Alzheimer's Disease Pathophysiology and Novel Treatment: An Update

Ashley Mo

The Harker School, 500 Saratoga Avenue, San Jose, CA, USA
Email: ashley4mo@gmail.com

Abstract—**Alzheimer's disease, a progressive and irreversible brain disorder predominantly affecting the elderly, is influenced by age, smoking, and head trauma. It disrupts memory, cognition, motor skills, speech, and more. Alzheimer's disease pathophysiology is caused by two main processes: the formation of misfolded amyloid-beta plaques and misfolded tau tangles. While tau is a naturally occurring, microtubule-associated protein, amyloid-beta peptides are cleaved fragments of the transmembrane amyloid precursor protein. Accumulation of these plaques and tangles result in various negative mechanisms. Regarding the relationship between the two proteins, evidence suggests that amyloid beta induces the conversion of tau from a normal to toxic state, but they ultimately work together to contribute to Alzheimer's disease pathogenesis. As of currently, there is still no cure for the disease, and patients rely on treatment methods that solely alleviate symptoms or benefit early stages to halt the disease's progression. The main medications for Alzheimer's disease are cholinesterase inhibitors such as Donepezil and Galantamine, but novel pharmacological and non-pharmacological treatments are being utilized as well, such as β-secretase inhibitors and deep brain stimulation respectively. This review investigates peer-reviewed publications on pathophysiology and treatment of Alzheimer's disease, with a focus on novel approaches for treatment and intervention.**

Keywords—**Alzheimer's disease, Tau, Amyloid-beta, treatment of Alzheimer's**

I. INTRODUCTION

Every 65 seconds, one person in the US contracts Alzheimer's Disease (AD) [1]. As one of the most prevalent irreversible neurodegenerative disorders, AD affects the brain's ability to think, remember, and coordinate the body's actions. Patients are unable to carry out tasks they were previously able to do as a result of cognitive decline and functional impairment [2].

AD is a major type of dementia, and there are two main categories of the disease: familial and sporadic [3]. Familial AD, or early-onset familial Alzheimer's disease (EOFAD), typically occurs in patients under sixty years of age, accounting for less than 1% of all AD cases [4]. Caused by inherited gene mutations in presenilin (PS1, PS2) and the Amyloid Precursor Protein (APP), EOFAD affects patients with a family history of AD [5]. Sporadic AD, on the other hand, is the most common type of AD and occurs spontaneously without a clear pattern of inheritance within families [6]. The risk for developing sporadic AD is influenced by a combination of factors including aging, genetic variations, and environmental risk factors such as head trauma, hypertension, smoking, psychological stress, or hypercholesterolemia [7]. EOFAD and Sporadic AD typically progress slowly over several years, with symptoms gradually worsening over time [6]. Regardless, patients with EOFAD decline at a faster rate compared to those with Sporadic AD [8].

Currently, AD dementia affects around 5.8 million Americans, or one out of eight seniors, but the impact of AD is not just limited to the United States [9]. Worldwide, over 40 million individuals are affected, and by 2050, rates are projected to quadruple, impacting approximately 106.8 million individuals across the globe [10].

Patients with AD experience a range of symptoms that can vary from subtle to severe. In early stages, the most common cognitive symptoms include memory problems, such as repeating questions or misplacing objects [11]. As the disease progresses into the stage of Mild Cognitive Impairment (MCI), patients may develop psychotic or behavioral symptoms such as hallucinations. For instance, they may have delusions that someone is stealing their belongings or constantly following them. Ultimately, in late stages, individuals might experience difficulty with communication and motor movements, sleeping, personality changes, poor judgment, worsening of memory, and loss of speech [12]. With mortality rates predicted to skyrocket in coming years due to population increase and aging, AD and its effects remain a growing concern in public health. Moreover, the COVID-19 pandemic has led to a shortage of dementia caregivers in the United States, creating a critical situation as the demand for AD dementia care is increasing with the rise in cases [9].

Although there is no definite cure for AD, effective diagnosis has become more possible with the use of physical exams, cognitive tests, and brain imaging techniques such as Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) scans [13]. Targeted medications, such as those used for treating inflammation or cholinergic deficiency, may offer short-term alleviation of symptoms. Despite the promising potential

of gene therapy and antioxidants, the field of AD treatment is still heavily researched [14].

II. METHODS

Publicly available databases such as PubMed, Scopus, and Web of Science were searched for peer-reviewed articles published in English from inception to 6th July 2023. Search terms were used including "Alzheimer's disease", "tau", and "amyloid". The title and abstract of published papers were screened for suitability. Relevant papers were selected, and after the full-text screening, data was extracted from final papers for inclusion in the review. Publicly available search engines such as Google and Google Scholar were searched with similar terms for additional resources. Figures were generated using Biorender.

III. DISCUSSION

AD is a type of proteinopathy, a neurodegenerative disease characterized by the buildup of misfolded proteins in the brain [15]. Protein misfolding in diseases such as AD and Parkinson's disease can occur when proteins undergo structural changes that disrupt their normal function, which occur due to genetic mutations, aging, and other environmental factors [16]. The two main features of AD pathogenesis are the accumulation of amyloid-beta (Aβ) plaques and the formation of neurofibrillary tangles made of misfolded tau protein [17] (Fig. 1). Aβ buildups develop outside the neuron within synaptic terminals, disrupting neuron communication and ultimately leading to cell death by apoptosis. Misfolded tau tangles, on the other hand, accumulate intracellularly in the microtubules within axons. In both cases, since neurons are unable to function properly, patients with AD will experience memory loss, which is a hallmark of the disease [18].
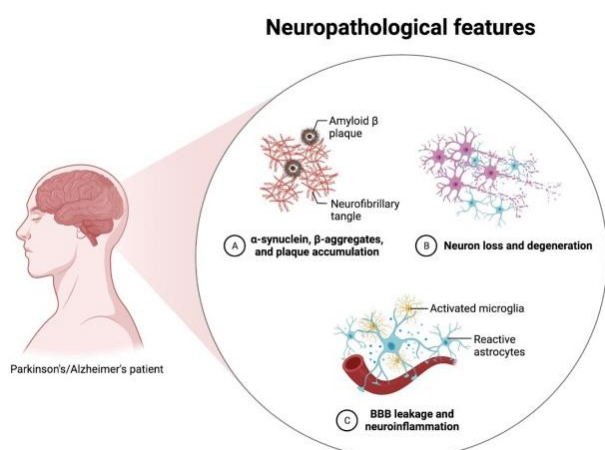

Fig. 1. Diagram of AD pathogenesis features. Neurological disorders including Alzheimer's Disease (AD) and Parkinson's disease are characterized by the accumulation of misfolded protein aggregates, such as Aβ plaques and tau tangles, which contribute to the degeneration of neurons and dysfunction of the Blood-Brain Barrier (BBB).

This review presents an interdisciplinary overview of current literature on the mechanisms of misfolded Aβ and tau proteins in AD. Furthermore, it discusses the specific processes of amyloid-beta and tau, and it outlines candidate treatments that may hinder the advancement of AD, providing a valuable perspective into the research on neurodegenerative diseases.

A. Mechanisms of Misfolded Aβ and Tau Protein

Aβ and tau proteins are naturally present in the human body; yet, their misfolded forms can result in neurodegenerative diseases like AD [19]. Accumulation of these misfolded proteins leads to oxidative stress in the brain, mainly through an increase in Reactive Oxygen Species (ROS) production, inflammation, and mitochondrial dysfunction [20]. These proteins typically build up in the areas of the brain responsible for memory and other cognitive functions, such as the cerebral cortex and hippocampus [21].

One of the most significant differences between the two proteins is their propagation patterns. Tau distribution in the brain is consistent in AD: beginning in layer II of the entorhinal cortex, the diffusion of tau is highly predictable and distributes hierarchically, propagating through the limbic and associative regions and eventually culminating in the hippocampus and neocortex. Known as "seeds of aggregation", tau can spread from the injection site to distant brain regions through prion-like seeding methods, enabling them to template the misfolding of normal, soluble tau. This process leads to the formation of endless new tau tangles, which can then spread to neighboring neurons in a self-propagating manner. The concept of tau spreading through prion-like mechanisms suggests that tau pathology in AD is similar to the spread of prions in diseases like Creutzfeldt-Jakob disease or mad cow disease [22].

On the other hand, Aβ plaques are initially found in the neocortex, but they can spread to the allocortex or subcortical regions of the brain and do not follow a consistent spreading pattern. It is hypothesized that abnormal Aβ proteins can spread from one neuron to another using synaptic connections or axonally interconnected brain regions [22].

Misfolded Aβ and tau can also trigger negative mechanisms in the brain [23]. Evidence has shown that soluble Aβ and tau collaborate to transform healthy neurons into their diseased states, regardless of their aggregation into plaques and tangles [22]. Primarily, neuroinflammation is a large component of AD pathogenesis. The presence of Aβ plaques and tau tangles triggers an inflammatory response in the brain which activates microglia and astrocytes, as well as the release of pro-inflammatory molecules, including cytokines such as interleukin-1 beta and interleukin-6, chemokines, and ROS. While these glial cells initially attempt to clear away the abnormal protein deposits, chronic activation of these cells can lead to excessive inflammation and damage neurons [23]. Secondly, AD protein misfolding disrupts cellular homeostasis and typical cellular processes, such as calcium regulation [24]. Calcium present in the blood or Extracellular Fluid (ECF), along with intracellular calcium found in mitochondria, plays a crucial role in enabling neurons to carry out their

functions effectively [25]. However, in AD, the presence of misfolded Aβ or tau can bind to calcium channels and mitochondrial structures, resulting in the disruption of their normal functions. Amyloid-beta has been shown to alter the activity of certain calcium channels on the cell membrane, influencing the influx and efflux of calcium ions in and out of neurons [26]. This dysregulation can lead to abnormal calcium concentrations inside the neurons, which can be toxic and harmful to neuronal function [25]. The detachment of tau from structures in the axon called microtubules also hinders the transport of substances along the axon, including calcium ions, and this transport impairment affects proper calcium signaling and overall calcium regulation [26].

Ultimately, patients with Alzheimer's disease often experience brain shrinkage due to loss of neuron function, which is caused by the misfolded Aβ and tau. This is exacerbated by the blockage of Cerebrospinal Fluid (CSF) movement, which can lead to ventricular enlargement and tissue loss, as shown in the top monochrome brain diagrams in Fig. 2 [3].
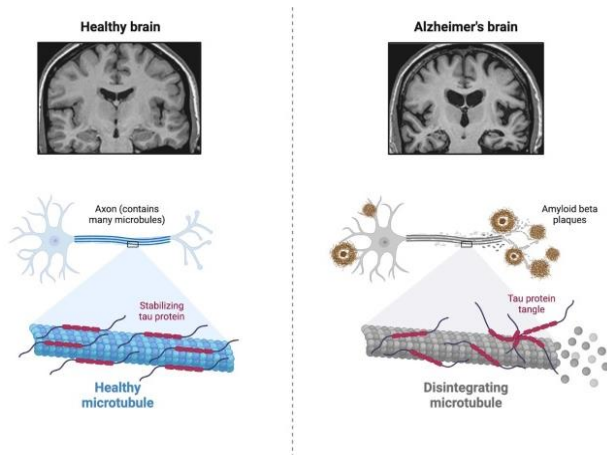
Fig. 2. Diagram of a healthy brain compared to an Alzheimer's brain. In healthy brains (left), neurons have open dendrite receptors and functioning. However, in Alzheimer's brains (right), loss of neurons leads to excess space and abnormal enlargement of brain cavities. The dendrites and synaptic terminals are obstructed by Aβ plaques, while neurofibrillary tau tangles in microtubules cause the axons to lose their original form and break apart.

B. Role of Misfolded Aβ

Aβ is developed from the Amyloid Precursor Protein (APP), a large transmembrane protein found in neuronal synapses and blood vessels [27]. Commonly expressed in neurons, Aβ regulates many brain functions including axonal guidance, neuroprotection, and synaptic functions [22]. Normally, during Aβ production, APP is cleaved by enzyme α-secretase to produce the APPsα and C83 proteins. From the latter arises two new proteins cut by the γ-secretase enzyme, namely P3 and the amyloid precursor protein intracellular domain (AICD) [28]. However, in amyloidogenic pathways, APP switches instructions, first using β-secretase to cut APP into Appsβ and C99. Then, γ-secretase once again cleaves C99 into AICD and the infamous Aβ protein (Fig. 3). Because C99 undergoes abnormal cleavage to form the Aβ protein, the result is the formation of different-lengthed Aβ peptides,

including Aβ42 and residues 38–41. These Aβ peptides are more prone to aggregation in the synapse and lead to the formation of Aβ plaques, which is considered a key factor in AD pathogenesis [29].
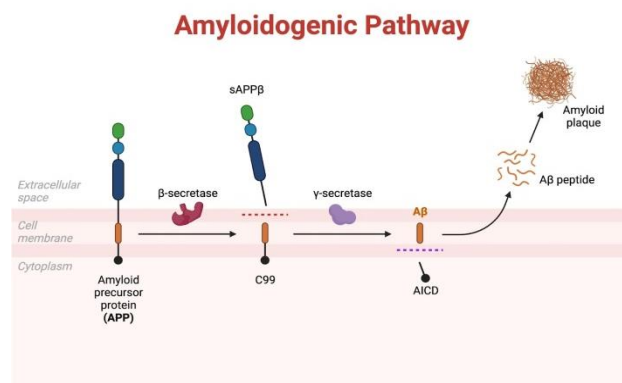
Fig. 3. Diagram of the multi-step process of Aβ creation, which occurs in the amyloidogenic pathway and requires the presence of enzymes β-secretase and γ-secretase.

However, the toxicity of Aβ is contingent on how it aggregates, as the formation of amyloid fibrils is necessary for its neurotoxicity; thus, Aβ aggregates that are amorphous do not have neurotoxic effects [30]. Monomeric Aβ can aggregate into many forms, including oligomers, protofibrils, and insoluble amyloid fibrils that accumulate to form toxic amyloid plaques. Because soluble monomeric and oligomeric Aβ coexist in AD brains, it is challenging to discern the toxic forms that contribute to the pathogenesis of AD [22].

Aβ plaques also affect synaptic plasticity and the communication of neurons. AD synaptic plasticity occurs when the space between neurons expands, leading to the weakening of certain synaptic linkages, impaired learning formation, and disrupted neuronal network connectivity. As these neurotoxic Aβ plaques accumulate in synaptic terminals, the blockage leads to synaptic loss and dysfunction [31] (Fig. 2). Neurons are unable to transmit electrochemical signals and neurotransmitters throughout the body, leading to cognitive deficits and neurodegeneration [32]. In relation to tau, Aβ oligomers have been found to induce the abnormal phosphorylation and formation of tau tangles in AD pathogenesis, but the precise nature of the two proteins' relationship is not fully understood [22].

Not only do Aβ plaques lead to synaptic dysfunction, they also result in neuron degeneration, which is achieved by triggering signals that initiate apoptotic pathways in the mitochondria and Endoplasmic Reticulum (ER) [28]. Over time, as Aβ builds up within the mitochondrial matrix, the level of mitochondrial toxicity rises [33]. Aβ causes a decrease in calcium levels in the ER, leading to an increased concentration of calcium in the cytosol, the fluid-like substance in the interior of a neuron. This increase in cytosolic calcium and mitochondrial toxicity disrupts the chemical potential of the mitochondrial membrane, leading to the activation of mitochondrial apoptotic events [28].

Despite the progress made in AD research, many questions still remain, particularly regarding the β-

secretase enzyme responsible for initiating the production of Aβ. Researchers are working to identify how β-secretase is activated, and targeting this enzyme is a promising field in Alzheimer's drug development [34]. Single nucleotide polymorphisms in APP or β-secretase, as well as an increase of oxidative stress or inflammation in the brain, are known factors that lead to the overproduction of Aβ [35]. However, recent studies also speculate that activation of viruses, such as the current SARS-CoV-2, may also trigger β-secretase [36].

C. Tau Pathology

Tau is a naturally occurring, brain-specific protein that is typically found in the axons of neurons [37]. In humans, tau is encoded by the MAPT gene, which is situated on chromosome 17 [38]. Tau's main role is to stabilize Microtubules (MTs), structures that make up the nerve cell cytoskeleton and are crucial to neuron stability and transportation [39] (Fig. 2). Additionally, tau enables proper communication and transport of electrochemical signals between nerve cells, acting as the backbone for sensory processing, motor control, and other cognitive functions [40]. From its soluble physiological state to its pathological aggregated formation, tau has several conformational states [38].

In order to maintain its function, normal tau undergoes a regulated process called phosphorylation, which is the addition of phosphate groups to specific amino acids of the protein through the kinase enzyme. However, in AD, tau becomes abnormally hyperphosphorylated and misfolded during excessive phosphorylation, causing it to detach from microtubules, aggregate, and lose its normal function [41]. Because misfolded tau has higher affinity and is more attracted to one another than to the MTs, they will combine to form Neurofibrillary Tangles (NFTs), or twisted fibers inside the neuron [42]. Dysfunctional enzymes that regulate tau phosphorylation, such as kinases and phosphatases, are the main causes for the production of misfolded tau [43]. As a result, the buildup of NFTs leads to disintegration of microtubules, disrupting the typical architecture of neurons and affecting their ability to transmit signals effectively [44] (Fig. 2).

Tau, like Aβ, also impacts synaptic plasticity: NFT accumulation leads to microtubule retraction [45]. Tau is implicated in the regulation of Long-Term Potentiation (LTP), a form of synaptic plasticity associated with long-lasting strengthening of synaptic connections between neurons, particularly in the context of repeated and persistent stimulation [46]. To prove this point, a 2013 study on JNPL3 (BL6) transgenic mice expressing mutant, hyperphosphorylated tau showed that impaired GABAergic function caused by pathological tau led to altered LTP synaptic plasticity and severe memory deficits [47]. During LTP, the strengthening of synaptic connections is often associated with an increase in the number and size of dendritic spines, which are small protrusions on dendrites that receive synaptic inputs. Tau has been found to influence dendritic spine morphology, and misfolded tau can lead to abnormal spine structure. Disrupted spine morphology can compromise the efficacy

of synaptic transmission and impair the ability of synapses to undergo plastic changes during LTP [48].

Moreover, misfolded tau plays a role in glutamate recycling [49]. Excitatory signals, including glutamate, acetylcholine, and dopamine, promote neuronal activation and firing. Contrastingly, inhibitory signals, such as GABA, regulate and moderate neuronal activity. This balance is crucial for proper information processing and coordination between different brain regions [50]. Glutamate is the primary excitatory neurotransmitter in the central nervous system, responsible for regulating memory and learning. To maintain the proper balance of glutamate levels in the synapse, glutamate undergoes glutamate recycling, where the neurotransmitter is taken from the synaptic cleft back into the presynaptic neuron, so that it can be repackaged into synaptic vesicles for subsequent release. However, in AD, misfolded, hyperphosphorylated tau affects proteasome, the organelle responsible for degrading proteins, and disrupts glutamate recycling. The exact mechanism of misfolded tau in this process is still unclear, but it is known that the alteration results in excitotoxicity and neuronal degeneration [51].

D. Novel AD Treatments

Currently, only a few drugs are FDA approved for AD treatment: acetylcholinesterase inhibitors Donepezil (Aricept), Galantamine (Rimanyl/Razadyne), Tacrine (Cognex), and Rivastigimine (Exelon), and N-methyl-D-Aspartate Receptor (NMDAR) antagonist Memantine (Namenda) [52]. However, the main issue when taking such medications is the possibility of side effects like diarrhea and nausea, which can be a large disincentive for elderly patients. The four acetylcholinesterase inhibitors are medications based on the cholinergic hypothesis, which presumes that a deficiency in the neurotransmitter Acetylcholine (ACh), which is crucial for memory and cognition, contributes to the progression of AD [53]. Memantine, on the other hand, functions by blocking the neurotransmitter glutamate, as excess amounts can lead to overactivation of NMDA receptors and nerve cell damage [54].

Moreover, in July of 2023, the FDA granted traditional approval of the new AD drug Leqembi (lecanemab-irmb) [55]. Leqembi is an advanced Immunoglobulin gamma 1 (IgG1) monoclonal antibody that targets both soluble and insoluble misfolded Aβ agglomerations, clearing the harmful protein from the brain and slowing down disease progression. Though clinical trials were successful, how the drug will perform in the long run is still unknown [56].

On a more general scale, AD treatment depends on the severity of the diagnosis. AD patients follow the global deterioration scale, which categorizes the 7 stages of dementia, as the terms "AD" and "dementia" are often used interchangeably. As levels of AD deteriorate, more advanced medication is used to target areas of treatment [57].

Thus, researchers are constantly working to discover more treatment methods, such as using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) or CRISPR-associated protein 9 (cas 9) gene

editing techniques. By editing specific genes, researchers hope to correct or mitigate the effects of genetic mutations that make certain people more prone to contracting AD; for example, if a gene mutation is responsible for an individual's increased probability of tau tangles, CRISPR could potentially be used to alter the single nucleotide polymorphism and reduce the production of misfolded tau [58]. Due to CRISPR's success in treating disorders and diseases such as sickle cell anemia, hemophilia, and malaria, and its various technological applications in our modern world, it remains one of the most promising and probable future cures for AD [59].

As for pharmacological interventions, researchers have discovered that targeting the relationship between the Lipoprotein Receptor-Related Protein-1 (LRP1) and Receptor for Advanced Glycation End products (RAGE) could lead to a probable cure for AD. A 2021 study investigated the effects of lycopene on LRP1 and RAGE in the Choroid Plexus (CP) of male Wistar rats with AD, and the results showed that lycopene administration reduced Aβ accumulation by increasing LRP1 levels and decreasing RAGE levels in the Cerebrospinal Fluid (CSF) and the CP. Lycopene, which pinpoints the levels of activation of LRP1 and RAGE, may be one of several future therapeutic approaches to improve Aβ clearance and prevent neuroinflammation [60]. Table I provides a summary of other novel pharmacological interventions for the treatment of AD.

TABLE I. SUMMARY OF NOVEL PHARMACOLOGICAL AD INTERVENTIONS

Category	Class of drugs	Compounds	Mechanism	Subjects	Summary	[Ref]
Anti-amyloid therapy	Secretase inhibitor	Verubecestat	BACE1 inhibitor	Prodromal to moderate AD	Lack of efficacy	[61, 62]
	Aβ aggregation inhibitor	PBT1	MPAC	MCI to moderate AD	Rescue of cognitive decline in severely affected patients (ADAS-cog ≥ 25), visual impairment	[63]
	Aβ immunotherapy	ACI-24	Aβ vaccine	Adults with Down syndrome	Lack of immunogenicity	[64]
Anti-tau therapy	Phosphatase modifier	Selenate	PP2A activator	Mild to moderate AD	Lack of efficacy	[65, 66]
	Kinase inhibitor	Roscovitine	CDK5 inhibitor	5XFAD mice	Prevention of tau phosphorylation	[67, 68]
	Tau aggregation inhibitor	MB	Disrupts polymerization	Mild to moderate AD	Cognitive improvement	[69]
	Microtubule stabilizer	EpoD	Enhances microtubule bundling	Mild AD	Discontinuation, frequent adverse effects without published data	[70]
	Tau immunotherapy	AADvac1	Tau vaccine	Mild AD	Completed, no published data	[71]
Anti-neuroinflammatory therapy	Microglia modulator	Thymoquinone	TLR4 inhibitor	AD mice induced by AlCl3	Rescue of cognitive impairment	[72]
	Astrocyte modulator	Stattic	STAT3 inhibitor	5XFAD mice	Rescue of learning and memory impairment	[73, 74]
	Insulin resistance management	Intranasal insulin therapy	Intranasal supplement	MCI to moderate AD	Cognitive improvement, modulation by APOE4 genotype	[75, 76]
	Microbiome therapy	Sodium oligomannate	Dysbiosis of gut microbiota	Mild to moderate AD	Cognitive improvement	[77, 78]
Neuroprotective agents	Antiepileptic drug	Levetiracetam	SV2A receptor	MCI	Ongoing	[79]
	NMDAR modification	Sodium benzoate	DAAO inhibitor	MCI	Cognitive and functional improvement	[80]
	Omega 3 polyunsaturated fatty acid supplements	DHA	Anti-oxidative effect	Mild to moderate AD	Lack of efficacy	[81]

Aβ, amyloid-beta; AD, Alzheimer's Disease; ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; APOE4, apolipoprotein E type 4; BACE1, β-secretase1; CDK5, Cyclin-dependent kinase 5; DAAO, D-amino acid oxidase; DHA, docosahexaenoic acid; EpoD, Epothilone D; FAD, Familiar Alzheimer's Disease; MB, methylene blue; MCI, Mild Cognitive Impairment; MPAC, metal protein attenuating compound; NMDAR, N-methyl-D-aspartate receptor; PBT1, clioquinol; PP2A, Protein phosphatase 2A; STAT3, Signal transducers and activators of transcription 3; SV2A, Synaptic Vesicle glycoprotein 2A; TLR4, Toll-like receptor 4.

In addition, non-pharmacological interventions have also become prominent in the last decade, such as different types of brain and nerve stimulation (Table II) [82]. These interventions specifically target different regions of the brain and involve diverse techniques, such as Deep Brain Stimulation (DBS), Vagus Nerve Stimulation (VNS), Transcranial Magnetic Stimulation (TMS), and Transcranial Electrical Stimulation (TES). Some of these intervention techniques are invasive, such as DBS, but others, like TMS, are non-invasive [52].

Though pharmacological and non-pharmacological interventions are crucial for treatment, active management of AD does not only consist of taking the proper medication to help with symptoms: it also encompasses treating coexisting conditions, creating a support group, and providing family caregivers with training to better manage the daily life of the care recipient [90]. With these novel treatments for AD, patient outcomes are expected to improve, slowing the progression of cognitive decline and potentially delaying the need for full-time care [91].

TABLE II. SUMMARY OF NOVEL NON-PHARMACOLOGICAL AD INTERVENTIONS

Category	Methods	Targeted Region	Protocol	Subjects	Summary	[Ref]
Deep brain stimulation	DBS	Fornix	Forneceal DBS	Mild AD	Slight cognitive benefit in the elderly	[83, 84]
Vagus nerve stimulation	VNS	Tenth cranial nerve	Invasive VNS	Probable AD	Cognitive stabilization and improvement, response rate 70%	[85, 86]
Transcranial magnetic stimulation	High-frequency rTMS	Left DLPFC	10 Hz/120% MT/3000 pulses per session/10 sessions/2 weeks	MCI	Executive functional improvement	[87]
Transcranial electrical stimulation	Transcranial direct current stimulation	Left DLPFC	2 mA/30 min per session/single session, Mild to moderate AD	Mild to Moderate AD	Improved recognition and memory	[88]
	Transcranial alternating current stimulation	Left DLPFC	40 Hz/1.5 mA/30 min per session/40 sessions/4 weeks	MCI to moderate AD	Improved cognitive performance	[89]

AD, Alzheimer's Disease; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

IV. CONCLUSION

AD pathophysiology is a complex process involving various cellular mechanisms. The hallmark features of AD, the accumulation of amyloid beta plaques and tau NFTs, contribute to the progressive degeneration of neurons and cognitive decline observed in affected individuals. Neuroinflammation, synaptic dysfunction, and impaired clearance mechanisms further exacerbate the disease's progression. Despite AD pathogenesis being multifactorial, targeting different aspects of its pathophysiology and areas of the brain through both pharmacological and non-pharmacological interventions can lead to effective treatment measures. Early diagnosis and intervention are crucial in optimizing treatment effectiveness, and novel medications, such as Leqembi and Lycopene, as well as gene editing technology like CRISPR offer hope for future breakthroughs. Despite the many advancements in the medical field over the past few decades, more research is required to understand the exact mechanisms of AD pathogenesis. Moreover, because the number of patients is increasing globally as the population is expanding and the lifespan increases, we are still in need of long-term resources to address the severe issue of AD. By better understanding the disease's underlying etiology, researchers can develop more effective therapies to prevent and slow AD progression, and ultimately pave the way towards a future where AD is no longer an insurmountable challenge.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

[1] N. Julia. (2023). Dementia & Alzheimer's disease statistics and facts (2023 update), CFAH. [Online]. Available: https://cfah.org/alzheimers-dementia-statistics/#:~:text=82%2C965%20people%20die%20from%20Alzheimer%E2%80%99s%20and%20its%20complications,to%20%24321%20billion%20by%20the%20end%20of%202022

[2] X.-L. Li, *et al.*, "Behavioral and psychological symptoms in Alzheimer's disease," *BioMed Research International*, pp. 1–9, 2014. https://doi.org/10.1155/2014/927804

[3] S. Lista, *et al.*, "Biomarkers in sporadic and familial Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 47, no. 2, pp. 291–317, 2015. https://doi.org/10.3233/jad-143006

[4] L. Wu, *et al.* (2014). *Early-onset familial Alzheimer's disease (EOFAD): Canadian Journal of Neurological Sciences, Cambridge Core*. Cambridge University Press. [Online]. Available: https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/earlyonset-familial-alzheimers-disease-eofad/AB96537F3AB11B3790F957D833CC9C04

[5] D. L. Price and S. S. Sisodia. (1998). Mutant genes in familial Alzheimer's disease and ... – Annual reviews. [Online]. Available: https://www.annualreviews.org/doi/abs/10.1146/annurev.neuro.21.1.479

[6] J. Dorszewska, *et al.*, "Molecular basis of familial and sporadic Alzheimer's disease," *Current Alzheimer Research*, vol. 13, no. 9, pp. 952–963, 2016. https://doi.org/10.2174/1567205013666160314150501

[7] Z. Stozická, N. Zilka, and M. Novák. (2007). Risk and protective factors for sporadic Alzheimer's disease. Europe PMC. [Online]. Available: https://europepmc.org/article/med/18197729

[8] P. K. Panegyres and H.-Y. Chen. (2013). Differences between early and late onset Alzheimer's disease. American Journal of Neurodegenerative Disease. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3852569/

[9] W. Thies and L. Bleiler. (2023). 2023 Alzheimer's disease facts and figures – Alzheimer's & dementia ... Alzheimer's Association. [Online]. Available: https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13016

[10] R. Brookmeyer, *et al.*, "Forecasting the global burden of Alzheimer's disease," *Alzheimer's & Dementia*, vol. 3, no. 3, pp. 186–191, 2007. https://doi.org/10.1016/j.jalz.2007.04.381

[11] O. L. López and S. T. DeKosky, "Clinical symptoms in Alzheimer's disease," *Dementias*, pp. 207–216, 2008. https://doi.org/10.1016/s0072-9752(07)01219-5

[12] E. Joe and J. M. Ringman, "Cognitive symptoms of Alzheimer's disease: Clinical management and prevention," *The BMJ*, 2019. https://doi.org/10.1136/bmj.l6217

[13] M. A. DeTure and D. W. Dickson, "The neuropathological diagnosis of Alzheimer's disease," *Molecular Neurodegeneration*, vol. 14, no. 1, 2019. https://doi.org/10.1186/s13024-019-0333-5

[14] R. S. Shah, *et al.*, "Current approaches in the treatment of Alzheimer's disease," *Biomedicine & Pharmacotherapy*, vol. 62, no. 4, pp. 199–207, 2008. Available: https://doi.org/10.1016/j.biopha.2008.02.005

[15] T. A. Bayer. (2015). Proteinopathies, a core concept for understanding and ultimately treating degenerative disorders? European neuropsychopharmacology: The journal of the European College of Neuropsychopharmacology. U.S. National Library of Medicine. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/23642796/

[16] C. M. Dobson. (2003). Protein folding and misfolding, Nature. U.S. National Library of Medicine. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/14685248/

[17] R. H. Takahashi, *et al.*, "Co-occurrence of Alzheimer's disease β-amyloid and tau pathologies at synapses," *Neurobiology of Aging*, vol. 31, no. 7, pp. 1145–1152, 2010. https://doi.org/10.1016/j.neurobiolaging.2008.07.021

[18] A. S. DeToma, *et al.* (2011). Misfolded proteins in Alzheimer's disease and type II diabetes, Chemical Society Reviews. The Royal Society of Chemistry. [Online]. Available: https://pubs.rsc.org/en/content/articlelanding/2012/cs/c1cs15112f/unauth

[19] A. L. Brand, *et al.*, "The performance of plasma amyloid beta measurements in identifying amyloid plaques in Alzheimer's disease: A literature review," *Alzheimer's Research & Therapy*, vol. 14, no. 1, 2022. https://doi.org/10.1186/s13195-022-01117-1

[20] S. Sharma, *et al.*, "Molecular interactions of resveratrol with AB 42 peptide and fibril during in-vitro AB 42 aggregation," *Advances in Redox Research*, vol. 7, 100060, 2023. https://doi.org/10.1016/j.arres.2023.100060

[21] H. Jahn, "Memory loss in Alzheimer's disease," *Dialogues in Clinical Neuroscience*, vol. 15, no. 4, pp. 445–454, 2013. doi:10.31887/dcns.2013.15.4/hjahn

[22] P. d'Errico and M. Meyer-Luehmann, "Mechanisms of pathogenic tau and AB protein spreading in Alzheimer's disease," *Frontiers in Aging Neuroscience*, vol. 12, 2020. doi:10.3389/fnagi.2020.00265

[23] S. Sharma, *et al.*, "Targeting neuroinflammation as disease modifying approach to Alzheimer's disease: Potential and challenges," *Mini-Reviews in Medicinal Chemistry*, vol. 23, 2023. doi:10.2174/1389557523666230511122435

[24] M. P. Mattson and S. L. Chan, "Dysregulation of cellular calcium homeostasis in Alzheimer's disease: Bad genes and bad habits," *Journal of Molecular Neuroscience*, vol. 17, no. 2, pp. 205–224, 2001. doi:10.1385/jmn:17:2:205

[25] S. Camandola and M. P. Mattson, "Aberrant subcellular neuronal calcium regulation in aging and Alzheimer's disease," *Biochimica et Biophysica Acta (BBA) – Molecular Cell Research*, vol. 1813, no. 5, pp. 965–973, 2011. doi:10.1016/j.bbamcr.2010.10.005

[26] L. Canevari, A. Y. Abramov, and M. R. Duchen, "Toxicity of amyloid β peptide: Tales of calcium, mitochondria, and oxidative stress," *Neurochemical Research*, vol. 29, no. 3, pp. 637–650, 2004. doi:10.1023/b:nere.0000014834.06405.af

[27] R. J. O'Brien and P. C. Wong. (2011). Amyloid precursor protein processing and Alzheimer's disease, Annual Reviews. [Online]. Available: https://www.annualreviews.org/doi/abs/10.1146/annurev-neuro-061010-113613

[28] L. Zuo, *et al.*, "The role of oxidative stress-induced epigenetic alterations in amyloid-β production in Alzheimer's disease," *Oxidative Medicine and Cellular Longevity*, pp. 1–13, 2015. https://doi.org/10.1155/2015/604658

[29] G. Chen, *et al.*, "Amyloid beta: Structure, biology and structure-based therapeutic development," *Acta Pharmacologica Sinica*, vol. 38, no. 9, pp. 1205–1235, 2017. https://doi.org/10.1038/aps.2017.28

[30] B. A. Yankner. (1996). Mechanisms of neuronal degeneration in Alzheimer's disease, Neuron. U.S. National Library of Medicine. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/8630250/

[31] E. A. Stern, *et al.*, "Cortical synaptic integration in vivo is disrupted by amyloid-β plaques," *The Journal of Neuroscience*, vol. 24, no. 19, pp. 4535–4540, 2004. doi:10.1523/jneurosci.0462-04.2004

[32] T. C. Südhof, "The cell biology of synapse formation," *Journal of Cell Biology*, vol. 220, no. 7, 2021. https://doi.org/10.1083/jcb.202103052

[33] J. N. Meyer, J. H. Hartman, and D. F. Mello, "Mitochondrial toxicity," *Toxicological Sciences*, vol. 162, no. 1, pp. 15–23, 2018. doi:10.1093/toxsci/kfy008

[34] R. Vassar, *et al.*, "The β-secretase enzyme BACE in health and Alzheimer's disease: Regulation, cell biology, function, and therapeutic potential," *The Journal of Neuroscience*, vol. 29, no. 41, pp. 12787–12794, 2009. https://doi.org/10.1523/jneurosci.3657-09.2009

[35] E. Lee, *et al.*, "Single-nucleotide polymorphisms are associated with cognitive decline at Alzheimer's disease conversion within mild cognitive impairment patients," *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, vol. 8, no. 1, pp. 86–95, 2017. https://doi.org/10.1016/j.dadm.2017.04.004

[36] G. Abate, M. Memo, and D. Uberti, "Impact of COVID-19 on Alzheimer's disease risk: Viewpoint for research action," *Healthcare*, vol. 8, no. 3, 286, 2020. https://doi.org/10.3390/healthcare8030286

[37] N. N. Naseri, *et al.*, "The complexity of tau in Alzheimer's disease," *Neuroscience Letters*, vol. 705, pp. 183–194, 2019. https://doi.org/10.1016/j.neulet.2019.04.022

[38] C. A. Brunello, *et al.*, "Mechanisms of secretion and spreading of pathological tau protein," *Cellular and Molecular Life Sciences*, vol. 77, no. 9, pp. 1721–1744, 2019. doi:10.1007/s00018-019-03349-1

[39] L. C. Kapitein and C. C. Hoogenraad, "Building the neuronal microtubule cytoskeleton," *Neuron*, vol. 87, no. 3, pp. 492–506, 2015. https://doi.org/10.1016/j.neuron.2015.05.046

[40] M. V. Aanandhi, *et al.* (2018). A comprehensive review on the role of tau proteins in Alzheimer's pathology. Research Journal of Pharmacy and Technology. A & V Publications. [Online]. Available: https://www.indianjournals.com/ijor.aspx?target=ijor%3Arjpt&volume=11&issue=2&article=071

[41] G. Lee, *et al.* (2004). Phosphorylation of tau by FYN: Implications for Alzheimer's disease. Journal of Neuroscience. Society for Neuroscience. [Online]. Available: https://www.jneurosci.org/content/24/9/2304.short

[42] J. Avila, "Tau phosphorylation and aggregation in Alzheimer's disease pathology," *FEBS Letters*, vol. 580, no. 12, pp. 2922–2927, 2006. https://doi.org/10.1016/j.febslet.2006.02.067

[43] D. B. Parekh, W. Ziegler, and P. J. Parker, "Multiple pathways control protein kinase C phosphorylation," *The EMBO Journal*, vol. 19, no. 4, pp. 496–503, 2000. https://doi.org/10.1093/emboj/19.4.496

[44] E. Köpke, *et al.*, "Microtubule-associated protein tau. abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease," *Journal of Biological Chemistry*, vol. 268, no. 32, pp. 24374–24384, 1993. doi:10.1016/s0021-9258(20)80536-5

[45] M. J. Rowan, *et al.*, "Synaptic plasticity in animal models of early Alzheimer's disease," *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, vol. 358, no. 1432, pp. 821–828, 2003. doi:10.1098/rstb.2002.1240

[46] O. A. Shipton, *et al.*, "Tau protein is required for amyloid β-induced impairment of hippocampal long-term potentiation," *The Journal of Neuroscience*, vol. 31, no. 5, pp. 1688–1692, 2011. doi:10.1523/jneurosci.2610-10.2011

[47] J. Levenga, *et al.*, "Tau pathology induces loss of GABAergic interneurons leading to altered synaptic plasticity and behavioral impairments," *Acta Neuropathologica Communications*, vol. 1, no. 1, 2013. doi:10.1186/2051-5960-1-34

[48] P. Merino-Serrais, *et al.*, "The influence of phospho-tau on dendritic spines of cortical pyramidal neurons in patients with Alzheimer's disease," *Brain*, vol. 136, no. 6, pp. 1913–1928, 2013. doi:10.1093/brain/awt088

[49] N. J. Allen, *et al.*, "Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GLUA1 AMPA receptors," *Nature*, vol. 486, no. 7403, pp. 410–414, 2012. doi:10.1038/nature11059

[50] R. Kandimalla and P. H. Reddy, "Therapeutics of neurotransmitters in Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 57, no. 4, pp. 1049–1069, 2017. doi:10.3233/jad-161118

[51] A. Armada-Moreira, *et al.*, "Going the extra (synaptic) mile: Excitotoxicity as the road toward neurodegenerative diseases," *Frontiers in Cellular Neuroscience*, vol. 14, 2020. doi:10.3389/fncel.2020.00090

[52] T.-W. Yu, H.-Y. Lane, and C.-H. Lin, "Novel therapeutic approaches for Alzheimer's disease: An updated review," *International Journal of Molecular Sciences*, vol. 22, no. 15, 8208, 2021. doi:10.3390/ijms22158208

[53] K. Sharma, "Cholinesterase inhibitors as Alzheimer's therapeutics (review)," *Molecular Medicine Reports*, preprint, 2019. doi:10.3892/mmr.2019.10374

[54] T. Kishi, *et al.*, "Memantine for Alzheimer's disease: An updated systematic review and meta-analysis," *Journal of Alzheimer's Disease*, vol. 60, no. 2, pp. 401–425, 2017. doi:10.3233/jad-170424

[55] Z. Chen and Z. Liu, "Alzheimer's drug Leqembi expected to be approved by the US FDA," *International Academician Association Communication*, vol. 1, no. 2, 2023.

[56] V. A. Canady, "FDA approves new treatment for Alzheimer's disease," *Mental Health Weekly*, vol. 33, no. 3, pp. 6–7, 2023. doi:10.1002/mhw.33505

[57] J. Wesson and J. Luchins, "An empirical evaluation of the global deterioration scale for staging Alzheimer's disease," *Am. J. Psychiatry*, vol. 149, pp. 190–194, 1992.

[58] T. Rohn, *et al.*, "The potential of CRISPR/Cas9 gene editing as a treatment strategy for Alzheimer's disease," *Journal of Alzheimer's Disease & Parkinsonism*, vol. 8, no. 3, 2018. doi:10.4172/2161-0460.1000439

[59] S. Bhardwaj, *et al.*, "CRISPR/Cas9 gene editing: New hope for Alzheimer's disease therapeutics," *Journal of Advanced Research*, vol. 40, pp. 207–221, 2022. doi:10.1016/j.jare.2021.07.001

[60] R. Wang, *et al.*, "Lycopene can modulate the LRP1 and rage transporters expression at the choroid plexus in Alzheimer's disease rat," *Journal of Functional Foods*, vol. 85, 104644, 2021. doi:10.1016/j.jff.2021.104644

[61] M. F. Egan, *et al.*, "Randomized trial of Verubecestat for mild-to-moderate Alzheimer's disease," *New England Journal of Medicine*, vol. 378, no. 18, pp. 1691–1703, 2018. doi:10.1056/nejmoa1706441

[62] M. F. Egan, *et al.*, "Randomized trial of Verubecestat for prodromal Alzheimer's disease," *New England Journal of Medicine*, vol. 380, no. 15, pp. 1408–1420, 2019. doi:10.1056/nejmoa1812840

[63] C. W. Ritchie, *et al.*, "Metal-protein attenuation with Iodochlorhydroxyquin (clioquinol) targeting AB amyloid deposition and toxicity in Alzheimer disease," *Archives of Neurology*, vol. 60, no. 12, 1685, 2003. doi:10.1001/archneur.60.12.1685

[64] F. Mantile and A. Prisco, "Vaccination against β-amyloid as a strategy for the prevention of Alzheimer's disease," *Biology*, vol. 9, no. 12, 425, 2020. doi:10.3390/biology9120425

[65] C. B. Malpas, *et al.*, "A phase IIA randomized control trial of vel015 (sodium selenate) in mild-moderate Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 54, no. 1, pp. 223–232, 2016. doi:10.3233/jad-160544

[66] B. R. Cardoso, *et al.*, "Supranutritional sodium selenate supplementation delivers selenium to the central nervous system: Results from a randomized controlled pilot trial in Alzheimer's disease," *Neurotherapeutics*, vol. 16, no. 1, pp. 192–202, 2018. doi:10.1007/s13311-018-0662-z

[67] H. S. Khalil, *et al.*, "Discovery and development of Seliciclib. How systems biology approaches can lead to better drug performance," *Journal of Biotechnology*, vol. 202, pp. 40–49, 2015. doi:10.1016/j.jbiotec.2015.02.032

[68] G. M. Leggio, *et al.*, "The antineoplastic drug flavopiridol reverses memory impairment induced by amyloid-ß 1-42 oligomers in mice," *Pharmacological Research*, vol. 106, pp. 10–20, 2016. doi:10.1016/j.phrs.2016.02.007

[69] C. M. Wischik, *et al.*, "Tau aggregation inhibitor therapy: An exploratory phase 2 study in mild or moderate Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 44, no. 2, pp. 705–720, 2015. doi:10.3233/jad-142874

[70] Study to evaluate the safety, tolerability and the effect of BMS-241027 on cerebrospinal fluid biomarkers in subjects with mild Alzheimer's disease (2014) CTG Labs – NCBI. [Online]. Available: https://clinicaltrials.gov/study/NCT01492374

[71] 24 months safety and efficacy study of AADvac1 in patients with mild Alzheimer's disease (ADAMANT) (2019) CTG Labs – NCBI. [Online]. Available: https://clinicaltrials.gov/study/NCT02579252

[72] Y. Zhou, *et al.*, "TLR4 targeting as a promising therapeutic strategy for Alzheimer disease treatment," *Frontiers in Neuroscience*, vol. 14, 2020. doi:10.3389/fnins.2020.602508

[73] M. Choi, *et al.*, "Inhibition of STAT3 phosphorylation attenuates impairments in learning and memory in 5xfad mice, an animal model of Alzheimer's disease," *Journal of Pharmacological Sciences*, vol. 143, no. 4, pp. 290–299, 2020. doi:10.1016/j.jphs.2020.05.009

[74] P. Millot, *et al.*, "STAT3 inhibition protects against neuroinflammation and BACE1 upregulation induced by systemic inflammation," *Immunology Letters*, vol. 228, pp. 129–134, 2020. doi:10.1016/j.imlet.2020.10.004

[75] S. Craft, *et al.*, "Effects of regular and long-acting insulin on cognition and Alzheimer's disease biomarkers: A pilot clinical trial," *Journal of Alzheimer's Disease*, vol. 57, no. 4, pp. 1325–1334, 2017. doi:10.3233/jad-161256

[76] K. I. Avgerinos, *et al.*, "Intranasal insulin in Alzheimer's dementia or mild cognitive impairment: A systematic review," *Journal of Neurology*, vol. 265, no. 7, pp. 1497–1510, 2018. doi:10.1007/s00415-018-8768-0

[77] T. Wang, *et al.*, "A phase II randomized trial of sodium oligomannate in Alzheimer's dementia," *Alzheimer's Research & Therapy*, vol. 12, no. 1, 2020. doi:10.1186/s13195-020-00678-3

[78] S. Xiao, *et al.*, "A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia," *Alzheimer's Research & Therapy*, vol. 13, no. 1, 2021. doi:10.1186/s13195-021-00795-7

[79] Study of AGB101 in mild cognitive impairment due to Alzheimer's disease (HOPE4MCI) (2023) CTG Labs – NCBI. [Online]. Available: https://clinicaltrials.gov/study/NCT03486938

[80] C.-H. Lin, *et al.*, "Benzoate, a D-amino acid oxidase inhibitor, for the treatment of early-phase Alzheimer disease: A randomized, double-blind, placebo-controlled trial," *Biological Psychiatry*, vol. 75, no. 9, pp. 678–685, 2014. doi:10.1016/j.biopsych.2013.08.010

[81] J. F. Quinn, *et al.*, "Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease," *JAMA*, vol. 304, no. 17, 1903, 2010. doi:10.1001/jama.2010.1510

[82] C.-H. Chang, H.-Y. Lane, and C.-H. Lin, "Brain stimulation in Alzheimer's disease," *Frontiers in Psychiatry*, vol. 9, 2018. doi:10.3389/fpsyt.2018.00201

[83] A. M. Lozano, *et al.*, "A phase II study of fornix deep brain stimulation in mild Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 54, no. 2, pp. 777–787, 2016. doi:10.3233/jad-160017

[84] J.-M. S. Leoutsakos, *et al.*, "Deep brain stimulation targeting the fornix for mild Alzheimer dementia (the advance trial): A two year follow-up including results of delayed activation," *Journal of Alzheimer's Disease*, vol. 64, no. 2, pp. 597–606, 2018. doi:10.3233/jad-180121

[85] M. J. Sjogren, *et al.*, "Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease," *The Journal of Clinical Psychiatry*, vol. 63, no. 11, pp. 972–980, 2002. doi:10.4088/jcp.v63n1103

[86] C. A. Merrill, *et al.*, "Vagus nerve stimulation in patients with Alzheimer's disease," *The Journal of Clinical Psychiatry*, vol. 67, no. 8, pp. 1171–1178, 2006. doi:10.4088/jcp.v67n0801

[87] P. R. Padala, *et al.*, "Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: A double-blind, randomized, Sham-controlled, cross-over pilot study," *Psychiatry Research*, vol. 261, pp. 312–318, 2018. doi:10.1016/j.psychres.2017.12.063

[88] P. S. Boggio, *et al.*, "Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in

Alzheimer disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 80, no. 4, pp. 444–447, 2008. doi:10.1136/jnnp.2007.141853

[89] L. Kehler, *et al.*, "The effect of transcranial alternating current stimulation (tacs) on cognitive function in older adults with dementia," in *Proc. 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, Preprint, 2020. doi:10.1109/embc44109.2020.9175903

[90] R. H. Lim and T. Sharmeen, "Medicines management issues in dementia and coping strategies used by people living with dementia and family carers: A systematic review," *International Journal of Geriatric Psychiatry*, vol. 33, no. 12, pp. 1562–1581, 2018. doi:10.1002/gps.4985

[91] S. P. Salloway, *et al.*, "Advancing combination therapy for Alzheimer's disease," *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, vol. 6, no. 1, 2020. doi:10.1002/trc2.12073