

Review

Advances in 3D Bioprinting for Neuroregeneration: A Literature Review of Methods, Bioinks, and Applications

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Abstract: Recent advancements in 3D-bioprinting technology have sparked a growing interest in its application for brain repair, encompassing tissue regeneration, drug delivery, and disease modeling. This literature review examines studies conducted over the past five years to assess the current state of research in this field. Common bioprinting methods and key parameters influencing their selection are explored, alongside an analysis of the diverse types of bioink utilized and their associated parameters. The extrusion-based 3D-bioprinting method emerged as the most widely studied and popular topic, followed by inkjet-based and laser-based bioprinting and stereolithography. Regarding bioinks, fibrin-based and collagen-based bioinks are predominantly utilized. Furthermore, this review elucidates how 3D bioprinting holds promise for neural tissue repair, regeneration, and drug screening, detailing the steps involved and various approaches employed. Neurovascular 3D printing and bioscaffold 3D printing stand out as the top two preferred methods for brain repair. The recent studies' shortcomings and potential solutions to address them are also examined and discussed. Overall, by synthesizing recent findings, this review provides valuable insights into the potential of 3D bioprinting for advancing brain repairment strategies.



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1. Introduction

The human brain is one of the most enigmatic and complex structures in the known universe, characterized by its intricate network of billions of neurons. Addressing neurological disorders poses a formidable challenge despite notable advancements in the field of neuroscience [1]. Among the conditions that profoundly impact the lives of millions worldwide, traumatic brain injury (TBI), neurodegenerative diseases like Alzheimer's and Parkinson's, and strokes are a few examples [1–4], frequently presenting limited treatment options and uncertain outcomes [1,4].

Given the imperative to confront these challenges, recent advancements in biomedical technologies have ignited optimism in this field. Among these innovations, 3D bioprinting has emerged as one of the most promising approaches for repairing and regenerating damaged neural tissues [1,3,4]. Three-dimensional bioprinting is based on tissue engineering and additive-manufacturing principles. It enables the precise placement of biological materials like cells and biomolecules, along with supportive scaffolds, to create an intricate three-dimensional structure resembling native tissues [1–3,5–7]. By leveraging customizable bioink formulations and high-resolution printing methods, the replication of the detailed architecture of the brain on a small scale is possible [5,6]. This facilitates the growth and integration of newly formed neural cells and networks in damaged areas. Additionally, personalizing treatment through the customization of bioprinted structures

according to individual needs has the potential to enhance effectiveness and minimize side effects [1,4–7].

The 3D bioprinting of neural tissue involves fabricating 3D structures composed of biomaterials and living cells to replicate the architecture and functionality of native neural tissue. Generally, with the preparation of bioink, which is a specialized material containing living cells, biomaterials, and growth factors, the 3D-bioprinting process starts [4–6]. Bioink provides structural support and biochemical cues for the structure of cell growth and tissue regeneration. Then, a computer-aided design (CAD) model is generated to define the spatial arrangement of cells and other components in the desired neural tissue structure [4,8]. Then, a bioprinting modality is applied to achieve a scaffold structure. There are various bioprinting techniques, among which extrusion-based, inkjet-based, or laser-based methods are popular [1–6,8]. In some cases, crosslinking is applied to the process to enhance the mechanical integrity of the structure [9]. For the sake of the post-processing phase, incorporating neurotrophic factors, growth factors, and signaling molecules into the bioink formulation can play a significant role in tissue development and maturation [3,7–9]. Alongside these basic steps, additional steps may be incorporated based on specific requirements dictated by the condition being addressed [8,9]. A general overview of the 3D bioprinting of neural tissue is depicted in Figure 1.

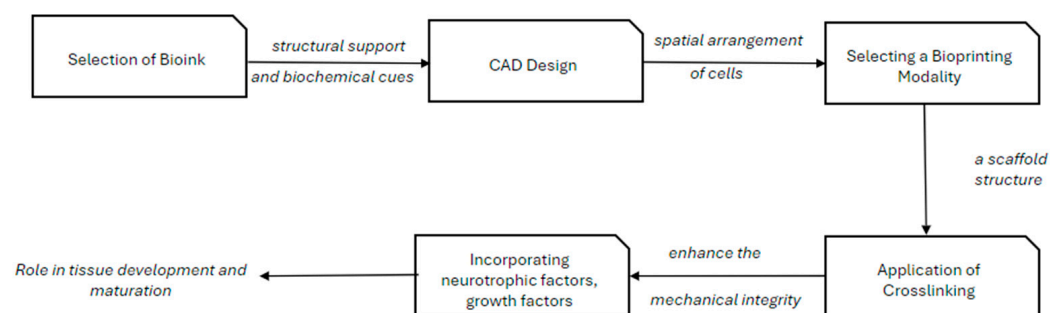


Figure 1. A general overview of 3D bioprinting of neural tissue.

In this literature review, we examine recent studies conducted within the past five years to assess the current state of research on the use of 3D bioprinting for brain repair, encompassing a range of applications from tissue regeneration to drug delivery and disease modeling. We investigate the common methods applied for 3D bioprinting over the past five years and identify the key parameters that need to be considered while choosing a modality. Furthermore, the diverse types of bioink used in these studies are analyzed, and their key parameters are also described in this literature review. Lastly, we focus on brain repairment, elucidating how this 3D bioprinting can be used for neural tissue repairment, tissue regeneration, and drug screening. The steps involved and different approaches for this are discussed.

By delving into key advancements, challenges, and future directions in the field, insights from a diverse array of studies are drawn in this literature review. By critically examining the existing literature, our aim is to elucidate the potential of 3D bioprinting as a transformative tool in treating neurological disorders and advancing the boundaries of regenerative medicine. Through this comprehensive exploration, our goal is to illuminate the growing field of neuro-bioprinting and its implications for future healthcare.

2. Background

Brain injury and neurological disorders encompass a broad spectrum of conditions that profoundly impact individuals' health and well-being. These conditions often result in significant impairments in cognitive, motor, and sensory functions, leading to disabilities and reduced quality of life for affected individuals [1,2]. Moreover, they pose substantial challenges to healthcare systems worldwide due to the complex and long-term nature of their management [3,4]. TBI represents a widespread and significant public health concern

on a global scale; it is the leading cause of death and disability worldwide, affecting approximately 70 million people from various demographic backgrounds [5–7]. Stroke stands as the second leading cause of mortality worldwide, with implications extending beyond death to include heightened risks of chronic disability, sustained physical and cognitive impairments, and diminished quality of life, impacting both stroke survivors and their caregivers [8]. Additionally, neurodegenerative conditions, such as Alzheimer’s and Parkinson’s, impact millions across the globe, resulting in progressive declines in cognition, learning, memory, executive reasoning abilities, and motor functions, as well as dementia, depression, and autonomic dysfunctions [9].

Despite the progress made in biomedical research, treatment choices for brain injury remain constrained, lacking any effective therapy for the restoration of both the structure and function of the injured brain. Conventional treatment approaches for brain injury and neurological disorders typically involve a combination of acute interventions, rehabilitation, and symptomatic management [3]. In the case of TBI, immediate medical attention is critical to stabilize the patient and prevent further damage [7]. Surgical procedures such as craniotomy and hematoma evacuation may be necessary to relieve pressure on the brain and mitigate secondary injuries. Following the acute phase, rehabilitation therapies play a crucial role in promoting recovery and maximizing functional outcomes [6]. Stroke management focuses on restoring blood flow to the affected area through thrombolytic therapy or mechanical thrombectomy, followed by rehabilitation to address deficits in mobility, communication, and cognition [8]. Neurodegenerative diseases, including Alzheimer’s and Parkinson’s, are often managed with medications to alleviate symptoms and supportive care to enhance quality of life. Surgical resection, radiation therapy, and chemotherapy are common treatments for brain tumors aimed at reducing tumor burden and prolonging survival [10].

Despite significant advancements in conventional treatments, there are several limitations. Many individuals experience incomplete recovery following brain injury or disease, with persistent deficits impacting their daily lives [11–13]. Surgical interventions carry risks of complications and side effects, and medications may have limited efficacy or intolerable side effects [14]. Delivering therapeutics to the brain is particularly challenging due to the blood–brain barrier, which restricts the passage of molecules into the brain tissue [11]. Additionally, responses to treatment can vary widely among patients, making outcomes difficult to predict. The long-term costs associated with ongoing care, rehabilitation, and support further compound the burden of these conditions on individuals and healthcare systems [3].

Given the shortcomings of traditional treatment approaches, there is a growing recognition of the need for innovative strategies to address brain injury and neurological disorders. In recent years, emerging technologies such as 3D printing have shown promise in advancing brain repair and regeneration [15]. The utilization of 3D printing is aimed at overcoming the limitations of existing treatments and enhancing outcomes for individuals with brain injuries and neurological conditions.

3. Classification in 3D Bioprinting of Neural Tissue

In neural tissue engineering, several 3D-bioprinting modalities are employed to create complex neural constructs. Extrusion-based, inkjet-based, and laser-based bioprinting and stereolithography are some of the modalities that are frequently used [13–20]. A succinct description of them is given below.

3.1. Types of Modalities of 3D Bioprinting

3.1.1. Extrusion-Based Bioprinting

Extrusion-based bioprinting is the most widely used technique in the field [13–15]. This method involves a process where cells are first mixed with a suitable hydrogel or polymer solution to create a bioink. The bioink is then loaded into a syringe or cartridge and extruded through a nozzle using continuous pressure, which can be pneumatic, mechanical,

or hydraulic. The extruded bioink is deposited layer by layer to build a 3D structure, which is often crosslinked chemically or physically to maintain its shape. This method offers high cell viability due to low shear stress and is versatile in handling a wide range of bioink viscosities. It also allows for the simultaneous printing of multiple cell types and materials, making it particularly useful for creating complex neural tissue constructs, such as neural networks [15]. The relatively low cost and simple operation of extrusion-based bioprinting contribute to its popularity. However, it does have limitations, including a lower resolution (typically 100–500 μm) compared to other methods, the potential for nozzle clogging with highly viscous bioinks, and the possibility of cell damage due to shear stress at the nozzle tip for some sensitive cell types.

3.1.2. Inkjet-Based Bioprinting

Inkjet-based bioprinting, also known as droplet-based bioprinting, was initially developed for producing neural tissue constructs from human-induced pluripotent stem cell (hiPSC)-derived neural cells [16,17]. In this process, a low-viscosity bioink containing cells is formulated and loaded into a printhead with multiple nozzles. Droplets are generated on demand using thermal or piezoelectric actuators and precisely deposited onto a substrate. Multiple layers are built up to create 3D structures. This method offers high printing speed and throughput, excellent control over cell deposition and spatial arrangement, and good resolution (typically 50–300 μm). It is particularly useful for studying neural development and function *in vitro*, as it allows for the formation of precise neural networks within printed constructs. The low cost per unit volume of bioink is another advantage. However, inkjet-based bioprinting is limited to low-viscosity bioinks and may cause cell damage due to thermal or mechanical stress. It also typically results in lower cell concentrations compared to extrusion-based methods.

3.1.3. Laser-Based Bioprinting

Laser-based bioprinting utilizes laser energy to precisely deposit cells and biomaterials. The process typically begins with the preparation of a donor slide, where a thin layer of cell-laden bioink is spread on a laser-absorbing layer. A focused laser pulse is then directed at the absorbing layer, creating a high-pressure bubble that propels a droplet of bioink. This droplet is collected on a substrate below, and the process is repeated to build up 3D structures. Laser-based bioprinting offers a very high resolution (<100 μm) and is a nozzle-free process, reducing the risk of clogging. It can print a wide range of bioink viscosities and causes minimal cell damage due to the absence of direct mechanical stress. These features make it particularly suitable for creating complex, high-resolution tissue models for disease modeling and drug screening [17,18]. However, this method has lower throughput compared to other techniques and higher costs due to the specialized equipment. There is also a potential for unintended cell heating from laser energy.

3.1.4. Stereolithography

Stereolithography is a light-based 3D-printing technique adapted for bioprinting. The process begins with the formulation of a photocrosslinkable bioink containing cells. A thin layer of this bioink is spread on a build platform, and a light source (often UV or visible light) selectively cures specific areas of the layer. The build platform is then lowered, a new layer of bioink is added, and the process is repeated until the 3D structure is complete. Stereolithography offers the highest resolution among the bioprinting techniques (<100 μm), a fast printing speed for complex structures, and an excellent surface finish and structural integrity. It is particularly useful for creating high-resolution neural tissue models, especially when using light-sensitive materials that mimic neural tissues after polymerization [19,20]. However, stereolithography has limitations in material selection due to the photocrosslinking requirement, potential cytotoxicity from photoinitiators and UV exposure, and difficulty in creating structures with internal voids or channels.

Each of these bioprinting methods has its own set of strengths and weaknesses, and all have found successful applications in neural tissue bioprinting to address various functional requirements. Figure 2 illustrates these 3D-bioprinting modalities, highlighting their key features and processes.

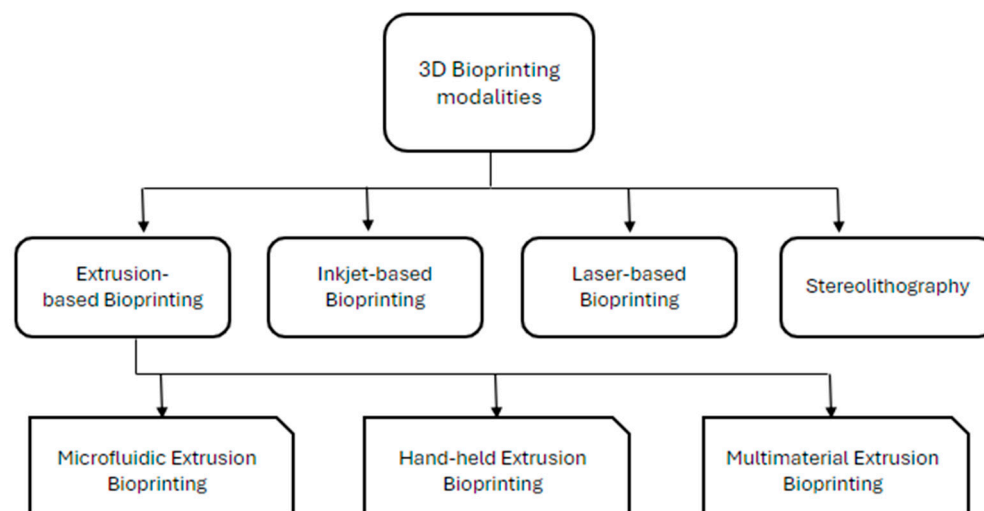


Figure 2. Different 3D-bioprinting modalities.

3.2. Extrusion-Based 3D-Bioprinting Method Classification

As mentioned earlier, the extrusion-based 3D-bioprinting method has been the most common one to use in recent years. This method can be further divided into three more types, Figure 1. These are discussed briefly.

3.2.1. Microfluidic Extrusion Bioprinting

This method involves using microfluidic channels to precisely deposit bioink containing neural cells and biomaterials, allowing for precise control over cell distribution and organization [13]. As it can handle delicate cell structures, it allows for high cell viability during printing. Furthermore, the simultaneous use of multiple biomaterials and bioactive molecules is possible. It is beneficial for creating complex tissue structures. One example of this method usage is in the direct stem cell differentiation [13].

3.2.2. Hand-Held Extrusion Bioprinting

This method involves extruding bioink-containing neural cells through a hand-held device. The most significant fact about this method is that it offers a more portable and accessible option, unlike other methods, which normally require large, specialized equipment [14]. This allows for its implementation in on-site applications or situations where access to advanced laboratory facilities is limited. Despite its simplicity, this method maintains cell viability and function post-printing, making it suitable for modeling neural tissue. Its application can be found in modeling cerebral cortex architecture [14].

3.2.3. Multimaterial Extrusion Bioprinting

This method allows for the deposition of multiple bioinks containing different cell types and biomaterials to create complex neural tissue constructs [15]. This approach enables the simultaneous extrusion of multiple biomaterials, such as growth factors and several types of neural cells, within the scaffold. Like other methods, it also provides precise control over spatial distribution and allows for the creation of a sophisticated scaffold. This method is mostly applied for modeling the spinal cord architecture, which is out of the scope of this literature review [15].

3.3. Biolinks

3.3.1. Classification of Bioinks

Bioink is one of the most utilized and most significant biomaterials in 3D bioprinting. Among several types of bioink, fibrin-based bioink and collagen-based bioink are mostly used. There are some others (Table 1).

3.3.2. Fibrin-Based Bioink

Fibrin-based bioink is typically derived from fibrinogen isolated from blood plasma [1]. Fibrin is a fibrous protein formed from fibrinogen [1]. Due to its cell-binding sites and ability to bind growth factors, fibrin enhances cell attachment, migration, and proliferation. Therefore, it exhibits good biocompatibility and bioactivity [1,2]. Furthermore, fibrin scaffolds facilitate tissue integration by gradual remodeling by cells and are progressively being replaced by native tissue during the healing process. Because fibrin-based bioink is injectable, it is commonly used in applications necessitating injectability and in scenarios such as wound healing and tissue repair where dynamic tissue remodeling is essential [2,3].

3.3.3. Collagen-Based Bioink

Collagen is also a protein that is found in the extracellular matrix of various tissues as their major structural component [4]. Collagen-based bioink usually consists of collagen extracted from natural sources. Similar to fibrin-based bioink, it also has high biocompatibility, making it suitable for tissue scaffolds [4–6]. Additionally, its resemblance to the native extracellular matrix offers a natural microenvironment conducive to cell growth. It is commonly used in bioprinting collagen-rich matrices, such as skin, cartilage, and blood vessels [5,6].

3.3.4. Gelatin-Based Bioink

Because gelatin is derived from collagen, gelatin-based bioink shares many of collagen-based bioink's properties, including high biocompatibility and biodegradability [7,8]. It also offers tunable mechanical properties. This type of bioink is usually used in tissue engineering to regenerate cartilage, bone, vascular tissue, etc. [7,8].

3.3.5. Alginate-Based Bioink

Alginate is a polysaccharide derived from seaweed. It is known for its biocompatibility and low immunogenicity [10]. It offers excellent printability and shape fidelity. Alginate-based bioinks are commonly used in bioprinting soft tissues, such as cartilage, adipose tissue, and liver tissue [11].

3.3.6. Decellularized ECM-Based Bioink

The decellularized ECM is derived from natural tissues that have been treated to remove cellular components [12]. While doing so, it preserves the native ECM architecture and biochemical cues. Similar to collagen-based bioink, as it resembles the native ECM architecture, it offers a biomimetic microenvironment for cell growth and tissue regeneration. It is used in bioprinting applications requiring tissue-specific microenvironments, such as cardiac tissue, skeletal muscle, and liver tissue engineering [12].

Overall, bioink plays a pivotal role in 3D bioprinting, with fibrin-based and collagen-based bioinks being the most commonly used due to their biocompatibility and ability to support tissue integration [1–6]. Additionally, other bioinks, such as gelatin-based, alginate-based, and decellularized ECM-based bioinks, offer unique properties and applications, contributing to the versatility of bioprinting in tissue engineering and regenerative medicine [7,8,10–12]. Figure 3 provides a general overview of various bioinks along with their respective advantages and disadvantages.

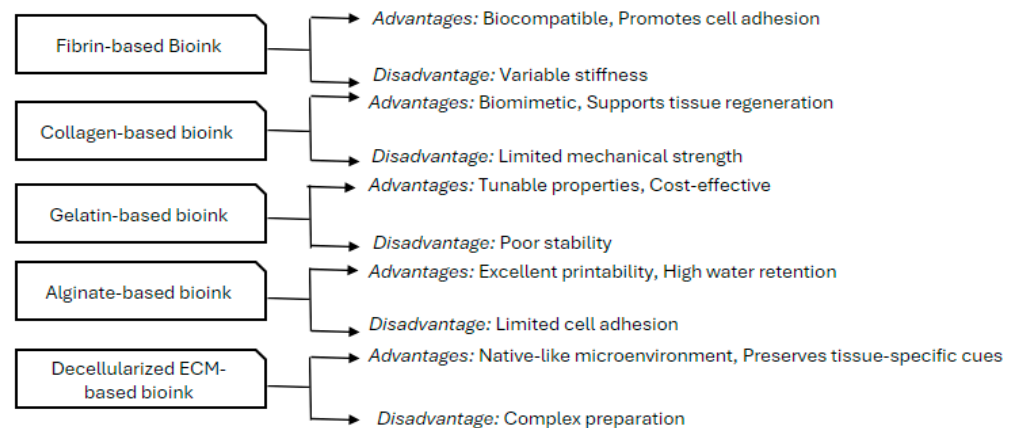


Figure 3. Advantages–disadvantages of different bioink.

3.4. Physicochemical Properties of Bioinks for Neural Tissue Engineering

The selection of appropriate bioinks is crucial for the successful 3D bioprinting of neural tissues, with each bioink requiring specific physicochemical properties aligned with the target tissue's requirements. Table 1 summarizes the key physicochemical properties of the major bioink types used in neural tissue engineering and their suitability for specific applications. Gelation mechanisms and kinetics play a vital role, ensuring structural integrity while maintaining cell viability. Common approaches include temperature-sensitive gelation (suitable for bioinks like gelatin methacrylate), ionic crosslinking (used in alginate-based bioinks), and photocrosslinking, which enables precise spatial control of gelation. Rheological properties, particularly the shear-thinning behavior and viscosity, are critical for both the printability and shape fidelity of neural constructs. Ideal bioinks should exhibit shear-thinning behavior to facilitate extrusion, have sufficient viscosity to maintain shape post-printing, and recover quickly after shear stress to preserve printed structures [1,2].

The stiffness of bioinks must match the mechanical properties of the target neural tissue, with elastic moduli requirements varying across different regions of the nervous system. Brain tissue requires softer bioinks (0.1–1 kPa), while spinal cord and peripheral nerves need moderately stiff (1–10 kPa) and stiffer (10–20 kPa) bioinks, respectively. Bioink degradation rates should align with tissue regeneration timelines, allowing for initial structural support, gradual replacement by native extracellular matrix, and facilitation of neurite outgrowth and network formation. Biocompatibility is crucial, with bioinks needing to support neural cell adhesion, growth, and differentiation through the presence of cell-adhesion motifs, the ability to incorporate growth factors and neurotrophic factors, and low immunogenicity.

Commonly used bioinks in neural tissue engineering include fibrin-based, collagen-based, alginate-based, and GelMA bioinks, each with distinct properties suitable for specific applications. Fibrin-based bioinks offer fast gelation, good cell adhesion, and controllable degradation, making them suitable for brain and spinal cord applications. Collagen-based bioinks provide tunable stiffness and natural ECM mimicry, ideal for brain and peripheral nerve engineering. Alginate-based bioinks excel in printability and cell encapsulation, suitable for spinal cord and drug delivery systems [11,21]. GelMA, with its highly tunable properties and good cell adhesion, is versatile and suitable for various neural tissues. By carefully considering these physicochemical properties, researchers can select or design bioinks that best suit the specific requirements of different neural tissue engineering applications, ultimately improving the success of 3D-bioprinted neural constructs [22].

Table 1. Physicochemical properties of common bioinks for neural tissue engineering.

Bioink Type	Gelation	Rheology	Stiffness	Degradation	Biocompatibility	Suitable Applications
Fibrin-based [1–3]	Fast gelation via enzymatic crosslinking	Shear-thinning	Tunable (0.2–50 kPa)	Controllable	Excellent cell adhesion	Brain, spinal cord
Collagen-based [5]	Temperature-sensitive gelation	Moderate shear-thinning	Tunable (0.1–10 kPa)	Slow	Natural ECM mimicry	Brain, peripheral nerves
Alginate-based [11,21]	Rapid ionic crosslinking	Good printability	Tunable (10–50 kPa)	Slow in physiological conditions	Good cell encapsulation	Spinal cord, drug delivery systems
GelMA [22]	UV crosslinking	Excellent shear-thinning	Highly tunable (0.5–100 kPa)	Controllable	Good cell adhesion	Versatile, suitable for all neural tissues

4. The Key Parameters

For the successful fabrication of functional constructs, some key parameters need to be carefully considered while choosing 3D bioprinting. Following is a brief overview of these parameters.

4.1. The Key Parameters of 3D Bioprinting

4.1.1. Bioink Formulation

Bioink is one of the most important elements in the 3D-bioprinting approach. Its selection is pivotal because it provides the necessary structural support and biochemical signals for the growth and function of neural cells [1,5,6]. Bioink selection should be prioritized by the cell adhesion, proliferation, and differentiation capability of the material [8]. Additionally, its resemblance to the native extracellular matrix (ECM) of neural tissue should also be considered [2]. Hydrogels derived from natural polymers like collagen, fibrin, and gelatin or synthetic polymers such as alginate are typically utilized [1–3,5,6].

4.1.2. Cell Source and Type

After the selection of the bioink, it comes to the selection of the appropriate neural cell type, which is essential for generating neural tissue and characteristics [23,24]. Some examples are neurons, astrocytes, oligodendrocytes, or neural progenitor cells (NPCs). Cell sources may include primary cells, stem cells, or neural cells [23].

4.1.3. Cell Density and Distribution

To achieve proper tissue architecture and functionality, it is important to prioritize the control of cell density and distribution [9–11]. Enhancing cell–cell interactions and neural network formation should be the aim for choosing the optimal cell density. Additionally, considering cell viability is essential in this process [10].

4.1.4. Bioprinting Technique

Once the cell characteristics and bioink are determined, it is important to select the appropriate bioprinting technique. The most popular techniques are extrusion-based, inkjet-based, and laser-based approaches, all used for creating neural tissue constructs [13–20]. Each technique offers unique advantages and drawbacks concerning resolution, speed, cell viability, and the ability to incorporate multiple cell types and biomaterials [13–20].

4.1.5. Crosslinking Method

To stabilize the printed structure and improve the mechanical strength, crosslinking agents or stimuli are commonly applied [9]. However, to ensure cell viability and functionality, the crosslinking method should be compatible with the chosen bioink and cells. Some examples of crosslinking methods are chemical crosslinking, physical crosslinking, photo-crosslinking, enzymatic crosslinking, etc. [9].

4.1.6. Neurotrophic Factors and Growth Cues

Following the printing of the structure, it is important to focus on tissue development and maturation. Incorporating neurotrophic factors, growth factors, and signaling molecules into the bioink formulation can be an effective strategy for enhancing the survival, differentiation, and growth of neurites in the cells [3–7,9].

These are the primary factors that require meticulous optimization to produce complex neural tissue constructs resembling native nervous tissue. Such constructs hold promise for applications in disease modeling, drug screening, and regenerative medicine.

4.2. The Key Properties of 3D Bioprinting

4.2.1. Biocompatibility–Bioactivity

Biocompatibility refers to the ability of the bioinks to facilitate cell adhesion, proliferation, and differentiation without triggering any negative reactions or immune responses [1–3,5,6]. As a result, biocompatible bioink can enhance cell viability [1,3]. On the other hand, bioactivity refers to the ability to interact with cells, thus affecting cellular behavior [4–6]. Bioactive bioink provides biochemical cues that can promote specific biological responses. For example, collagen-based bioinks are both biocompatible and bioactive [4–6].

4.2.2. Mechanical Properties

The physical characteristic of the printed construct is referred to as the mechanical properties. It includes the stiffness, elasticity, and tensile strength. These characteristics are crucial for maintaining structural integrity and facilitating cell attachment and movement [10,11]. In the context of nervous tissue, it is essential for the mechanical properties of the bioink to closely resemble those of natural neural tissue [13]. This ensures proper cell response and tissue development. For example, a softer hydrogel should be considered for brain tissue repair, whereas stiffer scaffolds may be preferred for spinal cord regeneration [10,11].

4.2.3. Biodegradability

The ability of the bioink to break down into non-toxic byproducts in the body over time is known as biodegradability [22]. This property is important for tissue repair because it enables the gradual replacement of the scaffold with native tissue during tissue regeneration, eliminating the necessity for surgical extraction [22,25]. A good example is gelatin methacrylate (GelMA), which is derived from natural gelatin. It degrades over time into byproducts, such as amino acids, that can be metabolized and excreted by the body [22].

4.2.4. Bioink Rheological Properties

Rheological properties encompass characteristics like viscosity and shear-thinning behavior, which determine how a bioink flows and changes shape when subjected to stress [7,8]. These properties affect extrusion, deposition, and the final structure of the printed construct. Controlling the rheological properties is essential for attaining precise printing outcomes [8]. For instance, gelatin-based hydrogel exhibits a decrement of viscosity when under shear stress, known as shear-thinning behavior, facilitating easier extrusion [8].

4.2.5. Electrical Conductivity

In neural tissue engineering, electrical conductivity is crucial because of the electrical functions of neurons and neural networks. Similarly, when designing bioinks, it is important to consider their electrical conductivity [4,26]. The incorporation of conductive biomaterials into bioink can enhance conductivity [4]. For example, conductive polymers (e.g., polypyrrole and polyaniline) or carbon-based nanomaterials (e.g., graphene and carbon nanotubes) can be incorporated for this purpose [4,26].

Optimizing these key parameters of bioink is essential for producing functional and biomimetic tissue constructs in 3D bioprinting, enabling applications in various fields, including tissue engineering, regenerative medicine, and drug discovery.

5. Brain Repairment

The brain is a complex structure with various intricate components. It is protected by a highly vascularized layer called the meninges, and its different regions have distinct functionalities and physical characteristics originating from unique developmental processes. Additionally, central nervous system (CNS) disorders can result from genetic factors as well as exposure to environmental toxins. These complexities pose challenges in comprehending brain development and modeling neurological diseases at the tissue level. Facing these challenges, this section focuses on the methods of utilizing 3D bioprinting to repair the brain and regenerate neural tissue. Furthermore, this section also discusses the integration of diverse types of neural cells into 3D-bioprinted structures and the utilization of 3D bioprinting for studying neurological disorders.

5.1. *Methods of Brain Repair Using 3D Printing*

5.1.1. Neurovascular 3D Printing

The neurovascular unit, consisting of neurons and glial cells in the neural segment and endothelial cells, pericytes, and vascular smooth muscle cells in the vascular segment, is essential for brain health [21]. The interface and interactions of neural and vascular elements play pivotal roles in regulating cerebral blood flow through mechanisms, such as neurovascular coupling, maintaining blood–brain barrier integrity, managing neuroinflammation, and preserving neuronal function [27]. Damage to this unit can disrupt cerebral blood flow regulation, leading to neurovascular dysfunction and neurodegeneration and resulting in various brain disorders, including Alzheimer’s disease, Parkinson’s disease, and stroke [1,3]. Hence, modeling both the function and dysfunction of the neurovascular unit is crucial for comprehending normal physiology and uncovering the molecular and cellular mechanisms that underlie various neurovascular and neurodegenerative diseases.

Neurovascular 3D printing is a rapidly evolving field that focuses on replicating and reconstructing the intricate vascular networks within the brain using advanced additive-manufacturing techniques. Three-dimensional printing provides the capability to construct patient-specific vascular models with geometric accuracy, facilitating clinical decision-making, including treatment planning [28]. By utilizing medical imaging data such as magnetic resonance imaging (MRI) or computed tomography (CT) scans, detailed three-dimensional models of cerebral arteries, veins, and capillaries can be created [29]. These models provide invaluable insights into the anatomical variations and pathological conditions affecting brain vasculature, aiding in both diagnostic and therapeutic decision-making processes. Moreover, neurovascular 3D printing facilitates preoperative planning and simulation for complex neurosurgical procedures. Patient-specific neurovascular models generated through 3D printing allow surgeons to visualize the unique vascular anatomy of individual patients; identify optimal surgical approaches; and simulate interventions, such as aneurysm clipping or arteriovenous malformation resection [30].

Various studies in the last five years have focused on clinical usage and research purposes related to 3D printing. Chopra et al. (2021) used CT, CT angiography (CTA), MRI, and diffusion tensor imaging (DTI) data from five patients to print 3D skull base tumor models with cranial nerves and blood vessels for surgical assistance and educational purposes [31]. Hudelist et al. (2024) introduced a new neurovascular surgical training platform by integrating synthetic 3D-printed models with placental vascular structures, resulting in a partially realistic surgical environment [32]. Another study evaluated the clinical effectiveness of a 3D-printed brain tumor model in presurgical planning, with a particular emphasis on variations in the extent of resection [33]. A study by Li and colleagues showed the effectiveness of using a 3D-printed cerebral aneurysm model for microcatheter shaping in neurovascular interventional training [34]. Another study devised a cost-effective and streamlined method to model intracranial aneurysms and the surrounding neurovasculature utilizing 3D-printing technology [35]. Saleh and colleagues created a highly anatomically accurate skull base model that proves valuable for educational purposes using 3D printing [36]. Another study developed a patient-specific 3D-printed model to simulate acute ischemic

stroke and study the effects of variations in clot location, composition, length, and arterial angulation using digital subtraction angiograms (DSAs) [28]. Wang and colleagues devised a two-stage approach for bio-fabricating functional 3D neurovascular constructs in vitro, featuring a low modulus of the extracellular matrix (ECM) for understanding the neurovascular unit function and screening neuro-drug [37]. Ye et al., 2020, fabricated a 3D model of the brain arteriovenous malformation as an educational and clinical tool using CTA and magnetic resonance venography (MRV) images [38].

5.1.2. Bioscaffold 3D Printing

Bioscaffold 3D printing represents an innovative approach in tissue engineering and regenerative medicine, utilizing advanced 3D-printing technology to fabricate intricate scaffold structures that closely mimic the natural ECM of biological tissues [39,40]. This technology holds significant promise for a wide range of applications, revolutionizing the field by providing precise control over scaffold composition, architecture, and functionality. Bioscaffold 3D printing allows for the fabrication of biomimetic scaffold structures that replicate the complex microenvironment of native tissues [41]. With 3D printing of the scaffolds, parameters such as scaffold porosity, pore size, and surface topography can be manipulated in order to tailor the scaffolds to promote cell attachment, proliferation, and differentiation [39,41]. These biomimetic scaffolds provide an ideal substrate for tissue regeneration and repair, offering a supportive environment for the development of functional tissue substitutes for transplantation and regenerative therapies. Moreover, bioscaffold 3D printing enables the incorporation of cells and bioactive molecules into the scaffold matrix, facilitating tissue engineering and regeneration [41]. Cells can be seeded onto or within the scaffold structure, where they interact with the scaffold material and neighboring cells to form organized tissue structures. This approach promotes cell viability, phenotype maintenance, and tissue-specific functionality, making it suitable for engineering various tissues, such as bone, cartilage, and skin [40]. Furthermore, bioscaffold 3D printing serves as a valuable tool for biomedical research and disease modeling. By engineering biomimetic scaffolds that recapitulate the structural and biochemical cues present in native tissues, researchers can study cell behavior, tissue development, and disease progression in a controlled experimental setting [42]. Bioscaffold-based models offer insights into physiological processes, disease mechanisms, and drug responses, facilitating the development of novel therapeutics and personalized treatment strategies [40,43].

In neurotrauma, the consequence from a tissue perspective is the formation of a cavitory defect or tissue discontinuity at the lesion site, disrupting the unidirectional architecture of nerve tracts and leading to the destruction of the neural network responsible for transmitting signals in the central nervous system [44]. Repairing the neural network requires functional tissue continuity at the lesion site, making 'bridging' the lesion a crucial step; however, the challenge lies in ensuring that the scaffold used as a 'bridge' closely mimics native tissue, both biologically and architecturally, in tissue engineering approaches. Recent studies have demonstrated the potential of 3D scaffolds for promoting brain tissue regeneration in various preclinical models of neurological disorders and injuries, including stroke, TBI, and neurodegenerative diseases. By providing a biomimetic microenvironment that recapitulates the complex architecture and biochemical cues of the native brain tissue, 3D scaffolds hold promise for enhancing endogenous repair mechanisms and restoring lost neurological function [45].

One of the key advantages of 3D scaffolds is their ability to provide structural support and guidance to regenerating neural cells [45]. An optimal microenvironment promoting cell adhesion and migration can be created by precisely controlling scaffold properties, such as the porosity, pore size, and mechanical stiffness [46]. This enhances the integration of transplanted cells or endogenous neural progenitors into the surrounding tissue, fostering the formation of functional neuronal networks. Moreover, 3D scaffolds can serve as carriers for bioactive molecules and growth factors, which play crucial roles in regulating cellular behavior and tissue regeneration [47,48]. By incorporating growth factor-releasing micro-

spheres or nanoparticles into the scaffold matrix, researchers can achieve spatiotemporal control over the delivery of bioactive cues, promoting cell survival, proliferation, and differentiation at the injury site [47]. Furthermore, advances in biomaterials science have enabled the development of biocompatible and biodegradable scaffold materials that can seamlessly integrate with the host tissue [49]. These materials provide temporary structural support during the early stages of tissue regeneration and gradually degrade over time, allowing for the remodeling of new tissue and minimizing adverse foreign body reactions.

Chen et al., 2022, studied the impact of implanting 3D-printed collagen/silk fibroin scaffolds loaded with mesenchymal stem cell secretome as a prospective therapy for spinal cord injury [50]. Their findings suggest that this approach indeed holds promise as a potential treatment. A study compared the effectiveness of 2D and 3D culture systems in generating functional motor neuron-like cells from adipose-derived stem cells [51]. The findings suggested that the 3D system might create a conducive environment for the proliferation of motor neuron-like cells. In their 2021 study, Elnaggar and colleagues explored the combined impact of extracellular matrix proteins fibronectin and laminin within a poly- ϵ -caprolactone nanofiber scaffold on neuronal adhesion and sprouting [52]. They compared this effect with scaffolds containing only a single immobilized protein.

Liu et al., 2022, conducted a study where they utilized 3D printing to fabricate injury-preconditioned secretome/collagen/heparan sulfate scaffolds [53]. Their findings demonstrated that these scaffolds facilitated the recovery of cognitive and locomotor function following TBI in rats. In another study, Liu et al. (2023) evaluated the effectiveness of a newly developed 3D-printed collagen/chitosan scaffold infused with exosomes obtained from neural stem cells pre-treated with insulin-like growth factor-1 [54]. Their study aimed to assess the scaffold's potential in enhancing TBI repair and promoting functional recovery in rat models of TBI. Parikh et al. (2020) conducted a study to investigate how scaffold surface features influence tumor-scaffold interactions [55]. Their aim was to enhance our understanding and optimize the development of scaffold-based chemotherapy applications. Another study examined intracellular calcium activity in neurons within 3D hippocampal cultures, comparing those interfaced with graphene to those without [56]. The findings indicate that although the resulting 3D neuronal networks had similar cellular composition and morphology, graphene had the capacity to modify the synaptic inhibitory control of emerging synaptic activity. Reginensi et al. (2020) aimed to gain insight into the distinctions among the extracellular matrices from three subregions, which could prompt specific cell responses [57]. They detailed the characterization of the resulting decellularized tissues and assessed their ability to foster neuronal attachment and growth through in vitro studies involving PC12 cells.

5.2. Steps for Brain Development

5.2.1. Direct Cell Integration in 3D-Bioprinted Scaffolds

The direct implementation of neural cells into hydrogel bioinks to make 3D-printed scaffolds has been found in several studies [13,22,23,58–60]. One such example is the lattice-shaped small tissue structures by 3D bioprinting human neural stem cells constructed by Gu and colleagues [58]. Additionally, hiPSCs have been a valuable tool in the field of 3D bioprinting because they have the capability to be expanded indefinitely and to differentiate into the various cell types present in the central nervous system (CNS). For instance, microfluidic patterned printing was utilized to create 3D-bioprinted fibrin-based structures containing hiPSC-derived neural aggregates [13]. During printing, the cells stayed healthy and continued to grow for 41 days afterward. They showed visible nerve growth and early signs of becoming neurons [13]. In another study a combination of fibrin-based bioink formulation with drug-releasing microspheres was found for bioprinting tissues, where a fibrin bioink incorporated with microspheres releasing guggulsterone was used to induce subtype-specific neuronal differentiation [23]. This controlled release promoted the differentiation of hiPSC-derived NPCs into dopaminergic neurons within a 30-day culture period [23]. In a different study, GelMA was modified with dopamine to

produce a bioink that enhanced the differentiation of neural stem cells [22]. Dopamine is an essential neurotransmitter that aids in regulating neuronal development and promoting neurite growth. However, GelMA possesses excellent biocompatible and biodegradable properties. A noticeable formation of neural networks and increased expression of neuronal genes was observed in the stem cells. This study highlighted two factors: firstly, the importance of including factors that mimic the natural biochemical environment of tissues, and secondly, the demonstration of 3D bioprinting as a support for different cell types in the brain [22]. Apart from these approaches, the direct integration of neural stem cells directly into bioprinted scaffolds is noticeable in several studies [59,60]. This direct integration did not impact negatively on the cells' viability and activity.

These advancements suggest the potential to include a wider variety of cell types to create scaffolds that closely mimic the complexity of neural tissue. Such scaffolds could provide a strong foundation for studying cell interactions and the factors influencing differentiation.

5.2.2. Bioprinting for Cerebral Cortex Modeling

Modeling the cerebral cortex requires considering its laminated neuronal layers, each with unique roles in information processing. Traditional 2D cultures lack cortical lamination characteristics, but recent studies using 3D bioprinting have shown progress [61]. Three-dimensional bioprinting offers user control over spatial organization, enabling precise formation of distinct layers, which was not possible in previous studies and approaches. For instance, in one study, a six-layer construction was made using the 3D print approach, specifically using a hand-held extrusion bioprinter [14]. In another study, to understand the cellular interactions during cortical development, a lipid-bilayer-supported droplet bioprinting technique was utilized to create scaffolds, which achieved precise cellular organization [62]. This method illustrated cell viability after printing [62].

5.2.3. Three-Dimensional Bioprinting for Cancer Modeling

The use of 3D bioprinting to model cancers has increased, particularly in studying how diseased cells interact with their surrounding microenvironment [63]. In one of the recent studies, a bioink containing alginate, gelatin, and glioma stem cells was developed to mimic the glioma microenvironment. This allowed for the study of tumor vascularization [64]. In a separate study, a scaffold-free 3D-bioprinting method was used to stimulate glioma invasion [24]. Spheroids were created from hiPSC-derived NPCs. Using 3D confocal microscopy, they observed the invasion of glioma cells into the neural progenitor population in real-time and in fixed samples.

This promising research later led to the possibility of creating patient-specific models for investigating tumor invasion [24]. Tang and colleagues investigated the possibility of adding additional neural cell types into the tumor system to better replicate the brain tumor microenvironment [64]. Their research indicated that this approach better replicated tumor transcriptional profiles than traditional 2D culture methods and successfully modeled tumor cell invasion, cellular interactions, and immune responses [64].

Gliomas, which can occur in both the brain and spinal cord, are being modeled using 3D-bioprinting techniques. This approach allows researchers to create more accurate representations of the tumor microenvironment. For instance, 3D-bioprinted glioma stem cell models have been developed to study brain tumors. These models can better mimic the complex structure and heterogeneity of gliomas, providing a more realistic platform for studying tumor behavior and testing potential treatments [65,66].

Three-dimensional bioprinting is being used to create models for various types of tumors, including soft, solid, and liquid tumors. This versatility is crucial because it allows researchers to study different cancer types in environments that more closely resemble their *in vivo* conditions. For solid tumors, like those found in the brain or spinal cord, 3D bioprinting can create scaffolds with tunable stiffness, mimicking the mechanical properties

of the original tissue. This is particularly important for studying how cancer cells migrate within these structures [67].

One of the key advantages of 3D bioprinting in cancer modeling is its ability to reconstitute the cancer microenvironment. This is crucial for gliomas and other brain or spinal cord tumors, as their behavior is heavily influenced by their surrounding environment. Additionally, 3D-bioprinted models can incorporate various cell types, extracellular matrix components, and even vascular structures, providing a more comprehensive view of tumor development and progression [66].

Research has also been conducted regarding neuroblastoma (NB). NB is a type of brain tumor that affects young children [68]. In one study, an alginate-gelatin bioink was developed in combination with NB cells, iPSCs, and neural stem cells, and the extrusion bioprinting method was utilized [68]. In another recent study, NB cells were incorporated into scaffolds, and the result was enhanced differentiation and neural network formation [10]. An alginate–collagen I bioink was used in another study to form a biomimetic scaffold with the purpose of investigating NB cell behavior [69].

Overall, these studies collectively underscore the capability of 3D-bioprinting methods to replicate the tumor microenvironment in laboratory settings and provide a strong, efficient platform for studying the behavior of cells and the pathophysiology of brain tumors.

6. Limitations and Future Directions

6.1. Limitations of the Literature

Despite its numerous advantages, 3D bioprinting has some limitations. Firstly, the structural fidelity and stability of 3D-bioprinted structures can be compromised by the soft tissue bioinks that have an unstable nature [70]. Additionally, prolonged printed times can result in the deformation or collapse as well as the dehydration of hydrogel constructs. Secondly, bioprinting techniques may subject cells to mechanical and thermal stresses on cells, leading to reduced viability and altered cellular behavior [17]. Thirdly, cellular damage can occur during the printing process. Fourthly, 3D bioprinting is constrained by printing resolution, with some techniques offering high resolution but often requiring lengthy printing durations and complex organization [71]. Nevertheless, the ability to achieve features smaller than 50 μm is still challenging [71]. Additionally, a 3D-printed model may not always be comparable with intraoperative observations. Furthermore, obtaining all the desired characteristics of the scaffold remains challenging due to limitations in fabrication techniques. Lastly, the absence of perfusable vascular networks in current bioprinting methods limits nutrient and oxygen transport potentially.

6.2. Limitations of This Review

This literature review focuses mainly on human studies. Additionally, non-English studies and animal studies were omitted from this review. Consequently, any potential findings and associations arising from these aspects are not represented in this review.

6.3. Future Directions

The field of 3D bioprinting for neuroregeneration is rapidly evolving, with several exciting trends on the horizon. Advanced biomaterials and smart bioinks are being developed to better mimic the complex extracellular environment of neural tissues, incorporating growth factors and cell-signaling molecules for enhanced functionality. The integration of artificial intelligence and machine learning in bioprinting processes promises to optimize print parameters and predict tissue behavior, potentially leading to more successful outcomes. In situ bioprinting techniques are being explored for direct application in the brain, which could revolutionize treatment approaches for acute brain injuries. Furthermore, the combination of 3D bioprinting with other cutting-edge technologies, such as optogenetics and organ-on-a-chip platforms, opens up new possibilities for creating more sophisticated and functionally relevant neural tissue models.

New technologies are expected to replace the ongoing techniques that offer unique advantages but also face distinct challenges [72,73]. Extrusion-based bioprinting excels in its ability to handle high-viscosity bioinks and create larger structures, making it suitable for producing bulk brain tissue. However, it often struggles with achieving high resolution and can subject cells to significant shear stress. Inkjet-based bioprinting, on the other hand, provides excellent precision and speed, allowing for the creation of intricate neural networks, but it is limited in its ability to work with high-viscosity materials and may face issues with cell viability due to the droplet ejection process [74]. Laser-based bioprinting, such as laser-induced forward transfer (LIFT), offers unparalleled resolution and cell viability, crucial for replicating the brain's complex microstructures, but it can be slow, expensive, and limited in scalability. Stereolithography, while capable of producing highly detailed structures with good resolution, often faces biocompatibility issues with its photopolymerizable materials and may struggle with incorporating living cells directly into the printing process [75–77]. Each of these techniques presents a trade-off between resolution, scalability, cell viability, and material versatility, with ongoing research aimed at overcoming their respective limitations to better replicate the intricate architecture and functionality of brain tissue.

Innovation in 3D bioprinting for neuroregeneration is driving the field toward groundbreaking approaches. The concept of 4D bioprinting, which incorporates time as the fourth dimension, is particularly promising for creating dynamic, stimuli-responsive neural constructs that can adapt to changing physiological conditions. Bioprinted neural organoids are emerging as powerful tools for personalized medicine and drug screening, offering the potential to model individual patients' neurological conditions and test treatment efficacy [72]. The integration of bioelectronics with 3D-bioprinted neural tissues is another exciting frontier, potentially enabling the direct monitoring and modulation of neural activity within engineered constructs. Perhaps most ambitiously, researchers are exploring the potential of bioprinted neural interfaces for brain–computer interactions, which could have profound implications for treating neurological disorders and enhancing human cognitive capabilities [63,68,72].

The complexity of 3D bioprinting for neuroregeneration necessitates strong interdisciplinary collaborations to drive meaningful advancements [25]. Partnerships between neuroscientists and materials scientists are crucial for developing next-generation bioinks that can better replicate the neural microenvironment and support functional tissue development. Collaborations between bioengineers and clinicians are essential for translating bioprinting technologies from bench to bedside, ensuring that engineered constructs meet clinical needs and regulatory requirements. The involvement of computer scientists working alongside biologists can lead to optimized bioprinting processes and more sophisticated tissue designs, leveraging computational modeling and machine learning algorithms. These cross-disciplinary efforts not only accelerate technological progress but also foster a more comprehensive understanding of the challenges and opportunities in neural tissue engineering. As these technologies mature, they may also contribute to broader applications in cognitive enhancement and brain–machine interfaces, opening up new frontiers in human–computer interaction and neural augmentation [73].

7. Conclusions

Recent advancements in 3D-bioprinting technology signify a paradigm in the framework of brain repair and regeneration. This literature review aims to provide a comprehensive analysis of studies conducted over the past five years, shedding light on the current state of research in this dynamic field. Through an exploration of common bioprinting methods, key parameters influencing their selection, and the diverse array of bioinks utilized, this review aims to underline the multifaceted nature of 3D bioprinting for neural tissue repair. Moreover, by elucidating the intricate process involved in the 3D bioprinting of neural tissue, from bioink preparation to scaffold fabrication and post-processing phases, there is tremendous potential for this technology in terms of addressing the complexities of

brain injury and neurological disorders. By leveraging customizable bioink formulations and high-resolution printing methods, 3D bioprinting offers the possibility of replicating the detailed architecture of the brain on a small scale, facilitating the growth and integration of newly formed neural cells and networks in damaged areas.

Furthermore, it is important to emphasize the importance of ongoing innovation and collaboration in advancing the field of neuro-bioprinting. By synthesizing key advancements, challenges, and future directions, this review underscores the transformative potential of 3D bioprinting as a tool for treating neurological disorders and contributing to advancements in regenerative medicine. In conclusion, it is evident that neuro-bioprinting and its implications for future healthcare are becoming increasingly clear and significant. By encouraging interdisciplinary work together and using new technologies, 3D bioprinting holds immense promise in revolutionizing the way we approach brain repair and regeneration, ultimately offering hope to millions worldwide affected by neurological conditions.

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