016/j.sleep.2015.10.016

Ooms, S., Overeem, S., Besse, K., Rikkert, M. O., Verbeek, M., & Claassen, J. A. H. R. (2014). Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: A randomized clinical trial. *JAMA Neurology*, *71*(8), 971–977. https://doi.org/10.1001/jamaneurol.2014.1173

Palmqvist, S., Schöll, M., Strandberg, O., Mattsson, N., Stomrud, E., Zetterberg, H., Blennow, K., Landau, S., Jagust, W., & Hansson, O. (2017). Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nature Communications*, *8*(1), 1214. https://doi.org/10.1038/s41467-017-01150-x

Papalambros, N. A., Santostasi, G., Malkani, R. G., Braun, R., Weintraub, S., Paller, K. A., & Zee, P. C. (2017). Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00109

Papalambros, N. A., Weintraub, S., Chen, T., Grimaldi, D., Santostasi, G., Paller, K. A., Zee, P. C., & Malkani, R. G. (2019). Acoustic enhancement of sleep slow oscillations in mild cognitive impairment: Enhancing sleep slow oscillations in MCI. *Annals of Clinical and Translational Neurology*, *6*(7), 1191–1201. https://doi.org/10.1002/acn3.796

Qiu, C., Kivipelto, M., & von Strauss, E. (2009). Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. *Dialogues in Clinical Neuroscience*, *11*(2), 111–128.

Rasch, B., & Born, J. (2013). About Sleep's role in memory. *Physiological Reviews*, *93*(2), 681–766. https://doi.org/10.1152/physrev.00032.2012

Reid, K. J., Baron, K. G., Lu, B., Naylor, E., Wolfe, L., & Zee, P. C. (2010). Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. *Sleep Medicine*, *11*(9), 934–940. https://doi.org/10.1016/j.sleep.2010.04.014

Roh, J. H., Jiang, H., Finn, M. B., Stewart, F. R., Mahan, T. E., Cirrito, J. R., Heda, A., Snider, B. J., Li, M., Yanagisawa, M., de Lecea, L., & Holtzman, D. M. (2014). Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer's disease. *The Journal of Experimental Medicine*, *211*(13), 2487–2496. https://doi.org/10.1084/jem.20141788

Ruch, S., Schmidig, F. J., Knüsel, L., & Henke, K. (2022). Closed-loop modulation of local slow oscillations in human NREM sleep. *NeuroImage*, *119682*, 119682. https://doi.org/10.1016/j.neuroimage.2022.119682

Santostasi, G., Malkani, R., Riedner, B., Bellesi, M., Tononi, G., Paller, K. A., & Zee, P. C. (2016). Phase-locked loop for precisely timed acoustic stimulation during sleep. *Journal of Neuroscience Methods*, *259*, 101–114. https://doi.org/10.1016/j.jneumeth.2015.11.007

Schneider, J., Lewis, P. A., Koester, D., Born, J., & Ngo, H.-V. V. (2020). Susceptibility to auditory closed-loop stimulation of sleep slow oscillations changes with age. *Sleep*, *43*(12), zsaa111. https://doi.org/10.1093/sleep/zsaa111

Shih, H. I., Lin, C. C., Tu, Y. F., Chang, C. M., Hsu, H. C., Chi, C. H., & Kao, C. H. (2015). An increased risk of reversible dementia may occur after zolpidem derivative use in the elderly population: A population-based case-control study. *Medicine*, *94*(17), e809. https://doi.org/10.1097/MD.0000000000000809

Shokri-Kojori, E., Wang, G.-J., Wiers, C. E., Demiral, S. B., Guo, M., Kim, S. W., Lindgren, E., Ramirez, V., Zehra, A., Freeman, C., Miller, G., Manza, P., Srivastava, T., De Santi, S., Tomasi, D., Benveniste, H., & Volkow, N. D. (2018). β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(17), 4483–4488. https://doi.org/10.1073/pnas.1721694115

Simon, K. C., Whitehurst, L. N., Zhang, J., & Mednick, S. C. (2022). Zolpidem maintains memories for negative emotions across a night of sleep. *Affective Science*, *3*(2), 389–399. https://doi.org/10.1007/s42761-021-00079-1

Staresina, B. P., Bergmann, T. O., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., Elger, C. E., Axmacher, N., & Fell, J. (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nature Neuroscience*, *18*(11), 1679–1686. https://doi.org/10.1038/nn.4119

Steinhubl, S. R., Muse, E. D., & Topol, E. J. (2015). The emerging field of mobile health. *Science Translational Medicine*, *7*(283), 283rv3. https://doi.org/10.1126/scitranslmed.aaa3487

Sterr, A., Ebajemito, J. K., Mikkelsen, K. B., Bonmati-Carrion, M. A., Santhi, N., della Monica, C., Grainger, L., Atzori, G., Revell, V., Debener, S., Dijk, D.-J., & DeVos, M. (2018). Sleep EEG derived from behind-the-ear electrodes (cEEGrid) compared to standard polysomnography: A proof of concept study. *Frontiers in Human Neuroscience*, *12*. https://doi.org/10.3389/fnhum.2018.00452

Tononi, G., & Cirelli, C. (2012). Time to Be SHY? Some comments on sleep and synaptic homeostasis. *Neural Plasticity*, *2012*, 1–12. https://doi.org/10.1155/2012/415250

Walsh, J. K., Zammit, G., Schweitzer, P. K., Ondrasik, J., & Roth, T. (2006). Tiagabine enhances slow wave sleep and sleep maintenance in primary insomnia. *Sleep Medicine*, *7*(2), 155–161. https://doi.org/10.1016/j.sleep.2005.05.004

Wennberg, A. M. V., Wu, M. N., Rosenberg, P. B., & Spira, A. P. (2017). Sleep disturbance, cognitive decline, and dementia: A review. *Seminars in Neurology*, *37*(4), 395–406. https://doi.org/10.1055/s-0037-1604351

Westerberg, C. E., Mander, B. A., Florczak, S. M., Weintraub, S., Mesulam, M.-M., Zee, P. C., & Paller, K. A. (2012). Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. *Journal of the International Neuropsychological Society*, *18*(3), 490–500. https://doi.org/10.1017/S135561771200001X

Whitmore, N. W., Harris, J. C., Kovach, T., & Paller, K. A. (2022). Improving memory via automated targeted memory reactivation during sleep. *Journal of Sleep Research*, *31*(6), e13731. https://doi.org/10.1111/jsr.13731

Winer, J. R., Mander, B. A., Kumar, S., Reed, M., Baker, S. L., Jagust, W. J., & Walker, M. P. (2020). Sleep disturbance forecasts β-amyloid accumulation across subsequent years. *Current Biology*, *S0960982220311714*, 4291–4298.e3. https://doi.org/10.1016/j.cub.2020.08.017

Wunderlin, M., Koenig, T., Zeller, C., Nissen, C., & Züst, M. A. (2022). Automatized online prediction of slow-wave peaks during non-rapid eye movement sleep in young and old individuals: Why we should not always rely on amplitude thresholds. *Journal of Sleep Research*, *31*(6), e13584. https://doi.org/10.1111/jsr.13584

Wunderlin, M., Züst, M. A., Fehér, K. D., Klöppel, S., & Nissen, C. (2020). The role of slow wave sleep in the development of dementia and its potential for preventative interventions. *Psychiatry Research: Neuroimaging*, *306*, 111178. https://doi.org/10.1016/j.pscychresns.2020.111178

Wunderlin, M., Züst, M. A., Hertenstein, E., Fehér, K. D., Schneider, C. L., Klöppel, S., & Nissen, C. (2021). Modulating overnight memory consolidation by acoustic stimulation during slow wave sleep – A systematic

review and meta-analysis. *Sleep*, *44*(7), zsaa296. https://boris.unibe.ch/151205/

Zambelli, Z., Jakobsson, C. E., Threadgold, L., Fidalgo, A. R., Halstead, E. J., & Dimitriou, D. (2022). Exploring the feasibility and acceptability of a sleep wearable headband among a community sample of chronic pain individuals: An at-home observational study. *Digital Health*, *8*, 20552076221097504. https://doi.org/10.1177/20552076221097504

Zhang, J., Yetton, B., Whitehurst, L. N., Naji, M., & Mednick, S. C. (2020). The effect of zolpidem on memory consolidation over a night of sleep. *Sleep*, *43*(11), zsaa084. https://doi.org/10.1093/sleep/zsaa084