

Review

Glia-Informed Design of Smart Biomimetic Biomaterials for Brain Repair and Neural Tissue Engineering

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Abstract

Smart biomimetic biomaterials are increasingly being developed to improve brain repair by providing structural support, localized therapeutic delivery, and biologically active microenvironments that promote tissue integration. However, their performance in the central nervous system is strongly influenced by the neuroimmune milieu, particularly by microglia- and astrocyte-mediated regulation of inflammation, extracellular matrix remodeling, and tissue homeostasis. This narrative review examines how glial biology can inform the design of neural biomaterials across major platform types, including hydrogels, nanoparticles, three-dimensional scaffolds, and neural interfaces. We synthesize current evidence showing that glial responses are not merely secondary reactions to implanted materials, but key determinants of biomaterial integration, regenerative permissiveness, and long-term functional compatibility. We further discuss how stimulus-responsive and extracellular matrix-mimetic materials can be engineered to sense local injury-associated signals and deliver temporally and spatially controlled therapeutic effects. Based on these observations, we outline a glia-informed design perspective centered on microenvironmental sensing, temporal regulation of neuroinflammation, biomimetic matrix architecture, and selective modulation of glial functions relevant to tissue repair. The review highlights translational considerations and biological readouts for evaluating biomaterial performance at cellular, tissue, and functional levels. By integrating advances in biomaterials science with glial biology, this article provides a biologically grounded design perspective for next-generation neural biomaterials with improved relevance for brain repair and regenerative neuroengineering.

Keywords: Neural biomaterials, biomimetic biomaterials, microglia, astrocytes, neuroinflammation, brain repair, neural tissue engineering, regenerative neuroengineering.

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Introduction

Biomaterials have become an increasingly important component of strategies aimed at repairing neural tissue, delivering therapeutics to the brain, and improving the performance of neural interfaces [1,2]. Advances in polymer chemistry, nanotechnology, and biofabrication have enabled the development of smart and biomimetic biomaterials capable of responding to physiological stimuli or mimicking structural and biochemical aspects of native tissue environments [3–5]. These developments have expanded the relevance of biomaterials to brain repair and neural tissue engineering, where materials are increasingly designed not only as passive carriers or structural supports, but as active regulators of cellular behavior, tissue integration, and local microenvironmental dynamics [6–8].

Despite significant progress in biomaterial design, the translation of many neural biomaterials remains challenging. One key reason is that the biological performance of

implanted materials depends not only on their intrinsic material properties but also on how they interact with the complex cellular and molecular environment of the central nervous system [9–11]. In particular, neuroimmune responses often play a decisive role in determining whether biomaterials integrate successfully with surrounding tissue or instead trigger persistent inflammation and tissue remodeling [9,11–13]. For biomaterials intended for brain repair and regenerative neuroengineering, successful design therefore requires attention not only to material architecture, but also to the biological systems that interpret and respond to the implanted material [11,14,15].

Glial cells, particularly microglia and astrocytes, are central regulators of these responses, coordinating inflammatory signaling, purinergic communication, and homeostatic regulation within the neural microenvironment [16]. Microglia act as the resident immune cells of the brain and rapidly respond to perturbations such as injury, infection, or

biomaterial implantation [17–19]. Astrocytes contribute to multiple aspects of neural homeostasis, including metabolic support, ion balance, and extracellular matrix regulation. Following injury or implantation, both cell types participate in inflammatory signaling, debris clearance, and structural remodeling of the neural microenvironment [18,19]. Because these glial responses shape inflammatory tone, tissue stability, regenerative permissiveness, and long-term material compatibility, they are increasingly relevant not only as biological readouts of biomaterial performance, but also as potential guides for biomaterial design [20–23].

Historically, many neural biomaterial strategies have focused primarily on neuronal outcomes while treating glial responses mainly as inflammatory reactions that should be minimized [9,24]. However, increasing evidence suggests that glial activity cannot be understood solely as a detrimental response. Instead, glial cells play important roles in regulating tissue repair, immune signaling, and extracellular matrix organization within the brain [18,25]. This shift has important implications for biomaterials research: rather than broadly suppressing glial activity, emerging design strategies may seek to selectively engage glial functions that support repair, controlled remodeling, and adaptive integration [22,26,27].

Several recent reviews have examined biomaterials for neural regeneration, neuroinflammation, neural interfaces, or glial modulation in specific disease settings [17, 28,29]. Prior work has also discussed biomaterial strategies for modulating neuroinflammatory responses in the central nervous system, nanomaterial-based regulation of microglial activity, and engineering approaches for neural repair or localized therapeutic delivery [9,17,28–30]. However, many of these reviews are organized primarily around individual material classes, specific technologies, inflammatory pathways, or isolated application settings. The specific contribution of the present review is to synthesize these areas into a glia-informed design framework in which microglia and astrocytes are treated not only as biological responders to implanted materials, but as active interpreters of material properties and regulators of downstream tissue outcomes. In this framework, biomaterial design variables such as stiffness, surface chemistry, degradation behavior, architecture, and stimulus responsiveness are linked to glial sensing, inflammatory timing, extracellular matrix remodeling, tissue integration, and measurable functional outcomes. This design-oriented synthesis distinguishes the present review from prior material-centered or neuroinflammation-centered reviews by using glial biology as an organizing logic for the development and evaluation of smart biomimetic neural biomaterials [6,7,20,21].

This narrative review addresses that need by examining how glial biology can inform the design of smart biomimetic biomaterials for brain repair and neural tissue engineering. By integrating findings from studies of hydrogels, nanoparticles, scaffolds, and neural interfaces,

we outline a glia-informed design perspective centered on microenvironmental sensing, temporal regulation of neuroinflammation, biomimetic matrix architecture, and selective modulation of glial functions. Rather than treating glial responses as secondary consequences of implantation, we consider them as biologically meaningful determinants of material integration, regenerative permissiveness, and long-term functional compatibility. We also discuss translational considerations and biological readouts that may help evaluate biomaterial performance at cellular, tissue, and functional levels. By bringing together insights from biomaterials science, neuroimmunology, and regenerative neuroengineering, this review aims to provide a biologically grounded framework for the development of next-generation neural biomaterials with improved relevance for brain repair.

To clarify the structure of the review, the manuscript is organized around a stepwise design logic. First, it summarizes the roles of microglia and astrocytes in regulating the neural microenvironment. It then examines how major neural biomaterial classes, including hydrogels, nanoparticles, three-dimensional scaffolds, and neural interfaces, engage glial responses. Building on these platform-specific interactions, smart and stimulus-responsive biomaterials are then discussed within the biomaterial platform section as glia-informed design strategies rather than as a separate topic. Finally, it discusses temporal and context-dependent glial responses before considering translational issues and measurement approaches that may help evaluate biomaterial performance at cellular, tissue, and functional levels.

Accordingly, the novelty of the proposed framework lies in connecting material-level design features to glial interpretation, temporally defined microglial and astrocytic responses, tissue-level remodeling, and experimentally measurable outcomes.

This conceptual framework is illustrated in Fig. 1, which summarizes the central role of glial cells as mediators of biomaterial–tissue interactions in the neural microenvironment.

Glia Regulation of the Neural Microenvironment

Glial cells play essential roles in maintaining neural homeostasis and coordinating responses to injury, infection, and disease. In addition to supporting neuronal function, glial cells regulate immune signaling, metabolic exchange, extracellular matrix organization, and vascular interactions within the central nervous system. These processes collectively shape the local microenvironment in which neural cells operate and respond to physiological or pathological stimuli [31,32].

When biomaterials are introduced into neural tissue, whether as drug delivery systems, scaffolds for tissue repair, or implanted neural devices, they interact not only with neurons but also with surrounding glial populations

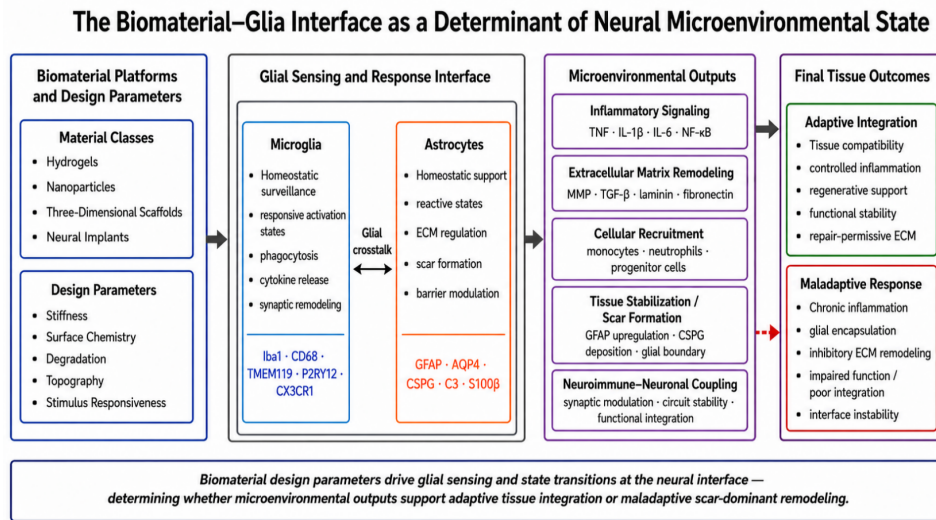


Fig. 1. The biomaterial–glia interface as a determinant of neural microenvironmental state. Schematic overview of the proposed glia-informed biomaterial design framework. Biomaterial classes and design parameters influence microglial and astrocytic sensing, state transitions, and functional outputs at the neural interface. These glial responses shape microenvironmental processes, including inflammatory signaling, extracellular matrix remodeling, cellular recruitment, tissue stabilization or scar formation, and neuroimmune–neuronal coupling. Depending on the timing, intensity, and context of these responses, biomaterial–glia interactions may support adaptive tissue integration or contribute to maladaptive scar-dominant remodeling. Created with Microsoft PowerPoint.

that regulate tissue responses. Glial cells rapidly detect perturbations in the neural environment and initiate signaling pathways that influence inflammation, tissue remodeling, and cellular recruitment. As a result, glial responses often play a decisive role in determining whether implanted materials integrate successfully with neural tissue, remain biologically stable, or instead provoke persistent immune activation and structural remodeling [9].

Understanding the regulatory roles of glial cells, therefore, provides an important biological framework for interpreting how biomaterials behave in the brain. Rather than acting solely as passive bystanders, glial cells actively shape the tissue environment in which biomaterials function. Examining the functions of microglia and astrocytes is therefore essential for understanding the mechanisms through which biomaterials influence neural repair, inflammatory signaling, and disease-related tissue changes.

Microglia: Immune Surveillance and Tissue Remodeling

Microglia are the resident immune cells of the central nervous system and serve as primary mediators of immune surveillance within neural tissue. In their resting state, microglia continuously extend and retract cellular processes to monitor the surrounding microenvironment, allowing them to detect subtle changes in neuronal activity, tissue integrity, or molecular signaling [31,33]. When disturbances occur, such as injury, infection, or the introduction of biomaterials, microglia rapidly transition into activated states characterized by morphological changes and altered gene expression [34–37].

Activated microglia perform several functions that

are important for maintaining neural tissue homeostasis, including purinergic signaling-mediated regulation of inflammatory responses, cellular communication, and tissue remodeling processes [16]. These include phagocytic removal of cellular debris, secretion of cytokines and chemokines that regulate inflammatory responses, and modulation of synaptic connectivity through processes such as synaptic pruning [31,38,39]. Through these mechanisms, microglia help coordinate immune responses while also influencing neuronal survival and tissue repair. Rather than existing as a single uniform activated population, microglia adopt context-dependent functional states shaped by local injury signals, extracellular cues, and intercellular communication [35,36,40,41].

In the context of biomaterial implantation, microglia are often among the first cells to interact with material surfaces or released molecular signals. Their responses may include phagocytosis of particulate materials, secretion of inflammatory mediators, and recruitment of additional immune cells. Depending on the characteristics of the biomaterial and the surrounding microenvironment, microglial activation may either contribute to tissue repair or promote sustained inflammatory responses that influence biomaterial integration [9,42].

Because microglial activity strongly influences inflammatory signaling and cellular recruitment within neural tissue, their responses represent an important biological factor that shapes the interaction between biomaterials and the brain microenvironment. Understanding how different biomaterials influence microglial behavior is, therefore, an important step toward designing materials that are

more compatible with neural tissue and capable of supporting therapeutic goals. Rather than viewing microglial activation solely as a detrimental foreign body response, it is increasingly important to recognize that microglia can also support debris clearance, inflammatory resolution, tissue remodeling, and adaptive repair depending on biological context [9,43,44].

Astrocytes: Structural Support and Tissue Remodeling

Astrocytes are among the most abundant glial cell types in the central nervous system and perform a wide range of functions that support neural physiology. They contribute to metabolic support of neurons, regulation of extracellular ion concentrations, neurotransmitter clearance, and maintenance of the blood–brain barrier. Through these roles, astrocytes help maintain the stability of the neural microenvironment and support proper neuronal signaling [32,45].

Following injury, disease, or the implantation of biomaterials, astrocytes can undergo reactive changes that alter their morphology, gene expression, and functional properties. Reactive astrocytes participate in inflammatory signaling, regulate extracellular matrix composition, and influence tissue remodeling processes within the brain [45,46]. These reactive changes are context-dependent and may contribute to both protective tissue stabilization and inhibitory remodeling, depending on the nature and duration of the local insult [47–49]. One well-characterized response is the formation of astrocytic scar structures that surround sites of injury or foreign material. These structures can help limit the spread of inflammatory signals but may also influence axonal growth and cellular migration within damaged neural tissue.

Astrocytic responses can therefore have important implications for biomaterial performance in the brain. Changes in extracellular matrix deposition, cytokine signaling, and structural organization around implanted materials may affect cellular infiltration, neuronal regeneration, and long-term material integration. Understanding how biomaterials influence astrocyte activation and tissue remodeling is therefore important for designing materials that interact more effectively with neural tissue [10,50]. In particular, because astrocytes regulate matrix architecture, metabolic support, and structural boundary formation, their responses are highly relevant to the design of biomaterials intended to promote repair-compatible microenvironments [21,51,52].

Glial Crosstalk and Neuroimmune Networks

Microglia and astrocytes do not function in isolation but instead operate within complex cellular networks that include neurons, endothelial cells, and infiltrating immune cells. Communication among these cell populations occurs through a wide range of signaling molecules, including cytokines, chemokines, growth factors, and metabolic intermediates. These interactions form dynamic neuroim-

mune networks that regulate inflammatory responses, tissue repair, and cellular homeostasis within the central nervous system [53,54]. In addition, emerging evidence highlights that glial crosstalk extends beyond classical immune signaling to include neuromodulatory interactions, such as dopamine–glia communication pathways that influence neuroinflammation and plasticity [55].

Within these networks, microglia and astrocytes influence each other's activity through reciprocal signaling pathways. Microglial activation can stimulate astrocytic responses, while astrocytes can modulate microglial behavior through the release of regulatory factors. These interactions contribute to coordinated responses to injury or disease and play important roles in shaping the cellular microenvironment of the brain. Because these reciprocal signaling relationships influence inflammatory timing, extracellular matrix remodeling, and tissue stability, they are also relevant to how biomaterials are perceived, integrated, and remodeled after implantation [21,56,57].

When biomaterials are introduced into neural tissue, they become part of this signaling landscape. Material surfaces, degradation products, and released therapeutic molecules may influence glial signaling pathways and alter the behavior of surrounding cells. Consequently, understanding glial crosstalk within neuroimmune networks is essential for interpreting how biomaterials interact with the brain and for designing materials that support beneficial tissue responses [56,58]. A biomaterial may therefore influence neural repair not only through direct effects on individual cell types, but also by reshaping the signaling interactions among glial, neural, vascular, and immune components of the local microenvironment [21,52,57].

Glial Responses to Neural Biomaterials

Experimental studies across multiple classes of biomaterials demonstrate that glial responses strongly influence the biological performance of implanted materials. When biomaterials are introduced into neural tissue, they interact with the surrounding cellular environment, including microglia and astrocytes that regulate inflammatory signaling, tissue remodeling, and immune surveillance. These interactions can shape the local microenvironment and ultimately affect the integration, stability, and therapeutic performance of biomaterial systems [15,59]. In this way, glial responses function not only as markers of tissue reaction but also as determinants of whether a biomaterial supports adaptive integration, repair-compatible remodeling, or persistent neuroinflammatory dysfunction [15,42,60].

As summarized in Fig. 2, distinct classes of neural biomaterials engage microglial and astrocytic responses through different mechanisms, yet converge on shared glial-mediated pathways that can be evaluated using representative biological readouts and linked to tissue-level outcomes.

The inclusion of these readouts is intended to make

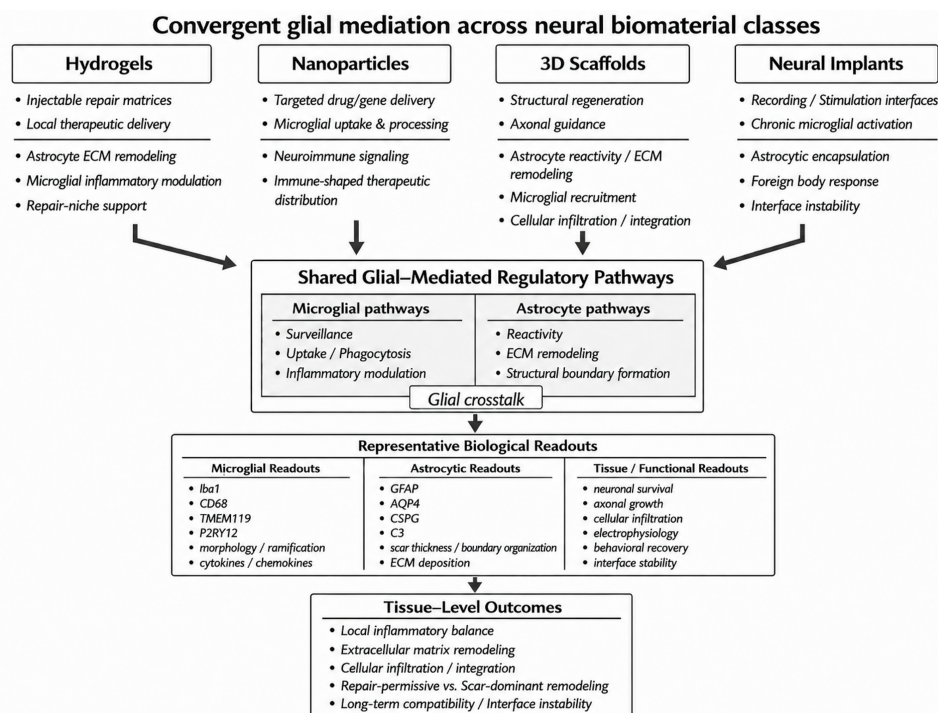


Fig. 2. Convergent glial mediation across neural biomaterial classes with representative biological readouts. Distinct classes of neural biomaterials, including hydrogels, nanoparticles, three-dimensional scaffolds, and neural implants, interact with the neural microenvironment through different application contexts and material properties, but converge on shared glial-mediated regulatory pathways. Across these platforms, microglial surveillance, uptake/phagocytosis, and inflammatory modulation, together with astrocyte reactivity, extracellular matrix remodeling, and structural boundary formation, function as common mechanisms linking biomaterial exposure to tissue response. Representative readouts that can be used to assess these responses experimentally are also shown. Microglial readouts include markers and measures such as Iba1, CD68, TMEM119, P2RY12, morphology/ramification, and cytokine or chemokine production. Astrocytic readouts include GFAP, AQP4, CSPG, C3, scar thickness or boundary organization, and extracellular matrix deposition. These glial measurements can be further linked to tissue-level and functional outcomes, including local inflammatory balance, extracellular matrix remodeling, cellular infiltration and structural integration, repair-permissive versus scar-dominant remodeling, neuronal survival, axonal growth, electrophysiological activity, behavioral recovery, and long-term compatibility or interface stability. These readouts should also be interpreted across temporal response windows, including acute microglial activation, subacute extracellular matrix remodeling, and chronic astrocytic scar formation or glial encapsulation. Created with Microsoft PowerPoint.

the framework experimentally actionable. Rather than interpreting glial responses only through broad terms such as activation or reactivity, biomaterial studies can use marker combinations, morphology, spatial organization, and functional assays to distinguish microglial uptake or inflammatory signaling from astrocytic matrix remodeling, scar organization, and tissue-stabilizing responses.

These measurements should be interpreted longitudinally because acute, subacute, and chronic glial responses may carry different implications for biomaterial integration, regenerative permissiveness, and long-term functional compatibility.

Evidence from different biomaterial platforms suggests that material properties such as surface chemistry, mechanical stiffness, degradation behavior, porosity, architecture, and molecular signaling cues can actively shape glial activation and immune responses [15,61]. Rather than being passive substrates that are merely surrounded by reactive glia, neural biomaterials can influence how

microglia migrate, adhere, internalize material fragments, secrete inflammatory mediators, and participate in debris clearance. They can also influence astrocyte morphology, extracellular matrix deposition, scar boundary formation, and tissue-stabilizing responses. Observations from hydrogels, nanoparticle systems, scaffolds, and neural implants therefore indicate that glial responses are not only biological readouts of biomaterial exposure, but also mechanistic intermediates through which material properties affect tissue repair, chronic inflammation, or long-term integration [15,42,59,60,62]. These findings support the need to evaluate biomaterial performance in terms of how specific design variables actively regulate microglial and astrocytic behavior across time. Table 1 provides a comparative summary of major neural biomaterial classes, with microglial and astrocytic responses presented separately to clarify cell-type-specific interactions, key design variables, and corresponding glia-centered design opportunities.

Hydrogels in Neural Tissue Engineering

Hydrogels are widely used in neural tissue engineering because their mechanical properties and structural characteristics can be tuned to resemble aspects of the native extracellular matrix. Their high water content and biocompatibility make them suitable for applications such as cell delivery, tissue scaffolding, and localized therapeutic release. Because hydrogels can be engineered to mimic the physical and biochemical properties of neural tissue, they are frequently investigated as platforms for neural regeneration [8,63,64]. This matrix-like adaptability makes hydrogels particularly attractive for biomaterial strategies aimed at supporting repair-compatible cellular organization and controlled local microenvironmental modulation [8,65,66].

Experimental studies have shown that hydrogel stiffness, composition, and degradation profiles can significantly influence glial responses within neural tissue. Changes in mechanical properties may affect astrocyte activation, extracellular matrix deposition, and the organization of surrounding cellular networks. In addition, microglial responses to hydrogel materials may vary depending on factors such as polymer composition, crosslinking density, and degradation products [15,61]. These findings suggest that the design of hydrogel-based biomaterials can influence glial signaling pathways and thereby shape the local inflammatory environment. Accordingly, hydrogels are not only structural platforms for repair, but also biologically active interfaces that may help regulate neuroinflammation, matrix remodeling, and tissue permissiveness after injury [15,61,67].

Nanoparticles and Drug Delivery Platforms

Nanoparticle-based systems are widely explored for the targeted delivery of drugs, nucleic acids, and imaging agents to the brain. Their small size and tunable surface properties allow nanoparticles to interact with biological barriers and cellular populations in ways that can improve therapeutic distribution within neural tissue [68,69]. Because nanoparticle behavior is strongly shaped by size, charge, coating chemistry, and targeting ligands, these systems offer unusual flexibility for modulating cell-specific interactions within the neural microenvironment [70–72].

Microglia often play an important role in the biological handling of nanoparticles introduced into the central nervous system. As immune surveillance cells, microglia can internalize nanoparticle systems through phagocytosis or receptor-mediated uptake. This interaction can influence the distribution, persistence, and cellular localization of nanoparticle-delivered therapeutics within neural tissue. In some cases, nanoparticle uptake by microglia may contribute to immune activation or modulation of inflammatory signaling pathways [68,69,73]. Several recent preclinical and proof-of-concept studies have explored this interaction as a potential strategy for directing cargo toward glial populations or influencing immune-state-dependent drug

release and signaling responses [70,74,75]. However, direct evidence that nanoparticle-mediated glial modulation improves neurological outcomes in large-animal models or clinical settings remains limited. Therefore, nanoparticle–microglia interactions should currently be interpreted as an emerging design opportunity rather than an established translational mechanism.

Understanding how nanoparticle characteristics such as size, surface chemistry, and coating materials influence microglial interactions is therefore an important aspect of designing drug delivery platforms for neurological applications. These interactions illustrate how biomaterial properties can shape immune responses and therapeutic outcomes within the brain microenvironment. In this respect, nanoparticles are especially informative examples of how material design can influence not only biodistribution, but also the cellular interpretation of a therapeutic platform within a glia-regulated tissue environment [71–73].

Three-Dimensional Scaffolds

Three-dimensional biomaterial scaffolds are widely investigated as structural platforms for neural regeneration and tissue repair. These scaffolds can provide physical support for cellular attachment, migration, and organization, thereby helping to guide the reconstruction of damaged neural tissue. Materials used for scaffold fabrication include natural polymers, synthetic polymers, and hybrid biomaterials designed to mimic aspects of the neural extracellular matrix [15,62]. Because they combine structural guidance with tunable biochemical and mechanical cues, three-dimensional scaffolds are especially relevant to neural tissue engineering strategies aimed at reconstructing repair-permissive microenvironments [15,62,76].

The structural properties of scaffolds, including pore size, mechanical stiffness, fiber alignment, surface topography, and spatial architecture, can actively influence how neural and glial cells populate and interpret the material. Surface chemistry and biochemical functionalization may further affect cellular adhesion, migration, and signaling pathways within the surrounding tissue environment. Importantly, scaffolds may influence microglial behavior as well as astrocytic remodeling. Scaffold porosity and architecture can affect microglial infiltration and spatial distribution within or around the material, while stiffness, degradation products, and surface chemistry may influence microglial inflammatory signaling, phagocytic activity, and cytokine release [15,42]. These microglial responses may then interact with astrocytic reactivity and extracellular matrix remodeling to determine whether the scaffold supports repair-compatible cellular organization or becomes associated with persistent inflammation, cellular exclusion, and scar-dominant tissue responses [15,62,76].

Table 1. Major neural biomaterial classes, cell-type-specific glial responses, and design-relevant variables.

Biomaterial class	Primary application context	Microglial responses	Astrocytic responses	Key design variables	Glia-centered design opportunities
Hydrogels	Injectable repair matrices; tissue engineering; local therapeutic delivery	Modulation of inflammatory signaling; altered microglial recruitment depending on polymer composition, stiffness, crosslinking, and degradation products; potential support of inflammatory resolution when appropriately tuned	Astrocyte activation and extracellular matrix remodeling; influence on scar architecture, tissue permissiveness, and astrocyte organization around the hydrogel interface	Stiffness and mechanical matching; composition and crosslinking; degradation profile; ligand presentation	Tune mechanical and degradation properties to limit chronic inflammation while supporting repair-compatible astrocyte organization and matrix remodeling
Nanoparticles	Targeted drug delivery; gene delivery; imaging-guided therapeutic platforms	Microglial uptake and intracellular processing; possible immune activation or immune-state-dependent cargo handling; preclinical exploration of microglial targeting and inflammatory modulation	Secondary effects on astrocytic responses through altered inflammatory signaling, therapeutic cargo release, or changes in the surrounding neuroimmune environment	Size and surface charge; surface functionalization; targeting ligands; coating chemistry; cargo release profile	Treat nanoparticle–microglia interactions as an emerging design opportunity; optimize biodistribution, uptake, and cargo release while monitoring downstream astrocytic and tissue responses
Three-dimensional scaffolds	Structural regeneration; axonal guidance; repair niche organization	Microglial recruitment, inflammatory signaling, and phagocytic activity are influenced by scaffold architecture, porosity, degradation products, and surface chemistry	Astrocyte reactivity, matrix remodeling, scar boundary formation, and regulation of cellular infiltration around or within the scaffold	Architecture and porosity; mechanical properties; surface chemistry and biochemical cues; degradation behavior	Design scaffold architecture to support cellular infiltration and repair-compatible remodeling while limiting scar-dominant organization and persistent inflammatory activation
Neural implants	Electrodes; neural interfaces; stimulation and recording devices	Chronic microglial activation, foreign body response, inflammatory mediator release, and peri-device immune remodeling	Astrocytic encapsulation, glial sheath formation, extracellular matrix deposition, and structural isolation of the device interface	Surface chemistry; mechanical mismatch; coatings; flexibility; interface topography	Reduce chronic foreign body reactivity and stabilize long-term glial–device interfaces by tuning mechanics, surface chemistry, and anti-inflammatory or biomimetic coatings

In addition to structural properties, scaffold degradation behavior can also affect glial responses. Degradation products may alter the biochemical composition of the local microenvironment, modify local pH or osmotic conditions, expose new surface motifs, or provide molecular cues that influence inflammatory signaling pathways. For microglia, these changes may affect material-fragment uptake, lysosomal activity, inflammatory mediator production, and recruitment of additional immune cells. For astrocytes, scaffold degradation and matrix remodeling may influence boundary formation, extracellular matrix deposition, and the degree to which cells can infiltrate the repair site. As a result, scaffold performance should be considered not only in terms of physical support, but also in terms of how scaffold architecture, material chemistry, and degradation kinetics actively regulate microglial and astrocytic behavior during tissue remodeling and long-term integration [15,62].

Neural Implants and Interfaces

Implanted neural devices such as electrodes and neural interfaces are increasingly used for recording neural activity, delivering electrical stimulation, and restoring neurological function. However, the long-term performance of these devices is often limited by biological responses that occur at the interface between the implant and neural tissue. One common challenge is the development of chronic neuroinflammatory responses around implanted devices [59,77]. In this setting, the material–tissue interface becomes a persistent site of glial activation, mechanical mismatch, and structural remodeling that can progressively compromise device function [60,78].

Following implantation, microglia and astrocytes are typically recruited to the implant site, where they participate in inflammatory signaling and tissue remodeling. Over time, these responses can lead to the formation of dense glial structures surrounding the implant, which may alter electrical signal transmission and reduce device functionality. This process can contribute to decreased recording stability and reduced therapeutic effectiveness of neural interfaces [59,77]. These responses illustrate that glial encapsulation is not simply a histological observation, but a central biological determinant of long-term interface stability and performance [60,78].

To address these challenges, researchers are increasingly exploring biomaterial coatings and surface modifications designed to improve the compatibility of neural implants with surrounding tissue. Strategies include modifying surface chemistry, incorporating bioactive molecules, and developing flexible or biomimetic materials that better match the mechanical properties of neural tissue. These approaches aim to modulate glial responses and promote more stable interactions between implanted devices and the neural microenvironment. From a design perspective, neural interfaces therefore provide a particularly clear exam-

ple of how biomaterial properties can shape chronic glial responses and, in turn, determine long-term functional outcomes [60,78].

Together, hydrogels, nanoparticles, three-dimensional scaffolds, and neural interfaces illustrate that neural biomaterials do not act as passive platforms after implantation. Instead, their stiffness, surface chemistry, degradation behavior, architecture, and released molecular cues are interpreted by microglia and astrocytes and can shape inflammatory tone, extracellular matrix remodeling, tissue integration, and long-term functional compatibility. Building on these platform-specific interactions, the following subsection discusses smart and stimulus-responsive biomaterials as design strategies that may allow more temporally controlled and microenvironment-sensitive regulation of glial responses.

Smart and Stimulus-Responsive Biomaterials as Glia-Informed Design Strategies

Recent developments in materials science have led to the design of biomaterials capable of responding to biochemical and physical cues within their surrounding environment. These systems are often referred to as smart or stimulus-responsive biomaterials because their properties or functions can change in response to specific local signals. In neurological applications, such materials are increasingly explored as platforms for controlled drug delivery, tissue engineering, and modulation of local cellular responses within the brain [3,79]. In the context of the present review, these materials are discussed not as a separate topic from glial biology, but as an extension of glia-informed biomaterial design. Their relevance lies in the possibility of linking material responsiveness to injury-associated cues, inflammatory timing, extracellular matrix remodeling, and microglial or astrocytic state changes. Within brain repair and neural tissue engineering, this responsiveness is especially attractive because it allows biomaterials to adapt to evolving local conditions rather than functioning as static therapeutic platforms [80,81]. The conceptual framework underlying stimulus-responsive biomaterials in the brain microenvironment is illustrated in Fig. 3.

This stimulus–response framework provides a mechanistic basis for glia-centered biomaterial design, linking microenvironmental sensing to adaptive therapeutic function. In particular, it supports the idea that biomaterials can be engineered to detect biologically meaningful signals associated with glial activation, injury progression, and tissue remodeling, and to translate those signals into context-dependent material actions [80,81].

Stimulus-responsive biomaterials are designed to detect changes in physiological conditions and trigger corresponding alterations in material behavior, such as drug release, degradation, or structural transformation. Because the neural microenvironment can vary dynamically during processes such as injury, inflammation, or tumor progres-

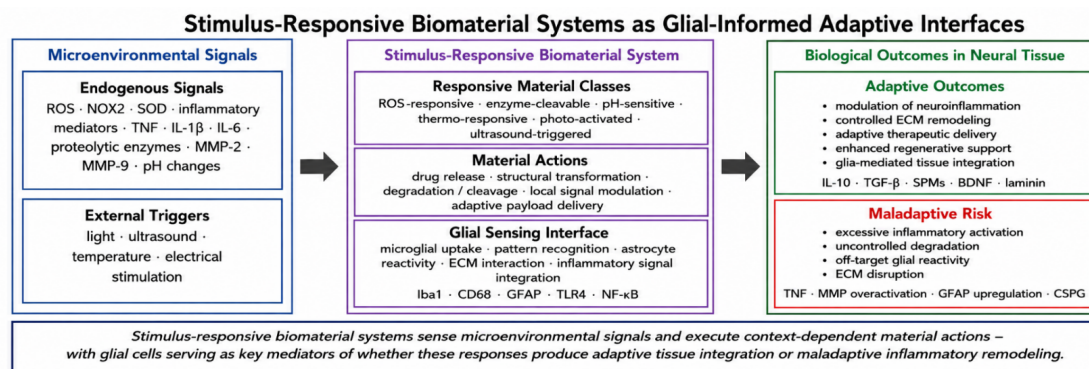


Fig. 3. Stimulus-responsive biomaterial systems as glia-informed adaptive interfaces. Schematic showing how endogenous microenvironmental signals and external triggers can activate stimulus-responsive biomaterial systems. These materials may respond through drug release, structural transformation, degradation or cleavage, local signal modulation, and adaptive payload delivery. The effects are interpreted through glial sensing interfaces involving microglial uptake, astrocyte reactivity, extracellular matrix interactions, and inflammatory signal integration. Depending on context, timing, and response magnitude, these processes may support adaptive outcomes such as controlled neuroinflammation and tissue integration or contribute to maladaptive inflammatory remodeling. Created with Microsoft PowerPoint.

sion, materials that respond to these changes may offer advantages over static biomaterial systems. By adjusting their activity in response to biological signals, these materials may enable more localized and temporally regulated therapeutic interventions [79,82]. This capacity is particularly relevant in the central nervous system, where the timing, magnitude, and spatial distribution of inflammatory and reparative signals can strongly influence tissue integration and regenerative outcome [80,81].

Several types of stimuli have been explored in the development of responsive biomaterial systems. Reactive oxygen species represent one commonly studied trigger, as oxidative stress often accompanies tissue injury and inflammatory responses. Materials engineered to respond to reactive oxygen species can release therapeutic agents or undergo structural changes when exposed to oxidative environments. Enzyme-responsive materials provide another approach, as enzymatic activity associated with inflammation or tissue remodeling can be used to trigger degradation or activation of biomaterial systems [79,83]. Because reactive oxygen species, proteolytic activity, and inflammatory mediators are often linked to glial activation states, such cues are especially relevant for biomaterials designed to interact dynamically with the neural microenvironment [80,81].

Changes in pH also provide useful biological signals for responsive biomaterial design. Local variations in pH may occur during inflammation, ischemia, or tumor progression, allowing pH-sensitive materials to release drugs selectively within affected tissues. Temperature-responsive materials have likewise been explored, particularly in systems designed to undergo reversible structural changes or controlled release in response to thermal variations [79,84,85]. These trigger systems broaden the range of material behaviors that can be coupled to biologically

relevant microenvironmental states [86–88].

In addition to endogenous signals generated within tissues, externally applied stimuli can also be used to control biomaterial behavior. Light-responsive systems, for example, allow spatially controlled activation of drug release or structural modification through optical stimulation. Ultrasound-responsive biomaterials represent another strategy in which externally applied acoustic energy can trigger drug release or alter material properties without invasive procedures [89–91]. Such externally controlled systems may be especially useful when precise temporal or regional modulation is needed within complex neural tissue environments [92–94].

In neural applications, these responsive biomaterial systems may offer opportunities to interact with dynamic biological processes occurring within the brain microenvironment. Because inflammatory signaling, oxidative stress, and enzymatic activity are often associated with glial activation, stimulus-responsive materials may provide new ways to influence the interactions between biomaterials and glial cells. Designing biomaterials that respond to such signals may therefore contribute to more adaptive strategies for therapeutic delivery and tissue repair in neurological contexts. More broadly, stimulus-responsive biomaterials support a shift from passive material implantation toward biologically interactive systems that sense, interpret, and respond to the evolving conditions of injured neural tissue [80,81].

Glia-Centered Design Principles for Neural Biomaterials

Building on the evidence reviewed above, we propose that glial biology can be translated into a set of design axes for neural biomaterials. This glia-centered framework

links microenvironmental signals to specific glial targets and material actions, thereby providing a more biologically grounded basis for biomaterial design across distinct neurological applications. Rather than treating glial responses as secondary consequences of implantation, this perspective considers them as functionally meaningful biological processes that can help guide the design of repair-compatible biomaterial systems [1,9,11].

Evidence from biomaterial–glial interactions suggests several principles that may guide the design of neural biomaterials. Observations from hydrogels, nanoparticle systems, scaffolds, and neural implants indicate that glial responses often shape the biological performance of biomaterials within neural tissue. These responses influence inflammatory signaling, extracellular matrix remodeling, cellular recruitment, and tissue integration. Translating these biological insights into engineering strategies may therefore help guide the development of biomaterials that interact more effectively with the neural microenvironment [4,9,12]. Table 2 summarizes glia-informed design principles with microglial and astrocytic targets presented separately, highlighting how each design axis may engage distinct cell-type-specific processes within the neural microenvironment.

By separating microglial and astrocytic targets, this framework emphasizes that glia-informed biomaterial design should not treat glial reactivity as a single uniform process, but should instead account for distinct cell-type-specific functions and their coordinated effects on tissue repair.

A conceptual framework integrating these glia-centered design axes across microenvironmental sensing, glial biological targets, and engineering actions is illustrated in Fig. 4.

This framework provides a unifying design logic that links the principles outlined in Table 2 to specific glial targets and functional biomaterial strategies. In doing so, it connects biological interpretation to practical design considerations, including how materials sense local tissue states, modulate inflammatory timing, and support structurally permissive repair environments [9,61,95].

Rather than focusing solely on neuronal survival or axonal regeneration, a glia-centered perspective emphasizes how biomaterials interact with the cellular networks that regulate immune responses and tissue homeostasis in the brain. Considering these interactions during biomaterial design may improve the ability of materials to support tissue repair, reduce chronic inflammation, and enhance long-term compatibility with neural tissue. This perspective is especially relevant for brain repair and neural tissue engineering, where functional recovery depends not only on neuronal preservation but also on the regulation of matrix remodeling, inflammatory resolution, and microenvironmental stability [1,8,11].

Importantly, glial cells perform diverse and context-

dependent functions that extend beyond inflammatory signaling alone. Microglia regulate immune surveillance, phagocytosis, and synaptic remodeling, while astrocytes contribute to extracellular matrix organization, metabolic support, and scar formation following injury [19,46,96]. Recognizing these cell-specific functions allows biomaterial design strategies to move beyond generalized immune modulation toward more targeted regulation of glial biological processes. This shift supports the development of biomaterials that do not simply suppress reactivity, but instead aim to engage beneficial glial functions while limiting maladaptive remodeling [9,11,19].

Microenvironmental Sensing

As illustrated in Fig. 4, microenvironmental sensing represents a primary entry point for glia-centered biomaterial design. Biomaterials capable of detecting biochemical signals within neural tissue may allow more context-dependent responses to local physiological conditions. Signals associated with oxidative stress, inflammatory mediators, and enzymatic activity often reflect changes in tissue state during injury, inflammation, or disease progression. Materials that respond to these signals can be engineered to alter their structure, release therapeutic agents, or modify cellular interactions in response to local environmental cues [83,97,98]. In this way, microenvironmental sensing provides a mechanistic bridge between evolving tissue conditions and adaptive biomaterial behavior [3,9,79].

In neural environments, oxidative stress and inflammatory signaling are commonly associated with glial activation. Designing biomaterials that respond to these signals may allow materials to adapt their activity to the state of surrounding tissue [98–100]. Such systems may help localize therapeutic delivery or regulate inflammatory responses in a manner that reflects the biological context of the implant site. This capacity is particularly important in injured neural tissue, where the spatial and temporal distribution of inflammatory and reparative cues can change rapidly during the course of remodeling [9,79,88].

From a glia-centered perspective, microenvironmental sensing may also enable biomaterials to respond specifically to signals generated by activated microglia or astrocytes. For example, materials responsive to reactive oxygen species, cytokine gradients, or matrix metalloproteinases may detect microglial inflammatory states and adjust therapeutic delivery accordingly [46,83,99]. Similarly, biomaterials that sense astrocyte-derived extracellular matrix components or proteolytic activity may dynamically respond to glial scar formation. These strategies suggest that biomaterials may eventually function as responsive interfaces that detect and react to glial signaling states within neural tissue. Such systems may be especially valuable for designing materials that align therapeutic activity with local injury stage, inflammatory state, and matrix remodeling status [79,83,88].

Table 2. Glia-informed design principles separated by microglial and astrocytic targets.

Design principle	Microglial targets / Responses	Astrocytic targets / Responses	Biomaterial strategies	Intended repair-oriented outcome
Microenvironmental sensing	Detection of inflammatory mediators, oxidative stress, cytokine gradients, phagocytic activity, and immune-state-associated cues	Detection of extracellular matrix remodeling, astrocyte-associated proteolytic activity, scar-associated matrix changes, and tissue-boundary signals	Stimulus-responsive release systems; ROS-, cytokine-, pH-, or enzyme-responsive materials; feedback-responsive coatings or injectable systems	Context-sensitive therapeutic delivery that responds to evolving injury or inflammatory states
Temporal regulation of neuroinflammation	Support early debris clearance and inflammatory resolution while limiting persistent microglial activation, chronic cytokine production, or maladaptive phagocytosis	Limit prolonged reactive astrocyte activation and chronic inflammatory amplification while preserving early tissue-stabilizing functions	Staged release profiles; degradable carriers; sequential delivery of anti-inflammatory, pro-resolution, or trophic cues	Controlled transition from acute injury response to repair-compatible remodeling
Biomimetic extracellular matrix architecture	Influence microglial recruitment, migration, inflammatory tone, and interaction with scaffold architecture or degradation products	Regulate astrocyte adhesion, scar architecture, extracellular matrix deposition, AQP4 organization, and boundary formation	Soft matrix-mimetic hydrogels; extracellular matrix (ECM)-derived ligands; tunable stiffness; porous scaffolds; controlled degradation	Repair-permissive matrix remodeling, cellular infiltration, and reduced scar-dominant organization
Selective modulation of glial functions	Time-limited debris or myelin clearance; inflammatory resolution; reduced excessive synaptic engulfment; modulation of microglial cytokine signaling	Support metabolic/trophic functions, tissue stabilization, and controlled matrix remodeling while limiting chronic CSPG-rich scar formation	Localized delivery of immunomodulatory or trophic cues; targeted cargo release; surface functionalization; glia-responsive material design	Engagement of specific beneficial glial functions without broad suppression of glial activity
Long-term compatibility and interface stability	Reduced chronic foreign body response, peri-material inflammatory accumulation, and persistent microglial clustering	Reduced astrocytic encapsulation, glial sheath formation, and inhibitory matrix deposition around long-term implants	Flexible materials; mechanically matched coatings; anti-inflammatory coatings; bioactive interface modification	Stable biomaterial–tissue integration with reduced chronic inflammation and improved functional durability

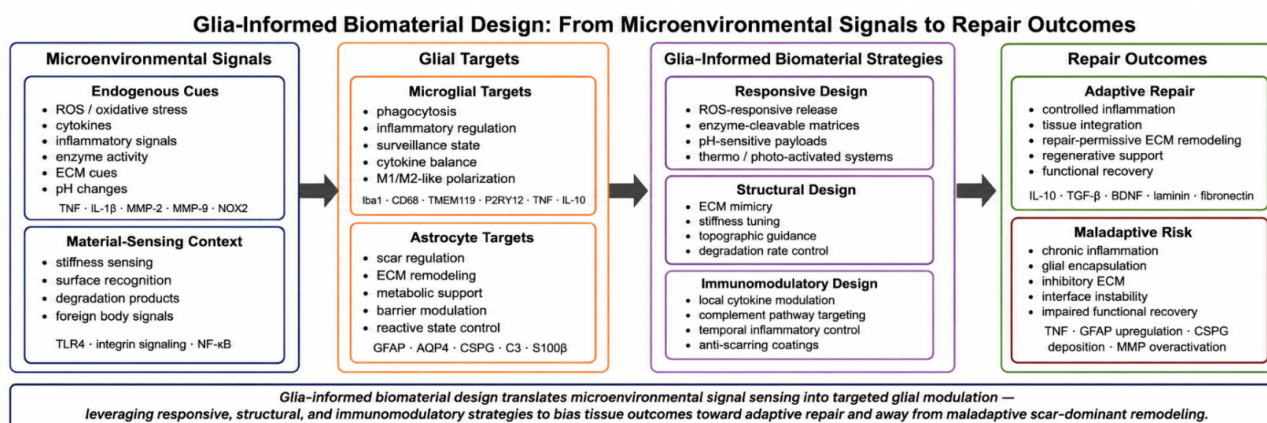


Fig. 4. Glia-informed biomaterial design: from microenvironmental signals to repair outcomes. Schematic summary of how microenvironmental cues and material-sensing contexts can be translated into glia-informed biomaterial strategies. Microglial and astrocytic targets provide design-relevant entry points for regulating inflammation, extracellular matrix remodeling, scar formation, and tissue integration. Responsive, structural, and immunomodulatory strategies may bias biomaterial–tissue interactions toward adaptive repair while reducing the risk of chronic inflammation, glial encapsulation, inhibitory matrix remodeling, and impaired functional recovery. Created with Microsoft PowerPoint.

Temporal Regulation of Neuroinflammation

Inflammatory responses within neural tissue often evolve over time following injury or biomaterial implantation. Early inflammatory signaling may contribute to debris clearance and immune activation, whereas prolonged or excessive inflammation can lead to tissue damage and impaired biomaterial integration. Biomaterials capable of modulating immune responses in a temporally controlled manner may therefore help support tissue repair while reducing the risk of chronic inflammation [9,12]. This temporal dimension is especially important in the brain, where the transition from acute injury response to chronic inflammatory remodeling can strongly influence regenerative outcome and long-term material compatibility [9,11,12].

Temporal regulation can be achieved through several material design strategies, including controlled release of therapeutic molecules, degradation-dependent signaling, or stimulus-responsive systems that change activity over time [9,100]. By aligning biomaterial behavior with the dynamic phases of neural inflammation and repair, such approaches may help promote more favorable interactions between biomaterials and glial cells within neural tissue. In this way, temporal control allows biomaterials to be designed not only for what they deliver, but also for when and under what tissue conditions they exert their effects [9,12,101].

This temporal perspective is particularly relevant for microglial biology. Early microglial activation is often associated with debris clearance and phagocytosis of damaged cellular components, processes that may support tissue recovery [19,102]. However, prolonged inflammatory activation may contribute to chronic neuroinflammation and tissue damage. Biomaterials that modulate microglial activity across these phases may therefore help preserve beneficial functions such as phagocytosis while limiting sus-

tained inflammatory signaling. Designing materials that influence the timing of microglial activation states represents an emerging strategy for aligning biomaterial function with the natural progression of neuroimmune responses. Such approaches may help shift biomaterial design away from indiscriminate immune suppression and toward phase-appropriate regulation of glial activity during tissue repair [9,12,101].

Biomimetic Extracellular Matrix Architecture

The extracellular matrix of the brain provides structural support and biochemical signals that influence cellular behavior within neural tissue. Its mechanical properties, molecular composition, and spatial organization contribute to the regulation of neuronal signaling, glial activation, and tissue remodeling. Glial cells in particular respond to changes in matrix stiffness, ligand availability, and structural architecture, which can affect inflammatory signaling and cellular migration [19,61]. These features make extracellular matrix architecture a central design variable for biomaterials intended to function within the highly sensitive neural microenvironment [1,9].

Biomaterials designed to mimic aspects of the native brain extracellular matrix may therefore improve compatibility with neural tissue. Materials with mechanical properties similar to those of neural tissue can help reduce mechanical mismatch between implants and surrounding tissue, which has been associated with inflammatory responses and impaired tissue integration [11]. In addition, biomaterials that incorporate extracellular matrix components or biomimetic ligands may influence glial adhesion, signaling pathways, and tissue remodeling processes. Such strategies are particularly relevant for biomaterials intended to support repair-compatible cell organization and permis-

sive tissue remodeling after injury [8,103,104].

By reproducing key features of the neural extracellular matrix, biomaterials may provide environments that better support cellular organization and functional integration within the brain. Such biomimetic strategies may also help regulate glial activation and promote tissue responses that are more compatible with neural repair. Accordingly, matrix-mimetic design is not only a structural consideration, but also a means of shaping how glial cells interpret and respond to implanted or injected biomaterials [1,9].

Astrocytes are particularly sensitive to extracellular matrix architecture and mechanical properties. Changes in matrix stiffness or ligand presentation can influence astrocyte activation states and the formation of reactive astrocytic structures surrounding injured tissue or implanted materials [46,61]. Designing biomaterials that reproduce the mechanical softness and biochemical composition of native brain matrix environments may therefore help regulate astrocyte-mediated scar architecture. In this context, biomimetic matrices may serve not only as structural scaffolds but also as regulators of astrocyte-driven tissue remodeling. This is especially important in neural tissue engineering settings, where astrocyte-dependent matrix organization may influence whether a material supports constructive repair or contributes to inhibitory boundary formation [50,61].

Selective Modulation of Glial Functions

Traditional approaches to neural biomaterial design often aim to reduce glial activation broadly in order to minimize inflammatory responses. However, glial cells perform a range of functions that are essential for maintaining neural tissue health and coordinating repair processes. These functions include debris clearance, release of trophic factors, regulation of synaptic environments, and resolution of inflammatory signaling [18,56,96]. This functional diversity suggests that glial activity should not be viewed solely as a target for suppression, but as a set of biological processes that may be selectively engaged or redirected during biomaterial design [12,105].

Rather than broadly suppressing glial activity, biomaterials may instead be designed to influence specific glial functions that contribute to beneficial tissue responses. For example, promoting debris clearance while limiting prolonged inflammatory signaling may help support tissue repair after injury. Similarly, encouraging the release of trophic factors from glial cells may contribute to neuronal survival and regeneration [25,106]. Such an approach is especially relevant in neural repair settings, where beneficial and maladaptive glial functions often coexist within the same evolving tissue environment [12,105].

Design strategies that selectively influence particular glial activities may therefore offer a more nuanced approach to biomaterial-immune interactions. By modulating specific cellular pathways rather than suppressing glial activity

altogether, biomaterials may help support regenerative processes while limiting detrimental inflammatory responses. In this sense, selective modulation provides a way to align biomaterial function with the biological complexity of the injured brain rather than imposing uniform immune inhibition [9,12,103].

Examples of such strategies remain largely preclinical, but they illustrate how selective glial modulation could be defined more specifically in biomaterial studies. For microglia, one design goal may be to support time-limited phagocytic clearance of cellular debris or damaged myelin after injury while avoiding persistent inflammatory activation or excessive synaptic engulfment. This could be evaluated using CD68 or other lysosomal markers, colocalization of microglia with debris or myelin fragments, preservation of synaptic markers, and time-course analysis of inflammatory mediator resolution. For astrocytes, selective modulation may involve promoting tissue-stabilizing or trophic functions while limiting chronic scar-dominant extracellular matrix deposition. Relevant readouts may include GFAP organization, CSPG deposition, AQP4 localization, astrocytic boundary thickness, neuronal survival, and neurite extension near the biomaterial interface [97,99,101,107,108]. These examples clarify that selective modulation should not be interpreted as simple enhancement or suppression of glial activity, but as experimentally defined regulation of specific glial functions within an appropriate temporal and tissue context.

Because many selective glial modulation strategies remain at an early experimental stage, claims regarding therapeutic benefit should be interpreted cautiously. Future studies will need to connect biomaterial-induced changes in glial function with downstream tissue repair, neuronal preservation, circuit activity, and functional recovery, ideally across multiple time points and increasingly translational models.

Context-Dependent Biomaterial Strategies

The biological environments encountered by neural biomaterials can vary considerably depending on the underlying disease or injury context. For example, neural tissues undergoing acute injury, chronic neurodegeneration, or other pathological remodeling states may exhibit distinct inflammatory profiles, cellular compositions, and extracellular matrix structures. These differences can influence how biomaterials interact with surrounding cells and tissues [9,103,109]. Accordingly, biomaterial design cannot be fully separated from the biological context in which the material is expected to function [4,12].

Because of this variability, biomaterial design strategies may need to be adapted to specific biological contexts. Materials intended for neural repair after injury may require properties that support cellular migration, tissue remodeling, and regeneration. In other settings, biomaterials may prioritize local immune regulation, structural stabilization,

or context-specific therapeutic delivery depending on the dominant features of the surrounding tissue environment [12,103].

Considering these contextual differences during biomaterial design may improve the ability of materials to interact effectively with neural tissue. Approaches that account for disease-specific microenvironments and glial responses may therefore help guide the development of biomaterials that are better suited to diverse neurological applications. From a glia-informed perspective, this means that the same general design principle may require different material implementations depending on the local balance among inflammation, matrix remodeling, cellular recruitment, and tissue stability [4,9,103].

For example, biomaterials designed for traumatic injury may aim to regulate early inflammatory signaling while supporting astrocyte-mediated tissue stabilization and neural progenitor recruitment. In other contexts, materials may instead be optimized to limit chronic inflammatory remodeling, support long-term tissue compatibility, or deliver therapeutic signals in a more spatially restricted manner. These differences highlight the importance of designing biomaterials that account for the distinct roles of glial cells across neurological disease states. Thus, context-dependent design should be understood not as a departure from glia-informed biomaterial principles, but as the condition under which those principles become biologically meaningful and therapeutically useful [9,12].

Temporal and Context-Dependent Glial Responses: From Repair Support to Maladaptive Remodeling

A central challenge for glia-informed biomaterial design is that many glial responses are not intrinsically beneficial or detrimental. Instead, their biological meaning depends on timing, intensity, duration, anatomical location, and the surrounding injury or disease context. Microglial activation, astrocytic scar formation, extracellular matrix remodeling, and inflammatory signaling may each support repair under some conditions while contributing to maladaptive remodeling under others. For biomaterial design, this means that the goal should not be universal suppression of glial activity, but temporal and context-sensitive modulation of specific glial functions [110–112].

A practical way to apply this principle is to interpret biomaterial–glial interactions across acute, subacute, and chronic response windows. In the acute phase, microglial activation may support surveillance, debris clearance, and early inflammatory coordination, but excessive or unresolved activation may amplify tissue injury. During the subacute phase, extracellular matrix remodeling, cellular infiltration, and astrocyte–microglia crosstalk may determine whether the local environment becomes repair-permissive or begins to shift toward inhibitory remodeling. In the chronic phase, persistent astrocytic scar formation, dense extracellular matrix deposition, chronic microglial

activation, and long-term glial encapsulation may compromise axonal growth, material integration, and neural interface stability [113,114]. These temporal distinctions are important because the same biomaterial property may have different consequences depending on when it acts within the evolving repair environment.

Microglial phagocytosis provides a useful example of this double-edged behavior. During the early phase after injury or implantation, microglial clearance of cellular debris, damaged myelin, or material-associated particles may help limit secondary damage and support tissue remodeling. However, if phagocytic activation is sustained, spatially misdirected, or associated with excessive complement-related signaling, it may contribute to synaptic loss, neuronal stress, or maladaptive circuit remodeling [112,115–117]. From a design perspective, biomaterials intended to engage microglial phagocytosis should therefore be evaluated not only by whether they increase or decrease microglial activation, but also by what is being cleared, when the response occurs, and whether the response resolves after the acute repair phase. Useful readouts may include temporal analysis of Iba1-positive microglial accumulation, CD68-associated lysosomal activity, debris or myelin clearance, synaptic marker preservation, and inflammatory mediator resolution [112,113,118].

Astrocytic scar formation also illustrates the need for temporal interpretation. In the acute phase, astrocytic boundary formation can help contain inflammatory spread, stabilize damaged tissue, and protect surrounding neural regions [110,112,119]. In the chronic phase, however, persistent astrocytic reactivity, dense extracellular matrix deposition, and accumulation of inhibitory molecules such as chondroitin sulfate proteoglycans may restrict axonal extension, cellular infiltration, and functional integration. Biomaterial strategies should therefore distinguish between early tissue-stabilizing astrocytic responses and chronic scar-dominant remodeling. For example, a repair scaffold may be considered more favorable if it supports early lesion stabilization while later permitting matrix remodeling, cellular infiltration, and neurite extension rather than maintaining a dense inhibitory boundary [58,120].

These examples suggest that glia-informed biomaterial design should be guided by response windows rather than fixed assumptions about “good” or “bad” glial activation. In practice, design strategies may include early anti-inflammatory or pro-resolution release profiles, delayed delivery of matrix-remodeling or trophic cues, degradable architectures that change as the lesion environment evolves, and surface or stiffness properties that limit chronic foreign body responses [58,111,113,121,122]. Although precise quantitative thresholds are likely to vary across models, tissue regions, and biomaterial classes, a practical design principle is to promote glial activities that are spatially restricted, functionally relevant, and capable of resolving or transitioning as repair progresses, while avoiding persistent

inflammatory amplification, chronic matrix inhibition, and long-term glial encapsulation.

Applications in Brain Repair and Neural Tissue Engineering

Glial responses play important roles in regenerative contexts within the central nervous system. In these settings, interactions among glial cells, neurons, vascular elements, immune components, and extracellular matrix structures shape the microenvironment in which biomaterials function [13]. Because biomaterials can influence inflammatory signaling, cellular migration, tissue remodeling, and structural integration, understanding glial responses is essential for interpreting how these materials perform in applications related to brain repair and neural tissue engineering. This is particularly relevant in injured neural tissue, where biomaterial success depends not only on material properties, but also on how effectively materials engage or modulate the biological processes that govern repair, inflammatory resolution, and microenvironmental stability [104].

Research in neural biomaterials has therefore increasingly focused on how material properties influence glial activity across different injury and repair settings. In particular, biomaterials designed for brain repair and neural tissue engineering operate within environments where glial signaling, extracellular matrix remodeling, and neuroimmune dynamics strongly influence therapeutic outcomes. Examining these application areas provides insight into how glia-informed design strategies may be translated into more effective regenerative and neuroengineering approaches [123]. Although related principles may also have relevance in other pathological brain microenvironments, the primary focus here is on repair-oriented applications in which biomaterials are used to promote tissue integration, regenerative permissiveness, and functional recovery [7,104].

Brain Repair After Injury

Biomaterials are actively investigated as therapeutic tools for the treatment of neurological injuries, including stroke, traumatic brain injury, and spinal cord injury. These conditions often involve extensive tissue damage, disruption of neural networks, and inflammatory responses that can impede natural regenerative processes. Biomaterials are explored in this context as platforms that may provide structural support for damaged tissue, deliver therapeutic molecules, or create microenvironments that support neural regeneration [124]. In this setting, biomaterials are increasingly viewed not only as passive supports, but as biologically interactive systems capable of shaping the repair environment after injury [81,104,125].

After neural injury, the key design challenge is not simply to suppress glial reactivity, but to influence whether the lesion environment progresses toward controlled in-

flammation, tissue stabilization, regenerative remodeling, or chronic inhibition. For biomaterial-based repair strategies, this means that material properties and delivered signals should be evaluated in relation to injury-stage processes such as inflammatory resolution, matrix remodeling, cellular recruitment, and preservation of repair-permissive tissue structure [13,44,104].

In injury-focused applications, biomaterials may therefore be used to localize therapeutic delivery, stabilize damaged tissue regions, and modulate early inflammatory or reparative signaling in a spatially controlled manner. Rather than emphasizing structural support alone, glia-informed repair strategies should consider whether the material helps shift the damaged microenvironment toward inflammation resolution, controlled matrix remodeling, and functional tissue integration [7,81].

In the context of stroke and traumatic brain injury, biomaterials have been investigated for their ability to promote tissue regeneration, reduce inflammatory damage, and support neuroregenerative processes through integrated biomaterial and neuroengineering strategies [104,125–127]. Materials designed with appropriate mechanical properties may help stabilize damaged tissue and support the migration of endogenous neural stem or progenitor cells. Similarly, biomaterial-based delivery systems can provide localized release of molecules that influence inflammatory signaling or enhance regenerative pathways. Such strategies illustrate how glia-informed biomaterial design may help couple local immune regulation with structural support for tissue repair [104].

Spinal cord injury presents additional challenges because damaged axonal tracts must reconnect across lesion sites [15,128]. Biomaterial scaffolds with aligned structures have been explored to guide axonal growth and support cellular organization within injured regions. In these applications, interactions between biomaterials and glial cells can influence whether the lesion environment becomes permissive or inhibitory to axonal regeneration. This highlights the importance of designing scaffolds that not only guide axonal extension, but also shape the inflammatory and matrix environment through which regeneration must proceed [15,80].

Although biomaterials show promise in these contexts, successful therapeutic outcomes depend on complex interactions between material properties and biological responses. Glial activation, extracellular matrix remodeling, and immune signaling all influence whether biomaterials promote regeneration or instead contribute to chronic inflammation. Understanding these interactions remains an important step toward designing biomaterials that support neural repair more effectively. Taken together, these findings support the view that brain repair applications provide one of the clearest translational settings in which glia-informed biomaterial strategies may improve tissue integration, regenerative permissiveness, and functional recovery

[7,34,104].

The following subsection extends this injury-focused discussion by considering neural tissue engineering more broadly as the construction of regenerative microenvironments in which material architecture, biochemical signaling, and glial regulation are integrated.

Neural Tissue Engineering and Regenerative Microenvironments

Neural tissue engineering aims to restore or support damaged nervous tissue by combining biomaterials, cellular strategies, and microenvironmental regulation to promote repair and functional integration. In contrast to the injury-specific focus of the previous subsection, this section emphasizes how biomaterials can be engineered to construct regenerative niches in which physical architecture and biological signaling are integrated [7,8].

A central goal of this approach is to create environments that support cellular infiltration, progenitor migration, neurite extension, vascular support, and long-term tissue integration while limiting chronic inflammation and inhibitory remodeling. Hydrogels, three-dimensional scaffolds, and matrix-mimetic biomaterials are especially relevant because their mechanical softness, hydration, ligand presentation, porosity, degradation behavior, and spatial architecture can be tuned to shape how resident and recruited cells interact with the repair site [7,15].

From a glia-informed perspective, the key issue is not only whether a material provides physical guidance, but whether its structural and biochemical features support a repair-compatible balance among inflammatory signaling, extracellular matrix remodeling, cellular recruitment, and tissue stabilization. In this way, neural tissue engineering can be viewed as the design of dynamic regenerative microenvironments rather than the placement of static scaffolds within damaged tissue [7].

Biomimetic matrix design is one important strategy in this context. Materials that approximate the biochemical and mechanical features of native brain extracellular matrix may reduce mechanical mismatch, influence astrocyte reactivity, and support more favorable patterns of cellular organization. Likewise, scaffold architecture, porosity, and degradation behavior can shape the movement of cells through the repair site, the distribution of signaling molecules, and the progression of matrix remodeling over time. In this way, neural tissue engineering depends not only on static material resemblance to tissue, but also on how biomaterials dynamically interact with evolving biological processes after implantation [15].

Another important feature of regenerative microenvironment design is the integration of structural and signaling functions. Biomaterials may be used to localize growth factors, anti-inflammatory mediators, or other therapeutic cues within repair sites while simultaneously providing structural support for tissue organization. This dual role is par-

ticularly valuable in the central nervous system, where regeneration depends on both the physical reconstruction of damaged regions and the regulation of inflammatory and extracellular matrix conditions that shape cellular behavior. Biomaterials that combine matrix support with controlled signaling may therefore help coordinate neuronal survival, progenitor recruitment, vascular ingrowth, and glial remodeling within the same regenerative niche [7].

Taken together, neural tissue engineering and regenerative microenvironment design illustrate how glia-informed biomaterial strategies can be translated into repair-oriented applications beyond immediate injury management alone. Rather than functioning solely as carriers or scaffolds, biomaterials in these settings may serve as biologically interactive platforms that organize structural, cellular, and immunological features of the repair environment. This perspective reinforces the broader principle that successful neural biomaterials should be designed not only to occupy damaged tissue space but also to help construct microenvironments that are permissive to regeneration, integration, and long-term functional recovery [7,8,15].

Context-Specific Translational Extension

Although the primary focus of this review is on brain repair and neural tissue engineering, related glia-informed biomaterial principles may also have relevance in other pathological brain microenvironments. One important example is glioblastoma, where the microenvironment includes complex interactions among tumor cells, glial cells, vascular components, and immune populations [129–131]. In this setting, the therapeutic objective differs fundamentally from regenerative applications: rather than promoting tissue integration and regenerative permissiveness, biomaterial strategies may instead aim to support localized therapeutic delivery, modulate immunosuppressive signaling, or disrupt tumor-supportive microenvironmental interactions.

Within the glioblastoma microenvironment, glial cells play important roles in shaping tumor behavior and therapeutic responses. Microglia and macrophage-like cells can accumulate within tumor regions and participate in signaling pathways that influence tumor growth, invasion, and immune regulation, while astrocytes may also contribute to tumor-associated signaling networks that affect cellular migration, extracellular matrix organization, and inflammatory responses within the tumor environment [50,123,131,132]. Because biomaterials can influence immune signaling and local cellular interactions, there is growing interest in designing biomaterial platforms capable of modulating these complex microenvironments [12,129,130]. Hydrogels, nanoparticle carriers, implantable materials, and three-dimensional biomaterial platforms have all been explored for localized therapeutic delivery or for modeling tumor–glia interactions within glioblastoma [29,129,133–141]. These examples suggest that the same general design principles discussed throughout this review, including mi-

croenvironmental sensing, selective glial modulation, and matrix-aware biomaterial design, may also be adapted to non-regenerative central nervous system (CNS) contexts in which the desired outcome is not repair, but targeted disruption of pathological signaling environments [132,142].

Translational Considerations and Measurement Strategies

Successful clinical translation of neural biomaterials requires careful evaluation of the biological responses that occur following implantation or therapeutic delivery. Although experimental studies have demonstrated promising interactions between biomaterials and neural tissue, translating these findings into clinically effective therapies depends on understanding how materials influence complex cellular and molecular processes within the brain. In particular, glial responses represent a critical component of these processes because microglia and astrocytes regulate inflammatory signaling, extracellular matrix remodeling, and long-term tissue compatibility within neural environments [9,143,144]. For biomaterials intended for brain repair and neural tissue engineering, such evaluation is especially important because material success depends not only on immediate biocompatibility, but also on whether the material supports repair-compatible remodeling and functional integration over time [7,8,145].

To avoid treating translational evaluation as a single general endpoint, the following section organizes measurement strategies into four linked modules: glial activation, inflammatory signaling, long-term tissue compatibility, and neural function. This structure separates cellular, molecular, tissue-level, and functional readouts while preserving their biological connection. From a glia-informed perspective, these measurements are not merely descriptive outcomes, but practical indicators of how biomaterial design features translate into biological performance within neural tissue [146–148]. Table 3 outlines a translational framework for evaluating glial, inflammatory, tissue-level, and functional responses to neural biomaterials.

Assessment of Glial Activation

Assessment of glial activation is a key component of evaluating biomaterial performance in neural tissue. Both microglia and astrocytes undergo changes in morphology, gene expression, spatial distribution, and functional behavior in response to injury or implanted materials. These responses can be assessed using immunohistochemistry, immunostaining, transcriptomic profiling, spatial profiling, and morphology-based image analysis [42,143,148]. For microglia, representative measurements may include Iba1-positive cell density, CD68 expression as an indicator of lysosomal or phagocytic activity, TMEM119 or P2RY12 expression as markers related to resident microglial identity or homeostatic features, and morphology-based analysis of ramification, soma size, and clustering around the biomaterial.

For astrocytes, relevant readouts may include GFAP intensity, AQP4 localization, CSPG deposition, C3 expression, astrocytic scar thickness, and the spatial organization of astrocytes around the material interface.

Importantly, glial assessment should not rely only on broad markers of reactivity. Where possible, measurements should distinguish general reactive changes from functionally relevant glial activities. For example, microglial phagocytic activity can be evaluated by CD68 or lysosomal marker expression, uptake assays, or colocalization of microglia with cellular debris, myelin fragments, or synaptic markers. Astrocyte-associated matrix remodeling can be evaluated by CSPG deposition, scar boundary organization, laminin or fibronectin distribution, and changes in extracellular matrix architecture. These more specific measurements help determine whether glial responses reflect unresolved inflammatory activation, debris clearance, inflammatory resolution, trophic support, matrix remodeling, or repair-compatible tissue stabilization [42,143,146].

Monitoring of Inflammatory Signaling

Monitoring inflammatory signaling is another important component of biomaterial evaluation. Following implantation or therapeutic delivery, neural tissues may produce cytokines, chemokines, complement-related signals, and other molecular mediators that regulate immune responses. These signals can help determine whether a biomaterial promotes balanced immune modulation, inflammatory resolution, or prolonged inflammatory activation [9,144]. Experimental approaches may include ELISA or multiplex cytokine assays for secreted mediators such as TNF- α , IL-1 β , IL-6, IL-10, and CCL2; qPCR or RNA sequencing to assess inflammatory and resolution-associated gene programs; and pathway-level analysis of NF- κ B signaling, inflammasome activation, complement-related pathways, or interferon-associated responses.

Because inflammatory signaling is highly time-dependent, measurement strategies should include defined time points after implantation or delivery rather than relying on a single endpoint. For example, an early increase in inflammatory cytokines after injury-associated implantation may not have the same biological meaning as persistent cytokine elevation weeks later. Similarly, a biomaterial designed for acute repair may be evaluated for whether it supports resolution of inflammatory signaling over time, whereas a neural interface may require assessment of whether chronic low-level inflammation persists around the device. These examples illustrate why inflammatory readouts should be interpreted together with time course, material type, injury model, and tissue-level outcomes [143,146,147].

Long-Term Compatibility Analysis

Long-term compatibility with neural tissue is a critical consideration for many biomaterial applications, partic-

Table 3. Translational evaluation framework for neural biomaterials.

Evaluation category	Biological readout	Measurement approaches	Translational relevance
Glial activation	Microglial and astrocyte activation states; morphology; state transitions	Immunohistochemistry and immunostaining (e.g., Iba1, GFAP); transcriptomics; spatial profiling; morphology-based image analysis [143,148]	Indicates whether biomaterials promote broadly reactive, resolving, or repair-supportive glial responses
Inflammatory signaling	Cytokines, chemokines, and immune pathway activation	ELISA; RNA sequencing; multiplex cytokine assays; pathway-level molecular analysis [9,144]	Helps determine whether biomaterials support balanced immune modulation or prolonged inflammatory activation
Tissue compatibility	Extracellular matrix remodeling; glial scar formation; cellular organization; interface stability	Histological analysis; immunostaining; <i>in vivo</i> imaging; structural assessment of peri-material tissue organization [143,150]	Evaluates long-term tissue integration, matrix permissiveness, and the risk of inhibitory remodeling
Neural function	Synaptic activity; network integrity; circuit-level responses; functional recovery-related output	Electrophysiology; calcium imaging; behavioral and functional assays [151]	Connects cellular and tissue-level findings to recovery, integration, and restoration of neural performance

ularly those involving implanted devices, slowly degrading scaffolds, or sustained therapeutic delivery systems. Chronic inflammatory responses, glial scar formation, progressive extracellular matrix remodeling, or cellular exclusion from the material interface may affect long-term material stability and biological performance [143,149]. These outcomes can be assessed by histological analysis of tissue structure, immunostaining for glial scar and matrix-associated markers, *in vivo* imaging, and spatial analysis of peri-material tissue organization.

Specific compatibility readouts may include peri-implant glial density, astrocytic scar thickness, CSPG accumulation, neuronal density near the material interface, axonal growth or exclusion, vascular organization, cellular infiltration into scaffolds, and persistence or degradation of the biomaterial over time. For neural implants, additional interface-specific measures such as encapsulation thickness, electrode impedance, recording stability, and inflammatory cell accumulation around the device may be especially relevant. For injectable hydrogels or degradable scaffolds, long-term compatibility may instead require analysis of degradation kinetics, matrix permissiveness, tissue cavity formation, and whether infiltrating cells organize into repair-compatible rather than scar-dominant structures [7,150].

Neural Function Evaluation

In addition to immune and structural responses, biomaterials may influence neural circuit function. Because neurons and glial cells interact closely within the brain, changes in the local microenvironment can affect synaptic activity, neuronal signaling, network organization, and functional recovery. Functional assessments may include

electrophysiological recordings, calcium imaging, evoked responses, behavioral assays, and neural interface performance measurements, depending on the application [42, 148,149]. For example, biomaterials intended for brain repair may be evaluated using behavioral recovery, neuronal survival, neurite extension, and circuit activity measures, whereas biomaterials used in neural interfaces may require assessment of recording stability, stimulation reliability, signal-to-noise ratio, and long-term device performance.

These functional readouts are important because they connect cellular and molecular measurements to the broader therapeutic goals of recovery, integration, and restoration of tissue performance [146,151,152]. A biomaterial that reduces glial activation but impairs neuronal activity would not represent an optimal repair strategy. Conversely, a material that produces transient early glial activation but supports tissue stabilization, axonal growth, and functional recovery may be biologically more favorable. Functional evaluation should therefore be interpreted together with glial, inflammatory, and tissue-level measurements rather than as an isolated endpoint.

Despite significant progress in biomaterial development, differences in experimental models, measurement techniques, and reporting standards can make it difficult to compare results across studies. Standardization should not mean applying one identical assay panel to all biomaterials. Instead, evaluation frameworks should include a shared core set of glial, inflammatory, tissue, and functional readouts, while also allowing material-specific measurements. For example, nanoparticle studies should report size, surface charge, coating chemistry, dose, biodistribution, microglial uptake, and cargo release behavior. Hydro-

gel and scaffold studies should report stiffness, porosity, degradation rate, ligand presentation, cellular infiltration, and matrix remodeling. Neural implant studies should report mechanical mismatch, surface coating, encapsulation, impedance, recording stability, and peri-device glial organization. This material-specific reporting would improve comparison across studies while preserving the biological context needed to interpret biomaterial–glia interactions.

Advancing such measurement frameworks will likely play an important role in guiding the development of neural biomaterials that are both biologically compatible and therapeutically effective. More broadly, translational progress will depend on connecting biomaterial design logic with measurable cellular, tissue-level, and functional outcomes that can guide iterative refinement of repair-oriented neural biomaterial systems [146,151].

Conclusions

Glial responses are central determinants of how implanted or delivered biomaterials interact with neural tissue. Microglia and astrocytes regulate inflammation, debris clearance, extracellular matrix remodeling, tissue stabilization, and long-term integration; therefore, their responses should be treated as functional components of biomaterial performance rather than merely adverse reactions to implantation. Across hydrogels, nanoparticles, three-dimensional scaffolds, and neural interfaces, glia-informed design requires attention to material properties, biological context, and response timing. The goal should not be broad suppression of glial activity, but selective promotion of repair-supportive functions while limiting persistent inflammation, inhibitory matrix remodeling, and chronic glial encapsulation. By connecting biomaterial design parameters with glial sensing and tissue-level outcomes, this framework provides a practical direction for developing smart biomimetic materials that promote repair-permissive microenvironments, stable integration, and improved repair-oriented functional outcomes.

Declaration of AI and AI-assisted Technologies in the Writing Process

During the preparation of this manuscript, AI-assisted tools, including ChatGPT and Claude, were used only for language editing, grammatical refinement, organization of wording, and improvement of clarity and readability. These tools were not used to generate original scientific data, fabricate references, create unsupported claims, or replace the author's scientific judgment. The author prepared, reviewed, edited, verified, and approved all manuscript content, including the scientific interpretation, reference selection, citation accuracy, figures, tables, and final wording, and accepts full responsibility for the integrity and accuracy of the submitted work.

Availability of Data and Materials

Not applicable. No new data were generated or analyzed in this study. Data sharing is therefore not applicable to this article.

Author Contributions

The author contributed solely to the article.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflicts of interest.

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