Neuroplasticity-Based Therapies for Alzheimer's Disease

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Abstract

Neuroplasticity is an innate feature of the brain that allows organisms to continuously adapt to their environment for survival. Although this ability naturally declines with age, plasticity is more severely disrupted by the onset of Alzheimer's disease (AD), a progressive neurodegenerative illness that affects millions globally. AD impairs synaptic plasticity through pathology, neuron loss, and inflammation (Mesulam, 1999). Provided that all of these factors ultimately contribute to reduced adaptive capacity, therapies focused on preserving plasticity offer promising results for delaying the onset of AD–especially considering that synapse loss occurs years before overt clinical symptoms. Research suggests both pharmacological and non-pharmacological methods can be used to promote synaptic remodeling and neurogenesis in order to enhance or potentially restore cognitive function and memory storage in patients with Alzheimer's disease. This paper explores the mechanism by which AD disrupts plasticity and evaluates the potential of targeted neuroplasticity-based therapies as an effective form of treatment for AD.

Introduction

Neuroplasticity is known as the brain's ability to change structure and function in response to experience, commonly referred to as the major cellular model of learning and memory. Neuroplasticity is a fundamental cognitive process essential for the human brain to grow and develop as we age. This allows us to modify behavior, learn new skills, and recover from injury. Unfortunately, this built-in superpower degrades over time. This decline can be attributed to structural changes, reduced efficiency, and hormonal alterations in the brain, but is ultimately an inevitable truth. However, Alzheimer's Disease International (2020) reports that, for 55 million people worldwide, the rate at which an individual loses their neuroplastic response is devastated by Alzheimer's disease, which rapidly accelerates the decline of mental capacity and strips away memory, autonomy, and identity. As the number is set to rise to 153 million by 2050 (Alzheimer's Disease International, 2020), the need for effective prevention and treatment is in high demand–yet no cure has been found.

Primarily, the disorder is characterized by amyloid-β (Aβ) plaques–formed by imbalances between production and clearance that lead to buildup of Aβ peptides–and neurofibrillary tangles–where tau protein becomes abnormally phosphorylated and aggregated (Teter & Ashford, p. 404, 2002). Simply put, these plaques and tangles are clumps of protein that block mechanisms of synaptic plasticity, which are essential for neural communication and connection. Moreover, the loss of cholinergic neurons in the basal forebrain impairs cortical and hippocampal plasticity, which is essential for memory storage and formation (p. 405-406). Additionally, disruptions of calcium homeostasis, oxidative stress, and inflammation all contribute to neuroplastic impairment (p. 411).

As all outcomes of Alzheimer's disease appear to directly damage plasticity, neuroplasticity-based therapies have gained significant recognition as a promising avenue for early diagnosis and intervention. Notably, ongoing research offers favorable results. Data has shown that plasticity remains and can be retained, especially early-on; experiments with animals show how learning and enriched environments aid with synaptic remodeling and neurogenesis, while potential plastic changes have been observed in human brain imaging and postmortem cases (p. 411).

Methodology

This paper conducts a literature review based on research and experiments conducted by scientific professionals. The sources were selected from Google Scholar and limited to 21st century publications of peer-reviewed studies and statistical reports from internationally recognized organizations to ensure credibility. The following keywords were emphasized when selecting papers: “neuroplasticity,” “Alzheimer’s disease,” “neurodegenerative disease,” “amyloid-β (Aβ) plaques,” “tau OR neurofibrillary tangles,” and “neuroinflammation.” Each text was summarized then categorized by concept and theme in order to ensure research was accurately represented and effectively integrated for organization and relevance.

Current Treatment and Diagnosis

Currently, Alzheimer’s disease (AD) has no cure. Approved treatments for AD are based on drugs acting on the cholinergic and glutamatergic systems, but have minimal efficacy for only half of its patients (Koch & Spampinato, 2022). Acetylcholinesterase Inhibitors (AchEIs) and memantin are most commonly used, but only relieve symptoms momentarily and fail to slow cognitive decline (Koch & Spampinato, 2022 as cited in Di Lazzaro et al., 2004). Despite the fact that treatment can prove to be more effective when applied early, forms of diagnosis are limited as well. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) (Koch & Spampinato, 2022 as cited in Mosconi et al., 2008), functional magnetic resonance imaging (fMRI) (Koch & Spampinato, 2022 as cited in Brickman et al., 2009), and electroencephalography (EEG) (Koch & Spampinato, 2022 as cited in Cook and Leuchter, 1996) are commonly used to detect synaptic dysfunction, but offer indirect estimates with low temporal

resolution, have high costs that require specialized facilities, lack standardization, and utilize techniques that are not yet validated or representative.

Although current diagnostic tools yield inconclusive results, their findings build the foundation for targeted therapies. Early diagnosis relies on detecting beta-amyloid and tau-related abnormalities; toxic Aβ and tau proteins are known to disrupt synaptic plasticity in the hippocampus, causing spine shrinkage, network disorganization, and cell death (Koch & Spampinato, 2022 as cited in Lasagna-Reeves et al., 2016). However, these observations have indicated there is a stronger correlation between the loss of synaptic density to AD symptoms than solely Aβ and tau pathology. Synaptic integrity and plasticity are essential for processes of cognitive function and memory formation: neurogenesis[1], as well as long-term potentiation (LTP) and long-term depression (LTD)[2]. Additionally, neuronal communication breaks down from the loss of synapses even without neuronal death, and some patients have plaques even without dementia; this suggests Aβ and tau pathology are consequences of plasticity loss, rather than the cause. Therefore, future treatment for Alzheimer's disease may benefit from not only focusing on biomarkers, but also boosting plasticity.

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[1] Growth and development of nervous tissue

[2] Synaptic connections strengthen (LTP) or weaken (LTD) from repeated stimulation

Pharmacological Approaches

Primarily, Alzheimer's disease is traditionally addressed with pharmacological interventions. For instance, "Therapeutic Strategies Aimed at Improving Neuroplasticity in Alzheimer Disease" by María F. Colavitta and Francisco J. Barrantes and "A Brief Overview on BDNF-Trk Pathway in the Nervous System: A Potential Biomarker or Possible Target in

Treatment of Multiple Sclerosis?" from the National Library of Medicine discusses how medicated treatment strategies target the underlying mechanisms of AD. One form of pharmacological intervention emphasizes neurotransmitter modulation; cholinesterase inhibitors (eg. donepezil) increase acetylcholine availability in order to boost synaptic signaling and NMDA receptor antagonists (eg. memantine) reduce excitotoxicity to preserve synaptic function. Another form of medicinal treatment targets protein aggregation, such as anti-Aβ immunotherapies–remove Aβ to prevent synaptoxicity–and tau-targeting agents–reduce tau aggregation to prevent synaptic destabilization. Similarly, gene and RNA based Therapy (eg. antisense oligonucleotides) also reduce synaptic proteins or toxic aggregation by delivering genes or RNA. Beyond this, neurotrophic approaches restore processes associated with signaling pathways. Neurotrophic factors (eg. BDNF mimetics) activate TrkB without BDNF binding to its receptor to activate intracellular signaling processes–MAPK/ERK pathway for synaptic plasticity, PL3K/Akt pathway for neuron survival, and PLC-γ pathway for LTP–while neurotrophin signaling pathways (eg. TrkB receptor agonists) stimulate synaptic plasticity. In contrast, anti-inflammatory agents are intended to reduce microglia or inflammatory cytokines that impair synaptic function. Taken together, all modern forms of Alzheimer's medication aim to preserve or enhance synaptic integrity and plasticity despite differing mechanisms. As plasticity appears to play a critical role in delaying the progression of AD, it could be more strongly emphasized in future treatment development to enhance the potency of medicine.

To continue, "Potential Effects of MSC-Derived Exosomes in Neuroplasticity in Alzheimer's Disease" published by researchers at Frontiers explore the application of mesenchymal stromal cells (MSCs) as a form of neuroplasticity based treatment. MSCs secrete exosomes that deliver proteins, lipids, and microRNAs to promote synaptic remodeling,

neurogenesis, and angiogenesis. MSC-exosomes play a crucial role in preserving neuroplasticity as they regulate neuroinflammation and microglial activation while exosomal cargo contains the miRNA that regulates plasticity pathways, neural rewiring, and cognitive recovery. Scientists conducted an experiment in which mice injected with Aβ and treated with MSC exosomes had increased neurogenesis in the subventricular zone (DCX and PSA-NCAM markers) and improved cognitive performance demonstrated by their performance in the Morris water maze and with object recognition. On the one hand, familial AD cell models cultured with MSC-exosomes had reduced Aβ expression and restored expression of synaptic plasticity genes (eg. BDNF, synaptophysin, NMDA). On the other hand, AD transgenic mice showed improved brain metabolism, cognitive function, synaptic gene expression, and reduced astrocytes through FDG-PET and cognitive tests; these enhancements delay AD progression. Overall, recent experiments involving MSCs have demonstrated improved cellular and behavioral symptoms in both cells and animals with similar AD pathology, aligning with the proposal for neuroplasticity-based treatment plans for Alzheimer's disease.

Moreover, PLOS One's research article, "Age-Dependent Neuroplasticity Mechanisms in Alzheimer Tg2576 Mice Following Modulation of Brain Amyloid-β Levels" documents the significance of reducing Aβ in rodents to enhance plasticity, which aids in the restoration of brain structure and cognitive function. The PLOS One (2013) experiment consists of young mice (4-6 months old) representing early plaque-rich stages of amyloid pathology contrasted with older mice (15-18 months) representing later stages, where all subjects are administered Aβ-lowering drug (+) -phenserine daily for 16 days. After the trial concluded, the younger mice displayed a 40% decrease in soluble Aβ40 and Aβ42 (Aβ buildup progresses AD), 35% increase in synaptophysin (synaptic marker), 50% increase in GAP-43 (synaptic marker), double

BrdU-positive cell count (indicates neurogenesis), and improved radial arm maze (displays cognition). While older mice also exhibited 40% decrease in soluble Aβ40 and Aβ42, as well as decreased GFAP (inflammation), there was no significant change in synaptophysin or GAP-43 nor cognitive improvement found. All in all, the scientists' experiment revealed how Aβ reduction can delay the progression of AD by targeting neuroplastic processes, but also highlights the importance of timing in intervention as lowering Aβ early on was more effective for younger mice.

Ultimately, Alzheimer's disease is characterized by several pathophysiology elements, but synaptic loss underlies all biological abnormalities. Therefore, pharmacological interventions should prioritize the preservation of plasticity to delay the degeneration of other mechanisms that contribute to the progression of Alzheimer's disease.

Nonpharmacological Approaches

Unfortunately, the sole dependence of pharmacological interventions is impractical due to accessibility and time constraints. Consequently, the additional nonpharmacological interventions should also be considered to amplify the effectiveness of treatment.

As aforementioned, "Therapeutic Strategies Aimed at Improving Neuroplasticity in Alzheimer Disease" by María F. Colavitta and Francisco J. Barrantes and "A Brief Overview on BDNF-Trk Pathway in the Nervous System: A Potential Biomarker or Possible Target in Treatment of Multiple Sclerosis?" from the National Library of Medicine also mentions how nonmedicated treatment strategies can target the underlying mechanisms of AD. For example, Transcranial Magnetic Stimulation (TMS) has been used to offset the implications of AD by promoting LTP-like effects, modulating neuronal activity, enhancing synaptic plasticity and

BDNF signaling. TMS is particularly effective when applied to regions responsible for memory and attention (eg. dorsolateral prefrontal cortex) and when combined with other forms of treatment, reinforcing the value of a multimodal approach. To add, a transcranial Direct Current stimulation (tDCS) modulates excitability of neurons, produces LTP-like (excitatory) and LTD-like (inhibitory) effects, and increases BDNF levels through low-intensity constant electrical current using electrodes placed on the scalp that shift membrane potential. Although tDCS still shows inconsistency, continued revisions promotes favorable results for the future of tDCS and treating AD–especially since the approach is non-invasive and low-cost. Even fun and easy mental activities that stimulate, train, and enrich the mind enhances synaptic activity and connectivity, supports neurogenesis and synaptic remodelling, increases synaptic density, and shows improved cognitive performance in animals. In addition to the previous articles, "Physical Exercise Enhances Neuroplasticity and Delays Alzheimer's Disease" by Tzu-Wei Lin, Sheng-Feng Tsai, and Yu-Min Kuo adds how physical exercise in particular can relieve AD symptoms. According to the report, meta-analysis shows physical activity reduces risk of dementia by 28% and AD by 45%. Researchers explain that exercise preserves essential mechanisms that are harmed by the onset of Alzheimer's disease; it boosts BDNF, supports neurogenesis in the hippocampus, increases synaptic and cerebrovascular plasticity, and decreases neuropathology and neuroinflammation. Chiefly, aerobic exercise has shown to increase hippocampal, prefrontal, and temporal cortical volume. As a result, evidence from human studies have depicted cognitive and structural enhancements. Meta-analysis reports that aerobic exercise improved cognitive performance in 42 studies of 3,781 adults aged 55+ and pattern separation (key element of hippocampal function). After 6 months of aerobic exercise, 120 older adults (65+) showed increased hippocampal volume and improved spatial memory;

after 12 months, reports showed improved default-mode connectivity and frontal executive network, which are typically disrupted by the onset of AD. Likewise, in-depth experimentation with animal subjects has displayed anatomical and behavioral benefits that can offset symptoms of Alzheimer's disease. Moreover, these conclusions have been supported by imaging, as fMRIs have also tracked enhanced activity in brain regions associated with attentional control. These articles convey how AD treatment can possess several forms, pharmacological or not, with the main priority being neuroplasticity. Plus, non-pharmological approaches can be helpful for a wider range of affected individuals because of its cost-effectiveness and accessibility.

Furthermore, Giacomo Koch and Danny Spampinato investigate how transcranial magnetic stimulation (TMS)–a magnetic field that induces electric currents in cortex–triggers neuronal depolarization to identify prominent alterations of neuroplasticity in AD in "Alzheimer disease and neuroplasticity." Koch and Spampinato (2022) describe how TMS can identify early elements of AD synaptic dysfunction and improve diagnosis accuracy by predicting disease progression and response to therapy. TMS does so by testing neurotransmitters, plasticity-like changes, brain rhythms and oscillations, connectivity between brain regions, and Short Afferent Inhibition (SAI) and Short Intracortical Inhibition (SICI) protocols. The researchers discovered sessions of repetitive Transcranial Magnetic Stimulation (rTMS) induced LTP- and LTD-like changes in plasticity to improve plasticity, memory (especially episodic), and slow progression. In particular, high-frequency rTMS may be especially helpful in early AD, while rTMS to the precuneus improves memory and network. While TMS only stimulates specific regions, combining TMS with fMRI can identify effects on other regions to study connectivity and target weak regions. The text acknowledges that current treatments that target synaptic loss are limited and inconclusive, but presents TMS as a new, non-invasive solution that prevents cognitive

decline and memory loss by targeting the central issue of AD through preventative and direct measures in real-time. The piece also brings attention to the benefits associated with combining treatment plans, such as pairing TMS with fMRI or EEG.

Limitations

As demonstrated, neuroplasticity-based therapies appear to be the best course of action for AD treatment, but wide-spread implementation has yet to become a reality because of logistical constraints. Experiments confirmed that plasticity-targeted therapies are less effective after severe synapse and neuron loss in advanced disease progression, indicating early diagnosis using biomarkers and imaging are fundamental for its success, but these procedures remain underdeveloped, invasive, and expensive. These obstacles can be overcome with the necessary recognition and funding for longitudinal experiments with human subjects to confirm results and long-term benefits. Research has shown pharmacological and non-pharamacological interventions that target synaptic degeneration can preserve plasticity and delay the progression of Alzheimer's disease, but this goal can only be achieved when affected individuals receive the widespread awareness and support they deserve.

Conclusion

Overall, neuroplasticity-based therapies become increasingly valued as early interventions for Alzheimer's disease, offering the potential to preserve or possibly restore cognitive function and memory by enhancing synaptic remodelling and neurogenesis. While traditional drug therapies aim to restore cholinergic neurotransmission and improve cognitive function using medication, non-pharmacological approaches have gained traction as a non-invasive, low-cost method for promoting synaptic changes through enrichment, stimulation, and training. As professionals continue to investigate, combining medicinal and behavioral approaches appears to be the most effective approach in targeting both the cellular and molecular mechanisms that underlie brain adaptation and repair. Despite current limitations in this emerging field of research, continued plasticity-focused studies and funding will confirm results and reinforce this promising concept.

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