Title: Central Nervous System Microstimulation: Towards selective micro-neuromodulation

Authors: Morgan E. Urdaneta[1], Andrew S. Koivuniemi[2], and Kevin J. Otto[1,3,4,5]
[1] Department of Neuroscience, The University of Florida
[2] Department of Neurological Surgery, Indiana University School of Medicine
[3] J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida
[4] Department of Materials Science and Engineering, The University of Florida
[5] Department of Neurology, The University of Florida

Correspondence:
Kevin J. Otto
1064 Center Drive, NEB 363, PO Box 116131
University of Florida, Gainesville, FL 32611
kevin.otto@bme.ufl.edu

Highlights:

- Electrical microstimulation to modulate neural activity has emerged as a critical tool in brain research, neurotherapeutics, and bidirectional neuroprostheses.
- Recent successes in sensory, motor, auditory, visual, and cognitive neuroprostheses demonstrate a need for more focal micro-neuromodulation technologies.
- Advances in electronics, optics, and magnetics are leading towards stable, high spatial-resolution interfaces.
- Advances in neuroprosthetic technologies may one day enable single neuron, whole-brain micro-neuromodulation.

Abstract:

Electrical stimulation technologies capable of modulating neural activity are well established for neuroscientific research and neurotherapeutics. Recent micro-neuromodulation experimental results continue to explain neural processing complexity and suggest the potential for assistive technologies capable of restoring or repairing of basic function. Nonetheless, performance is dependent upon the specificity of the stimulation. Increasingly specific stimulation is hypothesized to be achieved by progressively smaller interfaces. Miniaturization is a current focus of neural implants due to improvements in mitigation of the body's foreign body response. It is likely that these exciting technologies will offer the promise to provide large-scale micro-neuromodulation in the future. Here, we highlight recent successes of assistive technologies through bidirectional neuroprostheses currently being used to repair or restore basic brain functionality. Furthermore, we introduce recent neuromodulation technologies that might improve the effectiveness of these neuroprosthetic interfaces by increasing their chronic stability and microstimulation specificity. We suggest a vision where the natural progression of innovative technologies and scientific knowledge enables the ability to selectively micro-neuromodulate every neuron in the brain.

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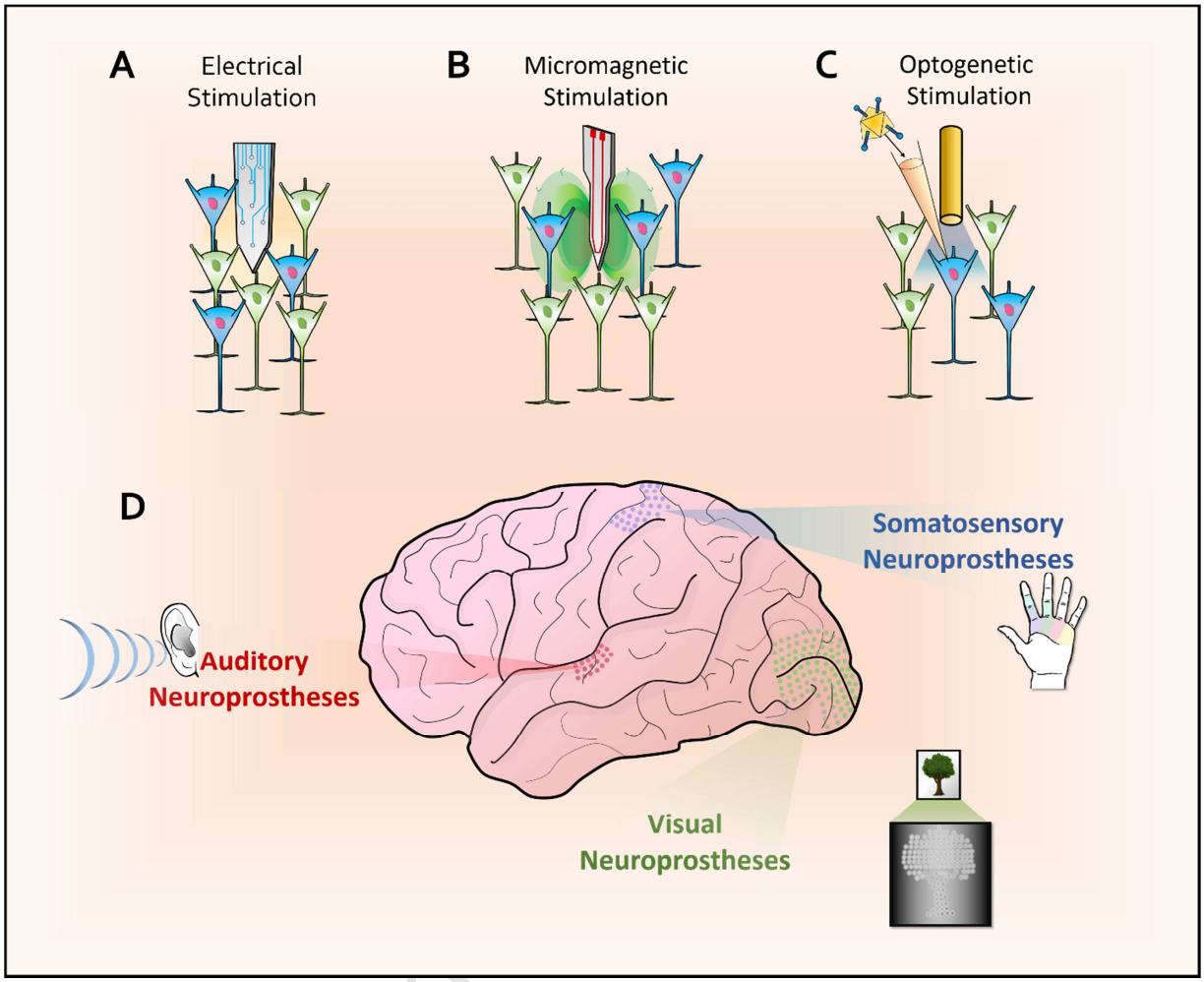

Graphical abstract

Introduction

The fields of neuroscience, medicine, and neural engineering have made great strides in how we interface the central nervous system to study normal function and treat injuries and diseases. The NIH Sponsored B.R.A.I.N. initiative aims to develop innovative technologies for studying individual cells and complex neural circuits [1,2]. These technologies aim for cellular and sub-cellular resolution, setting ambitious goals that include recording from every neuron in a single brain simultaneously. However, in addition to recording, the **activation** of these individual cells offers the promise of propelling forward both basic science and medicine. We envision technologies that will enable independent modulation of every neuron in a single brain, i.e., "whole-brain micro-neuromodulation." In this review, we will first highlight advances in science and engineering that are developing higher resolution stimulation approaches to enhance performance and translation of recent neuroprosthetic successes. Subsequently, we will detail several promising new technologies that may enable even larger-scale and cellular-resolution micro-neuromodulation in the near future.

Current neuromodulation offers various clinical approaches that provide powerful alternatives to patients otherwise refractory to available treatments. Clinical neuromodulation therapies, such as deep brain stimulation (DBS), have been widely used for the treatment of Parkinson's disease [3–5] and essential tremor [6]. DBS has also shown great potential for the treatment of a variety of neurological disorders, including, obsessive-compulsive disorder [7], Tourette's syndrome [8,9], Alzheimer's disease [10,11], alcoholism [12]**,** and depression [13]. Similarly, less invasive approaches such as transcranial magnetic stimulation (TMS) has demonstrated neurorehabilitation potential [14], as well as, effectiveness in the treatment of depression [15,16], and neuropathic pain [17,18]. However, both DBS and TMS performance are limited by their poor spatial resolution: namely, the inability to focally microstimulate specific neurons or neuronal clusters [19]. For instance, DBS macroelectrodes are estimated to excite approximately 500,000 neurons simultaneously [20]. This low specificity is likely a source off-target stimulation [21–23] which has been attributed as a source of neuropsychological post-stimulation side effects [24], such as increased impulsivity [25,26] and verbal fluency decline [27,28]. Even though the precise effects of stimulation on the activity of neuronal populations remains controversial (see [29–31] for a discussion of clustered vs. distributed population activation by microstimulation), it can be assumed that advances in interfacing technologies will gradually allow for more selective microstimulation. Regardless of whether microstimulation activates clusters of neurons local to the implanted device, or sparse, widespread populations, it is likely that advanced technologies will allow more selective activation of specific neuronal populations. This focal microstimulation, providing high-resolution activation of small neuronal populations, will offer unparalleled advantages in neuromodulation [32]. These advantages, including more selective activation of the intended target, may result in both fewer off-target effects in neuromodulation therapeutics [21,22,27], as well as futuristic assistive technologies for sensory, motor, and cognitive repair [11,33–35].

Existing microstimulation technologies, such as intracortical microelectrodes, must overcome critical challenges in order to achieve chronically stable whole-brain micro-neuromodulation. One of these challenges is the design of high-resolution interfaces through advanced materials and state-of-the-art microfabrication techniques (see [36]). Another challenge is the development of chronically stable devices capable of withstanding abiotic factors related to device breakdown [37] and biotic failures associated the foreign body response (FBR). The FBR is characterized by neuronal death, tissue encapsulation, and reduced functional longevity [37–40]. Multidisciplinary efforts for advanced device

manufacturing for greater abiotic stability [41–43] as well as mitigation of the FBR [44–59] are concurrently being investigated.

The requirements from the latest breakthroughs in microstimulation-based neuroprostheses, as well as state-of-the-art advances in neuromodulation technologies, suggest that the field is naturally progressing towards multichannel micro-neuromodulation. These technologies are shifting the stimulation spatial resolution scale from the network level to the cellular (and sub-cellular) level. The perceived quality and adaptability of future prosthetics will be bolstered by advances in neuroscience, the consolidation of functional maps with neuronal resolution, and the ability to selectively modulate those neurons. For the remainder of this review, we will discuss current successes in sensory, motor, and cognitive prostheses. We will then highlight novel technologies that are overcoming drawbacks that may one day enable whole brain micro-neuromodulation.

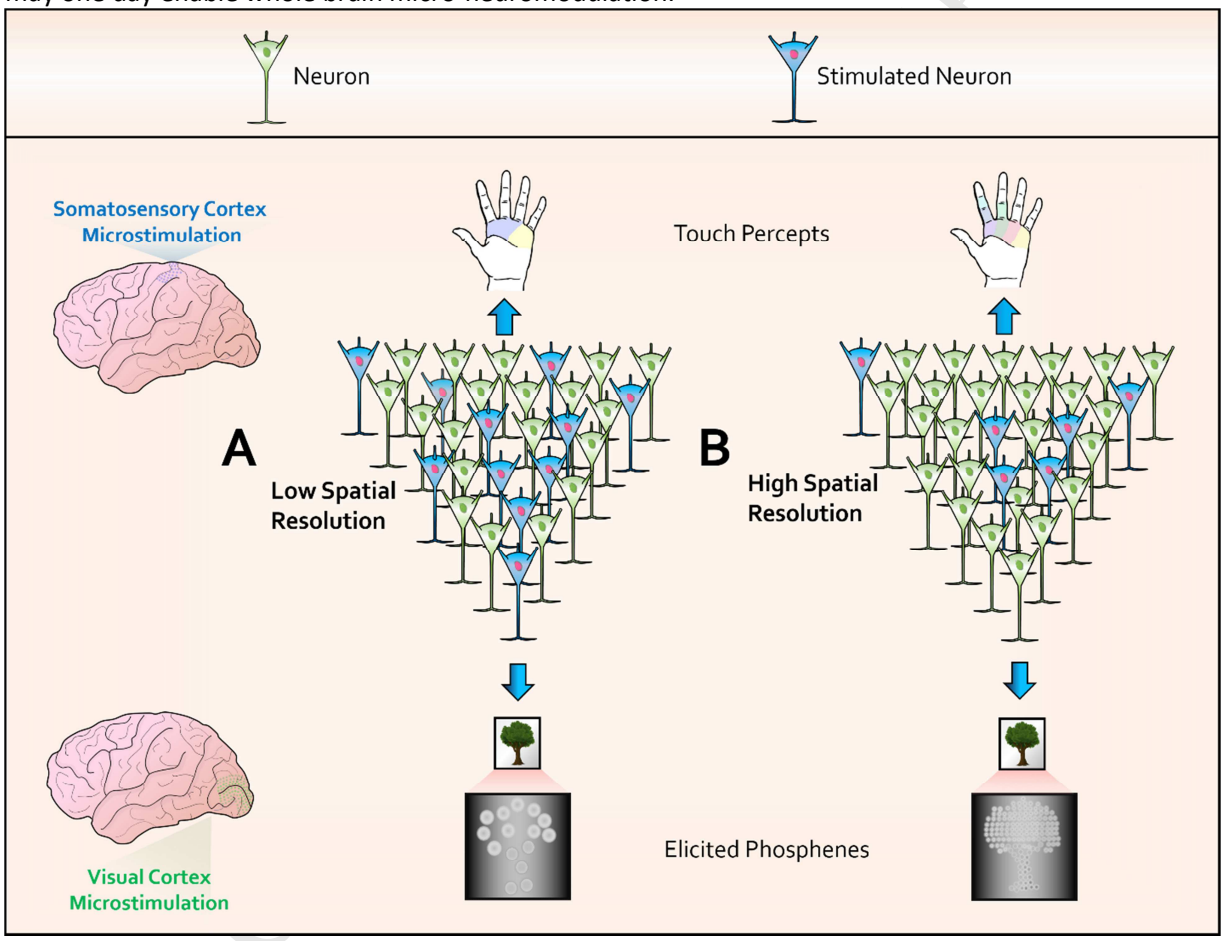

Figure 1.
Overview of stimulation spatial resolution and its effects on somatosensory and visual neuroprostheses. (A) Low spatial resolution stimulation inducing blunt visual and sensory percepts. (B) High spatial resolution neuromodulation showing discrete activation of neuronal clusters. This increase in stimulation specificity will likely allow for higher quality, more naturalistic neuroprostheses.

Recent Microstimulation Success

Advances in brain-machine interfaces (BMI) have resulted in continually improving assistive technologies to increase the quality of life of patients with neurological deficits [60]. BMI's progress has been possible

by innovations in computational algorithms, neuroscience knowledge, and predominantly, interfacing neuroprosthetic technologies (namely, the ability to record and/or microstimulate neuronal activity). Likewise, novel microstimulation technologies and targets may potentially propel forward advances and translational efforts in neuroprosthetics for patients with sensorimotor, visual, auditory, and cognitive deficits. In the following sections, we will briefly describe some of latest breakthroughs and assess critical challenges facing microstimulation neuroprostheses.

Somatosensory Neuroprostheses

Interfacing intracortical motor recordings [61,62] with complex decoding and prediction computer algorithms [63–65] has allowed tetraplegic patients to control robotic prosthetic limbs with several degrees of freedom [66–68]. Nevertheless, touch feedback is crucial for the proper biomimetic operational control of these interfaces [33]. Pioneering studies in non-human primates (NHP) by Romo *et al*. [69] demonstrated that microstimulation of somatosensory cortex (S1) could reproduce behaviors similar to the sense of touch [69–73]. Moreover, NHP somatosensory cortex microstimulation has led to further advances such as integrating sense of touch into a prosthetic hand [74] through bidirectional BMI [75,76] (For an extended review: see [33]). Less than two decades after Romo's seminal breakthrough [69], penetrating microelectrodes [77] and electrocorticographic (ECoG) arrays [78,79] were implanted into somatosensory cortices of human volunteers to restore the sense of touch. The results of both of these studies demonstrated that, even with the status of neuromodulation technologies, somatosensory microstimulation is capable of eliciting naturalistic percepts of pressure, as well as, discrete spatial discrimination of touch. The detection thresholds, as well as the perceived quality of these percepts, depended on the stimulation parameters used [77,78]. Over time, spontaneous percepts were mitigated, and the patient was able to detect percepts from a higher number of electrodes. Similarly, the number of independent electrodes that the patient could discriminate gradually increased [77], suggesting an important role for neuroplasticity in the adaptation of these implants. Moreover, advances in sensory topographies [80], biomimetic feedback [81], and selective micro-neuromodulation have the potential to drive improvements in artificial somatosensation and spatial discrimination elicited by these devices (Fig. 1B- Top).

Auditory Neuroprostheses

The use of neuroprostheses to restore hearing is one of the oldest clinically available neuroprosthetic technologies. Worldwide, more 300,000, cochlear implants (CI) have allowed patients with auditory deficits to restore hearing and improve their quality of life [82]. Due to neurophysiological properties of the cochlea and the limited neural interface, CIs have many inherent drawbacks that compromise their performance. These include impaired pitch and music perception, speech comprehension in noisy backgrounds, and sound localization [35,83]. Approaches to overcome these challenges such as augmenting the number of effective electrodes and mitigating current spillover through focal stimulation have shown only modest results [35]. Alternative stimulation targets with direct neuronal interfacing may contribute to more naturalistic auditory neuroprostheses. For instance, interfacing directly with the auditory nerve offers several potential advantages over CI, including a broader frequency range, reduced interference, and lower activation thresholds [84].

Other alternatives such as the auditory brainstem implants (ABI) [85] and auditory midbrain implants (AMI) [86] targeting the cochlear nucleus and inferior colliculus, respectively, have also been tested clinically. Although far less common and less effective than CI, ABI and AMI have been shown as a suitable approach to patients to whom CIs or auditory nerve implants are not feasible [87,88]. An additional potential target for auditory neuroprostheses is the medial geniculate nucleus of the thalamus. Animal studies have shown that thalamic stimulation might elicit ranges similar to CIs with

lower stimulation thresholds than AMI and ABI [89]. Lastly, primary auditory cortex microstimulation stands as a prospective target for auditory neuroprostheses. Otto *et al*. used a discrimination task to assess intracortical microstimulation of the auditory cortex of behaving rats. The results of these experiments indicated that the tonotopic location of the microelectrode correlates with the perceived frequency of the stimulus [90,91]. Moreover, microstimulation evoked faster responses than natural hearing [91]. Similar tonotopic activation has been reported in human electrical stimulation [92], and fMRI studies [93], suggesting potential translatability of these interfaces.

The aforementioned experiments have identified promising auditory neuroprosthetic targets that might, one day, restore normal hearing of deaf patients. The emergence of massively parallel micro-neuromodulation channels that can stimulate small neuronal populations independently will likely continue to add to the quality of auditory sensation, limiting the perceived frequency spread and enhancing the temporal resolution.

Visual Neuroprostheses

The potential of microstimulation to restore sight for the blind was established after the finding more than 80 years ago that stimulation of the visual cortex elicited localized phosphenes [94]. Since then, several potential visual neuroprosthetic targets along the visual pathway have been identified. Moreover, neural implants have shown substantial restoration of sight in low-vision patients. Retinal implants have shown great clinical and commercial success, enabling substantial improvements in motion detection, word recognition, and acuity tasks in blind patients [95,96] (See: [97] for an extended review). Despite these successes, due to anatomical constraints, retinal implants may never offer extreme high-resolution artificial vision. However, the visual cortex offers great potential for high-resolution visual prostheses [98]. The feasibility of visual cortex implants was recognized by human trials [99–101]. These experiments led to important insights and considerations for future developments of visual cortex prostheses and neural implants in general, including the importance of spatial resolution and proper neuromodulation parameters. For instance, the charge necessary to reach threshold and evoke phosphenes of intracortical (penetrating) electrodes was orders of magnitude lower compared with cortical surface stimulation [101,102]. Likewise, high stimulation currents disrupted the color and quality of evoked phosphenes [101]. Furthermore, electrodes separated by at least 0.5 mm were able to elicit independent phosphenes. Currently, multidisciplinary efforts to develop a reliable visual cortex implants have been recently proposed [103–105] (see [106] for a review). Yet, several scientific and technological challenges must be overcome before the implementation of fully functional visual cortex prostheses. For instance, a detailed understanding of the encoding used within the primary visual and striate cortices can result in enriched receptive field mapping [107] and phosphene prediction models [108]. Combining these topographic models with specific spatiotemporal neuromodulation can potentially elicit real-time, high-quality percepts. Along the same lines, experiments in NHP suggest that microstimulation of visual association areas influences object perception, including direction [109] and faces [110]. Hence, coordinated neuromodulation of visual cortex with visual association areas could potentially alter the perception and connotation of elicited phosphenes. See [111] for an extended review. Moreover, future prosthetic implementations must take into account the role of training and plasticity in chronic functional implants. Additionally, alternative stimulation targets, such as the optic nerve [112,113] and lateral geniculate nucleus (LGN) [114], have been studied for neuroprosthetic interfaces. Though still in development, advances in high-resolution brain mapping and micro-neuromodulation will likely improve the visual resolution of the perceived images, as well as the spatial patterns observed during natural vision, in all of these visual prosthesis targets [101] (Fig. 1 - Bottom).

Motor Neuroprostheses

Even though direct neuromodulation of motor cortex for locomotion has been challenging due to the lack of fine motor tuning [115] and its impracticality in spinal cord injury patients [116], it has been widely used for brain mapping [117,118] and functional neurorehabilitation [119,120]. Typically, motor cortex serves as the efferent component of bidirectional brain-machine interfaces. Recordings from primary motor cortex serve to direct neuromodulation of specific targets, including the spinal cord (via intraspinal microstimulation (ISMS) or epidural stimulation) and functional electrical stimulation for the periphery [121]. These approaches have recently allowed paralyzed NHPs to reach and grasp [122,123], and effectively restore leg locomotion [34]. Moreover, recent human trials have shown successful limb control in paralyzed patients [124,125]. Although, aside from ISMS, these stimulation techniques are not strictly classified as microstimulation, high spatiotemporal resolution neuromodulation has the potential to continue to improve the overall sustainability and naturalistic performance of these interfaces. Focal neuromodulation can substantially help overcome some of the challenges facing current motor prostheses. These include the need to drastically reduce muscle fatigue, electrical spillover, and high power consumption [126]. Moreover, micro-neuromodulation in combination with functional mapping would drastically enhance selective control of independent muscular bundles for fine motor control [127]. Finally, the chronic stability of both recording and stimulating interfaces (see Invasive Neuromodulation section) is necessary for closed-loop motor and touch integration in the translation of future, fully-functional clinical motor neuroprostheses [75]**.**

Cognitive Neuroprostheses

Restoration of cognitive abilities has emerged as an intriguing micro-neuromodulation target. Microstimulation of hippocampal cells demonstrated enhancements in memory performance tasks in rodents [128] and NHPs [129]. These microstimulation experiments were feasible by a nonlinear multi-input multi-output (MIMO) model that allowed online extraction of the patterns of firing of hippocampal cells during memory tasks to provide effective pulses of microstimulation in real time [128]. Similarly, human studies have shown that neuromodulation via DBS of other potential targets such as the medial temporal lobe can significantly improve tasks of verbal recall [130] and spatial memory [11,131]. More recently, Ezzyat *et al.*, demonstrated that these memory enhancements via neuromodulation are dependent on current brain encoding state [132], further supporting the importance of bidirectional (afferent and efferent) BMI [133]. These findings indicate that controlled neuromodulation of specific brain targets may be used in the future to treat patients with memory disorders and cognitive dysfunctions. As we expand our understanding of the circuitry involved in the acquisition, consolidation, and retrieval of memories, the efficacy of current cognitive prostheses can improve significantly by using micro-neuromodulation with high spatial and temporal precision. Even though the implementation of these type of neuroprostheses might have unparalleled clinical applications, several ethical questions are important to discuss [134].

Recent neuromodulation technologies

Invasive Neuromodulation

Electrical

The advancement of neuroscientific research and therapeutic performance of current neuroprostheses are dependent on the robustness, reliability, and predominantly the spatiotemporal resolution of the interfacing neuromodulation technology. Due to its long history of usage, safety profile, cortical depth selectivity, and low threshold currents [101,135], penetrating electrical

stimulation has been the gold standard for the vast majority of aforementioned neuroprosthetic successes [60](Figure 3A). Novel silicon microelectrodes [136–138] have systematically become denser by decreasing the size and increasing the number of electrode sites [32]. Even though performance variability occurs among different site locations [46,139], when compared to regular single-site microelectrodes [135], high-density microelectrodes allow independent placing of electrode sites within a single shaft, improving focal selectivity within cortical layers [140]. Task-specific design of microelectrodes can greatly benefit the selectivity and functionality necessary for particular neuroprosthetic applications. Advances in design and microfabrication, such as electron-beam lithography [141] and active CMOS electronic units [142] would allow for an increased number of traces and independent stimulation channels [143]. This next generation of microelectromechanical systems (MEMS) would greatly propel forward both microstimulation and recording capabilities [143]. In addition to conventional MEMS, the mechanical, electrical, and particularly, dimensional properties of carbon fibers have proven to be an attractive alternative to the manufacture of chronic electrical microelectrodes [144–146](Figure 3B). Even though these penetrating electrodes have been mostly developed as recording devices (essential for bidirectional BMI) [133], discrete modifications can be done to achieve electrostimulation [147,148]. Additionally, advances in material composition, compatibility, and deposition techniques have allowed a variety of microelectrode designs with different substrate profiles [36]. These advances have led to novel electrode designs that can potentially mediate the scale of the FBR, such as: mechanically dynamic probes [45], ultraflexible nanoelectronic threads [149], injectable mesh electrodes [150,151], as well as, endovascular stent electrodes [152]. Further studies are necessary to assess the chronic performance of these novel interfaces, as well as, their potential ability to neuromodulate surrounding neurons. Despite their obvious functional and theoretical advantages, penetrating microelectrodes face several practical challenges, primarily, biocompatibility-related. Device implantation inherently causes trauma, including blood-brain-barrier disruption [15], and neuronal death [38]. This initiates a FBR [37] by the immune system that triggers microglia [154,155] and astrocyte activation [156] leading to the formation of an indwelling glial sheath that surrounds the electrode [38–40] (Figure 2). Even though, this encapsulating glial sheath, as well as neuronal death, has been primarily associated with chronic decline in recordings [157,158] and not in stimulation [77], there is literature suggesting that the FBR might have a role in, hindering chronic performance of focal micro-neuromodulation [140] (Figure 3A).

Several multidisciplinary efforts are currently developing strategies to mitigate these effects [44], including electrical [47,48,159], mechanical [45,49–51], and chemical approaches [52,55–59] that may result in more biomimetic interfaces. A less invasive electrical microstimulation alternative is the use of intracranial electrode grid placed over the cortical surface denominated electrocorticography (ECoG) arrays. Microstimulation in humans with these devices have shown success [78] (see Somatosensory Neuroprostheses section). Likewise, novel reduced-size µECoG arrays [160,161] have shown great potential. However, the spatial resolution and effective neuromodulation of these are limited to the cortex, excluding critical deeper neuromodulation targets.

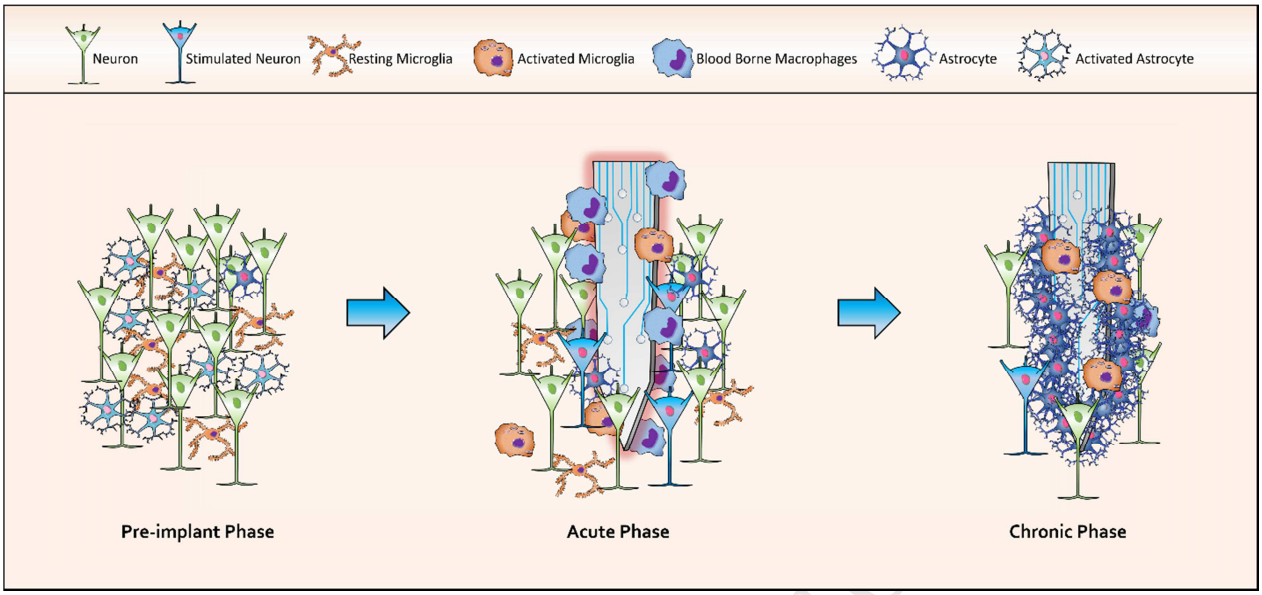

Figure 2.
Overview of foreign body response to intracortical microelectrodes.
Pre-implant phase (left) showing undisrupted tissue. Post-implant acute phase (center), characterized by mechanical brain blood barrier disruption and local bleeding (depicted in red), neuronal death, and activation of microglia. Chronic phase (right), characterized by additional neuronal death and astrocytic glial sheath surrounding the electrode, potentially impairing its performance.

Magnetic

A conventional alternative to standard electrical stimulation is the use of induced electric fields from magnetic stimulation to modulate neural activity; such is the case of TMS. Through large hand-held coils that induce strong magnetic fields, TMS is able to modulate brain activity through the scalp [162]. TMS is commonly used for the treatment of neurological disorders, including, depression [15] and stroke [120]. Analogously, implantable-sized microcoils are capable of reaching neuronal activation thresholds through micromagnetic stimulation (µMS) [163]. This novel µMS technology offers several advantages over conventional electrical stimulation, including, potential MRI compatibility [163] and, high spatial resolution (<60 µm) [164]. Additionally, the focused spatial selectivity due to the asymmetric nature of elicited magnetic fields can selectively activate [164,165], or suppress [166] neurons depending on the coil orientation (Figure 3C). Moreover, neuronal modulation through the FBR may improve chronic performance of µMS relative to micro-electrical stimulation. Compared to conventional microelectrodes, these microcoils require a much higher power input to modulate neuronal activity [164,166]. Novel microcoil designs and materials can potentially reduce this power, as well as, dramatically increase their selectivity. Furthermore, additional longitudinal *in vivo* studies will help to validate the potential of µMS as a viable and safe micro-neuromodulation mechanism.

Optical

Optical neuromodulation, through cell-type specific genetically-inserted light-sensitive proteins (opsins) [167], opened the door for a different microstimulation paradigm, known as optogenetic neuromodulation [168]. In the past decade, optogenetics has been established as a powerful tool for neuroscience research [168,169]. Advances in optogenetic systems [170], as well as the ability to selectively activate or inhibit specific cell types [167](Figure 3D), has increased interest in optogenetic neuromodulation technologies [171]. Yet, this nascent technology faces many challenges for neuroprosthetic implementation, including low temporal resolution, complex interfaces, and more importantly, the necessity to genetically manipulate cells [167,168,172,173]. In this manner, multidisciplinary efforts to overcome some of these challenges have shown recent success. These include, subverting the need for genetic manipulation through gold nanoparticles [174], as well as the development wireless [175,176], fully implanted systems [176,177], and improved flexible multifunctional probes [178]. Similarly, implantable μECoG arrays for optogenetic recording and microstimulation have shown recent success [179]. Faster and more sensitive opsins will continue to increase the temporal resolution of this technique [143]. Analogously, the spatial resolution could be drastically improved by reductions in probe size and highly selective genetic labeling. Furthermore, advances in high-resolution genetic tagging efforts analogous to nucleotide barcoding [180] and Brainbow labeling [181], might one day allow micro-neuromodulation at cellular and sub-cellular resolution.

Chemical and Thermal

Alternatively, chemical and thermal neuromodulation technologies have also been proposed. Optically-induced thermal neuromodulation technologies, such as infrared neural stimulation (INS) [182] do not require genetic manipulation [139]. *In vivo* studies have shown that INS is able to effectively modulate neuronal activity of visual cortex [183] and peripheral nerves [182] with high selectivity [184]. Nevertheless, absence of thermally induced damage, spatiotemporal resolution, and chronic stability are yet to be proven in longitudinal studies [139]. On the other hand, selective injection of neurotransmitters [185], charged ions [186], or temperature-sensitive magnetic nanoparticles (MNP) [187,188] are capable of modulating neuronal activity with high precision [19]. Recently, a method of stimulation called magneto-thermal genetic stimulation was tested for the first time in freely behaving rats. Combining MNPs with non-invasive alternating magnetic fields, this stimulation method allows for high specificity of genetically-modified cells [189]. However, these technologies require further improvements in stimulation onsets. Currently, poor temporal resolution renders these neuromodulation technologies unfeasible for real-time neuroprostheses.

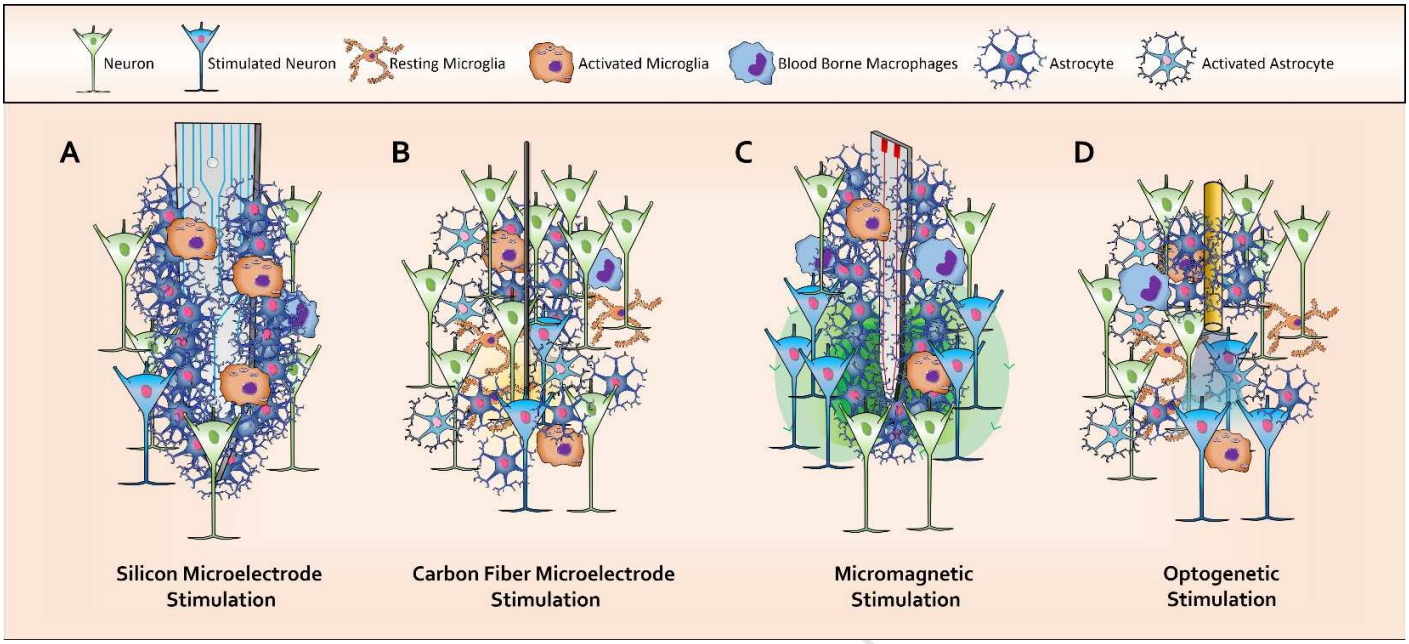

Figure 3.
Representative biostability and chronic performance of current intracortical neuromodulation technologies..
Electrical microstimulation by (A) silicon and (B) carbon fiber microelectrodes showing different foreign body responses and relative performance (stimulated neurons). (C) Implantable-sized microcoil eliciting orientation-based selective activation of neurons by micromagnetic stimulation (μMS) capable of passing though the glial scar. (D) Optical fiber probe eliciting cell type-specific optical stimulation after genetic modification (not shown).

Non-invasive Neuromodulation

Non-invasive neuromodulation technologies such as TMS [120] and transcranial current stimulation [122] have been available in the clinic for more than a decade. Even though these methods have the advantage of not requiring invasive procedures, these transcutaneous neuromodulation techniques have poor temporal and spatial resolution. Further, the unwieldy equipment necessary in the case of TMS renders these impractical for chronic neuroprostheses. Nevertheless, recent non-invasive neuromodulation alternatives have emerged with improved spatial resolution. For example, transcranial focused ultrasound (tFUS) has demonstrated neuromodulation recently in human studies that has successfully elicited discrete somatosensory [190,191] and visual [192] percepts. Likewise, temporal interference (TI) electrical stimulation has recently demonstrated that transcranial electric field interference stimulation is capable of neuromodulation at a selective depth [193]. Further studies will look to demonstrate the practicality and spatiotemporal resolution of these technologies for their application in micro-neuromodulation.

Conclusion

In conclusion, modern developments from the fields of medicine, neuroscience, and neural engineering are bringing the possibility of micro-neuromodulation closer for prosthetic and science applications. Recent studies in both human and animals have demonstrated the power of high-density, high-resolution neural interfaces to provide sensory, motor, and cognitive effects. Simultaneously, technologies from electronics, optics, and magnetics are continually being miniaturized to provide high-density, robust interfaces that avoid some biotic failures associated with the FBR. As non-invasive stimulation techniques gradually improve, Short-term solutions to the spatial resolution obstacle will most likely be overcome through invasive penetrating electrodes. Like DBS and cochlear implants, the drawback associated with the implantation of these devices will be outweighed by their clinical success. Furthermore, technological advances in computational power, artificial intelligence, and microelectronics must be developed in parallel as stimulation neuroprostheses become more reliable and precise. As the BMI spotlight shifts from academic and biomedical grounds towards commercial endeavors within the next decade, we will see an inevitable shift from assistive technologies and therapeutics towards sensory augmentation, performance enhancement, and faster-than-thinking communications. Emerging companies such as Neuralink and Kernel are leading pioneering efforts towards these goals. As the incentives for innovation and development of neuroprosthetic interfaces increase, strides towards super-high resolution integrative BMI will continue to flourish. Truly, the ability to selectively micro-neuromodulate every single neuron in the brain will one day become a pillar of neuroscientific research, adding a functional layer of complexity to current multidisciplinary brain mapping initiatives.

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