Neurotechnology for monitoring and restoring sensory, motor, and autonomic functions

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ABSTRACT

The rapid and exponential advances in micro- and nanotechnologies over the last decade have enabled devices that communicate directly with the nervous system to measure and influence neural activity. Many of the earliest implementations focused on restoration of sensory and motor function, but as knowledge of physiology advances and technology continues to improve in accuracy, precision, and safety, new modes of engaging with the autonomic system herald an era of health restoration that may augment or replace many conventional pharmacotherapies. DARPA's Biological Technologies Office is continuing to advance neurotechnology by investing in neural interface technologies that are effective, reliable, and safe for long-term use in humans. DARPA's Hand Proprioception and Touch Interfaces (HAPTIX) program is creating a fully implantable system that interfaces with peripheral nerves in amputees to enable natural control and sensation for prosthetic limbs. Beyond standard electrode implementations, the Electrical Prescriptions (ElectRx) program is investing in innovative approaches to minimally or non-invasively interface with the peripheral nervous system using novel magnetic, optogenetic, and ultrasound-based technologies. These new mechanisms of interrogating and stimulating the peripheral nervous system are driving towards unparalleled

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spatiotemporal resolution, specificity and targeting, and noninvasiveness to enable chronic, human-use applications in closed-loop neuromodulation for the treatment of disease.

Keywords: neural interface, neuromodulation, brain-computer interface, optogenetics, nanoparticles, neurotechnology, nervous system, biomedical

1. INTRODUCTION

1.1 The Nervous System: Anatomy and Function

The human nervous system comprises two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS is composed of the brain and the spinal cord while the PNS contains the nerves that connect the CNS with peripheral structures such as muscles, skin, and viscera.[1] In general, the PNS receives sensory information from the body via afferent nerves to the CNS for processing, while efferent nerves transmit control signals to muscles, glands, and other effectors. The autonomic nervous system (ANS), a specific component of the PNS that regulates end organ functions, communicates motor and sensory information with visceral organs and tissue. The ANS regulates heart rate and blood pressure, respiration, digestion, and other organ system functions that operate mainly without conscious control.[1]

The neuron is the main signaling cell in the nervous system. The cell wall or membrane of neurons is composed of a phospholipid bilayer that maintains an electrical gradient (approximately -70 mV) between the cell interior relative to the extracellular environment. Neuronal communication occurs via electrochemical signals; neurotransmitters are released from the axon terminals of the neuron at synapses, which form the junctions between neurons. Neurotransmitters then diffuse across the synapse to bind to receptors on an adjacent neuron's dendrites, which serve to collect input signals from other neurons. Binding of the neurotransmitter to receptors triggers the opening of ion channels in the neuron's cell membrane to allow ions to cross the membrane, altering the transmembrane potential for the neuron. Once the transmembrane potential for the neuron depolarizes to a critical threshold (approximately -55 mV), the neuron will fire an action potential from the soma at the axon hillock, which proceeds along the axon to the axon terminals, which deliver neurotransmitters to synapses with other neurons and other effector cells, such as muscles and glands. In general,

the action potential manifests as a transient influx of Na^+ ions that depolarize the cell followed by a sustained efflux of K^+ ions that repolarize the cell. This highly specialized electrical signal traverses the axon by self-generating at each gap in the myelin sheath and occurs rapidly in just a couple milliseconds.[1, 2]

Bioelectrical signals, such as the action potential provide a direct record of the information processing and communication functions performed by neurons, prompting the development of various technologies to measure the electrical state of neurons. Conversely, the sensitivity of neurons to electrical and chemical signals has inspired techniques for modulating neural activity via electrical stimulation. Techniques for monitoring and modulating activity in the nervous system have evolved from simple devices to study the basic functions of neurons in the laboratory to clinical applications of neural recording and stimulation to monitor and treat neurological disease. Ongoing efforts to advance new capabilities for interfacing with neurons are aimed at improving the spatial and temporal resolution at which neural activity can be measured or regulated, as well as the scale at which interfaces can communicate with large populations of neurons. To support more widespread use of neural interfaces in treating neurological disease, significant emphasis is being placed on reducing invasiveness and improving reliability of neural interfaces for long-term use in humans.

1.2 System Design Considerations

Interactions with the nervous system require a neural interface system capable of transducing neural activity (both measuring and stimulating) into modalities readily interpretable by digital systems. Key considerations to designing a neural interface system include safety, invasiveness, signal modality, source, detector, data rates, and power. Collection and stimulation of neural activity may require direct physical contact with the nervous system (e.g., via electrodes) or non-contact methods (e.g., optical). Early implementations included invasive electrodes in direct physical contact with the nervous system, but emerging non-electrical opportunities exist in both minimally invasive (e.g., injectable) and non-invasive approaches. Non-electrical modalities include optical, thermal, and acoustic techniques (or combinations thereof), which represent appealing alternatives to traditional electrode-based neural interface systems. System design requirements for signal detection (signal-to-noise ratio) and data rates appropriate to the neurophysiology must be considered when integrating the signal modality, transducer, and detector in the final implementation. Power sources for implanted systems must meet stringent battery life, power density, and packaging requirements, which determine battery size and, by extension, implant size. Large implants require more invasive surgery, increasing the barriers to use.

Conversely, injectable implants can be safely and easily delivered to the patient requiring only small incisions and increasing the benefit to risk ratio. Recent advances in wireless[3, 4] or acoustic[5, 6] power may open the door to ultra-miniaturized injectable or standoff neural interface systems requiring no battery. While all of these system design considerations are intricately intertwined, this paper will focus exclusively on the current and emerging trends in neural interfaces rather than complete systems.

2. Current Applications of Neural Interface Technologies

State-of-the-art neural interface technologies applied to clinical settings revolve around treatment of neurological disorders or prosthesis applications. Growing acceptance of existing commercial technologies applied to autonomic dysfunction has led to several notable clinical trials, including one on obesity[7]. Regardless of clinical indication, neural interface therapies involve stimulating neurons whereas neural recording technology typically is implemented with prosthetic or assistive technologies. In both cases invasive and non-invasive approaches exist.

2.1 Stimulation

Non-invasive brain stimulation for therapeutic intervention originated in the late 18th century[8], but recent advances have refined treatment options to be more effective, with minimal side effects such as headache and dizziness. Transcranial direct current stimulation (tDCS) applies a constant, battery-powered current across the skull between two electrodes. The biophysical mechanisms of action for tDCS are unknown, but two variants are generally used, with anodal and cathodal tDCS believed to have differing effects on the membrane potential of neurons. Anodal usually depolarizes the cells and makes them more likely to fire an action, whereas cathodal usually hyperpolarizes the cells making action potential less likely. Alignment of the neuron with the electric field most significantly affects the membrane potential and, in turn, the probability of neuronal firing.[8] Transcranial alternating current stimulation (tACS) is thought to interrupt neuronal oscillations, but like tDCS, the mechanism is not fully understood. Though promising, non-invasive electrical brain stimulation produces inconsistent outcomes that may result from differences in electrode placement, duration, frequency, and current density. Diffusion of current through the skull and brain tissue also limits the spatial resolution and the ability to target specific brain regions.

Magnetic stimulation can also be used to stimulate the brain non-invasively. Transcranial magnetic stimulation (TMS) has been studied as a therapeutic intervention for treatment-resistant major depressive disorder and neuropathic pain.[9, 10] TMS involves placing a coil adjacent to the head and applying a brief, but very strong, magnetic field to generate electrical currents in the tissue through electromagnetic induction.[11] Despite this general understanding, the exact biological mechanism is not well understood and the functional effects seem to be frequency dependent.[12] TMS permits targeting of brain regions that are deeper than can be stimulated effectively with electrical methods, which are generally limited to regions near the cortical surface.

In contrast with non-invasive stimulation methods, deep brain stimulation (DBS) boasts high spatial resolution. Implantation of large penetrating electrodes into the brain also permits targeting specific brain regions including those several centimeters below cortical surface. While DBS is capable of high spatial selectivity, risk of infection, seizures, and bleeding accompany this technique. Therefore, clinicians usually view DBS as a last resort option for severe medical conditions including drug-resistant Parkinson's Disease[13-15], epilepsy[13, 16], depression[13, 17, 18], and Obsessive Compulsive Disorder (OCD)[18-20].

Vagal nerve stimulation (VNS) has been used clinically for treatment of epilepsy[21, 22], depression[23], and stroke[24]. This stimulation interface indirectly influences brain activity via the peripheral nerve, and is believed to activate neuromodulatory regions of the brain that in turn regulate downstream cortical changes. Alterations in brain activity[25, 26] and neurotransmitters[27, 28] have been demonstrated following VNS, but the exact mechanisms of action remain unclear. The side effects are often less severe than with DBS and include voice alterations, cough, hematoma, and bradycardia[29], although implanting the electrodes and pulse generator does pose a surgical risk. To further minimize risk, more recent advances have explored non-invasive methods of stimulating the auricular[30, 31] and cervical branches[32, 33] by placing electrodes on the skin. Initial data seem promising, but further investigation into the biological mechanism and parameter space is required to fully understand the potential benefits and limitations of VNS.

2.2 Recording

Typically, neural recording interfaces require signal transduction, amplification, denoising, and processing algorithms, such as for prosthetics applications.[34] Non-invasive recording by electroencephalography (EEG) can produce both 2D[35] and 3D[36] movement signal control by collecting signals through the skull with electrodes placed on the scalp. Signal

attenuation through the bone limits the amplitude and spatial resolution of EEG, which is also susceptible to noise from electromyographic (EMG) and electroocular (EOG) signals.[37]

Electrocorticography (ECoG) provides greater signal-to-noise ratio (SNR) sufficient for demonstrating online brain computer interface (BCI) control.[38] Two types of ECoG, distinguished by the placement of the electrodes, exist, but both are invasive and require a craniotomy or opening of the skull. Epidural ECoG places electrodes on top of the *dura mater* and exhibits spatial resolution of ~1.4 mm[39], whereas subdural EGoG places electrodes beneath the dura and produces a spatial resolution of ~1.25 mm[40, 41]. While a spatial resolution improvement over EEG, ECoG cannot achieve the spatial resolution of penetrating electrodes nor can it detect single action potentials.[37] Other advantages over EEG include larger bandwidth (up to 500 Hz) and higher SNR[37, 42]. Moreover, ECoG arrays can produce more stable chronic recordings compared to penetrating electrodes.[43]

The first demonstration of implantable penetrating electrodes to control prosthetic limbs in humans with tetraplegia occurred in 2006.[44] While several types of electrode arrays exist for prosthetic control applications, the Utah style is the only high-density implantable recording array approved by the FDA for clinical use.[34] A silicon-based array of penetrating microelectrodes, the Utah array contains one contact at the tip of each electrode. In contrast, the silicon-based Michigan array uses a thin film design that allows for multiple contacts per shank in either single-shank or multi-shank implementations. The multiple contacts per shank enable the Michigan arrays to achieve tighter spacing between electrodes, improving the spatial resolution for neuronal recording.[34] Similar to the Utah arrays, metal microwires also boast a single contact at the tip. Overall, implantable electrodes exhibit excellent temporal resolution (< 1ms)[45], 50 – 150 μm spatial resolution and single action potential detection[46]. Despite the advances in spatiotemporal resolution afforded by implantable electrode arrays, localization and cell type specificity remain major technical challenges[47], which are being addressed by the emerging genetic interfaces discussed later.

Despite the early successes of implantable interfaces for prosthesis control, reliable detection of high-quality signals decreases over time, and many have even reported device failure[48-50]. One possible cause is the neuroinflammatory response activated by the highly invasive nature of these interfaces. Penetrating the blood-brain barrier initiates a cascade of complex events including immediate activation of microglia and macrophages that signal astrocytes into a reactive state; in some cases, neuronal death has been reported.[51] Mechanical failure and material degradation may also

influence the life of the device.[34, 52] Despite concerted efforts to overcome these technical limitations, including novel materials[53-55], flexible tissue compliant devices[56-59], and design size,[60, 61] challenges remain.

3. EMERGING TECHNOLOGIES

While sensorimotor restoration presents a clear path for nervous system intervention for patients, illnesses associated with end-organ dysfunction or a loss of homeostasis governed by the autonomic nervous system are typically treated with pharmacological and surgical interventions. As physiological and mechanistic understanding of the autonomic reflexes and their control over visceral dysfunction improves, non-pharmacological intervention by precise, targeted autonomic neuromodulation moves closer to treating inflammatory disease[62-66], chronic heart failure[67, 68], and other conditions[69]. Realizing this vision requires novel neural interfaces capable of overcoming the following limitations of electrode-based technologies: 1) poor targeting, 2) limited scale, 3) invasiveness, and 4) chronic unreliability. Technical approaches to overcome these challenges can broadly be classified according to the interface's primary signal modality, namely optical, magnetic, acoustic, or hybrid approaches. The following sections summarize emerging minimally and non-invasive neural interface technologies potentially applicable to peripheral neuromodulation for autonomic control.

3.1 Optical

Genetic Transducers

Advances in genetic engineering have enabled optical stimulation or recording of neurons with high specificity and selectivity.[47, 70] Optogenetics involves genetically modifying neurons to make them light sensitive for photic stimulation or to generate photic signals for measuring neural activity. For photic stimulation, neurons are genetically altered to express light-responsive channel proteins in the plasma membrane. The protein channels, originally discovered in photosynthetic algae and bacteria, open in response to light, permitting ions to flow into or out of the cell, thus triggering changes in the neuronal membrane potential.[71] Depending on the specific protein and the corresponding ionic flux, light activation either excites or inhibits the neural action potential. Since its first demonstration in neurons in 2005[72], optogenetics has expanded rapidly and advanced in lock-step with improvements in microbial opsin engineering, genetic

methods for cell-type targeting, and optical strategies for guiding light through tissue[71]. One critical advantage potentially afforded by optogenetics is high cell-type specificity based on promoter selection. Cell-type specificity enables multiplexing based on wavelength, differential activity (firing vs. inhibition), specific neurotransmitter production, and other cell type-specific functions.

Early demonstrations with microbial opsins produced millisecond channel opening, thus enabling control of single spikes and even synaptic events.[72] Despite such high temporal resolution, the early efforts suffered prolonged deactivation and rapid inactivation, which produced extra spikes, plateau potentials, and limited the firing rate to ~40 Hz.[73, 74] Recent improvements in temporal precision and the ability to sustain higher frequency firing resulted from engineering microbial opsin variants with faster deactivation kinetics.[73, 74] On the other end of the temporal spectrum, stabilized step function opsins (SSFO) permit on-off switching with a brief pulse of blue light to activate for up to 30 minutes, and deactivation by yellow or green light, thus enabling long timescale experiments.[74]

Another genetic tool for visualizing and recording neuronal signals optically is through genetically encoded indicators. The two classes, Genetically Encoded Voltage Indicators (GEVIs) and Genetically Encoded Calcium Indicators (GECIs), both require transduction of an endogenous signal to a fluorescent indicator. These are notoriously difficult to calibrate due to nonlinearities of fluorescence. Typically, these include an analyte-binding or sensor domain combined with a reporter element containing a fluorescent protein.[47]

GEVIs offer unique capabilities for large-scale recording[47] and exhibit better spatial resolution than traditional electrical recordings[70]. However, current GEVIs are dim, resulting in only moderate sensitivity. Rhodopsin variants have made some improvement, but require further modification and will likely need to be paired with brighter retinal chromophores.[75] Another factor limiting sensitivity is that they must be paired with additional imaging techniques to visualize the signal. Unfortunately, GEVIs cannot be paired with two-photon imaging and must be performed with wide-field microscopy, thus limiting the SNR. One report of two-photon imaging with a rhodopsin variant exists, but required extensive trial averaging to detect the signal.[76]

GEVIs typically exhibit poor kinetics[75] on timescales greater than 1 ms[77] leading to moderate temporal resolution. Protein engineering has incrementally improved the kinetics, but ultimately the tradeoffs between brightness, kinetics, and SNR require continued optimization. High-performance GEVIs have yet to be demonstrated in awake and mobile

animals, although high SNR and fast Voltage-sensitive Fluorescent Proteins (VSFPs) have been applied in animal models.[47] These consist of a voltage-dependent conformational change of a voltage-sensor domain coupled to a pair of fluorescent proteins.[77] GEVI's are also limited by their need to remain contained in the cell wall rather than the cytosol.[47]

GECIs are the most widely used genetically encoded indicator for *in vivo* imaging[47] and were first reported in 1997[78]. Despite their success over GEVIs, calcium indicators serve only as proxies for action potentials. Ca^{2+} ions can only enter the neuron through a subset of channel proteins, such as NMDA and nicotinic receptors. Therefore, Na^{+} ion influx may occur through other channel proteins to initiate an action potential without involving Ca^{2+}.[78] Measuring Ca^{2+} instead of voltage also limits the temporal resolution because voltage changes rapidly during neuronal signaling whereas Ca^{2+} dynamics are much slower.[79] Extended Ca^{2+} transients can indicate an integrated signal[75] and make it difficult to discern spike rate, especially during high frequency or bursting activity. However, protein engineering has recently improved the kinetics and single action potential resolution has been reported.[80]

Protein engineering has also produced bright GECIs[81] with high enough SNR to exploit two-photon imaging[80]. As such, these boast good spatial resolution and single action potential detection from hundreds of cells. In addition, expansion of the available color palette to at least five distinct wavelengths[47, 75] greatly extends the specificity and experimental applications of GECIs within basic neuroscience.

Two critical SNR-limiting factors hamper optogenetics and genetically encoded indicators: expression levels and a secondary method of signal detection. Low expression levels require higher power lasers and exposure times, but this inevitably leads to photo-bleaching or cytotoxicity. In contrast, high expression levels can also result in cytotoxicity. Despite these constraints, optogenetic neural interfaces have evolved rapidly and facilitated a wealth of knowledge including cell specific roles in complex behaviors[75] and neural dynamics[47]. Their applicability for human use remains unclear due to the genetic modifications required.

Direct Approaches

In contrast to the previously described methods, which require optical transducers, direct optical interrogation and stimulation can occur without an intervening transducer. Non-invasive, non-contact, label-free approaches are appealing for their lack of direct physical contact with the neural tissue, thereby significantly limiting the technical challenges associated with biocompatibility that typically plague traditional, invasive approaches. *In vivo* direct optical approaches

use near infrared (NIR) or infrared (IR) signals due to their transmissivity through water and tissue, while the penetration depth's dependence on wavelength provides a potential means for targeting fascicles.[82, 83] Despite the high spatial resolution afforded by focused illumination and the transparency of tissue to NIR and IR wavelengths, optical approaches are still limited to penetration depths on the order of ~10^2 μm, limiting their use to research applications.[84, 85] Infrared neural stimulation[84] and refractive index-based neural recording[86] represent two non-invasive, direct optical approaches.

Direct optical recording of neural activity typically probes local changes in the membrane's optical properties when active. Such changes, which manifest as perturbations to the refractive index[79, 86], have been probed using various optical scattering, birefringence, optical coherence tomography, or similar techniques.[87-90] Other approaches may also relay neural activity by exploiting nonlinear optical processes, such as Raman spectroscopy of membrane lipid components[91] to monitor perturbations to the lipid vibrational modes as the lipid bilayer accommodates the membrane potential activation. A critical technical challenge to directly interrogating neural activity using optical approaches rests with the low sensitivity, thus requiring signal averaging to increase SNR, which fundamentally limits the temporal resolution. Optical system-level optimizations may mitigate the SNR technical challenges for example, searching for approaches to minimize the optical source noise.[92] Spontaneous Raman scattering approaches cannot measure neural activity *in vivo* due to the damage-inducing power required to produce a measurable Raman signal. Optical coherence tomography (OCT) or optical coherence microscopy (OCM) approaches are appealing for their sensitivity to small perturbations to the target optical properties, especially phase-domain measurements, which more accurately and sensitively probe slight changes in nerve displacement resulting from action potential generation.[89] The in-plane resolution achievable through OCT is limited to approximately 10-20 μm, while OCM employs high numerical aperture objectives that enable 1 μm resolution. Signal integration is not the sole hindrance to high temporal resolution measurements. These techniques can be limited in their temporal resolution depending on mechanism of activity being probed by the system, such as the membrane swelling response to compound action potential generation or physical realignment of the membrane proteins.[89] Despite these limitations, as the state of the art in optical source, detector, and system design continues improving, the potential application of *in vivo*, real-time optical neural recording techniques seems increasingly possible.[88]

Several groups have demonstrated direct IR stimulation of neural activity[83, 87, 93-96], but the precise physical mechanism by which direct IR stimulation activates neural activity remains unclear. Several hypotheses exist, including thermal disruption of the membrane ion and TRPV channels, photon absorption by the membrane proteins, and perturbations to the membrane, with the consensus converging on a combination of thermal effects and the membrane capacitance stimulating nerve activity.[87, 94, 95] Early experiments demonstrated nerve propagation to be temperature-dependent and governed by a process driven largely by temperature gradients localized to the nerve membrane, which may increase the Na^+ ion channel conduction upon opening or activate heat-sensitive channels.[83, 97] In contrast, more recent efforts by Shapiro, *et al.* suggest that the localized heat produced by IR absorption in the surrounding water increases the local temperature and reversibly increases the membrane capacitance, thereby depolarizing the cell.[82] Along with the murky origins of thermally induced neural stimulation by IR excitation, a key technical challenge to safe, direct optical stimulation of peripheral nerves *in vivo* remains the tradeoff between stimulation and tissue damage energy. Early studies determined that at wavelengths coinciding with minimal tissue absorption (4 μm and 2.1 μm), stimulation thresholds are highest relative to the threshold intensities resulting in tissue damage. The authors conclude that the low absorption wavelengths offer the greatest safety margin between stimulation and damage.[83]

Emerging approaches in both neural recording and stimulation through direct optical techniques suggest a potential avenue for achieving non-invasive, non-contact, non-destructive *in vivo* neuromodulation. Core to both technologies remains a thorough understanding of the mechanisms of action to inform engineered solutions that meet the spatiotemporal requirements while addressing the system-level challenges for delivering the light safely to the target.

Nanoparticle Transducers

Light incident on nanoparticle transducers produces concentrated thermal energy, and their injection to the desired stimulation site localizes the effect and enables targeted stimulation. However, the frequency of incident light affects the signal penetration depth irrespective of how deeply the transducers are injected.

Plasmonic gold (Au) nanoparticles (NPs) have been applied *in vivo* for many medical fields, including targeted cancer therapy and neuromodulation. Au nanoparticles can produce heat when irradiated by light tuned to their localized surface plasmon resonance – the quantization of a metallic nanoparticle's free electron density oscillations in response to incident electromagnetic radiation. Metallic nanoparticles exhibit enhanced absorption of light tuned to their localized

surface plasmon resonance, which in turn generates heat due to electron scattering and subsequent phonon-phonon interactions.[98] For cancer therapies, the localized heat produced by the excited plasmonic nanoparticles destroys tumor cells. In contrast, application of plasmon resonant nanoparticles for optically induced neural stimulation decreases the required intensity by leveraging the intrinsic enhancement produced by the plasmon resonant modes to generate heat and trigger neural activity. The plasmon resonance of these nanoparticles can be tuned by their geometry (i.e., dimensions and shape) and owing to Au's significant interband losses in the visible spectrum, its plasmon resonances tend to be limited to red and longer wavelengths (NIR to IR)[99]. These longer wavelengths coupled with Au's intrinsic chemical stability make these nanoparticles promising candidates for *in vivo* use. Furthermore, their small dimensions render Au nanoparticles ideally suited for minimally invasive delivery *via* direct injection to the target site. Such localized delivery prevents off-target neural activity as it ensures that the resonant nanoparticles act on only the neurons in their local vicinity.

Demonstrations of localized Au NPs coupled with IR or NIR stimulation can generate neural activity at lower laser powers than direct optical stimulation alone owing to the NP-mediated thermal enhancement.[100] Previous efforts have also demonstrated the importance of tuning the nanoparticle plasmon resonance to the incident light to maximize effect. Spherical Au NP off resonant from the NIR laser produce less neural activity relative to Au nanorods with longitudinal plasmon modes resonant with the incident field.[100] The spherical nanoparticles produce less heat and therefore stimulate less activity due to less efficient (non-resonant) coupling of the incident light to the plasmonic modes. The key advantages to combining plasmonic nanoparticles with NIR or IR stimulation are the lower laser power, which mitigates the risk of tissue damage[101], more precise nerve targeting based on nanoparticle location, and the potential to combine the NPs with binding elements to target nerve membrane. Nanoparticle-based neural interfaces are a promising technology buoyed by early demonstrations of thermal stimulation of neurons, but their clinical application requires further investigation into their safety, delivery, targeting, persistence, and efficacy. System engineering considerations such as optimization of the temporal resolution and monitoring power requirements, heat dissipation, and potential downstream activation also warrant further study.

3.2 Magnetic

Nanoparticle Transducers

An alternative to photothermally induced neural stimulation, magnetothermal stimulation relies on magnetic nanoparticles that locally generate heat when exposed to alternating magnetic fields (AMF), thus causing nearby heat-sensitive TRPV channels to open and activate the neuron.[102] This is an appealing technology capable of deep penetration *in vivo* since it exploits the transparency of the body to low frequency (100 kHz – 1 MHz) AMF to heat *in vivo* nanoparticles with limited attenuation. In a 2015 demonstration of this novel nanoparticle-based neural interface technology, magnetic nanoparticles delivered to the ventral tegmental area (VTA) in anesthetized mice yielded reversible neuronal activation in mice with TRPV1-expressing neurons.[102] The minimal cytotoxicity of these iron oxide (Fe_3O_4) nanoparticles coupled with their *in vivo* persistence for over a month suggest their potential for chronic use[102], but given the bulky magnet required to provide the 15 kA/m AMF this technology may remain limited to research applications.

Genetic Transducers

A recent genetic approach to magnetic neuromodulation combines TRPV4 channels with a paramagnetic ferritin protein.[103] Termed Magneto, this fused construct actuates neural activity in response to applied magnetic fields that the authors hypothesize torques the ferritin protein, which in turn places a mechanical strain on the mechanosensitive TRPV4 channel.[103] *In vitro* and *in vivo* experiments successfully demonstrated activation of nerve activity in response to the applied static magnetic field (~50mT-250mT), even in awake, freely behaving animals.[103] These magnetogenetic constructs exhibit faster dynamics and generate neural activity at physiologically relevant timescales – a key challenge hindering optogenetic techniques. Still in its nascent stages, the Magneto technology represents the newest contribution to the suite of emerging, non-invasive neural interface technologies.

3.3 Acoustic

Direct Approaches

A deeply penetrating modality capable of beam focusing and steering, acoustic or ultrasound signals may overcome the depth and scattering limitations that plague optical approaches while achieving spatial resolutions at the millimeter-scale. Early demonstrations of acoustic neuromodulation, typically inhibitory and performed in cortex, built off prior focused ultrasound uses for therapeutic and surgical interventions.[104] The intensities required to elicit nerve activity are several orders of magnitude lower than the high-intensity focused ultrasound used to lesion tissue (mW/cm^2 *vs.* kW/cm^2). Legon, *et al,* stimulated activity in the primary somatosensory cortex using transcranial focused ultrasound (FUS).[105] In the periphery, FUS need not be limited to long acoustic wavelengths to accommodate the high acoustic impedance of bone compared to soft tissue and can achieve greater penetration depths. While the low intensities applied for FUS neuromodulation typically fall below the $720mW/cm^2$ safety limit, long-term and/or repeated application remains unstudied and the safety of such use will affect its tractability as a treatment for chronic conditions.[106] Acoustic neuromodulation has achieved centimeter-scale penetration depth coupled with focusing capabilities without requiring any *in vivo* components; however, latencies on the order of $\sim 10^1$ ms reveal slower kinetics compared to electrical or optical modalities.[69, 106] The slower kinetics likely reveal some information about the mechanisms of action; however, the exact mechanism remains unclear and optimization of the parameter space a challenge.[106, 107]

Major hypothesized mechanisms include heating, cavitation, strain-induced opening of ion channels, and neuromechanical perturbation of membrane capacitance. Localized heating triggers nerve activity due to absorption of the applied acoustic energy.[108] Secondary effects[109] beyond the elastic heating mechanism can occur with focused ultrasound, but their impact tends to be small compared to absorption. A recent hypothesized cavitation-based mechanism[110] suggests mechanical forces generate pores in the cell membrane and the subsequent intramembrane cavitation perturbs its capacitance, which produces a displacement current that triggers an action potential. This so-called neuronal bilayer sonophore (NBLS) model has been validated *in vivo* in mouse primary motor cortex via front limb EMG.[111] Interestingly, membrane bilayer capacitance perturbation has previously been described by Shapiro, *et al.* to describe the mechanism by which IR-induced heating stimulates neurons, and the possibility that mechanical pressure may also be involved in the phenomenon is left for future study.[82] These membrane capacitance mechanisms may

converge to elucidate two diverse stimulation approaches, which could generate a more fundamental understanding of both modalities. Other hypothesized mechanisms rely on mechanical perturbations of the bilayer membrane, such as strain-induced opening on mechanosensitive ion channels[111, 112] and ultrasound-mediated effects that alter membrane conductance due to the viscoelasticity of the neurons[109]. Despite an abundance of hypothesized mechanisms, limited consensus exists and further detailed study of the mechanism of acoustic neuromodulation is needed.

Nanoparticle Transducers

Analogous to transducing optical stimulation *via* metallic nanoparticles, Marino, *et al.* demonstrated the use of ultrasound-stimulated piezoelectric nanoparticles to produce neural activity.[108] While the precise mechanism is not yet clarified, the influence of the piezoelectric barium titanate nanoparticles is not caused by local heating. The presence and absence of the nanoparticles yielded nearly identical temperature increases, but produced significant variation in Ca^{+2} transient amplitude and subsequent neurite outgrowth *in vitro*.[108] As with other modalities coupled to nanoparticle transducers, the targeting, safety, and efficacy of acoustic nanoparticle transducers requires further investigation.

Acoustic neuromodulation presents an intriguing potential avenue for deep, targeted, non-invasive or minimally invasive interface with the nervous system. Early demonstrations of its efficacy for cortical and peripheral modulation can inform further efforts to elucidate the biophysical mechanism of action and ultimately to develop technologies and protocols for potential clinical use.

3.4 Hybrid/Multi-modal

Hybrid approaches combining different modalities also offer a path to novel, non-invasive approaches to neuromodulation. No single modality has yet been demonstrated to meet all the technical requirements to achieve precise, single-axon resolution without trauma and at large scales. By integrating multiple modalities in a single interface technology, engineers can exploit the various physical tradeoffs to improve overall performance of such hybrid neural interfaces. Some examples of hybrid systems include electro-optical hybrids[95, 113-115] and acousto-electric hybrids[116]. As single modality neural interface technologies advance, improvements in performance enabled by hybrid implementations likely will follow.

3.5 Conclusion

Optical, magnetic, and acoustic signal modalities represent exciting opportunities for high spatiotemporal resolution, non-invasive neural interface technologies. As these technologies advance and novel transducers emerge, their appropriateness for clinical application must also be examined thoroughly. Multi-modal approaches offer an appealing engineering solution to overcome fundamental technical challenges hampering any of the single-modality approaches discussed in this paper. With the growing interest in advancing neuromodulation technologies away from solely sensorimotor restoration and towards remedying autonomic disorders, the development of minimally and non-invasive neural interfaces is critical for promoting neurotechnologies to frontline therapies rather than treatments of last resort.

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