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Short Review

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Neuroinflammation and Cognitive Decline in Alzheimer's Disease
Current Evidence and Future Directions

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ABSTRACT

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by progressive memory loss, cognitive decline, and behavioral impairment. Growing evidence indicates that chronic neuroinflammation, particularly mediated by dysregulated microglia, is a central contributor to disease progression. Simultaneously, advances in artificial intelligence (AI) and machine learning (ML) are transforming translational neuroscience by improving biomarker discovery, behavioral phenotyping, and early diagnosis. This review summarizes recent evidence on neuroinflammation, microglial biology, synaptic plasticity, AI-enabled translational neuroscience, digital phenotyping, and ML-based behavioral assessment in rodent models, and discusses future research directions.

Keywords: Alzheimer's Disease, Neuroinflammation, Microglia, Synaptic Plasticity, Cognitive Decline, Artificial Intelligence, Machine Learning, Digital Phenotyping, Translational Neuroscience, Behavioral Assessment.

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Introduction

Alzheimer's disease affects millions worldwide and remains the leading cause of dementia. Classical pathological hallmarks include extracellular amyloid-beta plaques and intracellular tau neurofibrillary tangles; however, increasing evidence demonstrates that immune dysregulation and synaptic dysfunction precede extensive neuronal loss. Integrating neuroscience with computational methods offers unprecedented opportunities for precision diagnosis and therapeutic development.

Neuroinflammation and Cognitive Decline

Microglia and astrocytes respond to injury by producing inflammatory mediators including IL-1β, IL-6, TNF-α, complement proteins, and reactive oxygen species. Persistent activation contributes to synaptic dysfunction, tau propagation, mitochondrial impairment, and neuronal death. Blood biomarkers such as Glial Fibrillary Acidic Protein (GFAP), neurofilament light chain, and phosphorylated tau complement PET and MRI for disease monitoring. Therapeutic strategies targeting inflammatory pathways are currently under active investigation. See Figure-1, where this figure illustrates how neuroinflammation, microglial activation, synaptic dysfunction, and artificial intelligence–driven analytics interact to influence cognitive decline in Alzheimer's disease, highlighting emerging biomarkers, translational neuroscience, and machine learning approaches for early diagnosis and therapeutic development [1-5].

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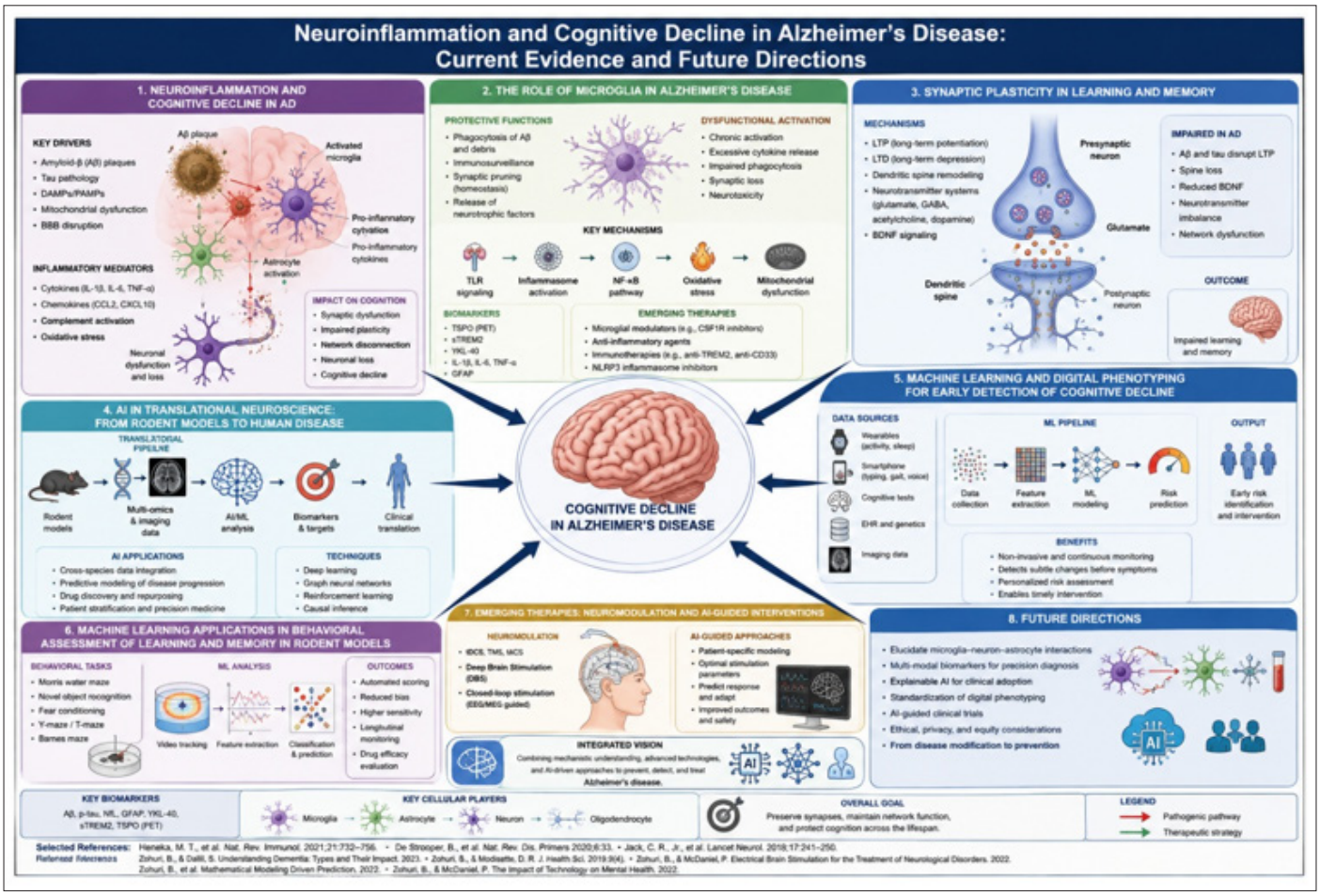

Figure 1: Integrated Overview of Neuroinflammation, Microglial Dysfunction, Synaptic Plasticity, and Artificial Intelligence for Early Detection and Translational Research in Alzheimer's Disease

GFAP is an intermediate filament protein that is primarily expressed by astrocytes, the most abundant glial cells in the Central Nervous System (CNS). It provides structural support to astrocytes and plays an important role in maintaining the integrity of the blood–brain barrier, regulating neuronal function, and responding to central nervous system injury. See Figure-1.

In Alzheimer's disease (AD):

- Elevated GFAP is a marker of astrocyte activation (reactive astrogliosis).
- Increased plasma and cerebrospinal fluid (CSF) GFAP levels are associated with early amyloid-β pathology, even before significant cognitive symptoms appear.
- GFAP is increasingly recognized as a non-invasive blood biomarker for the early detection and monitoring of Alzheimer's disease progression, with plasma GFAP showing a stronger association with amyloid-β pathology than tau aggregation, reflecting amyloid-related astrocyte activation.
- When combined with biomarkers such as phosphorylated tau (p-tau), amyloid-β, and neurofilament light chain (NfL), GFAP improves the accuracy of Alzheimer's disease diagnosis and prognosis.

Because of its sensitivity to early neuroinflammatory changes, GFAP has become one of the most promising biomarkers for identifying individuals at risk of developing Alzheimer's disease and other neurodegenerative disorders before irreversible neuronal damage occurs [6-8].

Microglia: Mechanisms, Biomarkers, Emerging Therapies, and Learning

Microglia regulate synaptic pruning, debris clearance, neurogenesis, and immune surveillance. Genetic variants involving TREM2, APOE, CD33, PLCG2, and complement pathways strongly influence AD susceptibility. Emerging therapies include TREM2 agonists, complement inhibitors, CSF1R modulation, nanoparticle drug delivery, gene editing, and cell-based immunotherapies. Properly regulated microglia facilitate learning by maintaining healthy synaptic remodeling, whereas chronic activation disrupts hippocampal memory circuits.

Genetic variants involving Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), Apolipoprotein E (APOE), Cluster of Differentiation 33 (CD33), and Phospholipase C Gamma 2 (PLCG2) influence the function of microglia and the brain's innate immune response, affecting the clearance of amyloid-β,

regulation of inflammation, and neuronal survival. Variations in these genes can increase or decrease an individual's risk of developing Alzheimer's disease by altering immune signaling, synaptic maintenance, and neuroinflammatory processes.

In summary, PLCG2 is an intracellular enzyme that mediates immune signaling in microglia. By regulating phagocytosis, inflammatory responses, and cell survival, it helps protect the brain from neurodegeneration. Protective genetic variants, such as PLCG2 P522R, are associated with a lower risk of Alzheimer's disease, making PLCG2 a promising target for future therapeutic development [8-10].

Synaptic Plasticity in Learning and Memory

Long-term potentiation and long-term depression represent fundamental mechanisms underlying memory formation. AD impairs N-Methyl-D-Aspartate (NMDA) receptor signaling, calcium homeostasis, dendritic spine stability, mitochondrial function, and brain-derived neurotrophic factor signaling. Exercise, cognitive training, sleep optimization, anti-inflammatory treatment, and neuromodulation may partially restore plasticity. Importantly, the NMDA receptor (NMDAR) is a specialized glutamate receptor and ligand-gated ion channel found on neurons throughout the brain. It plays a fundamental role in synaptic plasticity, learning, memory formation, and Long-Term Potentiation (LTP), which are the cellular mechanisms underlying memory storage. See Figure-2, where this figure illustrates the mechanisms of synaptic plasticity, emphasizing the role of NMDA receptor-mediated signaling in long-term potentiation and memory formation, the disruptions caused by Alzheimer's disease, and therapeutic interventions that may restore synaptic function and cognitive performance.
In summary, NMDA (N-Methyl-D-Aspartate) is a glutamate-activated receptor that is essential for synaptic plasticity, learning, and memory. Proper NMDA receptor function strengthens neuronal communication, whereas abnormal activation contributes to neuronal injury and cognitive decline in Alzheimer's disease. Consequently, the NMDA receptor is both a key component of normal brain function and an important therapeutic target in neurodegenerative disorders [11-12].

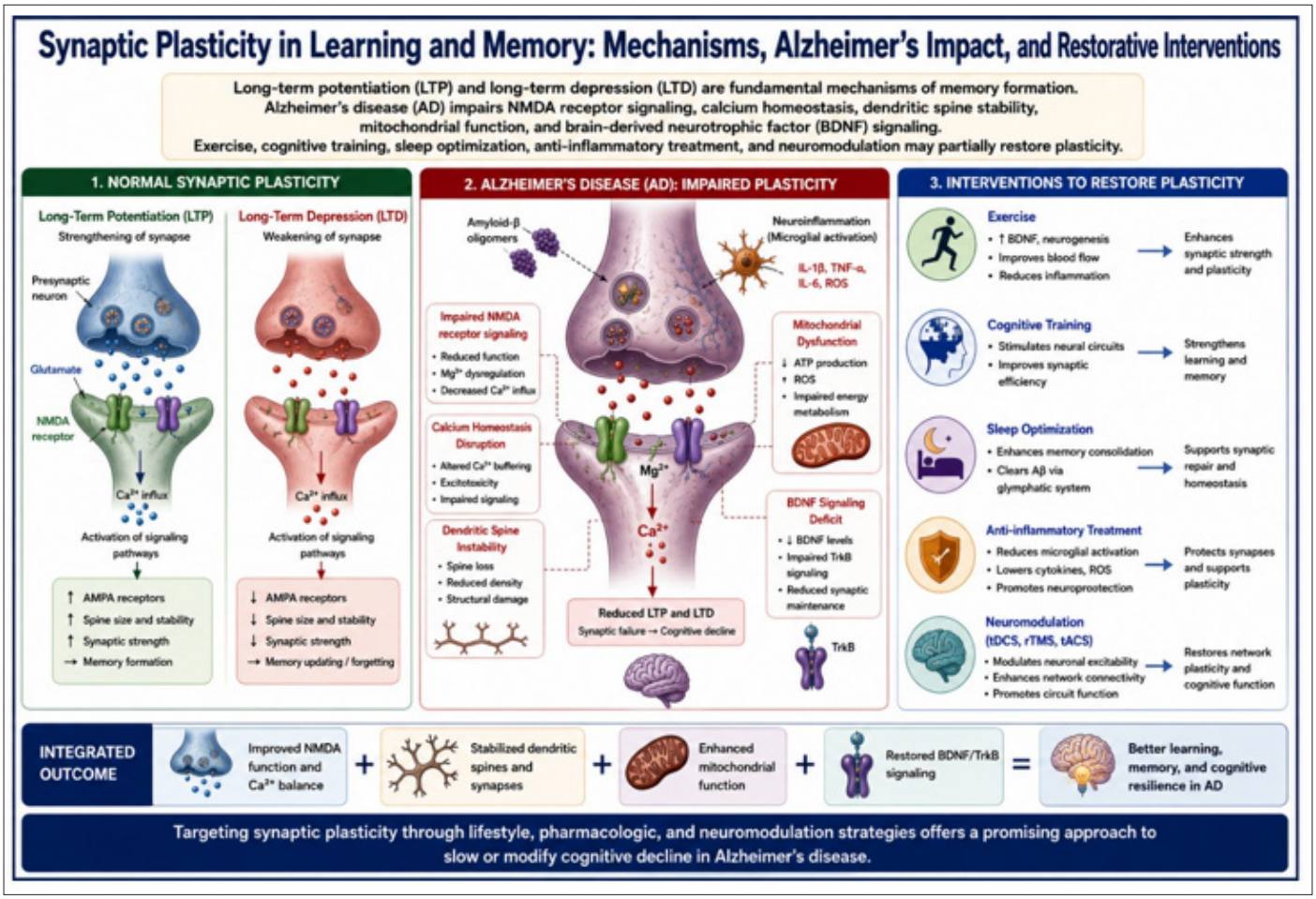

Figure 2: Synaptic Plasticity in Learning and Memory: NMDA Receptor Signaling, Alzheimer's Disease Pathophysiology, and Therapeutic Restoration Strategies

AI in Translational Neuroscience

Deep learning algorithms now analyze multimodal neuroimaging, pathology slides, genomics, transcriptomics, proteomics, and electronic health records. AI improves patient stratification, biomarker discovery, target identification, and prediction of therapeutic

response. Foundation models and explainable AI are expected to accelerate translation from rodent studies to human clinical trials. See Figure-3, where this figure illustrates how artificial intelligence integrates multimodal biomedical data to improve biomarker discovery, patient stratification, therapeutic prediction, and the translation of neuroscience research from preclinical models to precision medicine for Alzheimer's disease.

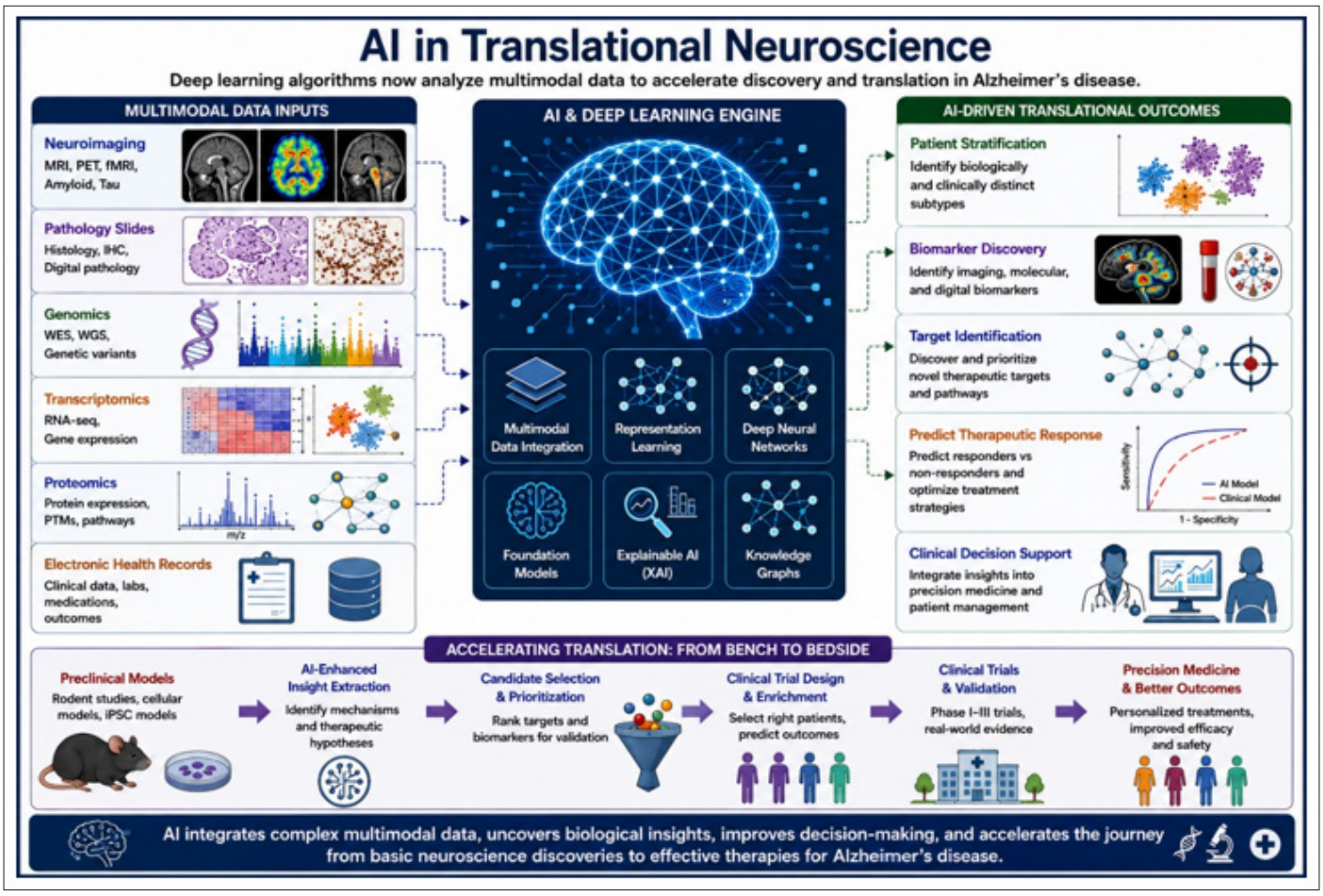

Figure 3: Artificial Intelligence in Translational Neuroscience: Integrating Multimodal Data for Biomarker Discovery, Precision Medicine, and Clinical Translation in Alzheimer's Disease

Machine Learning and Digital Phenotyping

Digital phenotyping integrates wearable devices, smartphones, speech analysis, gait monitoring, typing behavior, sleep tracking, and passive sensing. Supervised and unsupervised learning detect subtle behavioral changes years before clinical diagnosis. Combining digital biomarkers with plasma biomarkers and neuroimaging supports personalized risk prediction.

ML-Based Behavioral Assessment in Rodent Models

Computer vision and pose-estimation systems automatically quantify the Morris water maze, Barnes maze, novel object recognition, Y-maze, T-maze, fear conditioning, open-field activity, and social interaction tests. Automated scoring reduces observer bias, improves reproducibility, enables high-throughput drug screening, and strengthens translational validity [12-14].

Future Directions

Future research should integrate longitudinal multi-omics, spatial transcriptomics, digital twins, federated learning, explainable AI, and multimodal biomarkers. Earlier intervention during preclinical disease stages may become possible through precision medicine approaches combining inflammatory biomarkers, synaptic biomarkers, and continuous digital monitoring

Conclusion

Neuroinflammation and microglial dysfunction have emerged as central mechanisms driving Alzheimer's disease progression. Preservation of synaptic plasticity remains essential for maintaining cognition. Artificial intelligence and machine learning provide powerful tools for biomarker discovery, early detection, and translational research, offering realistic opportunities for precision neuroscience and disease-modifying therapies.

References

1. Bahman Zohuri, Patrick J McDaniel (2022) Transcranial Magnetic and Electrical Brain Stimulation for Neurological Disorders. Academic Press; 1st edition.

2. Heneka MT, Carson MJ, Khoury JE, Landreth GE, Brosseron F, et al. (2015) Neuroinflammation in Alzheimer's disease. Lancet Neurology 14: 388-405.
3. Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer's disease: where do we go from here? Nature Reviews Neurology 17: 157-172.
4. De Strooper B, Karran E (2016) The Cellular Phase of Alzheimer's Disease. Cell 164: 603-615.
5. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, et al. (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 14: 535–562.
6. Topol EJ (2019) High-Performance Medicine: the convergence of human and artificial intelligence. Nature Medicine Nature Medicine 25: 44–56.
7. Taeho Jo, Kwangsik Nho, Andrew J Saykin (2019) Deep Learning in Alzheimer's Disease: Diagnostic Classification and Prognostic Prediction Using Neuroimaging Data. Front Aging Neurosci 11: 220.
8. Mathys H, Davila-Velderrain J, Peng Z, Gao F, Mohammadi S, et al. (2019) Single-cell transcriptomic analysis of Alzheimer's disease. Nature 570: 332-337.
9. Cummings J, et al. Alzheimer's disease drug development pipeline: 2025. Alzheimers Dement 11: e70098.
10. Zohuri B, Dalili S (2023) Understanding Dementia: Types and Their Impact. Sci Set J of Med Cli Case Stu 2: 01-04.
11. Zohuri B, Modisette DR (2019) Electrical Brain Stimulation to Treat Neurological Disorder. Journal of Health Science 7: 123-128.
12. Zohuri B, McDaniel P (2019) Electrical Brain Stimulation for the Treatment of Neurological Disorders. Apple Academic Press; 1st edition. ISBN: 978-1771888516
13. Zohuri B. Mathematical Modeling Driven Prediction.
14. Zohuri B, McDaniel P. The Impact of Technology on Mental Health.