The Novel Use Of 3D Bioprinting and Artificial Intelligence to Further Alzheimer's Disease Detection Methods and Treatment

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Received October 23, 2024
Accepted February 28, 2025
Electronic access March 15, 2025

Alzheimer's Disease (AD) has been an increasing issue for centuries. Although it was first recognized around 2000 B.C. by ancient Egyptians, AD was considered a natural part of aging until the 20th century. Alois Alzheimer, a German psychiatrist and pathologist, initially identified dementia in 1906, which caused research on Alzheimer's to have advanced significantly. However, over the centuries, researchers have still been trying to find ways to delay, prevent, or improve ways of detecting AD. Currently, Alzheimer's is ranked as the seventh leading cause of death in America. Furthermore, AD is the most common cause of memory loss or dementia among older adults. As of now, it has very few treatments available. However, recent advancements in technology may provide the key to treating this disease as more possible treatments are being made and improved. Through analyzing research studies from various sources, this literature review aims to discuss the use of 3D bioprinting and Artificial Intelligence (AI) in potentially improving the detection of Alzheimer's Disease. Current studies on bioprinting have been shown to have the potential to create 3D structures that replicate the tissue environments and can be used as a tool in disease modeling or drug screening. These developments will make it easier to diagnose and treat Alzheimer's in the future. This review aims to explore the novel integration of 3D bioprinting and AI in advancing Alzheimer's disease detection and treatment methods to address current limitations in the field and pave the way for more effective interventions.

Keywords: Artificial Intelligence, Alzheimer's Diagnosis, Alzheimer's Treatment, 3D Bioprinting, Bioink

Background

AD is a progressive neurological disorder affecting multiple brain functions, most prominent in people over the age of 60. Throughout the early stages of Alzheimer's, there is an unusual buildup of proteins which forms tau tangles and amyloid plaques[1]. Over time, Alzheimer's causes brain cell communication and the cells themselves degenerate and die. These changes in the brain may begin before symptoms, such as the ones mentioned previously appear, making it hard for early detection. The first areas of the brain that appear to sustain injury are the entorhinal cortex and the hippocampal regions, which are crucial for memory formation. As time goes on, further areas of the brain become damaged and begin to shrink as more neurons die. At the last stage of Alzheimer's, brain tissue will have shrunken significantly and there will be extensive damage to the brain[1]. After being diagnosed, people with Alzheimer's Disease typically live for three to eleven years.

Alzheimer's is difficult to detect; however, one of the first symptoms is memory loss and confusion, although it can affect a variety of brain functions like language and thought as well[2]. Although MRIs help detect the loss of neurons—such as brain atrophy in the basal forebrain and hippocampus during the early stages of AD—there is no complete cure yet for Alzheimer's disease. Atrophy of the forebrain is believed to reflect the loss of cholinergic neurons which are essential for optimal brain function, including attention, and memory[3]. Nonetheless, using bio-inks, living cells, and other materials, 3D bioprinting—a computer-assisted method that produces three-dimensional constructs that resemble natural tissue—shows potential to advance a cure for Alzheimer's[4,5]. This review will explore 3D bioprinting and AI in the enabling of computers and digital devices to learn and grow with programmed languages. By examining the intersection of both these technological advances in Alzheimer's disease research, this review underscores the transformative potential of these technologies to revolutionize diagnostic techniques and further developments, setting the stage for groundbreaking advancements in combating this complex neurodegenerative disorder.

Methodology

Research papers have a wide range of ways to gather and compile comprehensive information. Regarding so, this literature review's methodology involves utilizing various research papers—mainly original and systematic reviews—-published in peer-reviewed journals and platforms. No restrictions were placed on the age, gender, or ethnicity of human subjects diag-

nosed with Alzheimer's Disease or other conditions. Furthermore, animal studies in vitro using Alzheimer's Disease models were considered. Ranging from the application of 3D bioprinting, including studies on drug delivery systems, and bioinks containing neural cells or tissues, to 3D printed scaffolds, numerous experimental scientific papers were included. In these experiments, the researchers employed techniques such as high-resolution microscopy to observe cellular interactions within the scaffolds and quantitative PCR to assess gene expression changes associated with neurodegeneration. Additionally, in vivo imaging and behavioral assays were used to evaluate the efficacy of the drug delivery systems in repairing cognitive function. In the AI domain, studies utilized a plethora of different techniques for machine learning. Some of these include convolutional neural networks, deep learning, biomarkers, or neuroimaging data related to Alzheimer's Disease. These approaches were assessed using accuracy metrics like area under the curve (AUC), sensitivity, and specificity. Such methods help to quantify the model's ability to predict Alzheimer's Disease progression and identify potential therapeutic targets. The primary outcomes of interest were improvements in the accuracy of diagnosis, staging, and prognosis of Alzheimer's Disease progression, cognitive and functional outcomes, changes in biomarkers, and the safety and biocompatibility of the investigated interventions.

Comprehensive searches were conducted in the PubMed, Embase, Web of Science, and IEEE Xplore databases from inception to March 2023. The search strings combined terms such as "Alzheimer's Disease," "3D bioprinting," "additive manufacturing," "artificial intelligence," "machine learning," and "neural networks." Additional studies were identified by manually screening the references of the included articles and relevant reviews. Studies were selected based on predefined inclusion criteria: (1) research articles published in English, (2) studies that specifically address the intersection of Alzheimer's Disease and technologies like 3D bioprinting or AI-driven methods, and (3) articles that report on empirical findings, excluding reviews, opinion pieces, and editorials. The exclusion criteria include studies not directly related to Alzheimer's Disease, those without a clear methodological framework, and those that did not focus on the technological aspects of 3D bioprinting or AI applications. Additional studies were identified through manual screening of references in the included articles and relevant reviews. Furthermore, the main origin of database research occurred on Google Scholar with the specific terms: "AD", "bioink", "CNN", "3D CNN", "BDNF", "neural tissue printing", "scaffolds", and "PCL". For the first general search, the inclusion of the Boolean Expression "OR" is used. Afterward, specific topics were grouped into clusters such as "AD", "CNN", "3D CNN", and "AI" which utilized the Boolean Operation AND to refine results.

The quality and relevance of the research to the present literature review are then independently assessed by two reviewers who also consider potential sources of bias. To eliminate potential biases, inter-rater reliability is utilized with various independent evaluators assessing material. Independent evaluators include research mentors and topic professionals. Data is then extracted from the studies using a systematic approach to objectively analyze research databases and sources to deliver reliable information. This method will thus effectively emphasize common themes and patterns of use in the application of 3D bioprinting and AI for research or treatment related to Alzheimer's Disease. Through this systematic approach, the review intends to offer a thorough but reliable summary of current knowledge in an ever-evolving area; coupled with identifying future research needs and opportunities.

AI and Alzheimer's Disease Detection

With the increasing prevalence of AI, specific types emerged to be more relevant to particular functions. In the case of disease diagnosis with numerous brain images, convolutional neural networks—a type of artificial neural network used primarily for image recognition and processing—have emerged as a possibility for creating an accurate yet effective detection method for AD. Currently, primary detection methods include doctors analyzing Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) images to find abnormalities in beta-amyloid levels, tumors, etc.[5]. However, with convolution neural networks and other AI advancements, new potential methods have been researched to further the detection process and accuracy for Alzheimer's Disease.

Progress in the Application of AI

To test how accurate artificial neural networks are, a study by Majdah Alshammari shows how convolutional neural networks work with MRIs[6]. In this study, they utilized a specific convolution neural network (CNN)—3D Convolutional Neural Networks (3D-CNN) to investigate the temporal region of gray matter instead of focusing on the whole brain. This novel experiment using 3D CNN is unique because currently creating detailed photos with 3D layers—while accessible—has certain drawbacks, such as computational limitations. The GPU constraint makes it challenging to build a large number of layers. As a result, 2D MRI is utilized in various networks for computational processing currently (Figure 1.). Nonetheless, this study provides a potential breakthrough using 3D-CNN despite its potential computational limitations[7].

The researchers in the study led by Majdah Alshammari coded their 3D-CNN AI with Python programming language and trained it in a machine-learning environment by employing open-source libraries like TensorFlow and OpenCV. This detection method can classify Alzheimer's Disease in stages, and lead to high performance accuracy. For instance, using a

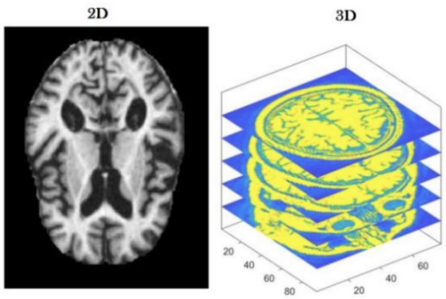

Fig. 1 2D vs. 3D Brain MRI Images - The 3D image images allow for more layers to provide high-quality representations of the database. Modified from S. Dubey et al. (2020) and M. Liu et al. (2018) [8,9].

regular MRI database resulted in an accuracy of 88.06% and a specificity of 82.09% [6]. The results found that with more trained AI, the detection accuracies can improve dramatically to grant efficient detection of Alzheimer's Disease.

In addition, an article published by the Alexandria Engineering Journal showed similar results with this detection method by conducting another study using AI and CNN [10]. The researchers in this study also employed a 3D-CNN architecture, also called a shallow CNN, to provide accurate diagnosis and classification of Alzheimer's Disease stages. A shallow CNN consists of typically one or two convolutional, or hidden, layers that apply a set of filters to what is imputed. These layers then will capture spatial hierarchies and patterns [7]. After a shallow CNN is employed, the article proposes that a supervised Deep Learning method is used to diagnose Alzheimer's using the various pre-trained shallow CNN models.

Although there was a data shortage for training the models, the researchers performed extensive experiments and compared their method for Alzheimer's diagnosis with several other methods. The article concluded that their experiments' results outperformed other methods of deep learning architectures like DenseNet121, ResNet50, etc. A similar study done by EL-Geneedy in 2023 showed matching results. The researchers found that there was high accuracy and suggested resilience, with an overall testing accuracy of 99.68% [10]. While both of the articles concluded with similar results, there is a lack of data. Thus, further research needs to be conducted on a larger database since limited data can increase the risk of overfitting in deep learning models. Overfitting occurs when a model learns using the training data too closely, which results in a high accuracy on the training set but poor performance on new, unseen data. Essentially, this is when the AI is "memorizing" the training data instead of generalizing it to new examples [10].

Furthermore, both studies conclude that this experiment is proof of a potentially fast and accurate AD diagnosis module that provides both global and local classification. Global classification means classifying whether the brain MRI suggests a normal brain, a MCI (Mild Cognitive Impairment), or Alzheimer's Disease. The local classification can stratify MCI into Visuospatial Mild Cognitive Decline (VMD), Memory Decline (MD), or Motor Decline (MoD) as the prodromal AD stage.

These studies conclude that utilizing Convolutional Neural Networks shows potential for doctors and patients to quickly and accurately diagnose Alzheimer's Disease. With these research articles showing an accuracy of high 80s to high 90s, the researchers finalized that a CNN detection model can provide more accurate Alzheimer's detection. However, while CNN and deep learning show significant promise in the detection of AD, a more nuanced analysis is required to explore how these AI technologies can be effectively integrated into clinical workflows.

CNN accuracy would benefit from a more critical evaluation of study limitations and potential biases. For instance, one key concern is selection bias. Due to the fact that not many CNN models are trained on fully representative diverse patient populations, this can lead to potentially biased predictions. Further research into cross-validation techniques is essential for assessing model robustness to ensure the reliability of results. Additionally, more studies into the accuracy of CNN models against current clinical diagnostic methods, such as neuroimaging or cognitive assessments, would provide a clearer context for evaluating the true potential and limitations of AI-driven approaches in clinical practice.

One major challenge is the need for large, diverse datasets to train robust models, which can be difficult to obtain due to privacy concerns and the variability of medical data across populations. Because medical data is often sensitive, there are stringent privacy laws, such as the Health Insurance Portability and Accountability Act (HIPAA) in the U.S., that restrict access to patient information. As a result, these regulations—which are important for protecting individual privacy—can limit the availability of the vast datasets needed to train AI models effectively.

Additionally, there are ethical concerns that include the use of personal medical data for the use of AI. To protect patient privacy, informed consent is a key ethical point that must be addressed throughout when collecting data to train AI. An ideal example of informed consent is when a patient is made completely aware of how their information will be used, and shared, as well as having the ability to withdraw if they wish. However, due to the novelty of AI patients may not understand the complete extent or implications, which should be considered as well.

Furthermore, the risk of overfitting could limit the clinical utility of AI tools, particularly in diverse real-world settings. This problem is particularly concerning in the context of AD detection because the clinical presentation of the disease can vary majorly across a plethora of different patient populations. Patients can vary in age, gender, genetics, coexisting conditions, and other factors. In real-world clinical settings, where the diversity of patient data is much broader, variable, and uncertain,

overfitting could result in reduced accuracy. This can go from misdiagnosis or missed diagnoses. This highlights the need for careful validation and regular updating of models, as well as the use of techniques like cross-validation and data augmentation to reduce the risk of overfitting and ensure that these novel AI tools remain effective in real-world applications.

Besides overfitting, medical professionals may also face technical barriers when adopting AI-based solutions, such as insufficient training, a reliance on complex algorithms that are not easily interpretable, and the the future need for seamless integration with existing electronic health record systems. Thus, before AI detection technologies can be fully integrated into modern society, addressing these challenges first is a critical step to ensuring that AI technologies not only show promise in research but can also be translated into practical, everyday use in clinical environments.Overall, there is a lack of data and testing that still needs to be done before this detection method can be implemented in the real world.

3D Neural Tissue Printing and AD

Aside from improving detection methods, the rise of another type of technology—3D bioprinting—has provided researchers with an incredible tool to study different portions of the brain and how they are affected by Alzheimer's Disease. Multiple methods involving the printing of neural tissue have emerged as potential solutions that could potentially reinvent the ways with which we understand, diagnose, and treat this debilitating condition. Through the use of 3D bioprinting models of neural tissue, researchers can study disease progression, screen for therapeutic targets, and test for Alzheimer's more accurately than ever before.

Progress in 3D Neural Tissue Printing for AD Treatment

Of critical importance are the 3D neural cell culture models, known as neurospheroids. These models have provided a promising way to recapitulate Alzheimer's Disease pathology. Neurospheroids are simplified miniaturized three-dimensional models of the brain. Unlike other 3D models, neurospheroids are composed of a diverse population of neural cells—including neurons, glial cells, and astrocytes—which allows them to more accurately simulate the complexity of the brain. These models are significantly valuable in Alzheimer's research because they can be derived from induced pluripotent stem cells (iPSCs) to study disease-specific cellular behaviors and other aspects in a more biologically relevant context. Through the use of animal studies and pluripotent stem cells (iPSC), neurospheroids can mimic the microenvironments of the brain. However, one common issue is that these models currently lack uniformity and reproducibility [10]. In their study, Jorfi et al. were able to generate uniform Neurospheroids from human neural stem cells by removing excess Matrigel matrix before solidifying. Solidifying means that the cells are then allowed to aggregate and mature into three-dimensional structures, using either familial Alzheimer's Disease-specific or iPSC-derived neural progenitor cells to model the disease in a more accurate cellular context. They incorporated Neurospheroids into a Matrigel matrix for better mimicry of the brain environment. Then, the researchers induced neural differentiation which led to the successful generation of neurospheroids that extended thick dendrites outwards to give rise to mature neurons over two to eight weeks. Remarkably, with this method of bioprinting, the neurospheroids showed Alzheimer-like pathology demonstrating their potential effectiveness for future drug screening. This makes it a reliable platform for studying and screening therapies in vitro [11].

Furthermore, an experiment conducted by Yuanwei Yan et al. showcases the potential of 3D bioprinting with functional connectivity in furthering Alzheimer's Disease research. Through the creation of layered neural tissue, the progenitor cells form synapses through the layers. The importance of the structure lies in its structural integrity. Bio-inks, specifically fibrin hydrogel, are the most compatible with neural cells. Using this bio-ink, the extrusion of the 3D bio-print would be able to mimic the brain structure with the laminations of the cortex. However, when the print's ink becomes too thick, it inhibits the growth of neurites, so the ideal thickness of printed neural tissue must be 100-200 mm. This ensures proper oxygen and nutrient transfer and the print remains relatively thin with defined cellular compositions and defined dimensions. For optimal concentration of fibrinogen and thrombin for the survival of human PSC, researchers used cortical NPCs. They found that as cell viability decreased and thrombin concentration increased, higher fibrinogen levels led to cell aggregation [12]. As a result, 85% of the cells survived after 6 hours and 80% of cells survived after 7 days. One limitation of printing technology is it does not allow for the orientation of mature neurons. The tissue is assembled by design, so the print would lack the intrinsic structural organization of brain organoids. However, some intrinsic properties are retained in the tissue and the cells in the bio-print mature rapidly, so it would still complement the existing organoids. The prints that are produced would allow researchers to understand neural networks not just Alzheimer's Disease as it serves as a platform for drug testing and even modeling pathological processes [12].

With the 3D co-axial bio-print, the print of an Alzheimer model could allow researchers to study how to improve human neural progenitor cells (NSCs) through self-assembling clusters and cell development [13]. The co-axial bioprint that is based on 3D extrusion is used to bio-print core-shell fiber, which would exhibit good cell proliferation. To construct a bioprinted Alzheimer's Disease, they developed APP-NSCs with familial Alzheimer's Disease mutation, then characterized the core-shell constructs for nutrient change. By doing so, the researchers in this study were able to evaluate the effect of the bio-printing

process on cell viability and growth while comparing the different microenvironments that were being mimicked. It also would provide functional tissue that mimics muscle fibers or nerve networks [13].

All three studies concluded that the creation of prints from 3D neural cell models can advance the understanding and treatment of Alzheimer's Disease. 3D bioprinting has been used to make artificial neural tissue structures that can be used to study Alzheimer's Disease in a lab setting. Bioprinted neurospheres and cortical layers make stem cells look like amyloid-beta plaques, which are a sign of several diseases, including Alzheimer's. Adding components like fibrinogen, alginate, and purmorphamine to bioinks makes these 3D neural cultures more like the environment in living organisms. Thus, these bioprinted tissues can be useful for testing drugs and learning more about how Alzheimer's works. They can mimic the microenvironments of the brain which create Alzheimer-like pathologies. Because they offer additional platforms for research and testing, these models have the potential to positively influence research in the Alzheimer's Disease community.

Nonethless, it's important to note that while the studies on 3D bioprinting and neural tissue models have the potential to provide valuable insights into short-term outcomes—such as cell viability over a few days—they fall short in exploring the long-term potential of these models, which is crucial for understanding Alzheimer's disease progression. Alzheimer's is a chronic, progressive disorder, and effective models must simulate disease development over extended periods to capture key aspects like amyloid plaque accumulation, tau aggregation, and neuronal degeneration. Thus, future research should primarily have a focus on creating 3D bioprinted models that mimic the long-term dynamics of Alzheimer's, incorporating chronic exposure to pathological factors and tracking changes in cellular behavior, neural network function, and disease markers over time. Such models would better reflect the disease's natural progression and could significantly improve the development and testing of therapeutic strategies.

Scaffolds and Bioink 3D Neural Tissue Printing and AD

While Alzheimer's research can benefit from 3D bioprinting, the materials needed for the procedure are crucial. The appropriate materials can improve the smoothness of research, while mismatched materials might have severe adverse consequences.

A study conducted by T Limongi focuses on investigating how different types of materials can improve treatments for Alzheimer's Disease [14]. Due to Alzheimer's being a progressive neurodegenerative disorder that's characterized by the buildup of amyloid beta plaques and various neurofibrillary tangles that contain hyperphosphorylated-tau, this first research article explores the use of biopolymers, specifically poly--caprolactone (PCL), as scaffolds to drive and promote neural regrowth and regeneration. These biopolymer scaffolds demonstrate the ability to allow and enable the upload and controlled release of active molecules and various medical drugs [14]. However, for further research on the study, a quantitative analysis of functional outcomes is for evaluating the efficacy of these PCL-based scaffolds in promoting neural regeneration. Measuring parameters such as neurite outgrowth, synaptic formation, and cellular viability would provide a clearer understanding of how well these scaffolds function in comparison to traditional cell culture methods. Additionally, it would be valuable to assess whether these biopolymer scaffolds outperform existing approaches in terms of tissue integration and long-term stability, helping to benchmark their potential for clinical application.

Analyzing the Impact on Disease Modeling and Testing

Notably, the study describes microfabricated PCL scaffolds optimized for the controlled release of the Neurotrophin Brain-Derived Neurotrophic Factor (BDNF). What BDNF is known for is that it plays a crucial role in promoting neuronal survival, differentiation, and synaptic plasticity, processes that are important for neuroregeneration. The dysregulation of BDNF has been linked to the pathophysiology of AD, since decreased levels of BDNF are often observed in areas of the brain affected by neurodegeneration like the hippocampus and cortex. Thus, the reduction in BDNF can contribute to impaired neuronal survival, synaptic plasticity, and beyond, which are all of which are hallmark features of AD [15]. PCL is a biocompatible and biodegradable polymer and is particularly well-suited for tissue engineering applications attributed to its ability to support cell adhesion and growth while gradually degrading in the body. The micropatterned PCL devices demonstrated sustained release of bioactive BDNF over 21 days in vitro, offering a promising approach to enhancing neuroregeneration [15]. In primary neuronal cultures, the released BDNF activated BDNF signaling pathways, increased synaptic density, and enhanced neuronal survival. This provides proof-of-principle evidence for the potential therapeutic use of these microfabricated biopolymer devices to enhance neuronal regeneration after injury or lesion [15]. Nonetheless, it is important to note that these results are based on in vitro studies, and further validation in animal models or clinical trials is necessary to confirm their therapeutic efficacy in vivo. The goal of this study was to make 3D structures that look and feel like the original tissue environment. These structures can be used to model diseases or test drugs for AD.

In the study conducted by Claire Benwood, human induced pluripotent stem cells (hiPSCs) were used. HiPSCs were taken from various healthy and sick patients. Afterword, these cells were then turned into neural progenitor cells (NPCs). The Aspect RX1 microfluidic printer was used to bioprint the NPCs into dome-shaped structures [15]. The bioink mixture used in this process included: cells, bio-ink, and puromorphamine (puro)-

releasing microspheres. The purpose was to mimic the environment in the brain and help the NPCs differentiate into cholinergic neurons that look like those in the basal forebrain (BFCN). In addition, the bioink used in this study is made up of several important parts, and each one is very important to the success of the 3D bioprinted AD models. For instance, fibrinogen, alginate, and chitosan are all-natural biomaterials that help cells survive and grow by giving them the support and structure they need. These natural biomaterials help neural progenitor cells multiply and differentiate into mature neurons when they are added to bio-ink. Furthermore, the bioink also has calcium chloride and thrombin in it to give it the right mechanical properties for cell encapsulation and long-term culture [15]. These parts allow the bioink to be chemically crosslinked, which creates the best conditions for cell growth and differentiation. Bioink has polycaprolactone (PCL) microspheres added to it so that the small molecule purmorphamine can be released slowly over time. For neuronal integrity, Purmorphamine is an important pathway. The reason is that it also helps guide the differentiation of neural progenitor cells into a basal forebrain cholinergic neuron phenotype. This is very important because basal forebrain cholinergic neurons are one of the first cell types to be affected by Alzheimer's Disease.

Overall, the structure made by the bio-ink, cells, and purmorphamine successfully resembles the structure of the human brain. This means that these models can be used to speed up research on AD in the future. The bioink's natural materials create a biomimetic environment (scaffolds) for neural cells to grow, and the crosslinking makes sure that the mechanical properties are just right. The purmorphamine microspheres help neurons differentiate into a type that is relevant to AD, which is why it has the potential to revolutionize AD research and treatment. The low viscosity of the bioink also helps keep cell viability high after bioprinting. This new way of 3D bioprinting AD models is a promising way to learn more about how the disease works and come up with possible treatments. For example, these models can be used for high-throughput drug screening, which can allow researchers to test potential Alzheimer's therapies in a more physiologically relevant system. In addition, by using AD-specific neural cell types from bio-inks, these models have the possibility to provide insight into regenerative therapies aimed at repairing or replacing damaged brain tissue in AD patients [16]. This new way of 3D bioprinting AD models is a promising way to learn more about how the disease works and come up with possible treatments.

Researchers have concluded that they created advanced biomaterial scaffolds that can help neurons grow again. Polymers like PCL allow the controlled release of neurotrophic factors like BDNF. However, turning these discoveries into useful clinical therapies is still a big challenge. For instance, further research on conducting meta-analysis is recommended to assess the overall effect sizes of AI-based methods for diagnosis or treatment outcomes across different studies. By doing so, more concrete confirmations can be done about potential consistency and the effectiveness of these technologies.

Conclusions

The objective of the literature review was to investigate how novel technologies 3D bioprinting and AI can be implemented in the diagnosis, treatment, or prevention of AD in the foreseeable future. AI and 3D bioprinting technology provide fresh approaches to managing the intricate nature of AD. When they work together, they make it possible to create more relevant models to understand how the disease works and find new treatments. For instance, CNN and bioink provide possible avenues of growth in diagnosing and treating AD.

However, some issues with these novel approaches are that they are still very new, hence the word novel. For example, it is very hard to print neural tissues that fully replicate the brain microenvironment in humans. To make sure that AI algorithms are ready for clinical use and free of bias, they need to be tested on more datasets. There are also regulatory barriers that need to be cleared before bioprinted tissues or AI-based diagnostics can be used in commercial settings.

To sum it up, this review shows how 3D bioprinting and AI could make huge steps forward in Alzheimer's Disease research and care. Possible next steps will be to get past the technical and regulatory problems that are stopping us from using these potent technologies to their maximum potential, as well as to get enough funding and people from different, various fields to work together. It is important to acknowledge key barriers such as issues with clinical transitions due to further research needed for consistent reproducibility. Additionally, regulatory hurdles and the need for patient-specific customization pose significant obstacles, because personalized treatments must navigate complex approval processes and be tailored to diverse patient populations to ensure both safety and efficacy in real-world settings. AD is still a vast problem for the healthcare industry with more and more people getting it as our population ages. The prevalence of Alzheimer's disease is rising, so we have to tackle it with all of our innovative strengths.

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