PILOT CLINICAL TRIAL PROTOCOL

A Pilot Clinical Trial Investigating the Safety, Feasibility and Proof of Concept of Deep Brain Stimulation of the Pedunculopontine Nucleus for the Treatment of Alzheimer's Disease

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General Information

Title:	A Pilot Clinical Trial Investigating Deep Brain Stimulation of the Pedunculopontine Nucleus for the Treatment of Alzheimer's Disease
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Contents

Protocol Summary

Full Title

A Pilot Clinical Trial Investigating Deep Brain Stimulation of the Pedunculopontine Nucleus for the Treatment of Alzheimer's Disease

Short Title

DBS-PPN-AD

Design

Multi-centre, single-cohort, non-randomized prospective pilot trial

Sample Size

N= 6

Study Population

Adults 60 years and older, diagnosed with Alzheimer's Disease.

Accrual Period

Up to 36 months.

Study Duration

Up to 48 months.

Intervention

Medtronic Model B35200 Percept™ PC Neurostimulator with BrainSense™ Technology deep brain stimulation device. The system delivers electrical stimulation to targeted regions of the brain, defined by anatomy or physiology, to suppress the symptoms associated with a neurologic disorder treatable by brain stimulation. The neurostimulator generates electrical current that is conducted through DBS extensions and leads to the distal lead electrodes. The electrical current leaves the lead's electrodes and interacts with the targeted brain tissue to achieve the desired effect.

Primary Objectives

i. *Feasibility*
Determined by assessing recruitment trends, adherence to study protocol and attrition rates;

ii. *Safety*
Assessed by monitoring adverse events, serious adverse events, or unanticipated problems related to the DBS device.

Secondary Objectives

i. *Electrographic Measures*
GO and theta-gamma coupling will be used as surrogates for PVIN activity. DBS-PPN ability to restore GO and theta-gamma coupling will be used as proof of concept for its ability to upregulate PVIN within the hippocampal-neocortical network.

ii. *Cognitive Measures*
Cognitive assessments will be used to correlate the anticipated effects of DBS-PPN to improvement in cognitive performance using the: Clinical Dementia Rating (CDR) Scale; the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog); the Montreal Cognitive Assessment (MoCA); the Neuropsychiatric Inventory (NPI);the Sleep Disorders Inventory (SDI); and Quality of Life in Alzheimer's Disease (QoL-AD).

Summary

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that gradually impairs memory, cognitive abilities, and daily functioning, placing a significant burden not only on patients but also on caregivers and the healthcare system. Despite extensive research, current treatments provide only symptomatic relief without halting or reversing the disease's progression.

Recently, a new class of treatments has emerged, targeting amyloid—a protein that accumulates abnormally in the brains of AD patients and is believed to play a role in the disease's pathology. While anti-amyloid therapies, such as Leqembi (lecanemab), have shown potential in targeting amyloid deposits, their clinical benefits remain modest. These drugs offer limited improvements in symptoms and come with a risk of significant side effects, including infusion reactions in around 25% of patients, as well as brain swelling and bleeding—collectively known as amyloid-related imaging abnormalities (ARIA)—affecting about 20% of users. Furthermore, these treatments necessitate frequent intravenous infusions and regular brain imaging, significantly increasing costs and limiting accessibility.

The limited efficacy, potential for adverse effects, and high costs have led to varied regulatory responses across countries. The Therapeutic Goods Administration (TGA) in Australia declined to approve Leqembi, citing an insufficient risk-benefit balance given the risks of ARIA. This mirrors the European Medicines Agency's (EMA) stance, which also opted not to approve the drug, expressing similar concerns regarding its risk-benefit profile. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) granted approval, yet the National Institute for Health and Care Excellence (NICE) has withheld a recommendation for funding by the National Health Service (NHS), effectively limiting access to private care. Japan has approved Leqembi for an initial round of treatment under national insurance, but subsequent doses require out-of-pocket payment. These decisions highlight a cautious global stance toward anti-amyloid therapies, raising ethical considerations regarding equitable access and the true impact of these treatments on AD progression.

Amid these developments, interest is growing in alternative approaches to treating AD by modulating brain wave activity, specifically gamma oscillations. Gamma oscillations are brain rhythms associated with cognition and memory, both of which are compromised in AD. Studies suggest that enhancing gamma activity could help slow AD progression. Techniques like visual or auditory stimulation can increase gamma waves, but their effects are often limited to sensory areas and may not fully engage the brain's natural gamma activity, potentially limiting therapeutic benefit.

This study investigates a novel approach using deep brain stimulation (DBS) to target the pedunculopontine nucleus (PPN), a region involved in generating and regulating gamma oscillations across the brain. By stimulating the PPN, we aim to enhance gamma activity in a more widespread and natural manner, potentially improving memory and cognition in AD patients. Preclinical studies have demonstrated that gamma enhancement has disease modifying effects in AD. While DBS of the PPN for AD is an emerging field, DBS itself is a well-established treatment for movement disorders and certain types of epilepsy, with expanding applications in other neurological conditions. In Parkinson's disease, for instance, PPN

stimulation has been associated with cognitive improvements and better sleep quality—benefits that could address similar deficits in AD and support cognitive health.

This study explores DBS-PPN as a promising intervention for AD, aiming to enhance cognition and overall quality of life for patients.

1.0 BACKGROUND

Alzheimer's disease (AD) is an insidious and devastating neurodegenerative condition that affects millions worldwide, placing a considerable burden on patients, families, and healthcare systems. In Canada, over 650,000 individuals are currently living with AD or another form of dementia. This number is expected to more than double by 2030, underscoring the urgent need for effective treatments that can slow or halt the disease progression.[1-3]

In 2020, the total annual economic burden of dementia in Canada was estimated to be $40B, including the impact upon informal caregivers (e.g., family members), which was estimated to be $25B. This includes costs from lost productivity (absenteeism and early retirement) and consideration of an estimated 472 million caregiving hours. If current trends continue, the annual economic burden could grow by 275% over the next 30 years.[4]

Recent advances in amyloid-depleting therapies represent a significant breakthrough in Alzheimer's research; however, their clinical benefits remain limited.[5] These treatments have demonstrated modest improvements in slowing cognitive decline, often accompanied by substantial drawbacks, including notable side effects, high costs, and logistical challenges.[5-8] For instance, frequent MRI surveillance for amyloid-related imaging abnormalities (ARIA) and biweekly intravenous administration are required, imposing a strain on healthcare systems that may lack the capacity to deliver such intensive care on a wide scale.[5-7] These challenges accentuate the necessity for alternative treatments that are accessible, safe, and effective for a broader patient population.

Over the last decade, emerging evidence has identified neuronal hyperexcitability as a critical factor in the pathogenesis of AD.[9,10] The loss of both the number and function of inhibitory interneurons has been shown to exacerbate amyloid deposition, leading to further interneuron impairment and creating a vicious cycle of inexorable cognitive decline.[9,10] Stimulation of interneurons at gamma frequencies has demonstrated disease-modifying effects in several preclinical studies.[11-14] Entraining gamma oscillations (GOs), the electrophysiological signature of interneuron activity,[15] has not only mitigated aberrant amyloid production but has also enhanced microglial and glymphatic clearance of amyloid deposits.[11,12] Furthermore, it has restored deficits in theta-gamma coupling, an emerging electrophysiological biomarker in AD crucial for successful memory processing in the hippocampus.[13,14,16]

The pedunculopontine nucleus (PPN), located in the brainstem, is recognized as a principal driver of endogenous GOs in the brain.[17] Our study aims to utilize deep brain stimulation (DBS) of the PPN to entrain inherent GOs, thereby harnessing the disease-modifying effects observed in preclinical studies. We support our proposal by identifying a neural network through which PPN stimulation would drive inhibitory interneurons and entrain the resultant GOs across extensive brain networks including the hippocampus, a key structure pertinent to memory and AD.[18] Furthermore, DBS of the PPN (DBS-PPN) has shown cognitive improvements in Parkinson's dementia patients with a firmly established safety profile, an important observation that has largely gone unnoticed in the cognitive neuromodulation field.[19-21] Thus, our study is grounded in robust preclinical and clinical evidence supporting the feasibility and safety of DBS-PPN in AD. Additionally, our study has been peer-reviewed by an expert panel of the Alzheimer's Society Research Program (ASRP), which has endorsed this project through the ASRP/Brain Canada Proof of Concept Grant (2024).[22]

1.1 Rationale

1.1.2 GOs, Theta-Gamma Coupling, and Parvalbumin Interneurons in Cognition

Cognitive processes such as memory encoding, attention, and sensory processing rely on GOs which occur in the 30-100 Hz frequency range.[23,24] These fast rhythms allow for precise coordination of neural activity across cortical networks.[23,24] Parvalbumin interneurons (PVINs), a subtype of GABAergic interneurons, play a key role in generating and maintaining gamma oscillations by providing fast, rhythmic, and temporally precise inhibition to pyramidal neurons.[15,25] This action helps regulate the timing of excitatory signals, allowing neurons to fire in synchrony.[15,23] Moreover, the interaction between GOs and slower theta rhythms (4-8 Hz), known as theta-gamma coupling, is crucial for organizing information flow in the brain.[26,27] Theta-gamma coupling enables the brain to segment and prioritize information, with gamma oscillations encoding fine details within theta cycles.[26,27] This coupling, facilitated by PVINs, underlies key cognitive functions such as working memory, navigation, and attention by enhancing the temporal coordination between hippocampal and cortical circuits.[28-30]

1.1.3 Disruption of GOs, Theta-Gamma Coupling, and PVINs Function in AD

The disruption of GOs and theta-gamma coupling is closely associated with cognitive decline in AD, particularly memory deficits and impaired attention.[16,23,31] PVINs dysfunction, driven by neurodegeneration and the accumulation of amyloid-beta and tau pathology, undermines the ability of neural circuits to generate gamma rhythms.[9,10] This loss leads to impaired theta-gamma coupling, which is crucial for the synchronization of hippocampal and cortical activity during cognitive tasks.[16,28,31] The loss of PVINs reduces inhibitory control over excitatory neurons, leading to network hyperexcitability and desynchronization.[9,10] The breakdown in theta-gamma coupling disrupts the brain's ability to encode and retrieve memories, as well as process information efficiently.[16,26,31] Furthermore, studies suggest that impaired GOs may accelerate amyloid-beta deposition and tau pathology, contributing to a vicious cycle of neural network degradation, ultimately exacerbating the cognitive decline in AD **(Fig. 1)**.[9,10]

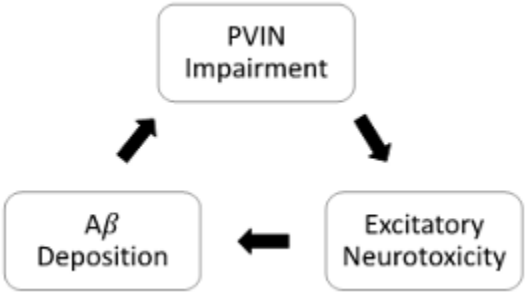

Figure 1: Aβ deposits impair the GABAergic parvalbumin interneurons (PVIN) inhibitory drive over glutamatergic pyramidal cells leading to excitatory neurotoxicity. The hyperexcitable pyramidal cells produce more Aβ creating a vicious cycle with inexorable cognitive decline.

1.1.4 GOs Entrainment as a Disease-Modifying Intervention in AD

Several studies have explored the potential of GOs entrainment as a therapeutic approach to modify the progression of Alzheimer's disease (AD), with a focus on reducing amyloid burden, restoring network dynamics, and enhancing amyloid-beta clearance.[32] A pioneering study by Iaccarino et al. (2016) demonstrated that non-invasive stimulation of GOs, using 40 Hz light flicker in a mouse model of AD, led to a significant reduction in amyloid-beta plaques.[12] This reduction was attributed to increased activation of microglia, the brain's resident immune cells,

which are crucial for clearing amyloid deposits. The study further suggested that gamma entrainment reestablished the balance between excitatory and inhibitory signaling, particularly by enhancing the activity of PVINs, which are essential for generating gamma rhythms. The restoration of PVINs function contributes not only to the normalization of network oscillations but also to the regulation of neural plasticity and cognitive performance.[32]

Subsequent studies have expanded on these findings by demonstrating that gamma entrainment can promote not only amyloid-beta clearance but also tau pathology reduction, which is another hallmark of AD.[33,34] Chronic gamma stimulation, delivered through auditory or visual sensory stimulation, has been shown to recruit microglia and astrocytes, both of which are implicated in the clearance of pathological protein aggregates.[33,34] The enhanced activity of these glial cells, triggered by synchronized GOs, increases their phagocytic capacity, leading to a reduction in amyloid-beta levels in the hippocampus and other cortical areas. Additionally, gamma stimulation has been linked to improved cerebrospinal fluid flow, which is critical for waste clearance from the brain, including amyloid-beta peptides.[11] Importantly, the therapeutic effects of gamma entrainment extend to the restoration of theta-gamma coupling, which is often disrupted in AD due to PVINs dysfunction.[13,14] By reestablishing the precise timing of neuronal firing and network synchronization, gamma stimulation helps restore the brain's capacity for efficient information processing and memory encoding.[32] These promising findings highlight the potential of GOs entrainment as a disease-modifying intervention in AD, offering a novel approach to targeting both the pathological and functional aspects of the disease.

1.1.5 Neural Circuitry Identifying the PPN as a Key Neuromodulation Target

The PPN located in the dorsolateral mesopontine tegmentum, plays a critical role in modulating GOs in the brain, acting as a key mediator of bottom-up control mechanisms.[17] The PPN's ascending glutamatergic projections, particularly targeting the basal forebrain, have been identified as the primary drivers of gamma oscillatory activity.[35] Studies have demonstrated that this PPN-basal forebrain pathway is pivotal for the initiation and regulation of GOs, which are essential for various cognitive functions, including attention and memory.[36] These projections stimulate cholinergic and GABAergic neurons within the basal forebrain, leading to widespread gamma entrainment across cortical and subcortical regions.[36] This makes the PPN an essential hub for the regulation of higher-order neural processes.[37]

Harmoniously, the basal forebrain is known to synchronize GOs through its extensive and direct projections to PVINs in both neocortical and hippocampal regions.[38,39] PVINs are crucial in generating and sustaining gamma rhythms due to their ability to precisely modulate excitatory pyramidal neuron activity.[25] By influencing PVIN function, the basal forebrain facilitates the entrainment of GOs across the neocortical-hippocampal network, which is critical for the encoding and retrieval of memory.[18] This interconnected system of the PPN, basal forebrain, and PVINs forms a coordinated neural circuit that supports cognitive processes through the modulation of gamma rhythms.[18]

In this framework, PPN glutamatergic projections upregulate the activity of the basal forebrain, which in turn recruits and synchronizes PVINs, thus driving gamma oscillatory activity throughout cortical and hippocampal networks **(Fig. 2)**.[18]

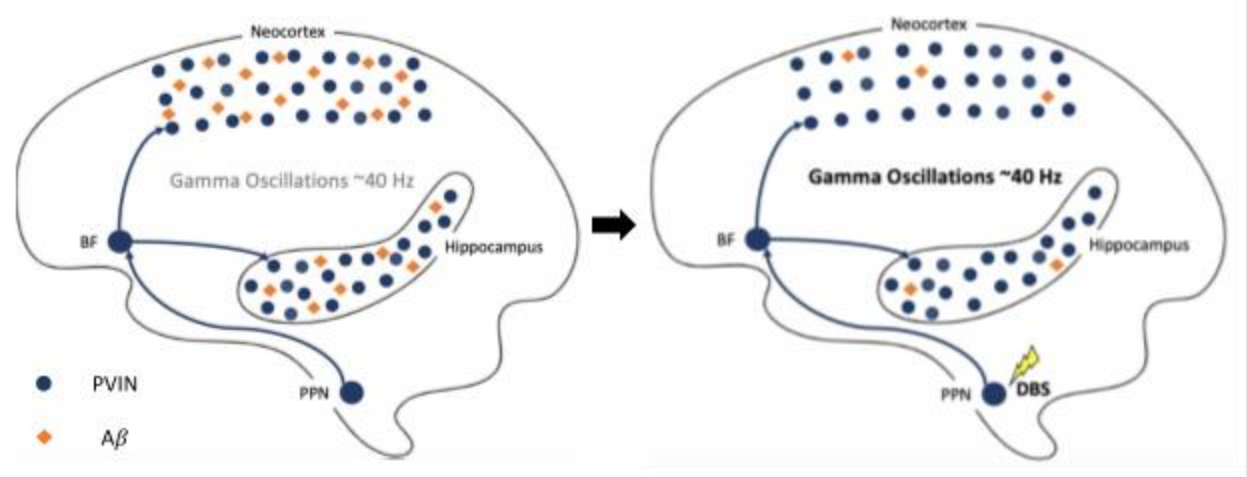

Figure 2: Pedunculopontine nucleus (PPN) is the main driver of gamma oscillations in the brain. PPN achieves this through ascending glutamatergic projections to the basal forebrain (BF), which in turn sends direct projections upregulating PVIN and the ensuing gamma oscillations within the hippocampal-neocortical network. **[Left]** Aβ deposits impair gamma oscillations and PVIN function of synchronizing pyramidal cells firing within the hippocampal-neocortical network, hampering memory processing and cognition. **[Right]** Deep brain stimulation (DBS) of the PPN would augment PVIN activity which has been shown to decrease the Aβ burden, restore gamma oscillations, and rescue memory in AD preclinical studies.

This cascading effect places the PPN at the core of a neuromodulatory network capable of enhancing cognitive function, particularly memory processing. Given its central role in regulating GOs, the PPN emerges as a highly promising target for neuromodulation therapies in AD, where GOs disruption is linked to cognitive decline.

This integrative neural network model underscores the PPN's role in orchestrating PVINs-driven gamma activity and its relevance to memory circuits. This model underscores the PPN's influence not only on basal forebrain and hippocampal circuits but also on the coordination of cortical regions, positioning it as a key factor in understanding memory-related dysfunctions in neurodegenerative diseases like AD (further details are available in our preprint). Importantly, this points to the potential of PPN-targeted therapies for restoring normal gamma oscillatory function and mitigating the cognitive deficits associated with AD.[18]

1.1.6 Preliminary Data from DBS-PPN Studies

DBS-PPN traditionally investigated in Parkinson's disease (PD) for motor symptoms, has also been shown to have significant non-motor benefits, particularly in areas related to sleep and cognition.[19-21] Studies indicate that DBS-PPN can improve the quality of sleep in PD patients, significantly increasing REM sleep which is critical for memory consolidation and cognitive function.[19-21,40-43] The PPN, as a key structure within the reticular activating system, plays an essential role in regulating arousal and maintaining the sleep-wake cycle.[17,36] Stimulating the PPN has been found to improve sleep architecture, facilitating a more restorative sleep that, in turn, supports cognitive performance.[19-21,44,45]

Some studies that included cognitive assessments alongside sleep measurements reported improvements in certain cognitive domains, particularly those related to executive function and attention.[19-21] For example, Costa et al. found that DBS-PPN stimulation significantly reduced response times in an *n-back task*, indicating enhanced processing speed, though accuracy remained unchanged.[46] Cervalo et al. demonstrated improvements in delayed recall, executive

function, verbal long-term memory, and verbal fluency with DBS-PPN.[40] Fischer et al. reported that low-frequency DBS-PPN stimulation enhanced basal attentional processing in patients with Parkinsonian disorders, increasing tonic alertness, a key factor in sustained attention.[47] Ricciardi et al. presented a case where deactivating DBS-PPN led to a decline in cognitive functions such as short-term memory, verbal fluency, and object naming.[19] Upon reactivating the stimulation, the patient's cognitive performance, including attention and memory, returned to baseline, restoring their prior cognitive profile and autonomy.

The connection between sleep disturbances and AD is indeed well-established. Poor sleep quality, particularly a reduction in REM sleep, is both a risk factor and a consequence of AD pathology.[48,49] Disrupted sleep accelerates the accumulation of amyloid-beta and tau proteins, key pathological features of AD, due to the impaired functioning of the glymphatic system during sleep.[48,50] Conversely, these pathological proteins further disrupt sleep architecture, creating a bidirectional relationship that exacerbates cognitive decline **(Fig. 3)**.[48,5039,41]

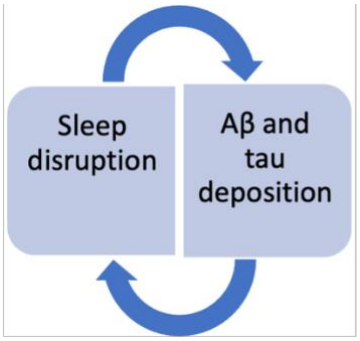

Figure 3: Bidirectional relationship between sleep disruption and Alzheimer's disease

Studies indicate that a 1% reduction in REM sleep heightens dementia risk by 9%, underscoring REM's crucial role in cognitive health.[49] DBS-PPN has been shown to almost double REM sleep duration without impacting other disease stages, suggesting it may help slow AD progression by enhancing REM sleep.[43] These findings highlight the potential of interventions targeting REM as a strategy to mitigate AD risk.

In this context, findings from DBS-PPN in Parkinson's patients are highly relevant to Alzheimer's research. Improved sleep measures, such as increased REM, could potentially delay or mitigate cognitive decline in AD by enhancing neural plasticity, promoting synaptic health, and facilitating the clearance of neurotoxic proteins during sleep.[42,43,48,50] Given the PPN's role in modulating both GOs and sleep-wake cycles, DBS-PPN presents a compelling neuromodulatory approach for addressing cognitive symptoms in AD.[17] By restoring a healthy sleep architecture, PPN stimulation could interrupt the vicious cycle of poor sleep and accumulating amyloid pathology, thus preserving cognitive function in neurodegenerative conditions.[18-21,43,48,50]

In conclusion, this **intersection of improved sleep, GOs, and cognition** provides **a holistic therapeutic approach** that targets not only symptomatic aspects of AD but also the underlying neural network disruptions that drive disease progression.

1.2 Novelty & Significance

1.2.1 Limitations of Anti-Amyloid Therapies and the Promise of DBS-PPN

Recently developed anti-amyloid drugs, which have shown cognitive improvements for the first time after decades of failure, have been well received both within and outside the scientific community.[5] However, the initial excitement has been tempered by concerns about their limited clinical impact, significant side effects, and poor cost-effectiveness.[5,6,8] Unlike these therapies, DBS-PPN represents a novel approach by addressing the underlying pathological processes that lead to amyloid-beta deposition, such as neuronal hyperexcitability and the disruption of glymphatic clearance during sleep, rather than directly targeting amyloid-beta itself.[18] This could not only prove to be a more efficient and effective strategy, but also avoids the brain inflammation associated with monoclonal antibodies directly targeting amyloid-betadeposits.[51-53] Such inflammation can lead to brain edema and hemorrhage, known as ARIA, which occur in about 20% of patients.[51-53] The high incidence of ARIA necessitates frequent MRI surveillance, further compounding the logistical and financial burdens of anti-amyloid therapies.[53] For example, the total cost of Lecanemab, including safety monitoring, can reach up to $88,728 USD per patient per year.[54] In contrast, DBS-PPN has one-time operative and device costs estimated at $20,000 to $26,000 USD.[55] Thus, DBS-PPN could offer a **more effective**, **more feasible**, and **safer** option at a significantly **lower cost**.

1.2.2 Comparative Efficacy of Non-Invasive Methods

Our proposal to entrain GOs using neuromodulation has been investigated, albeit through a non-invasive approach known as Gamma ENtrainment Using Sensory Stimulation (GENUS).[56] GENUS is a technique that uses sensory inputs, such as 40 Hz auditory or visual stimuli, to induce GOs in the brain.[56] While GENUS has shown some promise, it is limited to effects within specific sensory regions of the brain, which may not be sufficient given the widespread nature of AD.[56-59] This method requires extensive treatment sessions, leading to patient non-compliance and potential disruptions to daily routines due to the cognitive load imposed by the auditory and visual stimulation.[56] Additionally, the benefits of GENUS are often short-lived, necessitating frequent sessions to maintain efficacy, and individual responses can vary significantly based on sensory processing capabilities.[56] In contrast, DBS-PPN offers a more targeted and sustained approach, engaging widespread brain networks, including critical areas like the hippocampus, without the need for exhaustive treatment sessions or environmental adjustments.[18] This ensures better patient compliance and reduces the impact on daily life, making DBS-PPN a potentially more effective and practical solution for addressing the cognitive deficits associated with AD. Furthermore, studies indicate that GENUS elicits gamma-like oscillations that lack the same stability, coherence, and network-wide engagement of the brain's native GOs.[58] Conversely, DBS-PPN directly targets neural structures that generate native GOs, leading to more stable and widespread entrainment.[17,18] This distinction is crucial for Alzheimer's research, as consistent engagement of endogenous GOs may be necessary to achieve meaningful cognitive improvements.

1.2.3 Emerging GABAergic agents

Emerging GABAergic treatments aim to restore inhibitory tone by enhancing PVINs activity, thereby addressing the neural hyperexcitability linked to AD progression.[10] However, these pharmacological approaches are often accompanied by systemic side effects, including sedation, dizziness, motor incoordination, and cognitive impairment, which pose significant risks, particularly for elderly patients already vulnerable to cognitive decline. In contrast, our DBS-

PPN approach offers a more targeted strategy by specifically GOs and enhancing PVINs activity in a spatially selective manner, minimizing the widespread and non-specific effects associated with GABAergic drugs.[18] Directly modulating PVINs via PPN stimulation bypasses the systemic disruptions associated with pharmacological treatments, providing continuous, long-term modulation without the daily fluctuations or compliance issues commonly encountered with oral medications.

1.2.4 Previous DBS Trials

Prior DBS trials targeting the nucleus basalis of Meynert (NBM) and the fornix for Alzheimer's disease have yielded inconclusive results.[60] DBS-NBM was based on the cholinergic hypothesis, which has been challenged by findings indicating that cholinergic degeneration occurs later in the disease process.[61,62] Fornix DBS stemmed from an incidental finding in a patient undergoing DBS for obesity who experienced vivid autobiographical memory recall upon fornix stimulation.[63,64] This reliance on a non-specific observation, without a comprehensive understanding of the underlying neural networks, led to less favorable outcomes.[65,66] In contrast, our DBS-PPN approach is supported by robust preclinical and clinical evidence highlighting: (1) the disease-modifying effects of GOs entrainment, (2) the critical role of PPN in this process, and (3) the cognitive benefits observed in humans.[11-13,17,19,34] Additionally, the proposed trial utilizes GOs entrainment and theta-gamma coupling as objective electrophysiological outcome measures to evaluate the disease modifying potential of DBS-PPN.[16,27,31,67]

1.2.5 Broader Implications

This pilot study serves as a precursor to a multicenter randomized controlled trial (RCT) that could establish the **first disease modifying neuromodulatory treatment for AD**. It also opens up opportunities to investigate DBS-PPN in other dementias, such as frontotemporal dementia and Parkinson's dementia, where PVINs dysfunction is observed.[19,68] The findings may extend beyond dementia, with relevance to conditions characterized by GOs and PVINs impairments, including epilepsy, schizophrenia, and autism.[69-71] Ultimately, this study aims to contribute to our understanding of brain excitation/inhibition networks, which play a crucial role in normal brain function and are significant in various neurological disorders.[69-71]

2.0 OBJECTIVES

2.1 Assess the Safety, Feasibility, and Preliminary Efficacy of DBS-PPN in AD

This aim focuses on evaluating the safety, tolerability, and feasibility of DBS-PPN as a neuromodulatory intervention for patients with AD. The goal is to gather essential data for the design of a future multicenter RCT. We will also assess preliminary efficacy by measuring electrophysiological outcomes and cognitive function.

2.2 Establish Proof-of-Concept for DBS-PPN's Ability to Modulate PVINs Function and its Potential Effects on Electrographic Markers Associated with AD

This study aims to demonstrate that DBS-PPN enhances PVINs function, thereby restoring GOs and theta-gamma coupling in patients with AD.[13,14,17,18] While the molecular effects of DBS-PPN, such as amyloid-beta clearance, will not be directly measured, electrographic outcomes will serve as surrogate markers, supported by preclinical studies showing a link between GOs and molecular processes involved in amyloid-beta clearance.[11,12,34]

3.0 HYPOTHESES

3.1 DBS-PPN Attenuates the Electrographic Signature of AD

GOs and theta-gamma coupling are critical neural rhythms that underpin successful memory processing.[23,26,27] Disruptions in these oscillatory patterns have been linked to cognitive deficits in AD patients.[16,23,67] Preclinical studies indicate that stimulation of PVINs at gamma frequencies restores theta-gamma coupling and improves memory in AD models.[13,14] We hypothesize that DBS-PPN will enhance PVINs function, restoring impaired GOs and theta-gamma coupling in AD patients, thereby attenuating the electrographic imprint of AD.[18]

3.2 DBS-PPN Modulates Electrographic Surrogates of Molecular Clearance Mechanisms in AD

Amyloid-beta deposition is a key pathological hallmark of AD, stemming from an imbalance between amyloid-beta production and clearance.[72] In preclinical models, gamma-frequency stimulation of PVINs has been shown to enhance microglial activity, promoting amyloid-beta clearance and reducing its burden.[12] Furthermore, gamma entrainment appears to decrease aberrant amyloid-beta production by restoring the excitation/inhibition balance in the brain.[12,34] GOs are also linked to the enhancement of the glymphatic system, which facilitates amyloid-beta clearance.[11] Although molecular changes will not be directly measured in this study, we hypothesize that DBS-PPN will modulate electrographic signatures (GOs and theta-gamma coupling) as surrogates for these molecular clearance mechanisms.[18]

3.3 DBS-PPN Improves Cognitive Function by Addressing the Electrographic Deficits Associated with AD

Cognitive decline in AD, particularly memory impairment, is closely associated with disruptions in GOs and theta-gamma coupling.[16,23] By enhancing PVINs function through DBS-PPN, we expect to restore these neural rhythms and subsequently improve cognitive performance in AD patients. We hypothesize that improved electrographic markers will correspond to gains in memory and overall cognition, providing evidence of DBS-PPN's therapeutic potential in AD.

4.0 STUDY METHODOLOGY

4.1 Design

This pilot study is designed as a single-centre, single-cohort, open-label, non-randomized prospective clinical trial. The open-label nature means that both the researchers and the participants will be aware of the intervention being administered, which is DBS targeting of the pedunculopontine nucleus (PPN). The trial will recruit a small group of participants to evaluate the safety, feasibility, and preliminary efficacy of DBS-PPN in treating AD.

The rationale for the choice of a single-cohort, open-label design allows for a focused, initial exploration of the intervention's effects without the complexities and costs associated with larger, multi-center, randomized controlled trials (RCTs). This design is appropriate for a pilot study where the primary goals are to gather preliminary data on feasibility and safety, and to identify any potential issues that could affect a larger trial in the future.

4.2 Patient Selection

4.2.1 Recruitment

The study will recruit a small number of participants (N=6) who meet specific inclusion and exclusion criteria. Each participant will serve as their own control, with outcome measures compared before and after DBS-PPN intervention. Recruitment will be performed through the Toronto Dementia Research Alliance (TDRA). Established in 2012, the TDRA is a collaboration among the University of Toronto, Baycrest, the Centre for Addiction and Mental Health (CAMH), Ontario Shores Centre for Mental Health Sciences (Ontario Shores), Sunnybrook Health Sciences Centre, Unity Health Toronto, and UHN.

The TDRA and the Alzheimer Society of Toronto (AST) have teamed up to make ongoing studies in AD more accessible to prospective participants, as their website provides a Research Studies section where patients and their caregivers can find information about AD studies that are open for participation. Prospective participants can browse for studies in plain language, or if they are not sure which study to sign up for, there is a questionnaire to help match them to a study. Click here to review their brochure. Any information entered and stored through these questionnaires will only be used for the purpose of connecting the patient with the specific study and providing the study team with the patient's contact information. The electronic forms and systems will be protected with standard safeguards as per CAMH privacy policy and will only be accessed by the TDRA team.

We aim to recruit a minimum of two patients per year to reach our goal of recruiting six patients in under 36 months, which is the threshold we will require to proceed with a larger RCT in the future.

4.2.2 Consent Process

Potential participants will be identified through the Toronto Dementia Research Alliance (TDRA). Initial contact will be made by the research team to provide information about the study.

Patients expressing interest will be referred to the neurosurgery/neuropsychology clinic at TWH (Dr. McAndrews) to screen for study eligibility based on our inclusion and exclusion criteria set forth below. If deemed eligible, informed consent will be obtained by the coordinator and baseline outcome measures will be collected (Figure 3; cognitive/electrophysiological/PET

scan). DBS-PPN implantation will be scheduled within 2 months of obtaining informed consent (Figure 3).

The study coordinator or designated study staff will obtain informed consent from participants. Detailed explanations of the study will be provided, and any questions or concerns will be addressed.

4.2.3 Inclusion Criteria

i. Adults over 60 years old;
ii. Satisfied the diagnostic criteria of the National Institute of Aging - Alzheimer's Association criteria for probable AD;
iii. Clinical dementia rating scale global score of ≤ 1; and
iv. Not taking an acetylcholinesterase inhibitor and/or memantine, or taking a stable dose for at least six months;
v. Fluent in English;
vi. Caregiver available.

4.2.4 Exclusion Criteria

i. Pre-existing structural brain abnormalities (e.g., significant white matter disease, tumor, infarction, or intracranial hematoma);
ii. Other neurologic or psychiatric diagnoses, or medical comorbidities that would preclude patients from undergoing surgery;
iii. Non-fluent in English (it will be very difficult to conduct standard cognitive tests in English on non-fluent English speakers. In addition, language barrier is significant hurdle in providing standard care with communication and cognition being a main outcome measure).

4.3 Intervention

The study will employ Deep Brain Stimulation (DBS), a neuromodulation therapy involving the precise application of electrical impulses to targeted brain regions to modulate neural activity. DBS is delivered through a surgically implanted neurostimulator, similar in function to a cardiac pacemaker, and is used to manage symptoms of specific neurological disorders.

Surgical Procedure: The DBS implantation procedure targeting the PPN involves a neurosurgical operation performed under general anesthesia. During the procedure, thin electrodes are implanted in the PPN with the aid of advanced pre-operative imaging (MRI and CT scan) to confirm precise targeting. These electrodes are connected to a neurostimulator device implanted subcutaneously in the chest. This device generates and transmits electrical impulses to the PPN, which can be adjusted to optimize therapeutic outcomes. A post-operative CT scan is used to confirm location of the implanted electrodes.

Postoperative Recovery: Following the procedure, patients are expected to stay overnight for monitoring, with most returning home the next day. A gradual return to normal activities is anticipated within 3 to 6 weeks, allowing time for recovery and initial device programming adjustments.

Device and Regulatory Information: This study will use the Medtronic Model B35200 Percept™ PC Neurostimulator with BrainSense™ Technology, a licensed device approved by Health Canada in 2020. Although the device is licensed for specific uses, it will be applied here for an off-label indication by targeting the PPN, which falls outside its standard approved indications. Given that this study is independently conducted and not sponsored by the manufacturer, it qualifies for an exemption from Health Canada's Investigational Testing Authorization (ITA) requirements. Per Health Canada's guidance on ITA applications (section 2.3.2.2), studies employing licensed devices off-label are exempt from ITA requirements if they are not manufacturer-sponsored (see link).[21,64,73-75]

4.4 Outcome Measures

The primary outcomes will focus on **safety** and **feasibility** metrics, serving to inform the design of a subsequent RCT. The secondary outcomes will assess **electrophysiological** and **cognitive** measures, providing proof-of-concept for the potential disease-modifying effects of DBS-PPN.

4.4.1 Safety

DBS is a neurosurgical procedure that utilizes stereotactic techniques to implant an electrode in a specific brain target, delivering electrical stimulation via a pulse generator.[76] As a minimally invasive intervention, most patients are discharged the day after surgery and can resume normal activities within 3–6 weeks.[77] DBS is considered a low-risk procedure and has become a widely accepted treatment for several neurological conditions, including Parkinson's disease and drug-resistant epilepsy.[76]

The most frequent complication associated with DBS is infection, occurring in approximately 3% of cases, with the most severe being intracranial hemorrhage or stroke, which remains rare (<1%).[76,78] Importantly, the incidence of complications is significantly reduced in high-volume centers. Toronto Western Hospital is internationally recognized for its expertise in DBS surgeries.

The use of DBS-PPN has been reported in over 100 published cases, establishing a favorable safety profile, including demonstrated tolerability in the pediatric population.[74,79] However, it is important to note that DBS-PPN is considered an off-label application for Alzheimer's disease. This study aims to further validate the safety and tolerability of DBS-PPN in individuals with Alzheimer's, laying the groundwork for a subsequent multi-center RCT.

Possible adverse events (AEs), serious adverse events (SAEs), or unanticipated problems related to the DBS device, related surgery and/or stimulation will be closely monitored and managed as per standard of care and definitions and classifications set forth in the following subsections.

4.4.1.1 Definition and Classification of Adverse Events (AEs)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device which includes:

a. Events related to the investigational medical device or the comparator; and
b. Events related to the procedures involved.

An SAE is an event that:

a. Led to death;

b. Led to serious deterioration in the health of the subject, that either resulted in:
    i. A life-threatening illness or injury;
    ii. A permanent impairment of a body structure or a body function;
    iii. In-patient or prolonged hospitalization; or
    iv. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.\
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect;
d. Could have led to death or a serious deterioration were it to recur.

4.4.1.2 AE Severity

All AEs will be assessed by the study team using The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 published by the U.S. Department of Health and Human Services (November 27, 2019) grading system. For AEs not included in the CTCAE defined grading system, the following guidelines will be used to describe severity:

- Grade 1, Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Grade 2, Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life (ADL)*;
- Grade 3, Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**;
- Grade 4, Life-threatening consequence; urgent intervention indicated; or
- Grade 5, Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

4.4.1.3 AE Relationship to Study Intervention

For all collected AEs, the study team will determine the AE's causality based on temporal relationship, alternative explanations (e.g. concurrent disease or other drugs) and clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study device use and cannot be explained by concurrent disease or other drugs, chemicals, or devices;
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after implantation/use of the study device, is unlikely to be attributed to concurrent disease or other drugs, chemicals or devices;
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after implantation/use of the study device. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate;

- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to implantation/use of the study device makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after implantation/use of the study device) and in which other drugs, chemicals, devices or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments); or
- Not Related – The AE is completely independent of implantation/use of the study device, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

4.4.1.4 AE Outcome

The outcome of the AE will be defined according to the following:

- Recovered/ Resolved: The event has fully resolved at the end of the study*;
- Recovering/ Resolving: The event is improving but has not fully resolved at the end of the study*;
- Recovered/ Resolved with sequelae: The event has resolved, but retained pathological conditions resulting from the prior disease or injury;
- Not recovered/ not resolved: The event is ongoing at the end of the study*;
- Fatal: This event is determined to be the cause of death; and
- Unknown: Outcome information could not be obtained.

*or at the time of last observation

4.4.2 Feasibility

4.4.2.1 Recruitment Rates

The effectiveness of recruitment strategies will be assessed by monitoring the rate at which eligible participants are enrolled. The target enrollment is six participants within a 36-month period. Recruitment progress will be regularly reviewed to identify potential barriers and optimize outreach methods.

4.4.2.2 Adherence to Study Protocol

To ensure procedural consistency across participants, adherence to the study protocol will be systematically monitored. Any protocol deviations will be documented and evaluated for their potential impact on study outcomes, ensuring the reliability and reproducibility of findings.

4.4.2.3 Attrition Rates

Participant retention will be assessed through an analysis of attrition rates, with particular attention to identifying the causes of dropout. Understanding these factors will provide critical insights into the feasibility of sustaining long-term participant engagement in future large-scale RCTs.

4.4.2.4 Feedback from Participants and Caregivers

Exit interviews will be conducted with participants and their caregivers to gather qualitative data on their experiences with the intervention and the research processes. This feedback will be instrumental in refining both the intervention and study design for subsequent trials.

4.4.3 Electrographic Measures

Objective electrophysiological outcome measures will be utilized to provide proof-of-concept for the disease-modifying potential of DBS-PPN. The ability of DBS-PPN to restore neural oscillations associated with cognition will serve as evidence not only for potential memory enhancement but also as a surrogate marker for improved amyloid-beta and tau clearance, as demonstrated in preclinical studies.

4.4.3.1 GOs Power and Synchrony

Description:

GOs are primarily generated by PVINs and play a key role in memory and cognitive processing. In AD, the disruption of these oscillations is associated with cognitive decline, impaired microglial function, and a reduction in glymphatic clearance efficiency. Restoring gamma power and synchrony may not only enhance cognition but also promote amyloid-beta and tau clearance, through upregulating microglial responses and improving glymphatic system function.

Measurement:

GOs power spectral density and synchrony will be assessed using scalp EEG and MEG during DBS-PPN "on" and "off" epochs. These recordings will be collected during resting-state periods at the first follow-up visit, 4 weeks post-implantation **(see device programming section)**. Increases in gamma activity during the "on" state will be evaluated to determine the effectiveness of DBS-PPN in entraining neural rhythms essential for cognitive restoration and amyloid/tauclearance.

Significance:

Preclinical studies have shown that gamma stimulation at 40 Hz promotes the activation of microglia, which are essential for clearing amyloid plaques and tau, and enhances CSF-ISF exchange within the glymphatic system, aiding amyloid/tau clearance. Given that impaired

gamma rhythms contribute to both cognitive deficits and the accumulation of AD-related pathology, restoring GOs offers a promising avenue for improving memory function and slowing disease progression.

4.4.3.2 Theta-Gamma Coupling During N-Back Memory Task

Description:

Theta-gamma coupling captures the interaction between slower theta rhythms (4–8 Hz) and faster GOs. This dynamic coordination is essential for memory encoding and retrieval, with particular relevance during working memory tasks such as the *n-back task*. Emerging evidence identifies theta-gamma coupling as a biomarker in AD, correlating with the degree of cognitive decline and reflecting the functional status of hippocampal-prefrontal networks . This methodology has been pioneered, with published data, by our collaborators at CAMH.[16,31,67,80]

Measurement:

Theta-gamma coupling will be measured using EEG and MEG recordings during an *n-back task*, which engages working memory and cognitive flexibility. Comparisons will be made between "on" and "off" states of DBS-PPN to evaluate whether stimulation enhances coupling and improves task performance. The analysis will focus on brain regions critical to memory processes, such as the hippocampus and prefrontal cortex, given their involvement in encoding and retrieval functions. This will be conducted at the first follow-up visit, 4 weeks post-implantation **(see device programming section)**. Thereafter the device will be turned “on” for the rest of the study and theta-gamma coupling will be examined at subsequent follow-up visits at 3, 6, 9, and 12 months to monitor long-term changes in cognitive performance. These longitudinal assessments will help determine whether DBS-PPN elicits sustained improvements in neural coupling and working memory performance, reflecting potential therapeutic benefits over time.

Significance:

Deficits in theta-gamma coupling are closely linked to impaired memory encoding and retrieval in AD, making it a key target for interventions aimed at cognitive restoration.[16,26,31,67] PVINs, through their inhibitory control, play a crucial role in coordinating theta and gamma oscillations.[13,14,28] DBS-PPN, by modulating PVINs activity, may enhance theta-gamma coupling, improving temporal coordination within memory-related networks, such as the hippocampus and prefrontal cortex.[18] By upregulating PVINs function, DBS-PPN holds potential for improving working memory and cognitive flexibility, offering mechanistic insights into how stimulation influences memory networks. Longitudinal theta-gamma coupling assessments will provide data on the durability of DBS-PPN’s effects and monitor disease progression over time.

4.4.4 Cognitive Measures

Cognitive assessments will be employed to correlate the anticipated effects of DBS-PPN with improvements in cognitive performance. The following validated tools will be used:

- ***Clinical Dementia Rating (CDR) – Sum of Boxes (CDR-SB)***:
  The CDR-SB will be used to provide a more granular assessment of cognitive and functional performance. It evaluates six domains, including memory, orientation, and problem-solving, and generates a total score that better captures subtle changes in disease severity.[81,82]
- ***Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-Cog)***:
  The ADAS-Cog is a widely used tool to measure cognitive dysfunction in Alzheimer’s

disease (AD). It assesses domains such as memory, language, and praxis, and is sensitive to detecting cognitive changes over time.[82,83]

- ***Montreal Cognitive Assessment (MoCA)***:
  The MoCA is a 30-item screening tool designed to detect early cognitive impairments across multiple domains. It is particularly effective in measuring executive functions, attention, memory, and visuospatial abilities, offering high sensitivity for identifying mild cognitive impairment.[84]
- ***Neuropsychiatric Inventory (NPI)***:
  The NPI assesses behavioral and neuropsychiatric symptoms frequently observed in AD, such as agitation, depression, and apathy. It is administered through a structured interview with caregivers, who report on the presence, frequency, and severity of symptoms, making it sensitive to treatment-related changes.[85]
- ***Sleep Disorders Inventory (SDI)***:
  The SDI expands upon the sleep-related item from the NPI. It captures the frequency, severity, and caregiver burden of sleep disturbances through caregiver reports.[6] Sleep disorders are common in AD and contribute to behavioral and emotional difficulties in both patients and caregivers.[86]
- ***Quality of Life in Alzheimer's Disease (QoL-AD)***:
  The QoL-AD is a validated tool designed to assess quality of life in individuals with Alzheimer's disease. It consists of both patient and caregiver versions, capturing perceptions of physical health, social interaction, and emotional well-being. Including this measure will provide a broader understanding of how DBS-PPN impacts both cognitive and non-cognitive aspects of the patient's life.[87]

4.4.5 Participant's Evaluation of Intervention

DBS-PPN-AD Trial Exit Interview: Interview conducted at end of the study to assess patients' and caregivers' evaluation of the pilot study, including their experience in the trial, benefits of DBS-PPN AD to emotion and cognition, and recommendations for[83-86,88]

5.0 STUDY TIMELINE

The study will span 12 months, with key milestones including patient recruitment, DBS-PPN implantation, DBS activation, and follow-up assessments at 3-month intervals. These follow-up visits will assess safety, feasibility, electrographic,and cognitive outcomes. DBS-PPN implantation will be performed within two months after obtaining informed consent from patients (Figure 3).

	Visit # (Month)						
Measure/Activity	Visit 1 (-2) Initial Assessment	Visit 2 (0)	Visit 3** (1)	Visit 4 (3)	Visit 5 (6)	Visit 6 (9)	Visit 7 (12)
DBS Implantation (CT + MRI Scan*)		■					
DBS Activation			■				
DBS Initial Programming			■				
Safety Monitoring		■	■	■	■	■	■
Feasibility Monitoring	■	■	■	■	■	■	■
Electrographic Measures (EEG & MEG)	■		■	■	■	■	■
Cognitive Assessments & Questionaires							
CDR	■			■	■	■	■
ADAS-Cog	■			■	■	■	■
MoCA	■			■	■	■	■
NPI	■			■	■	■	■
SDI	■			■	■	■	■
QoL-AD	■			■	■	■	■
Exit Interview							■
Patient Time Commitment (Hours/Visit)	3	5 + Overnight Hospital Stay	3	3	3	3	3

Figure 3. Study timeline and Schedule of Research Activities. Cognitive Assessments and Questionnaires: Clinical Dementia Rating Scale (CDR); Alzheimer's Disease Assessment Scale - Cognition Subscale (ADAS-Cog); Montreal Cognitive Assessment (MoCA); Neuropsychiatric Inventory (NPI); Sleep Disorder Inventory (SDI); Quality of Life in Alzheimer's Disease (QoL-AD). * Ideally, an MRI is done in a 1-hour hospital visit 1-4 weeks before the surgery, but can be done on day of surgery. **Visit 3 may be divided into two sessions within the same week.

6.0 Statistical Considerations

The planned sample size (N=6) is consistent with similar pilot clinical trials in the literature.[62,64] Descriptive summaries of variables will be provided where appropriate. Variance and confidence intervals of the outcome measures will be used to guide the power analysis of a larger RCT. Each patient will serve as their own control and repeated measures ANOVA will be used for the analysis of outcome measures change over the 12 months course of the study. All statistical tests will be performed at the 0.05 level.

Safety will be assessed by analyzing the rates of procedure-related WHO grade 3-5 AEs and summarized descriptively. Additional summaries may be performed.

7.0 Quality Control & Quality Assurance Procedures

Site monitoring will be conducted to ensure that the rights and well-being of participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

The study coordinator will ensure that the study is conducted and documented properly by carrying out the activities outlined in International Council for Harmonisation E6, Section 5.18.4 and as detailed in the study Monitoring Plan.

Types of monitoring will include:

- targeted data verification
- confirmation of completion of eCRFs in REDCap
- query resolution
- eligibility criteria review
- adverse event review
- screening/enrolment data

8.0 Ethical Considerations

This trial will be conducted in compliance with the protocol, Good Clinical Research Practice (GCP) and all applicable regulatory requirement(s). The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the UHN REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the UHN REB before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

Participants will be provided with detailed information about the study, including its purpose, procedures, potential risks, and benefits. Informed consent will be obtained prior to participation.

8.1 Termination of Participation/Withdrawal Criteria

The following criteria apply to participants who have been enrolled in the study. An enrolled participant will be automatically withdrawn from the study if their treatment plan is modified such that they no longer meet the study eligibility criteria. A participant may verbally withdraw at any time by contacting the PI (surgeon) or appropriate study staff (e.g. study coordinator, surgeon's administrative coordinator).

The PI may terminate a patient's participation in the study if: any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

Reasons for withdrawal or termination will be recorded in the participant's study record.

All data collection relating to a withdrawn or terminated participant will cease at the time of withdrawal/termination. Clinical care in all withdrawn or terminated participants will continue as per standard of care. Any participant that withdraws or is terminated prior to completion of the Month 9 visit will be replaced.

8.2 Potential Risks

The risks of DBS surgery can generally be grouped into surgical, device-related, and stimulation-related complications.

8.2.1 Surgical Risks

Infection

Approximately 3% of patients experience infection at the site of implantation. This may require removal or replacement of the DBS hardware in severe cases. [76,78]

76,78

Intracranial Hemorrhage/Stroke

There is a risk of bleeding in the brain, which can lead to stroke. The incidence of stroke or significant hemorrhage in DBS procedures is less than 1%, which can lead to neurological deficits or, rarely, death (0.2%). Small bleeds are often asymptomatic, but larger bleeds can cause significant issues depending on the area affected.

Seizures

Seizures occur in about <1% of patients as a rare postoperative complication.

Hardware-related Complications

Lead fractures or displacement occur in around 2% of cases which may require surgical correction.

8.2.2 Device-Related Risks

Device Infection

As with surgical risks, device-related infection occurs in around 3% of patients, often requiring antibiotic treatment or device related.

Battery Issues

Patients require battery replacement every few years, depending on usage, which involves minor surgical procedures and carries similar infection risks.

8.2.3 Stimulation-Related Risks (Adjustable with Programming)

Adverse Effects

Potential reversible side effects associated with DBS stimulation and implantation include sensory phenomena, oscillopsia “shimmering vision”, limb myoclonus, headache, dizziness, and urinary incontinence.

8.2.4 Risk of Study-related Procedures

8.2.4.1 CT Risk

As part of this study, you will undergo imaging of your brain using a CT scan. CT scans involve exposure to a small amount of ionizing radiation, which carries a very low risk of potential harm. Additionally, some people may experience claustrophobia or discomfort during the scan. Commonly, patients experience a warm feeling or a metallic taste in the mouth during the injection of the contrast dye. These side effects disappear quickly and do not require any treatment. More rarely, patients may experience short-term side effects such as nausea, vomiting, headache, rash. You may develop an allergic reaction to the dye used for the CT scan.

If you are eligible for the study, safety checks will be conducted before any imaging, and a healthcare professional will be available to address any concerns during the procedures

8.2.4.2 EEG and MEG Risk

EEG and MEG are safe, non-invasive methods to monitor brain activity. EEG uses small electrodes on the scalp to detect electrical signals, while MEG measures the magnetic fields generated by brain activity without direct contact. Both are painless, but patients may experience mild discomfort from wearing the EEG cap or lying still during the MEG scan, which could cause slightly anxiety or restlessness. Our team will prioritize patient comfort and monitor for any signs of distress throughout these procedures.

8.2.4.3G MRI Risk

An MRI scan is painless but noisy. If you have any metal in your body, for your safety, please tell the staff. There is no radiation. Some people may feel a little 'closed-in' the MRI machine, but you will be able to speak with someone at all times and can stop the test at any time. Gadolinium contrast is not safe to use in people who have kidney problems. If you have had a problem with your kidneys, please inform the study team of this problem before the procedure. There is a small risk quantify of allergic reaction with gadolinium that can include symptoms of itchiness or rash. Rarely, a serious reaction may develop involving your kidneys leading to hardened skin lesions all over your body and stiffening of your joints. You must seek medical attention immediately if you develop any symptoms of allergic reaction.

8.3 Risk Mitigation

8.3.1 Close Monitoring

Participants will be closely monitored for any adverse events. Any serious adverse events will be managed promptly according to standard clinical procedures.

8.3.2 Follow-up Visits

Regular follow-up visits will help in early detection and management of any complications.

8.3.3 Informed Consent

Participants will be fully informed of the potential risks before consenting to the study

9.0 DATA MANAGEMENT & RECORD KEEPING

UHN's *validated* REDCap instance will be used to capture study assessments and data [electronic case report forms (e-CRFs)]. REDCap is a secure web platform for building and managing online databases and surveys. REDCap's streamlined process for rapidly creating and designing projects offers a vast array of tools that can be tailored to virtually any data collection strategy. Electrophysiological data (including related PET scan files) will be uploaded into an electronic image database created in UHN's MS OneDrive.

The study coordinator or other delegated study staff will enter data into the eCRFs. Training will be provided for the electronic data capture (EDC) system. All study staff using the EDC system must have the necessary education, training, and experience or any combination of these. The program manager will be responsible for documenting employee education, training, and previous experience that pertain to the EDC system for all staff using the EDC system. The program manager must maintain adequate security of the EDC system, including documentation that all users have been trained and a list of authorized users. To ensure all data entries can be tracked, all personnel responsible for data entry must obtain a unique user identification (user

ID) and password before any data can be entered in the eCRFs. Authorized study staff will be assigned a unique user ID only after receiving training.

Data collection is the responsibility of the program manager and PI. They are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Source documents include:

- Signed informed consent forms
- Study data collection questionnaires
- Electrophysiological data
- PET scan files
- Participant's medical files (MRN, EPIC)
- DBS device-specific data, i.e. make, model, DBS parameter settings

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official study record.

In Canada, essential study documents will be maintained for a period of 25 years, in accordance with section C.05.012 of Canada's Food and Drug Regulations - Division 5 "Drugs for clinical trials involving human subjects".

10.0 DELIVERABLES, SIGNIFICANCE & BENEFITS

This pilot study sets the stage for a multicenter RCT with the potential of providing the first disease modifying neuromodulatory treatment for AD. Moreover, it paves the way for exploring DBS-PPN in other forms of dementia, for example frontotemporal dementia where PVIN dysfunction has been reported, and Parkinson's dementia where preliminary evidence supports a beneficial role.15,32. Our findings could be translatable to other pathologies where GO and PVIN impairment is a common denominator such as epilepsy, schizophrenia, and autism.33–35 This study will teach us immensely about the brain excitation/inhibition networks that are the nucleus of normal brain functioning and are at the center of a broad spectrum of brain pathologies.

10.1 Potential Benefits

10.1.1 Benefits to Participants

Improvement in Cognitive Function

Participants may experience improvement in cognitive functions, such as memory and attention, due to enhanced PVIN function and modulation of gamma oscillations.

Reduction in AD Symptoms

The intervention has the potential to reduce the molecular and electrographic imprints of AD, thereby alleviating symptoms associated with the disease.

10.1.2 Benefits to the Community/Public:

Advancement in AD Treatment

Successful results from this pilot study could pave the way for a new, effective treatment modality for AD, potentially benefiting hundreds of thousands of Canadians.

Economic Impact

If DBS-PPN proves to be effective, it could reduce the overall burden of AD on the Canadian healthcare system by decreasing the need for long-term care and associated healthcare costs.

10.1.3 Benefits to UHN & The Krembil Brain Institute:

These following benefits underscore the potential of this pilot study to catalyze significant advancements in AD treatment and neuromodulation:

Research Leadership & Innovation

This study positions the Krembil Brain Institute at the forefront of ground-breaking research in neuromodulation and AD treatment. Leading such innovative research enhances Krembil's reputation as a pioneer in developing novel therapeutic strategies, attracting top-tier talent and fostering a culture of excellence and innovation.

Increased Funding & Grant Opportunities

Positive outcomes from this pilot study are likely to attract additional funding and grant opportunities from national and international funding bodies, including government agencies (CFI, CIHR), private foundations, and industry partners. This can significantly boost the institute's research budget, enabling further advancements and expansion of research programs.

Strategic Collaborations & Partnerships

Success in this pilot study could lead to strategic collaborations with other leading research institutions, pharmaceutical companies, and medical device manufacturers. These partnerships can facilitate knowledge exchange, resource sharing, and joint ventures in large-scale clinical trials and research projects.

Publication & Academic Prestige

Ground-breaking results from this study are expected to result in high-impact publications in prestigious scientific journals. Such publications not only enhance the academic prestige of UHN and Krembil, but also contribute to the global scientific community's understanding of AD and neuromodulation.

Clinical Impact & Patient Care

Establishing DBS-PPN as a viable treatment for AD could significantly improve patient care protocols and outcomes. The institute's involvement in this research translates to direct clinical benefits for patients treated at its affiliated hospitals, reinforcing its commitment to improving patient care through cutting-edge research.

Economic Benefits & Cost Savings

By demonstrating the cost-effectiveness of DBS-PPN compared to existing treatments (can be proposed in the larger RCT), the institute can position itself as a leader in developing economically viable healthcare solutions. This can lead to substantial cost savings for healthcare systems, enhancing the institute's value proposition to healthcare providers and policymakers.

Educational & Training Opportunities

Leading this research project provides invaluable educational and training opportunities for medical students, residents, and fellows. It fosters a learning environment that emphasizes translational research and clinical application, preparing the next generation of clinicians and researchers.

Long-term Institutional Growth

The success of this pilot study and potentially a subsequent larger RCT can, catalyze long-term growth for the Krembil Research Institute, enabling the establishment of new research centres, recruitment of additional expert faculty, and expansion of research infrastructure.

11.0 REFERENCES

1. Statistics Canada. Alzheimer's Awareness Month. Jan 12, 2024 (https://www.statcan.gc.ca/o1/en/plus/5374-alzheimers-awareness-month).
2. Alzheimer Society of Canada. Landmark Study Report #1: Navigating the Path Forward for Dementia in Canada. 2022. (https://alzheimer.ca/sites/default/files/documents/Landmark-Study-Report-1-Path_Alzheimer-Society-Canada_0.pdf).
3. Alzheimer Society of Canada. Landmark Study Report #2: The Many Faces of Dementia in Canada. 2024. (https://alzheimer.ca/sites/default/files/documents/ASC_The%20Many%20Faces%20of%20Dementia%20In%20Canada_Landmark%20Study_Vol2.pdf).
4. Canadian Centre for Economic Analysis. Dementia in Canada: Economic Burden: 2020 to 2050. 2023. (https://www.cancea.ca/wp-content/uploads/2023/07/CANCEA-Economic-Impact-of-Dementia-in-Canada-2023-01-08.pdf).
5. Lecanemab for Alzheimer's disease: tempering hype and hope. Lancet 2022;400(10367):1899. DOI: 10.1016/S0140-6736(22)02480-1.
6. Nadeau SE. Lecanemab Questions. Neurology 2024;102(7):e209320. DOI: 10.1212/WNL.0000000000209320.
7. Nguyen HV, Mital S, Knopman DS, Alexander GC. Cost-Effectiveness of Lecanemab for Individuals With Early-Stage Alzheimer Disease. Neurology 2024;102(7):e209218. DOI: 10.1212/WNL.0000000000209218.
8. Nelson SE, Lopez OL. Lecanemab for Alzheimer Disease: Is It Worth It? Neurology 2024;102(7):e209265. DOI: 10.1212/WNL.0000000000209265.
9. Hijazi S, Smit AB, van Kesteren RE. Fast-spiking parvalbumin-positive interneurons in brain physiology and Alzheimer's disease. Mol Psychiatry 2023;28(12):4954-4967. DOI: 10.1038/s41380-023-02168-y.
10. Xu Y, Zhao M, Han Y, Zhang H. GABAergic Inhibitory Interneuron Deficits in Alzheimer's Disease: Implications for Treatment. Front Neurosci 2020;14:660. DOI: 10.3389/fnins.2020.00660.
11. Murdock MH, Yang CY, Sun N, et al. Multisensory gamma stimulation promotes glymphatic clearance of amyloid. Nature 2024;627(8002):149-156. DOI: 10.1038/s41586-024-07132-6.
12. Iaccarino HF, Singer AC, Martorell AJ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 2016;540(7632):230-235. DOI: 10.1038/nature20587.
13. Etter G, van der Veldt S, Manseau F, Zarrinkoub I, Trillaud-Doppia E, Williams S. Optogenetic gamma stimulation rescues memory impairments in an Alzheimer's disease mouse model. Nat Commun 2019;10(1):5322. DOI: 10.1038/s41467-019-13260-9.
14. Park K, Lee J, Jang HJ, Richards BA, Kohl MM, Kwag J. Optogenetic activation of parvalbumin and somatostatin interneurons selectively restores theta-nested gamma oscillations and oscillation-induced spike timing-dependent long-term potentiation impaired by amyloid beta oligomers. BMC Biol 2020;18(1):7. DOI: 10.1186/s12915-019-0732-7.
15. Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 2007;8(1):45-56. DOI: 10.1038/nrn2044.
16. Goodman MS, Kumar S, Zomorrodi R, et al. Theta-Gamma Coupling and Working Memory in Alzheimer's Dementia and Mild Cognitive Impairment. Front Aging Neurosci 2018;10:101. DOI: 10.3389/fnagi.2018.00101.
17. Garcia-Rill E, Mahaffey S, Hyde JR, Urbano FJ. Bottom-up gamma maintenance in various disorders. Neurobiol Dis 2019;128:31-39. (In eng). DOI: 10.1016/j.nbd.2018.01.010.
18. Elsawy A, Valiante T. The Missed Potential of Deep Brain Stimulation of the Pedunculopontine Nucleus for the Treatment of Alzheimer's Disease [Internet]. OSF Preprints 2023. DOI: https://doi.org/10.31219/osf.io/h84kp.
19. Ricciardi L, Piano C, Rita Bentivoglio A, Fasano A. Pedunculopontine nucleus stimulation in Parkinson's disease dementia. Biol Psychiatry 2015;77(8):e35-40. DOI: 10.1016/j.biopsych.2014.07.027.
20. Stefani A, Peppe A, Galati S, Bassi MS, D'Angelo V, Pierantozzi M. The serendipity case of the pedunculopontine nucleus low-frequency brain stimulation: chasing a gait response, finding sleep, and cognition improvement. Front Neurol 2013;4:68. DOI: 10.3389/fneur.2013.00068.
21. Ricciardi L, Sarchioto M, Morgante F. Role of pedunculopontine nucleus in sleep-wake cycle and cognition in humans: A systematic review of DBS studies. Neurobiol Dis 2019;128:53-58. DOI: 10.1016/j.nbd.2019.01.022.

22. Valiante T, Elsawy A. DBS-PPN-AD: A Pilot Clinical Trial Investigating Deep Brain Stimulation of the Pedunculopontine Nucleus for the Treatment of Alzheimer's Disease. Alzheimer Society of Canada Brain Canada; 2023.
23. Mably AJ, Colgin LL. Gamma oscillations in cognitive disorders. Curr Opin Neurobiol 2018;52:182-187. DOI: 10.1016/j.conb.2018.07.009.
24. Fries P. Rhythms for Cognition: Communication through Coherence. Neuron 2015;88(1):220-35. (In eng). DOI: 10.1016/j.neuron.2015.09.034.
25. Hu H, Gan J, Jonas P. Interneurons. Fast-spiking, parvalbumin(+) GABAergic interneurons: from cellular design to microcircuit function. Science 2014;345(6196):1255263. DOI: 10.1126/science.1255263.
26. Colgin LL. Theta-gamma coupling in the entorhinal-hippocampal system. Curr Opin Neurobiol 2015;31:45-50. DOI: 10.1016/j.conb.2014.08.001.
27. Brooks H, Goodman MS, Bowie CR, et al. Theta-gamma coupling and ordering information: a stable brain-behavior relationship across cognitive tasks and clinical conditions. Neuropsychopharmacology 2020;45(12):2038-2047. DOI: 10.1038/s41386-020-0759-z.
28. Wulff P, Ponomarenko AA, Bartos M, et al. Hippocampal theta rhythm and its coupling with gamma oscillations require fast inhibition onto parvalbumin-positive interneurons. Proc Natl Acad Sci U S A 2009;106(9):3561-6. DOI: 10.1073/pnas.0813176106.
29. Amilhon B, Huh CY, Manseau F, et al. Parvalbumin Interneurons of Hippocampus Tune Population Activity at Theta Frequency. Neuron 2015;86(5):1277-89. (In eng). DOI: 10.1016/j.neuron.2015.05.027.
30. Lopez-Madrona VJ, Perez-Montoyo E, Alvarez-Salvado E, et al. Different theta frameworks coexist in the rat hippocampus and are coordinated during memory-guided and novelty tasks. Elife 2020;9. DOI: 10.7554/eLife.57313.
31. Patterson RA, Brooks HJ, Mirjalili M, et al. Theta phase-gamma amplitude coupling during working memory and its relationships with demographic, clinical, genetic, neurochemical, and neurostructural measures in older adults at risk for dementia. Alzheimer's & Dementia 2021;17(S5):e050923. DOI: https://doi.org/10.1002/alz.050923.
32. Guan A, Wang S, Huang A, et al. The role of gamma oscillations in central nervous system diseases: Mechanism and treatment. Front Cell Neurosci 2022;16:962957. DOI: 10.3389/fncel.2022.962957.
33. Martorell AJ, Paulson AL, Suk HJ, et al. Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. Cell 2019;177(2):256-271 e22. DOI: 10.1016/j.cell.2019.02.014.
34. Adaikkan C, Middleton SJ, Marco A, et al. Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection. Neuron 2019;102(5):929-943 e8. DOI: 10.1016/j.neuron.2019.04.011.
35. Fuller PM, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. J Comp Neurol 2011;519(5):933-56. DOI: 10.1002/cne.22559.
36. Saper CB, Fuller PM. Wake-sleep circuitry: an overview. Curr Opin Neurobiol 2017;44:186-192. DOI: 10.1016/j.conb.2017.03.021.
37. Garcia-Rill E, Kezunovic N, Hyde J, Simon C, Beck P, Urbano FJ. Coherence and frequency in the reticular activating system (RAS). Sleep Med Rev 2013;17(3):227-38. DOI: 10.1016/j.smrv.2012.06.002.
38. Király B, Domonkos A, Jelitai M, et al. The medial septum controls hippocampal supra-theta oscillations. Nat Commun 2023;14(1):6159. (In eng). DOI: 10.1038/s41467-023-41746-0.
39. Kim T, Thankachan S, McKenna JT, et al. Cortically projecting basal forebrain parvalbumin neurons regulate cortical gamma band oscillations. Proc Natl Acad Sci U S A 2015;112(11):3535-40. DOI: 10.1073/pnas.1413625112.
40. Ceravolo R, Brusa L, Galati S, et al. Low frequency stimulation of the nucleus tegmenti pedunculopontini increases cortical metabolism in parkinsonian patients. Eur J Neurol 2011;18(6):842-9. DOI: 10.1111/j.1468-1331.2010.03254.x.
41. Boyce R, Glasgow SD, Williams S, Adamantidis A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science 2016;352(6287):812-6. DOI: 10.1126/science.aad5252.
42. Li W, Ma L, Yang G, Gan WB. REM sleep selectively prunes and maintains new synapses in development and learning. Nat Neurosci 2017;20(3):427-437. DOI: 10.1038/nn.4479.
43. Lim AS, Moro E, Lozano AM, et al. Selective enhancement of rapid eye movement sleep by deep brain stimulation of the human pons. Ann Neurol 2009;66(1):110-4. DOI: 10.1002/ana.21631.

44. Klinzing JG, Niethard N, Born J. Publisher Correction: Mechanisms of systems memory consolidation during sleep. Nat Neurosci 2019;22(10):1743-1744. DOI: 10.1038/s41593-019-0507-z.
45. Klinzing JG, Niethard N, Born J. Mechanisms of systems memory consolidation during sleep. Nat Neurosci 2019;22(10):1598-1610. DOI: 10.1038/s41593-019-0467-3.
46. Costa A, Carlesimo GA, Caltagirone C, et al. Effects of deep brain stimulation of the peduncolopontine area on working memory tasks in patients with Parkinson's disease. Parkinsonism Relat Disord 2010;16(1):64-7. DOI: 10.1016/j.parkreldis.2009.05.009.
47. Fischer J, Schwiecker K, Bittner V, et al. Modulation of attentional processing by deep brain stimulation of the pedunculopontine nucleus region in patients with parkinsonian disorders. Neuropsychology 2015;29(4):632-7. DOI: 10.1037/neu0000179.
48. Wang C, Holtzman DM. Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors. Neuropsychopharmacology 2020;45(1):104-120. DOI: 10.1038/s41386-019-0478-5.
49. Pase MP, Himali JJ, Grima NA, et al. Sleep architecture and the risk of incident dementia in the community. Neurology 2017;89(12):1244-1250. DOI: 10.1212/WNL.0000000000004373.
50. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. Science 2020;370(6512):50-56. DOI: 10.1126/science.abb8739.
51. Honig LS, Sabbagh MN, van Dyck CH, et al. Correction: Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. Alzheimers Res Ther 2024;16(1):159. DOI: 10.1186/s13195-024-01507-7.
52. Honig LS, Sabbagh MN, van Dyck CH, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. Alzheimers Res Ther 2024;16(1):105. DOI: 10.1186/s13195-024-01441-8.
53. Hampel H, Elhage A, Cho M, Apostolova LG, Nicoll JAR, Atri A. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. Brain 2023;146(11):4414-4424. DOI: 10.1093/brain/awad188.
54. Lin GA, Whittington MD, Wright A, et al. Beta-Amyloid Antibodies for Early Alzheimer's Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, 2023. (https://icer.org/assessment/alzheimers-disease-2022/#timeline).
55. Health CAfDaTi. Appendix 2, Deep Brain Stimulation Reported Costs. Pharmacoeconomic Review Report: Levodopa/Carbidopa. Ottawa (ON): 2018. (https://www.ncbi.nlm.nih.gov/books/NBK539446/).
56. Manippa V, Palmisano A, Filardi M, et al. An update on the use of gamma (multi)sensory stimulation for Alzheimer's disease treatment. Front Aging Neurosci 2022;14:1095081. DOI: 10.3389/fnagi.2022.1095081.
57. Khachatryan E, Wittevrongel B, Reinartz M, et al. Cognitive tasks propagate the neural entrainment in response to a visual 40 Hz stimulation in humans. Front Aging Neurosci 2022;14:1010765. DOI: 10.3389/fnagi.2022.1010765.
58. Soula M, Martin-Avila A, Zhang Y, et al. Forty-hertz light stimulation does not entrain native gamma oscillations in Alzheimer's disease model mice. Nat Neurosci 2023;26(4):570-578. DOI: 10.1038/s41593-023-01270-2.
59. Schneider M, Tzanou A, Uran C, Vinck M. Cell-type-specific propagation of visual flicker. Cell Rep 2023;42(5):112492. DOI: 10.1016/j.celrep.2023.112492.
60. Majdi A, Deng Z, Sadigh-Eteghad S, De Vloo P, Nuttin B, Mc Laughlin M. Deep brain stimulation for the treatment of Alzheimer's disease: A systematic review and meta-analysis. Front Neurosci 2023;17:1154180. DOI: 10.3389/fnins.2023.1154180.
61. Davies P. Challenging the cholinergic hypothesis in Alzheimer disease. JAMA 1999;281(15):1433-4. DOI: 10.1001/jama.281.15.1433.
62. Kuhn J, Hardenacke K, Lenartz D, et al. Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. Mol Psychiatry 2015;20(3):353-60. DOI: 10.1038/mp.2014.32.
63. Hamani C, McAndrews MP, Cohn M, et al. Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol 2008;63(1):119-23. DOI: 10.1002/ana.21295.
64. Laxton AW, Tang-Wai DF, McAndrews MP, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 2010;68(4):521-34. DOI: 10.1002/ana.22089.
65. Lozano AM, Fosdick L, Chakravarty MM, et al. A Phase II Study of Fornix Deep Brain Stimulation in Mild Alzheimer's Disease. J Alzheimers Dis 2016;54(2):777-87. DOI: 10.3233/JAD-160017.
66. Rios AS, Oxenford S, Neudorfer C, et al. Optimal deep brain stimulation sites and networks for stimulation of the fornix in Alzheimer's disease. Nat Commun 2022;13(1):7707. DOI: 10.1038/s41467-022-34510-3.

67. Brooks H, Wang W, Zomorrodi R, et al. Cognitive function based on theta-gamma coupling vs. clinical diagnosis in older adults with mild cognitive impairment with or without major depressive disorder. Transl Psychiatry 2024;14(1):153. DOI: 10.1038/s41398-024-02856-5.
68. Assogna M, Sprugnoli G, Press D, et al. Gamma-induction in frontotemporal dementia (GIFTeD) randomized placebo-controlled trial: Rationale, noninvasive brain stimulation protocol, and study design. Alzheimers Dement (N Y) 2021;7(1):e12219. (In eng). DOI: 10.1002/trc2.12219.
69. Jiang X, Lachance M, Rossignol E. Involvement of cortical fast-spiking parvalbumin-positive basket cells in epilepsy. Prog Brain Res 2016;226:81-126. DOI: 10.1016/bs.pbr.2016.04.012.
70. Juarez P, Martinez Cerdeno V. Parvalbumin and parvalbumin chandelier interneurons in autism and other psychiatric disorders. Front Psychiatry 2022;13:913550. DOI: 10.3389/fpsyt.2022.913550.
71. Nahar L, Delacroix BM, Nam HW. The Role of Parvalbumin Interneurons in Neurotransmitter Balance and Neurological Disease. Front Psychiatry 2021;12:679960. DOI: 10.3389/fpsyt.2021.679960.
72. Knopman DS, Amieva H, Petersen RC, et al. Alzheimer disease. Nat Rev Dis Primers 2021;7(1):33. (In eng). DOI: 10.1038/s41572-021-00269-y.
73. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 2002;43(6):603-8. DOI: 10.1046/j.1528-1157.2002.26001.x.
74. MacLean JA, Nataraj J, Davies J, et al. Novel utilization of deep brain stimulation in the pedunculopontine nucleus with globus pallidus internus for treatment of childhood-onset dystonia. Front Hum Neurosci 2023;17:1270430. DOI: 10.3389/fnhum.2023.1270430.
75. Cheema S, Ferreira F, Parras O, et al. Association of Clinical and Neuroanatomic Factors With Response to Ventral Tegmental Area DBS in Chronic Cluster Headache. Neurology 2023;101(23):e2423-e2433. DOI: 10.1212/WNL.0000000000207750.
76. (AANS) AAoNS. Deep Brain Stimulation – Advantages, Risks and Conditions Treated. (https://www.aans.org/patients/conditions-treatments/deep-brain-stimulation/).
77. Krembil Brain Institute, University Health Network. Deep Brain Stimulation: Information for Patients and Families. 2022.
78. Fenoy AJ, Simpson RK, Jr. Risks of common complications in deep brain stimulation surgery: management and avoidance. J Neurosurg 2014;120(1):132-9. DOI: 10.3171/2013.10.JNS131225.
79. Hamani C, Lozano AM, Mazzone PA, et al. Pedunculopontine Nucleus Region Deep Brain Stimulation in Parkinson Disease: Surgical Techniques, Side Effects, and Postoperative Imaging. Stereotact Funct Neurosurg 2016;94(5):307-319. DOI: 10.1159/000449011.
80. Tamura M, Spellman TJ, Rosen AM, Gogos JA, Gordon JA. Hippocampal-prefrontal theta-gamma coupling during performance of a spatial working memory task. Nat Commun 2017;8(1):2182. DOI: 10.1038/s41467-017-02108-9.
81. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43(11):2412-4. DOI: 10.1212/wnl.43.11.2412-a.
82. Ellison TS, Cappa SF, Garrett D, et al. Outcome measures for Alzheimer's disease: A global inter-societal Delphi consensus. Alzheimers Dement 2023;19(6):2707-2729. DOI: 10.1002/alz.12945.
83. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141(11):1356-64. DOI: 10.1176/ajp.141.11.1356.
84. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-9. DOI: 10.1111/j.1532-5415.2005.53221.x.
85. Cummings J. The Neuropsychiatric Inventory: Development and Applications. J Geriatr Psychiatry Neurol 2020;33(2):73-84. DOI: 10.1177/0891988719882102.
86. Tractenberg RE, Singer CM, Cummings JL, Thal LJ. The Sleep Disorders Inventory: an instrument for studies of sleep disturbance in persons with Alzheimer's disease. J Sleep Res 2003;12(4):331-7. DOI: 10.1046/j.0962-1105.2003.00374.x.
87. : Quality of life in Alzheimer's disease: Patient and caregiver reports. 5.
88. Juva K, Sulkava R, Erkinjuntti T, Ylikoski R, Valvanne J, Tilvis R. Usefulness of the Clinical Dementia Rating scale in screening for dementia. Int Psychogeriatr 1995;7(1):17-24. DOI: 10.1017/s1041610295001815.