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Functional and Histological Effects of Chronic Neural Electrode Implantation

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Objectives: Permanent injury to the cranial nerves can often result in a substantial reduction in quality of life. Novel and innovative interventions can help restore form and function in nerve paralysis, with bioelectric interfaces among the more promising of these approaches. The foreign body response is an important consideration for any bioelectric device as it influences the function and effectiveness of the implant. The purpose of this review is to describe tissue and functional effects of chronic neural implantation among the different categories of neural implants and highlight advances in peripheral and cranial nerve stimulation.

Data Sources: PubMed, IEEE, and Web of Science literature search.

Review Methods: A review of the current literature was conducted to examine functional and histologic effects of bioelectric interfaces for neural implants.

Results: Bioelectric devices can be characterized as intraneural, epineural, perineural, intranuclear, or cortical depending on their placement relative to nerves and neuronal cell bodies. Such devices include nerve-specific stimulators, neuroprosthetics, brainstem implants, and deep brain stimulators. Regardless of electrode location and interface type, acute and chronic histological, macroscopic and functional changes can occur as a result of both passive and active tissue responses to the bioelectric implant.

Conclusion: A variety of chronically implantable electrodes have been developed to treat disorders of the peripheral and cranial nerves, to varying degrees of efficacy. Consideration and mitigation of detrimental effects at the neural interface with further optimization of functional nerve stimulation will facilitate the development of these technologies and translation to the clinic.

Key Words: Acute, chronic, tissue response, intraneural, perineural, epineural, stimulation.

Level of Evidence: 3.

INTRODUCTION

Permanent paralysis of a cranial nerve can substantially diminish quality of life and impact any of the twelve pairs of nerves, including the facial, vagus, spinal accessory, and hypoglossal nerves, among others. With an annual incidence of 70 cases per 100,000 and 127,000 new cases diagnosed annually in the United States,[1] facial paralysis, for instance, can arise from trauma, infection, tumor, surgery, or birth defects and cause substantial functional deficits.[2] Rehabilitation of a dysfunctional nerve such as the facial nerve is a rapidly evolving field with substantial clinical potential, and can be achieved through methods of nerve regeneration, reinnervation and muscle transfer, and neuroprosthetic technologies. Facial nerve regeneration with progenitor cells has been achieved *in vitro*, but has yet to be translated to the clinical arena.[3] While reinnervation and muscle transfer procedures such as the hypoglossal-facial nerve anastomosis or microvascular gracilis transfer are commonly performed around the world and provide meaningful aesthetic improvements, their functional and cosmetic outcomes are still limited compared to normal facial function.[4] To date, facial nerve stimulation through bioelectric interfaces, such as in intraneural implantation, has yet to be thoroughly investigated and may be a promising avenue for functional cranial nerve rehabilitation.

Chronic neuroprosthetic implants have already been widely employed in motor nerve neuromuscular systems. For instance, the United States Food & Drug Administration recently approved the Inspire Upper Airway Stimulation system, an implantable hypoglossal nerve stimulator for patients with severe obstructive sleep apnea.[5] The Medtronic InterStim Therapy System is an implantable sacral nerve stimulator to assist patients with bowel incontinence.[6] Furthermore, the application of direct nerve stimulation for patients with

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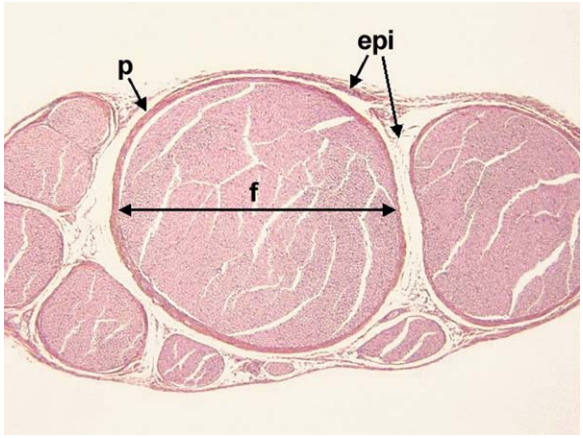

Fig. 1. Histology of the peripheral nerve showing the nerve fascicles (f) grouped in bundles surrounded by perineurium (p) and epineurium (epi). Image courtesy of Stephen Gallik, Ph.D.

disuse muscle atrophy, multiple sclerosis, and spinal cord injury is currently underway.[7] Direct stimulation of the nervous system can also address other pathologies.[8,9] Chronic spinal cord stimulation, for example, has been shown to alleviate severe neuropathic pain.[10] Moreover, selective stimulation of nerve roots with a Finetech-Brindley neurostimulator has been shown to improve bladder, bowel and sexual function in clinical trials.[11] Furthermore, supraorbital transcutaneous stimulation of the trigeminal nerve has reduced migraine duration.[12] Even the intrascalar electrode of the widely-used cochlear implant (CI) may eventually be supplemented or replaced with an array that interfaces with the cochlear nerve directly.[13,14]

Despite these advances, the long-term consequences of electrode implantation have yet to be fully characterized. Chronically implanted electrode arrays can induce neural injury through both mechanical trauma and continuous high frequency stimulation.[15] In this review, we first discuss frequently utilized electrode materials and composition. We then review categories of neural implants, which include intraneural, epineural, perineural and intranuclear interfaces (Fig. 1). Further, we describe the morphological and histological tissue response following chronic device implantation. We end by reviewing current trends in peripheral and cranial nerve stimulation.

Foreign Body Reaction to Biomaterial Implants

The host response to implants is a complex sequence of events that begins with implantation of any foreign material.[16,17] Blood/material interactions result in protein adsorption onto the material surface. An environment surrounding the implant is subsequently created that promotes the cascade of events in the inflammatory and wound healing response. A milieu of bioactive molecules such as cytokines, chemoattractants, and growth factors both attracts and actives inflammatory cells, including neutrophils, monocytes, and lymphocytes. The tissue surrounding the implants subsequently moves through the acute inflammatory phase consisting of polymorphonuclear cells, the chronic inflammatory phase consisting of predominantly monocytes and lymphocytes, and granulation tissue phase consisting of fibroblasts and neovascularization. Granulation tissue subsequently leads to a well-organized fibrous capsule encapsulating the implant.

Infiltrating monocytes and macrophages during the inflammatory response adhere onto biomaterial surface, differentiate, and fuse to form foreign body giant cells (Fig. 2).[18,19] The single layer of monocytes, macrophages, and foreign body giant cells separates the material from the surrounding fibrous capsule. Rather than being an inert layer of cells that help wall off the offending foreign material from the body, the activated macrophages and foreign body giant cells produce bioreactive molecules such as reactive oxygen species, degradative enzymes, and acid.[17] Depending on the material composition, this could result in breakdown of the implanted material. Therefore, the inflammatory and wound healing response, along with the destructive microenvironment at the material surface, can potentially lead to structural and functional failure of the implant.

Electrode Materials and Composition

Neural electrodes inject a charge through reactions that utilize either *capacitive* or *faradaic* materials, both of which bear specific limitations.[20] Capacitive materials include titanium nitride, tantalum, and tantalum oxide, among others, and in contrast to faradaic materials, do not generate any electrochemical reactions at the electrode surface. In general, capacitive materials are preferred over faradaic because charge species are neither created nor destroyed during stimulation. Faradaic materials are composed of noble metals such as platinum, platinum-iridium alloys, or iridium oxide. While faradaic materials provide greater charge-injection capacity, they can lead to irreversible electrode or tissue damage. Intrinsically conducting polymers and carbon nanotubes may be a newfound solution to these issues. The most commonly used intrinsically conducting polymer, poly(ethylenedioxythiophene) or PEDOT, offers diversity by possessing both ionic and electronic conductivity. Carbon nanotubes are particularly advantageous due to their immense double-layer charge capacity. For instance, one study reached charge-injection capacities up to 1.6 mC through vertical alignment of several nanotube electrodes.[21] Carbon nanotubes also allow surface customization that may improve biocompatibility, as mitigating the foreign body response is a critical aspect of an intraneural implant, and will be further discussed below.

Intraneural Implants

An intraneural implant is inserted directly into or adjacent to the axons of the nerve. Because of its location, intraneural implants offer selectivity of unique fiber populations within the same nerve, enabling improved specificity in motor or sensory nerve activation. Due to proximity to the neural elements, intraneural implants also require lower current thresholds when compared to other electrode types (e.g., cuff electrodes).[22] Precise placement and reduced current thresholds result in a lower risk of

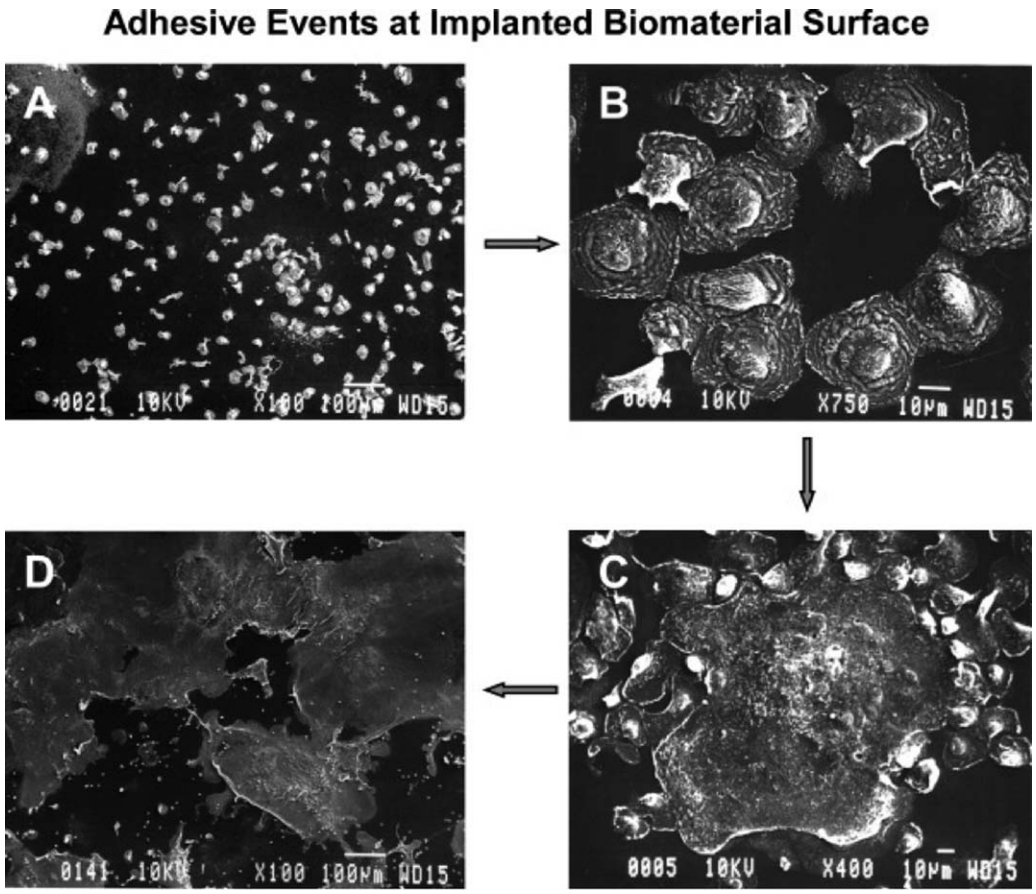

Fig. 2. Scanning electron microscopy images depicting foreign-body giant cell development on a Elasthane 80A Polyurethane surface in subcutaneous cage implants in rats. Blood-borne monocytes (A) become biomaterial-adherent macrophages within 3 days (B), then macrophages fuse at 7 days (C), and then become foreign body giant cells after 14 days (D).[18]

inadvertent stimulation of surrounding nerves. In contrast, cuff electrodes circumferentially wrap around a nerve, offering limited selectivity and possible scar tissue formation. However, the invasiveness of intraneural implants increases the risk of neural injury.[23] Intraneural implants include standard linear microarrays, the longitudinal intrafascicular electrode, the transverse intrafascicular multichannel electrode, and micro-electrode arrays (MEA).[24] Tissue response to these implants is varied and will be further explored here.

Passive tissue response

Neural tissue response to a penetrating electrode can be either passive (generated due to electrode presence), or active (response derived from stimulus current). The passive response refers to the cellular reaction to surgical trauma, electrode presence, as well as the electrode chemical and material properties. Cellular changes resemble those of any foreign body tissue response: the early development of granulation tissue followed by late scar formation mediated by macrophages and foreign body giant cells as an end-stage inflammatory and wound healing response.[17,18]

In addition to tissue reaction to the electrode, the implanted electrode itself can potentially damage the tissue due to shearing forces of the implanted electrode within a peripheral nerve residing in mobile soft tissue. One study examining the median nerve trunk in humans demonstrated substantial longitudinal displacement of the trunk during upper limb movement, resulting to potential nerve entrapment.[25] This normal movement of the nerve with an implanted electrode array has the potential to cause shear damage to the nerve. Although shear-damage is of considerable concern in chronic electrode implantations, it has not been well-investigated to date. Of note, implantation of a penetrating electrode array into the easily-accessible and immobile vertical (mastoid) segment of the facial nerve would result in minimal neural damage due to shearing forces.

Active tissue response

The active tissue response is the result of electrical stimulation from the implant and is generated by implant-induced electrochemical gradients and resulting changes in physiological function. Two electrode material characteristics directly correlate to the degree of active tissue response: *charge-per-phase* and *charge density.* The extent of neuronal activation (i.e., the number and distribution of activated fibers) by the implant is determined by its charge-per-phase, or the intensity of charge injected with each pulse. The charge density, or charge over area of nerve-electrode contact, is based on the type

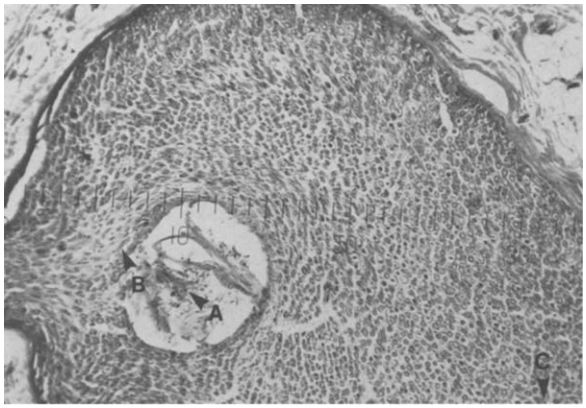

Fig. 3. Formation of bulbous fibrous connective tissue in the peroneal nerve of a cat which had a non-stimulating intraneural electrode implanted for 48 months. This is a cross-section between the entry and exit sites of the electrode. Fibrous tissue is seen by the electrode (A), and some demyelination is seen directly around the electrode (B). Luxol fast blue-hematxylin, 96X.[29]

and rate of electrochemical gradients formed at the nerve-electrode interface. The degree to which these characteristics ultimately influence neural tissue is highly variable, and is dependent on the particular neural substrate and stimulation parameters.[26] Activity-dependent changes in neuronal excitability and neuronal damage can occur following non-physiologic patterns of activation.[27]

Chronic immunological and functional changes

In the peripheral nervous system (PNS), chronic implantation of microelectrodes leads to a macrophage-mediated foreign body immune response. This response similarly alters cellular morphology, genetic transcription and cell function. To characterize the active response in peripheral nerves, Lefurge and associates chronically implanted intrafascicular platinum-iridium recording electrodes coated with polytetrafluoroethylene, or Teflon, within the radial nerves of six cats over six months.[28] Despite implant biocompatibility, adverse active responses were observed, including axonal caliber reduction, demyelination, mild foreign body response, and increased endoneural connective tissue.

Nevertheless, other studies reported few, if any, functional deficits as a result of the tissue response. Bowman et al. implanted intraneural nylon-coated stainless steel electrodes into the posterior tibial nerves of 18 rabbits for nine weeks to characterize the tissue response.[29] One experimental group had an electrode inserted and immediately removed in one leg, while the other leg retained the electrode. The other experimental group had chronically-implanted electrodes in both legs, but only one implant actively delivered stimulation. No significant changes in nerve conduction velocities were observed in either the stimulated or non-stimulated nerves at the time of implantation or nine weeks post-implantation, although minor motor current threshold increases were observed 10 days post-implantation. Additionally, nerves showed little or no demyelination or denervation. Notably, 40% of the nerves showed bulbous connective tissue formation at the array entry and exit sites with minor corresponding demyelination (Fig. 3). These results were reproduced in cats, in which the posterior tibial and peroneal nerve of each leg was implanted over a four-year period. There were minimal current threshold changes during implantation, minimal muscle fiber changes, and negligible demyelination around the electrode.

Levels of short and long-term neuronal excitability, determined by stimulation thresholds, are critical in establishing implant safety and efficacy. Changes in thresholds post-implantation have been studied in short-term (weeks to months) and long-term (years) experiments (Table 1).[30–32] Short-term threshold changes were found to be abrupt, reversible threshold increases that return to baseline within weeks;[30] Pfingst and colleagues observed this phenomenon in nonhuman primates.[31] In a later study, Pfingst et al. characterized two types of long-term changes following chronic cochlear implantation in nonhuman primates.[32] In their studies, threshold changes either 1) increased slowly over weeks to months prior to stabilizing, or 2) showed more significant threshold increases rapidly (days or weeks). However, this latter type of change showed remarkable threshold stability both before and after the abrupt increase, suggesting at least two different mechanisms for threshold changes post-implantation.

Epineural and Perineural Implants

Electrodes can also deliver current to other nerve components, including the epineurium and perineurium. Unlike intraneural implants, epineural and perineural implants interface with connective tissue surrounding the nerve instead of directly penetrating the fascicles. Epineural electrodes can be microsutured to the outer nerve sheath (epineurium), while perineural implants are attached to the inner neural sheath (perineurium). Even though the microsuturing of epineural implants may shear the nerve due to excessive tension, the impact to the nerve trunk is typically minimized by atraumatic and minimally invasive surgical techniques.[33]

Design and engineering

One example of an epineural electrode is the flat interface nerve electrodes (FINE), which flattens and reshapes the nerve, increasing electrode contact surface area. Tyler et al. implanted Teflon-coated platinum FINE electrodes into rat sciatic nerves and found that electrode-induced alterations in nerve structure, including decreases in axonal density, myelin thinning, and axon clustering, did not lead to any functional alterations.[34]

Implants may also have a slot-design, such as book electrode interfaces, which consist of silicone blocks with slots containing platinum electrodes. These have been used in the dorsal sacral roots of the human spinal cord to rehabilitate bladder function. The Resume system from Medtronic is an example of an epidural spinal cord implant that has been shown to effectively treat neuropathic pain in 116 patients, with over 40% of patients

TABLE 1.
Change in nerve stimulation thresholds over time. Threshold changes remain relatively stable as far out as 12 months after implantation.

	Change in Threshold (compared to baseline) in MicroA			
Months Post-Implant	Intraneural Wire Microelectrode (Rabbit)[94]	Intraneural Coiled Microelectrode (Cat)[44]	Intraneural Coiled Wire Electrodes (Rabbit)[29]	Utah Slanted Electrode Array (Cat)[95]
0	0	0	0	+25
1	+50	−300	−80	+65
2	+90	−280	−100	+79
3	+120	−300	−100	+74
4	+110	−300	−120	+80
5	+150	−300	−120	+75
6	+140	−300		
7		−300		
8		−300		
9		−300		
10		−300		
11		−300		
12		−300		

experiencing symptomatic improvement.[35] Epidural implants within the CNS are analogous to epineural implants in the PNS, as the dura mater surrounding the spinal cord and nerve roots within the spinal column invaginates the nerve as it exits the CNS to become epineurium.[36]

Epineural implants can also be helicoidal, consisting of flexible, platinum ribbons that circumscribe the nerve to minimize mechanical trauma. While such helical structures minimize selectivity, they are clinically used for gross hypoglossal nerve stimulation in treating obstructive sleep apnea, and vagal nerve stimulation in treating epilepsy and depression.[37–39] Another example is the BioControl CardioFit system,[40] which is an investigational device aimed at the treatment of congestive heart failure. It consists of a dual-cathode circumneural multi-polar stimulation lead and a sensor lead (Fig. 4). Agnew et al.[26] implanted helical electrodes in the cat peroneal nerve to observe the passive tissue response and identify stimulation parameters that induce permanent damage. Three weeks post-implantation, epineurium thickening due to implant presence was identified, as well as permanent damage following continuous stimulation for 8–16 hours above 50 Hz. Twenty hertz stimulation over the same duration, however, resulted in a return of neuronal excitability to baseline within one week of stimulation cessation.

Fig. 4. Image of the CardioFit system, an investigational device aimed at the treatment of congestive heart failure. It consists of a dual-cathode circumneural multi-polar stimulation lead and a sensor lead. The sensor lead is placed in the hearts right ventricle and the stimulation lead wraps around the vagus nerve. The system sends electrical pulses from the stimulator to the vagus nerve, and detects changes in heart activity to modulate the stimulation (Courtesy of BioControl Medical, Yehud, Israel).[40]

Tissue response and histological changes

Chronic implantation of perineural and epineural electrodes results in reactive responses in local tissue. Microscopically, considerable histological changes of both nerve and musculature have been shown, with a fibrous tissue layer typically seen in the electrode tract following implant removal. In a study of neural changes following epineural, nonpenetrating spiral platinum-silicone cuff electrode implantation in the sciatic nerve of seven cats,[41] normal histology proximal and distal to the cuff electrode was observed, with the most significant changes noted on the leads interfacing with the nerve trunk. Five cats exhibited histological changes, including a reduction in myelinated axon density, endoneural fibrosis, and perineural thickening (Fig. 5). In another study, implanted epineural electrodes composed of Teflon-coated stainless steel stimulated the lower extremities of five sheep for eight hours per day for 26 weeks.[42] The stimulated muscles exhibited physiological and histological changes, transition towards aerobic metabolism, and contained more type I fibers (type II remained unchanged) compared to contralateral control muscles, documenting the change in muscular physiology and composition resulting from epineural stimulation.

Girsch and colleagues assessed the impact of non-stimulating chronic epineural electrode implantation[43] to

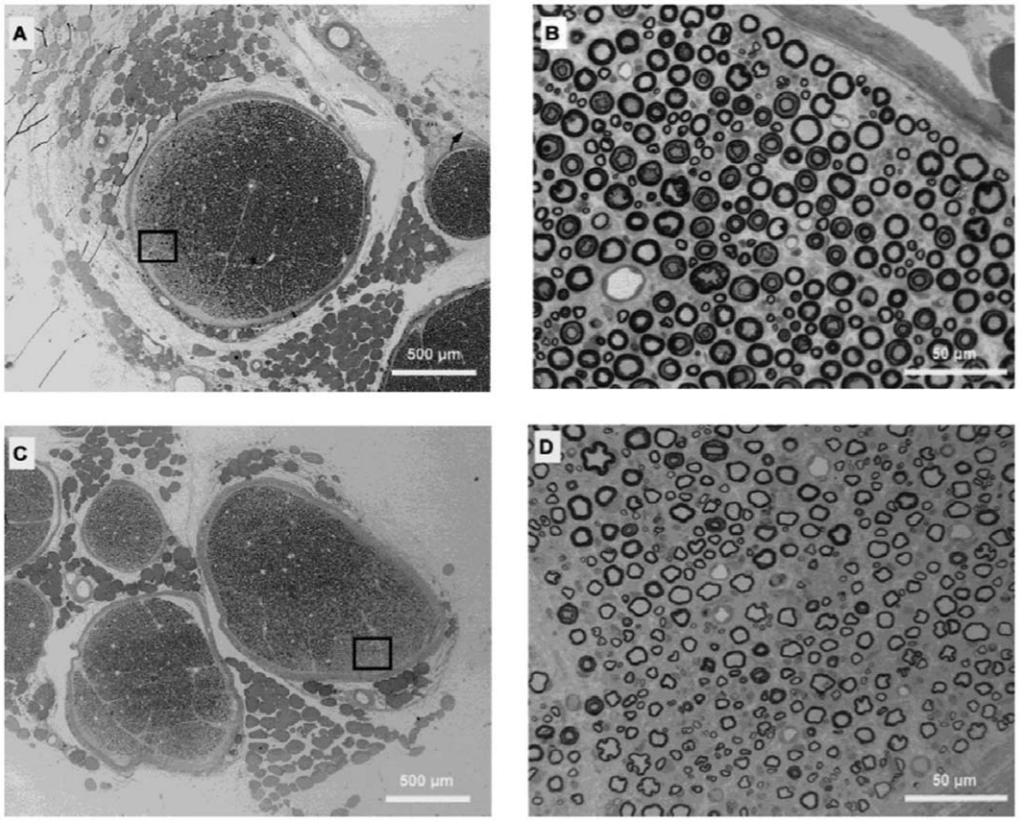

Fig. 5. (A) Microscopic image of feline sciatic nerve 1cm distal to the spiral nerve cuff electrode, containing 12 electrode contacts, following implantations of duration between 28 to 34 weeks. (B) High power view of (A) showing thickening of the perineurium, increased subperineurial connective tissue, edema, fewer and thinner axons, and Schwann cell proliferation. (C) Sciatic nerve at level of the cuff electrode, showing two of the three abnormal fascicles with these morphological changes. (D) High power view of (C) showing thin myelination of axons and increased endoneurial connective tissue.[41]

determine whether peripheral nerve damage was caused by electrical stimulation or electrode presence alone. In 36 rats with stainless steel-lead epineural electrodes unilaterally implanted in the sciatic nerve, the presence of reactive damage was evaluated at different time points in three groups. The first group received the implant for 10 days (Group A), the second group for three weeks (Group B), and the third group for three months (Group C). None of the implants emitted electrical stimulation. In Group A, 75% of the rats had histological evidence of lesions, which included signs of degeneration (e.g., myelin fragmentation, connective tissue increase, nerve fiber density reduction) or regeneration (e.g., small fibers and thin myelin). In Group B, 72% had lesions, while Group C had lesions in only 41% of nerves. This reduction in rate over time was likely due to nerve regeneration. Nevertheless, these results illustrate that even without electrical stimulation, peripheral nerve fibers can undergo histological damage due to reactive processes from the physical presence of the electrode alone.

Functional changes in epineural electrodes

Unlike intraneural implants, the link between physiological and functional motor changes in the context of chronic epineural and perineural electrode stimulation has not been well-characterized. Koller et al. attempted to identify motor deficits in seven rats by chronically stimulating their sciatic nerves for one year using ring-shaped, stainless steel epineural electrodes.[44] Only one rat required a higher stimulation current to elicit lower limb movement, and none of the rats exhibited motor deficits. Similarly, Grill et al. did not report any significant functional changes in the seven cats they examined following chronic sciatic nerve implant stimulation.[41]

Intranuclear Implants

Auditory brainstem implants (ABIs). Intranuclear electrodes directly stimulate neuronal cell bodies in the CNS and have been successfully used to rehabilitate hearing in patients with specific causes of profound hearing loss. While the CI has produced remarkable audiologic results in both pediatric and adult populations,[45] many patients, particularly those with genetic or anatomic abnormalities, such as neurofibromatosis type 2 (NF2), lack a viable auditory nerve for rehabilitative cochlear implantation. NF2 patients routinely develop bilateral vestibular schwannomas (VS) that routinely

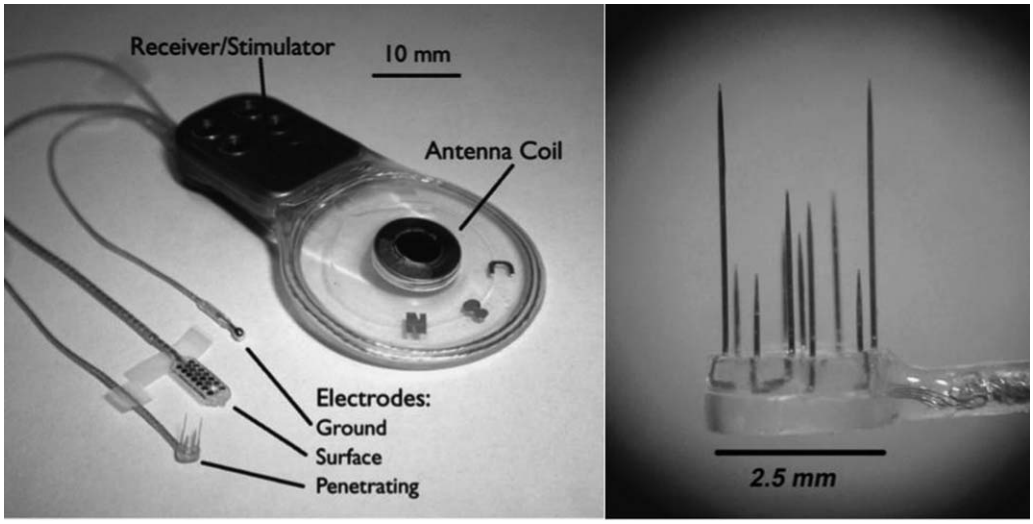

Fig. 6. Penetrating auditory brainstem implant (PABI) design showing penetrating and surface electrode arrays (left) and a microscope image of the penetrating array (right).[47]

lead to hearing loss secondary to VS growth or surgical removal.

To address hearing loss in this population, auditory brain stem implants (ABIs) were developed, and to date[45] over 1,000 patients worldwide have received ABIs, which stimulate second-order auditory neurons in the cochlear nucleus. However, improvement in hearing performance has been underwhelming when compared to that of CIs.[45] Additionally, ABIs bear a flat, non-penetrating electrode array that rests on the surface of the cochlear nucleus, and as such, threshold current levels are relatively high, access to the tonotopic organization of the auditory pathway is limited, and post-operative speech recognition has been shown to be comparatively poor.

To address these shortcomings, Otto et al. conducted a prospective study of a novel penetrating auditory brainstem implant (PABI) in NF2 patients (Fig. 6). The PABI employs eight or 10 penetrating activated iridium microelectrodes in conjunction with 10 or 12 surface electrodes.[46,47] In 10 NF2 patients implanted with PABI, threshold excitation levels were decreased, while range of pitch detection increased. However, a significant improvement in speech recognition was not accomplished. Notably, ABI has recently been found to enable substantial speech perception in non-VS patients, suggesting the aforementioned lack of speech improvement may be a consequence of damage to the cochlear nucleus by VS removal or by the tumor itself.[47]

Auditory midbrain implants (AMIs). To address the poor audiologic outcomes of ABIs in NF2 patients, Lim and associates introduced the auditory midbrain implant (AMI), a linear penetrating array with 20 platinum-ring electrodes that stimulates the inferior colliculus (IC).[48,49] The IC represents the convergence of all ascending auditory projections at the midbrain, and maintains tonotopic organization for frequency-specific stimulation.[48] Nevertheless, in both human trials and guinea pig models, they were unable to achieve favorable audiometric outcomes.[48,49] Of note, activating regions medial and ventral to the IC was found to cause spontaneous pain, temperature, and pressure sensation throughout the body.[48]

Deep brain stimulation. The deep brain stimulator (DBS) is a highly-effective type of intranuclear array implant system used in the treatment of neurodegenerative disorders. It functions by providing chronic stimulation to the nuclei within the basal ganglia. This topic, however, is outside the scope of this review.

Mitigating the foreign body response. The electrode surface composition can contribute to the degree of macrophage activation and foreign body response to chronic implants, and biomolecules such as anti-inflammatory cytokines, cytokine-inhibitors, or immunomodulatory proteins, can be incorporated onto electrode surfaces to diminish the immune response. For instance, CD200, a ubiquitous endogenous immunomodulatory protein, can be immobilized on the electrode surface to inhibit the macrophage-mediated foreign body response.[50] Other coatings that decrease the inflammatory response include a variety of inert compounds, including Teflon, which has been shown to reduce the immune response to wire electrode implants in rat[51] and monkey cortex.[52] More recently, Rousche et al. and Kim et al. reported promising results in vitro and in vivo with a tri-layer coating composed of polyimide, gold, and polyimide.[53]

Coatings that release anti-inflammatory drugs appear to be the most effective at reducing the neuroimmune response following electrode placement. Zhong et al. found that nitrocellulose-based coatings that steadily release dexamethasone attenuated immune reactivity and local neuronal loss following silicon electrode implantation in rat cortex.[54]

Current Trends in Cranial and Peripheral Nerve Stimulation

Recent advances in cranial and peripheral nerve stimulation have led to the development of a variety of new

TABLE 2.
Description of cranial nerve (e.g., cochlear, hypoglossal, trigeminal, recurrent laryngeal, vagal) and peripheral nerve devices with their functional, electrophysiologic, and histologic effects.

Cranial Nerve Devices											
Experimental Model				Electrode Characteristics					Results		
Citation	Model	Nerve Interfaced	Implant Length	Electrode Category	Insulator Material	Conductor Material	Electrode Coating	Shape	Functional Outcomes	Electrophysiological Outcomes	Histomorphological Outcomes
Strollo et al. 2014, 2015 Woodson et al. 2014, 2015 Soose et al. 2016[96–100]	Clinical (Obstructive sleep apnea)	Hypoglossal nerve	12-36 Months	Epineural	Silicon	Platinum	N/A	Cuff	1) ↑ median AHI (29.3 respiratory events/ hour to 6.2-9.7) and ODI score (25.4 respiratory events/ hour to 4.8-8.6). 2) ↑ subjective sleep quality (FOSQ/ESS tests).	No nerve alterations.	No nerve/muscle alterations. Some infection noted.
Schoenen et al. 2013 Riederer et al. 2015 Magis et al. 2016[12,101,102]	Clinical (episodic migraine)	Trigeminal and ophthalmic nerves (suborbital stimulation)	3 months	Trans-cutaneous	Cefaly® external transcutaneous supraorbital nerve stimulation device (eTNS)				1) 50% pain reduction was higher in experimental vs. control group. 2) 69 migraine patients had ↓ in total headache days but not in perceived severity. 3) 4.3% of patients reported minor side effects/discomfort while using device.	Possible blockage of ascending impulse of pain pathways.	1) 3 month treatment with eTNS ↑ metabolic activity in orbitofrontal/rostral anterior cingulate cortices of migraine patients. 2) ↑ fronto-temporo metabolism aids migraine reduction 3) Some allergic reactions to gel used to place the elec-trode-pad.
Middlebrooks et al. 2007, 2010[13,14]	Animal (cat)	Cochlear nerve	N/A	Intraneural	N/A	Platinum–iridium	N/A	8 channel banded penetrating array	1) Significant phase locking at higher limiting pulse rates compared to cochlear implants in the central nucleus of inferior colliculus. 2) Compared to classical cochlear implants, ↓ interference between electrodes stimulated simultaneously.	1) ↑ percentage of neurons at lower characteristic frequencies are selectively activated. 2) Neurons with ↓ limiting pulse rates have ↑ characteristic frequencies (CFs).	1) ↓ CFs, short latencies, and high-fidelity transmission of periodic stimula-tion can characterize high-temporal-acuity brainstem pathways. 2) ↑ temporal acuity in humans, and ↑ in speech perception/ pitch.
Michelson et al. 1971[30]	Clinical (dead ear and tinnitus)	Cochlear Implant	N/A	Intraneural	N/A	Steel	N/A	Needle	Tinnitus temporarily halted in 2/13 patients; 7/13 patients gained momentary hearing.	1) Short-term neuronal changes were abrupt and reversible thresh-old increases that return to baseline. 2) Low frequency stimuli ↑ tinnitus pitch.	N/A
Pfingst et al. 1979, 1990[31,32]	Animal (nonhuman primates)	Cochlear Implant	1-8 months	Intraneural	Silicone-rubber	Platinum-iridium	N/A	Multichannel scalar electrode	N/A	Threshold changes either 1) ↑ slowly over weeks to months prior to stabilizing, or 2) showed more significant ↑ rapidly (days or weeks).	N/A

TABLE 2.
(*Continued*)

Cranial Nerve Devices											
Experimental Model				Electrode Characteristics					Results		
Citation	Model	Nerve Interfaced	Implant Length	Electrode Category	Insulator Material	Conductor Material	Electrode Coating	Shape	Functional Outcomes	Electrophysiological Outcomes	Histomorphological Outcomes
Penry et al. 1990 [38]	Clinical (epilepsy)	Vagus nerve	12 months	Epineural	Silicone	Platinum	N/A	Helicoidal	Complete control of epileptic seizures in 2 of 4 patients (both complex and simple partial seizures), 40% decrease in frequency of attacks in another, and no change in the last.	Modulation of EEG frequencies during sleep and blockage of sleep spindle.	1) Severe vagus nerve edema and partial paralysis of vocal cords in one patient 2) Muscle spasms
Anholt et al. 2011 [40]	Animal (pig)	Vagus nerve (right cervical)	6 months	Epineural	Liquid silicone resin	Platinum–iridium	Liquid silicone resin	5 channel cuff	8/9 pigs showed 60% ↓ in A-fiber compound action potentials.	1) Unidirectional ↓ of A-fiber compound action potentials 2) B-fiber max excitation.	N/A
Peripheral Nerve Devices											
Holzer et al. 2008 [6]	Clinical (Bowel control)	Sacral nerve	1-12 Months	Epineural	Polyurethane	Platinum-iridium	Polyurethane adhesive	Cylindrical	1) ↑ median Wexner constipation score (from 23 to 8-11). 2) ↑ in bowel movements for slow transient cases.	1) Spontaneous perianal/perirectal region activity. 2) Afferent signals transmitted to spinal cord/Onuf's nucleus in spinal S2 region.	N/A
Lefurge et al. 1991 [28]	Animal (cat)	Radial nerve	6 months	Intraneural	Teflon	Platinum-iridium	Polytetrafluoroethylene	Intrafasicular sheet	1) 6/8 implanted electrodes remained functional, others had broken leads. 2) ↑ in impedance after the first month which stabilized afterward. 3) ↑ signal to noise ratio after 4 months.	Electrical properties of connective tissue around the electrode may be affecting signal to noise ratios.	Axonal caliber reduction, demyelination, mild foreign body response, and increased endoneural connective tissue.
Bowman et al. 1985 [29]	Animal (rabbit)	Posterior tibial nerves	9 weeks	Intraneural	None (deinsulated wire)	Stainless steel	Nylon	Coiled wire	1) No loss of plantar flexion function or change in favorability. 2) Despite wire passing over active joint, no wires were broken or electrodes pulled out.	1) No nerve conduction velocity changes. 2) Minor ↑ in motor current threshold 10 days post-implantation.	1) Little/no demyelination or denervation. 2) 40% of nerves had bulbous connective tissue formation at array entry/exit sites with minor demyelination.
Bowman et al. 1985 [29]	Animal (cats)	Posterior tibial and peroneal nerve	4 years	Intraneural	None (deinsulated wire)	Stainless steel	Nylon	Coiled wire	No observable extraneural scar anywhere along the wire in 1 cat.	Minimal current threshold changes.	1) Minimal muscle fiber changes. 2) Negligible peri-electrode demyelination. 3) No bulbous enlargement, unlike rabbit study.

TABLE 2.
(*Continued*)

Cranial Nerve Devices											
	Experimental Model			Electrode Characteristics					Results		
Citation	Model	Nerve Interfaced	Implant Length	Electrode Category	Insulator Material	Conductor Material	Electrode Coating	Shape	Functional Outcomes	Electrophysiological Outcomes	Histomorphological Outcomes
Tyler et al. 2003 [34]	Animal (rat)	Sciatic nerves	28 days	Epineural	None (no stimulation in this study)	None	None	FINE	Small forces externally applied to nerve can reshape and chronically disfigure the nerve without altering its function and electrophysiology	No implants emitted electrical stimulation, however neuropraxia with high clamp strength FINE electrode was observed, and normalized after 14 days.	1) All clamp strength FINE electrodes reshape fascicles and nerve diameter. 2) Small ↓ in axon density but no evidence of demyelination with moderate strength FINE electrode. 3) No change in blood-nerve barrier, or physiological alterations with low strength FINE
Agnew et al., 1989 [26]	Animal (cat)	Peroneal nerve	3 weeks	Epineural	Silicone rubber elastomer	Platinum ribbon	N/A	Helicoidal	Prolonged stimulation of the nerve at high frequencies damages axons and myelin, while at low frequencies this is avoidable.	1) Damage following stimulation for 8-16 hours above 50 Hz. 2) Interrupted high frequency stimuli of 50 Hz caused less damage than continuous stimulus. 3) Twenty Hz stimulation returned neuronal excitability to baseline within one week of stimulation cessation.	1) Degeneration of axons due to collapsed myelin-to-myelin ovoid. 2) Partial/complete demyelination, macrophage activity, and fiber loss 3) After healing, epineurium thickened.
Grill et al. 2000 [41]	Animal (cat)	Sciatic nerve	28 - 32 weeks	Epineural	Silicone rubber	Platinumfoil	N/A	12 electrode spiral cuff	1) 4/7 cats destroyed the electrode. 2) One cat walked abnormally after the implant, but recovered after 2 days. 3) Spiral cuff electrodes can be implanted even if internal diameter is smaller than nerve.	N/A	1) Normal histology proximal and distal to cuff electrode. 2) Significant changes noted on leads interfacing with nerve trunk. 3) Axonal/perineural changes.
Bijak et al. 2001 [42]	Animal (sheep)	Sciatic nerve	26 weeks	Epineural	Teflon	Stainless steel	Silastic glue	Coiled wires	1) No change in isometric force generation observed. 2) Selective stimulation of muscle, but muscle recruitment dependent movement.	N/A	1) ↑ type I but ↓ type IIc fibers compared to contralateral control muscles. 2) Foreign body response.

TABLE 2.
(*Continued*)

Cranial Nerve Devices											
	Experimental Model			Electrode Characteristics					Results		
Citation	Model	Nerve Interfaced	Implant Length	Electrode Category	Insulator Material	Conductor Material	Electrode Coating	Shape	Functional Outcomes	Electrophysiological Outcomes	Histomorphological Outcomes
Girsch et al. 1991 [43]	Animal (rat)	Sciatic nerve	10 days, 3 weeks, and 3 months	Epineural	Silastic tube	Stainless steel	Silastic tube	Annular	1) 22/36 nerves showed altered morphology regardless of duration of implantation. 2) Nerves appeared damaged initially, but began regeneration as duration of implantation increased.	No implants emitted electrical stimulation.	1) At 10 days 75% had lesions (myelin fragmentation, connective tissue ↑, nerve fiber density ↓) or regeneration (small fibers and thin myelin). 2) At 3 weeks, 72% had lesions and small/degenerated myelin sheaths. 3) At 3 months, 41% of nerves were damaged or in advanced state of repair. 4) Some ↑ in connective tissue around electrode.
Koller et al. 1992 [44]	Animal (rat)	Sciatic nerve	1 year	Epineural	Silicone	Stainless steel	Dow Corning Silastic 602®	Annular	1) One rat required higher stimulation current to elicit lower limb movement. 2) None exhibited motor deficits.	N/A	1) No changes proximal to implant. 2) Thinned myelin observed at level of electrode. 3) 2 rats had ↑ endoneurial connective tissue and 3 showed alterations distal to electrode. 3) All alterations were in advanced stages of repair.

devices that directly interface and stimulate these nerves (Table 2). From treating pain[55] and neuropathy, to epilepsy, stroke,[56] heart failure,[57] and arthritis,[58] neuroprosthetics have the potential to modulate a host of pathologies. With respect to Otolaryngology-focused devices, vagal nerve stimulators, for example, were first employed to treat epilepsy,[59] but have evolved into a neurostimulation technique that is being applied to migraine headaches,[60] fibromyalgia,[61] Crohn's disease,[62] depression,[63] and anxiety disorders.[64,65] In contrast, trigeminal nerve stimulation has been traditionally applied to epilepsy[66] and psychiatric disorders,[67] while hypoglossal nerve stimulation has been used to treat obstructive sleep apnea,[68] with limited applicability to other pathologies. Cochlear nerve stimulation is an emerging field within Otolaryngology that has been demonstrated to provide frequency-dependent stimulation of cochlear nerve fiber subpopulations without significant long-term functional or morphological deficits in the cat model.[13,14] Newer preclinical neuroprosthetic devices such as intraneural facial and recurrent laryngeal nerve stimulators[69] to treat facial and vocal fold paralysis, respectively, as well as pteryopalatine fossa and trigeminal ganglion neurostimulators to treat cluster headaches and post-stroke pain are currently in the pipeline.[70,71]

Studies investigating the functional and histomorphological changes of long-term electrical stimulation of any of the cranial nerves have demonstrated the long-term safety, efficacy, and tolerability of these devices as long as electrical stimulation parameters are tightly controlled to inject the minimal current necessary to elicit the desired clinical effect.[72,73] Even 2029 hours of charge balanced biphasic current pulses to the cochlear nerve in cats did not adversely affect spiral ganglion cells or result in any significant difference compared to normal unstimulated cochlear nerves.[74]

Peripheral nerves are also current and future neuroprosthetic targets. Classically, peripheral nerves, such as the tibial and sacral nerves, have been directly stimulated to treat reflex sympathetic dystrophy,[75] urinary[76] and fecal[77] incontinence, and pain.[78] Recently, stimulation of the brachial[79] or lumbar[80] plexuses has been shown to restore tactile sensation, treat amputee[81] and back[82] pain, and neuropathies[83] throughout the body, with the only major drawbacks involving electrode migration or failure.[84,85]

Electrical stimulation in both the cranial and peripheral setting must account for device or battery failure, as well as program or pulse generator malfunction and migration. Biological consequences of improper device implantation or overstimulation include biofilm formation, subcutaneous hematomas, skin erosion, pain/numbness, foreign body reactions, paresthesias, and muscle cramps.[86,87] As previously discussed, a variety of electrode surface modifications have been developed for intracortical electrodes; however, since the majority of peripheral nerve neurostimulators are nonpenetrating cuff electrodes, the foreign body response is less of a concern. More attention has been dedicated to the electrical stimulation parameters of these neurostimulators since they are relatively biocompatible. Nonetheless, further modifications to electrode surfaces, such as cross-linking polyelectrolyte films,[88] neural stem cell-seeded electrodes, and fibrin hydrogel coatings, have been tested to varying degrees of efficacy in improving the stimulation, recording, and biocompatibility profiles of neurostimulators.[89]

Efforts to improve the biocompatibility of implantable electrodes are ongoing, and range from developing new electrode materials, substrates, and coatings that can enhance electrode longevity and functionality. Classically, implantable electrodes were composed of included tungsten, iridium oxide, tantalum oxide, grapheme, carbon nanotubes, polymers, and hydrogels, with substrates that include silicon, silicon oxide or nitride, silk, Teflon, polyimide, and silicone.[90] Commonly, platinum or platinum alloys (e.g., platinum-iridium) are used due to their biocompatibility, inertness, radiopacity, and mechanical properties that allows for fabrication of thin or complex shapes.[91] However, enhancing the biocompatibility of neuroprosthetic implants has led to several innovations that can enhance the longevity and functionality of implanted electrodes. As previously mentioned, surface coatings such as Teflon, CD200, or drug-eluting nitrocellulose based coatings can modulate the neuroinflammatory response in implanted electrodes.[50,51,54] Other coatings, including polymer coatings such as poly-3,4-ethylenedioxythiophene (PEDOT) doped with *para*-toluene sulfonate (pTS), have demonstrated superior signal-to-noise ratios and biostability compared to other doped conducting polymers or bare iridium electrodes. Furthermore, new electrodes, such as those made from liquid dispersions of graphene oxide or platinum-elastomer composites, are mechanically more pliable then crystalline silicon or noble metal electrodes, and have been shown to reduce glial scarring and eventual electrode loss of function.[92,93] These efforts are ongoing, and may yield significant improvements in the biostability and electrical properties of neuroprosthetics.

At present, the incorporation of intraneural electrode arrays into cranial and peripheral nerves is a promising approach that offers exquisite selectivity of neural fiber stimulation at the cost of increased invasiveness when compared to extraneural cuff electrodes. However, the long-term biocompatibility and immunomodulation of the nervous tissue response to the implanted foreign body must be considered when using this approach, and the application of existing or newly developed surface coatings will likely need to occur prior to the clinical implementation of intraneural electrodes in cranial and peripheral nerve simulation.

CONCLUSION

A variety of chronically implantable electrodes have been developed to treat disorders of the peripheral nervous system, to varying degrees of efficacy. Options for interfacing with neural tissue include intraneural, epineural, perineural, intranuclear, and cortical electrodes, all of which carry certain risks and benefits. Consideration of the histological and functional effects due to the foreign body response at the neural interface is critical to the development of novel bioelectric devices. The mitigation of the foreign body immune response, potential tissue damage, histological changes, and the further optimization of

functional nerve stimulation will facilitate the translation of these technologies to the clinic. In recent decades, efforts to prevent the adverse consequences of chronic electrode implantation and stimulation have yielded noteworthy improvements in the long-term efficacy of electrode implants. Such changes include modification of the electrode surface, modulation of stimulation frequency and duration, and the incorporation of an intermittent duty cycle. Although further exploration of the safety and efficacy of neural implants is warranted, advances in emerging technologies show promise in treating peripheral and cranial nerve pathologies.

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