Use of Acoustic Stimulation to Increase Slow-Wave Activity in Alzheimer's Disease Patients

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Abstract

Alzheimer's disease (AD) is a degenerative brain disease that affects patients' memory, thinking and behavior with age. As of 2023, 6.7 million Americans over the age of 65 have been diagnosed with AD. The complexity of the neurodevelopmental disease and unknown causation has led to limitations in treatment options and consequent lack of a cure. A rising suspect for the development of AD is the gradual depletion of glymphatic clearance in the brain associated with biological senescence. Auditory sleep stimulation is a method of directing acoustic stimuli within the N3 phase, focusing on promoting the glymphatic response in neurodegenerative patients. In this project, pink noise capable of maximizing stimulation without triggering an arousal response is to be played during upstate phases in N3 sleep, thereby optimizing glymphatic promotive effects. Through a wearable device, pink noise will acoustically stimulate and increase slow-wave activity (SWA) to improve sleep and cognitive consolidation in AD and mild cognitive impairment (MCI) patients. The device was created through a series of prototyping and ideating, while including technical constraints and target population considerations. This project covered the initial stages of the long-term design process in hopes of mitigating AD and MCI development and for potential use in expanding research on sleepwear designs for older adults.

Keywords: Alzheimer's disease, Mild Cognitive Impairment, acoustic stimulation, slow-wave activity

Introduction

Alzheimer's disease (AD) is a degenerative brain disease in older populations that introduces neurocognitive decline - generally involving difficulties in memory retention and rational thinking. AD lacks a definite etiology, with medical professionals hypothesizing genetic, environmental or natural causes[1]. A popular hypothesis for the development and progression of AD is the decline in glymphatic response associated with aging. Discovered within the last decade, the glymphatic system is mainly active during deep sleep, where it removes debris from brain tissue into the lymphatic system[2].

The underlying mechanism of the glymphatic system relies on declining norepinephrine levels that allow for expansion of extracellular cavities within the brain, thereby improving cerebrospinal fluid (CSF) flow to drain out waste. The Amyloid-beta Cascade Hypothesis defines the buildup of amyloid-beta proteins to result in a feedback loop that promotes formation of neurofibrillary tau tangles associated with AD[3]. Specifically, the aggregation of these plaques may cause neuronal cell death that consequently leads to cognitive impairment. However, not all cases of amyloid-beta and tau tangle accumulation develop into AD as the two conditions are not causatively correlated to cognitive decline.

Slow-wave Sleep (SWS) or "deep sleep", is of the N3 phase in non-rapid eye movement (nREM) in which low-frequency, high-amplitude slow-waves are observed[4]. Slow-wave activity (SWA) is characterized by the 0.5-4.0 Hz frequency of sleep electroencephalograms (EEG), known as delta waves, during SWS[5]. N3 sleep is associated with memory consolidation due to the slow oscillations and sleep spindles that enable memory reactivation. Slow oscillations alternate between active upstates and quiet downstates; where upstate phases in particular, are indicative of memory reactivation and consolidation[6].

Pink noise is a type of noise that operates at a consistently low frequency to create lower waves that filter high sounds[7] and has been associated with enhancement of SWS. By directing acoustic stimulus via pink noise towards this sleep phase, the objective of this project is promotion of the glymphatic response to assist in the removal of plaques associated with AD[8]. Pink noise was selected due to its intrinsic property of maximizing stimulation without triggering an arousal response.

Mild cognitive impairment (MCI) is a potential precursor to AD, in which the patient experiences an unusually greater decline in cognitive function given their age[1]. MCI does not interfere with social behavior, but increases the risk of dementia/AD development. The onset of MCI can be predicted using the Montreal Cognitive Assessment (MoCA)[7]. This is a cognitive test that assesses short term memory, visuospatial abilities, language, orientation, and executive functions through a series of questions and objectives, such as drawing a clock. This test has become a commonly used diagnostic for MCI, and thus as an indicator for AD.

Mitigative treatments exist primarily in the form of pharmacological drugs, but there has been a rising interest in stimulative therapies. Donepezil, Galantamine, and Rivastigmine are cholinesterase inhibitors approved for use by AD patients to help mitigate associated symptoms[8]. Alternative treatments in the form of cognitive or stimulative therapies have had inconclusive results[9,10]; this project is motivated by the lack of effective, non-pharmaceutical treatments to AD. In 2022, the cost of care for AD/dementia patients 65 and older was $321 billion, of which 65% came from Medicaid and Medicare and a quarter from out-of-pocket[11]. Our goal is to target individuals with MCI to prevent or delay the onset of AD before it develops into irreversible stages. By doing so, we aim to reduce the economic burden of the disease on caregivers and the healthcare system, as well as alleviate the mental burden on geriatric patients through the use of our device.

Many acoustic stimulation studies are focused on employed middle-aged adults or sleep-deprived students. Diep et al. developed and tested an automated acoustic stimulation device capable of monitoring real-time EEG[12]. In their study of healthy adult males with depleted SWA, the device was able to improve executive function. Executive function is the use of mental activities to conduct common cognitive tasks such as planning, focusing, multitasking and memory recollection[13]. Ngo et al. studied auditory stimulation on a sample of children with Attention Deficit Hyperactivity Disorder (ADHD), a neurodevelopmental disorder with hindered memory function possibly due to obstructed SWA[14]. Reviews of literature and similar studies led to the conclusion that improvements in memory recollection and executive function were successfully observed after nights of auditory stimulation relative to non-stimulatory conditions[12].

The deliverable developed through this capstone project will be an innovative product specifically designed for use by geriatric patients with an onset of AD. While unable to provide a cure to the cognitive disease, the aim of the project is to introduce a preventative solution starting from the early indications of the disease. As amnestic MCI patients have shown improved short-term memory recollection through auditory stimulation applied during deep sleep, there is hope in doing the same for AD patients. The device produced from the project will contribute to the developing field of sleep therapeutics by targeting deep sleep - notably, of SWA and the upstate phase. Subsequently this will promote glymphatic activity to maintain cognitive performance in geriatric audiences with AD[15]. The goal of this project is to create an independent, biotechnical device capable of self-use by the geriatric patient, thereby promoting an efficient non-pharmaceutical tool for amplifying slow-waves to accordingly mitigate cognitive decline. This wearable device will be able to record and interpret brain activity during sleep, while also delivering appropriate acoustic stimulation to enhance SWA and thus glymphatic activity.

Materials and Methods

The design thinking process was applied to address the main clinical concern stated. We first identified the problem and then defined constraints by using literature research and target population considerations through surveys. Additionally, a verbal interview was held with Laura Byer, a project manager at the Alzheimer's Association, to better understand the behavioral needs and expectations of the target population. The last aspect that determined technical constraints were electrode placements and integration with the brain computer interface (BCI). With these constraints and considerations in mind, we brainstormed designs based on wearable headwear we have seen before and created a series of sketches. The sketches were then created into more detailed, 3D computer-aided designs (CAD) of which some were further rendered in Blender, which added more realistic features such as textures and lighting. Subsequently, we considered different materials to be used for 3D-printing and prototype assembly. Thermoplastic polyurethane (TPU) was originally the material of choice due to its flexibility and durability, but technical malfunctions with 3D printers narrowed our choices to polylactic acid (PLA), a hard plastic. The first prints were used as a reference to guide future prints, based on their size, weight, and feel of material choices. The printed prototypes were assembled with fabrics and tested on ourselves to gauge design comfortability.

To understand the requirements and expectations of target users of our device, a survey was created and advertised for feedback. Surveys were catered towards caretakers or family members of senior individuals with or

without neurodegenerative conditions. The responses from the surveys gave insight on the perspective of caregivers. Demographical data verified the collection of responses from the desired target population such as age, neurocognitive diagnoses (if any), and sleep conditions. Inquiries regarding sleep behavior were included to iterate upon our designs where necessary. In addition, ranking of technological comfort and use of common devices were requested for guidance in designing an intuitive device interface.

Results

Design Constraints

By reviewing relevant literature on acoustic stimulation and prior art, key design constraints were identified. The leading features relevant to form factor were comfortability, location of EEG electrodes, and adjustability. While other specifications were included for the device functionality, prioritizing the form factor was crucial for the target population to accept and adopt the device. To ensure comfort, we considered factors such as material choice, weight, and balance. When determining the location of the EEG electrodes, we followed the standard 10-20 EEG system (Fig. 1) where F_p, F_z, and/or F_c locations were prioritized for collecting delta waves and A_1 and A_2 were prioritized for reference signals.

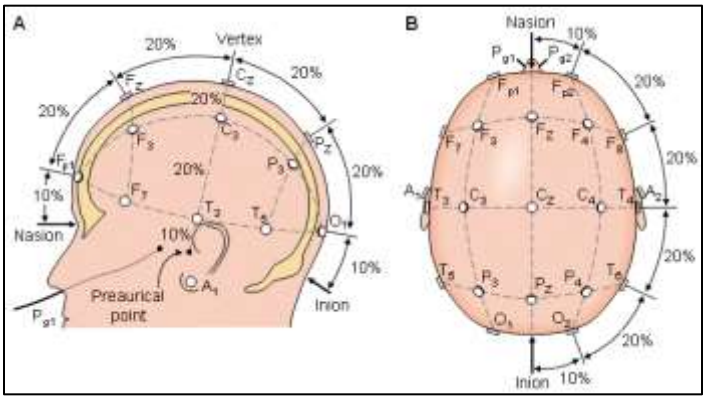

Figure 1. 10-20 EEG system. A) Lateral and B) Crown views of the 10-20 EEG system.

Form Factor Designs and Assembly

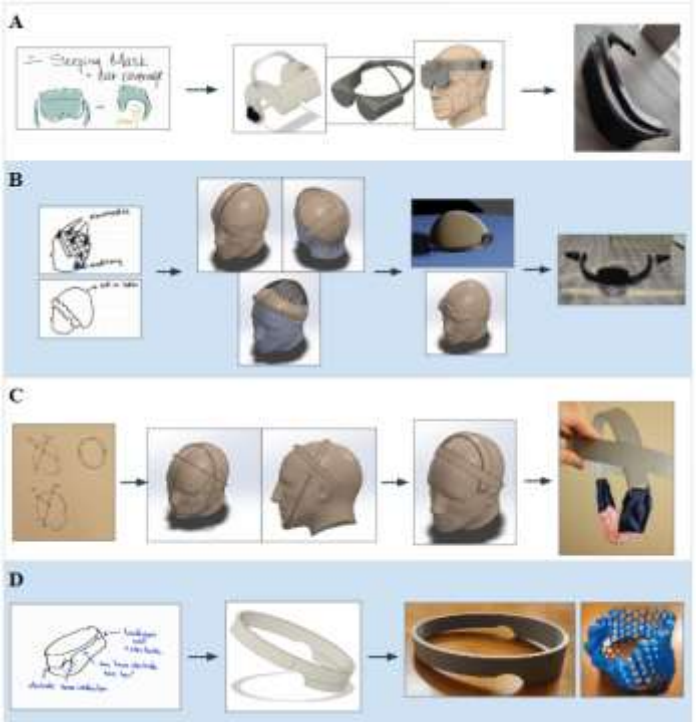

Figure 2. Prototype Designs. A) Sleep Mask. B) Sleep Cap. C) Sleep X/Y. D) Sleep Headband.

Sleep Mask

Figure 2A shows the 'Sleep Mask' design and its progression from ideation to a printed model. This design was selected due to its familiarity as a common sleeping headwear and its intuitive orientation. The sleep mask at the front of the design facilitates easy orientation, making it beneficial for patients with MCI who might have difficulty understanding the proper placement of the device. Based on feedback from our surveys, it was noted that many older adults are against the use of a sleep mask or coverage over the face during sleep. In response, the sleep mask cover was altered to be detachable according to the preference of the user. The presence of the main band also facilitates a stable support that can provide anterior electrode coverage where necessary.

To improve the functionality and comfort of this design, several issues have been identified with the current prototype. One of the main issues is the dimensions, which will need to be addressed to ensure the device fits comfortably on different head sizes. Additionally, the type of material used in the prototype (PLA) is too stiff and does not conform to the shape of the head, making it uncomfortable to wear. To address this, softer materials like TPU or other more malleable materials will need to be explored in future designs to increase flexibility, softness, and lightness, ultimately improving the device's comfort

and functionality.

Sleep Cap

Figure 2B shows the 'Sleep Cap' design and its progression from ideation to form factor prototype. The largest advantage of this design over others is the full coverage of the head that expands electrode placement capability similar to an EEG cap. The availability of easy access to F_z and C_z locations for electrodes allows for accurate EEG readings. Full coverage of the head not only provides better balance, but also reduces the likelihood of the wearable prototype becoming displaced during sleep if secured properly. After generating ideas through the design thinking process, various mockup iterations were developed using SolidWorks (CAD) software. To visualize the design more realistically, a rendered mockup was created in Blender (Fig. 2B).

One important factor to consider with this design is the requirement of scalp coverage, which could present challenges for users with thicker hair to properly orient, fit, and wear the device. To enable secure contact between the electrodes and the scalp, users will need to ensure that each electrode is able to reach past their hair and maintain contact with the scalp. This may be difficult for patients with MCI or hindered motility. Furthermore, changes in hairstyle and hair length may also impact how the device fits, necessitating resizing edits over time.

Sleep X/Y

Figure 2C shows the 'Sleep X/Y' design characterized by the main bands which follow the lines across that head (from side to side) which intersect the F_z and C_z locations (Fig. 1). These locations are ideal for collecting slow wave oscillations. The front band also extends towards the back of the ear where an electrode could reach A_1 and A_2. The design also takes into account the comfort of users who prefer to sleep on their backs by avoiding the use of hard materials near the back of the head. The design was based on simple shape and line designs combined with the goal of connecting a chin strap to a band that would cover an electrode at the top of the head. Multiple mockup iterations of 'Sleep X/Y' variations were designed in SolidWorks followed by 3D-printing and assembly (Fig. 2C). In initial fit testing, it was found that the 'Y' design would easily fall forward and was unbalanced. Therefore, the final prototype of the 'Y' design was modified to allow for straps near the back of the head, thus creating an 'X' design.

In the initial fit testing, both these designs were difficult to orient which may nullify the benefits of aligning the bands with the C_Z and F_Z locations. Additionally, the use of cloth fabric may prove difficult to clean but it served well as a demonstration that the bands are meant to be adjustable or stretchy. In the future, different materials and systems of adjustability (e.g., Velcro, strap fastener) may have to be considered.

Sleep Headband

Figure 2D shows the 'Sleep Headband' design that incorporates full EEG coverage and accommodates users with diverse hair textures. Additionally, the removable exterior of this design facilitates washing and reuse, which aligns with sustainability goals. Unlike many of our other designs that rely on direct contact with the scalp, which may pose challenges for patients with thicker hair, this device accounts for that obstacle and enhances its accessibility. Silicone was determined to be the optimal material choice for the interior due to its high elasticity, compressibility, and ability to provide a cooling effect during sleep.

An area for improvement lies in the challenging operation and orientation, particularly for older adults who may struggle to identify the correct side to place on their forehead. Furthermore, the absence of the C_z electrode location in this design is a point to consider, as it has been identified as a significant factor for a successful design. However, without additional testing, we cannot conclusively determine how the EEG readings will be impacted by the electrode omission.

Survey and Interview Results

To gain insight into the potential user population of our device once it reaches the medical market, data pertaining to sleep habits and technological comfortability were gathered through surveys. The surveys were specifically addressed to caretakers and relatives knowledgeable with the behaviors of a senior adult.

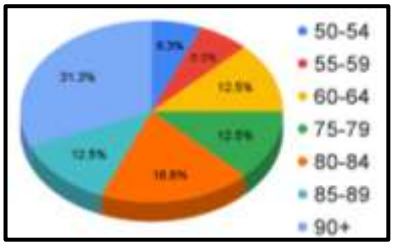

Figure 3. Breakdown of senior adult ages by survey respondents.

The age of older adults in the survey ranged from 50 to 90 and older with at least one senior in every age range increment of four years each (Fig. 3). Additionally, nine of the adults had an age related neurodegenerative disorder, with an even distribution of cases with AD, MCI or

dementia. This verifies that the survey data did include our target demographic of potential users. From the survey responses regarding sleep conditions, nine of the senior adults had a diagnosed sleep disorder, eight napped multiple times per day, and five only slept for 3-5 hours at night. These findings indicate the necessity of ensuring that our device is able to activate within at least three hours of sleep to be effective for some users. Without considering this factor, the device will be ineffective or less effective on patients that do not get enough hours of sleep to transition into the required N3 stage or experience very few cycles of deep sleep. The surveys also revealed that the majority of respondents typically slept on their back which suggests that the design should prioritize comfort in that position. This means that our designs should avoid hard materials, especially near the back of the head and ensure that the device is not too heavy or bulky in that area. Another important question asked was about willingness to wear a sleep mask. This was asked as sleep masks were thought to be the simplest and most analogous sleep headwear to our device in addition to the basis for the 'Sleep Mask' design. The majority of the older adults from the surveys were uncomfortable with wearing a sleep mask, some would consider it for medical reasons, and a rare few were open/willing to use sleep masks. This exemplifies the difficulty of designing and marketing a device where many senior adults are resistant (and sensitive) to sleep headwear. For questions regarding the use of different technologies including radio, television, and computer, varying levels of comfort and frequency were found (1-5 scale). Overall, computers were found to be both the least used and least comfortable device among the older adults. Thus our product should minimize the complexity of user interface features, making it intuitive and easy to use even for users who have difficulty handling technology.

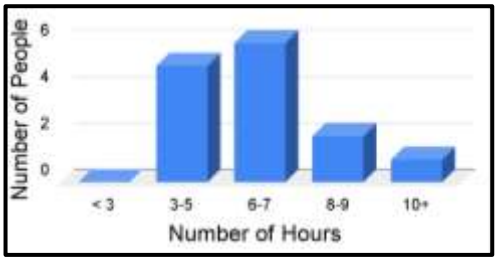

Figure 4. Number of hours slept per night by the senior adult, according to survey responses.

From our interview with Laura Byer, we gained insight into the lives of people living with AD/dementia. When asked about sleep habits, she presented many stories about wakefulness being a common issue for caretakers and safety in general. This demonstrates the need of our device to be resilient to user wakefulness - especially in being secured in position regardless of whether the user wakes up, walks around, or does various activities around their living space. Byer also emphasized how generally, caretakers were more trusted over relatives. From a marketing perspective, this shows the importance of convincing caretakers that our device is effective and comfortable so they can convince their patients to adopt our device. During the interview, we learned that as the disease progresses, many patients experience increased paranoia, making it crucial to convince a trusted caretaker to introduce the device early on. Doing so can help slow the progression of the disease and establish a pattern of device use that patients can become accustomed to before their condition worsens to the point where establishing a new routine becomes challenging.

Discussion

This project provided us a better understanding of the design process, including the realization that it can be long and unpredictable, indicating the need to allocate time for potential disruptions and unforeseen events. We faced many procedural difficulties, including technological failures and incorrect sizing of prototypes. The process of 3D-printing the designs took significantly longer than intended and these delays were incorporated into our initial planning to create a more accurate schedule. We also learned how to iterate on designs and assess their advantages and disadvantages. Many of our initial designs were improperly sized and were unstable when first printed, but after assessing the problems with each design, we were able to make necessary corrections in CAD and successfully reprint them. Additionally, a male head model was imported and used as a basis for designs. Since a majority of people with AD are women, future designs may have to be adjusted to be able to fit both typical male and female heads. Continuous ideation and iterations are vital to the design process, as we learned how to interpret problems and troubleshoot to create improvements.

Our prototypes are just one step in the overall design process of creating a wearable device to increase slow-wave activity in AD patients. We are aiming to create a more accessible device for patients who lack the means to afford current treatments for the disease or who cannot make it to the many appointments necessary for treatment. This device will be a one-time prescription device that patients can take home and use every day, without the need to renew a prescription or pay multiple times. Within the field of sleepwear devices, this project serves to inform future form factors and their considerations from an older adults perspective. Some of our designs were built based on

previous devices, but most were built based on common headwear, such as headbands, wig caps, and sleep masks. This could help future engineers integrate everyday objects into their designs and prototypes.

Future work includes incorporating the Unicorn Naked BCI and testing the effectiveness of the form factor in keeping electrodes in place during sleep. Following BCI assembly is software development to store and interpret sleep EEG data and apply consequent real-time acoustic stimulation. The integration of both hardware and software would allow for the creation of a functional prototype that can be validated through testing and data analysis. As the final steps, the device needs to undergo real-time testing during sleep, which should be accompanied by interviews with the target population to evaluate device comfort and usability.

This project focused on increasing accessibility to preventative AD treatments and therapeutics by creating a wearable device that will measure brain activity during sleep and deliver appropriate acoustic stimulation to increase slow-wave activity. In doing so, older adults with MCI will be able to take the device home and use it every night or during naps, all without having to attend frequent doctor appointments to renew prescriptions. The device is intended to be used on adults who are in the early stages of AD, such as MCI, as a measure to slow disease and mitigate cognitive decline associated with age by maintaining consistent glymphatic activity.

End Matter

Author Contributions and Notes

All authors contributed to survey and interview preparations. Teevan-Kamhawi and Yi contributed to the Sleep Mask. Donis Barrera and Lee contributed to the Sleep Cap and Sleep X/Y. Livingston designed the Sleep Headband.

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