Acoustic stimulation as a promising technique to enhance slow-wave sleep in Alzheimer's disease: results of a pilot study

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*All authors have seen and approved the manuscript

Funding

This work was supported by the Funds Malou Malou, Perano, Georgette Paulus, JMJS Breugelmans and Gabrielle, François and Christian De Mesmaeker, Managed by the King Baudouin Foundation of Belgium, [No, 2021-J1990130-222081] to Maarten Van Den Bossche and Laura Van den Bulcke, and by the ―Klinische onderzoeks- en opleidingsraad (KOOR)‖ of the University Hospitals Leuven to Maarten Van Den Bossche.

Conflict of interest

The authors have no conflicts of interest to declare.

Clinical trial registration:

The study was registered and validated in the UZ/KU Leuven central clinical research database of the Clinical Trial Center of UZ Leuven/KU Leuven (S65612) and the Belgian national authority for clinical trials, the Federal Agency for Medicines and Health Products (FAMPH).

Number of tables: 2

Number of figures: 2

Abstract word count (if applicable): 249

Brief summary word count (if applicable): 94

Manuscript word count: 1994

Abstract

Study Objectives: Sleep disturbances are common in people with Alzheimer's disease (AD), with a reduction in slow-wave activity (SWA) being the most striking underlying change. Acoustic stimulation has emerged as a promising approach to enhance SWA in healthy adults and people with amnestic mild cognitive impairment. In this phase 1 study we investigated, for the first time, the feasibility of acoustic stimulation in AD and piloted the effect on slow-wave sleep (SWS).

Methods: Eleven adults with mild to moderate AD first wore the DREEM2 headband (DH) for two nights to establish a baseline registration. Using machine learning, the DH automatically scores sleep stages in real-time. Subsequently, the participants wore the headband for 14 consecutive 'stimulation nights' at home. During these nights, the device applied phase-locked acoustic stimulation of 40 dB pink noise delivered over two bone-conductance transducers targeted to the up-phase of the delta wave or SHAM, if it detected SWS in sufficiently high-quality data.

Results: Results of the DH algorithm show a significant average increase in SWS (minutes); $t(3.17) = 33.57$, $p = 0.019$ between the beginning and end of the intervention; almost twice as much time was spent in SWS. Consensus scoring of EEG data confirmed this trend of more time spent in SWS; $t(2.4) = 26.07$, $p = 0.053$.

Conclusion: Our phase 1 study provided the first evidence that targeted acoustic stimuli is feasible and could increase SWS in AD significantly. Future studies should further test and optimize the effect of stimulation on SWS in AD in a large randomized controlled trial.

Key Words

ALZHEIMER'S DISEASE; SLEEP; SLOW WAVE SLEEP; ACOUSTIC STIMULATION; WEARABLE DEVICE

Brief summary

Disturbances of sleep are a very common and debilitating symptom of AD. A reduction in SWS is one of the most striking underlying changes. Our study provides the first evidence that acoustic stimulation could lead to a considerable increase in SWS in AD. Enhancement of SWS in AD provides exciting perspectives as this may not only lead to better sleep without the risks associated with sleep-inducing medications, less mood, cognitive and behavioral problems, but could even, given the role of SWS in the pathophysiology of AD, be considered a disease-modifying therapy in the future.

INTRODUCTION:

Besides the cognitive impairments, one of the most striking features of Alzheimer's disease (AD) is sleep disturbances. These disturbances can lead to mood[1], behavior[2] and cognitive problems[3] reducing patients' quality of life and increasing caregiver burden[4]. In AD, a reduction in the slow-wave sleep (SWS) stage (or N3) is one of the most notable changes in sleep[5]. The glymphatic system, a system particularly active during SWS, has been described in rodents as a pathway underlying the clearance of solutes, including Aβ, from the brain's extracellular space[6]. In humans, studies have indicated evidence for pathways that closely resemble the glymphatic system outlined in rodents[7]. A reduced clearance of pathological protein aggregates from the brain by the glymphatic system, influenced by a reduction in SWS, could be a shared phenomenon in neurodegeneration[8].

In recent years, several, primarily single-night, in-lab interventions have reported the beneficial effect of acoustic stimuli on slow wave enhancement and declarative memory consolidation in a (mostly young and healthy), small group of participants[9–13]. Furthermore, mobile devices provide the opportunity to move findings from well-controlled lab studies to more longitudinally in-field applications. Patients with AD could be of specific interest because of their pronounced reductions of SWS; moreover, effective and safe treatment of sleep disturbances in dementia remains an unresolved challenge[14,15]. Risks associated with the use of sleep-inducing medications in dementia include risk for falls, confusion, and declining ability to care for oneself[14]. Slow wave enhancement by acoustic stimuli may lead to better sleep without the risks associated with sleep-inducing medications, less mood and behavior problems, and could even

slow down the cognitive impairment. However, sound might also influence sleep in an undesirable way[16].

To date, no study has investigated the effect of acoustic stimulation in patients with dementia. In this study, we focused on people with AD; the primary aims of our phase 1 trial were to examine the feasibility of acoustic stimulation in the home environment during multiple nights and pilot the effect on SWS by using a commercially available sleep monitoring and feedback-controlled slow wave modulation device.

METHODS:

Thirteen patients (5 females, mean age 76.31 (SD 5.39), range: 63-84) living at home and their partners were included. The involvement of partners allowed for a more reliable application of the study intervention. Participants fulfilled the criteria of a neurocognitive disorder due to AD, according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), ranging from mild to moderate (as defined by a score of one or two on the Clinical Dementia Rating Scale)[17]. Exclusion criteria included other types of dementia, unstable medical or psychiatric conditions, and alcohol or substance abuse. The presence of pre-existing sleep disturbances and use of sleep-inducing medication were no exclusion criteria; however, no alterations in the use of psychopharmacological drugs were made during the study. The study was approved by the Ethics Committee of UZ Leuven and UPC KU Leuven (S65612) and conducted in accordance with the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Eligible participants were equipped with a commercially available headband device (DREEM2). The device was worn at home and participants respectively activated and deactivated the device themselves at their habitual sleep and wake time. The device uses machine learning to assess the data of its built-in sensors, including 5 EEG dry electrodes, a 3-D accelerometer, and a pulse oximeter, and automatically scores sleep stages. Additionally, the device has an inbuilt feature enabling acoustic stimulation through bone conduction. Participants first wore the device for two consecutive nights with the feature for stimulation turned off to establish a baseline registration. Then, they wore the headband for 14 consecutive 'stimulation nights.' The device applied phase-locked acoustic stimulation targeting slow wave up-phases at the 45° ascending condition. During these nights, the device either stimulated with two consecutive SO

phase-locked stimulation of 40 dB pink noise (STIM) or only marked the wave (SHAM) if the device detected SWS in sufficiently high-quality data. SHAM and STIM, each 50%, were randomly displayed throughout the night[18]. The device has proven to be accurate in detecting N3 sleep compared to polysomnography (PSG) (specificity: 0.90, sensibility: 0.70) and has a precise algorithm for stimulation (45 ± 52° reached on average for a 45° targeting)[18]. At the end of the study, participants were systematically debriefed to identify any adverse events and technical issues. A representation of the DH device and the flowchart of the study intervention is shown in Figure 1.

Independently and blinded from the DREEM annotations, two expert sleep scorers also manually scored the raw EEG data. SeqSleepNet-was used to aid the manual scoring of the sleep experts based on predictions from a machine learning model[19]. Using sequences of 10 consecutive epochs, we pre-trained SeqSleepNet on an open-access dataset of 25 adult volunteers measured with the Dreem Headband[20]. We used four EEG channels (Fp1-O1, Fp1-F7, F8-F7, F7-O1), accelerometry, and respiration of this dataset consisting of simultaneous PSG and DREEM headband measurements. Sleep stages are annotated based on PSG. Using the PSG annotations as ground truth, we trained the network on the DREEM data of this source dataset in a supervised way. Then we used unsupervised adversarial domain adaptation to adapt SeqSleepNet to each participant of our dataset.[21] The automatic sleep stage classification was followed by two independent manual expert reviews of these classifications based on visual scoring of the raw EEG data. Scorings were based on the AASM guidelines[22]. If the scorings of the two sleep experts were not concordant, a third scorer took the final consensus decision.

Duration (in minutes) and percentage of time spent in stage N3 of sleep, total sleep time (TST) (in minutes), sleep onset latency (SOL) (in minutes), and wake after sleep onset

(WASO) (in minutes) was calculated for night two and 16, the last night of the experimental procedure. To overcome the first-night effect, a common occurrence when using PSG, the initial night of registration was discarded from the analysis. First-night recordings are often characterized by decreased TST, lower sleep efficiencies, reduced rapid eye movement (REM) sleep, and longer REM latencies, an effect that is resolved during the second night of recording[23]. The results from the second night were thus used as baseline registration.

For between-night differences, paired two-sample t-tests were used. Where normality assumptions were violated, a non-parametric Wilcoxon signed rank test for paired data was applied. The pairwise deletion was implemented for handling missing data.

RESULTS:

Of the thirteen participants, two discontinued the study after three nights of recording for respectively experiencing pain behind the left ear and increased agitation during the day. Eleven participants completed the entire protocol. Data of four nights were excluded from the final analysis data set; two due to an unusually short total record time compared to previously recorded nights (less than 2.5h), this as a result of the removal or dislodging of the device during that specific night; one due to internal memory storage issues of the device and one due to the refusal of the participant to wear the device during that night. Sleep data of the remaining seven participants, who had sufficient data for both night two and night 16, were subsequently analyzed. The basic demographics of these participants are shown in Table 1.

In the debrief interviews with the eleven participants, no severe side effects were reported. The device was found to be comfortable to wear, with only four nights in total (out of 176) of non-use due to patient refusal. However, 60% of the participants reported that the headband became loose overnight at least once during the study. Suggested improvements included adding adjustable straps. Additionally, 80% of patients expressed the need for clear guidelines on pairing the headband with a personal device through Bluetooth and suggested simpler pairing methods.

The results generated by the DREEM headband showed a significant increase in the time spent in N3 (min) on night 16 (M = 68.64, SD = 46.64) compared to night 2 (M = 35.07, SD = 38.67), $t(3.17) = 33.57$, $p = 0.019$. Thus, in night 16, almost twice as much time was spent in N3 compared to night two. Also an increase in the percentage of TST spent in N3 (%) on night 16 (M = 15.80, SD = 9.90), compared to night 2 (M = 8.76, SD = 9.98) could be seen; $t(2.39) = 7.04$, $p = 0.054$. The consensus scoring of the raw EEG data confirm this trend of more time spent in N3 (min) on night 16 (M = 66.93, SD =

15.28), compared to night 2 (M = 40.86, SD = 27.28), t(2.4) =26.07, p = 0.053. Additionally, on night 16, the percentage of TST spent in N3 (%) (M = 14.35, SD = 3.15) compared to night 2 (M = 8.83, SD = 4.92) is significantly greater; t(2.74) = 5.52, p = 0.034. This means a 1.63 fold increase in the percentage N3 of TST between our interventions' beginning and end. There were no significant differences between baseline registration and night 16 in TST, SOL, or WASO (see Table 2).

The results of the scoring by the algorithm of the DREEM headband and those of the consensus scoring are shown in Table 2. A representation of the effect of the intervention on N3, both in absolute time and percentage of total sleep, is shown in Figure 2.

DISCUSSION:

We provided the first evidence that using a self-applied device at home for multiple nights, targeting SWS by acoustic stimuli is a usable and acceptable approach in AD and could considerably increase SWS by a factor of 1.6-2. Although enhancement of SWS was considered an important intervention target, no study has previously investigated the potential to enhance SWS by acoustic stimulation in patients with dementia[15]. It was considered questionable if enhancement of slow waves would be feasible in patients with AD, given the reduced baseline SWS and increased sleep fragmentation[10]. Moreover, given the reduced anticipated patient participation in patients with AD, using a self-applied headband device at home was considered challenging.

Limitations

At-home devices provide the opportunity for longitudinal in-field applications. However, they suffer from the absence of control over the subjects' behavior; e.g. pairing difficulties, refusal to wear the device, removal or dislodging of the devices. These have been previously reported and present a continuous challenge to measure sleep in people with dementia[24]. Feasibility measures may include the implication of a cognitively healthy partner in the study design, clear guidance on how to pair the headband with a personal device via Bluetooth, and general troubleshooting for technical issues. To ensure comfort and accuracy of data, adjustable straps should also be provided.

As we chose a commercially available device, no individualized alternations to the closed-loop stimulation technique could be made. We thus cannot exclude that an even more significant effect on SWS could be achieved with further (personalized) adjustments to the stimulation technique. Finally, since the primary aim of this phase 1

study was to investigate the feasibility of acoustic stimulation in AD and pilot the effect on SWS, our study was conducted in a small patient cohort without a control group.

Future directions

We have shown that acoustic stimulation could be a feasible and promising technique to enhance SWS in AD. Given the encouraging results of our phase 1 study, a large randomized control trial is warranted to further test and optimize the effect of acoustic stimulation on SWS in AD. Enhancement of slow waves in AD provides exciting perspectives, as improving sleep could possibly also result in improved mood, cognition, and quality of life of patients and their caregivers. A decrease in SWA, a quantitative measurement of SWS, has furthermore been correlated with the severity of cognitive decline and reduced cerebrospinal fluid clearance of Aβ and tau tracers in patients with AD[5,25]. As SWS seems to play an important role in the pathophysiology of AD, possibly mediated by the glymphatic system, enhancement of slow waves in AD could even be considered a disease-modifying therapy in the future.

Abbreviations

AD	Alzheimer's Disease
aMCI	amnestic mild cognitive impairment
DH	Dreem Headband
PSG	Polysomnography
REM	Rapid eye movement
SOL	Sleep onset latency
SWA	Slow-wave activity
SWS	Slow-wave sleep
TST	Total sleep time
WASO	Wake after sleep onset

Acknowledgments

The authors want to thank all participating patients, their partners, and their treating physicians.

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Figure legends

* Figure 1. Representation of the DH device and the flowchart of the study intervention

(A; we used the DREEM2 headband device (DH) to record sleep data and to stimulate the SWA by closed-loop acoustic stimulation. The DH was worn at home and self-applied by participants. Participants activated and deactivated the device at their habitual sleep and wake time. The device uses machine learning to assess the data of its built-in sensors, including 5 EEG dry electrodes, a 3-D accelerometer, and a pulse oximeter, and automatically scores sleep stages. Additionally, the device has an inbuilt feature enabling acoustic stimulation through bone conduction.

B; Participants first wore the device for two consecutive nights with the feature for stimulation turned off to establish a baseline registration (OFF). Then, they wore the headband for 14 consecutive 'stimulation nights.' The device applied phase-locked acoustic stimulation targeting slow wave up-phases at the 45° ascending condition. During these nights, the device either stimulated with two consecutive SO phase-locked stimulation of 40 dB pink noise (STIM) or only marked the wave (SHAM) if the device detected SWS in sufficiently high-quality data. SHAM and STIM, each 50%, were randomly displayed throughout the night.)

* Figure 2. Representation of the effect of the intervention on N3 both in absolute time and percentage of total sleep.

(Left; results by the embedded automatic algorithm of the DREEM headband (DREEM), Right; results of the consensus scoring of the raw EEG (CONSENSUS) data)

Tables

Table 1. Demographics of the study participants (N=7)	
	Frequency (%)
Gender	
Male	5 (71.43)
Female	2 (28.57)
Age, years	
60-70	1 (14.29)
70-80	4 (57.14)
80-90	2 (28.57)
Staging dementia (CDR*)	
Very mild dementia (3.0 - 4.0)	0
Mild dementia (4.5 - 9.0)	4 (57.14)
Moderate dementia (9.5 - 15.5)	3 (42.86)
Severe dementia (16 - 18)	0
Highest level of attained education	
Uneducated	0
Primary School	0
High School	3 (42.86)
Graduate	4 (57.14)
Smoking	
Active	0
Stopped	2 (28.57)
Never	5 (71.43)
Alcohol use	
Never	0
Daily	5 (71.43)
Weekly	2 (28.57)
Monthly	0
Coffee consumption	
Never	0
1-5/Day	7 (100)
>5/Day	0
*Staging dementia using clinical dementia rating scale sum of boxes scores	

Table 2. Sleep macrostructure for nights 2 and 16

	DREEM			CONSENSUS		
	NIGHT 2	NIGHT 16	p-value	NIGHT 2	NIGHT 16	p-value
Total sleep time (min)	397.43 (79.39)	421.29(65.23)	0.394	468.18 (82.73)	473.91 (70.39)	0.774
Sleep Onset Latency (min)	41.07(40.52)	30.64(38.47)	0.236	12.32(4.93)	9.30(3.71)	0.093
Wake after sleep onset (min)	116.79(45.19)	88.86(73.17)	0.237	77.68(43.43)	60.34(28.36)	0.275
Stage N3 (min)	35.07(38.67)	68.64(46.64)	0.019	40.86(27.28)	66.93(15.28)	0.053
Stage N3 (%)	8.76(9.98)	15.80(9.90)	0.054	8.83(4.92)	14.35(3.15)	0.034

*** Two-sided p values are mentioned (SD) of the paired t-tests / of the non-parametric Wilcoxon signed rank test for the DREEM results of SOL and WASO**

*** The results as shown represent respectively those by the embedded automatic algorithm of the DREEM headband (DREEM) and those of the consensus scoring of the raw EEG (CONSENSUS) data.**