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Magnetic Strategies for Nervous System Control

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Abstract

Owing to the low conductivity and negligible magnetic susceptibility of organic matter, magnetic fields can pass through tissue undiminished and without producing harmful effects. Their resulting ability to deliver stimuli wirelessly to targets of arbitrary depth in the body has motivated their use as a minimally invasive means to control neural activity. Here, we review mechanisms and techniques that couple magnetic fields to changes in electrochemical potentials across neuronal membranes. Biological magnetoreception, the underlying mechanisms of which remain an active area of study, is discussed as a potential source of inspiration for artificial magnetic neuromodulation schemes. The emergence of magnetic properties in materials is briefly reviewed to clarify the distinction between biomolecules containing iron or other transition metals and ferrite nanoparticles that exhibit significant net moments. We then describe recent developments in the use of magnetic nanomaterials as transducers that convert magnetic stimuli to forms more readily perceived by neuronal signaling machinery, and discuss opportunities for multiplexed and bi-directional control, as well as the challenges posed by delivery to the brain. The broad palette of magnetic field conditions and the array of mechanisms by which they can be coupled to neuronal signaling cascades serves to highlight the desirability of interchange between magnetism physics and neurobiology, and the necessity of continued dialogue between the engineering and neuroscience communities.

INTRODUCTION

Systems neuroscience and nearly all physiologically based interventions in psychiatric patients rely on the upregulation or downregulation of the activity of specific neural circuits or neuronal subtypes. Historically, this has been accomplished via pharmacology or surgical lesions. In the past several decades, however, a variety of neuromodulation approaches have emerged, some of which have found wide clinical use. For example, deep brain stimulation (DBS) with chronically implanted electrodes is an approved therapy for Parkinson's disease (Obeso et al. 2001) and is being investigated as a treatment for psychiatric disorders. Other methods, such as optogenetics, are mainly employed in basic neuroscience research

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(Deisseroth 2015). This review focuses on a class of neuromodulation approaches that rely on magnetic fields as stimuli.

As compared to other signals such electric fields, light, or ultrasound that may be used to deliver stimuli to the brain, magnetic fields are appealing due to their limited coupling to biological tissue (Young et al. 1980). A notable exception are the magnetic fields with large time-derivatives, which are used for transcranial magnetic stimulation and discussed in Inductive Methods section. The ability of magnetic fields to pass through the body undiminished and without deleterious effects suggests their use in wireless delivery of stimuli to deep targets. For many organisms, though not all, magnetic stimuli should be imperceptible, a desirable feature for behavioral experiments in which the subject's ability to sense the application of a stimulus may compromise the results. An example is optogenetics, in which visible light scattered by waveguides or tissue may be seen peripherally by the subjects. Medical interventions would also benefit from completely remote stimulation methods, and indeed one of the goals of magnetic neuromodulation strategies is to offer a means of DBS with a system that does not rely on a physical connection to sites of stimulation. This would reduce the invasiveness of DBS therapy and the tissue damage associated with implanted hardware.

Some organisms exhibit magnetoreception, the ability to perceive magnetic fields (Ritz et al. 2000, Wiltschko & Wiltschko 2005). Though the biophysical mechanisms underlying magnetoreception remain poorly understood (Johnsen et al. 2005), its existence suggests that reverse engineering could be an intriguing approach to developing tools for magnetic control over neural activity, especially if the necessary genetic machinery could be transferred to specific neural circuits to permit selective activation with magnetic stimuli.

Alternatively, magnetic fields can be used as an intermediary for almost every type of stimulus to which neurons have evolved to respond. Because all neurons are capable of communicating electrically and chemically, it is natural to consider coopting these mechanisms for external modulation of their activity. One approach to do this using magnetic fields entails inducing electric currents in the brain that can either elicit or suppress action potentials, as in transcranial magnetic stimulation (TMS). Alternatively, localized actuation of voltage gated ion channels by magnetic fields may be made possible by the introduction of nanoscale magnetoelectric composite materials (Guduru et al. 2015).

Other routes are suggested by specialized neurons that exhibit sensitivity to physical cues by incorporating ion transporting proteins that respond to a specific stimulus, such as light, mechanical forces, or temperature changes. Such channel proteins can be transgenically introduced where they would otherwise be absent, as is done in optogenetics with opsins, microbial optically-sensitive ion channels and pumps, to sensitize neurons to light. By analogy, proteins native to mammalian sensory neurons can be artificially expressed in neurons deep in the brain to sensitize them to mechanical force or heat. Using magnetic materials as transducers, the magnetic field energy can be locally converted to heat (Chen et al. 2015, Munshi et al. 2017, Munshi et al. 2018) or force (Tseng et al. 2012, Mannix et al. 2008, Lee et al. 2014).

It is worth noting that magnetic approaches represent a subset of a broader effort to identify wireless means of stimulating neurons, such as transcranial focused ultrasound (Legon et al. 2014), temporally interfering high frequency electric fields (Grossman et al. 2017), near infrared (NIR) light illumination, and NIR coupled to upconverting nanoparticles that allow for transcranial light delivery for optogenetic stimulation of deep brain structures (Chen et al. 2018). None of these approaches, however, match the combined resolution and penetration depth afforded by magnetic fields.

NATURAL MAGNETORECEPTION AS A MODEL

Behavioral studies suggest the ability of a variety of animals to perceive the Earth's magnetic field, including insects, amphibians, reptiles, fish, and birds. Migratory birds, for instance, have been suggested to not only orient themselves by sensing the inclination of the field (Wiltschko & Wiltschko 1972) but also may deduce location by discerning minute local variations in the geomagnetic field (Kishkinev et al. 2015). By analogy to other sensory input such as light or sound, the existence of specialized receptor cells has been thought to enable the detection of magnetic field direction and intensity. The biophysical mechanisms that underlie magnetoreception in nature would be an appealing source from which to draw inspiration for the development of effective technologies to enable magnetic control of the nervous system. One can imagine either emulating these mechanisms indirectly, or perhaps manipulating cells of interest to artificially produce the requisite biomolecules for magnetic sensitivity. Though it has its merits, this line of reasoning has thus far encountered practical difficulties for two likely reasons: 1) it fails to account for the dissimilarity between natural magnetic cues and the magnetic stimuli available in the laboratory, and 2) unequivocal mechanisms for natural magnetoreception remain elusive despite decades of research and debate.

The geomagnetic field is relatively weak (50 to 60 μT) and can be regarded as uniform at the scale of an organism and constant at the timescale of animal behavior. Aside from a rare transient magnetic field pulse associated with lightning strikes at very close range (Fuchset et al. 1998) or weak electromagnetic signals linked to human technology or solar wind (LaBelle & Treumann 2002, Engels et al. 2014), the geomagnetic field seems to be the principal magnetic stimulus of evolutionary significance to animals in their natural habitat. In contrast, the types of magnetic fields available in the laboratory are orders of magnitude stronger in field strength (e.g. ~1 T for TMS), can exhibit dramatic gradients (e.g. >100 T/m), and can act dynamically, for instance by rotating or alternating (Figure 1). While examining biological magnetoreception presents an exciting research avenue, leveraging the full palette of magnetic fields accessible in the laboratory may offer a more expedient and robust route to controlling the nervous system than direct emulation of magnetically sensitive molecular and cellular machinery.

Despite many decades of scientific search for biophysical mechanism underlying magnetoreception, consensus has not been forthcoming and key questions remain unanswered (Mouritsen 2018). There are two main hypotheses for mechanisms of magnetoreception in terrestrial animals (Figure 2): 1) magnetically influenced radical pair chemistry, typically thought to involve cryptochrome (Hore & Mouritsen 2016), and 2) the

use of biomineralized magnetic nanoparticles or assemblies formed from them to actuate mechanotransduction (Kirschvink et al. 2001). A third hypothesis suggests that elasmobranch fishes such as sharks may perceive magnetic fields via sensitive detection of induced electric potentials (Kalmijn 1981, Paulin 1995).

Many regard radical pair formation as a likely explanation of “compass sense” in at least some organisms, and a growing body of biophysical, genetic, and behavioral evidence is consistent with this hypothesis and with the notion that cryptochrome is necessary for magnetoreception (Gegear et al. 2008, Muheim et al. 2016). Cryptochrome is thought to mediate the formation of metastable radical pairs upon exposure to photons of ultraviolet or visible light with suitable energy and polarization, a nonequilibrium state that soon proceeds along reaction paths toward one of two possible sets of products (Muller & Ahmad 2011). Because radicals contain unpaired electrons, they exhibit a net magnetic moment, and the presence and orientation of the geomagnetic field can plausibly influence the fraction of these radical pairs existing in either singlet or triplet states. This, in turn, biases the products resulting from their reaction, and a currently unknown mechanism downstream is imagined to use this shifting balance of products to transduce neural activity. One compelling form of evidence based on a magnetic stimulus is the use of alternating magnetic fields varied over a wide frequency band in the low MHz to induce transitions between the singlet and triplet states that apparently interfere with magnetosensation (Ritz et al. 2004, Wiltschko et al. 2015). The full radical pair hypothesis is conceptually richer and is discussed in detail in a recent comprehensive review by Hore and Mouritsen (Hore & Mouritsen 2016). For the present discussion, the most intriguing aspect of this theory is the elegant way in which it plausibly circumvents the intrinsic energetic weakness of magnetic interactions with individual spin moments, merely requiring it to bias the path of a metastable state toward possible equilibria.

The second hypothesis of magnetoreception circumvents the energetic weakness of biomolecular interactions with magnetic fields by instead supposing that biomineralized magnetic materials could play a role. The magnetic moments of these particles, which are orders of magnitude larger than the moment of an unpaired electron, are capable of interacting with the geomagnetic field at energies significantly exceeding the ambient thermal noise. This principle is illustrated by magnetotactic bacteria, which contain magnetosomes, cellular membrane invaginations filled with chains of magnetite (Fe_3O_4) nanoparticles, which align with the local geomagnetic field. While magnetite of suspected biogenic origin has also been identified in other organisms (Gould et al. 1978, Walcott et al. 1979, Kirschvink et al. 1985), including humans (Kirschvink et al. 1992, Gilder et al. 2018), it likely serves a metabolic rather than a sensory function, and evidence of magnetite-dependent cell signaling remains elusive (Treiber et al. 2012, Edelman et al. 2015). Perhaps the most compelling evidence for this hypothesis comes from the reversal of the magnetic compass sense in a variety of organisms upon application of a millisecond magnetic pulse, a phenomenon that could be straightforwardly explained by remanence magnetization in magnetic particles or their assemblies and not by any of the other theories (Holland 2010).

In an effort to draw useful lessons from the progress in the field, it is worth considering the implications each hypothesis could have for informing magnetic stimulation technology if it

were true. Note that the hypotheses discussed above are not mutually exclusive, and that additional unanticipated mechanisms are likely at work. The cryptochrome-dependent radical pair mechanism requires the formation of metastable chemical intermediates via optical excitation at wavelengths absorbed and scattered by tissue. An approach requiring both illumination and magnetic field to stimulate cell populations in the central nervous system does not offer clear advantages over existing optogenetic methods. If the hypothesis of magnetoreception via cellular interaction with nanoscale biogenic magnetite crystals holds true in some instances, then natural magnetoreception could share an underlying mechanistic similarity with the methods reliant on synthetic magnetic nanoparticles discussed at length in a later section.

MAGNETOGENETICS

The desire for facile “magnetogenetics” methods has drawn significant interest in recent years. In concept, these techniques would be analogous to optogenetics (Deisseroth 2015) or chemogenetics (Rogan & Roth 2011), relying solely upon expression of a single protein responsive to magnetic field. This vision is appealing because such methods would be readily adoptable by the neuroscience community, allowing for the retention of many of the established methodologies used in optogenetics, while eliminating the need for the implanted optical waveguides or light-emitting devices that deliver stimuli in behavioral experiments.

This goal has been pursued by fusing the iron-binding protein ferritin to ion channels from the transient receptor potential vanilloid (TRPV) family. The earliest published example fused ferritin to the capsaicin receptor, TRPV1, and showed that exposure to a weak (5 mT) rapidly alternating (465 kHz) magnetic field triggered intracellular calcium ion (Ca^{2+}) influx (Stanley et al. 2012). Because the TRPV1 is a heat-responsive, Ca^{2+} permeable cation channel (Caterina et al. 1997), hysteretic heating of the ferritin was suggested as a putative mechanism for actuating the channel (Stanley et al. 2012). In a follow-up study the same ferritin-fused TRPV1 appeared to be actuated by applying comparatively large (~0.5 T) static magnetic fields (Stanley et al. 2014). An independent study presented evidence that a similar fusion of ferritin to another TRPV channel, TRPV4, was sufficient to produce a similar effect at ten times lower applied field magnitudes (50 mT) (Wheeler et al. 2016). The ability of TRPV1 and TRPV4 to respond to mechanical stimuli has led to a hypothesis that the mechanism underlying the observed effects of magnetic fields on cellular signaling and rodent behavior was mechanical (Stanley et al. 2014, Wheeler et al. 2016). A single amino acid substitution in the pore of the modified TRPV1 was subsequently reported to convert this protein to a chloride-selective channel activated by similar magnetic stimuli to produce inhibitory effects (Stanley et al. 2016).

The energy scale of interaction between ferritin and the magnetic fields with magnitudes employed in these studies was, however, shown to be 4–10 orders of magnitude below the ambient thermal fluctuations (Meister 2016) (Figure 2c), which is far too weak to directly generate mechanically induced conformational changes in a protein. While these articles appear careful in their experimental execution, the attempts to identify mechanisms should be regarded as tentative. For instance, the functional equivalence of the ferrihydrite core of

ferritin and magnetite nanoparticles implicitly posited by this work is not substantiated by the body of literature characterizing ferritin (Chasteen & Harrison 1999). Magnetic fields generated at length scales of centimeters, and alternating at frequencies corresponding to electromagnetic radiation with a wavelength of more than half a kilometer are referred to as “radio waves”, which is imprecise given their quasimagnetostatic nature (Stanley et al. 2012, Stanley et al. 2014, Stanley et al. 2016). For these methods to be properly understood and disseminated, additional experimental and theoretical studies are necessary to uncover the biophysical principles at the core of the observed physiological effects.

Another strategy for developing magnetogenetics has been to attempt to identify a previously unknown magnetic receptor. If valid, such a discovery would simultaneously enhance understanding of magnetoreception and offer a valuable technology for genetically targeted magnetic stimulation. It was recently claimed that iron-sulfur cluster assembly 1 (IscA1) protein isolated through a genome-wide screening of *Drosophila* and renamed as MagR interacts with cryptochrome to generate torque in magnetic fields and act as a “magnetic protein biocompass” (Qin et al. 2015). Concerns have been raised over the underlying mechanisms of magnetoreception reported in this work, especially since data displayed in the same article showed the magnetization of MagR to be about a thousand times lower than that of ferritin (Meister 2016, Winklhofer & Mouritsen 2016). Independent efforts to reproduce the key findings from this work have not yet succeeded (Panget et al. 2017).

These studies highlight the strong the impetus that exists to offer magnetogenetics as a tool for the neuroscience community (Long et al. 2015) and the discussions they have sparked highlight the need for refinement or revision of our understanding of the basic physics of these systems.

INDUCTIVE METHODS

Electromagnetic induction is a phenomenon described by Faraday’s law, in which a time-varying magnetic flux induces electric fields in a conductive medium. Transcranial magnetic stimulation (TMS) is based on this effect, but electromagnetic induction also plays a central role in several other types of wireless brain stimulation techniques.

TMS, transcranial direct current stimulation (tDCS), and electroconvulsive therapy (ECT) all rely on passing current through the brain to alter neural firing patterns. It is hypothesized that this gives rise to neuroplasticity (Nitshe et al. 2008, Lefaucheur et al. 2017), though the exact mechanism by which long-term behavioral changes are manifested is still unclear. Understanding the effects of TMS is further complicated by inhomogeneity in the induced current, the likely significance of the orientation of the axons being stimulated, the influence of pulse duration (which can either potentiate or depress activity), and the indirect activation of other brain regions (Yasuo 2002, Ruff et al. 2009). Some efforts to elucidate the mechanisms involve combining TMS with fMRI to correlate behavioral changes to hemodynamic signals as a proxy for neural activation (Bergmann et al. 2016). TMS has shown promise for treating depression (Brunoni et al. 2017, McClintock et al. 2018) and

neuropathic pain, while emerging applications such as the treatment of stroke and Alzheimer's disease require further investigation (Lefaucheur et al. 2014).

TMS involves placing a magnetic field coil close to the scalp and applying millisecond pulses of current through the coil to produce time derivatives of magnetic field ($dB/dt \approx 3\times10^4$ T/s, peak field amplitude ~2 T) that induce currents in the brain (Wagner et al. 2007) (Figure 3a). Only the top 1 – 2 cm of cortex directly below the coil will be stimulated, and by engineering the coil shape the field can be concentrated to spot sizes smaller than the coil diameter. A common coil geometry is the figure-eight or butterfly coil, which has two slightly overlapping coils wound in opposite directions (Figure 3b). This geometry produces a concentrated field at the point of overlap between the coils. Regardless of the TMS coil shape, magnetic field decreases with distance from the center of coil, which implies that superficial brain structures will consistently receive a stronger stimulus than deeper brain structures (Wagner et al. 2007).

While TMS cannot reach deep brain structures without stimulating cortical tissue with greater intensity, the implantation of miniature magnetic coils has been suggested as an alternative to DBS electrodes. An example of such a device consisted of a ~1 mm solenoid connected by wires to a battery pack, and generated a magnetic field that caused electromagnetic induction in neighboring neural tissue (Figure 3c). This device is thought to be potentially immune to eventual failure caused by glial scarring that plagues implanted electrodes, due to the fact that the induced fields extend for several hundred microns (Bonmassar et al. 2012). This would also mitigate safety concerns associated with electrochemical reactions at direct interfaces between electrodes and neural tissue (Park et al. 2013, Lee et al 2016).

Related alternatives to DBS electrodes include inductively powered implanted devices. Such devices use a pickup coil to couple to an external primary coil through mutual inductance, and power is transferred via an alternating magnetic field in a manner analogous to a transformer. One example of a miniaturized implantable device has been demonstrated to work 7.5 cm away from the power coil in a rat model (Figure 3d). It has approximate dimensions of 2×0.5×0.5 mm, and operates by rectifying induced voltages at a predetermined resonance frequency (e.g. 10 MHz) to produce a DC electric field capable of depolarizing adjacent neurons (Freeman et al. 2017). Like TMS, this device relies on external application of magnetic fields, but in this case the field is used solely as a source of wireless power for an electrical device. Other types of miniature implanted inductively powered electrical devices have also been designed, for example to drive microscale LEDs (μLEDs) for optogenetics (Kwon et al. 2015).

MAGNETIC MATERIALS

Basis for the Utility of Magnetic Particles

Techniques employing magnetic materials to stimulate the central nervous system tend to rely on coupling magnetic fields to other stimuli that are more readily detected by neuronal biochemical machinery. The role of the magnetic material in this approach is to provide an energetically plausible handle upon which a magnetic field can act. The dissimilarity in

magnetic properties between the magnetic material and the tissue surrounding it serves as the basis for selective influence of the field. To appreciate why the interaction of a magnetic field with such materials differs from its interaction with biomolecules or clusters of atoms, it is helpful to consider the origins of their magnetism (Figure 4).

While certain elements such as iron or rare earth metals exhibit higher magnetic moments than other atoms, their presence in a system alone does not constitute a magnet. A magnetic field applied to a population of such atoms, responding in effective isolation from one another, results in paramagnetic behavior (Cullity & Graham 2009) (Figure 4a). This is observed at room temperature in FeO (wüstite), which contains iron and oxygen atoms in a rock-salt crystal arrangement. The competition of thermal fluctuations with the energetic influence of an applied magnetic field determines the extent to which such a population of moments aligns with the field. For a paramagnetic material, the energies of interaction between the field and individual atoms are so small that even an applied field as strong as 1T will typically produce a magnetization value <1% of saturation (complete alignment). Because paramagnetism is an inherently weak effect, such materials are suboptimal handles for magnetic actuation (Figure 4a).

When atoms are arranged in close proximity, for example in a crystal, the possibility for spontaneous ordering of their magnetic moments sometimes arises (Figure 4b). Magnetic moments of atoms can interact with one another through “exchange interaction,” a quantum mechanical phenomenon that can occur either between nearest neighbors or can be mediated via neighboring nonmagnetic atoms (Cullity & Graham 2009). Because it requires overlapping wave functions, exchange interactions between atoms are appreciable only when they are separated by sub-nanometer distances. If this interaction causes neighboring magnetic moments in a crystal to align in parallel, for instance as in a body centered cubic crystal of metallic Fe, the material is referred to as “ferromagnetic” (Figure 4b). If, instead, the exchange interaction drives antiparallel alignment and their moments cancel, the material is referred to as “antiferromagnetic,” (Figure 4b) such as FeO at temperatures below −80°C (Fischer et al. 2009). Intermediate “ferrimagnetic” cases are possible, with antiparallel alignment of dissimilar moments or antiparallel alignment of unequal subpopulations of moments so that an overall net magnetization remains (Figure 4b). Biomineralized crystals of Fe_3O_4 (magnetite) and gregite (Fe_3S_4) fall into this category (Roberts et al. 2011). Crystal defects and surface effects in sufficiently small nanoscale crystals can play a significant role in determining properties. While the protein shell of ferritin has been used as a nucleation site for the growth of a variety of synthetic nanomaterials (Jutz et al 2015), in humans and other mammals its mineralized 5.5-6.0 nm core consists of ferrihydrite ($5Fe_2O_3\ 9H_2O$) (Chasteen & Harrison 1999). The Fe^{3+} ions in the ferrihydrite crystal are antiferromagnetically ordered, but defects and surface states lead to incomplete cancellation, leaving a weak residual moment of approximately 300 bohr magnetons (Jutz et al 2015). Magnetic ordering is an effect that emerges from structure and cannot be reduced to the presence or absence of certain elemental constituents. The above examples of paramagnetic, ferromagnetic, antiferromagnetic, and ferrimagnetic materials all derive their magnetic properties from iron, and yet the behavior of these materials differs markedly.

In a macroscopic object, the presence of magnetic ordering at the scale of the crystal often does not result in an overall net magnetization. This is because, in the absence of an applied field, magnetostatic energy can be reduced through the spontaneous formation of opposing domains (Figure 4c). These domains are separated by domain walls, where the local magnetization turns gradually from one direction to another. These walls have a characteristic width that depends on the strength of the exchange interaction and other material properties. In particles much smaller than this width, the energy cost associated with forming a domain wall outweighs the resulting reduction in magnetostatic energy, so multiple domains do not form. For magnetite, the approximate cutoff for single domain behavior is approximately 80 nm (Moskowitz & Banerjee 1979). Notably, in structures with linear dimensions within this range, behaviors intermediate between single and multidomain states can emerge, including the possibility for vortex states (Liu et al. 2015, Yang et al. 2014).

Simply because a particle is uniformly magnetized does not imply that its moment maintains a fixed direction. Indeed, the moments of sufficiently small particles fluctuate rapidly with respect to their crystal axes at a rate that decreases exponentially with increasing particle volume for a given temperature (Neél 1949). When a magnetic field is applied, if the timescale is longer than the characteristic rate of fluctuation, a population of these particles will show behavior similar to paramagnetism, with the important distinction that saturation occurs at field magnitudes thousands or tens of thousands of times smaller (millitesla to tens of millitesla), depending on their volume and the magnetization of the material (Figure 4d). This behavior is known as “superparamagnetism,” because the population of single domain magnetic nanoparticles acts as a collection of magnetic moments that are individually many thousands of times larger than those of individual atoms (Bean & Livingston 1959).

It is these large effective moments, made possible by ferro- or ferrimagnetic ordering in the crystals, that make these particles so useful for external magnetic manipulation. This is reflected in the chains of high quality, biomineralized magnetite or gregite nanoparticles that natural selection has favored in magnetotactic bacteria (Moskowitz et al. 1993, Schüler & Frankel 1999, Faivre & Schüler 2008).

Synthesis of Magnetic Nanoparticles

The observation that high quality magnetic nanoparticles can be generated by cells led to the hope that the requisite genes could be transferred to mammalian cells to artificially induce magnetoreception. This vision has not yet been realized, but some progress has been made, including the induction of iron oxide nanoparticle synthesis in human mesenchymal stem cells (Elfick et al. 2017). One barrier to transfecting brain cells with magnetosome genes in vivo is their large size, which presents a challenge to their packaging into viral vectors.

An alternative to genetically engineering cells to produce magnetite is to introduce synthetic magnetite into an organism, such as by injecting a solution of magnetite nanoparticles directly into the target brain area (Chen et al. 2015, Munshi et al. 2017). Magnetite nanoparticles can be synthesized via a variety of means, each offering certain advantages. For instance, co-precipitation cheaply produces large quantities of magnetite and hydrothermal methods can create interesting morphologies, such as hollow structures (Wu et

al. 2015). To achieve a high degree of size uniformity and a high saturation magnetization (a measure of the particles' magnetic moments) high-temperature thermal decomposition methods are often preferred (Kim et al. 2009, Park et al. 2004). During thermal decomposition synthesis, a solution of high-boiling point organic solvents and organometallic precursor (such as iron oleate or iron acetylacetonate) is heated until the decomposition of the organometallic precursor leads to the nucleation and growth of iron oxide nanoparticles (van Embden et al. 2015). By choosing solvents that undergo radical decomposition to favor an oxidative environment, the production of phase pure Fe_3O_4 can be promoted (Chen at al. 2016, Hufschmid et al. 2015). The magnetic properties of nanoparticles can be influenced not only by altering their shape and dimensions but also by introducing other transition metal atoms including Co, Mn, and Zn. While partial substitution of Fe^{2+} by Zn^{2+} allows for increased saturation magnetization as compared to magnetite (Jang et al. 2009, Noh et al. 2012), the other two atoms are typically used to modify magnetic anisotropy, a property that is discussed in greater detail below in the context of nanoparticle heating. Akin to pure magnetite, tertiary ferrite nanoparticles doped with these atoms ($Me_xFe_{3-x}O_4$, Me = Mn, Co, Zn) are readily produced via thermal decomposition at similarly high uniformity and crystallinity (Sun et al. 2004, Chen et al 2013).

Magnetomechanical Methods

Magnetic nanoparticles in a uniform magnetic field experience a torque that pulls their magnetization in the direction of the applied field, and magnetic nanoparticles in a magnetic field gradient experience a translational force (as in magnetic tweezers) (Figure 5a). These two mechanisms of interaction of magnetic nanoparticles with magnetic fields allow particles attached to biomolecules, organelles, and cells to exert forces on these structures (Pankhurst et al. 2003, Monzel et al. 2017). Sensory neurons in the peripheral nervous system express mechanosensitive ion channels that are responsible for our sense of touch, balance (via neurons in the inner ear), and painful pressure (Delmas et al. 2011, Coste et al. 2010) (Figure 5d). Mechanosensitive ion channels open in response to tension in the membrane or to directly applied mechanical force. In principle, akin to opsins in optogenetics and designer receptors in chemogenetics, these channels could be transfected into the central nervous system to allow for magnetic nanoparticle-mediated force-based control of the nervous system.

The use of magnetic nanoparticles to activate mechanosensitive ion channels has been demonstrated in vitro via patch clamp studies (Hughes et al. 2007) and calcium imaging (Lee et al. 2014, Tay et al. 2017). These studies have relied on devices similar to magnetic tweezers (Seo et al. 2016) that generate high magnetic field gradients on the order of 100 T/m. This implies that the cells being stimulated have to be in close proximity to the magnetic elements (within 10s to 100s of microns), and for this reason the high-magnetic field gradient approach does not translate easily to studies in vivo.

In contrast, it is possible to create low-gradient magnetic fields over volumes large enough to fit a human, for example those in an MRI magnet. As noted above, uniform magnetic fields can exert torques on magnetic nanoparticles, especially anisotropic ones. This torque-based

approach has been used to trigger necrosis in cancer cells, using both anisotropic particles such as discs (Kim et al. 2009, Shen et al. 2017) as well as chains of isotropic particles (Cheng et al. 2017) in combination with low frequency uniform fields (<20 Hz) 10s of mT in amplitude. By analogy with magnetothermal neural stimulation, which was originally inspired by magnetic hyperthermia treatment of cancer, magnetomechanical neural stimulation may work most effectively by adapting this torque-based approach to tumor destruction and tuning down the applied forces to physiologically safe levels.

Another interesting application of magnetic nanoparticles as force transducers is in neural regeneration scaffolds that can be wirelessly actuated. Neurons respond to mechanical cues (Lamoureux et al. 2002), and neural regeneration may be enhanced by mechanical actuation (Smith et al. 2001, Abraham et al. 2018). Prototype neural regeneration scaffolds actuated by magnetic nanoparticles have been developed that enhance the growth of cultured sensory neurons (Tay et al. 2018). These comprise hydrogels impregnated with magnetic nanoparticles that stretch periodically in response to periodic magnetic field application and removal, exerting forces on the neurons. In the future, it may be possible to implant such scaffolds to bridge nerve injuries, and then externally and non-invasively apply a slowly varying magnetic field to actuate the scaffold and promote growth. Such hydrogel scaffolds would be resorbable, and thus magnetic actuation would enable devices that are powered remotely and do not require explantation.

Magnetoelectric Composites

Since all neurons express voltage-gated ion channels, which are necessary for propagating an action potential, it could be advantageous to develop nanomaterials capable of transducing externally applied magnetic fields into localized electric fields in the vicinity of the membrane, at the scale of the relevant cellular machinery (Kargol et al. 2012, Yue et al. 2012) (Figure 5b,e). This method does not rely on electromagnetic induction, which is fundamentally electrodynamic in character, instead finding its basis in quasi-electrostatic and quasi-magnetostatic behavior. In intrinsically magnetoelectric materials, coupling is typically weak and is manifested only at temperatures far lower than the physiological environment (Brown et al. 1968). Magnetoelectric (multiferroic) composites offer a more feasible approach, and combine a material in which strain and magnetization are coupled (magnetostriction) to a material in which strain and electrical polarization are coupled (piezoelectricity) (Nan et al. 2008). Strain within the composite structure then links magnetization and electric polarization (Figure 5b). In practice, macroscopic versions of such composites exhibiting high coupling coefficients are typically driven at mechanical resonance in order to maximize the strain amplitude (Nan et al. 2008). In contrast, studies aiming to apply magnetostrictive-piezoelectric nanoscale composites for neural stimulation have driven these particles with slowly varying magnetic fields with frequencies from 0–20 Hz and amplitudes of 10mT (Guduru et al. 2015). Because the magnetoelectric response of a composite can be limited by the materials properties of either component, it is important to select constituents that are strongly magnetostrictive and piezoelectric. Unfortunately many strongly piezoelectric materials contain lead, which poses toxicity concerns for deployment in biological settings. Composite nanoparticles designed for neural stimulation at the stage

of exploratory experiments have incorporated $CoFe_2O_4$ as the magnetostrictive component and $BaTiO_3$ as the piezoelectric component (Guduru et al. 2015).

Magnetothermal Methods

A number of minimally invasive neural stimulation strategies have recently emerged that either directly or indirectly make use of heat dissipated by magnetic nanoparticles in alternating magnetic fields with frequencies ranging from tens of kHz to the low MHz and amplitudes in the 10s of mT. This heating arises from the work done by magnetic torque against dissipative forces during the cyclic response of the magnetization (Figure 5c). These dissipative forces can include either friction with the surrounding liquid medium when the entire particle physically rotates with the magnetization vector or damping processes internal to the crystal when the magnetization vector rotates independently of particle motion (Rosensweig 2002). Whichever of these occurs more rapidly will dominate the behavior of the system, but the latter tends to dominate when alternating magnetic field amplitudes are sufficiently large. This is because nanoparticles exhibit preferred orientations of their magnetic moment with respect to the crystal, a phenomenon called “anisotropy,” and applied fields lower the energy barriers separating preferred axes (Neél 1949). The symmetry of these these “easy axes” and the height of the energy barriers separating them can be influenced by properties of the crystal, particle shape (Usov & Barandiaran 2012), strain (Suzuki et al 1999), or surface effects (Peddis et al 2008). Among particles with similar material properties and different size, the anisotropy barrier approximately scales with volume (Neél 1949), a fact that helps explain the crucial importance of size control and monodispersity for synthetically produced magnetic nanoparticles.

Viewing the magnetic nanoparticles from a macroscopic vantage point, the periodic lag in response between their population-averaged magnetization and the rapidly alternating magnetic field has a convenient graphical representation in the form of hysteresis loops, which assume shapes that reflect the particular response of the magnetization. Despite their differences, models describing the heat dissipation of magnetic nanoparticles predict hysteresis loops and find their area, which corresponds to energy dissipated per cycle of the field. Examples of common models with differing domains of validity include linear response theory (valid at low field amplitudes compared to the Stoner-Wohlfarth coercive field, the “anisotropy field”) (Rosensweig 2002), dynamic hysteresis (valid at frequencies low compared to the precession of the particle moment) (Carrey et al. 2011), and stochastic Landau-Lifshitz-Gilbert models (most general, but still containing simplifying assumptions) (Usov 2010).

The suitability of ferrimagentic particles for heat dissipation compared to biomolecules and weakly magnetic nanoparticles like the ferrihydrite core of ferritin can be anticipated by considering the influence of their magnetic properties on hysteresis loops. A magnetite nanoparticle 20 nm in diameter contains ~500,000 iron atoms in a ferrimagnetic inverse spinel lattice. This ferrimagnetic ordering results in a higher magnetization compared to other phases of iron oxide, stretching the scale of the vertical axis. The anisotropy energy barrier increases with the volume of the particle and enables larger coercive fields at sufficiently high applied amplitudes. Both of these influences tend to increase the hysteresis

loop area and result in greater dissipated power. In contrast, the ferrihydrite core of ferritin that contains ~2500 iron atoms exhibits a low saturation magnetization that arises only because of a small number of uncompensated spins in crystal defects of its otherwise antiferromagnetic arrangement. Furthermore, its minute anisotropy barrier, evidenced by a low blocking temperature of 40K, ensures that it should be expected to exhibit virtually no hysteresis at physiological temperatures (Chasteen & Harrison 1999).

Local increases in temperature are capable of triggering the response of temperature sensitive channel proteins such as TRPV1, and several studies have demonstrated stimulation following injections of magnetic nanoparticles and viral delivery of *trpv1* transgenes (Huang et al. 2010, Stanley et al. 2012, Chen et al. 2015). Applications making use of hysteretic heat dissipation can be divided into two categories: those relying on bulk heating effects and those relying on nanoscale heating effects (Figure 5f). The former requires a highly concentrated and localized droplet of injected nanoparticles to heat itself and the surrounding tissue, and, combined with TRPV1 expression, this has been demonstrated as a viable approach for neuromodulation (Chen et al. 2015). On the other hand, the possibility for nanoscale heating is less intuitive when considering the effect of scaling relationships on the expected surface temperature of a heat-dissipating nanoscale sphere. Indeed, an extrapolation of macroscopic heat transport equations to the nanoscale suggests rapid equilibration on the timescale of hundreds of nanoseconds and an infinitesimal temperature change that drops off inversely with distance (Keblinski et al. 2006, Meister 2016). Nevertheless, a growing and varied body of experimental evidence contradicts this prediction, instead suggesting that temperatures at nanoscale interfaces reach steady state far more slowly (seconds or even tens of seconds) and can achieve effective temperature increases of 10s of °C in the nanometer vicinity of the nanoparticle surfaces before dropping off rapidly in solution (Huang et al. 2010, Riedinger et al. 2013, Dong & Zink 2014).

The use of nanoscale heating to wirelessly actuate the response of temperature sensitive channel proteins for neuromodulation precedes not only the bulk heating approach for neuromodulation, but also much of the work that has recently produced compelling evidence of nanoscale heating in similar situations. In principle, the main advantage of systems based on nanoscale heating is that they require lower quantities of magnetic material and avoid bulk heating effects on surrounding tissue. This work often includes targeting moieties that link the magnetic nanoparticles to the cell membranes or even the heat-sensitive channel, a design feature consistent with the close proximity that seems to be a requisite for the nanoscale heating effects to be relevant (Huang et al. 2010, Stanley et al. 2012). The technique has been demonstrated to trigger TRPV1 and drive neural activity and behavioral responses in awake, freely moving mice (Munshi et al. 2017). More recently, the concept was extended to neural inhibition by actuating a temperature gated chloride channel, TMEM16A (Munshi et al. 2018), offering a route to bi-directional neuromodulation analogous to chloride channels leveraged for optogenetics (Deisseroth 2015).

Nanoscale effects of hysteretic heating have also been used as a means of triggering release of chemical payloads from a variety of carriers, including temperature sensitive liposomes (Amstad et al. 2011) (Figure 5g), mesoporous silica particles (Rühle et al 2016), and

individual magnetic nanoparticles functionalized with thermally labile bonds (Riedinger et al. 2013). If the chemical species released can act as an agonist or an antagonist for a channel protein, then it is possible to couple magnetic stimulus to chemical actuation or downregulation of neuronal activity, mediated by heat. This concept has been demonstrated for *in vitro,* when an agonist of TRPV1, allylisothiocyanate anchored to the surface of magnetic nanoparticles via thermally sensitive azide bonds was used to stimulate neurons expressing this cation channel (Romero et al. 2016). While conceptually promising, this approach was restricted to payloads suited for chemical fusion to nanoparticle surfaces via thermally labile bonds, and the quantity available for release was quickly exhausted. Future work in this area could further develop the concept by making use of release schemes that are less chemically restrictive and focus on receptor-agonist pairs that respond sensitively and consistently to a wide range of concentrations.

In coming years, an appreciation of the physics underlying nanoparticle heat dissipation in magnetic fields could offer opportunities to extend the functionality of these techniques. For instance, dynamic hysteresis models have revealed the possibility for magnetothermal multiplexing, the ability to selectively heat magnetic nanoparticles with distinct physical or chemical properties using different alternating magnetic field conditions (Christiansen et al. 2014). This may enable bidirectional neural control, whether through actuating the separate release of excitatory and inhibitory compounds from carriers or selectively actuating TRPV1 or TMEM16A.

The spatial selectivity of stimulation offered by magnetothermal methods is presently limited by the localization of the injection, but foreseeable opportunities exist for more precise targeting enabled by superimposed magnetostatic gradient fields. For such a configuration, in regions with a large magnetostatic contribution, the net field would oscillate with an offset and magnetic nanoparticles would remain saturated and largely unresponsive to the superimposed alternating component of the field. At the point or line where the magnetostatic field vanishes, the magnetic nanoparticles would be able to undergo hysteretic heat dissipation. Precisely the same kind of superposition of alternating and static magnetic fields is currently employed in magnetic particle imaging to isolate signal from voxels (Knopp & Buzug 2014), though the amplitude and frequency of the alternating field would need to be increased. While efficiently producing strong alternating magnetic fields at frequencies in the hundreds of kHz in medically relevant working volumes is nontrivial, there is no fundamental barrier to scaling (Christiansen et al. 2017), and these technical opportunities for multiplexed and site specific neuromodulation techniques may spur on further development of the necessary instrumentation.

CONCLUSION AND OUTLOOK

Magnetic fields offer unparalleled access to the signaling processes occurring at arbitrary depths within the body because of the negligible magnetic permeability and low conductivity of tissue. Harnessing magnetic field energy as a means to control neuronal activity, however, requires transducing imperceptible magnetic fields into stimuli capable of triggering endogenous or genetically engineered signaling cascades within these cells. The enigmatic magnetoreception of migratory animals continues to inspire a vigorous search for

genetically encoded machinery that responds directly to magnetic fields. The cryptochrome-dependent radical pair mechanism proposed to underlie the magnetic compass sense in birds and insects appears to necessitate an optical stimulus, and thus cannot be implemented within the body without implanted light sources. Magnetosomes produced by magnetotactic bacteria, while suitable for transduction of weak magnetic fields into mechanical or thermal stimuli, require the amount of genetic material too large to be delivered by a single viral vector.

Paralleling the basic study of biological magnetoreception, the use of synthetic nanomaterials is a promising and expanding means for controlling neuronal activity. Magnetic nanoparticles can mediate interactions between magnetic fields and cellular machinery equipped to respond to heat, forces, and chemical stimuli. Magnetic neuromodulation methods can, in many cases, be implemented without transgenes, relying solely on endogenously expressed ion channels in mammalian neurons. Furthermore, nanomaterials composed of magnetite are considered biocompatible with notable examples being used as approved MRI contrast agents (Wang 2011) and promising means to treat brain tumors in a recent Phase II clinical trial (van Landeghem et al 2009). One outstanding issue is that of delivering nanomaterial to targets in the brain, which at present requires direct injection. While not a significant concern for experiments in animal models, the need for direct injection into neural tissue may slow down the translation of otherwise promising magnetic neuromodulation methods to clinical application. Challenges posed by delivery across the blood brain barrier are a topic of active research, and a number of strategies including monovalent antibodies (Niewoehner et al. 2014) and temporary permeabilization of the barrier with focused ultrasound (Hynynen et al. 2001, Szablowski et al. 2018) or chemical compounds (Cosolo et al. 1989) have recently emerged to aid transport of molecules or viruses injected systemically. Such methods may require additional engineering to account for the sizes of magnetic nanoparticles needed to effectively transduce magnetic fields into thermal (tens of nm), electrical (tens to hundreds of nm), or mechanical (hundreds of nm) stimuli.

The emerging interest in magnetic neuromodulation approaches demands close interactions between physicists, chemists, engineers, and neurobiologists to appreciate the advantages and overcome the challenges associated with these methods. Understanding of biophysical mechanisms governing the transduction of magnetic stimuli into cellular responses is essential not only for delivering robust and reliable magnetic neuromodulation tools for basic neuroscience community, but is key to refining these tools as future means to understand and treat diseases of the nervous system.

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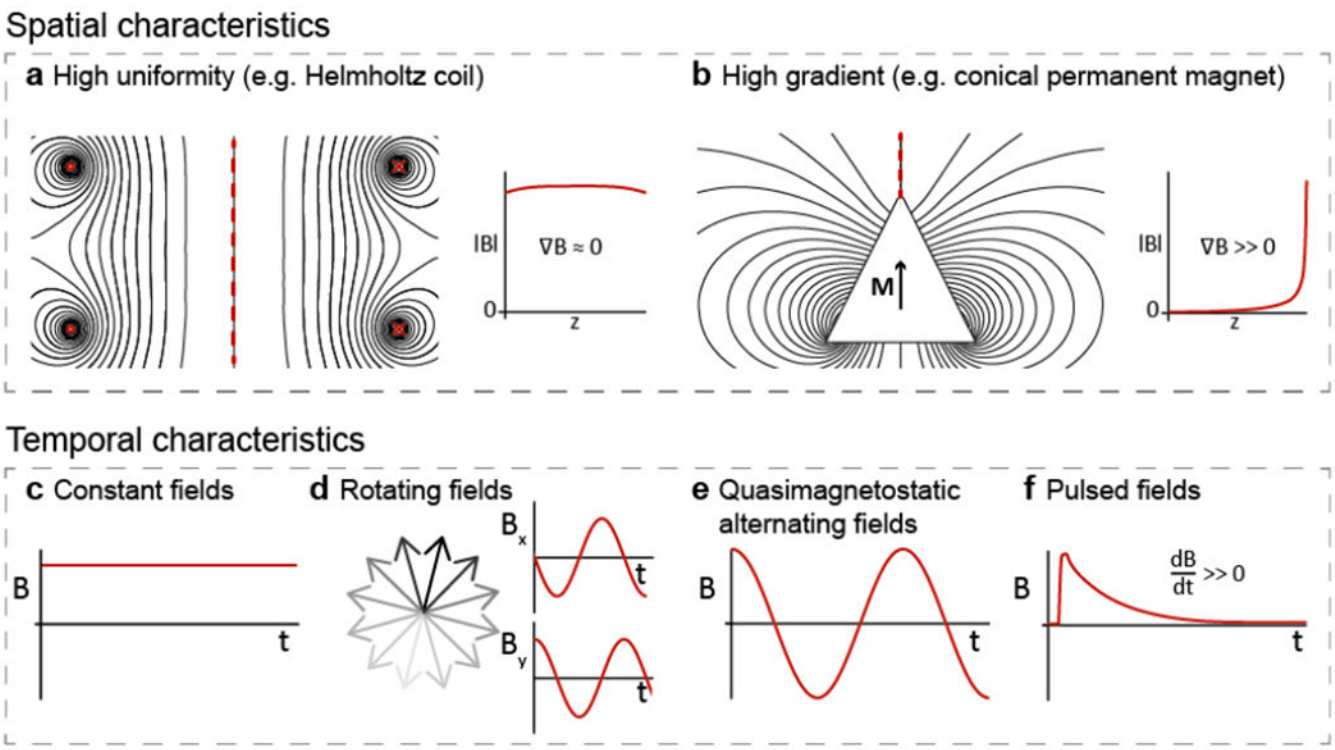

Figure 1.

A palette of artificial magnetic stimuli, categorized according to spatial and temporal characteristics. (*a*) Nearly uniform fields can be created, for example, using a Helmholtz coil (two current carrying rings separated by a distance equal to their radius). (*b*) A conical permanent magnet magnetized along its azimuthal axis produces a field at the tip that decays rapidly with distance, resulting in a high magnetic field gradient. Fields with various spatial distributions can also be categorized by how they vary in time. (*c*) Magnetic fields can remain constant over the timescale of interest. (*d*) Rotating fields maintain a constant magnitude while changing direction, revolving around some axis. A simple, planar rotation is shown. (*e*) Alternating magnetic fields sinusoidally change polarity, and are typically generated by applying AC current to a solenoid. If the linear dimensions of the solenoid are much less than the corresponding wavelength of electromagnetic radiation, the field is quasimagnetostatic. (*f*) Pulsed fields, which exhibit high dB/dt, can be generated by discharging a momentary burst of current through a coil. This approach is often used in TMS pulses.

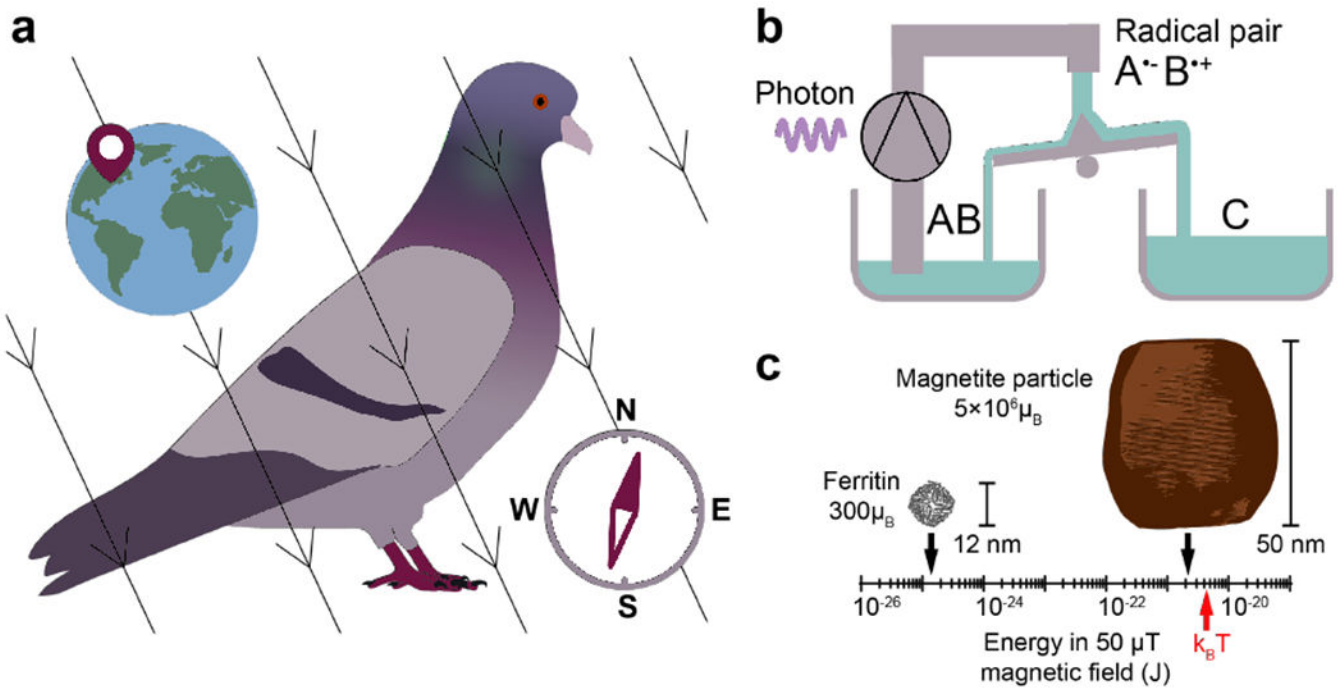

Figure 2.

Lessons offered by hypothesized mechanisms of magnetoreception. (*a*) Pigeons are an example of organisms that sense the inclination of the Earth's magnetic field and also possess a "map sense." They are thought to to detect minute local variations in the magnetic field and remember those variations to help navigate. (*b*) In the radical pair hypothesis, cryptochrome generates radical pairs when exposed to ultraviolet or blue light, and weak magnetic fields bias the proportion of radical pairs in the triplet or singlet state, altering the generation of downstream products detectable by neurons. (*c*) Magnetite nanoparticles have been reportedly found in many animals and could perhaps interact with the Earth's magnetic field strongly enough to produce forces detectable by neurons. A 50 nm magnetite particle is contrasted with the mineralized core of ferritin in terms of interaction energy with the Earth's magnetic field (50 μT). Thermal energy at room temperature is marked as k_BT, where k_B is the Boltzmann constant and T is temperature.

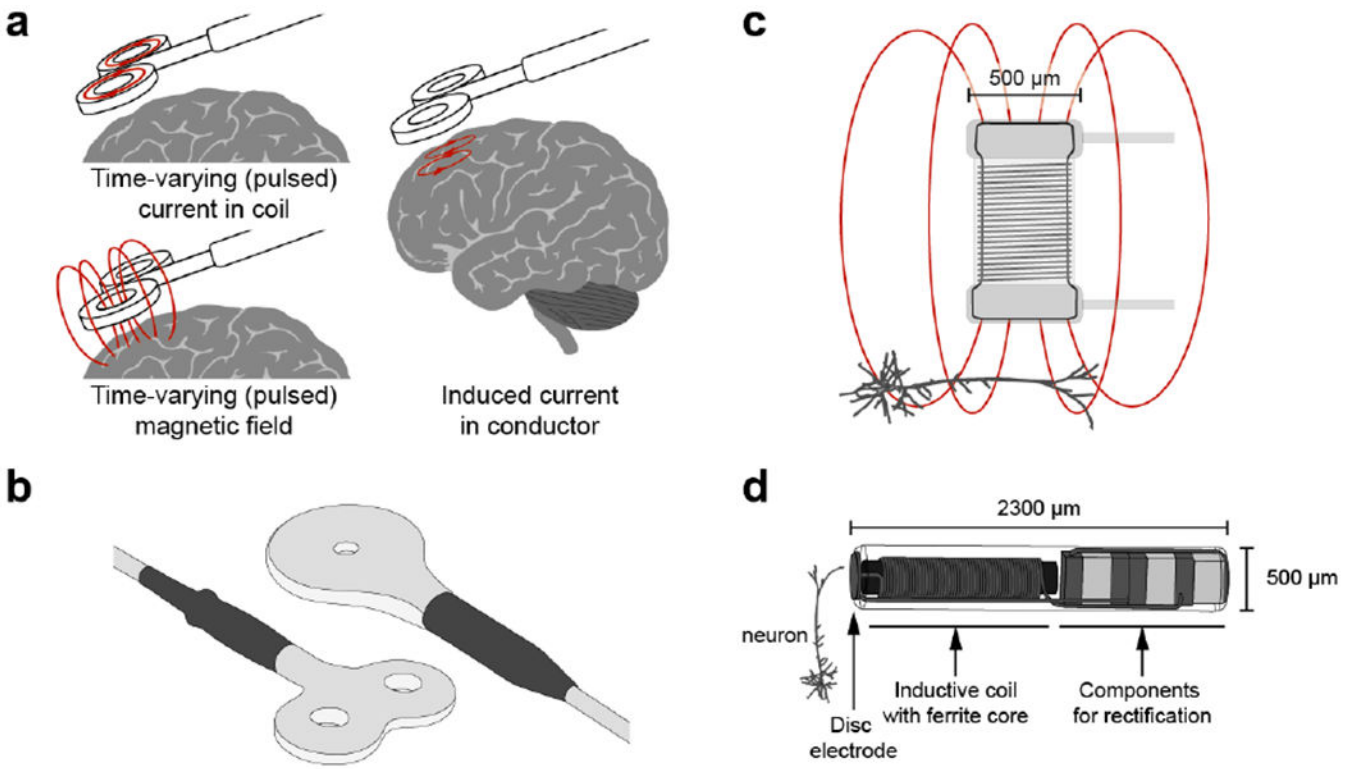

Figure 3.

Electromagnetic induction can be used to control neural activity. (*a*) Schematic of the electromagnetic induction in the context of TMS. A butterfly coil is held over the head of a human and a pulsed current is applied, resulting in a rapidly increasing magnetic field that induces a current in the brain (from Wagner et al. 2007). (*b*) Examples of TMS coils, single and butterfly (from magstim.com). (*c*) Electromagnetic induction could be used to stimulate deep brain structures via implanted millimeter-scale solenoids (from Bonmassar et al. 2012). (*d*) Implanted devices may be powered using electromagnetic induction. This device may be implanted into an animal and rectifies the induced voltage from an externally applied alternating magnetic field into a DC current that can stimulate neural activity (from Freeman et al. 2017).

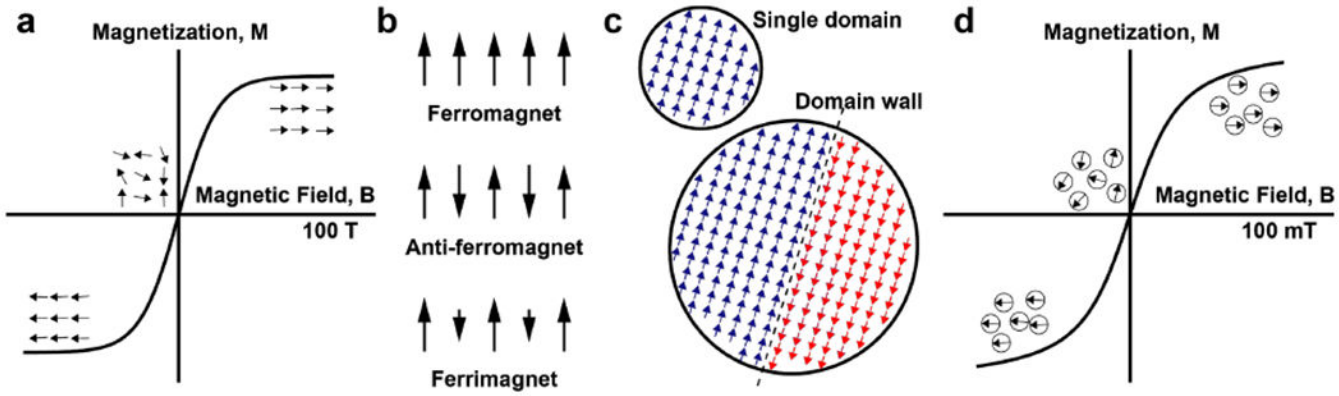

Figure 4.

Forms of magnetic ordering. (*a*) **Paramagnetism:** uncoupled spins are randomly oriented in the absence of applied field, but they asymptotically approach complete alignment with the application of large magnetic fields. (*b*) In **ferromagnetic** materials, magnetic moments spontaneously align to give the material a net magnetic moment. In **anti-ferromagnetic** materials, adjacent magnetic moments align anti-parallel to perfectly cancel, resulting in zero net magnetization. In **ferrimagnetic** materials, adjacent magnetic moments align anti-parallel but have unequal magnitude, resulting in a net magnetic moment for the material. (*c*) Single and multi-domain particles: below a critical size determined by the material properties, all moments within a ferromagnetic particle are aligned. At larger sizes, particles develop multiple domains to minimize their magnetostatic energy. For simplicity, the domain wall is illustrated as if it were abrupt; in reality, there would be spins of intermediate orientation between the two opposing domains. (*d*) **Superparamagnetism:** an ensemble of singledomain particles of ferromagnetic or ferrimagnetic material has zero net magnetization at zero applied field, but upon the application of moderate magnetic fields, the particle moments align with the applied field.

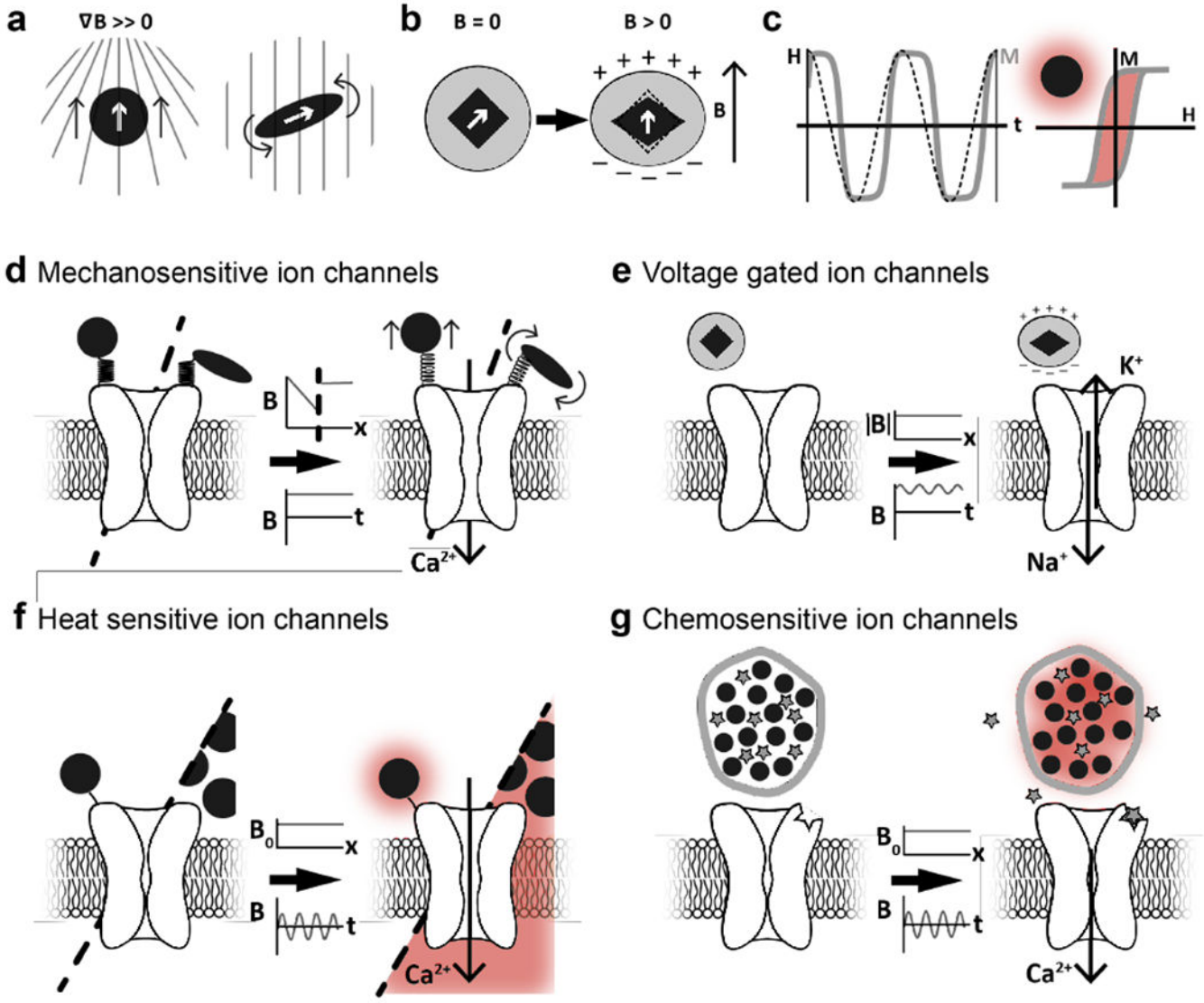

Figure 5.

Strategies for using synthetic nanomaterials for neuronal stimulation with magnetic fields. (*a*) Forces may be applied to magnetic particles in highly nonuniform fields, and torques may be generated if particles exhibit anisotropy. (*b*) Magnetoelectric composite nanoparticles couple the strain resulting from magnetostriction of their core to a piezoelectric shell, producing a change in electric polarization. (*c*) The lag in response of magnetization to an applied alternating magnetic field, which can be graphically represented by hysteresis loops, results in dissipated heat. (*d*) Force or torque may be used to actuate mechanosensitive ion channels. (*e*) Magnetoelectric composite particles can, in principle, be used to trigger the response of voltage gated ion channels. (*f*) Temperature-sensitive channel proteins may be actuated by the heat dissipated by magnetic nanoparticles, whether through nanoscale or bulk effects. (*g*) Heat may also be used to trigger the release of chemical agonists or antagonists that actuate ion channels.