Development of a Wearable Therapeutic Device for the Treatment of Alzheimer's Disease using Magnetic Stimulation Induced Gamma Oscillations

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Gaia Di Bernardini, Niharika Mahesh Dhande, Kyla Frenia, Abby Kuelker, Ilisha Prasad, and Srusti Sain

BIOE5850 – Design of Implants

Professor Sumner Barenberg

April 9th, 2023

ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disease that affects one in nine people over the age of 65 in the United States. The two major pathologies of AD are the accumulation of neurofibrillary tau tangles and amyloid-beta plaques in the brain. AD patients experience cognitive decline and progressive memory loss and there are currently no approved therapies that can cure or slow the disease progression. The induction of gamma oscillations can be achieved through transcranial magnetic stimulation (TMS) and has shown promise in the treatment of AD. Gamma oscillations are repetitive changes in the local field potential (LFP) of the brain, and are generated by GABAergic interneurons, which are inhibitory neurons that regulate neural circuit activity. Gamma oscillations play a key role in memory retrieval and thus hold valuable potential for the treatment of AD. Current TMS treatment must be performed in a clinical setting, making this therapy limiting for patients. As such, a cap design for a minimally invasive, at-home, and wearable TMS device for the treatment of AD has been developed and outlined in this proposal. Potential avenues for the development of smaller electrical components including coils and power supply for TMS are discussed. The expected outcomes of using the proposed TMS therapy for AD include reduced hippocampal long-term potential (LTP) impairment and spatial memory, relieved symptoms of memory loss associated with AD, reduced neurogenesis, and increased recovery action of lost neural populations.

I. UNMET CLINICAL NEEDS

a. Background

Alzheimer's disease (AD) is a neurodegenerative disease that is estimated to affect more than 131.5 million people worldwide by 2050 [1]. AD is the most common form of dementia and results in cognitive decline as well as symptoms such as agitation, hallucinations, depression, sleep disturbances, and apathy [2]. AD is a primary tauopathy, which is a class of neurological disorders defined by intracellular accumulation of the protein tau [3]. Tau proteins attach to microtubules to stabilize the internal skeleton of nerve cells [4]. When tau proteins become hyperphosphorylated, they form intraneuronal aggregates that are known as neurofibrillary tangles (NFTs) [3]. This is one of two primary pathologies in AD, with the accumulation of amyloid-beta plaques as the second common pathology. Amyloid-beta plaques form when the amyloid precursor protein (APP), meant to aid in cell-cell attachment, is improperly cleaved by gamma secretase, releasing amyloid-beta peptides that stick together extracellularly. It is proposed that neuronal synapses are blocked by the NFTs and plaques, however, what spurs the initiation of these mechanisms is unknown. Furthermore, it is also unclear if the brain atrophies because of these accumulations or, conversely, if these accumulations cause the brain to atrophy. Despite decades of research, there are still no drugs that can slow the progression of AD or cure it [4]. Promising preclinical results repeatedly fail when translated to humans, and the large focused on amyloid-beta plaques is being debated currently as to whether its importance is misplaced.

i. Current Treatments

There have been several advances in recent years toward better understanding Alzheimer's and developing new treatment methods. Currently, there are two main types of medications that have been approved to treat AD: medications that slow the progression of the disease, and medications that ease symptoms temporarily (Mayo Clinic, 2022). Numerous prescription drugs have already been approved by the FDA to help mitigate symptoms associated with AD. Cholinesterase inhibitors and Memantine are approved for use in mitigating AD symptoms and have varying efficacy depending on the stage of AD progression in the individual. Cholinesterase inhibitors work by increasing the amount of acetylcholine available in nerve cells and by limiting its breakdown in the brain (Mayo Clinic, 2022). Though this drug has shown some efficacy, cholinesterase inhibitors cannot reverse AD and eventually loses effectiveness, as well as causing unpleasant side effects in patients such as nausea, diarrhea, and vomiting (Deardorff et al., 2015). Memantine is approved in the US and the EU for patients with moderate to severe AD, and is used to lessen symptoms of cognitive decline and function (Robinson and Keating, 2006). Memantine works by regulating glutamate, which is a chemical associated with brain functions such as memory and learning (Mayo Clinic, 2022). This medication is often taken as a pill or syrup and, like cholinesterase inhibitors, is associated with side effects such as confusion, agitation, headache, and dizziness. On June 7th, 2021, the FDA accelerated the approval of aducanumab, a drug that may help slow the progression of AD by reducing amyloid deposits in the brain (NIH, 2021). This is the first drug of its kind, it is an intravenous infusion therapy that has been approved for patients with mild dementia and cognitive impairment. The benefits of the drug on memory and daily functioning still are not clear, and repeated MRIs of the brain are needed to detect changes in amyloid related abnormalities (Mayo Clinic, 2022). Overall, though there are various therapeutic treatments current approved for AD, they only offer mild alleviation of symptoms and are currently not disease-modifying (Frozza et al., 2018).

ii. Unmet Needs

Alzheimer's disease is a debilitating neurodegenerative disorder that affects millions of people worldwide. While transcranial magnetic stimulation (TMS) has been proposed as a potential treatment for Alzheimer's disease, there are several unmet clinical needs that must be addressed to optimize its therapeutic potential. This section highlights the critical unmet clinical needs for TMS in Alzheimer's patients.

Table 1: Unmet Clinical Needs of TMS for Patients with Alzheimer's Disease and Relevancy to Proposed Solution

Unmet Clinical Need	Description	Proposed Solution
Developing Reliable Biomarkers for Patient Selection	The need to identify biomarkers that can identify patients with early-stage Alzheimer's disease who are most likely to benefit from TMS. (Weiler et al., 2020)	✓ (provides targeted stimulation to the hippocampus)
Ethical guidelines for treating patients unable to provide informed consent	There are significant ethical concerns around providing TMS to Alzheimer's patients who are unable to provide informed consent. Therefore, there is a need to develop ethical guidelines to guide the treatment of these patients. These guidelines should ensure that TMS is provided in the best interest of the patient while ensuring their autonomy is preserved. (Illes & Racine, 2005)	✓ (an at-home device may reduce ethical concerns)
Timing of TMS Intervention	The need to identify the optimal timing for TMS intervention to produce the most significant benefit. Early intervention in patients with mild cognitive impairment and later intervention in patients with advanced disease may produce different outcomes. (Lin et al., 2019)	✓ (proposed device can be used at home, allowing for more flexibility in timing)
Combination of TMS with Other Treatments	The need to explore the combination of TMS with other treatments for Alzheimer's disease. Identifying the best combination of treatments and determining the optimal timing and sequence of treatments. (Freitas et al., 2011)	N/A (not directly addressed by the proposed solution)
Reliable Measures of Patient Outcomes	Developing standardized cognitive tests, functional assessments, and quality of life measures will help evaluate the effectiveness of TMS in Alzheimer's. (Buss et al., 2019)	✓ (proposed device can be used to monitor cognitive changes and track progress)
Optimal Targets for TMS in Alzheimer's Disease	Optimizing stimulation parameters and identifying the best target for each patient is critical to improving outcomes. (Cotelli et al., 2006; Weiler et al., 2020)	✓ (proposed device targets the hippocampus)

Criteria for Patient Selection	Identifying patients who are most likely to benefit from TMS for Alzheimer's disease, including patients with mild to moderate Alzheimer's disease who have not responded to other treatments. (Brem et al., 2014; Weiler et al., 2020)	✓ (proposed device can be used for patients with mild to moderate Alzheimer's disease)
Safety and Efficacy of TMS	Establishing the long-term safety and efficacy of TMS for Alzheimer's disease. (Lin et al., 2019; Rabey et al., 2013; Weiler et al., 2020)	N/A (not directly addressed by the proposed solution)
TMS Devices Specifically Designed for Alzheimer's Disease	The need for smaller, more precise coils and more advanced stimulator systems may help improve outcomes for Alzheimer's patients. (Iyer et al., 2005)	✓ (proposed device is specifically designed for use in Alzheimer's disease)
Cost-Effective TMS Devices	Developing cost-effective TMS devices and using materials that are safe and cost-effective will help improve access to this treatment. (Chail et al., 2018)	✓ (proposed device is designed to be at-home, reducing the cost of clinic visits)

II. PROPOSED SOLUTION

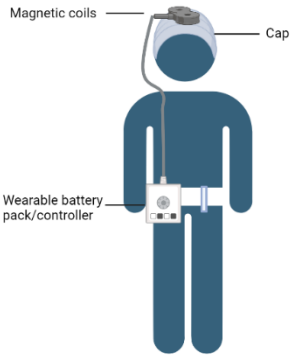

Figure 1: Concept sketch for design of wearable TMS for Alzheimer's

The proposed solution is an at-home TMS device which stimulates the hippocampus through the application of a magnetic field generated by coils. This device will deliver 40Hz stimulation for 1 hour to induce gamma oscillations in the brain. The device will be a non-invasive wearable in the form of a cap, which ideally connects to a battery pack that can be worn at the patient's hip to allow for mobility during treatment as shown in Figure 1. To position the coils reproducibly over the target region of the brain, the cap will be designed to the size of the patient's head and will attach around the ears and chin. A method of cooling the coils will also be integrated into the cap; this can take the form of fans, heat-sink materials surrounding the coils, a fluid cooling system, or some combination of these elements. A major design challenge for this system will be reducing the power supply system to a wearable size, so it can be expected that initial iteration of the design might require continuous connection to wall power.

Figure 2: Example cap design to ensure reproducible coil placement

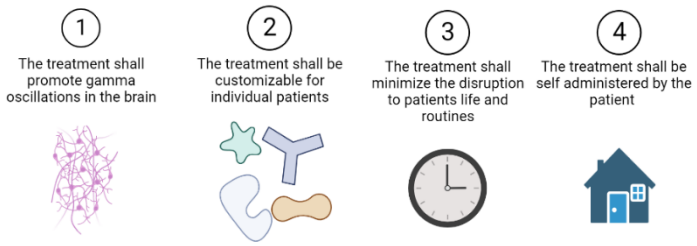

Figure 3: Design Requirements

The design requirements for this device are that it shall (1) stimulate gamma oscillations in the brain (2) allow for treatment customization (3) minimize the disruption of the treatment to the patient's life, and (3) be self-administered. All these requirements are met in the initial proposed design.

a. Brainstorming

Several potential avenues of development were explored by the team. Unmet needs were grouped into three major categories: invasiveness of DBS surgery, effectiveness of DBS treatment, and the uncertainty around effectiveness and mechanism of action associated with DBS.

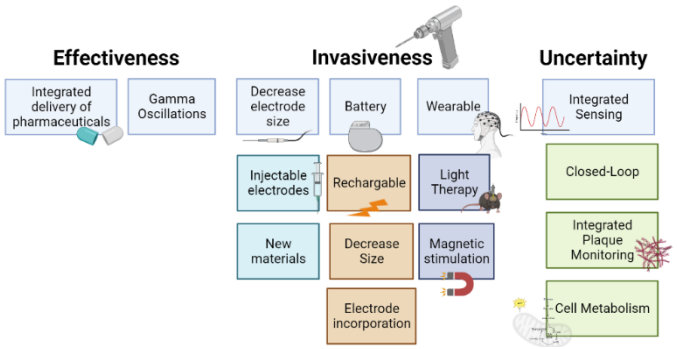

Figure 4: Brainstormed solutions to meet unmet clinical needs associated with DBS treatment for Alzheimer's.

b. Gamma Oscillation

Gamma oscillations are a synchronization of neural activity that causes rhythmics changes in the LFP around a set of neurons. These oscillations occur at a range of frequencies and are generally grouped into two categories, slow oscillations having a frequency between 25-50 Hz, and fast oscillations having a frequency of 55-100 Hz (Mably & Colgin, 2018). Gamma oscillations are generated locally but are often coupled with similar activity in other areas of the brain. Slow gamma oscillations, those of most interest to the treatment of Alzheimer's, are generated in the hippocampal subfield CA3 which is necessary for the retrieval of memories, is coupled with similar oscillatory patterns in the hippocampal CA1 region of the brain. Research has shown in both humans and mouse models that disruptions of gamma oscillations between the CA1 and CA3 hippocampal regions are common in the brains of patients with Alzheimer's (Traikapi & Konstantinou, 2021). Several methods of inducing gamma oscillations in the brain have been explored including light, audio, magnetic, and ultrasound stimulation. In mouse models, magnetic, light, and audio stimulation have been shown to be effective in inducing gamma oscillations when 40 Hz stimulation is used (Chan et al., 2022) (Zhen et al., 2017). The use of ultrasound to stimulate

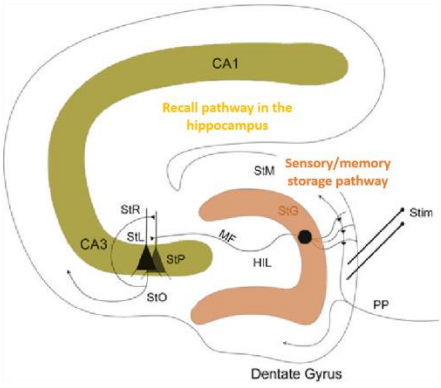

Figure 5: Pathway of memory recall and storage in the hippocampus

gamma oscillations has been explored but has not been shown to be effective in mouse models (Park et al., 2021).

c. **Materials**

Biomaterials are essential in TMS and DBS implant design because they can interact with the surrounding tissue, impact the implant's performance and longevity, and influence the imaging compatibility of the device. The biomaterials specifically in our proposed device are evaluated based on coils and their safety and biocompatibility. Due to the proximity of our device to the brain, we are proposing using material that can sustain the electrical stimulation capabilities at a close range along with having low heat dissipating capabilities. Making smaller coils capable of magnetic oscillations will provide consistent stimulation over extended periods of time without harming the patient. The magnetic coil used in deep brain stimulation (DBS) is typically made from copper wire wrapped around a ferromagnetic material such as iron or nickel and may also be encased in protective plastic or metal to ensure safe handling and prevent damage. Overall, these technologies represent significant advancements in their respective fields and offer new opportunities for research and medical applications.

Currently, the materials used in TMS comprise mechanically stable and imaging compatible metals including Titanium and its alloys. This is often used for making the outer casting of the device. Generally, ceramic materials can be used for outer casing of devices or internal insulation. However, since our device is a wearable cap, we will be using a lightweight and stretchable fabric made from textile that is comfortable instead of the usual hand-held device. One example is a textile made of 97% cotton and 3% lycra, which incorporates an elastic band at the back of the neck for added comfort. This cap will incorporate copper wires and ferromagnetic material. This cap will be connected to a battery pack that will power the coils for stimulation. The material used for making this battery pack is a possible future work to make the stimulations long lasting and powerful. One possible solution can be using a dual power for consistent power supply using zirconium and lithium-ion generator.

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d. **Human Factors**

Wearable devices that stimulate gamma oscillations in the brain may provide an easy-to-use non-invasive treatment option for Alzheimer's patients. The devices can be designed to emit light, magnetic fields, or audio at specific frequencies, and can collect data on the patient's brainwave activity during treatment sessions. It is important to note that for the purposes of the proposed design, Cognito has patented audio and visual stimulations. Additionally, clinicians can use this data to assess the effectiveness of the treatment, adjust treatment parameters, and identify any

adverse effects. Family members can also use the data to monitor treatment progress, offer emotional support, and advocate for the patient's needs. It is important for family members to educate themselves about the treatment and the patient's condition to provide informed support.

e. **Achilles Heels**

The biggest challenges to the development of an at-home TMS device for the treatment of Alzheimer's are the miniaturization of the coils, and the development of an appropriate portable power supply.

The coils used in the smaller system must be able to generate high-intensity magnetic fields from a compact form without overheating to a level that would either destroy the coils or cause injury to the patients. One potential solution to the design of smaller coils is to use additive manufacturing to make multi-layered 3D printed coils out of the superconducting materials discussed previously (Mohtadi Jafari & Abdolali, 2018). This would allow for the design of coil configurations that have high magnetic intensity and depth resolution and allows the design to be customized for applications to Alzheimer's and potentially to individual patients.

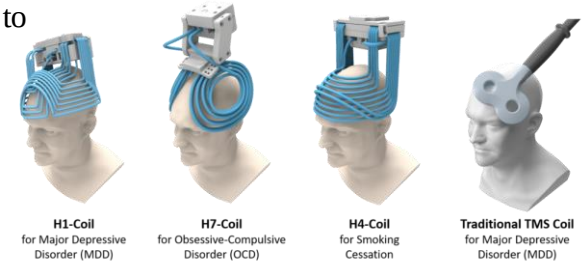


Figure 6 Traditional TMS coils. These coils are large and not suitable for application to an at-home device.

The second design challenge is creating a portable battery system. For TMS, the battery system must be able to release high bursts of energy quickly to induce the 40Hz magnetic field oscillation, but also be able to operate continuously and reliably for at least one hour. To achieve this, a capacitor must be coupled with a sustained energy source. Traditional capacitors used in TMS are large and bulky, and many power sources that can sustain the treatment duration are also large and heavy (Cloud TMS, TMS Technical specifications). One solution could be the coupling of an electrochemical capacitor with a lithium-ion battery (Epstein, 2008). Electrochemical capacitors can release the amount of power needed to generate a magnetic field in a quick burst, and recharge quickly (Science Direct, Electrochemical capacitor). By coupling one or more electrochemical capacitors to a battery, the capacitors can be used to discharge the pulses needed for the 40 Hz treatment and then be quickly recharged by the battery.

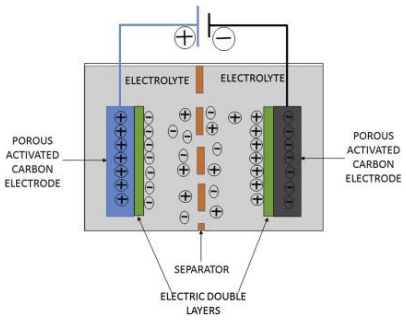


Figure 7 Electrochemical Capacitor

While there are possible solutions to reduce coil size and create better power supplies for TMS, these are two design challenges which will take expertise in electrical engineering, magnetics, and metallurgy to address and will be major choke points in the development of the proposed device.

III. DUE DILLIGENCE

a. Intellectual Property (patents)

i. Cognito

The company Cognito Therapeutics is leading the field of using gamma oscillations to treat AD. Currently, Cognito has four viable patents surrounding their brain stimulation device. The patents pertain to a device that evokes gamma oscillations in the brain through supply visual and auditory stimulation. The device looks similar to the top right image in Fig. 8 below. The device in this proposal will not infringe on the intellectual property of Cognito as this device has a different mode of action (magnetic stimulation) as well as design [1]. REMED, an electroceutical company based in Korea, has patented the tube system seen below for cooling fluid to flow through to cool their coils (shown in the top left of Fig. 8). Our device does not infringe on this IP either because it incorporates various smaller coils into a wearable cap, rather than two larger coils that are positioned above the head.

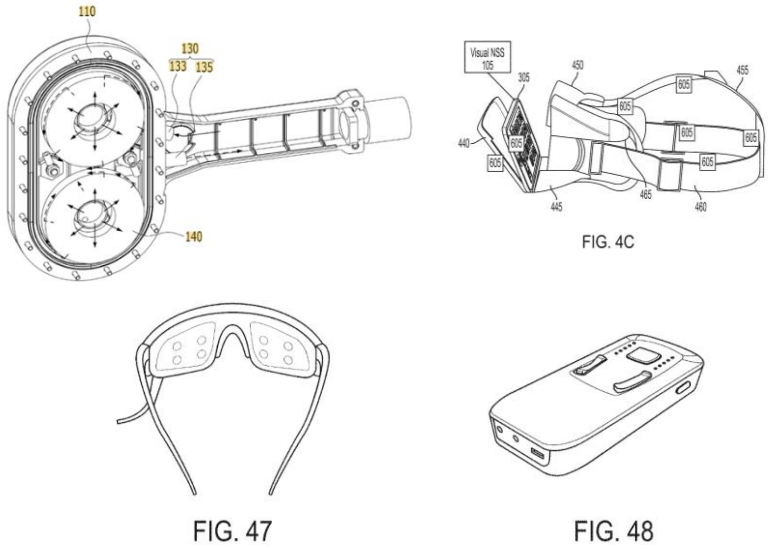


Figure 8:Patent images from Cognito Therapeutics and REMED

ii. Other Patents

As Cognito has patented the use of light and audio stimulation, other patents related to treating AD using magnetic stimulation were investigated. Surprisingly, there were not many patents that used TMS specifically to treat AD, as most current TMS therapies are more focused on treating depression. The first patent that was investigated was submitted by Teijin Pharma Limited in Tokyo, Japan and was approved in 2020. The purpose of Teijin's invention is to provide a small excitation coil with increased safety than the coils presently being used for magnetic stimulation therapy.

In Figure 9, a transcranial magnetic stimulation system schematic is shown, the TMS system (1) has an excitation coil that is electrically connected to the coil drive power supply (24) through a cable (23). The patient's head is fixed while receiving this treatment, and the excitation coil is placed on the scalp depending on what the treatment purpose is. The coil case (28) is divided into sections, with various mechanisms for cooling the coil as well as a temperature sensor for the excitation coil (Midorikawa and Okayama, 2017).

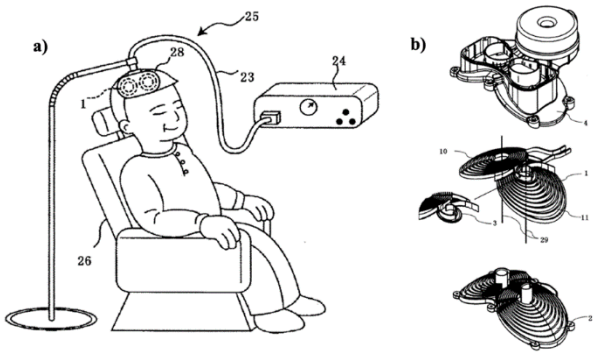
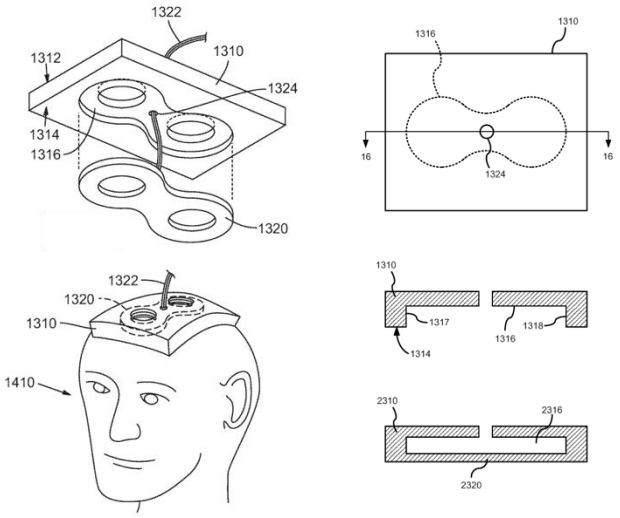


Figure 9: Device setup. (a) schematic view of the transcranial magnetic stimulation system. (b) exploded view of an example excitation coil and coil case for the invention (Midorikawa and Okayama, 2017).

Contrary to our design, this invention design has the limitation of a patient having to sit in a chair while receiving TMS treatment. TMS treatments can last up to two hours, multiple times a week; having a patient sitting during this time is limiting and disruptive to their daily lives.

The second patent that was investigated was filed by the NIH and was approved with priority in 2013. The purpose of this invention is to create a flexible housing for TMS coils to treat depression, Parkinson's disease, stroke recovery, autism, PTSD, or schizophrenia (Radman, et al., 2013).



IV. ANIMAL MODELS

Aim: The scope of our animal model would be to investigate the therapeutic effects of TMS on an AD mouse model using a control group.

Methods: The model of AD will be induced in the mice by injecting them with intracerebroventricular amyloid beta 42 oligomer (Aβ42). This is done because TMS has been shown to reverse the depletion of nerve growth factors caused by amyloid beta 42, thus injecting this on the initial mouse model will make it so that we can test the efficacy of TMS in this aspect.

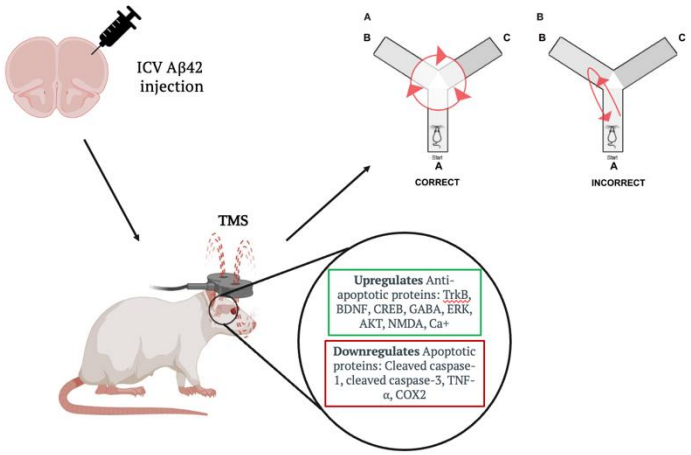


Figure 10: Experimental design depicting Aß42 injection and the main anti apoptotic proteins upregulated by TMS treatment, and the apoptotic proteins downregulated by TMS. Y-maze behavioral assessment shown with A: the correct solution to the maze showing cognitive improvement and B: the incorrect solution to the maze.

After injection, the mouse will be subject to TMS therapy using H-coil magnetic coils which were previously discussed.

Levels of Aβ (amyloid beta), neurotransmitters, neurotrophins, and markers of neurogenesis will be measured and analyzed after 5 days of TMS and 2 weeks, these time intervals were chosen based on past studies that showed that efficacy of TMS can be adequately demonstrated at these times (Choung, 2021).

A behavioral assessment using a Y-maze test will be conducted to show differences in cognitive recovery after TMS. The test occurs in a Y-shaped maze as shown in Figure 10 with arms are 120° angles from each other (Stanford Medicine, n.d.). The mouse will initially be allowed to explore all three arms of the maze, and a mouse will intact prefrontal cortical functions will remember the arms previously visited. Spatial reference memory will be tested by closing off one arm of the Y-maze and placing the mouse in it. After one hour, the mouse will be placed back in the original configuration to the maze and should remember which arm it had not previously explored and visit this arm more often (Kraeuter, 2019). A mouse with cognitive decline, or the AD model mouse, should instead only visit two arms rather than all three showing back of spatial reference memory.

Expected results: Reduced hippocampal long term potential (LTP) impairment and spatial memory, relieved symptoms of memory loss associated with AD, reduced neurogenesis and recovery action of lost neural populations, significantly improved neural functioning (Choung, 2021).

V. COST AND MARKET

TMS therapy has demonstrated promising benefits for individuals who have previously been resistant to other forms of treatment, and it is a relatively new type of therapy that can significantly improve symptoms. When considering these new therapy options, the biggest concern is the cost of the treatments and the coverage of these treatments under insurance. In the United States, typically an upfront treatment for TMS can be expensive, however the recent costs of treatment per session have reduced. Furthermore, when considering wearable brain device markets, the cost can go anywhere in the range from $35,000 to $100,000. This range usually includes the hospital costs such as hospital fees, implanted device and surgery. Depending on the specific surgeries there may be additional costs.

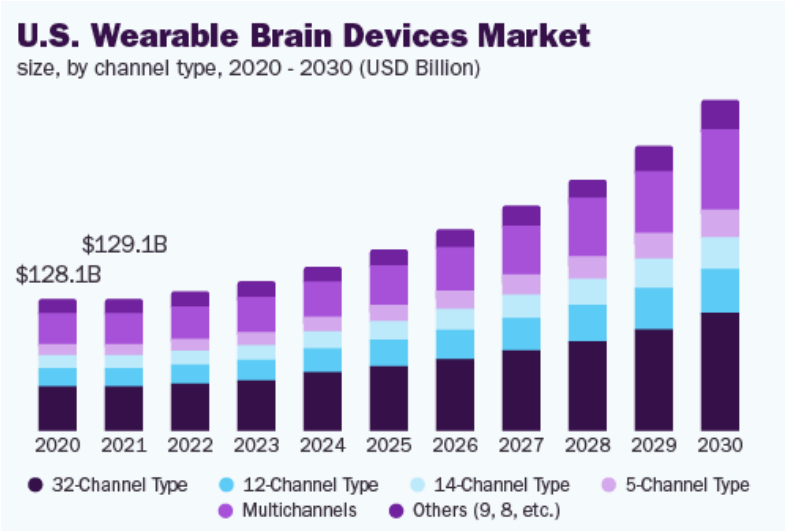


Figure 11: US wearable brain device market projected until 2030.

The market size of deep brain stimulation devices globally reached USD 1.05 billion in 2021, and it is projected to grow at a compound annual growth rate (CAGR) of 9.8% from 2022 to 2030. Market growth is expected to be driven by an increasing number of patients experiencing involuntary movements associated with Parkinson's disease, dystonia, and multiple sclerosis. The market is also being fueled by a high demand for minimally invasive techniques, which lead to better patient outcomes. Furthermore, the use of telehealth consultations and eHealth apps to monitor patients with Parkinson's disease during the COVID-19 pandemic is expected to further support the growth of the deep brain stimulation devices market over the forecast period.

Cognito Therapeutics started clinical trials for noninvasive neuromodulation techniques to alleviate symptoms of Alzheimer’s disease. As of March 2023, funding of 73 million has been secured by Cognito to progress its pivotal study of a non-invasive neuromodulation device, which administers gamma frequency light and sound stimulation developed to treat Alzheimer's Disease with their Phase II trials called HOPE and aim to enroll about 500 people. With such a competitive and much needed demand in the industry, our device will be a unique addition to a less researched patient base and bring cheaper treatment options for patients. Due to its immense impact on the patient's health and the large income for hospitals, our device will be a valuable addition in the wearable brain device market.

VI. REGULATORY

a. Accelerated Aging

Accelerated aging will be done according to standard ASTM F1980. The purpose of accelerated aging for the proposed device is to expose the device to harsh environmental conditions to determine if it will continue to perform adequately over time. The accelerated aging test will be conducted over three cycles, each lasting 7 days in an accelerated aging chamber at a temperature of 55°C ± 2°C and 95% relative humidity ± 3% according to the guidelines outlined in the ASTM standard. The device will be tested for performance after each cycle and results will be analyzed to determine if there is any difference in performance comparing the use of the device before and after the aging test.

b. Classification and Regulatory Pathway

Although specialized for the treatment of Alzheimer's, the finalized design for the medical device design is similar that of a traditional transcranial magnetic stimulation (TMS) cap. TMS caps as a general class of device are classified by the FDA as a class II medical device (2019 The Federal Register). The safety of the device is comparable to traditional TMS caps, however the novel application for the treatment of Alzheimer's, as well as the unique coil and wearable design which is not normally seen in TMS Caps, would require the collection of clinical trial data.

As there is no substantially equivalent therapy available and considering that clinical trial data would be needed to determine effectiveness, the FDA would likely classify this device as a class II device but still require pre-market approval to assure safety and efficacy.

Due to the novelty of the device, and the intense need for novel Alzheimer's treatments, the device would be likely to qualify for break through designation, which would help to expedite the PMA process (Center for Devices and Radiological Health, Breakthrough devices program).

There are several standards and regulations that apply to the device. The standards applied during the development, manufacturing, and sale of the device are enumerated in Table 3.

Table 3: Applicable standards

Standard	**Relevance**
IEC 60601-1:2005	Ensures electrical safety of the device.
ISO 10993-1:2018	Evaluation of biological compatibility
IEC 62304:2006	Standard for medical device software
IEC 62366-1:2015	Requires usability testing for medical devices
ASTM F3357-19	Cleanability of reusable devices.
ASTM F1980	Guides for accelerated aging studies
ISO 17.220.01	Standards for magnetic safety.
ISO 13485:2016	Establishment of a quality management system.
ISO 14971:2019	Standard for application of risk management.
ISO 20417:2021	Labeling requitements

VII. FUTURE WORK

As outlined in this paper, there are various Achilles heels involved with our current design that require additional feasibility testing. First, materials testing will need to be conducted to find an optimal material for the smaller coil design proposed. Superconducting materials have extremely specific and limited temperature specifications, therefore testing will need to be done on these materials to test their feasibility in this application. Some examples of crucial materials testing that will need to be done are included in Table 4.

Table 4: various examples of materials testing that will need to be done to test the feasibility of using superconductive materials for small coil TMS application.

Test	Scope	Procedure
Critical Temperature (T_c) Measurement	To determine if a material is superconductive	Cooling the material and measuring the temperature at which it transitions from a normal conductor to a superconductor
Critical Magnetic Field (H_c) Measurement	To determine the maximum magnetic field strength that a superconductive material can withstand before it loses its superconductivity	Performing a magnetization measurement using a magnetometer
J_c measurement	To determine the critical current density of a superconductive material.	Applying an external magnetic field to a superconductive material and measuring the current density that can flow throughout the material without losing its superconductivity
Mechanical Testing	To determine the material's strength and resistance to fracture	Tensile testing, compression testing, and bending testing using an apparatus such as a Mark-10
Electrical Testing	To determine the material's resistivity, conductivity, and other electrical properties	Measuring the electrical resistance of a material as a function of temperature, current, and magnetic field

VIII. REFERENCES

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