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Treating Alzheimer's disease with brain stimulation: From preclinical models to non-invasive stimulation in humans

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ABSTRACT

Alzheimer's disease (AD) is a severe and progressive neurodegenerative condition that exerts detrimental effects on brain function. As of now, there is no effective treatment for AD patients. This review explores two distinct avenues of research. The first revolves around the use of animal studies and preclinical models to gain insights into AD's underlying mechanisms and potential treatment strategies. Specifically, it delves into the effectiveness of interventions such as Optogenetics and Chemogenetics, shedding light on their implications for understanding pathophysiological mechanisms and potential therapeutic applications. The second avenue focuses on non-invasive brain stimulation (NiBS) techniques in the context of AD. Evidence suggests that NiBS can successfully modulate cognitive functions associated with various neurological and neuropsychiatric disorders, including AD, as demonstrated by promising findings. Here, we critically assessed recent findings in AD research belonging to these lines of research and discuss their potential impact on the clinical horizon of AD treatment. These multifaceted approaches offer hope for advancing our comprehension of AD pathology and developing novel therapeutic interventions.

1. Introduction

In 1906 Alois Alzheimer described some disorders of one of his patients as "a peculiar severe pathological process of the cerebral cortex" (Mirzayi et al., 2022). In particular, he was referring to a constellation of symptoms affecting his patient, from drastic memory loss to sleep disturbances and personality changes (Mirzayi et al., 2022). Currently, this condition is recognized as Alzheimer's disease (AD), a critical and progressive neurodegenerative disorder that has several deleterious effects on brain activity (Mirzayi et al., 2022).

With advancing age, the incidence of dementia and neurodegenerative diseases increases, with 6.7 million people (over the age of 65 and older) being affected by AD in the United States alone in 2023, (Alzheimer's Association, 2023a). The projected number of AD cases could increase to 13.8 million by the year 2060, unless there are significant advancements in research that can prevent, decelerate, or find a cure for AD (Alzheimer's Association, 2023a). AD is recognized as the seventh leading cause of death (Alzheimer's Association, 2023a), affecting a total of about 44 million people over the world (Dumurgier et al., 2020). AD is a costly disease: it is estimated that $345 billion US dollars were spent worldwide in 2023 for this condition (Alzheimer's Association, 2023a).

Currently, AD aetiology is unclear. It is well known that neuronal circuits and synaptic plasticity are the most affected in AD, but the exact mechanisms causing AD remain relatively unclear (Suresh et al., 2021). An important factor that characterizes AD is the presence of beta-amyloid (Aβ) plaques and tangles of neurofibrillary tau proteins that appear in distinct locations within the brain (Selkoe, 2001). Plaques, made up of Aβ peptides, occur outside the neurons, while neurofibrillary tangles, composed of tau protein, develop within neurons (Selkoe, 2001). Aβ plaques and tangles of neurofibrillary tau proteins are naturally produced by our brain; however, the pathological factor in AD is their overproduction (Hardy and Selkoe, 2002). The pathological process appears to result from an imbalance in the production of these

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elements (Hardy and Selkoe, 2002), which progresses into neuronal degeneration (Fig. 1) (Selkoe, 2002; Shankar et al., 2007) and consequent memory impairment and cognitive decline (Lesné et al., 2006; Walsh and Selkoe, 2004).

To date, there is no effective treatment for AD patients. The Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Italian Medicine Agency (AIFA) approved treatments are Memantine (a drug with complex mechanism of action including antagonism of the N-methyl-D-aspartate receptor), cholinesterase inhibitors (including Donepezil, Rivastigmine and Galantamine), Suvorexant (antagonist of orexin receptors) and Brexpiprazole, an atypical antipsychotic medication that has received approval for treating agitation linked to moderate to severe AD (Alzheimer's Association, 2023b; National Institute on Aging, 2023). Another possible strategy that has been considered to reduce Aβ in Alzheimer's patients is the breakdown of peptides (Alzforum, 2023; Zhang et al., 2023). However, the most promising solution has turned out to be immunotherapy, based on the use of monoclonal antibodies with high affinity and specificity. Unfortunately, this approach requires high costs (Lemere, 2013).

In June 2021, a new drug for AD was approved by the FDA: Aducanumab, a recombinant monoclonal antibody for human IgG1, which binds to soluble Aβ and insoluble fibrils. Aducanumab, administered through intravenous infusion, was the first approved monoclonal antibody directly targeting Aβ (Coerver et al., 2022). However, the FDA did not provide indications regarding the category of patients who can be treated with this drug. The EMA advised against granting marketing authorization for Aducanumab, stating that although the drug reduces Aβ in the brain, this reduction does not correlate with clinical improvement (European Medicines Agency, 2022). Clinical trials showed conflicting results and did not clearly demonstrate the drug's effectiveness in treating AD. Additionally, the safety of Aducanumab was questioned due to amyloid-related imaging abnormalities (ARIA) seen in some patients, which may be due to cerebral vasogenic oedema leading to microbleedings (Wojtunik-Kulesza et al., 2023). The EMA remained unconvinced that these abnormalities could be effectively managed in clinical practice and concluded that the benefits of Aducanumab did not outweigh its risks (European Medicines Agency, 2022). Today, Biogen Netherlands B.V. retracted its request for approval to market Aducanumab as a treatment for AD (European Medicines Agency, 2022). Biogen explained that it withdrew the application because the Committee for Medicinal Products for Human Use (CHMP) indicated the data provided were insufficient to support a positive opinion on Aducanumab's marketing authorization (European Medicines Agency, 2022).

Today, the FDA has approved Leqembi (Lecanemab-irmb) through the accelerated approval process. Researchers evaluated the effectiveness of Leqembi treatment in patients with mild cognitive decline; in the package insert, it has also been stated that there is no safety or efficacy data for the initiation of treatment in earlier or later stages of the disease other than those studied in clinical trials (Alzheimer's Association, 2023b). Lecanemab is a humanized monoclonal antibody IgG1, which has a high binding selectivity for soluble Aβ aggregate species compared to monomeric Aβ; furthermore, Lecanemab also shows moderate binding selectivity for fibrillar Aβ. The most common serious adverse effects

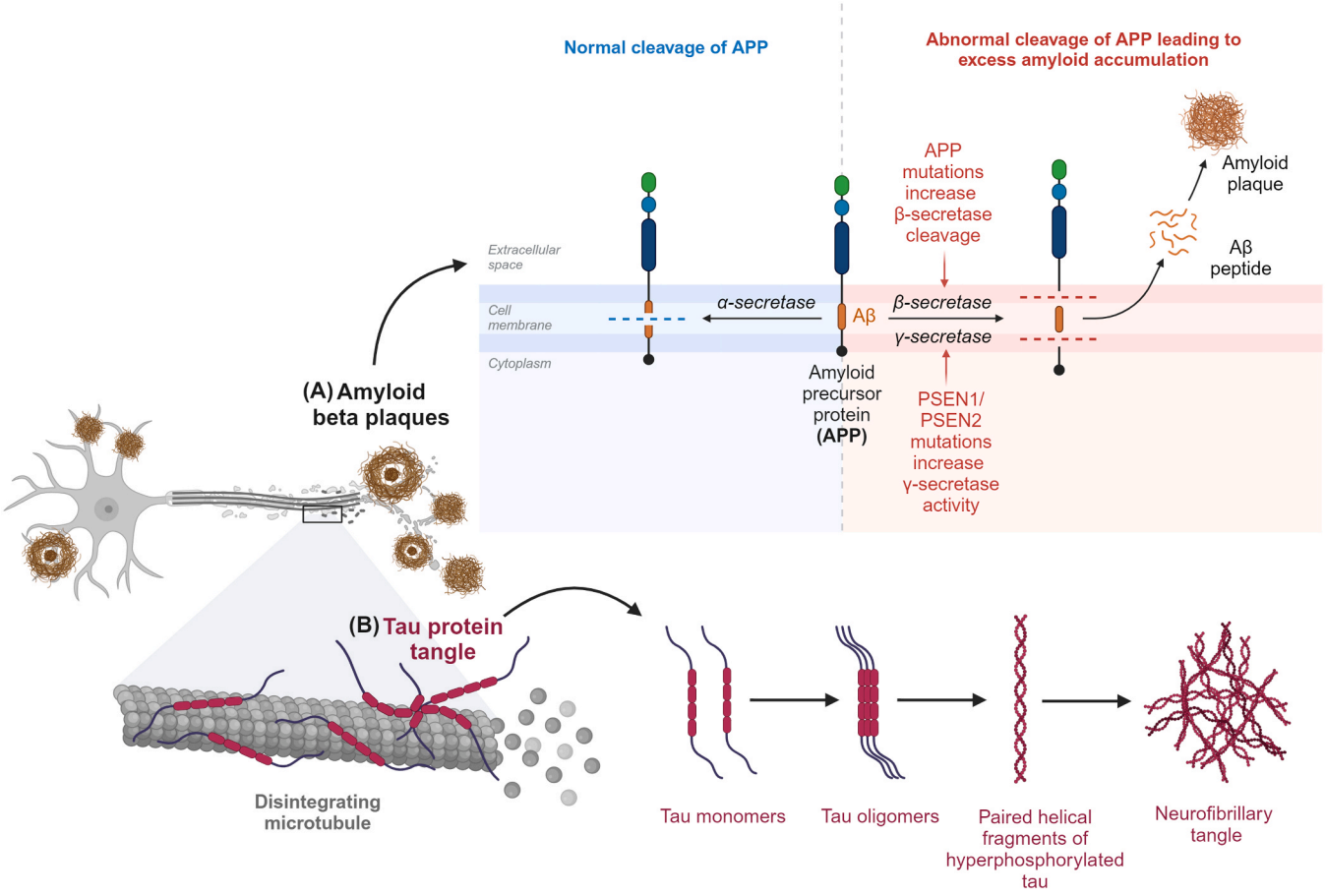

Fig. 1. Molecular Pathogenesis of Alzheimer's Disease. The figure illustrates the formation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) involving tau protein. (a) Amyloid precursor protein (APP) is cleaved by beta-secretase and gamma-secretase, resulting in the production of amyloid-beta peptides, which aggregate to form extracellular plaques. (b) Abnormally hyperphosphorylated tau protein dissociates from microtubules and aggregates to form intracellular neurofibrillary tangles. These pathological features contribute to neuronal dysfunction and cell death in Alzheimer's disease.

reported include ARIA, infusion-related reactions (the administration route used for this drug), atrial fibrillation, syncope and angina pectoris. Other adverse events observed include micro and macro cerebral haemorrhages, superficial siderosis and headaches (Van Dyck et al., 2023). The EMA is still in the process of evaluating whether to approve this drug.

Recently, the US FDA has also issued a positive opinion for Donanemab-azbt (Kisunla), an experimental anti-amyloid drug for AD, deeming it effective for the treatment of patients with early symptomatic disease (mild cognitive impairment or mild dementia) (Nature Reviews Drug Discovery, 2024). Donanemab is a humanized IgG1 monoclonal antibody designed to target Aβ plaques in the brain (Eli Lilly and Company, 2024). Specifically, it binds to an epitope (N-terminal of pyroglutamate Aβ), a form of Aβ present in amyloid plaques, and once bound, Donanemab induces the removal of these plaques (Eli Lilly and Company, 2024). The opinion was based on the results of the TRAILBLAZER-ALZ 2 phase III trial, in which the drug significantly reduced amyloid plaque burden in the brain and substantially slowed cognitive and functional decline compared to placebo (Nature Reviews Drug Discovery, 2024). The study enrolled approximately 1.700 subjects with early symptomatic AD, exhibiting amyloid and tau pathology (Nature Reviews Drug Discovery, 2024). Participants were randomized to receive either Donanemab or a placebo, administered intravenously every four weeks for up to 72 weeks (Nature Reviews Drug Discovery, 2024). Volunteers treated with Donanemab were switched to a placebo when their amyloid levels fell below a predefined threshold (Nature Reviews Drug Discovery, 2024). The primary endpoint of the trial was the change in the Integrated Alzheimer's Disease Rating Scale (iADRS) score (a 144-point measure of cognition and function) from baseline to 76 weeks (Nature Reviews Drug Discovery, 2024). Patients treated with Donanemab experienced a statistically significant 2.92-point slower decline compared to those receiving the placebo (Nature Reviews Drug Discovery, 2024). The antibody reduced amyloid plaque levels by an average of 61 % at 6 months, 80 % at 12 months, and 84 % at 18 months, according to the company (Eli Lilly and Company, 2024). Donanemab, like Lecanemab, includes a boxed warning about the potential for ARIA, which involves temporary brain swelling that can be fatal. To reduce this risk, baseline brain magnetic resonance imaging (MRI) and regular MRI monitoring are advised (Eli Lilly and Company, 2024). Donanemab may also trigger allergic reactions, some of which can be severe and life-threatening, typically occurring during or within 30 minutes after the infusion (Eli Lilly and Company, 2024). Headache is another common side effect (Eli Lilly and Company, 2024). However, as determined by the FDA, the benefits outweigh the risks. Donanemab is the first anti-amyloid drug that allows therapy to be discontinued once amyloid plaques are removed, resulting in fewer infusions and lower treatment costs.

In 2022, Ho et al. proposed an immunotherapeutic approach based on the down-regulation of activin, which is involved in protein aggregation in AD patients (Ho et al., 2022). Currently, no drugs based on this principle are in development.

However, the response to these treatments is limited, as they act on symptom control rather than on the disease course and have a diverse range of adverse effects (Shafqat, 2008). For this reason, the development of alternative and innovative treatments is necessary.

In this review, we examined the contribution of two different lines of research. The first one relies on the use of animal studies and preclinical models to the understanding and treatment of AD. In particular, the effectiveness of Optogenetic, Chemogenetic and Transcranial Brain Stimulation interventions was explored, as well as their clear implications for a broader understanding of pathophysiological mechanisms for future therapeutic interventions. The second line relies on the therapeutic effects of non-invasive brain stimulation (NiBS) techniques (Fig. 2) on AD patients. Evidence demonstrated that cognitive functions related to various neurological and neuropsychiatric disorders (including AD, as shown by encouraging findings; see e.g. Chang et al., 2018), can be successfully modulated by NiBS.

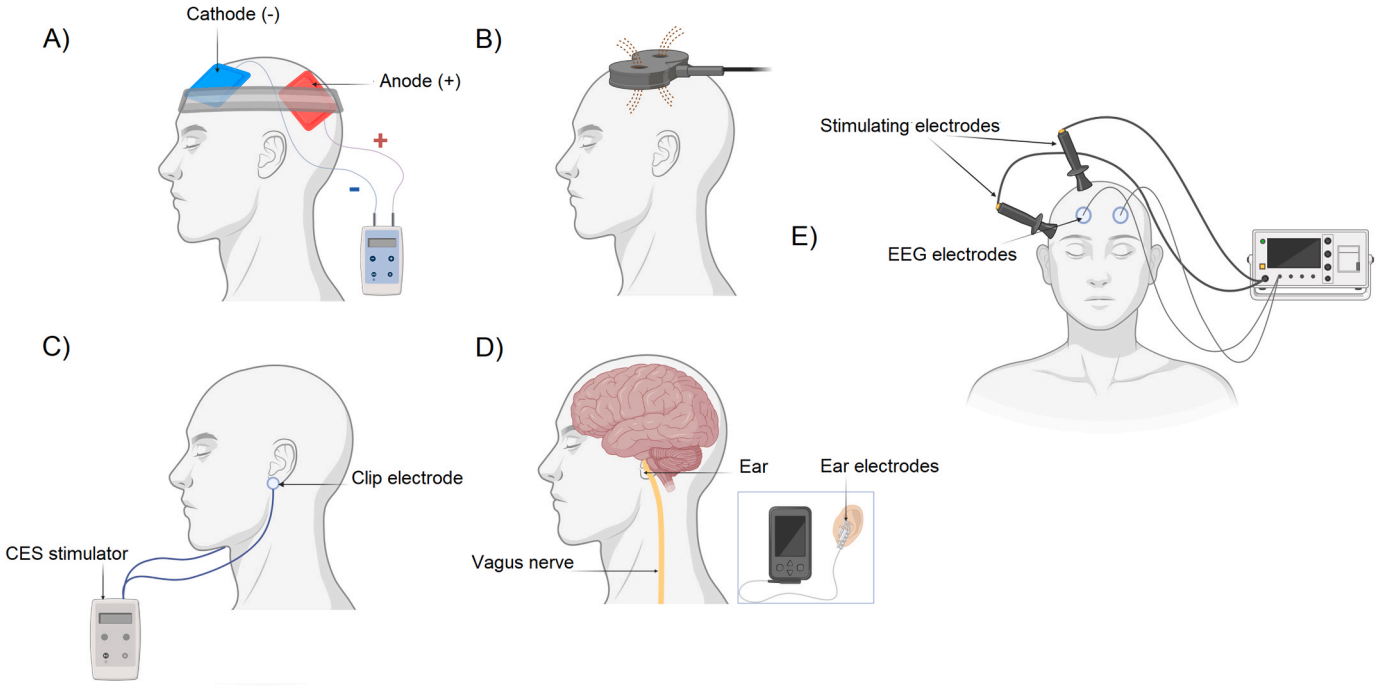

Fig. 2. Examples of Non-invasive Brain Stimulation Techniques. tDCS (Transcranial Direct Current Stimulation): it works by applying a negative (cathode) or positive (anode) electrode to an area. TMS (Transcranial Magnetic Stimulation): the coil (in this figure an eight-shaped one) delivers magnetic pulses in the region of application. CES (Cranial Electrotherapy Stimulation): it uses clip electrodes to earlobes to apply pulsed electrical currents. tVNS (Transcutaneous Non-Invasive Vagal Nerve Stimulation): this is a portable device that can stimulate the vagus nerve through the ear. ECT (Electroconvulsive Treatment): it consists in administering an electric current through a pair of electrodes.

2. Preclinical models

2.1. Optogenetics

The functioning of optogenetics relies on genetically modified cells that express photosensitive proteins that respond to light (Fig. 3) (Boyden et al., 2005; Kim et al., 2017). These transmembrane proteins, called rhodopsins, are present in all organisms and contain a sensitive molecule called opsin (Kato et al., 2012). For this reason, rhodopsins can respond to different wavelengths of electromagnetic light, thus allowing to alter the characteristic potential of the plasma membrane through the initiation of ionic exchanges (Mirzayi et al., 2022). The basic idea of optogenetics is precisely the use of proteins to induce changes in the membrane potential by exploiting light, through the adaptation of rhodopsins to specific subpopulations of cells (Cho and Li, 2016).

In-site light sources and distant light sources can be used for the introduction of light into the tissue (Mirzayi et al., 2022). In-site light sources work directly on the cortical surface (Huber et al., 2008; Ruiz et al., 2013) or can be implanted (Kim et al., 2013), while distant light sources generally work through the optical fiber and require infiltration of the tissue (Mirzayi et al., 2022). The use of the fibers requires a control, in order to minimize heat and damage on the tissue exposed to light, but at the same time it is necessary to have a sufficient beam of light to power the optics (Appasani and Appasani, 2017). For in-site light sources, LEDs and lasers are commonly used as they are less expensive, easier to use, and have broad efficacy than distant light sources. The disadvantage is that in order to independently activate two spectrally different opsins, two different devices must be used, since they have a spectrally narrow bandwidth (Wang et al., 2015a).

Microbial opsins are generally used in optogenetic studies as they are moderately simpler to engineer and respond to efficiency in kinetics (Guru et al., 2015). These include ion channels, such as channelrhodopsins, and ion pumps, such as halorhodopsins and bacteriorhodopsins (Govorunova et al., 2017). There are several methodologies for the transfer of opsin-encoding genes. Typically, the most used to deliver the opsin gene in the target cell population are lenti- and adeno-associated viral vectors (Cho and Li, 2016; Zhang et al., 2010). Viruses are incredibly effective in invading living cells and allow to simultaneously induce activation or inhibition in neural cells belonging to the same class, even if these are scattered throughout the tissue (Boyden et al., 2005). Currently, the efficacy of non-viral vectors is also being investigated, as they are cheaper, safer and moderately easier to use, but have

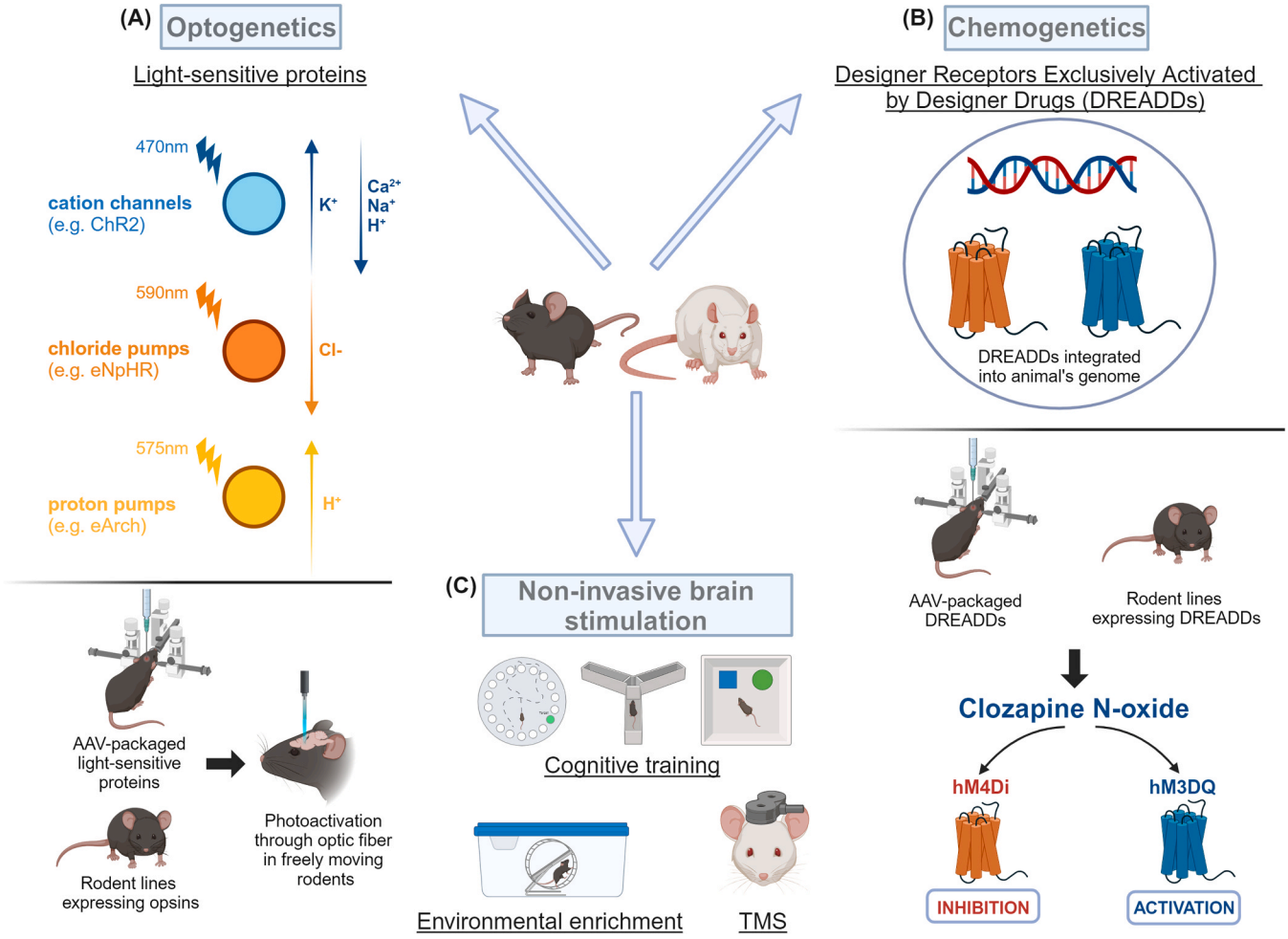

Fig. 3. Methods for Modulating Brain Activity in Preclinical Animal Models. The figure depicts various techniques used to study and influence brain function in animal models. (a) Optogenetics: Light-sensitive proteins are genetically targeted to specific neurons, allowing precise control of neuronal activity through light stimulation. (b) Chemogenetics: Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are used to selectively activate or inhibit neuronal activity in response to synthetic ligands. (c) Non-invasive brain stimulation methods: (i) Cognitive training comprises structured tasks and exercises designed to enhance cognitive abilities and brain health. (ii) Environmental enrichment involves providing a stimulating environment with enhanced sensory, cognitive, and motor activities to promote brain plasticity and function. (iii) Transcranial Magnetic Stimulation (TMS) uses magnetic fields to induce electric currents in the brain, modulating neuronal activity. These methods are employed to investigate neural circuits and potential therapeutic interventions for neurological and psychiatric disorders.

lower expression rates and delivery efficacy (Ramamoorth and Narvekar, 2015).

On the whole, optogenetics is an efficient methodology in the targeted modulation of molecular events, precisely because of the ability of opsins to control intracellular signaling through neuronal excitation or inhibition (Airan et al., 2009; Fenno et al., 2011).

2.1.1. Role of optogenetics in Alzheimer's disease treatment

Theoretically, in the future optogenetics could be an alternative therapeutic strategy for AD treatment. In fact, compared to pharmacological therapies or conventional electrical techniques, optogenetics has further advantages such as: reduced off-target effects, greater precision in targeting neural subpopulations and higher temporospatial and cellular specificity (Gradinaru et al., 2009; van Duuren et al., 2007).

Promising results have been demonstrated by various AD mouse model studies, which reproduce some of the biological and cognitive aspects of the disease. The future potential of these studies is exceptionally encouraging. The dentate gyrus (DG) has been extensively manipulated in the context of animal models of AD. For instance, optogenetic stimulation of neural ensembles within the DG has been shown to improve memory retrieval (Perusini et al., 2017) and to restore dendritic spine density and long-term memory, particularly at early AD stages (Roy et al., 2016). This implies a promising avenue for mitigating memory deterioration in AD patients.

Conversely, Wang and coworkers did not observe improvements in long-term memory but did report enhancements in short-term and working memory. These improvements were associated with increased glutamate receptor expression in the hippocampus, achieved through optogenetic stimulation of glutamatergic neurons in bilateral DG regions (Wang et al., 2019; Cui et al., 2020). These findings suggest that the impact of optogenetic interventions may vary based on specific cognitive functions and hippocampal regions, highlighting the need for a diversified approach in AD therapy.

Other animal studies have implemented a preventive approach, manipulating neuronal activity prior to the onset of symptoms. For example, Yang and colleagues reported significant results in Tg2576-APPswe mice, a genetically modified line carrying a transgene encoding the 695-amino acid isoform of the human amyloid precursor protein (hAPP) with the Swedish mutation, resulting in plaque pathologies similar to those seen in AD patients. The authors have shown that selective optogenetic activation through theta-burst stimulation of layer II pyramidal neurons of the entorhinal cortex (EC), whose direct innervation to parvalbumin-positive neurons of hippocampus CA1 region has been implicated in spatial memory, improves memory functions and spatial learning and prevents synaptic decay (Yang et al., 2018).

It is possible to take advantage of optogenetics to induce gamma band oscillations (GBO, 30–80 Hz, typically ~ 40 Hz), which are known to be disrupted in several neurological diseases. As such, induction of GBO in hippocampal PV interneurons of 5XFAD mice, a well-established model of AD, reduces Aβ plaques and induces microglia to increase Aβ uptake. Similar results were obtained when 40 Hz oscillations were replicated by non-invasive visual stimulation, opening intriguing perspectives to the treatment of human AD (Iaccarino et al., 2016). In a follow-up study, it was explained that GBO induction reduces the Aβ and tau presence throughout the neocortex due to the grouping of microglia around the plaques (Martorell et al., 2019). Also, the induction of theta waves in the hippocampus can enhance learning and memory by activating glutamatergic neurons (Robinson et al., 2016). Altogether, these findings suggest that manipulating neural oscillations could be a valuable strategy for addressing cognitive deficits in AD.

Beyond the hippocampus, other brain regions have been implicated in AD through optogenetic studies. For example, Omoluabi and colleagues reported that phasic stimulation of locus coeruleus (LC) neurons preserved axonal density and mitigated spatial and olfactory discrimination deficits associated with persistently phosphorylated pretangle tau, a hallmark of AD (Omoluabi et al., 2021).

In line with the proposal of GABA receptor modulators as a treatment for AD, studies have investigated the effects of optogenetic manipulation of GABA transmission in mouse models of AD. APP/PS1 mice show a reduction in Aβ plaques, recovery of learning impairment, induction of autophagy and decreased neuroinflammation as a consequence of GABAergic neurons stimulation in the hippocampus (Zhang et al., 2020). GABA manipulation has been studied also in prodromal AD, also known as the preclinical stage of Alzheimer's (pAD). This phase represents an early, pre-symptomatic stage of AD. During pAD, although patients may not exhibit symptoms, brain changes characterising the disease have already been set in motion (Osborn et al., 2016; Skaper, 2007). Alongside the accumulation of Aβ, this initial stage of the disease has also been associated with glial alterations and acute neuroinflammation (Heneka et al., 2015; Janelidze et al., 2018; Cribbs et al., 2012; Carter et al., 2012; Hoozemans, 2006; Verkhratsky et al., 2017). This phase can persist for many years before the onset of pronounced dementia symptoms, such as difficulties with short-term memory, spatial-temporal disorientation, language and planning issues, as well as changes in personality and behavior. In this context, hippocampus GABAergic activation in young APP/PS1 mice decreased the effects of Aβ pathology (Sun et al., 2012).

Overall, the prodromal phase of AD offers a crucial time frame within which it may be possible to potentially reduce both the risk and onset of the disease (Dubois et al., 2016; Scheltens et al., 2016; Williams et al., 2010; Crous-Bou, 2017; Kozauer et al., 2013). Numerous studies have indeed suggested that the loss of long-term memory over a span of days or weeks could serve as a reliable predictive indicator for AD diagnosis (Wearn et al., 2020; Walsh et al., 2014; Weston, 2018; Manes et al., 2008). It seems that tests assessing long-term memory functionality pose a greater challenge to mnemonic circuits compared to assessments involving the recall of information after a 30-minute delay. This phenomenon, referred to as "accelerated long-term forgetting", may result from deficits in memory consolidation processes, as outlined by Hoefeijzers et al. (2013). In these processes, information can be temporarily retained, but its conversion into long-term memory becomes problematic.

In conclusion, these studies collectively underscore the immense potential of optogenetics in advancing our understanding of AD and developing innovative therapeutic strategies. They offer hope for addressing memory deficits, synaptic decay, amyloid plaques, and tau abnormalities, both in the early stages of the disease and as preventive measures, heralding a promising future for AD research and treatment.

2.2. Chemogenetics

Chemogenetics is based on the use of genetically modified receptors that alter cellular signal transduction through interaction with specific molecules or synthetic ligands (Fig. 3) (Atasoy and Sternson, 2018). Some receptors, such as G-protein-coupled receptors (GPCRs), no longer react to their natural ligands, as they are modified by site-directed or random mutagenesis, but their activation is given by synthetic chemicals (Atasoy and Sternson, 2018). For example, the signaling pathways of GPCRs can be precisely controlled by DREADDs (Conklin et al., 2008). The most used DREADDs receptors are the human M3 muscarinic receptor (hM3Dq), which has excitatory effects, and the human M4 muscarinic receptor (hM4Di), which has inhibitory effects. Due to their mutations, hM3Dq and hM4Di can only be activated via a modified compound, namely clozapine N-oxide (CNO) (Alexander et al., 2009; Stachniak et al., 2014). CNO can only activate hM3Dq and hM4Di without altering the functions of endogenous receptors, as long as a high dose of CNO is not administered (Ying and Wang, 2021). In fact, it has been shown that CNO micromolar concentrations (10 μmol/L) do not alter several other receptors (including dopamine D1 and D2, histamine H1, 5-HT2A and muscarinic M1, M3, M4) (Gomez et al., 2017). As CNO has been reported to be back-metabolized in clozapine, an antipsychotic drug with affinity for many neurotransmitter receptors, more recently

new activating molecules have been developed, including compound 21 (C21), perlapine (PLP), olanzapine (OLP), JHU37152 (J52), JHU37160 (J60) and deschloroclozapine (DCZ) (Zhang et al., 2022).

Chemogenetics, with respect to optogenetics, offers prolonged manipulation of neuronal activities and their respective circuits, although it does not allow to acquire precision in time control (Rodriguez et al., 2020). The main advantage of this methodology is that the stimulus can be administered orally or through intraperitoneal injection, therefore through less invasive pathways with respect to optogenetics (Alexander et al., 2009; Todd et al., 2018; Rodriguez et al., 2020).

2.2.1. Chemogenetics manipulation in experimental models of Alzheimer's disease

To investigate AD underlying mechanisms and explore new strategies for early diagnosis and intervention, chemogenetics has recently been used on preclinical models of AD, since it allows to modulate the activities of specific neurons or neural circuits.

A treatment plan to prevent the progression of AD and its connection to memory-related circuits may be chemogenetic inhibition of the circuits with the highest expression of pathological Aβ and tau (Wu et al., 2016). In their study, Rodriguez and colleagues virally released hM4Di DREADDs into the entorhinal cortex (EC) of transgenic mice overexpressing mutant hAPP, then CNO was injected intraperitoneally. The authors reported a significant attenuation of EC neuronal activity and a consequent reduction in the accumulation of hAPP / Aβ and in the spread of pathological tau in the hippocampus (HIPP), along the EC-HIPP network (Rodriguez et al., 2020). This suggests that targeted interventions aimed at sustained modulation of neuronal activity could potentially serve as a viable therapeutic strategy for AD.

In the research conducted by Yuan and Grutzendler it was shown that using hM4Ds DREADDs through subarachnoid infusion in two AD-like mouse models (5XFAD and PS/APP), Aβ aggregation significantly decreases thanks to the reduction of neural activity, especially in regions presenting dendrites or axons of DREADDs-expressing neurons (Yuan and Grutzendler, 2016). This research has revealed a significant breakthrough by showing that chronically reducing neuronal activity over time can substantially decrease the accumulation of amyloid deposits. Moreover, it highlights that the regulation of Aβ release can take place in both axonal and dendritic regions, implicating both synaptic and non-synaptic mechanisms in Aβ release. Additionally, these reductions in neuronal activity resulted in the alleviation of synaptic abnormalities commonly associated with amyloid plaques. Consequently, the persistent reduction of neuronal activity could potentially serve as an innovative therapeutic strategy for AD (Yuan and Grutzendler, 2016).

The findings by Zheng and colleagues suggest a promising avenue for the future of AD research and potential therapies. Their chemogenetic inhibition of excitatory GABAergic interneurons in the DG led to substantial reductions in phospho-tau accumulation and the impairment of adult hippocampal neurogenesis (AHN) in mouse models of AD (3xTg AD) (Zheng et al., 2020). These factors are crucial contributors to cognitive decline in AD. This research underscores the potential of targeted neuronal modulation in mitigating key pathological aspects of AD. By addressing phospho-tau accumulation and promoting AHN, these interventions could offer novel strategies to slow down or even reverse cognitive decline in AD patients.

Rorabaugh and colleagues conducted a study on the effect of chemogenetic techniques on the activation of LC neurons induced by hM3Dq DREADDs (Rorabaugh et al., 2017). The hM3Dq DREADDs allows selective activation of tonic LC activity (Vazey and Aston-Jones, 2014), which appears to improve reversal learning (McCall et al., 2015). Tonic LC activation induced by DREADDs in TgF344-AD rats was reported to restore normal reversal learning by improving cognitive deficits. The results suggest that LC chemogenetic activation can rescue cognitive impairment in AD, even when there is already LC impairment (Rorabaugh et al., 2017).

By demonstrating the feasibility of attenuating AD-related pathology through such interventions, these researches open doors to the development of novel treatments that may slow down or even halt the progression of the disease. However, further studies and clinical trials will be essential to validate and refine these findings for potential translation into human therapies. Nevertheless, these studies represent a significant step forward in our understanding of AD and offers hope for more effective treatment approaches in the future.

In conclusion, these data strongly support the utility of optogenetic and chemogenetic neuromodulatory approaches in improving AD pathology.

2.3. Transcranial magnetic stimulation on murine models of Alzheimer's disease

In 1985, Barker and colleagues (1985) reported the first application of transcranial magnetic stimulation (TMS) on the motor cortex. TMS operates by generating short, high intensity magnetic pulses (up to 300 μs and 2.5 Tesla, respectively) through a copper wire coil applied to the leather scalp, based on Faraday's law of electromagnetic induction (Chang et al., 2018). This technique delivers rapidly changing electric current to specific brain regions, primarily in the superficial layers of the cortex (Hallett et al., 2007; Rossi et al., 2009). Cortical neuron modulation and dosage are determined by the stimulation intensity and by the individual's motor-evoked potential threshold (Sandrini et al., 2011). Repetitive TMS (rTMS) involves delivering bursts of continuous pulses at the same intensity over a period of time. This can include both low-frequency ($\leq$1 Hz) and high-frequency ($\geq$ 5 Hz) protocols (Rossi et al., 2009). Low-frequency pulses generally inhibit cortical excitability, while higher frequency pulses can increase it (Hallett et al., 2007; Sandrini et al., 2011). However, it should be noted that the relationship between TMS frequency and cortical inhibition or excitability is not always straightforward. For example, Caparelli et al. (2012) demonstrated that low-frequency pulses do not always result in cortical inhibition.

The beneficial effects of TMS on cognitive functions have been demonstrated in patients with AD (Cotelli et al., 2006; Hsu et al., 2015). Although this approach is routinely used in humans, its application to laboratory animals is rare, and little is known about the specifics of animal TMS for AD treatment. Tan and his team employed a rat model of AD induced by Aβ1–42 in the DG area of the dorsal hippocampus bilaterally, and administered rTMS treatment (round coil, 1 Hz at 100 % RMT) 14 days post-injection (Tan et al., 2013). Following 14 days of treatment, the rats exhibited recovery in hippocampal long-term potentiation (LTP) and improvements in spatial memory deficits. This recovery was linked to an increase in the levels of hippocampal neurotrophic factors (NGF and BDNF) and N-methyl-D-aspartate (NMDA) receptor expression (Tan et al., 2013). Similarly, in another study using mice models with Aβ1–42-induced toxicity, 14 days of rTMS treatment at various frequencies (1 Hz or 10 Hz at 30 % maximum output (1.26 T)), starting one day after Aβ1–42 injection, facilitated recovery. This was achieved by inhibiting neuronal apoptosis, activating β-catenin signaling, and raising brain levels of BDNF, NGF, and doublecortin (Chen et al., 2019).

These positive effects were further corroborated by multiple studies on genetically modified rodent models. In an APP23/PS45 mouse model of AD-like disease, Huang et al. (2017) evaluated the impact of low-frequency rTMS (round coil, 1 Hz at 100 % RMT). Mice received rTMS starting at 1.5 months of age, and two weeks of low-frequency treatment significantly reversed cognitive and synaptic deficits, as well as LTP impairment in the hippocampal CA1 region. The underlying mechanisms likely involve reductions in β-site APP-cleaving enzyme 1 (BACE1) and amyloid-β precursor protein (APP) processing (Huang et al., 2017).

In another study, TMS was applied at 1, 10, or 15 Hz daily for 4 weeks to young AD model mice (3xTg) that accumulate intracellular soluble Aβ (Wang et al., 2015a). Following behavioral tests,

hippocampal LTP was assessed (Wang et al., 2015a). TMS improved spatial learning deficits and enhanced LTP in a frequency-dependent manner (Wang et al., 2015a). In 3xTg mice, TMS restored the suppressed activity of large conductance calcium-activated potassium (Big-K; BK) channels in a frequency-dependent manner (Wang et al., 2015a). These changes were associated with corresponding increases and decreases in cortical excitability (Wang et al., 2015a). TMS also frequency-dependently boosted the expression of the scaffold protein Homer1a, which in turn enhanced BK channel activity (Wang et al., 2015a). A reduction in Aβ levels was observed after TMS in 3xTg mice; however, this reduction was not seen in 3xTg mice lacking Homer1a, even though TMS still affected BK channel activity and, consequently, LTP (Wang et al., 2015a). The study concluded that TMS enhances BK channels both through Homer1a-dependent and independent mechanisms, thereby boosting hippocampal LTP and reducing cortical excitability (Wang et al., 2015a). This reduced excitability contributed to lowering Aβ levels. The interconnected processes triggered by TMS likely improved learning in 3xTg mice (Wang et al., 2015b).

Notably, mice treated with high-frequency rTMS exhibited better outcomes. Choung et al. demonstrated that early administration of rTMS (round coil, 1 Hz or 20 Hz at 1.26 T) improved cognitive behavioral deficits induced by Aβ1–42 injection in mice by activating the dopaminergic system and upregulating neurogenic signalling. Additionally, enhanced recovery effects were observed with high-frequency rTMS, as proven in their in vivo experiments (Choung et al., 2021).

In another study led by Lin and colleagues, researchers investigated the impact of high-frequency rTMS treatment for 14 consecutive days on cognitive functions and pathological changes in the brains of 4–5 month old 5xFAD mice, which represent an early stage of pathology characterized by significant amyloid buildup and cognitive deficits. Each day, mice underwent 100 sessions of rTMS treatment with an inter-session interval of 5 seconds. During each session, they received 40 burst trains of 20 Hz stimulation, with the magnetic stimulation intensity set at 1.38 Tesla. Control groups, both wild-type and 5xFAD mice, underwent identical procedures, including restraint and exposure to noise from the magnetic stimulator, but were not positioned under the coil for actual stimulation. The findings revealed that rTMS treatment effectively prevented the decline in long-term memory related to novel objects and spatial locations in these mice. Notably, rTMS treatment significantly improved the efficiency of the brain's clearance pathways, including the glymphatic system within the brain parenchyma and the meningeal lymphatics, in the 5xFAD mouse model. Furthermore, the treatment led to a notable decrease in Aβ deposits, reduced activation of microglia and astrocytes, and prevented the decline in neuronal activity, as evidenced by increased c-FOS expression, observed in the prefrontal cortex and hippocampus of 5xFAD mice treated with rTMS. These findings collectively provide new insights into how rTMS regulates brain drainage systems and enhances Aβ clearance in the 5xFAD mouse model. Moreover, they suggest that the clearance rate of contrast tracers in cerebrospinal fluid could potentially serve as a prognostic biomarker for assessing the efficacy of rTMS treatment in AD patients (Lin et al., 2021).

Cao and colleagues discovered that 25 Hz rTMS improved cognitive function in 3xTg-AD model mice (Cao et al., 2022). This treatment also reduced hippocampal levels of Aβ1–42, alleviated oxidative stress, and enhanced glucose metabolism. The authors administered 25 Hz rTMS treatment to 6–8-month-old WT and 3xTg-AD mice for 21 days to investigate the neuroprotective effects on 3xTg-AD mice and explore the role of the phosphatidylinositol 3-kinase (PI3K) / protein kinase B (PKB/Akt) / glutamate transporter 1 (GLT-1) pathway in rTMS therapy. They observed that in 3xTg-AD mice, 25 Hz rTMS improved cognitive function, reduced Aβ1–42 levels, alleviated oxidative stress and neuroinflammatory responses, enhanced energy metabolism and synaptic plasticity, reduced neuronal loss, and increased PI3K/Akt activity and GLT-1 expression. However, when 3xTg-AD mice were treated with the PI3K-specific inhibitor LY294002 alongside rTMS, the treatment did not improve cognitive function, reduce Aβ1–42 levels or neuronal loss, nor did it increase GLT-1 expression. Therefore, the authors concluded that 25 Hz rTMS exerts multiple protective effects on 3xTg-AD mice, and its therapeutic benefits rely on the involvement of the PI3K/Akt/GLT-1 pathway (Cao et al., 2022).

Intermittent theta burst stimulation (iTBS), a new and highly effective form of rTMS, has been shown to reduce cognitive impairment in AD. To explore whether iTBS has long-term effects on AD-related pathologies, 6-month-old APP/PS1 mice received 30 consecutive days of iTBS treatment. After a 2-month break, brain morphological changes were assessed using immunohistochemistry and immunofluorescence staining, and protein levels were measured by Western blot at 9 months of age. The findings revealed that iTBS treatment significantly reduced Aβ burden in the cerebral cortex and hippocampus of APP/PS1 mice. Additionally, iTBS treatment was found to inhibit BACE1 expression and increase anti-insulin-degrading enzyme (IDE) levels, suggesting that the reduction in Aβ load is due to both decreased Aβ production and enhanced Aβ degradation. Furthermore, iTBS treatment alleviated neuroinflammation, neuronal apoptosis, and synaptic loss in APP/PS1 mice. Overall, these results indicate that a month of iTBS treatment improves brain pathologies in AD mice for at least 2 months, providing new evidence that iTBS may exert lasting effects on AD-type pathologies by inhibiting Aβ production and promoting Aβ degradation (Huang et al., 2023).

In summary, the available evidence indicates that rTMS has a beneficial impact on slowing the pathological progression of AD, particularly in enhancing synaptic plasticity and cognitive function. Moreover, high-frequency rTMS has shown greater therapeutic effectiveness compared to low-frequency rTMS.

2.4. Natural brain stimulation in preclinical models of Alzheimer's disease

Studies have shown positive effects of enhanced physical activity and computerised cognitive training (CCT) on cognition in patients with mild cognitive impairment (MCI) or even AD (Panza et al., 2018; Hill et al., 2017). Additionally, cognitive stimulation, often referred to as 'brain training', has been studied as an intervention to protect against cognitive decline associated with normal aging (Young et al., 2015; Lampit et al., 2014). Numerous effects have been documented following physical activity and enrichment in housing environments in transgenic mice expressing mutations associated with AD. In contemporary laboratory settings, environmental enrichment (EE) is defined as enhancing the quality of animal care by providing stimuli that promote both physiological and psychological well-being in captive animals (Coleman and Novak, 2017). Over the last decade, numerous reviews have underscored the efficacy of EE in combating AD progression (Wahl et al., 2019; Shepherd et al., 2018; Llorens-Martín, 2018; Robertson, 2013; Cutuli et al., 2022; Alanko et al., 2022). Particularly noteworthy is the evidence demonstrating that EE can reverse Aβ pathology and decrease senile plaque accumulation in transgenic AD mice (Lazarov et al., 2005; Balthazar et al., 2018).

Extensive evidence highlights the positive effects of enrichment and exercise on memory in familial AD (fAD) mice. When exercise is introduced before cognitive impairment appears, it generally enhances performance in the Morris water maze (MWM) test of spatial long-term memory (Rao et al., 2015; Chao et al., 2015), with one exception in APP23 mice (Wolf et al., 2006). Exercise also shows improvements in short-term spatial memory in the Y-maze (Richter et al., 2008; Bo et al., 2014), although some studies report no change (Miki Stein et al., 2017; Pietropaolo et al., 2008). Similarly, EE before cognitive decline consistently improves MWM performance across various transgenic models (Wolf et al., 2006; Cracchiolo et al., 2007; Ziegler-Waldkirch et al., 2018), with improvements also observed in short-term memory tasks like the Y-maze (Cao et al., 2018) and novel object recognition (Polito et al., 2014; Hüttenrauch et al., 2016; Verret et al., 2013; Huang et al., 2018; Görtz et al., 2008). Interventions applied after cognitive

impairment also show positive effects, with most exercise studies reporting improvements in MWM (Cho et al., 2015; García-Mesa et al., 2014; Ke et al., 2011; Zhao et al., 2015; García-Mesa et al., 2011; Cho et al., 2003; Nichol et al., 2007), Barnes maze (Herring et al., 2016), and Y-maze (Parachikova et al., 2008) performance. However, some studies show no change in MWM performance with late-stage exercise (Zhang et al., 2016; García-Mesa et al., 2016; Marlatt et al., 2013). One study found that voluntary exercise improved short-term memory, while forced exercise impaired memory and induced stress (Yuede et al., 2009; Kennard and Woodruff-Pak, 2012; Svensson et al., 2016).

Overall, EE appears to have a greater impact on synaptic plasticity, neurogenesis, and cognition than exercise. This is likely because EE stimulates both physical and cognitive functions. Studies investigating EE later in disease progression in mice suggest it is less effective at this stage, indicating that EE must be applied early, before plaque development, to maximize benefits. In contrast, exercise studies show more inconsistent results when used preventatively but more consistent benefits when applied therapeutically. This suggests that both cognitive and physical activities are crucial early in life, before plaques develop, to support neurogenesis and synaptogenesis.

3. Non-invasive brain stimulation in Alzheimer's disease patients

In recent years, NiBS techniques have attracted considerable public and scientific interest in the treatment of AD patients, given their role in modulating neural activity and their promising effects in terms of restoring pathophysiological aspects. Based on previous literature studies, we will discuss in the following paragraphs the opportunities of using NiBS to improve cognition and reduce symptoms in AD patients.

3.1. Transcranial magnetic stimulation

TMS is the most commonly used NiBS technique in the clinical setting to understand the pathophysiology of brain networks (Chang et al., 2018). Various studies have shown promising effects of rTMS on modulating cognitive functions in AD patients (Cotelli et al., 2006; Hsu et al., 2015). For example, in a study by Eliasova et al. (2014), high-frequency (10 Hz) rTMS was applied over the right inferior frontal gyrus (IFG) and vertex, in random order, in ten early AD patients. The protocol included the administration of 2250 pulses per session, and all participants received 2 rTMS sessions. The study reported a significant improvement in executive functions after applying 10 Hz rTMS over the right IFG, as measured by the performance on the Trail Making Test, a neuropsychological measure of executive functions (see, e.g., Bowie and Harvey, 2006).

Analogously, Zhao et al. (2017) reported a significant improvement in various neuropsychological tests in AD patients. These tests included the World Health Organization and University of California-Los Angeles Auditory Verbal Learning Test, the Mini-Mental State Examination (MMSE), and the Cognitive Subscale of the Alzheimer's Disease Rating Scale. The improvement was observed after 30 sessions of high-frequency (20 Hz) rTMS delivered over the posterior temporal and parietal cortex for 6 weeks compared to a sham (placebo) TMS treatment, but only when cognitive deficits were mild. Notably, AD patients were retested only 6 weeks after treatment, and therefore the maintenance of the effects over time is unknown. In addition, scores in a moderate treatment group did not improve significantly compared with the sham condition. Similar findings were reported by Cotelli et al. (2006) who applied rTMS to the dorsolateral prefrontal cortices (DLPFCs), bilaterally: rTMS improved accuracy on action naming in 15 AD patients. Building on this, the same research group conducted a follow-up study with 24 AD patients (divided according to the level of AD severity, mild to moderate and severe AD) who received bilateral rTMS over the DLPFC (Cotelli et al., 2008). The results showed that both groups improved in action naming, consistent with previous findings. Furthermore, patients with moderate to severe AD demonstrated a significant improvement in object naming accuracy, while those with mild AD did not. Since previous studies were conducted using single sessions of rTMS, Cotelli et al. (2010) conducted further research to evaluate the long-term cognitive effects derived from multiple sessions of rTMS on 10 AD patients. The study involved two groups of participants: the first group received 20 Hz rTMS to the left DLPFC five times a week for four weeks, while the second group received 20 Hz rTMS for two weeks, preceded by two weeks of placebo administration of rTMS (Cotelli et al., 2010). The results demonstrated that patients treated with real rTMS had significantly higher rates of correct auditory sentence comprehension compared to those treated with placebo rTMS. Furthermore, they observed a long-term improvement at a follow-up conducted 8 weeks after the end of treatment (Cotelli et al., 2010).

In a similar vein, Ahmed and colleagues (2012) conducted a study involving 45 AD patients who satisfied the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (Dubois et al., 2007). They were randomly divided into three groups. The first group received five sessions of high-frequency (20 Hz) rTMS on the DLPFC, bilaterally (right first); the second group received five sessions of low-frequency (1 Hz) rTMS on the DLPFC; and the third group received a placebo (sham) rTMS. The results showed that AD patients who received high-frequency (20 Hz) rTMS on the DLPFC exhibited a significantly higher rate of correct responses in the MMSE compared to the other groups.

Lee and colleagues (2016) conducted a study involving 26 patients with mild or moderate AD, based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. They targeted six brain regions with high-frequency (10 Hz) rTMS: bilateral DLPFC, Broca's area, Wernicke's area, and bilateral somatosensory cortices (R-pSAC and L-pSAC, respectively). The participants were randomly assigned to two groups: the first group received 30 rTMS sessions over a period of six weeks, while the second control group received sham rTMS. The treatment group showed significant improvements in ADAS-Cog scores after the six-week intervention, as well as in the MMSE and CGIC scores. Subgroup analysis revealed that the effects were more pronounced in the mild AD group, particularly in the domains of memory and language.

Positive results were obtained also using low-frequency rTMS. Turriziani and colleagues (2019), indeed, conducted a study involving 24 patients with mild AD, who showed improvement in recognition memory after two weeks of treatment targeting bilateral DLPFC, and this improvement persisted at one-month follow-up. Jiang and colleagues (2022) reported a study involving 32 AD patients who satisfied the criteria of the NINCDS-ADRDA (Dubois et al., 2007) and exhibited psychobehavioral symptoms. These patients were divided into two groups, one receiving high-frequency (10-Hz) and the other low-frequency (2-Hz) rTMS treatments, twice daily for four weeks, targeting the prefrontal cortex, bilaterally. After two weeks of treatment, the high-frequency rTMS group showed significantly reduced scores on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and Abilities of Daily Living (ADL) scores compared to their pre-treatment scores. These improvements persisted and deepened after four weeks of treatment. Similarly, the low-frequency rTMS group also exhibited significantly lower BEHAVE-AD and ADL scores compared to their baseline scores. Furthermore, when the two treatment groups were compared at different time points, the high-frequency rTMS group achieved significantly lower BEHAVE-AD and ADL scores compared to the low-frequency rTMS group. Additionally, the researchers found that the MMSE scores of the high-frequency rTMS group increased significantly after treatment, indicating improved cognitive function. In contrast, the MMSE scores of the low-frequency rTMS group did not show significant changes compared to their pre-treatment scores. These findings suggest that high-frequency rTMS offers advantages such as rapid results, efficacy, and a high level of safety in treating

psychobehavioral abnormalities in AD patients. Moreover, the study suggests that high-frequency rTMS interventions may have the potential to improve cognitive function in AD patients.

In another intriguing study conducted by Bentwich and colleagues (2011), a novel treatment approach called rTMS-COG, which combined high-frequency rTMS with cognitive training, was developed. rTMS was applied to six specific brain regions: bilateral DLPFC, Broca's area, Wernicke's area, and bilateral somatosensory cortices (R-pSAC and L-pSAC, respectively). Eight patients diagnosed with early or moderate AD, based on the DSM-IV criteria, underwent daily rTMS-COG treatment for six weeks, followed by two sessions per week of rTMS-COG treatment for three months. The researchers observed that the combined approach had a positive impact on cognitive function in these patients. This was shown by significant improvements in both mean Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) scores and Clinical Global Impression of Change (CGIC) scores.

Finally, in a study by Zhang et al. (2019), 15 patients with mild or moderate AD, based on the criteria of the NINCDS-ADRDA (Dubois et al., 2007), received 10 Hz rTMS on the left DLPFC and the left lateral temporal lobe. After four weeks of rTMS-COG treatment, patients showed improvements on several cognitive assessments, including the ADAS-cog, MMSE, and Addenbrooke's Cognitive Examination-III (ACE-III). Specifically, there were improvements in the word recall memory subscale of the ADAS-cog and in the attention and visual-spatial domains of the ACE III. Remarkably, these improvements were still evident at the four-week follow-up assessment (see, for consistent findings, Brem et al., 2020; Li et al., 2021).

Taken together, these studies suggest that various types of rTMS, whether high or low frequency, alone or in combination with cognitive training, hold promise as potential interventions for improving cognitive function in patients with AD, particularly in the early stages of the disease. However, no control group performing the COG treatment alone was tested in the above-mentioned studies. Further research in this area may provide valuable insights into the development of effective therapeutic strategies for AD patients in order to improve the quality of life of those affected by this condition. One clear limitation of all these studies is represented by the low-reliability tests used to evaluate improvements, such as the MMSE. Echological measures are lacking.

3.2. Low-intensity transcranial electrical stimulation

While TMS acts by directly inducing neural activation/inhibition within a specific brain region, low-intensity transcranial electrical stimulation (tES) delivers electrical currents through the scalp to modulate axonal or neuronal membrane polarization (hyperpolarization or depolarization; Paulus, 2011). Using surface electrodes of different polarities (cathodic or anodic) placed in special conductive media, such as sponges soaked in saline solution, tES works by decreasing (i.e., cathodal stimulation) or increasing (i.e., anodal stimulation) the probability that large populations of neurons (located between the electrodes) will fire, depending on the duration and intensity of the stimulation. The different ways in which electric current can be delivered, stimulating neuronal activity in different ways, allows us to distinguish three forms of tES: transcranial Direct Current Stimulation (tDCS), transcranial Alternating Current Stimulation (tACS), and transcranial Random Noise Stimulation (tRNS), a subform of tACS in which a low oscillatory current is delivered with random variations in its frequency and intensity (Antal and Herrmann, 2016).

Most studies in AD have been conducted using tDCS, which is now considered tolerable and safe for patients (Bikson et al., 2016; Ko, 2021). What is more, tDCS is a low-cost technique that can be efficiently used to develop protocols of daily stimulation sessions, thus to assess the long-term stability of tDCS-related effects (see next section). In contrast, little evidence has been gathered so far on tACS for the treatment of gamma oscillatory activity in AD, based on studies from animal models (Brechet et al., 2021; Dhaynaut et al., 2020; Iaccarino et al., 2016), while no studies – to the best of our knowledge – have used tRNS in AD studies.

3.2.1. Transcranial direct current stimulation

By delivering electrical current (typically between 1 and 2 mA; Woods et al., 2016), tDCS can modulate neuronal activity with a polarity change (anodal or cathodal), thereby altering membrane polarization (Brunoni et al., 2012; Kronberg et al., 2017). Generally, cathodal tDCS reduces cortical excitability in the brain region underneath and around the electrode placement, whereas anodal tDCS increases it (Stagg et al., 2018).

Numerous studies have suggested promising effects of tDCS in enhancing specific cognitive functions in AD patients (see, for reviews, Chang et al., 2018; Menardi et al., 2022). Typically, stimulation aiming at improving cognitive performance is delivered at a current intensity of 2 mA. For instance, Boggio et al. (2008) stimulated 10 AD patients with anodal tDCS (atDCS) for three sessions of 30 min each, including real stimulation of the left DLPFC and temporal cortex or sham stimulation. The authors found that atDCS to the left DLPFC and temporal cortex significantly improved visual recognition memory in their AD patients (Boggio et al., 2008). Subsequently, the same authors adapted the study design to evaluate the long-term stability of atDCS stimulation (Boggio et al., 2012). To this aim, AD patients received bilateral atDCS stimulation over the temporal regions for 30 minutes per day, 5 days per week. After 5 days of treatment, a significant improvement in visual recognition memory was observed, and this improvement was maintained for 1 month after treatment. However, no significant improvement in visual attention or general cognitive performance was found.

Similarly, Khedr et al. (2014) randomly assigned 34 AD patients to: atDCS on the left DLPFC, ctDCS applied on the left DLPFC, or sham stimulation. Both groups were administered daily sessions of 25 minutes of stimulation for 10 consecutive days. The authors found that both atDCS and ctDCS improved MMSE scores compared to sham, whereas ctDCS improved IQ performance, up to a 2-month follow-up (see, for similar findings, Khedr et al., 2019). Again, Roncero et al. (2017) applied atDCS stimulation for 30 minutes to the left inferior parietal cortex of 10 anomic AD patients. The authors observed a small but persistent (in a 2-week follow-up) increase in untrained picture-naming and digit span task after atDCS, whereas performance decreased after sham. Im et al. (2019) reported consistent findings. In 18 patients with early AD, 30 minutes of daily atDCS for 6 months resulted in improvement in the MMSE and Boston Naming Test, but not in delayed recall. This atDCS protocol was found to marginally prevent decline in executive functions. Analogously, Gangemi et al. (2021) conducted two separate studies in which AD patients received bilateral atDCS stimulation to the temporal lobe. In the first study, 26 participants received daily stimulation (real or sham) for 10 days. In the second study, 18 participants received daily stimulation (real or sham) for 8 months (10 days per month). The results demonstrated that the participants receiving real stimulation maintained the same level of neuropsychological performance (positive effect on temporal and personal orientation, attention, calculation, recall, and in preventing the worsening of apraxia symptoms tested with the MMSE), while the participants in the sham group showed a significant decline. This was true for both the short- and the long-term intervention.

It has become evident, however, that tDCS is more effective when combined with cognitive training than when delivered alone. Accordingly, Cotelli et al. (2014) randomly assigned 36 AD patients to three conditions: atDCS and individualized memory training, sham tDCS and individualized memory training, and atDCS and motor training. atDCS stimulation was applied to the left DLPFC for 25 minutes per day for 2 weeks (5 days per week). The results showed that both the atDCS group combined with individualized memory training and the sham group combined with individualized memory training showed significantly improved performance after 2 weeks compared to the atDCS group combined with motor training (Cotelli et al., 2014). This study suggests

that combining tDCS with cognitive training, especially targeting memory-related functions, may have the potential to enhance cognitive performance in AD patients, but what seems to work is in fact the cognitive training since combined with sham it was equally efficient. Lu et al. (2019) instead combined atDCS with working memory training. The authors recruited a large sample of 201 AD patients who underwent either atDCS and working memory training or sham atDCS and control cognitive training. atDCS stimulation was applied to the left temporal cortex for 20 minutes per session (12 sessions over 4 weeks). The results showed that atDCS combined with working memory training showed greater improvement in memory performance after a 4 weeks intervention, and at 8 weeks of follow-up. There were also transfer effects to a wide spectrum of cognitive functions, including attention and language. Unfortunately, there was no condition of sham combined with WM training.

Importantly, however, some evidence appears to be inconsistent with the above literature. For instance, Suemoto et al. (2014) recruited 40 AD patients who received two sessions, including atDCS to the left DLPFC for 20 minutes per session or sham stimulation. The authors found no significant differences in apathy over time between the atDCS and sham group. Similarly, Bystad et al. (2016) administered atDCS or sham tDCS to 25 AD patients during six sessions of stimulation over the left temporal cortex for 10 days, for 30 minutes per session. Changes in verbal memory (as assessed by means of the California Verbal Learning Test, CVLT) were not significantly different between atDCS and sham. Furthermore, there were not significant differences in MMSE, clock-drawing test, and TMT scores. In the same vein, Inagawa et al. (2019) observed no significant changes in MMSE and ADAS-Cog scores in 19 AD patients who received real tDCS compared to those who received sham treatment (Inagawa et al., 2019).

3.2.2. Transcranial alternating current stimulation

Transcranial alternating current stimulation (tACS) delivers a current that oscillates above and below zero with a specific stimulation intensity (i.e., the so-called peak-to-peak amplitude) at a given frequency (Chaieb et al., 2011). While tDCS modulates the excitability thresholds of neuronal membrane potentials (Nitsche et al., 2000; Kuo et al., 2012), tACS directly interacts with ongoing neuronal activity during cognitive and/or sensorimotor processes, leading to entrainment or synchronization of brain network oscillations (Chaieb et al., 2011; Reato et al., 2013). tACS is a safe form of neuronal modulation, although subjects may report mild - but transient - side effects, with no serious adverse events (Antal et al., 2017).

tACS has been shown to modulate higher-order cognitive processes, including working memory (Reinhart and Nguyen, 2019), long-term memory (Jones et al., 2018), episodic memory (Sandrini et al., 2016; Sandrini et al., 2017), and decision making (Herrmann et al., 2013). Similarly, tACS has been used to improve cognition in AD patients. For instance, Zhou et al. (2021) tested the clinical effects of tACS on the temporal lobe in a variety of cognitive functions in AD patients. They demonstrated that 30 sessions of daily 20-min tACS treatment for 6 weeks significantly improved cognitive functions (word recall, recall of test instructions, ideational praxis) in patients with mild to moderate AD symptoms, with significant changes in MMSE and ADAS-Cog scores. These results support the potential role of gamma swing as a therapeutic strategy for AD treatment.

In another study, tACS applied in the gamma band to DLPFC/DMPFC partially improved cognitive performance in most subjects with MCI, but not in AD patients (Naro et al., 2016). A 2-year follow-up showed that MCI subjects who did not respond to tACS treatment converted to AD (Naro et al., 2016). As this evidence remains highly preliminary, ongoing clinical trials are further investigating the impact of prolonged daily exposure to gamma-tACS. Recently, Liu et al. (2023) combined tACS with sound stimulation to treat moderate AD symptoms in a single 73-year-old female patient (Liu et al., 2023). The patient received tACS at a gamma frequency (40 Hz) and a peak-to-peak amplitude of 1.5 mA 15 times in 20-minute sessions over 3 weeks (21 days). Two electrodes (4 × 6 cm) were placed in the dorsolateral prefrontal cortex and the contralateral supraorbital area. At the same time, patients received sound stimulation through earphones with a sound tone set at 40 Hz. The authors observed a significant improvement in cognitive scale scores after 15 sessions and - most importantly - at a 4-month follow-up (Liu et al., 2023). Although the evidence for the performance-enhancing effects of tACS is still very preliminary, these results encourage more in-depth studies to further support the efficacy of this new therapy.

3.3. Electroconvulsive treatment

Electroconvulsive Treatment (ECT) consists of inducing a controlled seizure by administering an electric current through a pair of electrodes (Madsen et al., 2000). The therapeutic function underlying ECT is not fully understood, although it is known to induce proliferative changes in the brain, such as neurogenesis, angiogenesis, and gliogenesis (Madsen et al., 2000).

One of the key brain structures involved in the formation and retention of long-term memory is the hippocampus (Squire, 1992). Crucially, the hippocampus is also one of the earliest regions to be affected by the progression of AD (Rao et al., 2022). Retrograde (O'Connor et al., 2008; Kho et al., 2006) or anterograde (Ingram et al., 2008; Nordanskog et al., 2014) amnesia is known to be a common side effect of ECT. For this reason, the effects of ECT on hippocampal function have been studied extensively (Madsen et al., 2000; Takamiya et al., 2018; Hellsten et al., 2005), although the specific effect of ECT to treat AD symptoms has not yet been investigated, which would be very important in the light of some evidence. For example, Bouckaert et al. (2016) reported an increase in hippocampal gray matter after ECT.

To date, several studies were conducted to clarify the effects of ECT on depression, which is also a common symptom in AD patients (Andersen et al., 2005; Burke et al., 2019). Hausner et al. (2010) recruited 44 elderly patients hospitalized with Major Depressive Disorder (MDD). Patients were divided into three groups: dementia group, MCI group, and no cognitive impairment (NCI) group. Patients received either unilaterally right at minimum of 250 % seizure threshold or bilateral at minimum of 150 % seizure threshold, two to three times a week for 6 months. In the dementia group, pre-ECT MMSE scores (22.7 +- 4.4) increased to 25.6 (3.0) at the 6-month MMSE measurement (Hausner et al., 2010). Consistently, a retrospective cohort study of 126 MDD patients treated with ECT reported that MMSE scores at 6 months were significantly higher than at baseline (Fernie et al., 2014). However, a study by Verwijk et al. (2014) of 42 depressed patients aged ≥55 years showed improvements in the TMT-A and Letter Fluency Test at 6 months, but not in the MMSE (Verwijk et al., 2014). Moreover, numerous studies have shown that ECT can increase levels of brain-derived neurotrophic factor (BDNF) in depressed patients (Rocha et al., 2016), and several meta-analyses have shown that AD is associated with low levels of BDNF (Querfurth et al., 2010; Scheltens et al., 2016).

Overall, however, further research should be conducted in AD patients to test the efficacy of these treatments.

3.4. Cranial electrotherapy stimulation

Cranial Electrotherapy Stimulation (CES) uses clip electrodes on the earlobes to apply pulsed electrical currents of low-amplitude (typically <1 mA; Chang et al., 2018).

Scherder et al. (2002) investigated the cognitive effects of CES in AD patients by randomly assigning 18 participants to a CES treatment group and a control group. Patients in the treatment group were administered low-frequency (0.5 Hz) stimulation with an intensity of 10–600 μA, 30 min a day, 5 days a week. However, after 6 weeks of CES treatment, no improvement in cognition was found. Therefore, Scherder et al. (2006) used high-frequency (100 Hz) CES in 21 AD patients, with a

similar protocol (intensity of 10–600 μA, 30 min per day, 5 days per week). However, the results still showed no cognitive improvement after 6 weeks of treatment. For this reason, not many other trials have been conducted using this specific technique.

3.4.1. Transcutaneous electrical nerve stimulation

Some studies have shown that Transcutaneous Electrical Nerve Stimulation (TENS) can improve certain cognitive functions in AD patients (Scherder et al., 1995; Scherder et al., 1999). TENS mimics CES but delivers stimulation through the patient's back rather than the earlobes (head). Scherder et al. (1995) divided 16 patients with early-stage AD into two groups: 8 participants in the experimental group and 8 in the sham group. Participants were stimulated with asymmetric biphasic square pulses in train bursts, 30 minutes a day for 6 weeks, through electrodes placed on the back between the Th1 and Th5 vertebrae (each on one side of the spinal column). Each stimulation train consisted of nine pulses with an internal frequency of 160 Hz. The reset frequency was 2 Hz and the pulse width was 40 μs. The authors observed a significant improvement in memory recognition tests after 6 weeks of treatment (Scherder et al., 1995). Based on these results, the same research group used the same protocol on 16 participants in the intermediate stages of AD, reporting, however, that TENS resulted in less beneficial effects at this stage of the disease (Scherder et al., 1999).

3.5. Non-invasive transcutaneous vagal nerve stimulation

Non-invasive transcutaneous Vagal Nerve Stimulation (tVNS) devices are portable and can stimulate the vagus nerve indirectly through the skin of the neck or ear (Kraus et al., 2013; Hein et al., 2013). To date, there have not been tVNS studies in AD patients. However, the use of non-invasive tVNS to improve memory is being investigated. In a study of 60 participants, tVNS stimulation was shown to improve performance on working memory tasks (Sun et al., 2021). Analogously, Jongkees et al. (2018) reported improved response selection during sequential actions in a group of 40 participants. Giraudier et al. (2020) reported improvements in high-confidence recognition memory after a single session of tVNS compared to sham stimulation, although overall word recognition and emotional word processing were unaffected. In a study by Kaan et al. (2021), tVNS induced greater accuracy on a word span task (Nittrouer and Miller, 1999), when applied to the ear tragus than when sham was applied to the earlobe or in the absence of stimulation. The authors observed that the tVNS affected cognition and attention and could potentially aid in the modulation of memory and language. Taken together, these findings may suggest a potential effect to improve memory-related symptoms in AD patients that should be assessed by future studies.

4. Conclusions

Although there are drugs available today that have been suggested to improve memory, they have no effect on a cluster of symptoms and do not affect the progression of the disease. As Alzheimer's research moves towards early diagnosis and intervention, it is critical to have accurate preclinical models to probe the mechanisms of the disease and test the efficacy of new therapies. Optogenetics and chemogenetics have tremendous advantages for functional studies of neural circuits. In combination with non-invasive stimulation techniques, one can identify functional connections between distinct neurons and evaluate their functional alterations in AD models. Together with behavioral tests, it is possible to find specific neural circuits involved in different stages of the memory process and to identify which circuit is responsible for AD-like cognitive dysfunction in various animal models of AD. Optogenetics and chemogenetics not only provide a deeper understanding of the pathogenesis of AD, but also open the door to using these tools to deliver treatment. The main obstacle is to transfer research results from the laboratory to the clinic. Despite all the challenges, optogenetics has been applied safely and effectively to arouse non-human macaque primates (Han et al., 2009, 2011), which is remarkable, as primate studies bring the field closer to the clinical.

The present work aims to contribute to the advancement of translational projects that are both ambitious and feasible. These projects, starting from preclinical studies, have the potential to culminate in effective clinical treatments for AD with minimal side effects. The possibility of saving memory capacities in AD through innovative and integrated approaches based on NiBS techniques, optogenetics and/or chemogenetics, could represent a significant step towards the development of new strategies and future therapeutic approaches to improve the treatment of disorders related to AD memory.

The methodology employed to assess the effectiveness of treatments in the context of AD raises some pertinent issues. A key criticism revolves around the overreliance on the MMSE, which could be influenced by a practice effect, making it challenging to distinguish between actual improvement in patient conditions and mere familiarity with the test itself. The MMSE might prove accessible even to individuals with advanced dementia, especially if they have a high level of education. Furthermore, the apparent lack of consideration for ecological measures raises doubts about the validity of the assessments, as these may not necessarily reflect the tangible impact of improvements in the daily lives of both the patient and the caregiver. It would be advisable for future studies to incorporate more comprehensive approaches and measure the effectiveness of treatments in a daily living context.

Another key aspect to consider is the limited use of these potentially promising techniques in the context of AD. Furthermore, it is important to note – as a major limitation – the inability to target deep brain nuclei with TMS. Among the techniques discussed, Magnetic Seizure Therapy (MST), as a derivative of TMS, presents an intriguing possibility. MST induces seizures using high-intensity rTMS, but with greater control than TMS. Despite its potential, no studies have investigated the application of MST in AD. Luber et al. (2013) examined the applications of TMS and MST in neuropsychiatric diseases related to brain aging. The authors suggested that MST may improve cognition or reduce amnesia. Therefore, MST needs further exploration for its potential effect on AD patients.

Furthermore, future research could delve into the study of memory in healthy individuals. Addressing the limitations associated with pathophysiological conditions, some authors propose investigating the neurobiological foundations of individuals with exceptional memory abilities (Santangelo et al., 2022). This approach introduces innovative methods for studying superior memory, focusing on three recent lines of investigation: individuals with highly superior autobiographical memory (HSAM; Santangelo et al., 2018, 2021), elderly individuals displaying exceptional memory (SuperAgers; de Godoy et al., 2021), and individuals trained in mnemonic techniques, such as memory athletes (Dresler et al., 2017). The argument posits that the fundamental mechanisms enabling enhanced memory performance in these groups may potentially enhance memory in pathological conditions. This line of research into superior memory has the potential to challenge the conventional approach to studying memory, which typically centers on memory disorders (Santangelo et al., 2022). This innovative approach might pave the way for future applied research into brain stimulation and other therapeutic interventions targeting memory impairments and memory loss in conditions like AD.

Declarations of interest

None

Author contributions

IL: Writing - original draft, Writing - review & editing; GC: Writing - review & editing; CP: Writing - review & editing; VS: Conceptualization, Writing - review & editing, Supervision, Funding acquisition; PC:

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