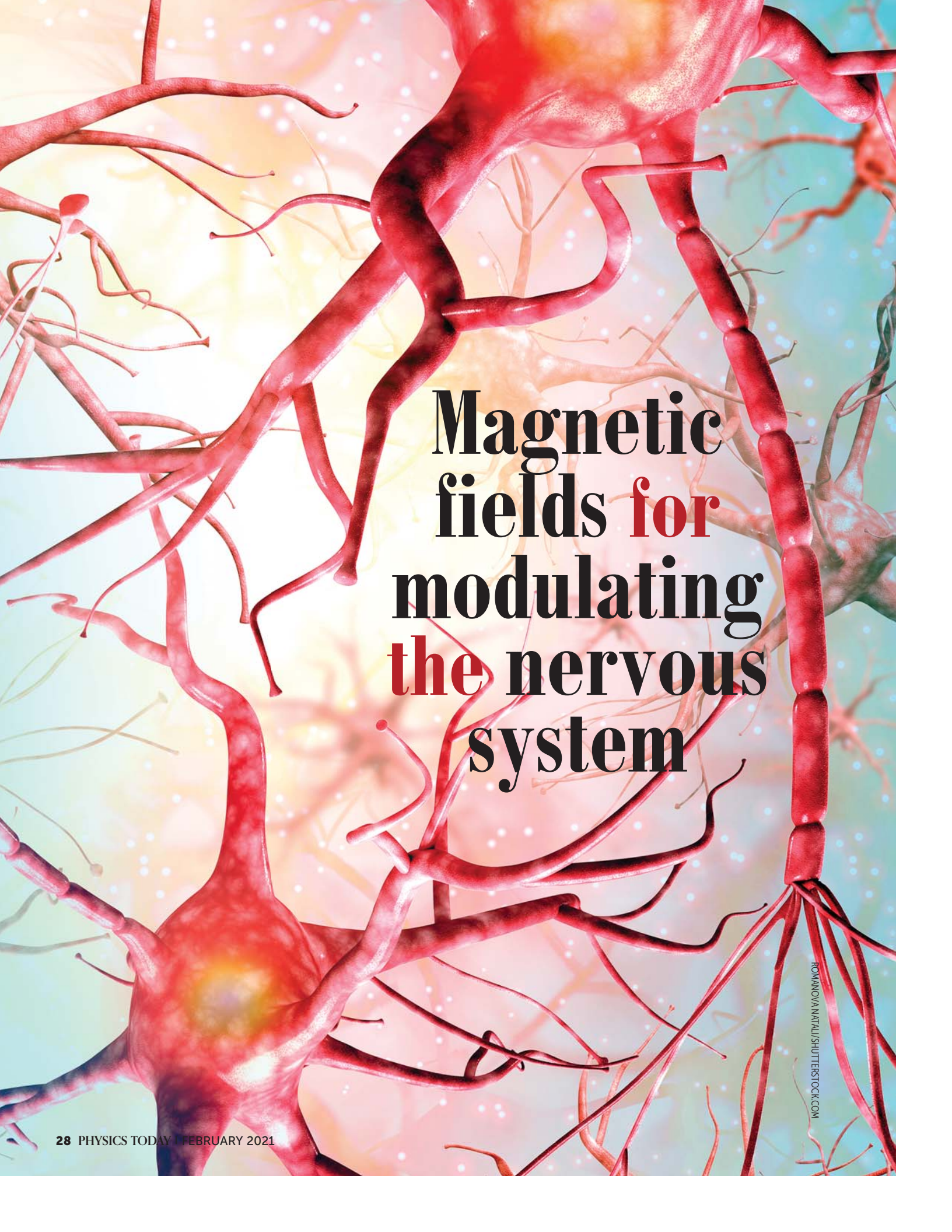




Magnetic fields **for** modulating **the** nervous system

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Although targeted actuation of neurons via magnetic fields may benefit neuroscience research and medicine, some approaches have sparked controversy.

Neuroscience research has grown rapidly in recent years, driven at least in part by the emergence of tools and techniques that enable scientists to pose experimental questions that not long ago would have been unanswerable. Methods for triggering activity in the nervous systems of living animal models have proven particularly useful for mapping networks, probing structure–function relationships, and connecting physiology to behavior. In addition, therapeutically controlling the activity of neurons in patients can offer relief from some diseases. For example, an approach that clinicians use to stimulate neurons deep in the brain to treat Parkinson’s disease has also shown promise for addressing persistent psychiatric disorders such as depression.

Technologies for stimulating neurons are poised to become increasingly significant, yet the presently employed methods have serious drawbacks. As is so often the case for biomedical technology, today’s innovations will appear primitive in the not-too-distant future. Currently, clinical deep-brain stimulation is conducted primarily by inserting millimeter-sized electrodes that are powered by devices implanted in the body. Although effective at offering relief for patients, such drastic measures are justifiable in only extreme cases. Technology for more commonplace neuron stimulation, whether for experiments in model organisms or clinical therapy in humans, should be noninvasive or minimally invasive, wireless, able to access regions deep in the brain, spatially targeted, and selective to particular cell types.

That vision has attracted numerous engineers and scientists to independently focus on developing devices and methods for coupling noninvasive stimuli—including ultrasound, near-

IR light, and time-varying electric fields—to the activity of neurons. Magnetic stimuli are especially appealing because of tissue’s weak magnetic properties and low conductivity, both of which ensure that magnetic fields can reach deep physiological targets undiminished.

Additionally, magnetic stimuli form a vast possibility space, as indicated in figure 1. Quasi-magnetostatic fields at the human scale can rotate, pulse, or oscillate with characteristic frequencies ranging from millihertz to megahertz. Spatially, the fields can be uniform, possess gradients, or exhibit points of vanishing magnitude. Any of those features or some combination

of them facilitates strikingly different approaches for actuation. The practical considerations for generating magnetic fields with those properties and the limits of feasible scalability can also vary profoundly.

Researchers have pursued the facile control of neurons via magnetic fields with such eagerness that soon afterward some of their claims have faced criticism, much of it framed in terms of the physical plausibility of the proposed mechanisms. Rather than avoid topics that have produced controversy, here we will consider their most discerning critiques.

The dream of magnetogenetics

Neurons propagate electrochemical signals by using voltage-gated biochemical machinery in their membranes. At the level of a single cell, a stimulus that depolarizes a small part of the membrane can cause an action potential that spreads throughout the cell. Some channel proteins function by locally increasing

or decreasing the membrane's polarization in response to a particular physical stimulus. Introducing genes that code for those channel proteins thus offers a way to program neurons to be inhibited or excited on demand.

In neuroscience, a broadly successful technique termed optogenetics has taken precisely that approach with visible light.¹ Typically, the necessary genes are introduced to neurons in a selected site or cell type of interest in an experimental organism, and optical fibers or light-emitting devices deliver light for stimulation. Could a similar magneto-genetic approach—one that employs biogenic magnetic materials and externally applied magnetic fields—be possible? If it were, the technique would eliminate the need for setups with tethers and visibly detectable stimuli, but it would leverage many of the same prolific methodologies that have made optogenetics so successful.

Although a magnetic variant of optogenetics appeals to many researchers in the field, a direct analogy fails to acknowledge some underlying physical restrictions. The key difference, illustrated in figure 2, is the energy scales expected for the different stimuli (see the article by Rob Phillips and Steve Quake, *PHYSICS TODAY*, May 2006, page 38). A photon of visible light carries enough energy to change the configuration or electronic state of a protein, as illuminated by examples ranging from fluorescent proteins to the opsins in our retinas that enable us to see. In contrast, realistic magnetic fields interacting with biomolecules or small biomineralized particles generate predicted energies of interaction that are far below the scale of background thermal fluctuations. That outcome is perhaps unsurprising when one recalls that the underlying motivation for using magnetic fields as stimuli is their ability to access deep physiological targets without appreciably interacting with tissue.

Reports of magnetogenetic techniques for neurons first appeared in prominent journals² in 2016. A common theme of the initial approaches was to modify the genetic blueprints for known channel proteins so that they also incorporated ferritin, an iron-storage protein. The authors then suggested, on the basis of known mechanical and temperature sensitivities of the unmodified channel proteins, that either heat flow in response to time-varying fields or magnetically mediated mechanical stimuli could trigger the channel to open and locally depolarize the neuronal membrane. Regardless of the suggested mechanisms, the studies presented numerous careful experimental controls that seemed to consistently suggest the existence of a real and reproducible effect.

However, those early studies of magnetogenetics soon drew criticism because they focused almost exclusively on demonstration and only loosely explained the possible basis for the observed effects.³ The core argument was that simplified physical models of ferritin ought to place realistic bounds on the expected energy of interaction with attainable magnetic fields. Without any need for heroic mathematics, the scale of those energies can be compellingly shown to be orders of magnitude

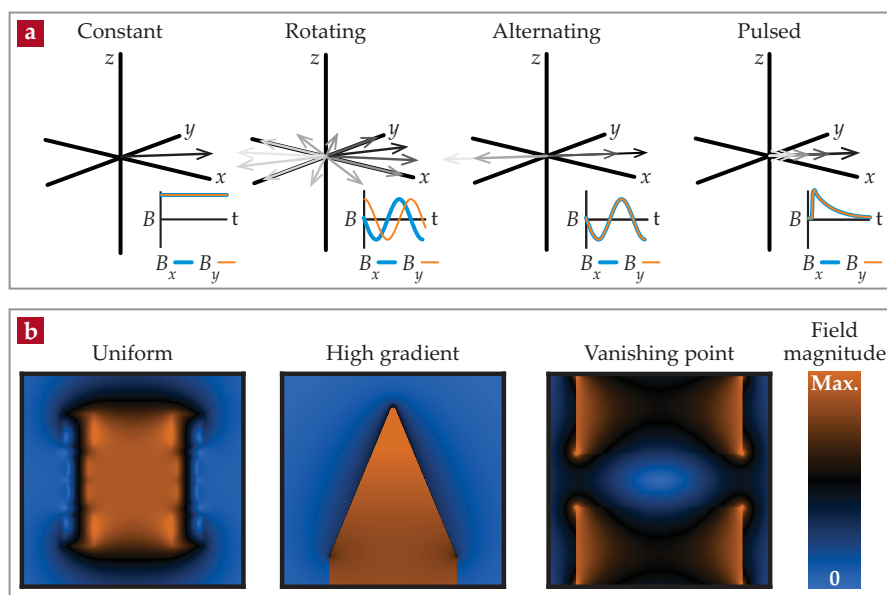


FIGURE 1. MAGNETIC FIELDS offer a large and diverse parameter space for engineering magnetic stimuli. **(a)** In addition to familiar temporally constant fields, quasi-magnetostatic fields can rotate, alternate, and pulse. **(b)** Distributions of field strength, such as uniformity, high gradients, and vanishing points, also offer various functionalities. The relative magnetic field magnitude is plotted for radial cross sections of several geometries with cylindrical symmetry: (from left) a Lee–Whiting coil, a conical permanent magnet, and two disk magnets with opposing magnetization. (Figure by Michael G. Christiansen; field plots created using FEMM software.)

too weak to actuate membrane proteins in the manner envisioned. Several independent research groups subsequently reported an inability to demonstrate similar magnetogenetic effects in their own laboratories, although a failure to replicate is not necessarily conclusive. The authors of the original works have since pointed out ways in which the replication attempts may have differed from their original experiments.

A conceptual rebuttal to the biophysical argument against ferritin-mediated magnetogenetics has been that the magnetic moment of ferritin may be about 75 times larger than expected, which would allow for an assortment of hypothetical actuation mechanisms.⁴ Such a large magnetic moment would be surprising given the extensive body of literature characterizing ferritin, although a fresh investigation may be warranted. Even if anomalously enhanced magnetic properties could be definitively ruled out by experiment, asserting the impossibility of magnetogenetics may be overly reductionist.

A feeble magnetic moment for ferritin at most precludes the possibility of direct actuation. Some of the relevant magnetic stimuli produce off-target effects, including induced voltages and mild nonselective heating. In principle, a modified channel protein that lowers the threshold of response to those influences by any means, magnetic or otherwise, might lead to selective actuation effects. An indirect mechanism of that sort might help explain experimental observations, although a strategy that depends on many external factors is likely to face difficulties in replication or routine use.

Recent experimental work has indicated a possible chemical pathway for actuation that involves iron released from ferritin.⁵

However, the way that magnetic fields alternating at kilohertz or megahertz frequencies might trigger ion release remains unanswered. Other experiments that used modified channel proteins suggest that extinguishing temperature sensitivity eliminates magnetic response and that having a magnetocaloric cooling effect may trigger a related channel sensitivity to cold rather than heat.⁶

An encouraging feature of recent efforts is a renewed focus on probing and explaining mechanisms. Nevertheless, one of the significant difficulties in making comparisons and drawing conclusions in the magnetogenetics literature is the sheer variety of magnetic stimuli, which allows every group to adopt its own seemingly unique stimulation paradigm. The situation is especially evident in the remarkable contrast between the magnetic conditions employed in the most recent experiments, ranging from 12 μT fields varying at 180 MHz to 250 mT fields varying at 800 MHz.

Yet another route to magnetogenetics that researchers have suggested draws inspiration from nature. Numerous organisms exhibit what's known as magnetoreception—the ability to sense Earth's comparatively weak 50 μT magnetic field, usually as a cue for migratory navigation (see the article by Sönke Johnsen and Ken Lohmann, *PHYSICS TODAY*, March 2008, page 29). Specialized magnetic receptor cells, similar to sensory systems that detect light or sound, have been hypothesized to exist. If such cells were unambiguously identified and thoroughly studied, perhaps their mechanism of sensation could be replicated through genetic modification. But that remains a remote possibility considering that decades of vigorous research and debate have yet to produce satisfactory explanations for natural magnetoreception.⁷

Mediation by magnetic materials

Another widespread category of techniques for magnetic stimulation of neurons employs synthetic nanomaterials. Usually introduced by direct injection, the materials offer an energetically plausible means of coupling an externally applied magnetic field to well-understood forms of stimulation. Whereas clusters of noninteracting atoms are expected to exhibit modest magnetic moments at best, collective ferro- or ferrimagnetic ordering mediated by exchange or superexchange interactions can lead to magnetic moments that are many orders of magnitude larger.

For magnetized particles smaller than a critical size range that depends on composition and geometry, opposing magnetic domains do not form, and the structures are approximately uniformly magnetized. The presence of magnetic order does not necessarily imply that the orientation of the magnetization remains constant. Rather, the magnetization orientation can rapidly precess and jump stochastically among certain preferred directions. Under conditions at which the rate of the stochastic jumps is much faster than the time scale of measurement, magnetic particles are said to be superparamagnetic.

Examples of magnetic nanoparticles do occur in nature, most famously in bacteria that employ chains of magnetite or greigite particles for coordinating their movement along magnetic field lines (see the article by David Dunlop, *PHYSICS TODAY*, June 2012, page 31). However, for neurostimulation methods based on magnetic nanoparticles, researchers typically prefer synthetic materials that can be produced in large quantities with tailorable surface chemistries. Because of their biocompatibility,

ferrites are common, especially maghemite, magnetite, and similar compounds doped with neighboring transition metal elements, such as manganese, cobalt, and nickel. Many approaches have been reported, so researchers find it helpful to classify them by the ways they transduce magnetic fields to detectable stimuli. Those categories, which are summarized in figure 3, include the production of forces or torques, magneto-electric coupling, actuation via dissipated heat, and triggered release of chemical agonists.

Sensory neurons in the peripheral nervous system contain channel proteins that respond to membrane tension or other mechanical cues to produce the sensation of touch. Combining magnetic and mechanical actuation is therefore a natural and intuitive idea. An extensive body of literature exists that addresses biological effects produced *in vitro* with magnetically applied forces, including examples of neural stimulation. But those methods typically require high field gradients, on the order of $10\text{--}10^3\text{ T/m}$, which prohibits scaling them to most *in vivo* contexts.

In contrast, mechanotransduction via torques generated by rotating or alternating uniform fields is a comparably scalable strategy. Particles suitable for applying torques must possess sufficiently large moments and anisotropy that links their physical orientation to their magnetization. For single-domain nanoparticles, large moments and high anisotropy tend to

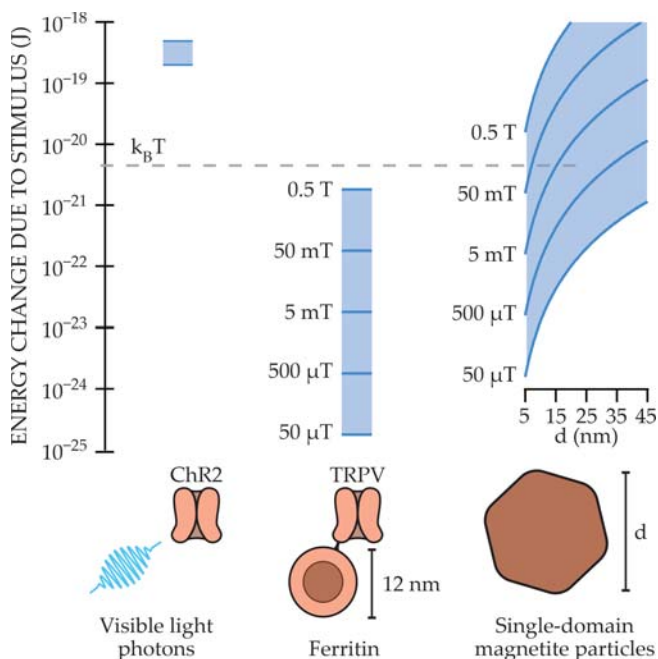


FIGURE 2. VARIOUS STIMULI can be used by researchers to affect the activity of neurons. Comparing the energy scales of the stimuli helps illustrate the fundamental challenge of using the genetically expressed protein ferritin and magnetic fields to stimulate neurons. Proteins such as ChR2 that respond to visible light (left) interact with photons that have an energy much higher than background thermal fluctuations $k_B T$, whereas the magnetic core of ferritin, attached to the channel protein TRPV (center), interacts only very weakly with magnetic fields. In contrast, single-domain synthetic magnetic particles made of magnetite (right), for example, have higher energies of interaction that also increase with particle size. (Figure by Michael G. Christiansen.)

increase the likelihood of aggregation and settling, but one potential work-around employs pseudo-single-domain nanostructures such as nanoscale disks. They exhibit intermediate vortex states between uniform magnetization and multiple domains, which, in the absence of an applied field, reduces the net magnetic moment and particle interactions.

Whereas mechanotransduction requires genes for introducing mechanically sensitive channel proteins into neurons that don't intrinsically express them, all neurons that propagate action potentials possess voltage-gated ion channels and respond to electric fields. Accordingly, researchers have suggested using nanoparticles with magnetoelectric properties to enable magnetic stimulation without requiring genetic manipulation. Magnetoelectric materials change their electric polarization in response to an applied magnetic field, and the strongest effects are seen in composite structures. They function by using strain fields to go between magnetic and electric properties: A magnetostrictive material, in which magnetization influences strain, is joined to a piezoelectric material, in which strain affects electrical polarization.

One reported use of magnetoelectric core-shell structures for stimulating brain activity in mice employed barium titanate as the piezoelectric shell and CoFe_2O_4 as the magnetostrictive core.⁸ Given that appreciable magnetostrictive properties typically require materials with high anisotropy, as is the case for CoFe_2O_4 , the low-frequency (0–20 Hz) magnetic stimulation in that work seems more likely to produce physical rotation rather than truly magnetoelectric effects. Additional study of nanoscale magnetoelectric composite materials with other magnetic stimulation paradigms may be warranted. Alternatively, researchers have recently investigated the use of magnetoelectric composites on a larger scale and saw promising results.⁹

In addition to containing voltage-sensitive channel proteins, many neurons have heat-sensitive ones. Magnetically, heat can originate from a hysteresis effect as the nanoparticles respond to alternating magnetic fields with frequencies ranging from kilohertz to low megahertz and amplitudes typically not exceeding 100 mT. The maximum permissible amplitude varies with frequency and is constrained by the need to limit off-target heating of tissue via weak eddy currents. Heat dissipation by magnetic nanomaterials is most familiar in the context of magnetic hyperthermia as a potential therapy for cancer, but the neuron-stimulation strategies discussed above avoid triggering cell death and have shifted the research focus toward wireless actuation of cellular activity. Wireless actuation is conceivable if a local temperature increase is sufficient to trigger a targeted, possibly genetically introduced, thermally responsive channel protein. But that temperature increase can't be high enough to cause cell damage.

In 2010 the first scheme for stimulating neurons with heat used low concentrations of magnetic nanoparticles bound to cellular membranes.¹⁰ The researchers employed a fluorescent dye as a thermal probe to show a change in temperature of several degrees Celsius at the surface of the nanoparticles. Since then, others have debated whether a localized temperature increase at the membrane is possible without surrounding bulk

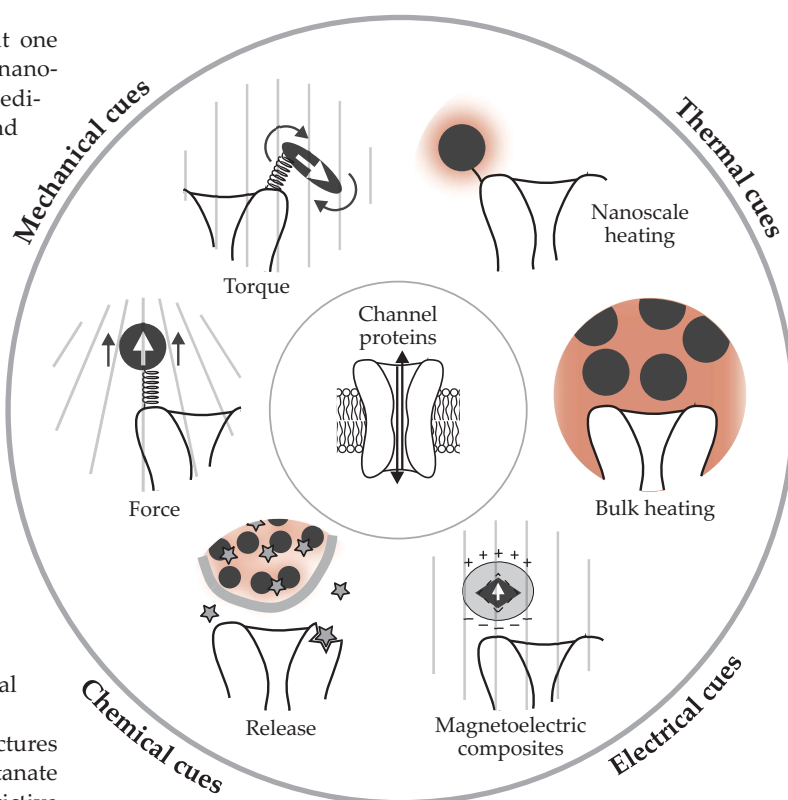


FIGURE 3. SYNTHETIC MAGNETIC NANOMATERIALS can couple to channel proteins, which respond to many types of stimuli, including heat, mechanical strain, electric fields, and chemical interactions. In response, the channels often open and allow the passage of ions, such as Ca^{2+} or Na^+ . That ion movement then triggers action potentials in neurons. (Adapted from ref. 18 by Michael G. Christiansen.)

heating. The standard heat-transfer equations suggest that the temperature difference between the surface of the nanoparticles and the solution should be more than a million times smaller than some experiments have suggested.

An intriguing clue to explain the discrepancy came nearly a decade later from a study that replicated a comparable methodology.¹¹ Rather than interpreting similar observations as an increase in surface temperature, the researchers suggested two types of experimental artifacts that may account for the original observation. Their findings and other recent negative results raise questions about the existence of nanoscale heating in similar systems. Nevertheless, heat-transfer effects peculiar to the nanoscale are studied extensively in solid systems and considered in terms of the transport of quantized phonon modes rather than classical heat flow. Moreover, various nanoparticle systems suspended in solution compellingly demonstrate carefully controlled heating effects and offer researchers an opportunity to reexamine physical models of nanoscale heat transport at crystalline-disordered interfaces.

Even without relying on nanoscale heating effects, heat can still stimulate targeted neurons. The classical heat-transport equations allow for bulk heating of concentrated ferrofluid droplets to stimulate neurons sensitized to increased temperature, an effect that has been demonstrated experimentally.¹² One recent paper suggested an extension of those methods

based on bulk-heating effects: Known as magnetothermal multiplexing, the approach heats adjacent ferrofluid droplets independently by pairing different types of magnetic nanomaterials with alternating magnetic field conditions that ensure selective heating.¹³

Another method readily extendable to chemical stimuli targeted at particular channel proteins is the magnetically triggered release of chemical payloads from nanoscale carriers. The concept was originally explored primarily for drug delivery and diagnostics. Available carriers include nanoparticle surfaces, thermally sensitive liposomes, and degradable polymer composites. In one instance, researchers controlled neural activity in freely behaving mice by triggering the release of neurochemicals from thermally sensitive liposomes.¹⁴ In the future, chemomagnetic methods could be coupled with superimposed magnetostatic selection fields, which offer spatial control in drug release.

Chemomagnetic methods are a relatively recent development compared with the other approaches highlighted in this section. Such chemomagnetic studies are affected by the uncertainty surrounding nanoscale heating because they are often performed at concentrations of magnetic nanoparticles that are far below that required for bulk heating. Whether the phenomenon triggered by an alternating field and leading to release can be exclusively attributed to heat is a question worth further consideration.

Electromagnetic induction methods

As described by Faraday's law, time-varying magnetic fluxes induce electric fields in conductive media, which generate currents that oppose the change in flux. The effect, already put to wide and varied technological use, offers a basis for neuronal stimulation through effects experienced at the tissue scale or via wirelessly powered devices.

Researchers have demonstrated that neurons in humans can be stimulated using magnetic fields pulsed at millisecond time scales—on the order of 10^4 T/s with a peak amplitude of up to 1 T—to produce rapid variations of the field strength.¹⁵

Figure 4 depicts how placing current-carrying coils close to the scalp stimulates neurons within the first few centimeters of the brain. The technique, called transcranial magnetic stimulation, or TMS, has shown promise for treating depression, neuropathic pain, and other disorders.

But researchers face several challenges when highly targeted stimulation is required. For example, changes in pulse duration and the physical orientation of the neurons can suppress neuronal activity rather than stimulate it. Superficial brain structures receive a stronger stimulus than deeper ones because magnetic field magnitude decreases with the distance from the coils. To improve spatial selectivity in their effects, researchers commonly use figure-eight or butterfly-coil geometries, both of which have two coils wound in opposite directions to focus stimulation effects near the point of overlap.

Others in the research community have suggested employing a similar effect in implanted devices as an alternative to the conventional electrodes used for deep-brain stimulation that apply potentials to inject small currents into their surroundings. The alternative electrodes remain tethered to an external power source and stimulate neurons in surrounding tissue through inductive effects generated by an approximately 1-mm-diameter solenoid.¹⁶ Although still invasive, the approach avoids scarring, in which brain cells called glia accumulate around an electrode and insulate it from its intended neuronal targets.

Inductively powered, untethered miniature devices implanted in the brain take the technology one step further and have been demonstrated for neural stimulation in animal models.¹⁷ Miniaturization is constrained fundamentally by both a device's requirement to reach induced voltages that are physiologically relevant and its reduced cross-sectional area. The most successful of those neural-stimulation devices have a highly permeable miniaturized ferrite core and a tightly wound solenoid. They use a simple circuit that resonantly couples to an alternating magnetic field with a frequency in the low megahertz range and that rectifies the resulting voltages for direct-current stimulation.

The excitation coils can be thought of as the primary windings

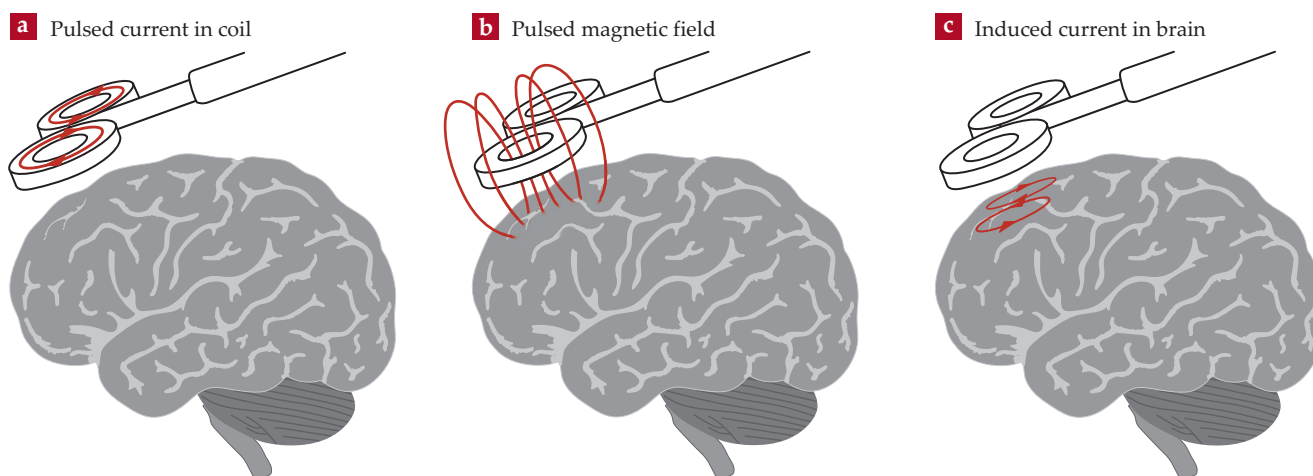


FIGURE 4. TECHNIQUES SUCH AS TRANSCRANIAL MAGNETIC STIMULATION, or TMS, use rapidly varying magnetic fields to induce voltages that trigger the voltage-sensitive channel proteins in neurons. In the representative scheme depicted here, (a) a current pulse is delivered to a coil that (b) generates a pulsed magnetic field. (c) Weaker currents opposing the change in magnetic flux are then induced in the brain tissue and produce neuronal stimulation. (Adapted from ref. 18 by Michael G. Christiansen.)

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of a transformer, and the device's inductive pickup acts as the secondary windings. A simple and compact resonant circuit rectifies the induced voltage, which allows the device to inject current into its surroundings and stimulate neurons. The degree of the transformer's inductive coupling is small compared with more familiar transformers optimized for power transfer. But the design of the device enables noninvasive stimulation over a reasonable area in which an animal can freely move. Other technical advantages of the approach include low power requirements for alternating magnetic field generation and the tunable resonance of the secondary coil. With multiple independently addressable devices, researchers may be able to stimulate different sites in the brain.

Accelerating progress

The present efforts to stimulate neurons with magnetic fields serve as a reminder that progress in science is rarely linear. Spurred by the unmet need for a tool useful to neuroscientists and clinicians alike, independent researchers have produced intriguing ideas and strategies to tackle the same underlying problem. Work that garners the greatest attention is the kind that seeks to shift existing paradigms, so perhaps it should be unsurprising when controversy follows closely behind some of the most prominent claims.

In those cases, a noticeable pattern emerges: Objections often center on foreseeable, fundamental explanatory shortcomings. Even when researchers have sought to defend the reproducibility of their results, they have frequently retreated from their initial statements about mechanisms. Arguably, that outcome is more a consequence of mindset than of expertise.

The fundamental orientation toward problem-solving often fostered in the physical sciences allows one to break difficult problems into solvable pieces and to test plausibility with simplified arguments rather than perfectly recapitulate reality. That way of thinking has already led independent researchers to make valuable contributions toward magnetic control over neurons, and additional engagement and dialog with physical scientists could help accelerate progress in neuroscience.

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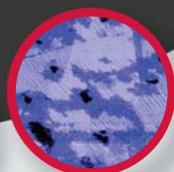
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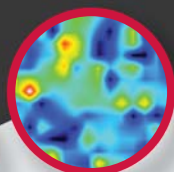
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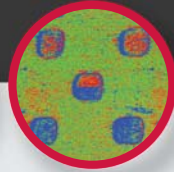
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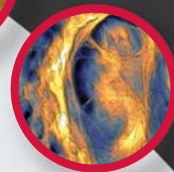
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