

Brain Organoids in Alzheimer's Disease Research: Applications, Limitations, and Future Directions

Qi Shi

The Oakridge School, Arlington, TX, USA
Email: 13910921634@139.com

How to cite this paper: Shi, Q. (2026)
Brain Organoids in Alzheimer's Disease
Research: Applications, Limitations, and
Future Directions. *Journal of Biosciences
and Medicines*, 14, 1-7.
<https://doi.org/10.4236/jbm.2026.147001>

Received: May 19, 2026

Accepted: June 29, 2026

Published: July 2, 2026

Copyright © 2026 by author(s) and
Scientific Research Publishing Inc.
This work is licensed under the Creative
Commons Attribution-NonCommercial
International License (CC BY-NC 4.0).
<http://creativecommons.org/licenses/by-nc/4.0/>



Open Access

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which molecular pathology, cellular stress and network dysfunction accumulate over many years before dementia becomes clinically evident. Because early AD biology cannot be directly followed in living human brain tissue, experimental models are essential for testing mechanisms and candidate interventions. Brain organoids, usually derived from human induced pluripotent stem cells (iPSCs), provide a three-dimensional human-cell-based system that can reproduce selected AD-like cellular phenotypes, including amyloid-beta ($A\beta$) changes, tau abnormalities, synaptic dysfunction and glial responses. However, organoids remain incomplete models. They are developmentally immature, variable between lines and batches, and lack full vascular, immune, systemic and behavioural complexity. This review discusses the applications, limitations and future directions of brain organoids in AD research, arguing that they are most powerful when used alongside animal models, human cohorts and biomarker studies.

Keywords

Alzheimer's Disease, Neurodegeneration, Brain Organoids,
Induced Pluripotent Stem Cells, Disease Modelling, Drug Screening

1. Introduction

Alzheimer's disease (AD) is one of the most common causes of dementia and is clinically associated with progressive memory decline, broader cognitive impairment and reduced ability to perform daily activities. Although AD has been studied extensively, its onset and progression involve interacting processes that are

still not fully understood. A central challenge is that researchers cannot easily observe the earliest stages of AD directly inside the living human brain or isolate one disease variable at a time in patients. For this reason, experimental models are needed to test mechanisms, evaluate therapeutic strategies and connect molecular pathology with cellular and network dysfunction.

Brain organoids have attracted attention because they offer a human-cell-based three-dimensional system for studying selected aspects of AD. They are not miniature human brains and should not be treated as complete replicas of human disease. Instead, their value lies in bridging simplified two-dimensional cultures and human disease by modelling human genetic background, multicellular organisation and experimentally tractable disease-related phenotypes [1] [2]. This review evaluates how brain organoids can be used in AD research, what they still fail to capture, and how future models may become more informative.

2. AD Pathogenesis and Why Models Are Needed

AD begins long before obvious clinical symptoms appear. Age and genetic factors, such as APOE status, can increase risk, while vascular health, sleep and lifestyle factors may also influence vulnerability. At the molecular level, A β peptides can accumulate in soluble and deposited forms, while tau proteins can become abnormally phosphorylated and form intracellular tangles. These changes are linked to synaptic stress, neuronal dysfunction and progressive damage to memory-related networks, particularly involving the hippocampus and connected cortical regions.

However, the presence of amyloid alone does not always match symptom severity, showing that AD cannot be explained by one molecule in isolation. Glial cells also contribute to disease progression. Microglia and astrocytes normally support neurons and respond to injury, but chronic activation may promote inflammation, synaptic loss and network dysfunction. As the disease advances, early synaptic changes are followed by neuronal loss, brain atrophy and clearer impairment in memory, cognition and daily function.

Biomarkers from imaging, cerebrospinal fluid and blood tests help detect AD-related biology, but they do not fully reveal cause-and-effect mechanisms. Human cohort studies and biomarkers show patterns in real patients, animal models provide whole-organism physiology and behaviour, and cell-based systems allow controlled mechanistic testing. Brain organoids occupy an important middle position: they improve human cellular relevance compared with many animal models and provide more tissue-like organisation than two-dimensional cultures, but they cannot reproduce the full clinical disease.

3. What Brain Organoids Are

An organoid is a self-organised three-dimensional tissue derived from stem cells that mimics selected structural or functional features of an organ. Brain organoids are commonly generated from embryonic stem cells or iPSCs. In a typical workflow, iPSCs are aggregated, directed toward neural fate, supported in a three-di-

mensional environment and matured over weeks or months. Guided protocols use specific signalling cues to generate more predictable regional identities, whereas unguided protocols allow broader self-patterning but are usually more variable [2].

For AD research, different organoid systems answer different questions. Organoids derived from familial AD lines or gene-edited isogenic lines are useful for testing mutation-driven mechanisms under controlled conditions. Organoids derived from sporadic AD donors may capture broader patient-specific genetic background, but they can also introduce line-to-line variability. Exogenously induced models, such as organoids exposed to AD patient brain extracts or synthetic A β /tau material, test how neural tissue responds to pathological stimuli rather than whether disease phenotypes arise intrinsically from the organoid. These model categories should therefore not be interpreted as equivalent evidence.

Different organoid formats are also suited to different research questions. Unguided organoids are useful for exploratory studies of mixed neural identities, whereas region-specific organoids provide more reproducible models of defined brain areas, such as cortical or hippocampal-like tissue. Vascularised organoids can improve nutrient delivery and support studies of neurovascular interactions. Microglia-containing organoids are especially relevant for neuroinflammation, but microglial origin, maturity and activation state require validation [3]. Assembloids, in which different organoids or cell populations are combined, can be used to study interactions between regions or cell types [4] [5]. Thus, the best model is not necessarily the most complex one, but the one most closely matched to the biological question.

4. Applications in AD Research

The most direct application of brain organoids in AD research is mechanistic disease modelling. Raja *et al.* reported that self-organising three-dimensional human neural tissue derived from AD patient iPSCs could show AD-like phenotypes, including A β aggregation and tau abnormalities [6]. This type of patient- or genotype-derived model is useful for asking whether intrinsic cellular or genetic factors can drive selected disease-related phenotypes *in vitro*. Importantly, such findings should be described as AD-like phenotypes rather than as a complete recreation of AD, because organoids do not reproduce the full ageing process, clinical course or behavioural features of the disease.

Organoids are also useful for drug screening. Compared with simple two-dimensional cultures, they provide a more tissue-like context for measuring A β levels, tau markers, neuronal stress, synaptic density and network activity. Park *et al.* developed a human iPSC-derived cerebral organoid platform that combined AD-related pathological features with network-based computational modelling for drug-screening purposes [7]. Such approaches can help identify candidate compounds or repurposed drugs that modify disease-relevant readouts. However, organoid screening remains less scalable than many two-dimensional assays, and

positive findings still require validation in other models and eventually in clinical studies. Organoids are therefore best viewed as one step in a wider testing pipeline rather than as a stand-alone route to therapy.

More complex organoid systems can model interactions between neurons, glia, vascular-like structures and disease-associated proteins. For example, Ji *et al.* reported that brain extracts from individuals with sporadic AD induced multiple AD-related changes in vascularised neuroimmune organoids, including A β plaque-like aggregates, tau tangle-like aggregates, neuroinflammation, increased microglial synaptic pruning, synapse or neuronal loss and impaired network activity [8]. This study is important because it uses an exogenous patient-brain-extract challenge to test whether complex human neural tissue can respond to diseased brain material with multiple AD-like phenotypes. It should not be presented as the same type of evidence as pathology arising spontaneously within patient-derived or mutation-carrying organoids.

A further application is personalised and patient-specific modelling. Because iPSCs can be generated from individual patients, brain organoids may be used to compare vulnerability or treatment responses across different genetic backgrounds. This is particularly relevant for AD, where risk is shaped by both inherited variants and environmental or vascular factors. At present, personalised organoid testing remains mainly a research goal rather than a routine clinical tool, but it provides a logical direction for precision medicine when combined with patient genotype, biomarker and clinical information.

5. Limitations

Despite their value, brain organoids have important limitations. The most important conceptual limitation for AD is the ageing problem. AD is mainly a late-life disease, but many iPSC-derived organoids resemble fetal or early postnatal neural tissue more than aged adult brain [9]. During iPSC reprogramming, adult somatic cells can lose age-associated molecular and epigenetic signatures, including DNA methylation age, mitochondrial stress features and accumulated cellular damage. This matters for late-onset AD because disease develops against decades of ageing, vascular change and metabolic stress. Therefore, organoids may model genetic vulnerability or early cellular mechanisms better than the full temporal trajectory of late-stage neurodegeneration.

A second limitation is incomplete physiology. Many brain organoids lack mature vasculature, blood flow, a complete immune environment and stable long-range circuits. Restricted diffusion of oxygen and nutrients can constrain organoid size, cell viability and maturation, and may lead to hypoxic or necrotic cores. Some organoids also lack mature oligodendrocytes and myelination, limiting their ability to reproduce adult network function. As a result, organoids cannot directly model clinical outcomes such as memory decline, behaviour, sleep disruption or whole-body interactions between the brain, immune system and metabolism [10] [11].

A third limitation is immune complexity. Microglia are central to AD, but they arise from a different developmental lineage from neurons and are often absent from standard brain organoids. Microglia-like cells can be added, co-cultured or generated within specialised organoid protocols, but the resulting cells may differ in origin, maturity and activation state. For example, organoids containing innately arising microglia and organoids with co-cultured microglia can respond differently to $A\beta$ challenge [12]. This means that inflammatory findings should be interpreted only after careful validation of microglial identity and culture-related stress.

A fourth limitation is variability. Organoid size, cellular composition, maturation state and regional identity can differ between iPSC lines, batches and laboratories. Patient-derived organoids also contain genetic background differences that may be useful for personalised modelling but problematic when trying to isolate one variant or mechanism. Strong experimental design therefore requires multiple cell lines, repeated differentiations, isogenic controls where possible, blinded quantification, careful quality control and validation in complementary systems [10] [11]. These limitations do not make organoids weak models; rather, they define the types of questions organoids can answer responsibly.

6. Future Directions

Future progress in AD organoid research will depend on improving both biological relevance and reproducibility. One direction is to increase cellular and structural complexity. Incorporating microglia-like cells, astrocytes, oligodendrocytes or vascular-like structures may help researchers study neuroinflammation, nutrient delivery, blood-brain-barrier-related biology and synaptic regulation in a more realistic context. Assembloids may also help model interactions between neural regions or cell populations. However, added complexity should be matched to a clear research question; a more complex model is not automatically a better model.

A second direction is to improve ageing relevance. Strategies such as prolonged maturation, stress-based induction, direct conversion approaches or methods that preserve age-related signatures may help organoids better reflect the biological context in which AD develops. Direct conversion from adult fibroblasts is one promising strategy because it may retain more age-related features than full iPSC reprogramming, although it also requires careful validation and comparison with conventional iPSC-derived organoids [13]. Artificial ageing-like stressors should also be used cautiously because they may create artefacts that resemble disease without reproducing its natural biology.

A third priority is standardisation. More consistent reporting of cell lines, differentiation protocols, organoid age, regional identity, cell-type composition, oxygenation, batch number and quantitative analysis methods would make studies easier to compare and reproduce. Shared benchmark datasets, reference controls and transparent quality-control criteria would also strengthen confidence in organoid-based findings [14]. In the long term, the strongest AD research will likely

combine organoids with two-dimensional systems, animal models, post-mortem tissue, biomarker data and clinical cohorts, allowing each model to answer the question it is best suited for.

7. Conclusion

Brain organoids have become an important tool for studying AD because they provide a human-cell-based three-dimensional system for testing selected molecular and cellular mechanisms. They are particularly useful for studying amyloid and tau-related changes, synaptic dysfunction, glial interactions, drug responses and patient-specific biology. However, they remain partial models that cannot reproduce full ageing, whole-body physiology, behaviour or the complete clinical course of AD. The most balanced conclusion is therefore not that organoids replace existing models, but that they complement them. When used with cautious interpretation and strong experimental design, brain organoids can help bridge the gap between simplified cell culture, animal models and human disease.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

- [1] Gerakis, Y. and Hetz, C. (2019) Brain Organoids: A Next Step for Humanized Alzheimer's Disease Models? *Molecular Psychiatry*, **24**, 474-478. <https://doi.org/10.1038/s41380-018-0343-7>
- [2] Papaspyropoulos, A., Tsolaki, M., Foroglou, N. and Pantazaki, A.A. (2020) Modeling and Targeting Alzheimer's Disease with Organoids. *Frontiers in Pharmacology*, **11**, Article 396. <https://doi.org/10.3389/fphar.2020.00396>
- [3] Zhang, W., Jiang, J., Xu, Z., Yan, H., Tang, B., Liu, C., *et al.* (2023) Microglia-Containing Human Brain Organoids for the Study of Brain Development and Pathology. *Molecular Psychiatry*, **28**, 96-107. <https://doi.org/10.1038/s41380-022-01892-1>
- [4] Paşca, S.P., Arlotta, P., Bateup, H.S., Camp, J.G., Cappello, S., Gage, F.H., *et al.* (2025) A Framework for Neural Organoids, Assembloids and Transplantation Studies. *Nature*, **639**, 315-320. <https://doi.org/10.1038/s41586-024-08487-6>
- [5] Kim, J., Imaizumi, K., Jurjuţ, O., Kelley, K.W., Wang, D., Thete, M.V., *et al.* (2025) Human Assembloid Model of the Ascending Neural Sensory Pathway. *Nature*, **642**, 143-153. <https://doi.org/10.1038/s41586-025-08808-3>
- [6] Raja, W.K., Mungenast, A.E., Lin, Y., Ko, T., Abdurrob, F., Seo, J., *et al.* (2016) Self-Organizing 3D Human Neural Tissue Derived from Induced Pluripotent Stem Cells Recapitulate Alzheimer's Disease Phenotypes. *PLOS ONE*, **11**, e0161969. <https://doi.org/10.1371/journal.pone.0161969>
- [7] Park, J.C., Jang, S.Y., Lee, D., *et al.* (2021) A Logical Network-Based Drug-Screening Platform for Alzheimer's Disease Representing Pathological Features of Human Brain Organoids. *Nature Communications*, **12**, Article No. 280. <https://doi.org/10.1038/s41467-020-20440-5>
- [8] Ji, Y., Chen, X., Wang, Z., Meek, C.J., McLean, J.L., Yang, Y., *et al.* (2025) Alzheimer's Disease Patient Brain Extracts Induce Multiple Pathologies in Novel Vascularized Neuroimmune Organoids for Disease Modeling and Drug Discovery. *Molecular Psy-*

- chiatry*, **30**, 4558-4575. <https://doi.org/10.1038/s41380-025-03041-w>
- [9] Hossain, M.K., Kim, H. and Chae, H.J. (2024) Aging Phenotype in AD Brain Organoids: Track to Success and Challenges. *Ageing Research Reviews*, **96**, Article 102256. <https://doi.org/10.1016/j.arr.2024.102256>
 - [10] Sainz, A., Pérez-Cerdá, F., Pérez-Samartín, A., Panicker, M., Ruiz, A. and Matute, C. (2025) Pros and Cons of Human Brain Organoids to Study Alzheimer's Disease. *Ageing and Disease*, **16**, 3483-3504.
 - [11] Urrestizala-Arenaza, N., Cerchio, S., Cavaliere, F. and Magliaro, C. (2024) Limitations of Human Brain Organoids to Study Neurodegenerative Diseases: A Manual to Survive. *Frontiers in Cellular Neuroscience*, **18**, Article 1419526. <https://doi.org/10.3389/fncel.2024.1419526>
 - [12] Wenzel, T.J., Desjarlais, J.D. and Mousseau, D.D. (2024) Human Brain Organoids Containing Microglia That Have Arisen Innately Adapt to a β -Amyloid Challenge Better than Those in Which Microglia Are Integrated by Co-Culture. *Stem Cell Research & Therapy*, **15**, Article No. 258. <https://doi.org/10.1186/s13287-024-03876-0>
 - [13] Kim, Y., Kim, H., Cho, B., An, S., Kang, S., Kim, S., *et al.* (2024) Modeling APOE E4 Familial Alzheimer's Disease in Directly Converted 3D Brain Organoids. *Frontiers in Aging Neuroscience*, **16**, Article 1435445. <https://doi.org/10.3389/fnagi.2024.1435445>
 - [14] Sandoval, S.O., Cappuccio, G., Kruth, K., Osenberg, S., Khalil, S.M., Méndez-Albelo, N.M., *et al.* (2024) Rigor and Reproducibility in Human Brain Organoid Research: Where We Are and Where We Need to Go. *Stem Cell Reports*, **19**, 796-816. <https://doi.org/10.1016/j.stemcr.2024.04.008>