

Future prospects of tissue engineering in the treatment of addiction related brain disorders: From modeling to regeneration

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Abstract

Addiction imposes a substantial global health burden, driving not only psychosocial dysfunction but also irreversible structural and neurochemical damage to brain regions including the prefrontal cortex, amygdala, and nucleus accumbens. Conventional pharmacotherapy and psychotherapy alleviate behavioral symptoms but fail to repair underlying neural deficits. Tissue engineering—an interdisciplinary pillar of regenerative medicine offers a transformative strategy for neural restoration. This review synthesizes current advances in biomaterial scaffolds, stem cell therapies, neurotrophic factor delivery, and three-dimensional bioprinting, which collectively support neuronal survival, axonal guidance, and synaptic reorganization. Additionally, brain organoids and brain-on-a-chip platforms enable high-fidelity modeling of addiction pathophysiology for drug screening and mechanistic studies. Preclinical evidence indicates that neural stem cell transplantation combined with growth factor-eluting scaffolds (e.g., BDNF, NGF) and controlled electrical stimulation promotes functional recovery and attenuates addiction-related behaviors. Early clinical reports show encouraging improvements in cognition, impulse regulation, and relapse prevention, though limitations including small cohorts, short follow-up, and protocol heterogeneity persist. We critically evaluate these biological and engineering principles, highlight translational hurdles—such as scalability, immunogenicity, and regulatory approval—and propose future research directions to bridge the gap between bench and bedside, ultimately advancing regenerative strategies for addiction.

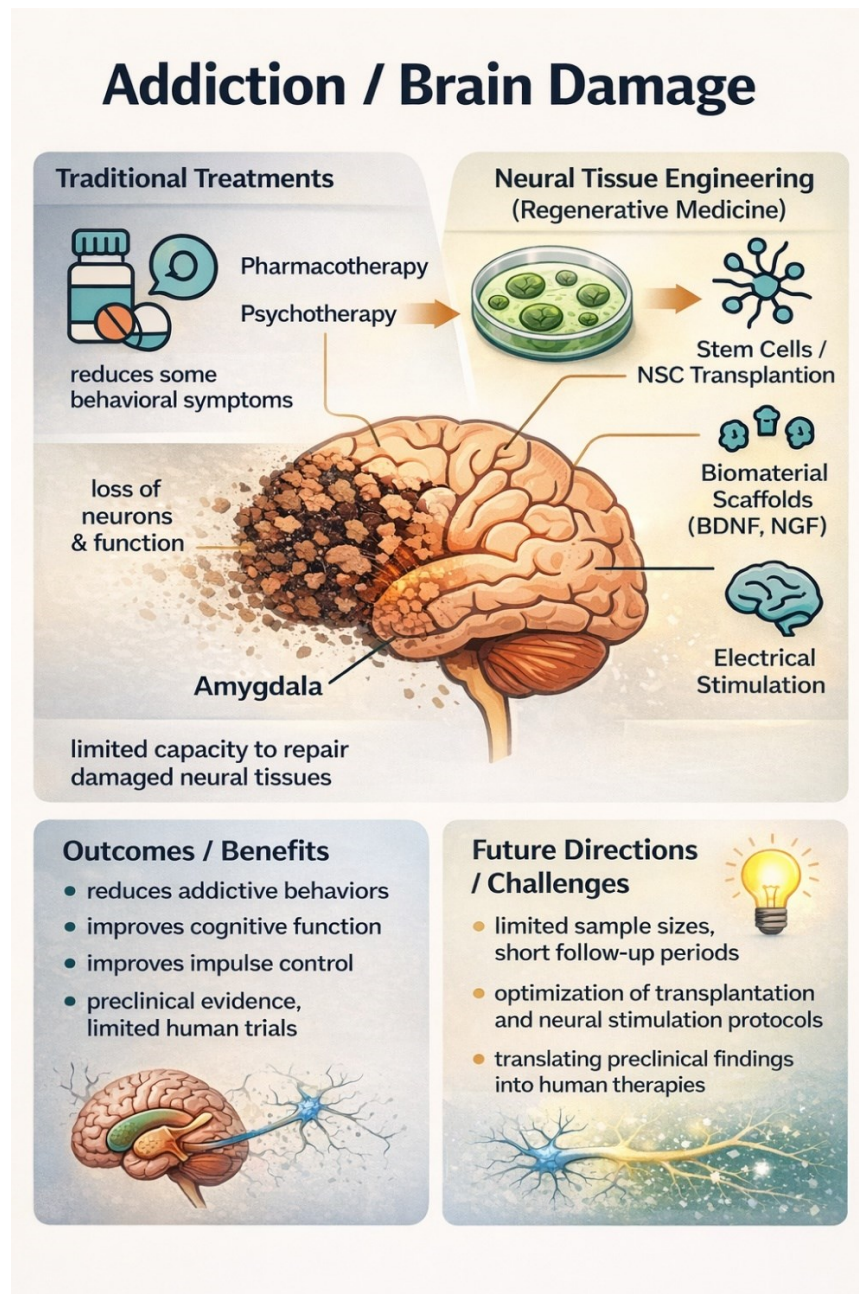
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Introduction

Addiction represents one of the most complex health issues, arising from the interplay of biological, psychological, and social factors (1, 2). This condition not only induces behavioral and cognitive changes but also profoundly affects the cellular and tissue structures of the brain (3). Recent research has shown that repeated exposure to addictive substances alters the brain's biological processes in ways that make returning to normal function challenging, and sometimes impossible (4).

These changes include neuronal death, reduced synaptic connectivity, neuroinflammation, and disruptions in neurotransmitter release and reuptake. From a neurobiological perspective, addiction is considered a chronic brain disease affecting reward, decision-making, and memory pathways (5). Substances such as nicotine, morphine, cocaine, and methamphetamine cause abnormal dopamine release in specific brain regions, disrupting the neural circuits involved in behavioral control (6)

Graphical abstract



Graphical abstract contrasts traditional symptomatic treatments for addiction (which primarily reduce behavioral symptoms but offer limited capacity to repair damaged neural tissues) with emerging regenerative strategies based on neural tissue engineering. The latter approach targets key brain regions such as the prefrontal cortex and amygdala through stem cell transplantation, bio-material scaffolds delivering neurotrophic factors (Brain-Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF)), and electrical stimulation. These interventions aim not only to alleviate addictive behaviors but also to restore cognitive function and impulse control by reconstructing damaged neural circuits. While preclinical evidence is promising, challenges remain in translating these findings into human therapies, including optimizing transplantation and stimulation protocols and addressing limitations in sample sizes and follow-up durations.

Over time, this dopaminergic dysregulation leads to dependency and diminishes the brain's capacity to experience pleasure from natural stimuli (2, 7).

Conventional addiction treatments primarily target behavioral and pharmacological aspects, including detoxification, psychotherapy, replacement therapies, and social support. However, these interventions often fail to repair structural brain damage (8). Restoring lost neurons, reestablishing neural connections, and correcting the cellular microenvironment remain major challenges for sustainable addiction recovery (6). Tissue engineering, as an emerging field of regenerative medicine, offers new hope for addressing these challenges (9). Its aim is to design and construct living structures capable of restoring the function of damaged tissues. In the context of brain disorders, tissue engineering can provide an environment for new neuron formation and network activation using neural stem cells, bio-material scaffolds, and growth factors (10, 11).

Advances in three-dimensional modeling and bioprinting technologies have further enabled detailed studies of cellular and molecular mechanisms underlying addiction (12). Researchers can now employ brain organoids and brain-on-a-chip systems to simulate the effects of addictive substances on neural cells and circuits (13). These models not only serve as valuable research tools but also help identify more effective regeneration strategies (14). Therefore, tissue engineering plays two critical roles in addressing addiction-related brain disorders: first, it allows precise modeling of tissue damage to better understand addiction mechanisms; second, it facilitates brain function restoration through the replacement or stimulation of new neural cells (15). The following sections review the biological foundations of addiction-related neural damage and the technologies used in neural tissue engineering, providing a comprehensive perspective on future regenerative approaches for addiction therapy.

Theoretical and Biological Foundations of Addiction-Induced Brain Disorders

From a biological perspective, addiction is a chronic disorder of the central nervous system resulting from persistent substance use, leading to lasting structural and functional changes in the brain (16). These alterations not only modify behavior but also induce cellular and molecular reorganization of neural networks (17). The human brain consists of billions of neurons interconnected through synapses, and any disruption in these connections can impair essential functions such as memory, decision-making, emotion regulation, and behavioral control

(6). A key pathway involved in addiction is the mesolimbic dopaminergic system, which extends from the ventral tegmental area to the nucleus accumbens and is responsible for reward and pleasure sensations (18, 19). Addictive substances overstimulate this pathway, causing abnormal dopamine release (6, 20). Consequently, the brain gradually loses sensitivity to natural stimuli, responding primarily to the substance to experience reward. This process establishes a reinforcing cycle of dependency that is difficult to break (8).

At the cellular level, addiction alters gene and protein expression related to neuronal survival (21). These changes often involve increased oxidative stress, neuroinflammation, and activation of apoptotic pathways, ultimately resulting in neuronal death (22). Regions such as the prefrontal cortex, amygdala, and hippocampus demonstrate reduced neuronal density and disrupted synaptic connectivity, contributing to cognitive deficits, impaired impulse control, and risky behaviors observed in addicted individuals (23, 24). Glial cells, which provide structural and metabolic support to neurons, are also affected. Normally, glial cells regulate the chemical environment and modulate inflammation, maintaining neural network stability (25). However, excessive activation of microglia and astrocytes during substance abuse leads to the release of pro-inflammatory cytokines, exacerbating tissue damage and creating an environment unfavorable for neurogenesis (3).

From a neuroplasticity standpoint, addiction can be viewed as a form of pathological learning, where reward and motivation circuits are abnormally reinforced while inhibitory pathways are weakened (24). This maladaptive plasticity consolidates addictive behaviors even after temporary abstinence (26). Therefore, effective therapies must restore balance within neural networks (27). Tissue engineering plays a crucial role here, as understanding the cellular and tissue-level mechanisms of addiction enables the design of artificial environments that support regeneration of damaged neurons and restoration of synaptic connections (28). Comprehending these biological foundations is the first step toward developing neural tissue engineering strategies, which will be further explored in this article.

Principles and Technologies of Neural Tissue Engineering

Neural tissue engineering is an interdisciplinary field aimed at repairing or replacing damaged components of the nervous system (29). Combining biotechnology, materials science, cellular biology, and neuroscience, it seeks to mimic the brain's

natural environment to promote neuronal growth, differentiation, and reconnection (30).

Core Components of Neural Tissue Engineering

A successful neural tissue engineering system comprises three fundamental elements: cells, scaffolds, and bioactive factors (31).

- **Cells:** Neural stem cells (NSCs) and induced pluripotent stem cells (iPSCs) are commonly used for neuronal regeneration (32). These cells can differentiate into neurons, astrocytes, or oligodendrocytes and form functional neural networks (33).
- **Scaffolds:** Biomaterial scaffolds provide a three-dimensional structure that supports cell growth (34). Natural polymers such as collagen, gelatin, chitosan, and alginate, or biodegradable synthetic polymers like Poly(lactic-co-glycolic acid) (PLGA) and Poly(ε-caprolactone) (PCL), facilitate mechanical and chemical signaling to the embedded cells (35-37).
- **Growth Factors:** Neurotrophic factors such as Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), and Glial Cell Line-Derived Neurotrophic Factor (GDNF) are essential for neuronal survival and growth (38). Controlled release of these molecules from scaffolds creates an environment conducive to repairing damaged neural tissues (39).

Bioprinting and 3D Scaffold Fabrication

Recent advances in neural tissue engineering have opened new possibilities for treating neurological disorders, including addiction-related brain damage (40). Addiction induces widespread structural, functional, and molecular changes in neurons and brain circuits (3). Conventional pharmacological and behavioral therapies often address symptoms without restoring tissue architecture or function (8). In contrast, technologies such as 3D bioprinting, smart drug delivery systems, nanotechnology, and targeted electrical stimulation enable precise reconstruction of neural networks (41, 42).

• 3D Bioprinting in Neural Tissue Engineering

Bioprinting allows the fabrication of scaffolds that closely mimic the structure, composition, and mechanical properties of natural brain tissue (43). Unlike traditional scaffold fabrication, bioprinting can precisely replicate the spatial arrangement of cells, nutrient channels, and neural pathways (44). Bioinks (composed of living cells, hydrogels, growth factors, and polymeric materials) are printed layer by layer to

form three-dimensional constructs (45). Neural stem cells or progenitor cells embedded in the matrix differentiate into interconnected neurons, forming functional networks (46). By adjusting parameters such as scaffold stiffness, porosity, and chemical composition, cell growth and differentiation can be precisely controlled (47).

A unique advantage of 3D bioprinting is the integration of microchannels for electrical guidance and nutrient transport, directing axonal growth along specific paths (48). For example, scaffolds can be designed to restore connections between the prefrontal cortex and nucleus accumbens, which are disrupted in addiction (49). Multi-material printing allows creating regions with distinct biological properties, supporting the growth of neurons, astrocytes, and glial cells separately yet cohesively, resulting in functionally and structurally complex tissues (50). Coupling bioprinting with computational modeling enhances alignment with physiological conditions of the human brain (51).

• Bioinks and Novel Materials

Selecting suitable bioinks is critical for neural tissue bioprinting. Bioinks must be biocompatible, promote cell adhesion, allow oxygen diffusion, and maintain 3D structure post-printing (52). Natural materials such as Gelatin Methacryloyl (GelMA), alginate, hyaluronic acid, and fibrin are widely used due to their similarity to brain extracellular matrix (53). Incorporating nanostructures or growth factors like NGF and BDNF improves neuronal differentiation and reduces cell death (54, 55). Emerging smart bioinks can respond to physiological stimuli such as temperature, pH, or electric fields, further enhancing tissue regeneration (56).

• Smart Delivery Systems

Precise delivery of growth factors and therapeutic agents is a major challenge in neural tissue engineering (57). Smart drug delivery systems using nanoparticles, microcapsules, and responsive hydrogels enable controlled, targeted release (58). Temperature- or pH-sensitive hydrogels can release factors like BDNF in acidic or damaged tissue environments, promoting neuronal differentiation, synaptic strengthening, and apoptosis prevention (59, 60). Magnetic nanoparticles can also deliver drugs under external magnetic guidance. Combining these systems with 3D-printed scaffolds creates multifunctional constructs that provide mechanical support and therapeutic delivery, enhancing neural regeneration (61).

• Nanotechnology in Neural Tissue Engineering

Nanotechnology plays a pivotal role in designing scaffolds and repair systems (62). Nanostructured surfaces can mimic the extracellular matrix topography, improving cell adhesion, axonal growth, and electrical signaling (63). Nanofibers and carbon nanotubes (<100 nm) replicate natural neuronal growth pathways, while metallic or semiconducting nanoparticles (e.g., silver, gold, graphene) enhance scaffold conductivity and mechanical properties, crucial for electrical stimulation (64, 65). Nanocarriers also enable targeted delivery of growth factors or genes, minimizing systemic doses and maximizing local efficacy (62).

- Electrical Stimulation and Neural Interaction

Neural function relies on electrochemical signaling; thus, targeted electrical stimulation is essential for functional regeneration (66). Conductive biomaterial scaffolds incorporating polyaniline, polypyrrole, or graphene facilitate weak electrical currents (67). Controlled stimulation promotes neural stem cell differentiation and accelerates functional synapse formation (40). Animal studies show that combining electrical stimulation with stem cell transplantation significantly improves cognitive and motor behaviors (68, 69). In addition, this approach can help restore dopaminergic reward pathways damaged by chronic substance use, rebalancing pleasure, motivation, and behavioral control (70).

Despite significant progress, clinical translation faces challenges, including cell survival post-transplantation, immune response management, and functional integration with host neural networks (71). Accurate delivery of scaffolds or cells to targeted brain regions without damaging healthy tissue requires advanced magnetic guidance, precision surgery, and live imaging (41). Establishing stable connections between transplanted and native neurons is essential for long-term functional recovery (72). Future integration of 3D bioprinting, nanotechnology, gene therapy, and artificial intelligence could produce smart neural tissues capable of real-time monitoring and modulation of neural activity (73).

Emerging neural tissue engineering technologies (including 3D bioprinting, smart delivery systems, nanotechnology, and electrical stimulation) offer promising avenues for regenerating addiction-damaged brain tissue (74). These approaches enable the design of artificial tissues closely resembling natural brain structures, precise control over cellular behavior, and reconstruction of disrupted neural circuits (29). While challenges remain, preclinical and early human studies indicate that combining these strategies may lead to safe, effective, and personalized regenerative therapies for

addiction-related brain disorders (75, 76). Neural tissue engineering not only provides a pathway for physiological repair but also deepens our understanding of addiction mechanisms and neural homeostasis restoration in humans (29).

Brain Tissue Modeling in Addiction

Studying the complex phenomenon of addiction represents one of the most challenging areas in neuroscience, as the human brain is a multi-layered, dynamic, and highly variable structure (77). Processes of dependency, tolerance, and withdrawal occur not only at the molecular and cellular levels but also across neural networks and interregional connections (78). However, ethical and practical limitations in direct access to human brain tissue have increasingly highlighted the need for alternative models (79). Consequently, brain tissue modeling using neural tissue engineering technologies has emerged as an advanced method to replicate brain environments and investigate the effects of addiction under controlled conditions (80). These models serve as powerful tools to study biological mechanisms, evaluate drug effects, and design regenerative therapies (81).

In engineered brain tissue modeling, researchers aim to reconstruct realistic brain conditions regarding cellular composition, spatial architecture, and electrophysiological characteristics (82). Such models may include neurons, glial cells, astrocytes, oligodendrocytes, and even brain endothelial cells to create a quasi-physiological environment. These systems are not only valuable for analyzing the direct effects of addictive substances but also for exploring neuronal regeneration and therapeutic responses after addiction (83).

Brain Organoids

Brain organoids have emerged as a remarkable biotechnological advancement over the past decade, revolutionizing disease modeling, including addiction (84). These small three-dimensional structures are generated from pluripotent stem cells (such as iPSCs or Embryonic Stem Cells (ESCs)) and can develop *in vitro* to mimic structural and functional brain characteristics (85). Organoids contain neurons, astrocytes, microglia, and other brain cell types that self-organize into active synaptic networks (86).

In addiction research, organoids provide an opportunity to investigate the long-term effects of addictive substances like cocaine, methamphetamine, nicotine, and opioids on neuronal growth, synaptic interactions, and expression of dopamine- and glutamate-related genes (87). For instance, a study

exposing human stem cell–derived brain organoids to methamphetamine found increased oxidative stress, dopaminergic neuron damage, and reduced synaptic markers (88). Such models can also precisely evaluate the effects of anti-addiction or regenerative drugs, including naltrexone, buprenorphine, and neurotrophic factors (89).

One key advantage of brain organoids is their customization potential, allowing the generation of organoids from stem cells of addicted individuals or those with a genetic predisposition to dependency (87). This approach introduces the concept of personalized regenerative medicine in addiction therapy. Nevertheless, limitations such as lack of vasculature, oxygen deprivation in deep tissue regions, and difficulty in simulating long-range brain connections remain significant challenges (90).

Brain-on-a-Chip Systems

Brain-on-a-chip systems combine microfluidic technology, biosensors, and cellular engineering, enabling researchers to simulate neural processes at a micrometer scale (91). In these platforms, neural cells reside in channels with precise fluid flow and are monitored in real-time via electrical, optical, and chemical sensors (92). In addiction studies, these systems provide an accurate model for examining synaptic changes, cellular responses to dopaminergic stimuli, and combined effects of multiple addictive substances (91). For example, one brain-on-a-chip model simulated dopaminergic pathways between the prefrontal cortex and nucleus accumbens to assess cocaine induced reward patterns, showing the system could replicate increased dopamine release, reduced reuptake, and altered synaptic responses (93, 94).

Other applications of Brain-on-a-Chip include evaluating the effects of rehabilitative drugs and addiction inhibitors (95). This technology enables precise monitoring of drug release, onset time, and synaptic impact (92). Moreover, these systems support designing combination therapies involving drug delivery, electrical stimulation, and targeted cellular nutrition (96). Future directions aim to integrate brain-on-a-chip with multi-organ systems to study brain-liver-immune interactions under substance exposure, providing a comprehensive understanding of systemic addiction effects and pharmacological responses (97).

3D Scaffold Models

Three-dimensional biological scaffolds are fundamental in neural tissue engineering, serving as platforms for neural cell growth and differentiation (98). These scaffolds are typically

fabricated from biocompatible materials such as collagen, alginate, gelatin, polycaprolactone, or conductive hydrogels, replicating the physical and chemical properties of brain tissue (51, 99). Carefully designed porosity, mechanical stiffness, and electrical conductivity allow cells to grow naturally and form active neural networks (100).

In addiction research, 3D scaffolds are powerful tools for simulating neuronal tissue damage, synaptic loss, and post-withdrawal regeneration (101). For instance, experimental studies using graphene oxide-containing nanocomposite scaffolds with neural stem cells demonstrated enhanced neuronal differentiation, improved electrical conductivity, and synaptic network regeneration (102, 103). The addition of growth factors like BDNF, NGF, and GDNF significantly accelerated regeneration of damaged neural pathways in animal addiction models (10, 104). 3D printing of region-specific neural scaffolds has enabled the *in vitro* reconstruction of discrete brain circuits, including the prefrontal cortex (PFC), amygdala, and nucleus accumbens (NAc) (105). This approach allows for controlled investigation of the functional contributions of each region to addictive behaviors, synaptic plasticity, and responses to therapeutic interventions, providing a platform for mechanistic studies of addiction-related neurocircuitry (106).

Injury Simulation and Therapeutic Response

Engineered brain tissue models are not only useful for understanding addiction mechanisms but also for evaluating novel treatments (107). Researchers can simulate chronic substance use, sudden withdrawal, and rehabilitation in controlled environments, assessing effects at cellular, molecular, and network levels (8). In organoid- and chip-based models, electrical stimulation using direct or alternating currents is precisely applied to examine its impact on synaptic recovery after substance exposure (84). Studies indicate electrical stimulation can increase neurotrophic gene expression, reduce neuronal apoptosis, and improve network functionality (108).

Neural stem cell therapy in three-dimensional engineered environments represents a promising strategy for brain regeneration post-addiction (109, 110). Preclinical studies showed that stem cell implantation in conductive biological scaffolds led to cortical tissue repair and restoration of dopaminergic pathways, paving the way for human clinical trials (111). Advantages of engineered brain tissue modeling include reduced reliance on animal studies, precise environmental control, high reproducibility, and access to detailed

synaptic and molecular data. These models also allow simultaneous evaluation of drugs, gene therapy, and neural stimulation (112). Nevertheless, limitations persist, including difficulty replicating the complex structure of the human brain, absence of real blood flow, and limited long-term viability of large organoids (84, 113). Challenges also exist in connecting organoids to sensory and motor systems to study behavioral responses (87).

Advances combining 3D bioprinting, nanotechnology, and microfluidics have opened new horizons for precise addiction-related brain modeling (62, 114). Future expectations include multiscale models integrating organoids with brain-on-a-chip, multi-organ systems, and AI-assisted neural data analysis (115). Artificial intelligence can reveal unknown patterns in neural signaling and drug responses from these complex models (116). Ultimately, brain tissue modeling in addiction provides a critical platform for understanding pathophysiology and developing regenerative therapies, intelligent drug delivery, and neural rehabilitation (117). Combining tissue engineering, neuroscience, biotechnology, and computational tools may realize a future where addiction-damaged brains are not only treatable but functionally restorable and reprogrammable (118, 119).

Strategies for Regenerating and Treating Addiction-Induced Brain Disorders

Brain tissue regeneration in addicted individuals is one of the major challenges in modern Regenerative Medicine and Neural Tissue Engineering (120). Addiction is not only a behavioral disorder but also a chronic neurological disease associated with molecular, cellular, and structural changes in areas such as the prefrontal cortex, amygdala, nucleus accumbens, and ventral tegmental area (21). These alterations disrupt reward, motivation, and decision-making systems, necessitating advanced biological and engineering technologies for repair (29, 121).

Cellular Regeneration via Stem Cells

Neural cell therapy has emerged as a promising approach for repairing addiction-damaged brains (118). NSCs and iPSCs can differentiate into various brain cells, including neurons, astrocytes, and oligodendrocytes (122). Studies have demonstrated that stem cell transplantation in reward-related brain regions can restore behavioral and cognitive functions (123). Preclinical studies indicate that exposure to addictive substances can significantly affect the proliferation, survival, and differentiation of neural stem/progenitor cells (NSPCs) in reward-related brain regions such as the NAc (124). Although

direct evidence for NSC transplantation fully restoring dopaminergic signaling and behavioral control in cocaine-exposed models is still limited, research suggests that NSCs can survive under stress conditions, integrate into striatal circuits, and support neurogenesis, potentially influencing reward-related behaviors (125). Furthermore, strategies utilizing patient-derived iPSCs differentiated into dopaminergic neurons may offer a personalized approach to modulate neural circuitry affected by addictive drugs (126). The use of autologous stem cells could additionally reduce immune rejection and enhance therapeutic feasibility (127).

Active and Smart Biomaterial Scaffolds

Biomaterial scaffolds play a crucial role in creating an environment conducive to cell growth, differentiation, and organization (128). Acting as a three-dimensional framework, scaffolds provide physical and chemical properties similar to native brain tissue (98). They are fabricated from biodegradable polymers like PCL, gelatin, chitosan, and alginate (129, 130). Recently, smart scaffolds capable of responding to environmental stimuli (such as pH, temperature, electrical fields, or light) have been developed to release growth factors in a targeted manner (131). For example, conductive hydrogels containing graphene or carbon nanotubes enhance scaffold conductivity and promote functional synapse formation (132). Microstructured scaffolds guiding axonal growth have successfully restored connections between prefrontal cortex neurons and subcortical structures typically damaged by chronic substance use (23).

Controlled Growth Factor and Drug Release

Neurotrophic factors like NGF, BDNF, and GDNF are crucial for neuronal survival and regeneration (54). Direct injection offers short-term effects and carries systemic risks. Therefore, controlled release systems have been developed for gradual, localized delivery (30, 133). Polymeric nanoparticles, liposomes, and microcapsules enable targeted transport of these factors to damaged brain areas (134, 135). For example, Preclinical studies have shown that BDNF-carrying PLGA nanoparticles are able to enhance BDNF transport into the brain and induce neuroprotective effects and improved neurological function in brain injury models, including traumatic injury (136) and ischemia (137). Magnetic-responsive systems allow remote, non-invasive drug release. Combined with 3D scaffolds, these technologies precisely control local neuron regeneration (138).

Electrical Stimulation and Neuromodulation

The brain operates as a complex electrochemical system, and electrical stimulation can enhance neuronal differentiation, strengthen synapses, and promote neurogenesis (139). Conductive scaffolds made from polyaniline, polypyrrole, or graphene are widely used for this purpose (140). Low-frequency electrical stimulation reactivates dopaminergic pathways, increasing dopamine release in the nucleus accumbens and modulating addictive behaviors (41). Neuromodulation techniques, such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS), complement engineered scaffolds to restore damaged structures through physiologic stimulation, modifying reward circuitry to combat addiction (141-143).

Integrating Tissue Engineering with Cognitive and Behavioral Rehabilitation

While biological treatments can repair brain structure, combining them with psychological and cognitive interventions is essential for full functional recovery and relapse prevention (8). Studies show that integrating cell therapy or electrical stimulation with cognitive-behavioral therapy (CBT) and mindfulness training enhances neural plasticity and prefrontal network function (144). Physical tissue regeneration without functional recovery yields limited outcomes (145). Hence, researchers are developing integrative tissue engineering and behavioral neuroscience models, combining cells, scaffolds, AI algorithms, and neurophysiological monitoring to dynamically personalize therapeutic responses (146).

Despite significant progress, neural tissue engineering for addiction faces challenges, including cell survival post-transplant in the complex brain environment. Immune reactions, chronic inflammation, and hypoxia threaten graft viability (29, 147). Encapsulating cells in biocompatible hydrogels protects them while facilitating nutrient exchange (148). Another challenge is ensuring functional integration of regenerated tissue with host neural networks; simply replacing cells is insufficient, as neurons must form proper connections and synchronized signaling (98). Axon-guiding scaffolds and localized electrical stimulation direct neuron growth along natural pathways (149).

Future therapies can be fully personalized, combining patient genomic data, custom organoid models, and AI-driven analysis to predict individual responses (150). 3D-bioprinted scaffolds from patient cells reduce immune rejection and enhance functional compatibility (151). Emerging technologies, including optogenetics, bio-nanorobots, and brain-on-a-chip systems, offer precise targeting of reward-

related neural circuits, controlling both regeneration and neural function (151).

Clinically, although many approaches remain preclinical, initial trials in patients with non-addiction neurological injuries (e.g., stroke or Parkinson's) show promising outcomes, supporting translation to addiction treatment (152). Overall, strategies for regenerating and treating addiction-induced brain disorders rest on three main pillars:

- Structural regeneration via stem cells and biomaterial scaffolds (29).
- Functional regeneration through electrical stimulation, neuromodulation, and growth factors (41).
- Behavioral and cognitive restoration through neural rehabilitation and psychotherapy (8).

Integrating these three aspects in a multifaceted approach enables comprehensive brain recovery—not only morphologically but also functionally and psychologically. Neural tissue engineering is now more than a repair tool; it is a gateway to understanding addiction's neural mechanisms and developing targeted, effective, and durable treatments.

Preclinical Studies and Clinical Trials

In recent years, tissue engineering has emerged as a promising strategy for addressing brain disorders associated with substance abuse (117). Preclinical studies indicate that 3D biomaterial scaffolds and hydrogels can provide a stable framework to guide neuronal growth and synapse formation (153). By enabling controlled release of neurotrophic factors such as BDNF, GDNF, and NGF, these systems facilitate the reconstruction of addiction-related neural circuits and reduce dependency-related behaviors (40, 154). Conductive scaffolds and systems for electrical or magnetic stimulation further enhance neurogenesis, promote axonal growth, and support the formation of new synapses, resulting in decreased drug-seeking behavior and addiction-related motivations in animal model (155). Polymeric nanoparticles and drug delivery systems capable of sustained release of growth factors have also demonstrated significant benefits (156, 157), particularly in models of methamphetamine and cocaine dependence, improving both cognitive and motor functions while supporting long-term reconstruction of reward circuitry (62). 3D bioprinted scaffolds, including GelMA or Poly(ethylene glycol) diacrylate (PEGDA)-GelMA composites, have been implanted in animal brain models with minimal inflammatory response, promoting cellular migration and angiogenesis and gradually replacing damaged tissue with regenerated struc-

tures (158). Recent studies further suggest that integrating these scaffolds with immunomodulatory molecules, such as exosomes, can reduce local inflammation and promote microglial polarization toward a reparative phenotype, thereby supporting synapse formation and functional restoration of reward pathways (159, 160).

At the clinical level, early studies have shown that implantation of hydrogels or 3D scaffolds loaded with growth factors, combined with cognitive and behavioral therapies, can improve memory, attention, mood, and strengthen reward-related neural pathways in patients with alcohol- or substance-induced brain damage (158, 161). These findings suggest that combining tissue engineering approaches with cognitive rehabilitation may offer a comprehensive strategy for restoring damaged neural circuits associated with addiction. Despite these promising outcomes, challenges remain, including long-term survival of implants, host immune responses, functional integration with existing neural networks, and high production and clinical implementation costs (162). Future research is likely to focus on developing multifunctional scaffolds with conductive and anti-inflammatory properties, advanced controlled-release systems, and 3D bioprinting platforms with tunable mechanical and physiological characteristics. The ultimate goal is to create tissue engineering strategies capable of effectively restoring addiction-damaged brain circuits and providing novel therapeutic options for patients (163).

Challenges and Future Studies

Neural tissue engineering offers promising avenues for treating addiction-related brain disorders, though it faces significant challenges (62). The complexity of the human brain, precise reconstruction of neural networks, and controlling immune responses after cell transplantation are among the main limitations (164). Producing organoids and complex scaffolds that mimic native tissue is costly and time-consuming, and maintaining long-term cell survival requires advanced technologies (165). Despite these challenges, there are considerable opportunities. Brain organoids and brain-on-chip systems enable precise simulation of reward pathways and the effects of addictive substances, aiding drug development and rehabilitation strategy design (166).

Technologies such as 3D printing, bio-nanoparticles, and conductive scaffolds create complex artificial environments that support neuronal growth and connectivity (167). Integrating these approaches with behavioral data and precision medicine allows for personalized treatment design and prediction of

patient responses (168). Neural tissue engineering in addiction therapy also requires adherence to ethical standards, safety regulations, and equitable access to advanced treatments (169-171). Overall, despite technical obstacles, innovations in modeling, technology, and integration with behavioral rehabilitation and personalized medicine provide hope for developing sustainable and effective therapies.

Conclusion

Addiction, beyond its behavioral and social consequences, induces significant biological and structural brain alterations, making treatment a complex challenge. Research has shown that chronic substance use leads to neuronal death, disrupted synaptic networks, and altered brain reward pathways. Traditional therapies, while effective in alleviating behavioral symptoms, cannot repair damaged brain tissue, highlighting the need for neural regenerative approaches. Neural tissue engineering, through technologies such as stem cells, bioengineered scaffolds, growth factors, 3D bioprinting of tissues, and brain-on-chip systems, enables reconstruction of damaged brain structures and functions. These technologies provide not only valuable research tools for understanding addiction mechanisms but also a foundation for designing novel and personalized therapeutic interventions.

Modeling brain tissue under addictive conditions, using brain organoids and brain-on-chip systems, allows researchers to simulate and analyze the effects of drugs and therapeutic responses with high precision. Combining these models with tissue engineering treatments and behavioral rehabilitation creates a new perspective for restoring cognitive and behavioral functions in individuals with addiction. Despite significant progress, major challenges remain, such as controlling immune responses, maintaining cell viability, ensuring integration of regenerated tissue with the host brain, and addressing ethical and social issues. However, technological advances, convergence with AI, the development of smart scaffolds, and personalized regenerative medicine provide a clear pathway to overcome these limitations. Ultimately, neural tissue engineering presents a promising future for treating addiction-related brain disorders. This scientific field could mark a turning point in clinical therapies, and by integrating biological knowledge, engineering technologies, and psychotherapeutic approaches, it offers the potential to improve the quality of life for individuals affected by addiction.

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Availability of data and materials

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors confirm that there are no conflicts of interest regarding the content of this article.

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