Journal of Neurology and Neurological Disorders
Volume 11 | Issue 1
ISSN: 2454-4981

Review Article Open Access

Modulation of Neuroinflammatory Responses to Neural Implants

Suhail Rasool[1,*], Joseph Haohang Sun[2], Minhua Zhou[1], Yue Sun[1], Chenxi Zheng[1], Junyi Zhao[1] and Dongxu Sun[1]

[1]Suninflam Ltd. Room 612, Building No.1, Shenzhen Institute of Advanced Technology, No.299, Huimao Road, Guangming Distct, Shenzhen China

[2]Palo Alto High School, 50 Embarcadero Rd, Palo Alto, CA, United States of America

[*]**Corresponding Author:** Suhail Rasool, Suninflam Ltd. Room 612, Building No.1, Shenzhen Institute of Advanced Technology, No.299, Huimao Road, Guangming Distct, Shenzhen China, Tel.: 7735160203, E-mail: suhail@suninflam.com

Citation: Suhail Rasool, Joseph Haohang Sun, Minhua Zhou, Yue Sun, Chenxi Zheng et al. (2025) Modulation of Neuroinflammatory Responses to Neural Implants, J Neurol Neurol Disord 11(1): 102

Received Date: July 31, 2025 **Accepted Date:** August 08, 2025 **Published Date:** August 22, 2025

Abstract

Neural implants have revolutionized neurology and neuroscience by offering novel therapeutic avenues for neurological disorders and functional restoration. However, their efficacy is often compromised by neuroinflammation, a complex and multifaceted response that adversely affects device performance and longevity. Understanding the mechanisms underlying neuroinflammation and its impact on neural implants are critical for developing strategies to mitigate these effects. Advances in biocompatible biomaterials and implant technologies, informed by neuroinflammatory research, hold promise for reducing immune reactivity and enhancing device functionality. Machine learning and novel signal processing methods are two of the most important recent advancements in software technology that have contributed to this quick progress. Application development in neuroscience is increasing as artificial intelligence (AI) systems get more sophisticated, effective, and quick. AI has the potential to enhance neural implant signal processing methods, such as the brain's interpretation of electrical impulses. The quality of life and long-term outcomes for people with neurological disorders may improve as a result of these important advancements in neurotechnology.

Keywords: Brain-computer interface; Neural implants; neuroinflammation

Neuroinflammatory Responses to Implanted Neurochemical Sensing Probes

According to studies, signal quality across all implanted central nervous system (CNS) sensors can be affected to differing degrees by insertion damage and foreign body response across both acute (seconds to minutes) and chronic (weeks to months) timeframes. Numerous intervention options for enhancing signal sensitivity and endurance result from an understanding of the biological processes at the cellular and molecular level that underlie the brain tissue response to the devices. Neurodegenerative diseases characterized by neurotransmitter signaling deficiencies can be effectively investigated using neurochemical sensing probes, which serve as both diagnostic tools and therapeutic platforms. However, the implantation of these biosensors often elicits adverse tissue reactions that disrupt the brain's neurochemical equilibrium. Within weeks post-insertion, a glial scar forms around the implant, creating a physical and biochemical barrier that contributes to progressive neurodegeneration and diminished signal sensitivity. This scar tissue impedes neuronal communication by obstructing the transmission of chemical messengers.

Recent studies highlight the pivotal role of non-neuronal cells in modulating the post-injury neurochemical environment. While astrocytes and microglia have been extensively characterized for their reactivity to implanted probes, emerging evidence suggests that other glial subtypes—including oligodendrocytes, their precursor cells, myelin structures, and vascular pericytes—also significantly influence this process. More recently, it was shown that both novel object recognition behavior and normal cortical gamma oscillations depend on astrocytic vesicular discharge [1] Furthermore, norepinephrine has been demonstrated to activate astrocytes, which improves the astroglial network's reaction to local neural network activity [2]. Another study shown that immunodeficient mice's larger and more complex human astrocytes improved learning, activity-dependent plasticity, and long-term potentiation [3]. During perceptional learning, microglial cells have also been shown to engage with dendritic spines and engulf synapses [4-6]. It is unclear how the immune system's reaction to foreign bodies affects brain activity overall, but it may change how nerves operate, particularly in the reactive glial sheath region.

The foreign body response triggered by probe implantation initiates a cascade of inflammatory events. Activated immune cells may attempt to degrade the implant within hours; if unsuccessful, fibroblasts and immune cells encapsulate the device within weeks, leading to tissue isolation. Regardless of the technology used, the breaching of the blood–brain barrier (BBB) to insert devices triggers a cascade of biochemical pathways resulting in complex molecular and cellular responses to implanted devices. The initial insertion trauma compromises the BBB, causing localized injury to parenchymal cells [7–14], capillaries, and the extracellular matrix [15–17]. Capillary damage can result in erythrocyte extravasation, platelet activation [15], and focal hematoma formation [18]. BBB disruption exacerbates neuroinflammation through multiple pathways: increased oxidative stress and mitochondrial dysfunction, extravasation of inflammatory plasma proteins, impaired local oxygen and nutrient delivery, microglial activation and recruitment [17–21], accumulation of neurotoxic metabolites in the parenchyma [17, 19–22]. Other initial reactions include microglia migration and activation toward the implant [23, 24, 25-27]. Additionally, local astrocytes are activated, undergoing morphological changes and becoming hypertrophied. [28, 29, 25, 30-32]. This reactive astrogliosis further contributes to the inflammatory milieu, establishing a feedback loop that perpetuates tissue damage and functional impairment. Regardless of technology, implantable device insertion invariably ruptures distant cells and vasculature, breaks the blood-brain barrier, tears through extracellular matrix, and punctures cell membranes. This is particularly true when insertion-related dimpling is seen [33, 34, 35]. Examining the inflammation biochemical cascades that are started by device implantation is essential to comprehending how damage variability affects inconsistent sensor performance. Numerous conditions might cause the original damage to result in increased inflammation : (i) breaking down the blood-brain barrier; (ii) decreasing blood flow, oxygenation, and the elimination of neurotoxic waste, which can result in ischemia or hypoxia; (iii) increasing pressure and mechanical strain due to hemorrhage, vasogenic edema, and device volume accommodativeness; (iv) surface biofouling and inflammatory cytokine accumulation; (v) steric inhibition of prosurvival signaling from the implant substrate.When the blood-brain barrier is disrupted, plasma proteins that are foreign to the central nervous system (CNS) are deposited. These include al-

bumin (40 mg/mL or approximately 55%), globulins (10 mg/mL or approximately 38%), fibrin/fibrinogen (3 mg/mL or approximately 7%), thrombin, plasmin, complement, and red blood cells (hemosiderin) [36-46]. Increases in hemoglobin (due to the breakdown of red blood cells) in the brain cause reactive oxygen species (ROS) and reactive nitrogen species (RNS) that can cause secondary injury by oxidizing cell lipids and proteins [47]. For instance, ROS downregulate tight junction proteins, which increases BBB permeability [48]. In parallel, the oxidative stress that results in the activation and upregulation of pro-inflammatory cytokines like interleukin (IL)-1β60. Overall, it has been demonstrated that device insertion and disruption of the blood-brain barrier instantly activate neighboring microglia. Glial cells exhibit persistently high levels of proinflammatory cytokines (interleukin1 and TNFα) and chemokines (monocyte chemotactic protein1, MCP1) throughout the implantation period, resulting in neuronal degeneration and demyelination [49–56].Consequently, it is probable that the long term (several weeks) installation of these devices will limit undesirable tissue conditions by employing techniques that minimize disruption of blood vessels. For many research, the shortand longterm consequences of reduced blood flow brought on by the implantation of a probe or electrode must be taken into account in order to obtain useful measurements.

Biomaterial-Dependent Modulation of Neuroinflammatory Responses

The magnitude and progression of neuroinflammatory responses to neural implants are critically influenced by the physicochemical properties of the biomaterials employed. Three key material characteristics govern this immune interaction: (1) mechanical properties, (2) surface topography, and (3) surface chemistry. Rough surface topographies, for instance, demonstrate increased pro-inflammatory potential due to greater surface area for protein adsorption and enhanced mechanical irritation of surrounding parenchyma. Conversely, smooth surfaces or engineered coatings (e.g., polyethylene glycol hydrogels) have shown efficacy in attenuating both acute neuroinflammation and chronic foreign body reactions [57].

In chronic recording applications utilizing silicon microelectrode arrays, the immediate "kill zone" of directly damaged neurons along the insertion track appears to have minimal impact on recording fidelity (57). More consequential is the subsequent reactive gliosis that dominates the peri-implant microenvironment during the critical 6-week post-implantation period. This multifaceted tissue response represents the CNS's attempt to stop neuronal loss, limit focal inflammatory reactions, and seal the injured area [31, 58-63]. The gliotic cascade involves Angiogenesis and revascularization of the surrounding region as well as the recruitment of astrocytes, microglia, and NG2-expressing glial precursors [60, 64, 65]. Notably, The first week after brain electrode or probe implantation may see a high concentration of reactive astrocytes, microglia, and laminin-labeled vessels in the vicinity of the implant [66-67]. This spatiotemporal progression underscores the dynamic interplay between material properties and biological responsesthat ultimately determine implant performance. A study that used implantable hydrous iridium oxide microelectrodes to record extracellular pH potentiometrically revealed histological correlations and variations in the local pH surrounding the electrode [68, 69]. There was significant variation in the pH level, pattern (biphasic alkaline-acidic and triphasic acidic-alkaline acidic), depth, and duration of acidosis when these pH detecting devices were transplanted into the brain. Specifically, when post-mortem histology was used, higher acidity levels were frequently linked to larger blood cell counts in the brain parenchyma [68].

Implanted Neural Electrodes as Essential Tools for Neural Signal Recording and Their Neuroinflammatory Consequences

High-density wire microelectrode arrays (MEAs) are indispensable miniature tools for recording neural activity at single-cell and sub-millisecond resolution, and they constitute a primary data source for dissecting neural circuit function. Beyond fundamental neuroscience, these devices underpin emerging clinical technologies such as brain–computer interfaces [70] and neuro-prosthetic systems [71], and they are under active investigation for the treatment of intractable neurological disorders [72, 73].

However, the implantation of MEAs triggers a cascade of adverse effects, beginning with disruption of the blood-brain barrier (BBB) [74]. This breach exposes the brain parenchyma to blood-derived substances that are normally excluded, thereby initiating an acute immune response characterized by rapid activation of astrocytes and microglia [75]. Over time, this response evolves into chronic neuroinflammation. Reactive microglia and hypertrophic astrocytes release pro-inflammatory cytokines and reactive oxygen species, ultimately leading to neurite retraction, neuronal apoptosis, and the formation of a dense glial sheath surrounding the implant [76]. This encapsulation increases electrical impedance and attenuates both signal recording fidelity and charge delivery during stimulation. Persistent BBB leakage can further sustain the inflammatory milieu and allow neurotoxic molecules to accumulate in the peri-implant region, exacerbating neuronal loss and functional degradation over time.

Chronic implantation of microelectrode arrays elicits a stereotyped, multi-cellular neuro-inflammatory response that evolves over weeks to months and ultimately compromises device performance. Across rodent and feline models, a dense sheath of reactive astrocytes consistently envelops the probe track [77–85]. Concomitantly, microglia undergo rapid activation and accumulate at the interface within minutes of insertion, whereas NG2-expressing oligodendrocyte precursor cells (OPCs) are recruited over the ensuing hours and subsequently proliferate [85–87]. The latter cells extend processes toward the implant, secrete axon-growth inhibitory extracellular matrix molecules, and—unique among glia—receive bona fide synaptic input from neighboring neurons [88]. Collectively, these events culminate in the formation of a compact glial scar that is rich in hypertrophic astrocytes whose thickened, interdigitated membranes constitute a diffusional and electrical barrier [89, 90]. Immunohistochemical analyses demonstrate a rapid and sustained up-regulation of glial fibrillary acidic protein (GFAP) beginning as early as three days post-implantation and persisting for at least several months [91]. Quantitative morphometry reveals a progressive decline in neuronal density within 0–50 μm of the electrode interface, with losses becoming statistically significant within 24 h and continuing to fluctuate thereafter (91). The inflammatory milieu is further amplified by activated glia that secrete pro-inflammatory cytokines—including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interferon-γ (IFN-γ)—thereby exacerbating neuronal injury and degrading recording fidelity [92]. Rigid silicon or metallic microelectrode arrays are particularly potent inducers of a foreign-body reaction. Beyond the acute stab wound, chronic presence of the device sustains an inflammatory cascade characterized by persistent astrogliosis (GFAP+ cells) and macrophage activation (ED1+/-MAC-1+ cells) within a 100–230 μm radius [93]. Notably, this zone exhibits marked neuronal loss relative to stab-wound controls, indicating that the continuous physical and biochemical insult of the implant, rather than the initial trauma, drives neurodegeneration. Elevated levels of monocyte chemoattractant protein-1 (MCP-1) and TNF-α at the interface corroborate the central role of prolonged cytokine signaling in mediating chronic tissue damage and functional decline. These findings underscore the critical need for strategies to mitigate neuroinflammatory responses while maintaining the functional integrity of neural implants.

The Impact of Mechanical Mismatch on Neuroinflammation and Strategies for Mitigation

The mechanical mismatch between rigid implants and soft brain tissue exacerbates neuroinflammation, leading to chronic tissue damage. Conventional neural probes with high bending stiffness induce shear stress upon implantation, disrupting local vasculature and promoting glial scar formation. This fibrotic encapsulation acts as an insulating barrier, elevating electrical impedance and increasing the physical distance between electrodes and viable neurons, ultimately degrading signal acquisition quality. While flexible probes with reduced cross-sectional dimensions elicit attenuated immune responses, their rigid counterparts trigger dense glial encapsulation and a pronounced "kill zone" characterized by significant neuronal loss [94]. Recent advancements in brain-computer interface (BCI) technology have focused on minimizing mechanical mismatch and reducing the implant footprint to mitigate tissue damage. Flexible polymer-based devices, such as those fabricated from polyimide (PI) or SU-8 substrates, have emerged as promising solutions. For instance, an ultrathin (1 μm) PI-based BCI device with bending stiffness comparable to that of neural axons [94] demonstrated a substantial reduction in glial activation and neuronal loss com-

pared to bulkier probes, enabling stable neural recordings for over 30 days post-implantation. Furthermore, ultraflexible nanoelectronic probes that closely match the mechanical properties of brain tissue have been shown to integrate seamlessly without inducing glial scarring [95].

Enhancing Biocompatibility through Material and Design Optimization

Neurotoxic materials lead to cellular rot and misfortune of neurons. It has been inspected the soundness and cytotoxic impacts of inserts made with gold (Au), platinum (Pt), iridium (Ir), indium tin oxide (ITO), and titanium (Ti) in coordinate contact with the tissue. Compared to a polystyrene tissue culture control, Au, ITO, and Ir appeared no diminish in neuronal movement or development taking after 72 h of coordinate contact. In spite of Pt and Ti tests diminishing the number of living cells, they were not labeled cytotoxic as over 75 % of cells remained [96]. Neural interfacing utilizing Tungsten have been utilized for a few decades. Be that as it may, within the nearness of oxygen or other oxidizing species, tungstic particles have poisonous impacts on the neural tissue close the implantation location. Tungsten's cytotoxic impacts, tall Young's modulus, and hardness challenge its utilize in BMIs [97,98]. Other metals, counting press, silver, copper, cadmium, manganese, lead, chromium, and nickel, appear hoisted neurotoxic impacts, most likely through free radical species formation [99, 100]. Other than metals and metalloids, later investigate endeavors investigated electrically conductive polymer-based microelectrode clusters [101]. These polymers, which can be talked about assist in this survey as potential coatings to upgrade biocompatibility, incorporate polypyrrolen [102], poly (3,4-ethylenedioxythiophene, (PEDOTor PEDT) [57], Poly-vinyl liquor (PVA) (103,104), poly-(lactic-co-glycolic corrosive) (PLGA) [103], Poly-D-Lysine (105), and poly(ethylene glycol) (PEG) (106). Within the form of graphene and carbon nanotubes (CNTs), carbon could be a promising fabric for neuro-prosthetic gadgets [107]. Graphene and CNTs have a tall Young's modulus, are not cytotoxic, and can be utilized to record and fortify neural movement. They moreover advance neuronal multiplication and attachment at the embedded location [108]. The mechanical properties permit adaptable, biocompatible BMI designs. Similar characteristics for silicon microelectrode inserts have been found, supporting their utilize in BMIs just like the UEA [109]. Surface modifications and electrode coatings play a critical role in improving device biocompatibility. For example, platinum-black (PtB) coatings significantly reduce electrochemical impedance while enhancing charge storage capacity, thereby improving signal fidelity. Additionally, optimizing implant geometry such as employing shuttle-assisted delivery systems—can minimize insertion-induced trauma [94]. A notable innovation involves a silicon shuttle with a microgroove structure, which ensures precise implantation of flexible probes while further reducing acute tissue damage [94].

Pharmacological Strategies to Suppress Neuroinflammation

In order to reduce the foreign body reaction and encourage tissue regeneration, pharmacological methods to reduce neuroinflammation surrounding neural implants concentrate on regulating the immune system. These tactics include the use of immunomodulators, cytokine inhibitors, corticosteroids, gene and RNA therapies, and stem cell therapies. Systemic injection of dexamethasone (DEX), a synthetic glucocorticoid that induces pleiotropic antiinflammatory functions through cellular glucocorticoid receptors, was the first way to directly modulate the immune system following microelectrode implantation. DEX is frequently used in the clinic to treat multiple sclerosis. The majority of cells, including microglia, express receptors for glucocorticoids like dexamethasone [110]. Adjunctive pharmacological interventions may further enhance BCI longevity. Minocycline, a microglial inhibitor, has been shown to attenuate TNF-α-induced blood-brain barrier (BBB) dysfunction [92]. However, long-term dosing of minocycline begets an increased risk of adverse events—including hyperpigmentation of the skin and other organs [111, 112]. Minocycline possesses an increased chance of serious adverse events relative to other tetracyclines [113]. Thus, minocycline could be part of a multi-faceted approach to reduce initial neuroinflammation, but less risky alternative therapies are needed for chronic applications. Similarly, localized delivery of anti-inflammatory agents, such as interleukin-1 (IL-1) receptor antagonists, could mitigate chronic inflammation around the implant site [114]. Targeted suppression of pro-inflammatory cytokines, including IL-6 and TNF-α, may also reduce glial activation without compromising the brain's innate ability to respond to genuine pathological threats. alpha-melanocyte stimulating hormone (Alpha-MSH) has been shown

to inhibit both nitric oxide and pro-inflammatory cytokines produced by activated microglia—both of which are detrimental to neuronal health [115]. Although flavopiridol stops cell cycle progression, glial activation has been found to re-enter the cell cycle, as seen by the overexpression of cell-cycle components [116]. Flavopiridol was therefore thought to result in better intracortical microelectrode recording performance and less glial activation. Using a knock-out mouse model, Kozai et al. showed that caspase-1 is a suitable immunomodulatory target for enhancing long-term single-unit recordings made by intracortical microelectrodes inserted into mice's visual cortex [117]. According to data collected by Kozai et al., pharmaceutical therapies that target the inflammasome's downstream actors and components may result in more stable long-term brain recordings. It was shown that employing a knockout mouse model to target monocyte chemoattractant protein1 (MCP1) reduced the inflammatory response to intracortical microelectrode implantation [118]. A chemoattractant called MCP1 draws monocytes to inflammatory sites, such the brain's reaction to a neural electrode. It was previously demonstrated that targeting the toll-like receptor (TLR)/cluster of differentiation 14 (CD14) pathways can improve both acute and chronic microelectrode performance using knock--out mouse models and a small-molecule inhibitor. Pattern recognition receptors are present on microglia, neurons, astrocytes, and blood-derived macrophages present at the probe interface and detect cellular damage and blood proteins [119, 120].

Galectin-3 (Gal-3) is a multifunctional protein implicated in neuroinflammation, microglial activation, and neurodegenerative diseases. Gal-3 is primarily secreted by activated microglia, where it modulates neuroinflammation by interacting with toll-like receptors (TLRs) and other immune pathways, exacerbating inflammation [105]. Inhibition of Gal-3 has shown promise in reducing neuroinflammation and neurodegeneration in preclinical models [121]. After investigating the effects of platinum implantation on neuroinflammation, we found that our antibody SIF001 targeting Galectin-3, a key proinflammatory factor, dramatically reduced neuroinflammatory markers of activated microglia and astrocytes in mice. When compared to an isotype control antibody, our SIF001 demonstrated significant decreases of both the scar tissue encapsulation of the platinum wire and microhemorrhage in brain sections, and it also dramatically increased neurogenesis, implying its potential application in neural implantation [122]. In Platinum wire insertion model, treatment with mSIF001 was able to significantly improves locomotor function test and significantly reduced neuroinflammatory activation of microglia and astrocytes. In addition, reduction in microhemorrhage there was also statistically significant increase in number of neurons by mSF001 Ab.

Conclusion

Neuroinflammation is a complicated, multidimensional problem that has a big influence on how well neural implants work and how long they last. Progress in the field of neural implants depends on comprehending the mechanisms underlying neuroinflammation and creating plans to lessen its effects. The performance and biocompatibility of neural implants can be enhanced by researchers investigating new biomaterials, surface modification methods, and drug delivery systems, which will ultimately improve the lives of people with neurological injuries or disorders.

References

1. Lee HS, Ghetti A, Pinto-Duarte A, Wang X, Dziewczapolski G et al. (2014) Astrocytes contribute to gamma oscillations and recognition memory. Proc. Natl. Acad. Sci. U. S. A. 111: E3343–3352.

2. Paukert M, Agarwa A, Cha J, Doze VA et al. (2014) Norepinephrine controls astroglial responsive- ness to local circuit activity. Neuron, 82: 1263-70.

3. Han X, Chen M, Wang F, Windrem M, Wang S et al. (2013). Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell, 12: 342–53.

4. Tremblay ME, Zettel ML, Ison JR, Allen PD, Majewska AK (2012) Effects of aging and sensory loss on glial cells in mouse visual and auditory cortices. Glia. 60: 541–58.

5. Tremblay, ME, Majewska AK (2011) A role for microglia in synaptic plasticity? Commun. Integr. Biol. 4: 220–2.

6. Tremblay MÈ, Lowery RL, Majewska AK (2010) Microglial interactions with synapses are modulated by visual experience. PLoS biology, 8: e1000527.

7. Hamani C, Luer MS, Dujovny M (1997) Microdialysis in the human brain: review of its applications. Neurological research. 19: 281–8.

8. Bungay PM, Newton-Vinson P, Isele W, Garris PA, Justice JB (2003) Microdialysis of dopamine interpreted with quantitative model incorporating probe implantation trauma. Journal of neurochemistry. 86: 932–46.

9. Benveniste H, Diemer NH (1987) Cellular reactions to implantation of a microdialysis tube in the rat hippocampus. Acta neuropathologica. 74: 234–8.

10. Benveniste H, Huttemeier PC (1990) Microdialysis--theory and application. Progress in neurobiology. 35: 195-215.

11. Ferguson M, Sharma D, Ross D, Zhao F (2019) A Critical Review of Microelectrode Arrays and Strategies for Improving Neural Interfaces. Advanced healthcare materials. 8: 1900558.

12. Anderson JM, Rodriguez A, Chang DT (2008) Foreign body reaction to biomaterials. Seminars in immunology, 20: 86–100.

13. Luttikhuizen DT, Harmsen MC, Van Luyn MJ (2006) Cellular and molecular dynamics in the foreign body reaction. Tissue engineering. 12: 1955–70.

14. Morais JM, Papadimitrakopoulos F, Burgess DJ (2010) Biomaterials/tissue interactions: possible solutions to overcome foreign body response. The AAPS journal. 12: 188–196.

15. Wellman SM, Kozai TDY (2017) Understanding the Inflammatory Tissue Reaction to Brain Implants To Improve Neurochemical Sensing Performance. ACS chemical neuroscience. 8: 2578–82.

16. Kozai TD, Jaquins-Gerstl, AS, Vazquez AL, Michael AC, Cui XT (2015) Brain tissue responses to neural implants impact signal sensitivity and intervention strategies. ACS chemical neuroscience. 6: 48–67.

17. Benveniste H (1989) Brain microdialysis. Journal of neurochemistry. 52: 1667–79.

18. Hawkins BT, Davis TP (2005) The blood-brain barrier/neurovascular unit in health and disease. Pharmacological reviews, 57: 173–185.

19. Lifshitz J, Sullivan PG, Hovda DA, Wieloch T, McIntosh TK (2004) Mitochondrial damage and dysfunction in traumatic brain injury. Mitochondrion. 4: 705–713.

20. Bennett C, Samikkannu M, Mohammed F, Dietrich WD, Rajguru SM, Prasad A (2018) Blood brain barrier (BBB)-disruption in intracortical silicon microelectrode implants. Biomaterials. 164: 1–10.

21. Bennett C, Mohammed F, Álvarez-Ciara A, Nguyen MA, Dietrich WD et al. (2019) Neuroinflammation, oxidative stress, and blood-brain barrier (BBB) disruption in acute Utah electrode array implants and the effect of deferoxamine as an iron chelator on acute foreign body response. Biomaterials, 188: 144–59.

22. Stence N, Waite M, Dailey ME (2001) Dynamics of microglial activation: a confocal time-lapse analysis in hippocampal slices. Glia. 33: 256–66.

23. Kozai TD, Gugel Z, Li X, Gilgunn PJ, Khilwani R et al. (2014) Chronic tissue response to carboxymethyl cellulose based dissolvable insertion needle for ultra-small neural probes. Biomaterials. 35: 9255–68.

24. Fawcett JW, Asher RA (1999) The glial scar and central nervous system repair. Brain research bulletin. 49: 377–91.

25. Loane D J, Byrnes, KR (2010) Role of microglia in neurotrauma. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics, 7: 366–77.

26. Benarroch EE (2013) Microglia: Multiple roles in surveillance, circuit shaping, and response to injury. Neurology. 81: 1079–88.

27. Benveniste H, Diemer NH (1987) Cellular reactions to implantation of a microdialysis tube in the rat hippocampus. Acta neuropathologica. 74: 234–8.

28. Benveniste H, Drejer J, Schousboe A, Diemer NH (1987) Regional cerebral glucose phosphorylation and blood flow after insertion of a microdialysis fiber through the dorsal hippocampus in the rat. Journal of neurochemistry. 49: 729-34.

29. Landis DM (1994) The early reactions of non-neuronal cells to brain injury. Annual review of neuroscience. 17: 133–51.

30. Sofroniew MV (2009) Molecular dissection of reactive astrogliosis and glial scar formation. Trends in neurosciences, 32: 638–47.

31. Eddleston M, Mucke L (1993) Molecular profile of reactive astrocytes--implications for their role in neurologic disease. Neuroscience. 54: 15-36.

32. Henze DA, Borhegyi Z, Csicsvari J, Mamiya A, Harris KD, Buzsáki G (2000) Intracellular features predicted by extracellular recordings in the hippocampus in vivo. Journal of neurophysiology, 84: 390–400.

33. Kozai TDY, Marzullo TC, Hooi F, Langhals NB, Majewska AK et al. (2010) Reduction of neurovascular damage resulting from microelectrode insertion into the cerebral cortex using in vivo two-photon mapping. Journal of neural engineering, 7: 046011.

34. Rohatgi P, Langhals NB, Kipke DR, Patil PG (2009) In vivo performance of a microelectrode neural probe with integrated drug delivery. Neurosurgical focus, 27: E8.

35. Bjornsson CS, Oh SJ, Al-Kofahi YA, Lim YJ, Smith KL et al. (2006) Effects of insertion conditions on tissue strain and vascular damage during neuroprosthetic device insertion. J. Neural Eng. 3: 196–207.

36. Zhong Z, Ilieva H, Hallagan L, Bell R, Singh I, Paquette N et al. (2009) Activated protein C therapy slows ALS-like disease in mice by transcriptionally inhibiting SOD1 in motor neurons and microglia cells. J. Clin. Invest. 119, 3437–449.

37. Zhong Z, Deane R, Ali Z, Parisi M, Shapovalov Y et al. (2008) ALS-causing SOD1 mutants generate vascular changes prior to motor neuron degeneration. Nat Neurosci. 11: 420-2.

38. Chen ZL, Strickland S (1997) Neuronal death in the hippocampus is promoted by plasmin-catalyzed degradation of laminin. Cell. 91: 917-925.

39. Mhatre M, Nguyen A, Kashani S, Pham T, Adesina A et al. (2004) Thrombin, a mediator of neurotoxicity and memory impairment. Neurobiol Aging. 25: 783–93.

40. Chen B, Cheng Q, Yang K, Lyden PD (2010) Thrombin mediates severe neurovascular injury during ischemia. Stroke. 41: 2348–52.

41. Cao L, Chang M, Lee CY, Castner DG, Sukavaneshvar S et al. (2007) Plasma-deposited tetraglyme surfaces greatly reduce total blood protein adsorption, contact activation, platelet adhesion, platelet procoagulant activity, and in vitro thrombus deposition. J. Biomed Mater. Res. A. 81: 827–37.

42. Alafuzoff I, Adolfsson R, Bucht G, Winblad B (1983) Albumin and immunoglobulin in plasma and cerebrospinal fluid, and blood-cerebrospinal fluid barrier function in patients with dementia of Alzheimer type and multi-infarct dementia. J. Neurol Sci. 60: 465–72.

43. Winslow BD, Christensen MB, Yang WK, Solzbacher F, Tresco PA (2010) A comparison of the tissue response to chronically implanted Parylene-C-coated and uncoated planar silicon microelectrode arrays in rat cortex. Biomaterials, 31: 9163-72.

44. Gasque P, Dean YD, McGreal EP, VanBeek J, Morgan BP (2000) Complement components of the innate immune system in health and disease in the CNS. Immunopharmacology. 49: 171–86.

45. Fitch MT, Doller C, Combs CK, Landreth GE, Silver J (1999) Cellular and molecular mechanisms of glial scarring and progressive cavitation: In vivo and in vitro analysis of inflammation-induced secondary injury after CNS trauma. J. Neurosci. 19: 8182–98.

46. Paul J, Strickland S, Melchor JP (2007) Fibrin deposition accelerates neurovascular damage and neuroinflammation in mouse models of Alzheimer's disease. J Exp Med, 204: 1999–2008.

47. Davalos A, Castillo J, Marrugat J, Fernandez-Real JM, Armengou A (2000) Body iron stores and early neurologic deterioration in acute cerebral infarction. Neurology. 54: 1568–74.

48. Abdul-Muneer PM, Chandra N, Haorah J (2015) Interactions of oxidative stress and neurovascular inflammation in the pathogenesis of traumatic brain injury. Molecular neurobiology, 51: 966-79.

49. Banati RB, Gehrmann J, Czech C, Monning U, Jones LL, Konig G, Beyreuther K, Kreutzberg GW (1993) Early and Rapid De-Novo Synthesis of Alzheimer Beta-A4-Amyloid Precursor Protein (App) in Activated Microglia. Glia, 9: 199–210.

50. Babcock AA, Kuziel WA, Rivest S, Owens T (2003) Chemokine expression by glial cells directs leukocytes to sites of axonal injury in the CNS. J. Neurosci. 23: 7922–30.

51. Giulian D, Li J, Li X, George J, Rutecki PA (1994) The Impact of Microglia-Derived Cytokines Upon Gliosis in the Cns. Dev. Neurosci, 16: 128-36.

52. Giulian D, Li J, Leara B, Keenen C (1994) Phagocytic Microglia Release Cytokines and Cytotoxins That Regulate the Survival of Astrocytes and Neurons in Culture. Neurochem. Int, 25: 227–33.

53. Sheng WS, Hu SX, Kravitz FH, Peterson PK, Chao CC (1995) Tumor-Necrosis-Factor-Alpha up-Regulates Human Microglial Cell Production of Interleukin-10 in-Vitro. Clin. Diagn. Lab. Immunol. 2: 604-8.

54. Chabot S, Williams G, Yong VW (1997) Microglial production of TNF-alpha is induced by activated T lymphocytes - Involvement of VLA-4 and inhibition by interferon beta-1b. J. Clin. Invest. 100: 604–12.

55. Nakajima K, Honda S, Tohyama Y, Imai Y, Kohsaka S et al. (2001) Neurotrophin secretion from cultured microglia. J. Neurosci. Res. 65: 322–31.

56. Elkabes S, DiCiccoBloom EM, Black IB (1996) Brain microglia macrophages express neurotrophins that selectively regulate microglial proliferation and function. J. Neurosci. 16: 2508–21.

57. Buffo A, Rite I, Tripathi P, Lepier A, Colak D et al. (2008) Origin and progeny of reactive gliosis: A source of multipotent cells in the injured brain. Proceedings of the National Academy of Sciences of the United States of America. 105: 3581–6.

58. .Okada S, Nakamura M, Katoh H, Miyao T, Shimazaki T et al. (2006) Conditional ablation of Stat3 or Socs3 discloses a dual role for reactive astrocytes after spinal cord injury. Nature medicine. 12: 829–34.

59. Sofroniew MV (2005) Reactive astrocytes in neural repair and protection. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry. 11: 400–7.

60. Vedam-Mai V, van Battum EY, Kamphuis W, Feenstra MG, Denys D et al. (2012) Deep brain stimulation and the role of astrocytes. Molecular psychiatry. 17: 124–15.

61. Sofroniew MV, Vinters HV (2010) Astrocytes: biology and pathology. Acta neuropathologica. 119: 7–35.

62. Szarowski DH, Andersen MD, Retterer S, Spence AJ, Isaacson M et al. (2003) Brain responses to micro-machined silicon devices. Brain research. 983: 23–35.

63. Alonso G (2005) NG2 proteoglycan-expressing cells of the adult rat brain: possible involvement in the formation of glial scar astrocytes following stab wound. Glia. 49: 318–38.

64. Magnus T, Coksaygan T, Korn T, Xue H, Arumugam TV et al. (2007) Evidence that nucleocytoplasmic Olig2 translocation mediates brain-injury-induced differentiation of glial precursors to astrocytes. Journal of neuroscience research. 85: 2126-37.

65. Stichel CC, Müller HW (1998) The CNS lesion scar: new vistas on an old regeneration barrier. Cell and tissue research. 294:

1-9.

66. Spataro L, Dilgen J, Retterer S, Spence AJ, Isaacson M et al. (2005) Dexamethasone treatment reduces astroglia responses to inserted neuroprosthetic devices in rat neocortex. Experimental neurology. 194: 289-300.

67. Sharifi MS (2013) Treatment of neurological and psychiatric disorders with deep brain stimulation; raising hopes and future challenges. Basic and Clinical Neuroscience. 4: 266.

68. Johnson MD, Kao OE, Kipke DR (2007) Spatiotemporal pH dynamics following insertion of neural micro- electrode arrays. J. Neurosci Methods. 160: 276–87.

69. Johnson MD, Langhals NB, Kipke DR (2006) Neural interface dynamics following insertion of hydrous iridium oxide microelectrode arrays. Conf Proc. IEEE Eng. Med. Biol. Soc. 1: 3178–81.

70. Guo Z, Wang F, Wang L, Tu K, Jiang C et al. (2022) A flexible neural implant with ultrathin substrate for low-invasive brain–computer interface applications. Microsystems & Nanoengineering, 8: 133.

71. Kozai TDY, Marzullo TC, Hooi F, Langhals NB, Majewska AK et al. (2010) Reduction of neurovascular damage resulting from microelectrode insertion into the cerebral cortex using in vivo two-photon mapping. Journal of neural engineering. 7: 046011.

72. Wang J, He T, Lee C (2019) Development of neural interfaces and energy harvesters towards self- powered implantable systems for healthcare monitoring and rehabilitation purposes. Nano Energy. 65: 104039.

73. Ji B, Liang Z, Yuan X, Xu H, Wang M et al. (2022) Recent advances in wireless epicortical and intracortical neuronal recording systems. Science China Information Sciences. 65: 140401.

74. Kozai TDY, Vazquez AL, Weaver CL, Kim SG, Cui XT (2012) In vivo two-photon microscopy reveals immediate microglial reaction to implantation of microelectrode through extension of processes. Journal of neural engineering. 9: 066001.

75. Williams JC, Hippensteel JA, Dilgen J, Shain W, Kipke DR (2007) Complex impedance spectroscopy for monitoring tissue responses to inserted neural implants. Journal of neural engineering. 4: 410.

76. Saxena T, Karumbaiah L, Gaupp EA, Patkar R, Patil K et al. (2013) The impact of chronic blood–brain barrier breach on intracortical electrode function. Biomaterials. 34: 4703-13.

77. Carter RR, Houk JC (2002) Multiple single-unit recordings from the CNS using thin-film electrode arrays. IEEE Transactions on Rehabilitation Engineering, 1: 175-184.

78. Edell DJ, Toi VV, McNeil VM, Clark LD (1992) Factors influencing the biocompatibility of insertable silicon microshafts in cerebral cortex. IEEE Transactions on biomedical engineering. 39: 635-643.

79. McCreery DB, Yuen TG, Agnew WF, Bullara LA (2002) A characterization of the effects on neuronal excitability due to prolonged microstimulation with chronically implanted microelectrodes. IEEE transactions on biomedical engineering, 44: 931-939.

80. Schmidt EM, Bak MJ, McIntosh JS (1976) Long-term chronic recording from cortical neurons. Experimental neurology. 52: 496-506.

81. Schmidt, Susan, Kenneth Horch, Richard Normann (1993) Biocompatibility of silicon-based electrode arrays implanted in feline cortical tissue. Journal of biomedical materials research. 27: 1393-9.

82. Schultz RL, Willey TJ (1976) The ultrastructure of the sheath around chronically implanted electrodes in brain. Journal of neurocytology. 5: 621-42.

83. Szarowski DH, Andersen MD, Retterer S, Spence AJ, Isaacson M et al.(2003) Brain responses to micro-machined silicon devices. Brain research. 983: 23-35.

84. Turner JN, Shain W, Szarowski DH, Andersen M, Martins S et al. (1999) Cerebral astrocyte response to micromachined silicon implants. Experimental neurology, 156: 33-49.

85. Sharafkhani N, Kouzani AZ, Adams SD, Long JM, Lissorgues G et al. (2022) Neural tissue-microelectrode interaction: Brain micromotion, electrical impedance, and flexible microelectrode insertion. Journal of Neuroscience Methods, 365: 10938838.

86. García-Revilla J, Boza-Serrano A, Espinosa-Oliva AM, Soto MS, Deierborg T et al. (2022) Galectin-3, a rising star in modulating microglia activation under conditions of neurodegeneration. Cell death & disease, 13: 628.

87. Wellman SM, Kozai TD (2018) In vivo spatiotemporal dynamics of NG2 glia activity caused by neural electrode implantation. Biomaterials, 164: 121-33.

88. Bradl M, Lassmann H (2010) Oligodendrocytes: biology and pathology. Acta neuropathologica, 119: 37-53.

89. Szarowski DH, Andersen MD, Retterer S, Spence AJ, Isaacson M et al. (2003) Brain responses to micro-machined silicon devices. Brain research. 983: 23-35.

90. Polikov VS, Tresco PA, Reichert WM (2005) Response of brain tissue to chronically implanted neural electrodes. Journal of neuroscience methods. 148: 1-18.

91. Kozai TD, Jaquins Gerstl AS, Vazquez AL, Michael AC, Cui XT (2015) Brain tissue responses to neural implants impact signal sensitivity and intervention strategies. ACS chemical neuroscience. 6: 48-67.

92. Wellman SM, Kozai TD (2017) Understanding the inflammatory tissue reaction to brain implants to improve neurochemical sensing performance. ACS chemical neuroscience. 8: 2578-82.

93. Pediaditakis I, Kodella KR, Manatakis DV, et al. (2022) A microengineered Brain-Chip to model neuroinflammation in humans. iScienc. 25: 104813.

94. Biran R, Martin DC, Tresco PA (2005). Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. Experimental Neurology.195: 115–26.

95. Guo Z, Wang F, Wang L, Tu K, Jiang C, et al. (2022) A flexible neural implant with ultrathin substrate for low-invasive brain–computer interface applications. Microsystems & Nanoengineering. 8: 133.

96. Selvakumaran J, Hughes MP, Keddie JL, Ewins DJ (2002) Assessing biocompatibility of materials for implantable microelectrodes using cytotoxicity and protein adsorption studies. In 2nd Annual International IEEE-EMBS Special Topic Conference on Microtechnologies in Medicine and Biology. Proceedings. 261-4.

97. Patrick E, Orazem ME, Sanchez JC, Nishida T (2011) Corrosion of tungsten microelectrodes used in neural recording applications. Journal of neuroscience methods. 198: 158-71.

98. Prasad A, Xue QS, Sankar V, Nishida T, Shaw G, Streit WJ, Sanchez JC (2012) Comprehensive characterization and failure modes of tungsten microwire arrays in chronic neural implants. Journal of neural engineering. 9: 056015.

99. Méndez-Armenta M, Rios C (2007) Cadmium neurotoxicity. Environmental toxicology and pharmacology. 23: 350-58.

100. Caito S, Aschner M (2015) Neurotoxicity of metals. Handbook of clinical neurology. 131: 169-89.

101. Bae SH, Che JH, Seo JM, Jeong J, Kim ET, et al. (2012) In vitro biocompatibility of various polymer-based microelectrode arrays for retinal prosthesis. Invest. Ophthalmol. Vis. Sci. 53: 2653–7.

102. Cui X, Wiler J, Dzaman M, Altschuler RA, Martin DC(2003) In vivo studies of polypyrrole/peptide coated neural probes. Biomaterials. 24: 777–87.

103. Pas J, Rutz AL, Quilichini PP, Slézia A, Ghestem A, et al. (2018) A bilayered PVA/PLGA-bioresorbable shuttle to improve the implantation of flexible neural probes. Journal of neural engineering, 15: 065001.

104. Chen A, Wu Y, Zhou S, Xu W, Jiang W, et al. (2020) High thermal conductivity polymer chains with reactive groups: a step towards true application. Mater. Advan.1: 1996–2002.

105. Ignatius MJ, Sawhney N, Gupta A, Thibadeau BM, Monteiro OR, et al. (1998) Bioactive surface coatings for nanoscale instruments: effects on CNS neurons. J. Biomed. Mater. Res. May.40: 264–74.

106. Bearinger JP, Terrettaz S, Michel R, Tirelli N, Vogel H, et al. (2003) Chemisorbed poly(propylene sulphide)-based copolymers resist biomolecular interactions. Nat. Mater. Apr. 2: 259–64.

107. Belyanskaya L, Weigel S, Hirsch C, Tobler U, Krug HF, et al. (2009). Effects of carbon nanotubes on primary neurons and glial cells. Neurotoxicology, 30: 702-11.

108. Vomero M, Castagnola E, Ordonez JS, Carli S, Zucchini E, et al. (2018). Incorporation of Silicon Carbide and Diamond-Like Carbon as Adhesion Promoters Improves In Vitro and In Vivo Stability of Thin-Film Glassy Carbon Electrocorticography Arrays. Advanced Biosystems, 2: 1700081.

109. Kristensen BW, Noraberg J, Thiebaud P, Koudelka-Hep M, Zimmer J (2001) Biocompatibility of silicon-based arrays of electrodes coupled to organotypic hippocampal brain slice cultures. Brain Res.896: 1–17.

110. Reichardt HM, Tuckermann JP, Gottlicher M, et al. (2001). Repression of inflammatory responses in the absence of DNA binding by the glucocorticoid receptor. The EMBO journal. 20: 7168–73.

111. Reed DN, Gregg FO, Corpe RS (2012) Minocycline-induced black bone disease encountered during total knee arthroplasty. Orthopedics. 35: e737–9.

112. Ochsendorf F Minocycline in acne vulgaris (2010) American journal of clinical dermatology.11: 327–41.

113. Yenari MA, Xu L, Tang XN, et al. (2006) Microglia potentiate damage to blood-brain barrier constituents: Improvement by minocycline in vivo and in vitro. Stroke. 37: 1087-93.

114. Galimberti D, Baron P, Meda L, et al. (1999) a-MSH peptides inhibit production of nitric oxide and tumor necrosis factor-a by microglial cells activated with β-amyloid and interferon γ. Biochemical and biophysical research communications. 263: 251–6.

115. Di Giovanni S, Movsesyan V, Ahmed F, et al (2005). Cell cycle inhibition provides neuroprotection and reduces glial proliferation and scar formation after traumatic brain injury. Proceedings of the National Academy of Sciences of the United States of America. 102: 8333–38.

116. Kozai TD, Li X, Bodily LM, et al. (2014) Effects of caspase-1 knockout on chronic neural recording quality and longevity: Insight into cellular and molecular mechanisms of the reactive tissue response. Biomaterials. 35: 9620–34.

117. Sawyer AJ, Tian W, Saucier-Sawyer JK, et al. (2014) The effect of inflammatory cell-derived MCP-1 loss on neuronal survival during chronic neuroinflammation. Biomaterials. 35: 6698–706.

118. Bedell HW, Hermann JK, Ravikumar M, et al. (2018) Targeting CD14 on blood derived cells improves intracortical microelectrode performance. Biomaterials.163: 163–73.

119. Hermann JK, Ravikumar M, Shoffstall AJ, et al. (2018) Inhibition of the cluster of differentiation 14 innate immunity pathway with IAXO-101 improves chronic microelectrode performance. Journal of Neural Engineering.15: 025002.

120. García-Revilla J, Boza-Serrano A, Espinosa-Oliva AM, Soto MS, Deierborg T, et al. (2022) Galectin-3, a rising star in modulating microglia activation under conditions of neurodegeneration. Cell death & disease. 13: 628.

121. Lozinski BM, Ta K, Dong Y (2024). Emerging role of galectin 3 in neuroinflammation and neurodegeneration. Neural regeneration research. 19: 2004–9.

122. Joseph Haohang Sun, Junyi Zhao, Yue Sun, Chenxi Zheng, Minhua Zhou, et al. (2025) Suppression of neuroinflammatory response to platinum wire implanted in mouse brain by monoclonal antibody SIF001 against Galectin-3. Am J Biomed Sci & Res. 27.