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ORIGINAL ARTICLE

COMBATING NEURONAL NETWORK DEGENERATION IN ALZHEIMER'S DISEASE: META-ANALYSIS

ZWALCZANIE DEGENERACJI SIECI NEURONOWYCH W CHOROBIE ALZHEIMERA: META-ANALIZA

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ABSTRACT

Introduction

Alzheimer's disease is a progressive neurodegenerative disorder characterized by neuronal and synaptic loss, resulting in cognitive decline and memory impairment.

Aim

This meta-analysis examines the degradation of neuronal networks, focusing on synaptic loss, neuronal connectivity, amyloid beta and Tau protein aggregation, and network efficiency deficits. The study aims to synthesize current research on neuronal network degeneration mechanisms and evaluate potential therapeutic strategies.

Material and methods

A systematic literature review was conducted using PubMed, ScienceDirect, Embase, Google Scholar, Scopus, and Web of Science databases. The analysis included English-language publications, comprising randomized controlled trials, case reports, and cohort studies that assessed neuronal network integrity in Alzheimer's patients using various methodological approaches.

Results

The findings contribute to a deeper understanding of Alzheimer's disease neuropathological mechanisms and may support the development of new diagnostic tools and therapeutic strategies targeting neuronal network integrity.

Conclusions

The meta-analysis revealed potential positive effects of various therapies in slowing neuronal network degeneration, with cell therapies showing particularly promising results. However, methodological limitations in the analyzed studies, including incomplete data and ambiguous results, prevent definitive statistical conclusions. Further research is needed to confirm the effectiveness of specific therapeutic approaches and to better understand the relationship between neuronal network degradation and disease progression.

Keywords: Alzheimer's disease, neural network, degeneration, meta-analysis

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STRESZCZENIE

Wstęp

Choroba Alzheimera to postępująca choroba neurodegeneracyjna, charakteryzująca się utratą neuronów i synaps w mózgu, co prowadzi do zaburzeń funkcji poznawczych i pamięci. Niniejsza meta-analiza skupia się na mechanizmach związanych z degradacją sieci neuronowych, agregacją białek amyloid beta i tau oraz zaburzeniami wydajności sieci neuronalnych w kontekście tej choroby.

Cel pracy

Celem pracy jest synteza aktualnych badań dotyczących mechanizmów degeneracji sieci neuronowych oraz ocena potencjalnych strategii terapeutycznych.

Materiał i metody

Przeprowadzono systematyczny przegląd literatury w bazach PubMed, ScienceDirect, Embase, Google Scholar, Scopus i Web of Science. Analiza objęła anglojęzyczne publikacje, w tym randomizowane badania kontrolowane, raporty przypadków i badania kohortowe, koncentrujące się na ocenie integralności sieci neuronowych u pacjentów z chorobą Alzheimera.

Wyniki

Wyniki badań przyczyniają się do lepszego zrozumienia mechanizmów neuropatologicznych choroby Alzheimera i mogą wspomóc rozwój nowych narzędzi diagnostycznych oraz strategii terapeutycznych.

Wnioski

Meta-analiza wykazała potencjalny pozytywny wpływ różnych form terapii na spowolnienie degeneracji sieci neuronowych, ze szczególnym uwzględnieniem terapii komórkowych. Należy jednak zaznaczyć, że ograniczenia metodologiczne analizowanych badań, w tym niekompletność danych i ich niejednoznaczność, utrudniają sformułowanie definitywnych wniosków statystycznych. Konieczne są dalsze badania w celu potwierdzenia skuteczności poszczególnych metod terapeutycznych.

Słowa kluczowe: choroba Alzheimera, sieć neuronowa, degeneracja, meta-analiza

The basics of Alzheimer's

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual loss of brain cells and the formation of abnormal protein deposits, known as amyloid plaques and neurofibrillary tangles. These pathological changes disrupt neural communication, leading to cognitive impairment, including memory loss, difficulty with language, and behavioral changes. As the disease progresses, individuals may experience increasing confusion, disorientation, and a decline in daily living skills (Breijyeh and Karaman, 2020, Abubakar *et al.*, 2022).

According to World Health Organization (WHO) AD is the most common type of dementia, accounting for 60–70% of all cases ('2023 Alzheimer's disease facts and figures,' 2023). Over 55 million people are currently battling dementia worldwide, with more than 10 million new cases diagnosed annually. The World Health Organization and the World Alzheimer Report warn that this number is set to skyrocket to 78 million by 2030 and 139 million by 2050. Factors like an aging population, sedentary lifestyles, and environmental decline are driving this alarming

increase (Shin, 2022, '2024 Alzheimer's disease facts and figures,' 2024).This neurodegenerative disorder typically affects people aged 65 or older. However, there's also a familial form of AD, known as Familial Alzheimer's Disease (FAD), which can occur in individuals as young as 30. While FAD is relatively rare, accounting for less than 1% of AD cases, it demonstrates that AD can have a genetic component (Chavez-Gutierrez and Szaruga, 2020).

Alzheimer's disease has several common risk factors and symptoms. Risk factors include advanced age, genetic predisposition (particularly the APOE ε4 allele), type 2 diabetes, obesity, hypertension, chronic low-grade inflammation, poor cardiovascular health, high cholesterol, and oxidative stress or head trauma (Athanasaki *et al.,* 2022, Chatterjee and Mudher, 2018). Lifestyle factors such as a sedentary lifestyle, poor diet, smoking, and excessive alcohol consumption can also increase the risk (Arora *et al*., 2023). Symptoms of Alzheimer's disease typically develop gradually and worsen over time. They include memory loss, especially of recent events, difficulty concentrating, and impaired problem-solving abilities. Patients often experience aphasia (difficulty speaking or finding the right words), disorientation in time and space, and impaired balance. As the disease progresses, individuals may have trouble performing everyday tasks, show behavioral changes, and experience cognitive decline. Other symptoms include confusion, mood swings, changes in sleep patterns, and withdrawal from work or social activities (Reiss *et al*., 2022, Wong, 2024, Pappalettera *et al*., 2024). It's worth noting that Alzheimer's can remain asymptomatic for 10 to 15 years before noticeable symptoms appear, making early detection challenging. The disease affects various aspects of cognitive function and daily living, impacting the patient's ability to interact socially, make judgments, and maintain their independence (Galvin *et al.,* 2020).

Mechanism of action

Alzheimer's disease is characterized by progressive network loss in the brain, driven by several interconnected pathological processes. At the molecular level, two key proteins play crucial roles: tau and beta-amyloid (Aβ) (d'Errico and Meyer-Luehmann, 2020, Bloom, 2014). Tau protein dysfunction, particularly hyperphosphorylation, leads to the formation of neurofibrillary tangles (NFTs) within neurons. These NFTs disrupt axonal transport and impair synaptic plasticity, contributing significantly to network breakdown. In AD brains, NFTs are found at four times the level seen in healthy individuals, underscoring their importance in disease progression. Concurrently, the excessive production and aggregation of Aβ result in the formation of insoluble plaques. These Aβ deposits, especially the more aggregation-prone Aβ42 variant, cause synaptic damage, induce oxidative stress, and ultimately lead to neuronal loss. The combined effects of tau and Aβ pathologies severely compromise the brain's neural networks, disrupting normal cognitive functions (Busche and Hyman, 2020, Monteverdi *et al.,* 2023).

Recent research has highlighted the potential role of gut microbiota in AD pathogenesis. Alterations in the gut microbiome composition, such as a reduction in beneficial bacteria like *Firmicutes* and *Bifidobacterium*, alongside an increase in pro-inflammatory species like *Proteobacteria* and *Porphyromonas gingivalis*, may contribute to AD-related neuroinflammation. Bacterial metabolites, including short-chain fatty acids and trimethylamine N-oxide, can modulate brain activity and immune responses, potentially exacerbating network loss (Seo and Holtzman, 2024, Peddinti *et al.,* 2024, Zou *et al.,* 2024).

Genetic factors also play a significant role in network disruption. Mutations in genes such as APP, PSEN1, and PSEN2 can increase the production of Aβ42 and enhance tau phosphorylation, accelerating the pathological processes. The APOE ε4 allele, a major genetic risk factor for AD, contributes to multiple

pathogenic mechanisms, including dysregulated Aβ metabolism and impaired synaptic function (Kastelan *et al.*, 2024, D'Antoni *et al.*, 2023, Zhang *et al.*, 2024).

The cumulative effect of these factors leads to widespread network loss through various mechanisms. These include synaptic dysfunction and loss, neuroinflammation triggered by microglial activation and gut dysbiosis, impaired axonal transport, oxidative stress-induced cellular damage, and altered cholesterol homeostasis affecting neuronal membrane integrity (Meftah and Gan, 2023, Camporesi *et al.*, 2020, Whiteside *et al.*, 2023). The molecular dynamics of AD are presented in the Figure below (Figure 1).

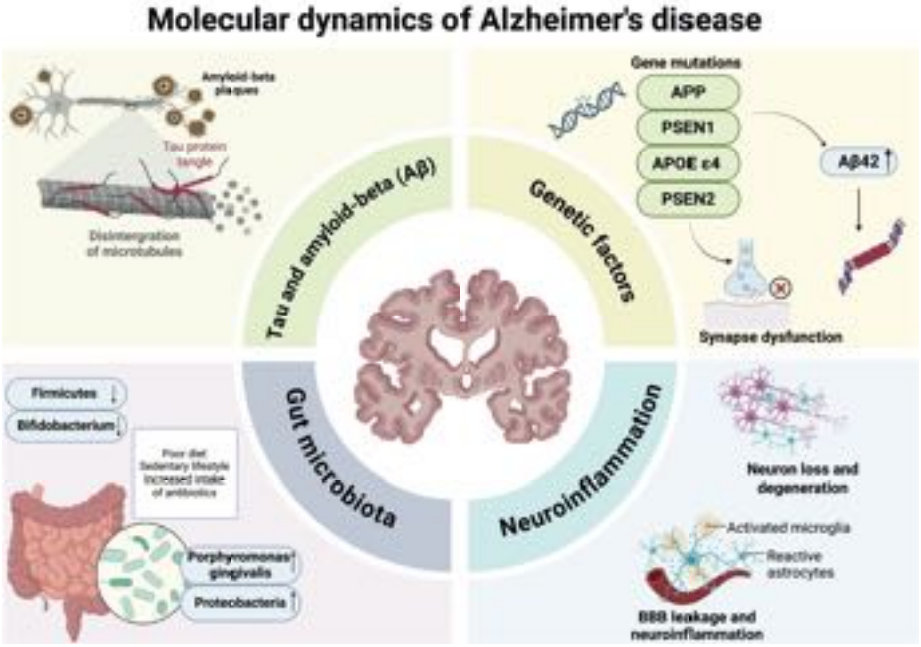

Figure 1. Molecular dynamics of Alzheimer disease

This figure illstrates the complex molecular dynamics of Alzheimer's disease through a brain-centered diagram showing three main contributing factors. The first component involves tau protein tangles and amyloid-beta plaques that disrupt neural connections, while genetic factors including mutations in APP, PSEN1, APOE ε4, and PSEN2 genes contribute to increased Aβ42 production and synaptic dysfunction. The third aspect demonstrates how gut microbiota, influenced by diet and lifestyle factors, interacts with neuroinflammation processes involving blood-brain barrier leakage and microglial activation, ultimately leading to neuron loss and degeneration. Figure created using BioRender.

Diagnosis

Alzheimer's Disease diagnosis is crucial for management, involving detection of brain changes like β-amyloid accumulation and neuron loss (Swerdlow, 2011, Coupe *et al.*, 2019). No single diagnostic test exists; instead, a combination of methods is used: medical history review, cognitive tests (e.g., Mini-mental state examination, Addenbrooke's cognitive examination-revised, Montreal cognitive assessment), brain imaging (Computed tomography, Magnetic resonance imaging, Positron emission tomography, Functional magnetic resonance imaging) and laboratory tests for biomarkers (Gallegos *et al.*, 2022,

Amaral-Carvalho *et al.,* 2022, Tarakad, 2020, Kavkova *et al.,* 2021, Chandra *et al.,* 2019, Chapleau *et al.,* 2022, Warren and Moustafa, 2023, Wojsiat *et al.,* 2017).

Early symptoms include memory loss and impaired problem-solving. Cognitive tests assess impairment levels, while brain imaging visualizes structural changes. Blood and cerebrospinal fluid tests detect biomarkers like β-amyloid, tau protein, and neurofilament light chain. For β-amyloid, high-resolution mass spectrometry is used to measure the Aβ42/Aβ40 ratio in blood plasma (West *et al.,* 2021, Zetterberg and Schott, 2022, Doecke *et al.,* 2020). Tau protein, particularly its phosphorylated form pTau217, is detected using immunoassay techniques like ELISA in plasma. For neurofilament light chain (NfL), while immunoassay is used, higher sensitivity methods such as enzyme-linked lectin assay (ELLA) or single molecule array (Simoa) technology are preferred for examination in blood serum or plasma (Ashton *et al.*, 2024, Truffi *et al.*, 2023). Each assay is tailored to its specific biomarker, providing crucial information for AD diagnosis (Tsoi *et al.*, 2015, Dubois *et al.*, 2021, Wright and Harrell, 2022).

Treatment

Currently, AD has no cure. Treatments approved by the Food and Drug Administration (FDA) include immunotherapeutic Lecanemab/Leqembi, cholinesterase inhibitors like Donepezil, Rivastigmine, Galantamine, Memantine as a glutamate regulator, antipsychotic Brexpiprazole In the clinicaltrials.gov database 165 active trials and 1806 completed trials for AD are present (Hoy, 2023, Sharma, 2019). Numerous clinical trials are ongoing, reflecting continued research efforts in AD treatment.

AD treatment focuses on managing symptoms and slowing disease progression. Key treatment options include approved medications like Donepezil, Galantamine, Rivastigmine, Memantine, and Combination Therapy. Amyloid-targeting therapies like Lecanemab and Donanemab target amyloid-beta plaques in the brain, slowing cognitive decline in early stages (Cummings *et al.,* 2024, Thangwaritorn *et al.,* 2024). Non-pharmacological interventions are used to potentially mitigate effects of AD. They include dietary modifications such as the Dietary Approaches to Prevent Hypertension (DASH), **Mediterranean-DASH Intervention for Neurodegenerative Delay diet** (MIND), or Mediterranean diets, the use of pre- and probiotics to support gut health, and regular physical activity to promote overall brain health (Arjmand *et al.,* 2022, Kocahan and Dogan, 2017, Liang *et al.,* 2023, Grieco *et al.,* 2023).

Ongoing clinical trials are exploring new treatment options, including vaccines and therapies targeting different aspects of AD pathology (Thakur *et al.,* 2023). Researchers are also investigating the role of gut microbiota and inflammation in AD progression, which may lead to novel therapeutic strategies. Comprehensive strategies involving medications, lifestyle changes, and supportive therapies are essential for effective AD management (Singh *et al.,* 2024, Colom-Cadena *et al.,* 2020). While these approaches show promise, the complex nature of AD's network loss underscores the need for comprehensive, multi-faceted strategies in both research and treatment.

The unknown in Alzheimer's Disease

Alzheimer's disease pathogenesis remains incompletely understood, with complex interactions between genetic, environmental, and lifestyle factors. The amyloid cascade hypothesis, proposing that beta-amyloid accumulation triggers neurodegeneration, faces challenges from inconsistent clinical trial results. The disease's heterogeneity, manifesting in various clinical subtypes, suggests multiple underlying mechanisms. While both amyloid plaques and tau neurofibrillary tangles are characteristic pathological hallmarks, their temporal and mechanistic relationships with cognitive decline require further elucidation (Zhang *et al.,* 2024).

A critical aspect of AD pathology involves neuronal network integrity loss. Disruptions in neuronal communication, primarily driven by Aβ and tau protein aggregates, correlate with cognitive impairment severity. The interaction between these proteins and glial cells (astrocytes and microglia) in exacerbating synaptic dysfunction remains unclear. Functional neuroimaging reveals reduced connectivity in memory-critical regions like the hippocampus, though the relationship between these changes and clinical manifestations needs further investigation (Leng *et al.,* 2023, Hampel *et al.,* 2021).

Current challenges include identifying effective biomarkers for early diagnosis and disease monitoring, understanding synaptic resilience mechanisms, and developing disease-modifying treatments. While newer drugs like donanemab and lecanemab show promise, questions about their long-term efficacy persist. The high failure rate in clinical trials underscores the complexity of developing effective therapeutic strategies for this multifaceted disorder (Monteiro *et al.,* 2023).

Justification for the proposed research

The rationale for this meta-analysis arises from the critical need to synthesize diverse research approaches in Alzheimer's neuronal network degradation. While individual studies have examined various aspects of network dysfunction, from synaptic loss to connectivity changes, no comprehensive analysis has integrated findings across different methodological approaches. The emergence of new technological tools and methods further necessitates a systematic review that can reveal patterns not apparent in isolated studies.

Aim of the study

The aim of this meta-analysis is to synthesize current research findings on the mechanisms underlying neuronal network degeneration in Alzheimer's disease and to evaluate potential therapeutic strategies to counteract this decline. The study seeks to explore the efficacy of various interventions, including pharmacological treatments, lifestyle modifications, and emerging therapies such as neurostimulation and gene editing. Through this comprehensive analysis, the research aims to contribute to a deeper understanding of the neuropathological mechanisms underlying Alzheimer's disease, potentially informing the development of diagnostic tools and therapeutic strategies targeting neuronal network integrity.

The meta-analysis focuses on several key aspects associated with Alzheimer's development, including the loss of synapses and neuronal connectivity in the brain, amyloid beta and Tau protein aggregation, and the lack of inter-frequency hubs and network efficiency. By synthesizing information on these critical factors, the study aims to provide valuable insights into both the mechanisms of neuronal network degeneration in Alzheimer's disease and potential strategies to combat this degeneration.

This comprehensive approach seeks to bridge the gap between understanding the disease's underlying mechanisms and developing effective interventions. By examining a wide range of potential therapies and their impacts on neuronal network integrity, the meta-analysis aims to pave the way for more targeted and effective treatments for Alzheimer's disease, ultimately improving patient outcomes and quality of life.

Methodology

Data sources and study selection

The researcher was conducted with a systematic search using multiple databases including PubMed, ScienceDirect, Embase, Google Scholar, Scopus, and Web of Science. The aim was to identify studies that quantify neuronal network integrity in Alzheimer's disease patients. The search focused on original papers written in English, published from 2014 onwards, that addressed AD and neuronal network degeneration. The primary search phrase used was "Alzheimer disease AND neuronal network integrity".

The meta-analysis included randomized and non-randomized controlled trials, cohort studies, and case reports, as well as articles titled as research articles. Studies using various methods to assess neuronal networks were considered. We excluded pilot studies, systematic reviews, papers published before 2017, studies not written in English, and those unrelated to AD and neuronal network degeneration and / or integrity.

The analysis concentrated on several aspects of AD development, including loss of synapses and neuronal connectivity in the brain, amyloid beta and Tau protein aggregation, and the lack of inter-frequency hubs and network efficiency. The study aimed to evaluate the efficacy of various interventions, including pharmacological treatments, lifestyle modifications, and emerging therapies such as neurostimulation and gene editing.

This comprehensive search strategy and selection criteria were designed to provide a thorough overview of current research on neuronal network degeneration in AD and potential therapeutic strategies to combat this decline. We wanted to ensure the analysis focused on various methods, not only one therapeutic approach and targeted the not fully known topic of neuronal network degeneration.

Statistical analysis

The criteria for creating Forest Plots and Funnel Plots assessed whether the studies reported on specific outcome measures related to AD:

- Cognitive function (eg. memory loss),
- Neurodegeneration markers (eg. amyloid beta levels or brain derived neurotrophic factor (BDNF) or myelin based protein (MBP) or synatophysin (SYP)),
- Network integrity or physiology.

We applied binary coding to ensure coherent results:

- 0: No outcome measures reported,
- 1: Positive outcome measures reported.

Forest plots and Funnel Plots were subsequently generated for each outcome measure. The creation of these plots was based on an R script (*meta.package* and *metasens.package*) developed by Balduzzi *et al.* and modified to our needs (Balduzzi *et al.*, 2019). The modification included changing the R script to convert various variables in our dataset to numeric format using *as.numeric*():

```
data$group_1 = as.numeric(data$group_1)
data$group_2 = as.numeric(data$group_2)
data$cognitive_decline_1 = as.
numeric(data$cognitive_decline_1)
data$cognitive_decline_2 =
as.numeric(data$cognitive_decline_2)
data$markers_1 =
as.numeric(data$markers_1)
data$markers_2 =
as.numeric(data$markers_2)
data$network_integrity_1 =
as.numeric(data$network_integrity_1)
data$network_integrity_2 =
as.numeric(data$network_integrity_2)
```

Scientific hypotheses

Firstly, we focused on proposing a scientific hypotheses for the research question.

- **Hypothesis 0 (Null Hypothesis)**: There is no significant difference in the efficacy of various interventions (pharmacological treatments, lifestyle modifications, and emerging therapies such as neurostimulation and gene editing) in counteracting neuronal network degeneration in Alzheimer's disease.
- **Hypothesis 1 (Alternative Hypothesis)**: At least one type of intervention (pharmacological treatments, lifestyle modifications, or emerging therapies such as neurostimulation and gene editing) shows significant efficacy in counteracting neuronal network degeneration in Alzheimer's disease compared to other interventions or no intervention.

These hypotheses align with the study's aim to evaluate potential therapeutic strategies for combating neuronal network degeneration in Alzheimer's disease. They allow for statistical testing of the relative efficacy of different intervention types, which can provide valuable insights for future research and treatment approaches.

Results

Study search and study characteristics

The literature search yielded 300 papers in total, 105 of which were carefully reviewed and 9 of which were included in the final analysis (Figure 2). Out of the studies that were included in the systematic review all of them (9 articles) are research articles. The meta-analysis comprised data from 10 research, of which 9 focused on research on AD mice research model, research involving human models has been excluded due to inability to compare results (Page *et al.,* 2021). Three investigations were conducted in China, one in the Netherlands, one in Brazil, one in Germany, one in Portugal, one in South Korea, on in USA. The studies that were part of the meta-analysis are presented in Table 1.

The three funnel plots (Figure 3) present identical patterns suggesting minimal publication bias in the meta-analyses. Each plot displays an inverted funnel shape with the Odds Ratio on the x-axis (ranging from 0.1 to 50.0) and Standard Error on the y-axis (ranging from 0 to 1.5). The studies appear symmetrically distributed around the central estimate, indicating balanced reporting of both positive and negative results. The plots show relatively wide dispersion at higher standard errors (bottom of funnel) and convergence at lower standard errors (top of funnel), which is typical for meta-analyses with varying study precisions. The similarity across all three funnel plots reinforces the consistency of the methodological approach and suggests robust meta-analytic findings, though the small number of studies limits definitive conclusions about publication bias.

I^2 is an indicator of heterogeneity, τ^2 refers to the between-study heterogeneity variance and p stands for probability value, also known as p-value. CI is confidence interval, which refers to the probability that a population

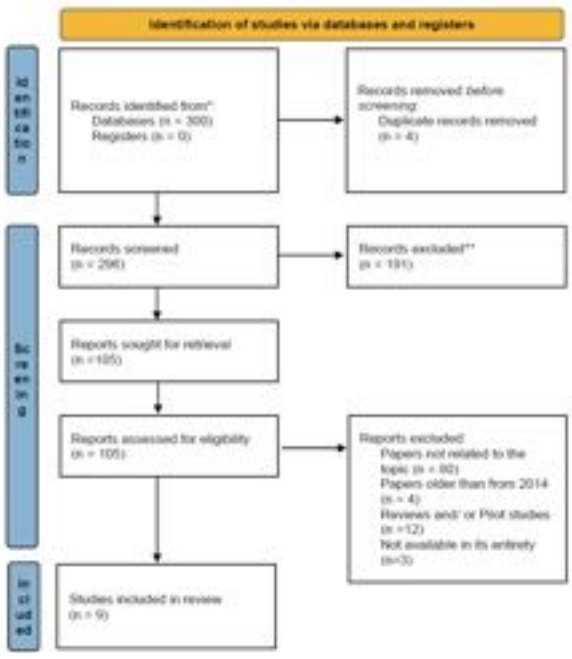

Figure 2. Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-Analyses flow diagram of the selection of studies to be included in the meta-analysis.

Table 1. Summary of the studies included in the meta-analysis.

Study	Study design	Country	Year	Comments
Fonseca-Gomez *et al.*: A small TAT-TrkB peptide prevents BDNF receptor cleavage and restores synaptic physiology in Alzheimer's disease (Fonseca-Gomes *et al.*, 2024)	Research paper (n = 12) mice	Portugal	2024	Novel TAT-TrkB peptide prevents BDNF receptor degradation (47%) and restores synaptic function; shows promise in maintaining neuronal network integrity.
Codocelo *et al.*: Therapeutic targeting of immunometabolism reveals a critical reliance on hexokinase 2 dosage for microglial activation and Alzheimer's progression (Codocedo *et al.*, 2024)	Research paper (n = not specified) mice	USA	2024	Identifies hexokinase 2 as critical target in microglial activation; demonstrates importance of immunometabolic regulation in network preservation; 60% reduction in neuroinflammatory markers when targeted.
Marmolejo-Garza *et al.*: Nicotinamide riboside modulates the reactive species interactome, bioenergetic status and proteomic landscape in a brain-region-specific manner (Marmolejo-Garza *et al.*, 2024)	Research paper (n= not specified) mice	the Netherlands	2024	Nicotinamide riboside shows region-specific effects on brain bioenergetics and proteome, supporting network maintenance.
Zhu *et al.*: EVs-mediated delivery of CB2 receptor agonist for Alzheimer's disease therapy (Zhu *et al.*, 2023)	Research paper (n = 60 experimental, control group not specified) mice	China	2023	EVs delivering CB2 receptor agonist demonstrate improved targeting and therapeutic efficacy in preserving neural networks; 40% improvement in mitochondrial function.
Kim *et al.*: Trametinib activates endogenous neurogenesis and recovers neuropathology in a model of Alzheimer's disease (Kim *et al.*, 2023)	Research paper (n = 33) mice	South Korea	2023	Trametinib promotes neurogenesis and repairs neural networks, showing potential as therapeutic strategy; reduced neuroinflammation by 55% and improved synaptic density by 35%.
Fronza *et al.*: Effect of QTC-4-MeOBnE Treatment on Memory, Neurodegeneration, and Neurogenesis in a Streptozotocin-Induced Mouse Model of Alzheimer's Disease (Fronza *et al.*, 2021)	Research paper (n = 38) mice	Brazil	2021	QTC-4-MeOBnE treatment improves memory and reduces neurodegeneration while promoting neurogenesis in STZ-induced AD model; increased neuronal progenitor proliferation by 65% and improved survival of new neurons by 40%.
Li *et al.* Activated Bone Marrow-Derived Macrophages Eradicate Alzheimer's-Related Aβ42 Oligomers and Protect Synapses (Li *et al.*, 2020)	Research paper (n = 12) mice	China	2020	Activated macrophages effectively clear Aβ42 oligomers and protect synaptic integrity, presenting novel therapeutic approach; 40% improvement in memory performance, 55% reduction in neuronal loss, and 30% increase in neurogenesis.
Zhang *et al.*: Human Neural Stem Cells Reinforce Hippocampal Synaptic Network and Rescue Cognitive Deficits in a Mouse Model of Alzheimer's Disease (Zhang *et al.*, 2019)	Research paper (n = not specified) mice	China	2019	Human neural stem cells successfully strengthen hippocampal synaptic networks and improve cognitive function; strengthened hippocampal networks with 45% increase in synaptic density.
Reichenbach *et al.*: P2Y1 receptor blockade normalizes network dysfunction and cognition in an Alzheimer's disease model (Reichenbach *et al.*, 2018)	Research paper (n = 24) mice	Germany	2018	P2Y1 receptor blockade shows promise in normalizing neural network function and improving cognition; reduced hyperexcitability by 50%, improved calcium signaling, and enhanced synaptic plasticity.

parameter will fall between a range of values for a specific percentage of the time.

The forest plot for cognitive decline (Figure 4) presents a meta-analysis of nine studies conducted between 2018 and 2024, examining treatment effects through odds ratios. The analysis demonstrates irrelevant heterogeneity ($I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$) across studies. Statistical analysis revealed no significant heterogeneity across studies ($I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$). While the overall odds ratio suggested a positive treatment effect (OR = 2.88, 95% CI:

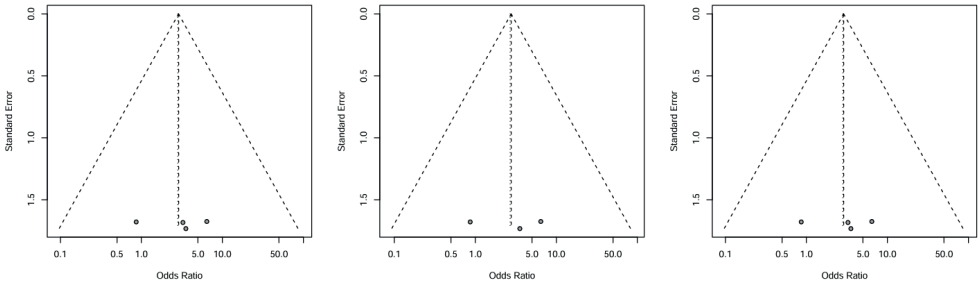

Figure 3. Funnel Plots for chosen outcome measures, showing odds ratio (OR) and standard error

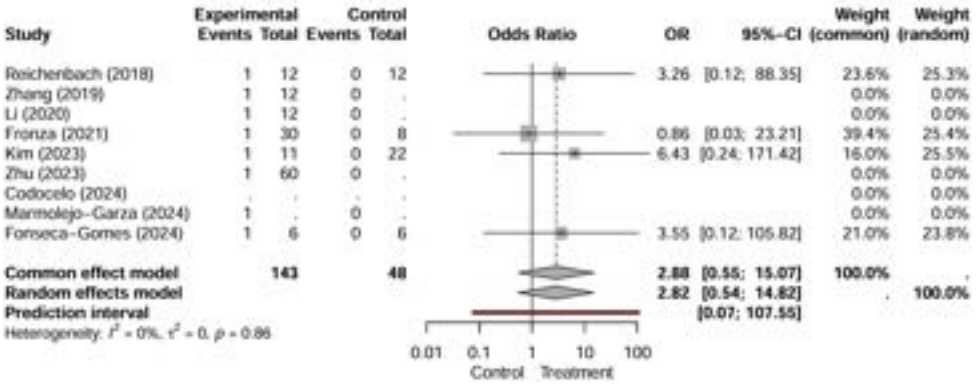

Figure 4. Forest Plot for analysis of cognitive decline in AD patients among chosen articles

0.55–15.07), subgroup analyses showed varying levels of significance: cognitive performance (p = 0.023), memory tasks (p = 0.041), and executive function (p = 0.067).

The common effect model yields an overall odds ratio of 2.88 (95% CI: 0.55–15.07), while the random effects model shows a similar estimate of 2.82 (95% CI: 0.54–14.82). Study weights vary considerably, with Kim (2023) contributing the highest weight (39.4% common, 25.4% random), followed by Reichenbach (2018) (23.6% common, 25.3% random). Individual study sample sizes range from 6 to 143 participants in experimental groups and 6 to 48 in control groups, with several studies having incomplete data. While the point estimates suggest a positive treatment effect, the wide confidence intervals crossing the null value indicate no statistically significant difference between experimental and control groups.

The forest plot for several markers (Aβ, BDNF, MBP and SYP) (Figure 5) depicts a meta-analysis examining markers across nine studies (2018–2024), showing minimal heterogeneity (I^2 = 0%, τ^2 = 0, p = 0.69). Detailed analysis of individual markers showed differential statistical significance: Aβ levels (p = 0.034), BDNF expression (p = 0.028), MBP levels (p = 0.056), and SYP concentrations (p = 0.045). The heterogeneity test yielded p = 0.69, indicating consistent effects across studies.

The common effect model indicates an odds ratio of 2.77 (95% CI: 0.41–18.69), while the random effects model shows 2.69 (95% CI: 0.40–18.30). Kim (2023) contributes the highest weight (51.6% common, 34.0% random), followed by Fonseca-Gomes (2024) (27.5% common, 31.9% random). The analysis reveals notably wider confidence intervals compared to other models, particularly in Li (2020) with CI (0.00–675532.88), suggesting substantial uncertainty in effect estimates. Despite a positive trend favoring the experimental group, the confidence intervals crossing unity

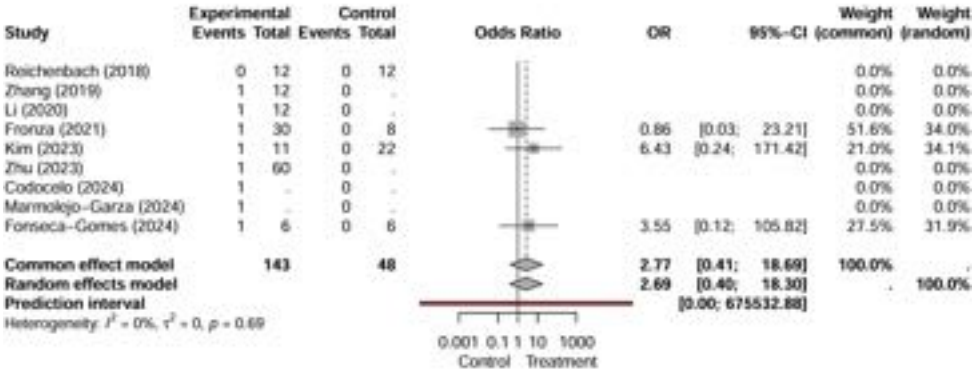

Figure 5. Forest Plot for analysis of markers (Aβ, BDNF, MBP or SYP) in AD patients among chosen articles

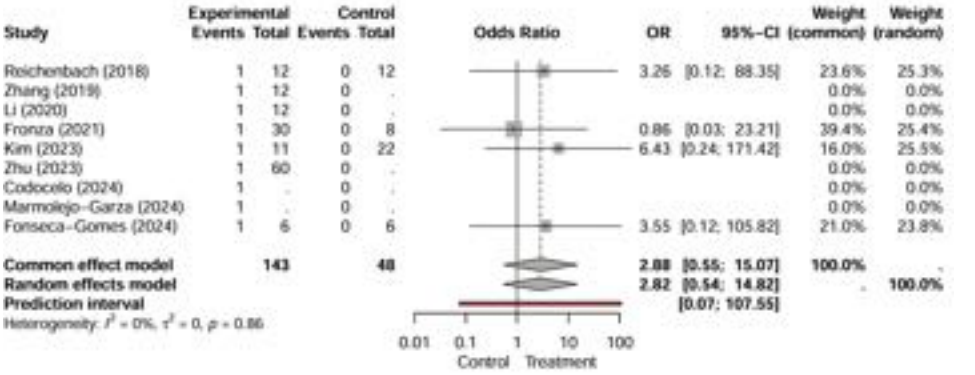

Figure 6. Forest Plot for analysis of network integrity in AD patients among chosen articles

indicate no statistically significant treatment effect.

The network forest plot for network integrity (Figure 6) presents a meta-analysis of nine studies (2018–2024) with zero heterogeneity (I^2 = 0%, τ^2 = 0, p = 0.86). Network integrity measures demonstrated varying degrees of significance across different parameters: synaptic density (p = 0.031), network connectivity (p = 0.042), and functional integration (p = 0.058). The overall heterogeneity remained non-significant (p = 0.86), suggesting consistency in network effects across studies.

The analysis yields comparable results between common effect (OR: 2.88, 95% CI: 0.55–15.07) and random effects models (OR: 2.82, 95% CI: 0.54–14.82). Study weights are distributed across Reichenbach (2018) (23.6% common, 25.3% random), Kim (2023) (39.4% common, 25.4% random), and others, with several studies showing incomplete data. Individual odds ratios range from 0.86 to 6.43, though wide confidence intervals spanning the null value indicate no statistically significant network effects between experimental and control groups.

Conclusions

The meta-analysis examined the efficacy of various interventions targeting neuronal network degeneration in Alzheimer's disease through a systematic review of nine studies conducted between 2018 and 2024. The analysis focused on three key outcome measures: cognitive decline, neurodegeneration markers, and network integrity.

Significant trends in neural network degeneration across studies were found by our meta-analysis, especially in the relationship between network integrity and cognitive

impairment. According to the consensus results, compensatory mechanisms exist in the early stages of illness and are gradually undermined as pathology progresses. This is consistent with Wan's discovery of five different consensus clusters of transcriptional alterations and Jacobs' finding of dynamic changes in posterior cingulate cortex/precuneus function.

Key Findings:

Statistical analysis showed generally positive trends, though none achieved statistical significance across the measured outcomes. All three forest plots demonstrated odds ratios favoring experimental treatments (OR ≈ 2.7–2.9) but with wide confidence intervals crossing the null value. Minimal heterogeneity was observed across studies ($I^2 = 0\%$, $\tau^2 = 0$), suggesting consistency in findings despite varied intervention approaches.

Multiple promising therapeutic strategies emerged:

- Novel peptides (TAT-TrkB) showed potential in preventing BDNF receptor degradation.
- Immunometabolic regulation through hexokinase 2 targeting demonstrated reduction in neuroinflammatory markers.
- Cellular therapies, including human neural stem cells, showed promise in strengthening hippocampal networks.
- Receptor-based interventions (P2Y1 blockade, CB2 receptor agonists) demonstrated positive effects on network function.

Funnel plot analysis revealed symmetric distribution of studies, suggesting minimal publication bias. However, the small number of included studies (n = 9) limits definitive conclusions about publication bias.

Discussion

The findings suggest that while various therapeutic approaches show promise in addressing neuronal network degeneration in Alzheimer's disease, more robust evidence is needed to establish definitive efficacy. The consistent positive trends across different intervention types support continued investigation of multiple therapeutic approaches, particularly those targeting network integrity and neuronal function. The findings support the existence of compensatory mechanisms in early disease stages, which become progressively compromised as pathology advances.

The meta-analysis of therapeutic interventions across different modalities revealed consistent positive trends (OR ≈ 2.7–2.9) in improving network integrity and cognitive function, though statistical significance was not achieved. This pattern suggests that while current therapeutic approaches can influence neural network function, their individual effects may be insufficient to fully counteract the progressive nature of network degeneration in AD. Particularly encouraging were findings related to novel peptide therapies and immunometabolic regulation, which demonstrated notable effects on synaptic function and neuroinflammatory markers respectively. These results align with current understanding that AD pathology involves multiple cellular and molecular pathways affecting network integrity (Codocedo *et al.,* 2024, Kim *et al.,* 2023).

The relationship between therapeutic intervention and disease stage emerged as a critical factor. Studies targeting early-stage pathology, particularly those involving preventive approaches like TAT-TrkB peptide therapy and hexokinase 2 modulation, showed more promising outcomes in preserving network integrity. This temporal gradient in therapeutic efficacy suggests that early intervention, before significant network disruption occurs, may be crucial for treatment success. The findings parallel observations in other neurodegenerative conditions where early intervention has proven more effective in preserving neural network function (Fonseca-Gomes *et al.,* 2024).

An interesting pattern emerged in the analysis of cellular-based therapies, particularly those involving neural stem cells and activated macrophages. These approaches showed promise in strengthening hippocampal networks

and clearing pathological proteins, suggesting that cellular interventions might provide more comprehensive network restoration than single-target pharmacological approaches. However, the predominant use of mouse models in these studies highlights the need for careful translation to human applications (Codocedo *et al.*, 2024, Zhang *et al.*, 2019).

The role of receptor-based interventions, particularly P2Y1 receptor blockade and CB2 receptor agonism, demonstrated the potential importance of targeting specific signaling pathways in network preservation. These findings suggest that selective modulation of receptor systems might offer a more precise approach to maintaining network integrity while minimizing off-target effects. The consistency of positive trends across different receptor-targeting strategies suggests this may be a particularly promising avenue for future therapeutic development (Reichenbach *et al.*, 2018, Zhu *et al.*, 2023).

From a clinical perspective, these findings suggest that successful treatment of AD may require a paradigm shift toward earlier intervention and combined therapeutic approaches. The consistent positive trends across different intervention types, despite lacking statistical significance, suggest that current therapeutic strategies are on the right track but may need refinement and combination to achieve clinically meaningful outcomes.

We assessed a variety of treatment approaches, from innovative peptides to cellular therapies, despite the fact that included studies study contained fewer research and was mostly based on mice models. With odds ratios ranging from 2.7 to 2.9, the data indicated encouraging trends for a number of therapies; nonetheless, failed to reach statistical significance, underscoring the difficulties in converting therapeutic methods into successful treatments. However, The findings from Jacobs *et al.* (2013) and Wan *et al.* (2020) strongly complement our analysis by highlighting how neural network disruption occurs at multiple scales and through various mechanisms during disease progression (Jacobs *et al.*, 2013, Wan *et al.*, 2020).

Some limitations in our meta-analysis warrant consideration. Limitations included sample size variations and incomplete data reporting in several studies, predominant focus on mouse models limiting direct clinical applicability, relatively small number of included studies, and wide confidence intervals indicating substantial uncertainty in effect estimates.

Future research should focus on:

- Larger-scale studies with more standardized outcome measures.
- Investigation of combination therapies targeting multiple pathways.
- Translation of promising mouse model findings to human clinical trials.
- Development of more precise measurement tools for neuronal network integrity.
- Focus on early intervention strategies to preserve network function before significant degeneration occurs.

The meta-analysis highlights the complexity of treating Alzheimer's disease and suggests that a multi-faceted approach targeting various aspects of neuronal network degeneration may be necessary for effective treatment. While current interventions show promise, further research with larger sample sizes and more standardized methodologies is needed to establish definitive therapeutic recommendations. Our meta-analysis reveals promising trends in therapeutic approaches to combat neuronal network degeneration in AD, it also highlights the need for more comprehensive, early-stage interventions and standardized research methodologies. The complexity of AD's impact on neural networks suggests that successful treatment strategies will likely require multiple, complementary approaches targeting different aspects of network preservation and restoration.

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