

Magneto-Optogenetic Deep-Brain Multimodal Neurostimulation

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Electrical neurostimulation has been used successfully as a technique in both research and clinical contexts for over a century. Despite significant progress, inherent problems remain, hence there has been a drive for novel neurostimulation modalities including ultrasonic, magnetic, and optical, which have the potential to be less invasive, have enhanced biointegration, deeper stimulus penetration from the probe, and higher spatiotemporal resolution. Optogenetics—the optical stimulation of genetically photosensitized neurons, enables highly precise genetic targeting of the stimulus. Specifically, it allows for selective optical excitation and inhibition via different wavelengths. As such, optogenetics has become a prominent tool for neuroscience. Herein, the complementarity between different forms of neurostimulation is explored with a focus on cranial magnetic and optogenetic stimulation. Magnetic stimulation is complementary to optogenetics in that it does not require an electrochemical tissue interface like in the case of electrical stimulation. Furthermore, if incorporated onto the same probe as one with light emitters, its stimulation field can be orthogonal to the light emission field—allowing for complementary stimulus fields. Herein, dual optogenetic and magnetic modalities are proposed that can unite to yield a powerful and versatile tool for neural engineering.

11.6% of the total globally) and the second leading cause of death after heart disease.^[1] With an aging population, degenerative neurological disorders in particular are projected to rise in prevalence globally.^[2] It is forecasted that the global market for neuromodulation will grow from \$5.6bn in 2020 to \$8.8bn, in 2025.^[3] These statistics clearly show the importance of the urgent development of novel treatments to complement and improve on existing treatments options.

Electrical neural stimulation therapy has been used for over 2000 years, the earliest recorded instance of which has been attributed to Scribonius Largus (47AD) who used torpedo fish as the source of electric discharges.^[4] Modern implantable devices became available with the first implantable heart pacemaker in 1958 at the Karolinska Institute, Sweden,^[5] followed by the first sub-cortical brain implant, in 1963, at the Institute of Experimental Medicine, USSR Academy of Medical Sciences.^[6,7]

Deep-brain stimulation—which involves long electrical leads being surgically implanted into the brain—is now a common treatment for conditions such as dystonia, tremors, Parkinson's disease, and epilepsy.^[8]

Figure 1a shows how different forms of neurostimulation can typically be used either to activate a neural signal (action potential) or to inhibit it. An action potential being a depolarization of a cell membrane which cascades across it by ions such as potassium and sodium passing through ion channels. Both activation and inhibition have important clinical uses: activation can be used to restore function to parts of the nervous system that have been damaged by trauma or a degenerative neurological disorder like Parkinson's disease, whereas the inhibition function could suppress, for example, the malfunctioning region of the brain during an epileptic seizure. This control is but one of many parameters of a hypothetical ideal device, which are shown in Figure 1b. It would be low power to prevent device heating and preserve battery life (or ideally wirelessly powered, but maintaining a sufficiently high and controlled level of power is a challenge^[9]), discreet, noninvasive and magnetic resonance imaging (MRI) compatible,^[10] precise, but controllable from a distance. It would not damage tissue, either by heating, photochemical damage, or by charge buildup. It would have neuronal selectivity, and have an effect which can be easily maintained, but also be

1. Introduction

Neurological disorders are the leading cause of disability-adjusted life years (DALYs) lost (276 million per annum and

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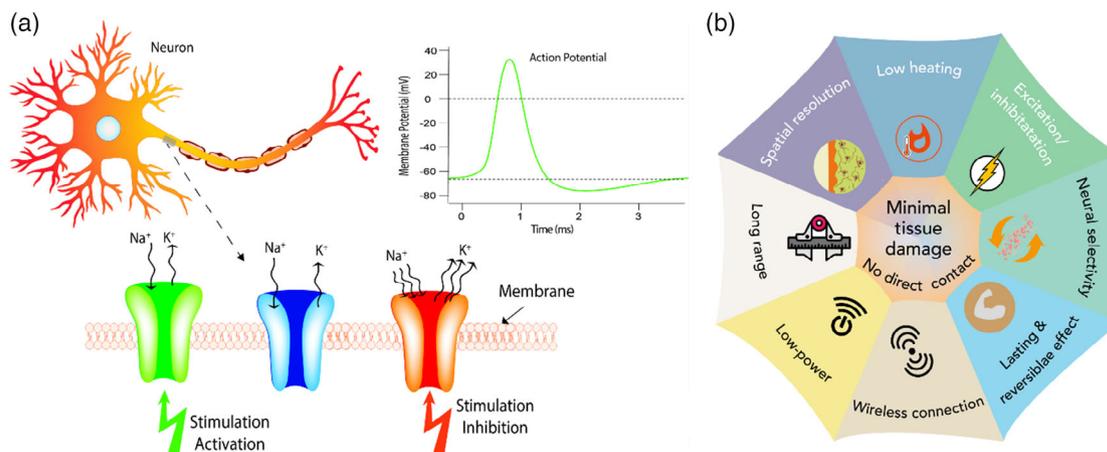


Figure 1. a) Depiction of electrical stimulation at the neuronal level, showing how action potentials can be manipulated by the hyperpolarization of the neuron cell membrane. b) Features of a hypothetical ideal implantable neuromodulation device: wireless power/communication, low-power, long-range, high spatial resolution, low heating, excitation/inhibition control, neuron directional selectivity, and a long-lasting but reversible effect.

completely reversible. Crucially, any implanted components of a device must be made of flexible, biocompatible materials that trigger a minimal immune response.^[9,11] Electrical recording and stimulation have had a venerable evolution as evidenced by technologies such as Neuralink (brain–computer interface)^[12] and Neuropixels (high density neural recording).^[13] However, all-electrical approaches have drawbacks such as the lack of functional control and potential tissue damage due to charge buildup, which sets limits on its neuroprosthetic clinical potential. Therefore, innovative types of other complementary modalities which lead to greater capabilities such as optical, magnetic, acoustic, thermal, and chemical techniques should be explored. In this perspective article, we will discuss these different modalities, with a particular focus on how optical (optogenetic) and magnetic stimulation techniques could work in tandem with electrical recording. We discuss this in terms of the implications to future implantable probes and thus clinical potential.

2. Development of Neurostimulation Techniques: From Macroscale to Nanoscale

2.1. Electrical

Modern developments in microfabrication and electronics have led to the creation of multielectrode probes,^[14] multidimensional Michigan^[15] and Utah arrays,^[16] and meshes,^[17] amongst a plethora of other designs. Devices have been implanted into different parts of the nervous system, including the brain, spinal cord, and peripheral nerves.^[18] Significant advances have been made recently in the miniaturization of and increasing the density of recording electrodes—such as the flexible “thread” electrodes of the Neuralink device^[12] and the high density Neuropixels probe.^[13] This marks a transition from simple macroscale devices to complex, nanofabricated devices with more advanced capabilities.^[19]

In contrast to electrical recording, electrical stimulation of neurons is more complex as the electrodes need to perform a

transient electrochemical exchange with the tissue. As such, to prevent electrolytic degradation, all stimuli need to be balanced. That is, an anodic (positive) pulse with equal integral charge is required to follow a cathodic pulse. This must be achieved in a time frame of the order of milliseconds with a current requirement determined by the volume of tissue to be stimulated.^[20] There is however a further limitation—the charge density limit set by the material.^[21] As stimulus strength/penetration is defined by the pulsed current injection, the density limit effectively presents boundary conditions on the minimum electrode size (which is not the case for recording electrodes operating at low currents). Furthermore, the tissue itself also has a limit in terms of the density of the electrical pulse it can safely receive. This is defined by the Shannon empirical theorem

$$\text{Log}(D) + \text{Log}(Q) \leq k \quad (1)$$

where Q is the charge density ($\mu\text{C cm}^{-2}$ phase), and D is the charge per phase ($\mu\text{C phase}^{-1}$) and $k \approx 1.9$. If this rule is not obeyed, then significant tissue damage can occur.^[22] As such, although electrical stimulation operates very well with pacemaker-class implants, it has significant challenges to scaling toward high density and high power interfaces.

2.2. Optical/Optogenetic Neurostimulation

Early optical stimulation was achieved via high powered lasers. In 1971, Fork demonstrated optical (488 nm) stimulation in the abdominal ganglion of an *Aplysia mollusc*.^[23]

Subsequently optical uncaging of neurotransmitters was used to optochemically stimulate cells. These techniques are still the subject of exploration today. There is ongoing exploration into the mechanism by which infrared (IR) light can stimulate cells, e.g., by Shapiro et al.^[24] Furthermore, there is exploration how IR light and nanoparticles can interact to stimulate cells, e.g., by De Boer et al.^[25] Similarly, optochemical methods are still being developed—albeit with genetic approaches such as that by Donthamsetti et al.^[26] to target photoswitchable ligands to

cellular sub-structures. IR and optochemical approaches both have merit, and with regards neuroprosthetics, IR has some interesting attributes with regards tissue penetration. Nevertheless, the current dominant approach optogenetics, which originated from the work on channelrhodopsin-2 by Nagel et al. in 2003.^[27]

Optogenetics involves the implantation of heterologously expressed opsin proteins into neuronal cell membranes. These opsins—derived from microorganisms are available in three varieties: – 1) light-activated ion channels (e.g., channelrhodopsin ChR2^[27]); 2) light-activated ion pumps (e.g., halorhodopsin NpHR^[28]); and 3) light-activated G-protein pathways (e.g., Melanopsin^[29]).

There are two primary advantages over traditional electrical stimulation. The first is simply that as a different modality, it has reduced potential to interfere with electrical recording. The second advantage relates the genetic method of incorporating such opsins into cells. Genetic methods allow targeting of photosensitivity and thus stimulus to specific cell types, and thus subcircuits of the nervous system. The suite of opsins that are now available gives a lot of flexibility in terms of the mechanism of action, light source required and choice of stimulation/suppression of signals. A common combination is to use ChR2^[27] for neural stimulation and NpHR^[28] for inhibition, as they absorb blue and green/yellow light, respectively, and so can be operated independently in the same system.^[30,31] An alternative to using microbial-derived opsins (rhodopsins) is to using mammalian opsins, which are g-protein coupled receptors (GPCRs) rather than ion channels.^[29] However, GPCRs require a complex amplification which slows down the response rate, typically in the seconds rather than milliseconds for optically activated ion channels.

Optogenetics is now a standard tool in neuroscience for use in animal models but there have been only two clinical trials to date: 1) Retrosense trials number NCT02556736 unpublished; 2)^[32] Using light to activate neurons overcomes some of the drawbacks of using electrical stimulation, with high neuronal specificity and less damage. But, if optogenetics is to become a widely used clinical technique, issues like heating and power consumption must be overcome.

The efficiency of μ LEDs used in some implantable optogenetic devices having been steadily advancing. But, heating remains a concern for optical probes—Owen et al. showed that local heating of as little as 0.2 °C can reduce the action potential generated by optogenetic stimulation in medium spiny neurons via the inward rectification of potassium ion channels.^[33] Dong et al. showed that to achieve sufficient tissue penetration and probe surfaces within the regulatory limits, light emitting diode (LED) efficiencies need to exceed 10%.^[34] As optogenetics is an optical technique, there is also potential for multiphase wavefront shaping approaches.^[35,36] This allows more precise excitation of neurons and reduces light being lost to scattering, which in turn reduces the energy required to drive the LEDs.

2.3. Magnetic

The activation of neurons via magnetism can be carried out transcranially with a powerful magnetic field,^[37] or locally in

an implantable device. The latter was pioneered by the likes of Fried, who have shown that similar effects to that of electrical stimulation can be produced using implantable microcoils.^[38] Using magnetism rather than electrical stimulation offers several advantages. First, the shape of the coil leads to anisotropic shaping of the electric field that accompanies the magnetic field—this brings forward the possibility of selectivity stimulating neurons of a particular orientation, increasing precision.^[39] Second, magnetic stimulation does not require contact with the targeted neurons; magnetic fields pass readily through biological tissues, enabling greater range, as well as reducing the damage to the electrode/coil and tissue due to high amounts of charge. Until recently, designing microcoils that produce sufficient field gradients has been a challenge, but this has been overcome.^[38] In addition, the tight bends in these microcoils have to far higher fields (50 kV m^{-2}) being produced than were expected at first (11 kV m^{-2}), enabling lower device power consumption. These reasons and the comparable power consumption to electrical neurostimulation make magnetic stimulation an obvious choice for precise neurostimulation. Using magnetic fields also lacks some of the specific functions of optogenetics where there is control over stimulation versus inhibition through the type of rhodopsin and light source used; this fact makes combining the techniques multimodally an appealing prospect.

2.4. Thermal

While thermal neuromodulation is constrained by safe temperature levels in the brain, it is possible to carry out cooling for inhibition and heating for neural stimulation. Although the impact of temperature change can be readily witnessed in neurons, the mechanism of action is not entirely understood. Temperature sensing in vivo has yielded encouraging results: an increase of 2 °C causes no tissue damage in one notable example.^[40] IR light may be used both as a tool for stimulation and inhibition of neural activity, through different avenues. Stimulation occurs due to a “spatiotemporal gradient of temperature.”^[41] Water has absorption peaks for IR radiation between 1 and 3 μm , and as such an IR laser can induce “rapid heat transients”^[42] in the cerebrospinal fluid, stimulating nearby neurons to produce action potentials. By contrast, there are a number of possible explanations^[43] for IR neural inhibition, culminating in a reproducible effect termed “heat block.”^[44] Peltier elements, which carry out thermoelectric cooling, have also been shown theoretically to reduce the temperature of brain regions as much as 15 °C.^[45]

2.5. Chemical

Using chemicals—or rather drugs—to affect the function of nervous system is a common technique but comes at the obvious disadvantage of requiring a physical payload of the chemical to be delivered. This is obviously trivial if drugs are taken orally, but using an implanted device comes with challenges. Drugs can carry out a wide variety of highly specific functions, so integrating this into an implantable device is highly desirable. For example, drugs which are targeted at part of the nervous system can be impregnated into polymer implanted, which allow controlled release over time for chronic implantation.^[46]

Implanting a more complex or powered device in part of the nervous system faces greater challenges, not least because of the invasive and expensive surgery required to place an implant in the brain for example.^[47] A hypothetical implant must be small and minimally invasive, and it would be highly beneficial to have control over the rate of release of the chemical. Existing applications include conducting polymers doped with nanoparticles, which can in turn be used as “a drug delivery reservoir,”^[48] and microfluidic electrodes with a maximum flow rate of $2 \mu\text{L min}^{-1}$.^[49] At the larger scale, payloads may be delivered via catheter into the deep brain.^[50] As we will see in the section on multimodal techniques, several techniques have been used to externally control this release, to avoid having to implant a bulkier device.

2.6. Acoustic (Ultrasonic)

Schaette et al. managed to reduce perceived loudness of noise in subjects with tinnitus, when the auditory nerves of subjects were stimulated acoustically.^[51] Other acoustic neurostimulation methods such as focused ultrasound (FUS) are promising and noninvasive. For example, Yoo and coworkers showed that function in targeted regions of a rat brain could be both stimulated and suppressed using FUS.^[52] While exciting, this technique is still very limited in terms of its precision, which is superior in magnetic, optical, and electrical methods. It could significantly benefit from being combined multimodally with an implantable device and a technique that is either more spatially precise, or more specific functionally.

Table 1 shows how aforementioned typical neurostimulation modalities (electrical, optical, magnetic, thermal, chemical, and acoustic) measure up to the key parameters of a hypothetical ideal device.

3. Multimodal Neurostimulation

It is worth clarifying some terminology used in this perspective: cross-modal refers to a transduction of energy from an external source, e.g., FUS to an internal stimulator, whereas multimodal is interpreted to mean two modalities that operate as stimulators independently or together on the same device. Several attempts have been made to combine the modalities discussed in the previous section to make use of the individual benefits each technique and overcome some of their limitations. These are shown in Figure 1b.

3.1. Acoustochemical

In chemical-based implants, the lack of control over the rate of chemical release can be solved by a deeply penetrating but minimally damaging remote control technology such as ultrasound. Shapiro and coworkers used acoustically targeted chemogenetics (ATACs), for example, where FUS is used like a precise surgical tool to enable the implantation of a designer–receptor exclusively activated by a designer drug (DREADD) through a specific location on the blood brain barrier.^[53] The DREADDs can then be activated weeks later using the chemogenetic drug clozapine-*n*-oxide. The technique impressively eliminates the need for

surgery and can be used to target specific cell types but lacks versatility and requires an abdominal injection of the drug for every stimulation run.

3.2. Acousto-Optical

External FUS has also been used to trigger optical emission from mechanoluminescent nanoparticles, named Sono-optogenetics.^[54] Hong and coworkers make use of the blood circulatory system to deliver mechanoluminescent nanoparticles which are externally recharged optically via surface vasculature but can also access deep into the brain. Once triggered, the nanoparticles emit blue light which can then activate optogenetic rhodopsins in the brain. The technique is complex but manages to overcome the drawback of implantation while retaining the functional specificity and control of optogenetics.

3.3. Chemomagnetic

Roa et al. have developed when they term “chemomagnetic modulation” which involves heating magnetic nanoparticles using an external field, which triggers the release of chemical from heat-sensitive vesicles.^[55] The method reduces the need for invasive and spatially imprecise injection via cannulae and infusion pumps. The chemomagnetic approach combines the specificity of function of the vesicle-enclosed chemicals, with the control of the external field and lack of need for an invasive implanted device. It does of course, come with the limitation of requiring a large magnetic field to function, but is nevertheless an exciting technique for the future.

3.4. Electrical—Optogenetic

LeChasseur et al. designed a multimodal microprobe that features fiber-optic based optical stimulation as well as electrophysiological recording.^[56] The fine $10 \mu\text{m}$ tip of the probe enabled single-neuron resolution, and the electrical recording was complemented by parallel optical Ca^{2+} recordings. The success of their device highlights the fact that electrical recording can be carried out passively, so it does not carry the potential for tissue damage that electrical stimulation does. Lugo et al. attempted to eliminate the need for genetic methods for optical stimulation by introducing quantum dots in an *in vitro* experiment.^[57] The mechanism they describe involves an electric dipole being generated on optical excitation, which is enough to cause hyperpolarization and depolarization of the neuronal cell membranes. Eliminating the need for genetic-modified organisms or vector-delivered RNA for rhodopsin expression significantly reduces the complexity of the technique, but it is hard to see how quantum dots made of toxic materials such as cadmium telluride could ever be used clinically. Rather than merging optical and electrical methods, the techniques are used in parallel on the same device.

3.5. Magnetothermal

Magnetic stimulation can be enhanced using other methods, such as what has been termed magnetogenetics. Nimpf and

Table 1. Limitations and complementarities of typical neurostimulation modalities.

References	Modality	Threshold power	Wireless potential	Tissue damage	Neuronal selectivity	Excitation/inhibition control	Direct contact	Lasting and reversible	Spatial resolution
[14]	Electrical	–	No	–	–	–	Yes	–	100 μm spacing between each electrode
[15]	Electrical	–	No	Single-unit spike activity	No significant tissue reaction, normal tissue between shanks	–	Yes	–	–
[16]	Electrical	–	No	Small populations of neurons	–	–	Yes	–	30–70 μm
[17]	Electrical	–	No	–	None	–	Yes	–	20 μm electrode spacing
[18]	Electrical	–	No	–	–	Stimulation	Yes	Pain relief extends up to 7 h	–
[13]	Electrical	–	No	Single-unit spike activity	–	–	Yes	–	15 μm centre-to-centre spacing
[74]	Electrical	20–100 nC phase ⁻¹	No	Highly localized areas of the cerebral cortex	Cellular encapsulation, presence of microglia	Stimulation	Yes	–	–
[75]	Electrical	5 mA, 1 V stimulation	No	–	–	Stimulation	Yes	–	Radius of activation of 100–200 μm
[76]	Optical/optogenetic	6.5 mW	No	–	–	Excitation	No	–	4–5 μm
[77]	Optical/optogenetic	0.9 J cm ⁻²	No	–	–	Excitation	No	–	–
[78]	Optical/optogenetic	>290 mW	No	Multiple number of selected neurons	None	Excitation	No	Low intensity long duration irradiation produces sustained depolarization, reversible	–
[29]	Optical/optogenetic	3 mW mm ⁻²	No	Targets GABAergic medium spiny neurons	–	Excitation	No	–	200 μm diameter optical fibre
[33]	Optical/optogenetic	3–15 mW	No	Medium spiny neurons	–	Both	No	Reversible	–
[39]	Magnetic	3.1 mW	–	Single neuron	Joule heating from coil	–	No	–	–
[79]	Magnetic	6.6 \times 109 A m ⁻²	–	–	–	Excitation	No	Spikes are invoked until 0.2 s after input	300 μm away from cell
[41]	Thermal	2.8–13.4 mW	No	Neurons in the vicinity of the irradiated regions	–	Both	No (“water as chromophore”)	Reversible	–
[45]	Thermal	200–400 mA	Yes	–	Damage above threshold 30–43°	Inhibition	No	–	–
[50]	Chemical	–	–	–	Possible protein deposition or local vasogenic edema	–	Yes	Lasts up to years and chemical effects wear off	–

Table 1. Continued.

References	Modality	Threshold power	Wireless potential	Tissue damage	Neuronal selectivity	Excitation/inhibition control	Direct contact	Lasting and reversible	Spatial resolution
[80]	Chemical	–	–	Retinal ganglion cells		Both	Yes	–	Spikes limited to 200 × 200 μm area
[52]	Acoustic	9.5 W cm ⁻² maximum acoustic intensity	–	Small tissue region	Max T rise 0.7 °C, BBB ^{a)} not disrupted	Both	No	Reversible	Acoustic focus 2.3 mm in diameter and 5.5 mm in length

^{a)}Blood–brain barrier.

Keays detailed two key magnetogenetic enhancement techniques: magneto-thermogenetics and force/torque methods.^[58] Magneto-thermogenetics involves the targeted implantation of magnetic nanoparticles like MnFe₂O₄ which generate heat when being excited by a magnetic field. Huang and coworkers showed that action potentials can be generated using this method in vitro, where the heating of the nanoparticles led to the opening of heterologously expressed thermosensitive TRPV1 ion channels. Like optogenetics, this method requires the expression of light-sensitive ion channels (or other types of rhodopsin) that are not native to the host organism. It should also be noted that this effect is thermal, although it is driven by a magnetic field. Force/torque methods involve implanting mechanoselective ion channels which are then coupled to nanoparticles that heat in response to a magnetic field. For example, Wheeler et al. showed that action potentials could be generated by implanting TRPV4 ion channels as well as the paramagnetic iron-conjugated protein ferritin, exciting them with a magnetic field.^[59] The mechanistic interpretation of these techniques has faced criticism—Markus Meister argued using an analytical approach that the magnetic fields could not produce the heating or motion that is seen experimentally.^[60]

3.6. Optical–Thermal

As was mentioned in the previous section, neural signals can be suppressed by local heating of neurons, intentionally or otherwise. Carvalho-de-Souza et al. opted for triggering the heating of implanted functionalized gold nanoparticles by exciting surface plasmons using green light.^[61] The technique shows excellent promise as an inorganic, thermal alternative to optogenetics but suffers from problems. Clustering of nanoparticles leads to changes in optical properties, and the authors report (despite some success, it should be acknowledged) damage to cell membranes, including “abnormal and persistent depolarization.” Remotely powered and triggered thermal neurostimulation remains an area with great potential.

3.7. Magneto-Optical

A multimodality that is yet to be explored in depth is magneto-optical stimulation. One exception to this statement is the magneto-luminescence microdevice (MLMD) of Chang and coworkers, where an external rotating magnetic field is used to drive the

rotation of a bar magnet, which excites mechanoluminescent nanoparticles.^[62] Of the main drawbacks of the fully implanted optogenetics approach is heating, which despite advances in the efficiency of μLEDs, remains a challenge. Although larger-scale blue LEDs for example can reach power conversion efficiencies of above 80%,^[63] multiple quantum well III-V μLEDs are reported to suffer from a drop in peak external quantum efficiency (EQE) with decreasing size.^[64] To the contrary however, the same data from Dawson and coworkers shows that for a current density $J > 10^2$ A cm⁻², smaller μLEDs have higher EQE. There is also a trend of better light emission efficiency with decreasing size, as well the lack of “thermal droop” that causes a drop in optical power density larger μLEDs which are run at higher current densities.^[65] There is certainly scope for an

Table 2. Summary of the discussed multimodal techniques, what benefits combining the techniques has brought, and what the remaining challenges are.

Multimodality	Benefits	Remaining issues
Acoustochemical	+Control +functional specificity	Physical payload
Acousto-optical	+Fully implantable +functional specificity +control	Complex
Chemomagnetic	+Functional specificity +noninvasive	Precision Cost External magnetic field Tissue Damage
Electro-optogenetic	+Neural activation/suppression	Possible toxic materials in body
Magneto-thermal	+Specificity +range +control +Noninvasive	Precision Cost External magnetic Tissue damage Temperamental
Optothermal	+Range, +control, +specificity	Heating tissue damage
Magneto-optogenetic	+Specificity, +control, +range, +orthogonality, +activation/suppression	Heating tissue damage

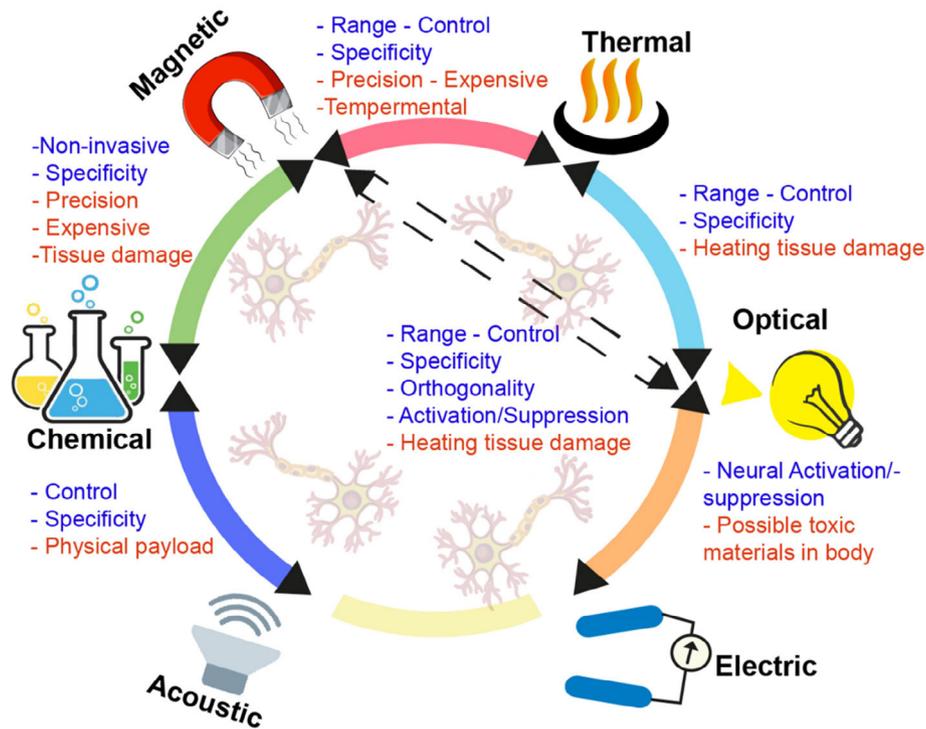


Figure 2. Infographic depicting the main neurostimulation modalities, with colored arrows depicting how they have been combined multimodally. The blue and red text details the benefits and remaining issues with the combined techniques as they stand.

optimization of device parameters than would allow significant miniaturization. A complementary approach to address the heating issue would be to use magnetic microcoils to effectively drop the activation threshold required—this could significantly mitigate any heating issues. Similarly, the control provided by the choice of rhodopsin and μ LED combination in optogenetics improves the comparative lack of control in magnetic stimulation. The remaining obvious downside of combining these techniques is power consumption—both techniques are already power-heavy when stand-alone in comparison with electrode-based devices, which limits their suitability as fully implantable devices. To get around this issue, novel approaches must be taken for efficient and miniaturized wireless power transfer, for example using magnetoelectric antennae and metamaterial-based transmitters.^[66]

The benefits and remaining issues with the multimodal techniques that we have covered are shown in **Table 2**. We propose that by grafting these established forms of neurostimulation into one nanofabricated multimodal device, the limitations of each can be overcome and benefits retained, potentially leading to a paradigm shift in modulation of neural signals, as shown graphically in **Figure 2**.

4. Future Perspective

Neurostimulation is a fast-paced field of research with enormous clinical and scientific potential, but challenges remain, which have been outlined in this perspective. Despite the extensive advances in electrical stimulation technology, the problem of

damage, inflammation and infection due to direct contact with stimulation electrodes will not go away. In contrast, recording electrodes do not tend to suffer from these problems as they operate at much lower currents. Thus, there is an urgent need to look to alternative techniques, whose limitations have the potential to be overcome. Multimodal approaches involving chemicals boast highly specific biochemical functionality but come with the distinct disadvantage of having a physical payload. Prominent examples of these techniques that have been covered here, affect remote triggering of the release of the chemicals either acoustically or magnetically. At the same time, while this makes the method less invasive, it then requires large external power-hungry pieces of equipment, limiting precision, and versatility. The magnetothermal approaches also require a sizable external coil to generate the field but can be made more precise with the implantation and/or genetic modification. This increases the complexity of the technique however, and any method that relies on heating as the mechanism of action comes with the apparent danger of tissue damage. Minimizing the possibility of heating may be a sensible choice. The field of optogenetics is moving forward rapidly, both in terms of device design, and the suite of rhodopsins that are becoming available commercially. These novel rhodopsins are increasingly diverse in terms of mechanism,^[67,68] have longer lasting effects,^[68] and have lower activation thresholds.^[68] Optogenetic methods have diverse functional control but have relatively high power consumption and heat from the LEDs could at worst damage tissue and best convolute the effect of the optical stimulation itself, preventing the acquisition of high-quality experimental data. The light also

has limited range, making the technique precise, but areas of the brain that require study or treatment may be more significant. Magnetism tends to be employed as an external trigger of another technique but can be used for bulk neurostimulation by itself. Recent developments in microcoil fabrication present opportunities, but high-power consumption and heating remain pressing issues. In the past, magnetic stimulation had been used as a transcranial technology for the treatment of neural disorders and the current density or magnetic flux density was used as an essential indicator to measure whether the large target tissue was activated.^[69,70] However, low spatial resolution and the selectivity of target neurons remain significant challenges. The mechanism of magnetic stimulation was also not very clear, limiting the progress of the technique. In 2011, Pashut et al. showed that the activation of a neuron is associated with the sign, magnitude, and stimulation time of the spatial derivative of the induced electric field along the axis of the axon using NEURON software.^[71] This understanding is important for improving the spatial resolution of magnetic neurostimulation and the selectivity of target neurons. Recently, Lee and Sun's work showed that advances in the design of implantable microcoils driven by low drive currents and high frequencies can induce a high spatial derivative of an electric field.^[72,73] Moreover, they fabricated different shapes of the coil to enhance the spatial derivative of the electric fields along the y -axis (dE_y/dy) instead of the x -axis (dE_x/dx) so that horizontally oriented axons from neighboring nerve cells would not be activated.^[72,73] However, a lot of challenges need to be explored such as what the optimal stimulation scheme is, optimal waveform, and the efficiency of the coil.

These developments have spurred interest in this topic—mainly how to realize reliable and effective magnetic stimulation such as the efficiency of the coil, the reliable frequency of activation and the penetration of magnetic stimulation. Magnetic and optical modalities have the advantage of not requiring direct contact, so they can be encapsulated in biocompatible materials that which cause minimal disruption to the fields, or even help shape the optical/magnetic fields. Combining the two techniques multimodally overcomes the control issue of magnetic stimulation and the range issue of optical stimulation. We put forward the hypothesis that the strong field gradients generated by state-of-the-art low-power magnetic microcoils will result in a reduced optogenetic activation threshold. Combined with the latest low activation threshold rhodopsins,^[67,68] we surmise that the heating issues which continue to plague fully implanted magnetic and optogenetic systems have the potential to be significantly mitigated. Considering the arguments that we have put forward here, a multimodal approach that combines magnetism and optogenetics seems to be an approach which has significant potential for advancing neurostimulation.

5. Conclusion

A broad range of techniques have been applied over the years for neuromodulation, with multimodal approaches being used to overcome some of the limitations of the standalone techniques. A number of these innovative approaches have been summarized with their benefits and drawbacks. There is clearly still scope for improvement, not least because most of these

technologies remain academic, with few being used for neuroscience, let alone for clinical deployment. Many of the techniques remain expensive, have heating and tissue damage issues, draw high currents, are not fully implantable and are limited in terms of their precision, cellular specificity, and functional specificity. We surmise that combining the magnetic and optogenetic approaches has strong potential to mitigate these issues and move neuromodulation forward in the quest to understand the brain and neurological disorders.

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Conflict of Interest

The authors declare no conflict of interest.

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