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### Title

Interfacing with the nervous system: a review of current bioelectric technologies

### Permalink

<https://escholarship.org/uc/item/0d6392r8>

### Journal

Neurosurgical Review, 42(2)

### ISSN

0344-5607

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### Publication Date

2019-06-01

### DOI

10.1007/s10143-017-0920-2

Peer reviewed

# Interfacing with the nervous system: a review of current bioelectric technologies

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Received: 13 July 2017 / Revised: 15 September 2017 / Accepted: 9 October 2017  
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**Abstract** The aim of this study is to discuss the state of the art with regard to established or promising bioelectric therapies meant to alter or control neurologic function. We present recent reports on bioelectric technologies that interface with the nervous system at three potential sites—(1) the end organ, (2) the peripheral nervous system, and (3) the central nervous system—while exploring practical and clinical considerations. A literature search was executed on PubMed, IEEE, and Web of Science databases. A review of the current literature was conducted to examine functional and histomorphological effects of neuroprosthetic interfaces with a focus on end-organ, peripheral, and central nervous system interfaces. Innovations in bioelectric technologies are providing increasing selectivity in stimulating distinct nerve fiber populations in order to activate discrete muscles. Significant advances in electrode array design focus on increasing selectivity, stability, and functionality of implantable neuroprosthetics. The application of neuroprosthetics to paretic nerves or even directly stimulating or recording from the central nervous system holds great potential in advancing the field of nerve and tissue bioelectric engineering and contributing to clinical care. Although current

physiotherapeutic and surgical treatments seek to restore function, structure, or comfort, they bear significant limitations in enabling cosmetic or functional recovery. Instead, the introduction of bioelectric technology may play a role in the restoration of function in patients with neurologic deficits.

**Keywords** Neural electrode · Neuroprosthetic · Nerve implant · Prosthetics · Nerve palsy · Bioelectric interface

## Introduction

The application of bioelectric stimulation to the nervous system has proven to be an effective option for restoring or augmenting some degree of function in patients with neurologic dysfunction [98]. In particular, functional stimulation of paretic nerves is a clinically vital and promising area of research that warrants significant investigation. At present, a variety of implantable nerve stimulators have been clinically employed and demonstrated to be efficacious in alleviating numerous pathologies. Several implantable devices are already in routine use, including hypoglossal nerve stimulation in patients with severe obstructive sleep apnea [76, 137]; chronic spinal cord stimulation in patients with severe neuropathic pain [153, 160]; direct electrical stimulation of peripheral nerves in patients with bladder, bowel, and sexual dysfunction [30, 40]; and even transcutaneous stimulation of the trigeminal nerve in migraine patients [35, 36, 75, 107, 125, 136, 142]. Deep brain stimulation (DBS) is arguably the most successful example of a bioelectric technology that has transitioned into the clinical realm to treat a variety of neurological disorders with an incredible degree of efficacy [59, 108]. DBS and other neuroprosthetic

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technologies represent only one example of the rapidly developing field of bioelectronic medicine, which broadly seeks to diagnose and treat disease by integrating the fields of neuroscience, bioengineering, and computer science with medicine [102]. Bioelectronic medicine, as a field, developed from work on modulation of neural networks to treat pathologies (e.g., vagus nerve stimulation has been used to successfully activate the inflammatory reflex and improve rheumatoid arthritis symptoms) [62]. Other examples of bioelectronic medicine include implantation of electrodes on the cortex itself to decode neural signals and drive movement of prosthetic limbs [16, 17].

This manuscript reviews the state of the art with regard to established or promising bioelectric therapies meant to alter or control neurologic function. First, we address the three potential sites for bioelectric technologies to interface with the nervous system—both peripheral and central—while exploring practical and clinical considerations. The three sites include, from distal to proximal, (1) the end organ, (2) the peripheral nervous system, and (3) the central nervous system. At each of these sites, electrodes can either record activity, deliver electrical current, or both, allowing for a broad degree of modulation of physiological activity to ideally mitigate dysfunction from a variety of pathological processes. We also discuss the emerging technologies that have potential in advancing the field of nerve and tissue bioelectric engineering to address a variety of clinical conditions. Lastly, we discuss the legal, engineering, and biological hurdles limiting the translation of bioelectric technologies to the clinical realm.

## Materials and methods

A systematic search was executed on PubMed, IEEE, and Web of Science databases from database creation to August 2017. PubMed, Ovid, and Cochrane databases were queried using the following keywords: (“bioelectric” or “stimulation” or “technologies” or “electrode” or “recording” or “neuroprosthetic” or “implant” or “interface”) and (“paresis” or “paralysis” or “neural” or “muscle” or “end organ” or “peripheral” or “nervous” or “system” or “central” or “brain” or “computer interface” or “nerve”). References of each manuscript were checked for additional manuscripts that were of potential relevance to our review. Three investigators independently screened each article according to title and abstract and included any article relating to the application of bioelectric technologies or neuroprosthetics in the peripheral or central nervous system. The full text of each selected article was obtained and analyzed. Because no patient information or animals were involved, Institutional Review Board approval and Institutional Animal Care and Use Committee approval were not required.

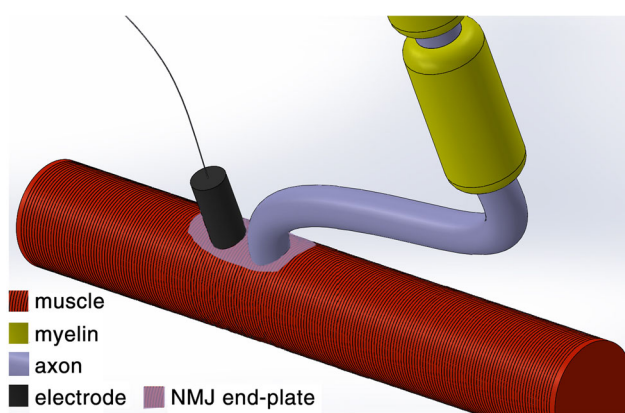
## Results and discussion

### Interfacing with the end organ

End-organ stimulation has gained recent prominence within the field of bioelectric technology and aims to stimulate or augment organ function (e.g., muscles, visceral organs) through electrodes implanted in the organ itself. The end organ can be a receptor organ that subsequently stimulates afferent nerve fibers (e.g., cochlea of the auditory system) or an effector organ (e.g., muscle). In both cases, an electrode can be placed either directly on the end organ or placed on the nerve associated with that organ (Fig. 1). In this section, the former approach will be discussed, while the latter approach will be explored in the section on peripheral nervous system stimulation. One benefit of interfacing with the end organ is that recorded signals are up to 100 times greater when compared to signals from peripheral nerve axons, facilitating signal input acquisition [63]. Further, the end organ is often better able to structurally interface with the mechanical composition of an electrode when compared to soft and delicate neural tissue [63] and oftentimes is more readily accessible than the associated nerve.

#### Muscle stimulation

Electrical stimulation of end organs, such as muscles, can be non-invasive, as in the case of transcutaneous electrical stimulation, or invasive, as in the case of implanted electrodes. For example, McDonnall et al. used transcutaneous electrodes to activate the *orbicularis oculi* muscle and restore blink function in patients with facial paralysis, while simultaneously minimizing painful sensations associated with the stimulation



**Fig. 1** A cartoon example of end-organ stimulation within the endplate, exaggerated in size, of a neuromuscular junction (NMJ) is shown. Here, the electrode is not in direct contact with the axonal nerve ending, which is depolarized through current spread. Muscle-electrode interfaces have proven more effective with sensory signal clarity due to an increased biocompatibility of the hard metal electrode and the tough mesodermal tissue [63]

[81]. Similarly, others have implemented transcutaneous muscle stimulation to treat post-surgical pain [24], disuse atrophy [44], as well as chronic back pain [57]. However, transcutaneous muscle stimulation to manage pain has yielded conflicting results, and the efficacy of this approach remains uncertain [34, 112].

For decades, implantable cardiac pacemakers and defibrillators have been in widespread clinical use and have proven efficacious in the long-term treatment of many cardiac disorders [1, 50, 71]. Recently, this technology has been adapted by Mueller et al. to serve as a laryngeal pacemaker system implanted directly into laryngeal muscles in patients with bilateral vocal fold paralysis to improve breathing and swallowing, without compromising vocalization [94]. In a rodent model, electrodes implanted within the gastrocnemius muscle reduced muscle atrophy without affecting motor reinnervation following tibial nerve transection and repair [159]. Electrodes inserted within muscles may also be able to record movements associated with limb tremors and stimulate the muscles to mitigate the tremors. End-organ stimulation of effector organs offers tremendous potential, but many of the advancements in the field are still within the realm of clinical research and are not yet routinely used in clinical practice. In contrast, end-organ bioelectric interfaces of receptor organs are already in routine clinical use, particularly within the auditory system. With the advent of miniature pacemakers, such as Medtronic's® leadless intracardiac transcatheter pacing system [119] or Nan et al.'s wirelessly chargeable ferromagnetic-piezoelectric antenna [96], we foresee increased versatility and wider application of such technologies in the near future.

#### *Cochlear, retinal, and vestibular implants*

In recent decades, electrodes implanted directly in the cochlea have restored hearing in patients with substantial sensorineural hearing loss, which is typically the result of irreversible damage to the cochlear sensory epithelium and auditory nerve. Cochlear implants (CIs) consist of a multi-channel electrode array that is surgically inserted deep into the scala tympani within the cochlea and connected to a receiver stimulator implanted beneath post-auricular soft tissue (Fig. 2). Electric current is delivered from select platinum electrode contacts to the spiral ganglion neurons within Rosenthal's canal, depolarizing these cells and generating a neural signal at the desired frequency to be propagated along the auditory pathway to the auditory cortex [109]. Approximately a half million deaf or hard-of-hearing children and adults have undergone cochlear implantation worldwide, leading to incredible personal, financial, and societal benefits [26, 56, 82, 139].

Retinal implants have also made their way into the clinical realm, with three retinal implant approaches in clinical trials: epiretinal, subretinal, and suprachoroidal implants, all of which relay visual input to the retina to stimulate surviving

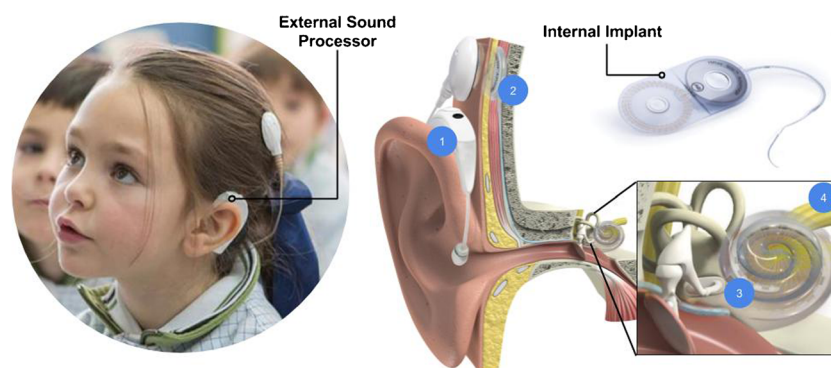
retinal neurons [99, 146]. Retinal implants are meant to treat degenerative disorders such as retinitis pigmentosa and age-related macular degeneration, which destroy photoreceptors in the retina. Although the functional restoration of vision is limited in resolution, these implants currently allow patients to perceive light and provide some degree of object recognition. However, further refinements and innovations will likely enhance the functional utility of retinal implants [23].

Bilateral vestibulopathy, or Dandy's syndrome, is a debilitating condition characterized by oscillopsia and unsteadiness during locomotion. Unsteadiness, due to a deficient vestibulo-spinal reflex, and oscillopsia, caused by bilaterally impaired vestibulo-ocular reflexes (VORs), both lead to severe impairment of postural control and image stabilization during head and body movement [60]. In recent years, cochlear implants have been modified to be used as vestibular prosthetics to restore inner ear balance and function in animal models [33, 83, 124]. Many of these experimental devices utilize inertial sensors to detect accelerations of the head, data from which is then used to provide specific electrical signals and patterns to the vestibular system in a compensatory manner.

Pelizzone et al. have recently translated this work to human trials in an effort to restore the VOR [106]. Using a modified cochlear implant with a standard intracochlear array and three additional electrode arrays, each of which to be implanted within the ampullae of the three semicircular canals (lateral, superior, and posterior), the authors electrically stimulated the vestibular end organs based on acceleration forces of the head detected by a gyroscope within the device. Electrical stimulation with the prosthesis, at 1 Hz, provided a significant VOR gain in three implanted patients with vestibular damage, reaching up to 98% of the average VOR gain in healthy patients. A similar clinical study is underway at Johns Hopkins University [19].

#### **Interfacing with the peripheral nervous system**

Both transcutaneous and invasive electrical interfaces with peripheral nerves have been implemented into routine clinical practice. From percutaneous cranial nerve stimulation to treat chronic [35, 36, 75, 136, 142] and episodic [107, 125] migraines and neuralgia, to epidural placement of leads in the dorsal root ganglion (DRG) for treatment of neuropathic pain [68], and to direct sacral anterior root stimulation to enhance bowel function post-spinal injury [117], electrical stimulation of nerves or nerve roots has been demonstrated to be a safe and efficacious clinical intervention. Although long-term repercussions of implantable neurostimulators have yet to be fully elucidated, the major shortcomings of implantable devices arise from the fibrotic foreign body response that develops following implantation, particularly following implantation within the peripheral or central nervous system [10]. Restricting the neuroprosthetic device to the epineurium can



**Fig. 2** A typical cochlear implant system consists of (1) an external sound processor, which accurately converts pressure changes in the air (soundwaves) into electromagnetic signals, (2) an internal implant, which converts the electromagnetic field into electrical current, and (3) an intracochlear multi-electrode array, which delivers the current and

depolarizes the first-order auditory neurons. The current from the electrode bypasses damaged cochlear hair cells and stimulates (4) the cochlear nerve, leading to sound perception and hearing. *Images provided by Advanced Bionics, Inc. and modified*

mitigate any ensuing foreign body response; however, long-term use with this approach can induce histological changes (e.g., fibrosis, perineural thickening, decrease in axon myelination) at the site of electrode lead placement [6]. The safest approach would be the utilization of minimally invasive transcutaneous devices, which at most cause minor irritation or an allergic reaction on the skin [130]. We will now explore several of these transcutaneous, epineural, and intraneural interfaces.

#### *Transcutaneous nerve stimulators*

The most neurologically relevant transcutaneous devices are Cefaly® Technology's cranial transcutaneous nerve stimulators (TNS) that treat two forms of neuralgia: episodic and chronic migraine. All three of their devices, the external trigeminal nerve stimulator [107], supraorbital transcutaneous nerve stimulator [35, 75], and the external occipital nerve stimulator [142], have been demonstrated to be efficacious in decreasing migraine intensity, frequency, and associated pain medication consumption [36]. The electrical stimulation from these devices is thought to block ascending impulses of trigeminal nerve nociceptors and may decrease metabolic activity of the orbitofrontal and anterior cingulate cortices, hence reducing pain signal generation and subsequent pain sensation [74, 125]. Deep neuromodulation has also been used to successfully treat primary headache. Although deep neuromodulation utilizes invasive electrode implantation (e.g., vagus nerve stimulation and sphenopalatine ganglion stimulation), it nonetheless is another approach being used to modulate autonomic pathways underlying the pathophysiological headache mechanisms [88, 114].

Other forms of TNS have been employed by Frigerio and colleagues in stimulating the distal facial nerve branches to elicit blinking of the eye [23]. Similarly, Antonio et al. used TNS to modulate activity within the auricular branch of the

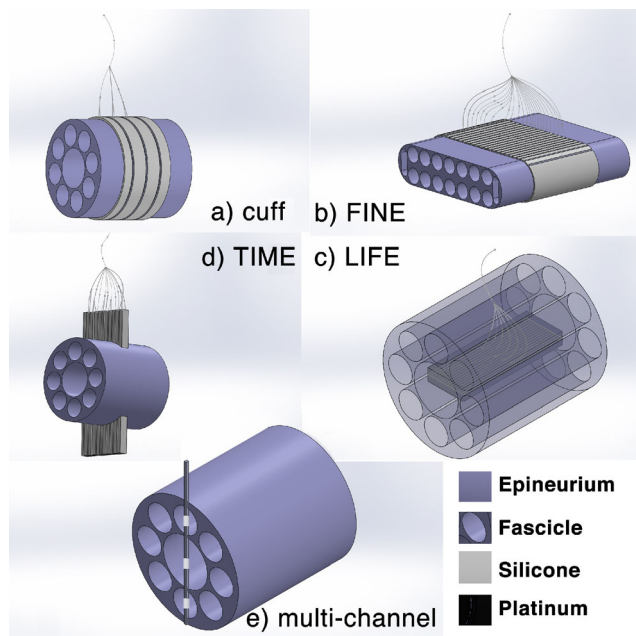
vagus nerve and treat spontaneous cardiac baroreflex sensitivity [7]. Additionally, transcutaneous vagus nerve stimulation has been demonstrated to reduce atrial fibrillation in humans [144].

#### *Cuff electrodes*

Cuff electrodes are the most basic type of epineural recording or stimulation device. The typical cuff electrode is comprised of a self-coiling, double-layer silicone cuff embedded with two to three platinum foil strips and is wrapped around the outer surface of the nerve, thus providing a direct interface for electrical stimulation (Fig. 3) [46, 73, 97, 128, 148, 149]. The electrode can operate at low stimulus thresholds, thus reducing the likelihood of detrimental nerve damage. Unfortunately, the cuff electrode generally elicits all-or-none neural activity and has a limited ability to target individual fascicles within the nerve fiber [63]. Cuff electrodes have been used safely for years, and although one study in rabbits found that long-term use of cuff electrodes had damaged myelinated axons, these axons were able to regenerate [64]. Furthermore, impedance and stimulation thresholds of cuff electrodes are stable over time, maintaining functionality for over 12 years in peroneal nerve stimulation experiments in hemiplegic patients [4, 149, 155, 158]. Peroneal nerve stimulation can also be accomplished via functional electrical stimulation (i.e., transcutaneous stimulation) of the peroneal nerve, which has been demonstrated to improve gait quality following stroke to the same degree as ankle foot orthotics [11, 135, 141].

The cuff electrode is routinely used in the clinical setting for vagus nerve stimulation (VNS), which has been shown to be effective in the management of epilepsy [31, 104], resistant depression [127], blood pressure control [110], as well as prevention of heart failure in patients with reduced ejection fractions [32, 43, 113]. Additionally, the Inspire® hypoglossal nerve stimulator, a Food and Drug Administration (FDA)-





**Fig. 3** **a** Cuff electrodes and **b** flat interface nerve electrodes (FINEs) are the most common epineural nerve-electrode interfaces: FINE compresses the nerve and thus has a higher resolution to excite specific fascicles. **c** Longitudinal intrafascicular electrodes (LIFEs) and **d** transverse intrafascicular electrodes (TIMEs) are the most common intraneural nerve-electrode interfaces. **e** Multi-channel electrodes have been used by our group to selectively activate fascicles within cranial nerves. For example, if implanted within the facial nerve, specific channels on the electrode array can activate specific fascicles and corresponding facial muscles

approved device used for obstructive sleep apnea, utilizes a cuff electrode wrapped around the hypoglossal nerve (Fig. 4). This implant is under clinical trials to augment the oropharyngeal airway by stimulating the motor nerve and lowering the tongue in coordination with the breathing cycle [54, 95]. Multiple mechanisms of action have been proposed to explain the various therapeutic effects of VNS, from emission of diffuse energy centrally towards the brain to disrupt the aberrant signals that contribute to uncontrolled epileptic seizures [13] to sympathetic and parasympathetic modulation of heart rate to prevent arrhythmia [32].

For purposes of sensory nerve stimulation, a tripolar or a modified monopolar or bipolar electrode would likely be required. Such designs can facilitate unidirectional action potential propagation while mitigating undesired signals in the opposing direction, though this has been difficult to reliably induce in practice. This contrasts with conventional monopolar or bipolar electrodes, which are impractical for administration of current to a single site (Fig. 5) [93]. Nonetheless, with regard to motor stimulation, bidirectional action potential propagation in stimulated efferent neurons can reliably elicit muscle activation and is less of an issue than with sensory nerve stimulation.

### Flat interface nerve electrodes

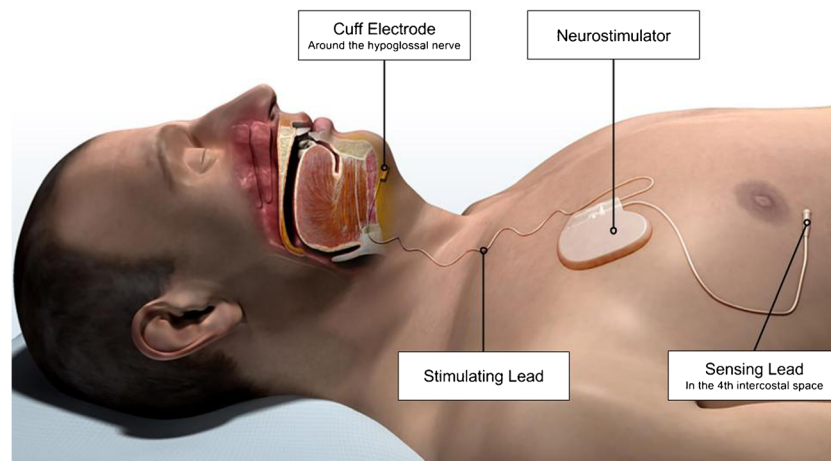
The flat interface nerve electrode (FINE) is a modified version of the cuff electrode. FINE can be designed in a multi-channel configuration and, moreover, compresses and reshapes the nerve into a flatter conformation, thereby allowing the central fascicles to be closer to the surface and providing more selective axonal population activation (Fig. 3) [63, 66, 105, 151, 161]. Additionally, intraoperative studies in the human femoral nerve showed that muscles innervated by the femoral nerve could be independently and selectively stimulated with a FINE device [133]. Surgical placement of FINE around the femoral trunk leads to selective activation of leg muscles, thereby aiding patients who suffer from lower trunk paralysis to stand from a sitting position [134]. Furthermore, the US Department of Defense has investigated the use of FINE in controlling neural prostheses in amputees [90]. Although FINEs have been used in several human studies without any deleterious consequences, FINEs have the potential to compress the nerve, reduce blood flow, or even cause neural damage [116].

### Longitudinal and transverse intrafascicular electrode

In contrast to FINE, intrafascicular electrodes pierce the protective epineurium of the nerve and can stimulate or record from peripheral nerves with higher sensitivity [89, 115]. Notably, a polymer-based, thin-film longitudinal intrafascicular electrode (tLIFE/polyLIFE) demonstrated no deleterious effects on nerve fiber count, diameter, or myelin thickness while providing higher recording selectivity than standard metal LIFE following 6 months of implantation in rabbit sciatic nerves [65]. LIFE has also been used to detect neural impulses from the median and ulnar nerves in an amputee to manipulate a robotic hand by the human patient [85, 122]. Transverse intrafascicular multi-channel electrodes (TIMEs) provide superior spatial selectivity than LIFE by enabling contact beyond one fascicle (Fig. 3) [14]. Specifically, TIME was developed to manage phantom limb pain in patients who required simultaneous excitation of multiple parallel fascicles within a nerve. This feat previously required the implantation of multiple LIFEs [14].

### Penetrating multi-channel arrays

Penetrating intraneural multi-channel arrays offer researchers vast access to diverse neural pathways (Fig. 3). Of note, investigators at the University of Utah have developed two types of multi-array electrodes: the Utah electrode array (UEA) and the Utah slanted electrode array (USEA) [25, 123]. Both are designed with the capacity to contain up to 100 microneedles which are implanted into neural tissue. Previous experiments with the UEA have reported successful recording of volitional



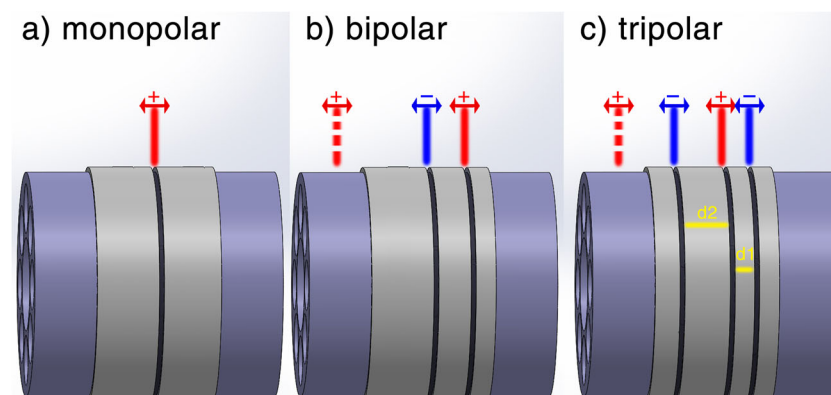
**Fig. 4** Diagram of the Inspire Upper Airway Stimulation (UAS) system. This is an implantable system that stimulates the hypoglossal nerve to treat obstructive sleep apnea (OSA). The components of the system include an implantable pulse generator (IPG), which is normally placed in the chest and is connected to two leads. The first lead is the sensing lead

and is placed into the fourth intercostal space. This senses intercostal muscle contraction and activates the stimulating lead, which is interfaced with the hypoglossal nerve. Additionally, external components that include the physician and patient programmer (sleep remote) make up the system. *Image provided by Inspire Medical Systems, Inc.*

motor commands from the central nervous system, among other accomplishments [101]. However, because this technique is highly invasive, it carries the risk of permanent neural damage [38]. Generally, the more invasive the neuroprosthetic interface, the greater the degree of selectivity of neural fiber activation at the sacrifice of potential injury to the nerve. As previously discussed, cuff electrodes, which gently wrap the nerve, generally activate the nerve in an “all-or-none” fashion with limited selectivity, while intraneural multi-channel microelectrode arrays violate the perineurium and may induce glial scarring, but offer exquisite selectivity of neural fiber activation.

Using a penetrating multi-electrode array developed at the University of Michigan, Middlebrooks et al. investigated intraneural cochlear nerve stimulation while recording the

downstream auditory pathway output at the brainstem’s inferior colliculus [86, 87]. The NeuroNexus (Ann Arbor, MI) stimulating array consists of 16 iridium-plated electrode contacts placed along a silicon shank, and in every critical auditory electrophysiological measurement in anesthetized cats, the penetrating intraneural array consistently outperformed a conventional intracochlear array. Furthermore, our group recently described the role of intraneural stimulation for facial nerve reanimation in the feline model. In short-term experiments, we achieved selective stimulation of facial muscles with the NeuroNexus multi-electrode array implanted into the main trunk of the facial nerve (Fig. 6) [129]. Electromyography (EMG) responses of four facial muscles were recorded following stimulation through the 16-channel penetrating array. Electrical pulses from each channel of the

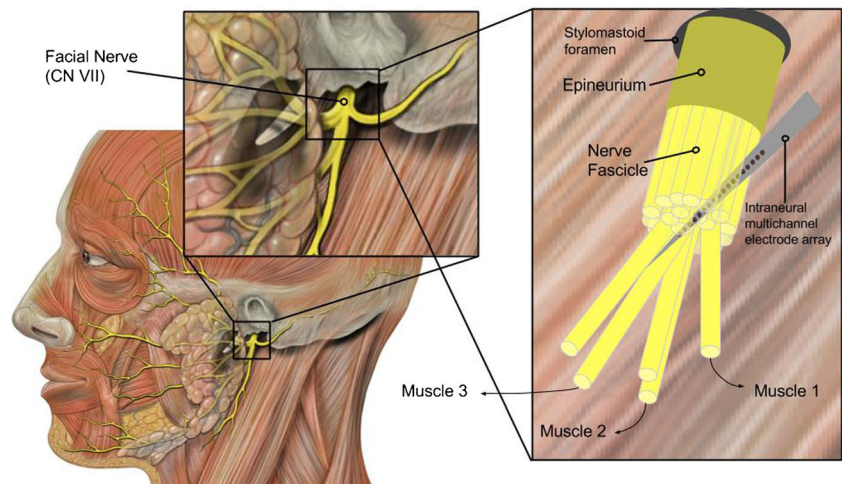


**Fig. 5** **a** Monopolar electrode configuration yields bidirectional action potential propagation due to uncontrolled depolarization of the contact point. **b** Bipolar electrode configuration aims to block one direction of action potential propagation by hyperpolarization of the nerve at the anode site. However, such magnitudes of anodic current induce a virtual cathode and negate the cancellation effect, thus yielding a

bipolar action potential. **c** An important aspect of tripolar electrodes is the platinum placements ( $d_2 > d_1$ ). Due to a time-shifted hyperpolarization at the further anode ( $d_2$ ), a virtual cathode beyond the closer anode ( $d_1$ ) will not form. However, a virtual cathode will be formed beyond the further anode, which results in a unidirectional action potential

**Fig. 6** Diagram depicting intraneural stimulation of the facial nerve with a multi-channel electrode array that can selectively activate discrete nerve fiber populations within the facial nerve and elicit selective stimulation of facial muscle groups.

*Image credit: Modified from Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD*



array selectively activated discrete neural populations within the facial nerve, resulting in independent activation of specific facial muscles. Increases in stimulation current levels resulted in corresponding increases in EMG voltage response. Moreover, long-term presence of the microelectrode array in the facial nerve confirmed the efficacy and stability of this intraneural stimulation approach [131]. Intraneural stimulation of restricted neural populations with one or more multi-channel arrays may play a role in reanimating the face for patients with permanent facial paralysis and may also help rehabilitate other motor and sensory functions throughout the central and peripheral nervous systems [129].

### Interfacing with the central nervous system

#### *Spinal cord stimulation*

Spinal cord stimulation (SCS) is an established therapy that has been readily investigated in the treatment of chronic severe pain. The complexity of the neural circuitry at the level of the spinal cord, however, has made it challenging to successfully achieve 50% or greater self-reported pain relief [163]. Beyond pain relief, SCS has been employed in the treatment of movement disorders. Epidural SCS has been successfully demonstrated to disrupt pathological circuit behavior and ultimately mitigates the motor symptoms of Parkinson's disease in marmosets [132]. This approach is less invasive than deep brain stimulation and may augment pharmacological dopamine replacement therapy in the treatment of Parkinson's patients. Furthermore, in human trials, restoration of voluntary movement following epidural SCS was achieved in patients with complete motor and sensory lesions [5]. Despite these successes, electrode migration is a common complication of SCS, and if stimulator reprogramming is insufficient in restoring function, surgical repositioning may be required [9]. Although SCS is a safe and effective approach to bioelectric restoration of function, electrode failure/fracture, cerebrospinal fluid leakage, spinal epidural

hematoma, and other complications may hinder the functional performance and ultimate utility of SCS [9].

#### *Brain computer interfaces*

Brain computer interfaces (BCIs) have been investigated for decades, leading to advancements in recording from various parts of the brain to restore a variety of functions [100, 152]. In essence, a variety of recording devices such as electroencephalogram (EEG), magnetoencephalogram (MEG), electrocorticography (ECoG), functional magnetic resonance imaging (fMRI), and functional near infrared spectroscopy (fNIRS) detect brain activity (e.g., electrical activity, magnetic activity, blood flow, metabolism) that serves as an input signal to a computer algorithm whose output affects the external environment. The spatiotemporal resolution and therefore the clinical applicability of such devices are dependent on invasive implantation within neural tissue [103]. Currently, non-invasive BCIs have been demonstrated to have therapeutic potential in enabling software-aided communication [20] and robot-assisted object manipulation (e.g., picking up a glass of water) [143] in advanced amyotrophic lateral sclerosis (ALS) patients with locked-in syndrome. Additionally, BCIs have exhibited great potential in aiding paraplegics with recovery [120, 162]. Nenadic et al. successfully used an EEG exoskeleton coupled with an augmented reality training platform to provide superior physical rehabilitation to a paraplegic spinal cord injury patient that enabled him to regain some gait function [61, 157]. Furthermore, Nenadic and colleagues have miniaturized their BCI system as well as decreased associated costs of production [78, 79]. Their goal is to advance their BCI into an implantable system for the complete recovery of gait post-spinal injury or stroke [79, 80].

Non-clinically, BCIs have been used by able-bodied users to control drones [58], smart homes [126], and augmented reality gaming [53]. In theory, non-invasive BCIs hold tremendous potential for human augmentation and alleviation



of disability, specifically as battery and other hardware/software technologies evolve; however, as of now, such devices are heavily hindered by signal processing algorithms, input signal differentiation and noise cancelation, and input-output signal mapping that conforms to unique individuals [103].

Intracranial brain computer interfaces (iBCIs) are invasive BCIs that directly interface with neurons to decode motor intent and elicit a response (e.g., artificial limb movement) [51]. iBCIs utilize microelectrodes implanted into the cortical surface, or ECoG grids to either bypass disrupted neural pathways and directly stimulate nerves and muscles or directly control artificial limbs. For example, tetraplegic patients have been able to volitionally control robotic arms [29, 49], while other patients have been able to control their own limbs via iBCI-based approaches [37, 91]. In addition to restoration of motor movement, enhancing communication, as in the case of ALS patients, for example, can also be achieved by iBCI [15, 42, 55].

Regardless of the higher spatiotemporal resolution of invasive iBCIs, no current electrode system can read and interact with individual neurons within the brain. Such a task, however, is anticipated with the introduction of a neural lace by Elon Musk's Neuralink (San Francisco, CA) [39], which is an ultrathin cortical mesh ultimately meant to enhance cognition by fusing the human mind with the internet [147]. This feat is not achievable with current technologies, and there is no clear understanding of how this system would process enormous bandwidths of neural activity, how it would be powered, and how it would chronically interface with neurons without damaging them; however, a proof of concept has been presented by Lieber et al., who achieved over 8 months of neural recording in a murine model via a syringe-injected nanoscopic self-assembling intracranial mesh, without causing neurological side effects [72]. Future research efforts directed at incorporating sensory feedback in iBCI setups and improving both recording and stimulation parameters is expected, as it can improve the efficacy of iBCI approaches in the clinical and human augmentation realms.

### *Cortical stimulation*

Additionally, intraparenchymal or subdural cortical electrodes have proven to be stable and effective implants for the treatment of chronic pain and long-term monitoring for seizure identification [67]. Non-invasive cortical stimulation has been repeatedly demonstrated to improve hand function following chronic stroke and has been utilized to varying degrees of success in neurorehabilitation regimens [52, 118]. More invasive subdural cortical stimulation, with a responsive neurostimulator connected to predetermined seizure foci, has been demonstrated to reduce the frequency of debilitating partial seizures in patients with medically intractable epilepsy

[92]. Furthermore, peri-infarct stimulation following cortical ischemic stroke, combined with rehabilitation, has been demonstrated to alleviate chronic motor deficits and enhance recovery in a primate model of ischemic stroke [111]. Recently, cortical stimulation combined with brain-state detection and haptic feedback has been demonstrated to augment iBCIs in neurorehabilitation of stroke patients with minimal hand function [41]. Although numerous histological changes (e.g., non-reactive, reactive, and toxic) at the brain implant boundary occur following chronic implantation of cortical electrodes, efforts to mitigate the fibrogliotic encapsulation of electrode leads may expedite the implementation of cortical stimulation technologies in the clinic [145].

### *Auditory nucleus and ganglion stimulation*

For patients with trauma or deformations of the cochlea or auditory nerve, the CI, which is designed to be placed in the cochlea and electrically activate the auditory nerve, is not an option for auditory rehabilitation. Most notably, patients with neurofibromatosis type-2 (NF2) suffer from bilateral vestibular schwannomas and as a result require more central activation of the auditory pathway at the brainstem's cochlear nucleus [84]. The auditory brainstem implant (ABI), again a modified cochlear implant with a flat array consisting of 12 (ABI by Med-El) to 21 (ABI by Cochlear Ltd.) platinum electrodes on a Dacron mesh backing, was created for NF2 patients [84]. To date, however, ABIs have proven most beneficial for adults without NF2 and in children with cochlear malformations [22, 28, 140]. In one study involving 48 non-NF2 (non-tumor) patients, a mean score of 59% was achieved on open-set speech perception tests [27]. For children suffering from bilateral, ossified cochlea secondary to meningitis, five out of the nine patients experienced a meaningful benefit from ABI, with access to conversational speech and sound field thresholds varying from 25 to 50 dB [8]. Although historically NF2 patients have had exceedingly limited benefit from ABIs due to the detrimental nature of the tumors, more recent studies from Europe have reported considerable success in ABI performance in NF2 patients, including a mean open-set speech perception of 41% at 24 months post-ABI activation in 18 NF2 patients [77]. Notably, a penetrating ABI and an auditory midbrain implant inserted into the inferior colliculus did not lead to an increased benefit over the ABI [69, 70, 138].

### *Deep brain stimulation*

DBS involves the implantation of microelectrodes into specific regions of the brain. An electrical pulse generator is connected to the multiple microelectrodes via microwires and, in the treatment of Parkinson's disease, will deliver biphasic current pulses (up to 30 microC/cm<sup>2</sup>) to the subthalamic nucleus (STN) or globus pallidus interna [47]. Surgical treatments for

Parkinson's disease were first described in the 1940s, but it was not until the 1990s that DBS was utilized to treat Parkinson's by targeting the STN [18]. Since the initial approval of DBS in 2002 by the Food and Drug Administration, over 70,000 patients have been treated with DBS to augment pharmacological dopamine replacement therapy [18]. Technical and surgical issues with DBS hardware are not uncommon, though a lack of standardized adverse event reporting protocols makes it difficult to fully understand the extent of DBS failure infection, lead migration, lead fracture, or skin erosion [18]. Refinements in lead design, placement, and stimulator programming may improve DBS efficacy, battery life, stimulation patterns, and electromagnetic field interference.

DBS has also been successfully used in the management of tremors, depression, obsessive-compulsive disorder, tinnitus, and other conditions, depending on the location of electrode implantation [21, 108, 156]. Developments in DBS technology, such as closed-loop stimulation strategies, have resulted in significantly enhanced management of Parkinson-related motor dysfunction [121]. Unlike traditional DBS approaches which deliver electrical impulses independent of neural feedback, closed-loop approaches constantly monitor neuronal activity to modulate the delivery of electrical stimulation [12]. Furthermore, coordinated reset of neural subpopulations (i.e., administering high-frequency pulse trains in a coordinated way to abolish pathological synchronization) has also been investigated to battle Parkinson's disease and essential tremor and may even be applicable in epilepsy [48, 150].

## Hurdles and conclusions

Despite the promise of the previously discussed bioelectric interfaces, a variety of biological and engineering hurdles must be addressed to implement and improve their clinical utility. Following implantation of any bioelectronic device, the host foreign body response will result in rapid protein adsorption onto the material surface, resulting in a cascade of inflammatory events mediated by cytokines, chemoattractants, and growth factors released by neutrophils, monocytes, and lymphocytes [2, 45]. The acute polymorphonuclear cell-mediated inflammatory phase transcends into a chronic inflammatory phase mediated by monocytes and lymphocytes. Fibrous encapsulation of the implanted electrode and the formation of a biofilm containing reactive oxygen species and degradative enzymes result in a variety of functional changes to electrical stimulation and recording, as well as possible structural failures [3]. For a more in-depth overview of the biological effects of chronic implantation of bioelectronic devices, we suggest a recent review by Sahyouni et al. [130].

In addition to mitigating the chronic foreign body response to implanted biomaterials, the development and optimization of hardware/software with a user-friendly and programmable interface remains an engineering challenge [154]. Developing closed-loop devices that can record real-time neural or physiological data and instantaneously modulate stimulation, or recording parameters, will help optimize the functional utility of bioelectronic devices. Ultimately, a multi-disciplinary approach between engineers, industry, and medical professionals will help expedite the translation of bioelectronic devices to the clinic. Applying the lessons learned from successful technologies, such as DBS, that have been implemented into routine clinical practice, will help expedite future technologies that target new pathologies. Although interfacing with the central and peripheral nervous systems offers incredible resolution and has tremendous potential in treating a wide variety of neurological disorders, the complexity and sensitivity of the brain, spinal cord, and nerves makes targeting the end organ an attractive alternative. With successes in the field of cochlear implantation, the extension of end-organ interfaces to effector organs (e.g., muscles) may be fully realized in the near future.

In conclusion, the application of neuroprosthetics to paretic nerves holds great potential in advancing the field of nerve and tissue bioelectric engineering and contributing to clinical care. Although current physiotherapeutic and surgical treatments seek to restore function, structure, or comfort, they bear significant limitations in enabling full recovery. Instead, the introduction of bioelectric technology may play a role in the restoration of volitional function in patients with nerve deficits.

**Funding information** This project was supported by grants from the American Neurotology Society, and the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1 TR001414.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This research did not involve any animals; therefore, Institutional Animal Care and Use Committee approval was not required.

**Informed consent** This research did not involve human participants or any patient information; thus, Institutional Review Board approval was not required.

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