Chapter 8

Image-guided Placement of Magnetic Neuroparticles as a Potential High-Resolution Brain-Machine Interface

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Abstract

We are developing methods of noninvasively delivering magnetic neuroparticles™ via intranasal administration followed by image-guided magnetic propulsion to selected locations in the brain. Once placed, the particles can activate neurons via vibrational motion or magnetoelectric stimulation. Similar particles might be used to read out neuronal electrical pulses via spintronic or liquid-crystal magnetic interactions, for fast bidirectional brain-machine interface. We have shown that particles containing liquid crystals can be read out with magnetic resonance imaging (MRI) using embedded magnetic nanoparticles and that the signal is visible even for voltages comparable to physiological characteristics. Such particles can be moved within the brain (e.g., across midline) without causing changes to neurological firing.

Keywords: magnetic, particles, image-guided MRI, brain-machine interface

1. Introduction

Brain-machine interfaces (BMIs) have made great progress as prostheses (e.g., for vision-impaired individuals). Those patients were willing to undergo major surgery, expense, and to have centimeter-scale electrical devices implanted in their nervous systems. The scope of influence of BMI of the future is clearly large, potentially including cognitive enhancement and memory storage, and quite likely with ramifications beyond anybody's present imagination [1, 2]. To fully exploit the power of BMI, some big steps need to be taken. For wide and long-term public use, the invasiveness of the implant procedure and toxicity of the implant materials need to be eliminated. The number of neuronal channels an implanted device must address needs to be increased by many orders of magnitude, and the entire nervous system must be accessible. The spatial resolution should be smaller or equal to the diameter of small groups of neurons (i.e., micron-sized), and the temporal resolution should be faster than or comparable to neurons in the native brain (i.e., sub-millisecond response time).

Most medical researchers attempt to translate therapeutic approaches from animal models to human use. Unfortunately, there are significant barriers to taking this approach to BMI. Optical dyes that are the mainstay of animal research do not work for animals larger than a few centimeters because of light scattering and the photon-stopping power of tissue. The multi-decade-long history of failure to bring optical mammography into clinical practice suggests that light scatter is not a problem that is easily solved [3]. Implanted tethered electrodes and high-intensity-focused ultrasound can only address one section of the nervous system at a time. Genetic manipulation of brain circuitry (e.g., with optogenetic or sonogenetic techniques) has significantly increased our understanding of preclinical neurosciences, but would still require invasive focal delivery of gene vectors, optical fibers, or ultrasonic transducers that would limit wide use in humans [4, 5].

Oscillating magnetic fields do not interact much with tissue, especially below several gigahertz in frequency, and therefore penetrate the human head readily. Magnetic resonance imaging methods that examine blood oxygen-level dependency (BOLD) rely on vascular changes that have a poor spatial and temporal resolution. Magnetic resonance imaging (MRI) pulse sequences that read out electrical current (e.g., from Lorentz forces causing neuronal displacement) can detect micro-amp levels (far from the nanoampere currents generated from individual or small neuronal bundles) although technical improvements such as fast magnetic gradients may improve performance in the future [6]. Imaging of electrical currents (magnetoencephalography) is limited to millimeter spatial resolution due to the variable impedance of the brain and the detector resolution [7].

In this chapter, we summarize contrast-enhancement approaches to BMI that could yield readout and writing of the entire brain with high spatial and temporal resolution. Contrast enhancement from radioactive and other materials has been used in radiology practices for the past century to explore and diagnose diseases of the nervous system. The contrast materials that appear the most promising are based on magnetic nanoparticles, which we attempt to describe more fully in this chapter.

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2. Brain access

To date, developers of the smart-dust [8] concept have constructed millimeter-sized particles using wafer-based lithographic methods typically employed for electronic circuitry (e.g., CMOS). Traditional electronic particles below a millimeter in size are difficult to power without a tether to the outside world, because of poor electromagnetic coupling to small antennas. In order to implant or remove electronic particles of these sizes, practitioners need millimeter-sized holes, requiring either surgery or interventional procedures to go through the vessels or subarachnoid spaces. Because of the potential for damage to eloquent nervous structures, such procedures carry risks and expensive and are therefore inappropriate for wide (e.g., consumer) applications.

As will be discussed below, we and others have formulated contrast solutions containing high concentrations of nano-sized particles with magnetic properties (e.g., spintronic, magnetoelectric) that do not need to rely on traditional approaches to enter or interact with the brain. As in drug delivery, we have shown that nanoscale particles can be delivered intranasally, which is considered a noninvasive administration mode in the clinical literature [9, 10]. The cribriform plate separates the nasal from the cranial cavities, with foramina that decline slightly in size with age, with an overall area of 6 mm^2 at age 25 and 4 mm^2 at age 66 [11]. Our group and others have demonstrated that magnetic particles with diameters of up to 250 nm readily enter the cranium with the assistance of a 20-mT magnetic gradient, with no appreciable intracranial entry in the absence of an imposed magnetic field (**Figure 1**). Minimally invasive routes other than intranasal are possible, for example, via lumbar puncture or via intravenous administration. However, both of these routes require overcoming countervailing current flows (of cerebrospinal fluid and blood, respectively) that make them less attractive.

Once in the intracranial cavity, magnetic particles can be manipulated using magnetic gradients for delivery to specific brain foci. The tracks that such particles make are micron-sized, unlike the millimeter scale holes made during conventional deep-brain stimulation surgery. Magnetic particle manipulation is difficult with a conventional MRI, since it is very hard to create magnetic gradients that can overcome the static MRI field strength. However, our group and others have constructed MRI systems where the static field can be temporarily

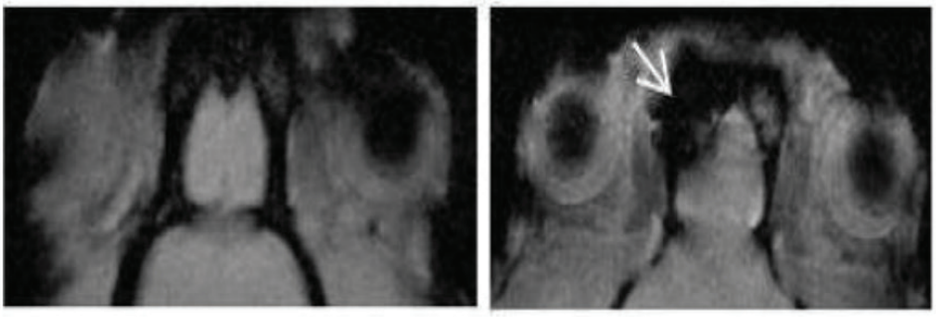

Figure 1. Transport into brain. Rat olfactory bulb before (left) and after (right) intra-nasal administration of particles under magnetic gradient.

eliminated in order to apply magnetic gradients without interference [12]. The MRI's static magnetic field can then be reapplied to assist in real-time image-guided manipulation.

In the past, it was believed that it was impossible to propel magnetic particles deep within tissues because of the particles' tendency to realign and become attracted to the propelling magnets and because particles tend to dissipate instead of aggregate when being pushed through tissue. With appropriate magnetic pulse sequences, it is possible to transiently polarize the particles in the direction opposite to the propelling magnets ("dynamic inversion"), so that the particles can be delivered deep into tissue [13]. With appropriate particle design choices, it is also possible to twist the particles during propulsion, which assists in penetrating tissues without increasing the particle track diameter [14]. Particles transported interstitially through the brain do not rely on vascular transport and therefore effectively bypass the blood-brain barrier.

Once the particles have been delivered to the intended location in the brain, the average distance between particles and neurons is inversely related to the local particle concentration. The distance between particles and neurons is critical to reading out or writing to the brain, since the electrical field decreases rapidly from kilovolts/meter (across the neuronal membrane) to tens of volts per meter (10 μm from the neuron). It may be possible to decrease the effective particle-neuron distance by coating the particle with materials in configurations that promote penetration of the neural membrane, as has been done with experimental brain electrodes [15].

3. Particle toxicity

For magnetic particles to become widely used, the particles must have a negligible potential for toxicity [16]. This very high bar is reflected in the Food and Drug Administration's (FDA) classification of devices for the brain as class III, requiring a premarket approval (PMA) application. In comparison, devices for the peripheral nervous system are often treated as class II devices. Note that particles are often treated by the FDA as drugs, although in Europe, they may be treated as devices. Studies of ex vivo vital rodent brain slices have shown that the presence of magnetic particles does not cause a measurable disruption of function [17]. In fact, it is not unusual for humans living in industrial cities to have magnetic particles in their brains, with no known related diseases [18]. It is also very common for humans over 50 years of age to have radio-dense "calcifications" in the basal ganglia, again with no definite disease association [19]. Small animal studies have examined the toxicity of magnetoelectric particles with no adverse effects [20].

4. Particle fabrication

Traditionally, implantable medical devices for neurostimulation have been built with CMOS processes (like other electronic devices). This approach is not scalable to nano-sized products that are needed for noninvasive access. Most of the magnetic particle literature was contributed in the field of bioassays, where particle uniformity is not critical. However, for medical applications (e.g., magnetic particle imaging), lack of particle uniformity is often a limiting factor [21].

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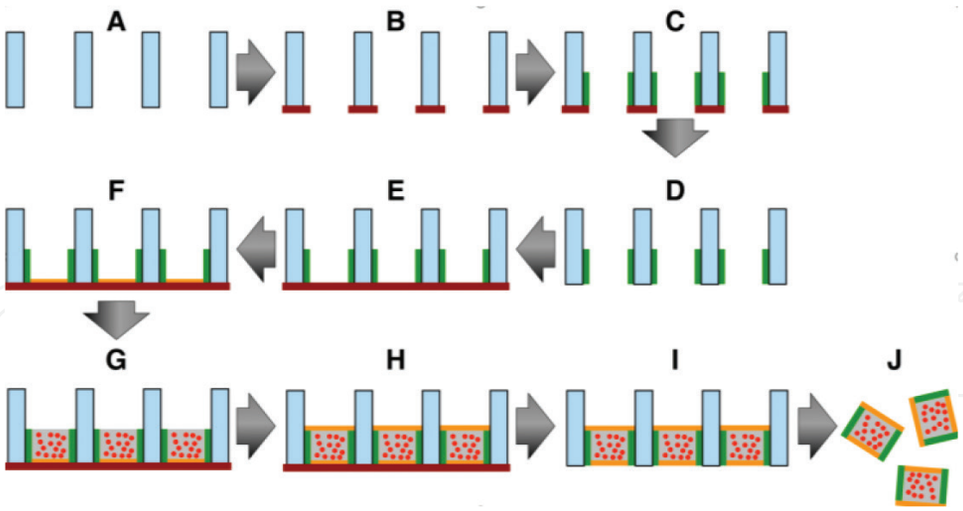

Figure 2. Example of template-guided shape-engineered synthesis of magnetic particles. Particles are made via sequential processing of polycarbonate track etched (PCTE) membrane films. PCTE films have pores extending through the thickness of the film. Templates (A) are first partially sealed on one surface with a conductive layer (B), followed by deposition of a polymer (e.g. poly-lactic-co-glycolic acid) shell inside the pores of the PCTE (C). Selectively etching the partially sealing conductive layer (D) and replacing it with a completely sealing conductive layer (E) allows for deposition of a conformal gold layer (F), after which a payload (e.g. liquid-crystal-magnetic composite) can be deposited by vacuum impregnation into the sealed pores of the PCTE film (G). Deposition of a final sealing layer (H), followed by selective etching of the conductive sealing layer (I) and removal of PCTE film (J) results in free-floating particles.

We have used template-guided methods to build shape-engineered highly uniform magnetizable particles with features important for transport and effectiveness [22] (**Figure 2**). For example, different sections of the particles can be built with aspect ratios that favor a particular magnetization direction. With appropriate use of precessing magnetic fields, the particles can be drilled through tissue [14]. The template-guided methods are also economical: it is possible to fabricate micromolar quantities of particles for less than $20 in raw materials. We have evaluated nanoscale spintronic devices for voltage sensing and stimulation, which have very tight tolerances. Transitioning these devices in their current morphologies to template-guided manufacturing (with tolerances of a few nm) may be challenging and may require device redesign.

5. Neuronal readout

Although neurons affect each other over nanoscale distances through chemical means (e.g., neurotransmitters), longer neuronal transmissions are electrical in nature. Noninvasive neuronal sensing in humans has generally employed either electrical methods to detect electrical fields or magnetic methods to detect electrical currents. Noninvasive external measurements of electrical fields from deep in the brain (e.g., with electroencephalography) yield centimeter-scale resolution because of the complicated impedance of the brain and surrounding tissues. Direct measurements of magnetic fields can be obtained with magnetoencephalography, but the resolution is limited to millimeter scales because of detector-size limitations.

Our working hypothesis is that the magnetic readout of contrast materials with magnetic resonance imaging (or the related field of magnetic particle imaging) is the way to go. With fast high magnetic gradients, magnetic resonance imaging (MRI) can achieve 30 μm spatial resolution (**Figure 3**) and kHz temporal resolution. In the past, it was believed that such rapid changes of magnetic fields would induce unwanted neurological stimulation, but we have shown in a prospective human study that if the frequency is high enough, such effects do not occur [23]. Magnetic particle imaging should theoretically be able to detect a single particle; however, experimentally, this has been difficult to achieve because of prior limits on gradient strength and particle uniformity [21, 24]. We have found that with very fast MRI pulse sequences that directly measure the reduction in local proton signal decay time, it is possible to detect as few as 1000 particles.

5.1. Readout with magnetic particle/liquid-crystal composites

There are several ways that magnetic particles can report on local electrical fields. The most promising in terms of field sensitivity takes advantage of liquid crystals, whose orientation can be used to detect low local electrical fields, for example, at a few volts per meter [25]. For purposes of comparison, voltage-sensitive dyes report on changes on the orders of kilovolts per meters (e.g., tens of millivolts across a 5-nm membrane) [26]. The high spatial and electrical field resolution of liquid crystals enables mapping of electronic layers with a sub-micron resolution [27]. Magnetic nanoparticles have been used to make the liquid crystals more sensitive to electric fields (dielectric permittivity) [28]. The liquid crystals' change in orientation (due to changes in local electric fields) can be transferred to magnetic particles, as validated with X-ray scattering methods (**Figure 4**) [29]. This orientation changes the local magnetic susceptibility, which can be detected with proton MRI (**Figure 5**) [30]. With MRI, we have detected electric fields as low as 20 V/m with this method.

5.2. Readout with piezoelectric magnetic particles

Particles have been built with magnetic cores and piezoelectric shells, where the magnetic moment of the core changes in response to an applied electric field. These magnetic moment

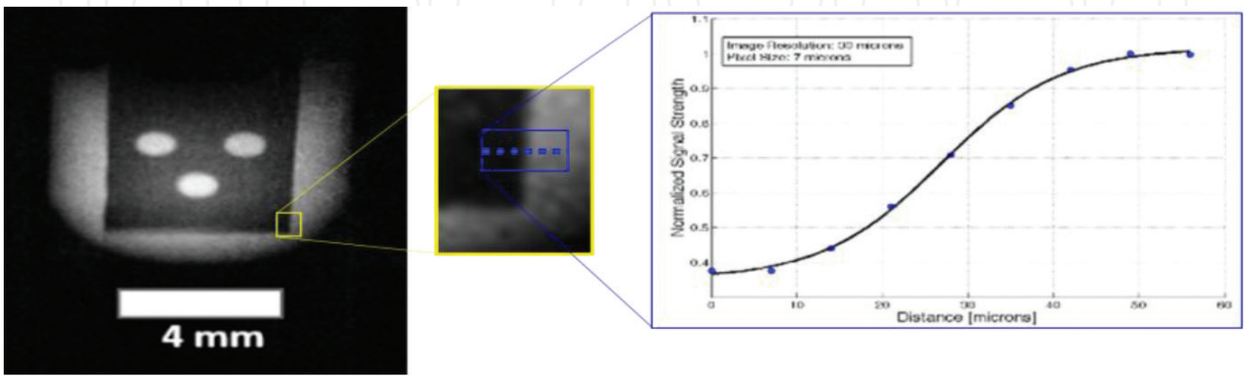

Figure 3. Spatial resolution of low-field MRI with high magnetic gradient strength. Left: spin echo sequence of a water phantom with 7-μm pixels in 2D projection. Right: calculation of spatial resolution of 30 μm.

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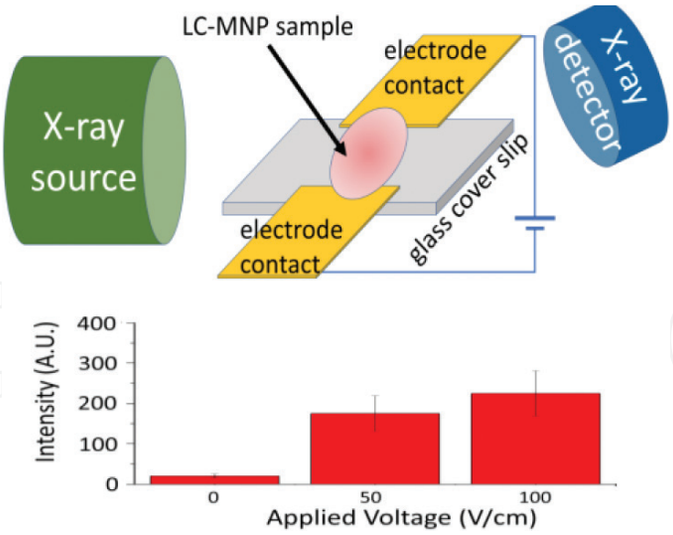

Figure 4. X-ray diffraction experiments with liquid crystal/magnetic particle composites (LC-MNP). Top: LC-MNP films placed in X-ray beam. Bottom: X-ray scattering measurements reveal changes in liquid crystal layer-to-layer spacings based on applied voltage.

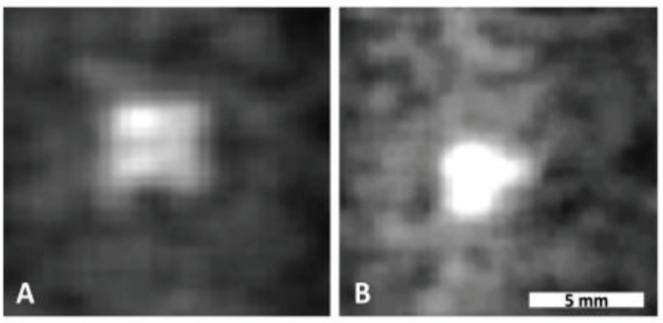

Figure 5. MRI of novel contrast agent. MRI results with no voltage applied (A) and with voltage applied (B). A 5% change in MRI signal is observed with electric fields of 20 V/m (comparable to the field within 10 μm of neurons).

changes can be read out with proton MRI (**Figure 6**). The same particles can be used to generate electric fields in response to an applied magnetic field (discussed subsequently in Section 6) [20, 31, 32].

5.3. Readout with spintronic particles

Spintronic devices act as nano-valves that convert electrical currents into radiofrequency (RF) waves. The devices are also sensitive to applied magnetic fields, which is important since the particles can thereby be localized by applying magnetic gradients (as in MRI). We have shown that a single nano-sized on-chip spintronic device can convert electrical currents in the micro-amp range into radio waves that can be detected centimeters away [33]. Spintronic devices can be ganged synchronously to amplify signals [34]. The micro-amp range is probably too low to detect the state of single neurons, but might be appropriate for tracts. Work needs to be done (e.g., with template-guided synthesis) on freeing the spintronic devices from substrates

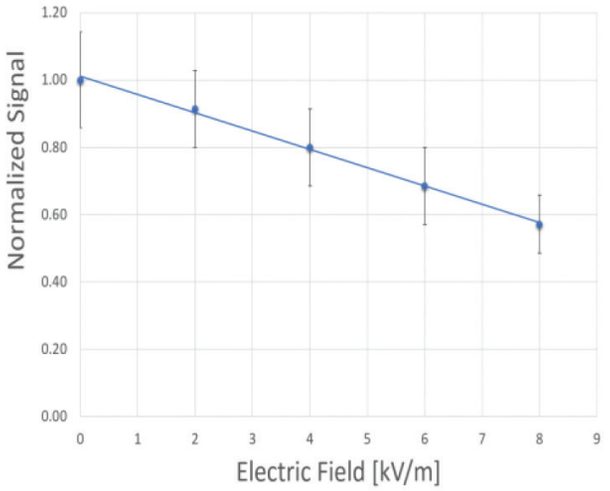

Figure 6. Voltage-sensitive MRI signal from piezo-magnetic particle.

for deployment as a contrast agent. The spintronic particles can be used in a reverse mode for stimulation (with radio-frequency energy converted to low-frequency currents) again with the possibility of localization with applied magnetic gradients [35].

6. Writing to the brain

The brain can be stimulated electrically, chemically and even mechanically. Most brain-machine interface work has been performed with electrical stimulation from invasive focal electrodes, which have advantages of high speed and spatial precision, but can only access a small portion of the brain. Noninvasive electrical stimulation has been performed with transcranial magnetic stimulation, where externally applied changing magnetic fields are used to induce electrical fields and currents in the brain. This technique yields relatively poor spatial resolution (e.g., centimeter scale) at the brain surface, with spatial resolution worsening appreciably in deeper parts of the brain. Externally applied electrical currents have even worse spatial localization capability, since the impedance of various tissues in the head is highly nonuniform. Theoretically, radio-frequency energy could be focused in small regions with high-field MRI, but this technique has not been intentionally used for stimulation [36]. Externally Administered chemical brain modulation is an ancient technique, practiced in pubs daily by millions of people. In a few rare cases, the focal concentration of receptors in certain sections of the brain allows chemical stimulants to target specific regions (e.g., substantia nigra by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin) [37]. Microinfusions of chemicals via brain-implanted catheters have been applied in animal studies for research. Catheters have been implanted in the neuronal sections of human brains to deliver cancer treatment (i.e., convection-enhanced delivery). Externally applied high-intensity-focused ultrasound (HIFU) has been used experimentally to stimulate the brain, although the exact mechanism is not well understood [38]. We hypothesize that magnetic particles may be useful in focal brain stimulation, with focality realized either through noninvasive selective placement of particles (e.g., after magnetically-assisted intranasal

administration) in desired locations or with diffusely delivered particles that can be addressed selectively. In the next sections, we list various candidate magnetic particles for brain stimulation, some of which overlap the prior section for brain readout.

6.1. Mechanical stimulation with magnetic particles

Anecdotal surgical data from the placement of deep-brain stimulation leads have shown that mechanical vibration can stimulate neurons [39, 40]. Cultured neuron studies have demonstrated mechanoreceptors that react by opening calcium channels [41]. Invertebrate experiments suggest that externally applied magnetic gradients can wiggle magnetic particles enough to cause nerve stimulation (**Figure 7**) [42].

6.2. Composite piezoelectric/magnetic particles

With appropriately designed piezomagnetic particles, externally applied magnetic fields can be applied to the particles in order to generate powerful electric fields focally (e.g., strong enough to electroporate cells) [32]. Indirect evidence of global brain stimulation has been collected through electroencephalography of animals [20].

6.3. Electret-based magnetic particles

Recent innovations in harvesting harvesting from mechanical motion have been driven because of the proliferation of wearable devices. Some of the principles of energy harvesting can be reversed in order to generate electrical currents and voltages. Electrets, which rely on changes in capacitance to generate power, are very efficient vibrational energy harvesters. Liquid crystals have been used as electrets for energy harvesting [43]. Typically, liquid crystals require very high magnetic fields to change their capacitance, but the addition of magnetic

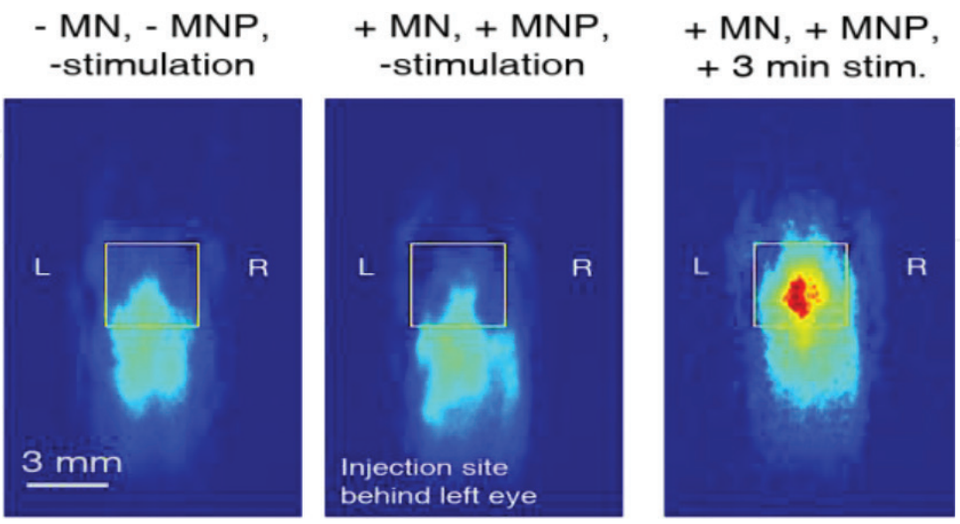

Figure 7. Magnetic particle neurostim-ulation visualized with manganese-enhanced MRI (MEMRI). Particles were injected behind the left eye of crawfish and stimulated for 3 min using magnetic wiggling of particles. Increased MEMRI signal is seen in the left brain.

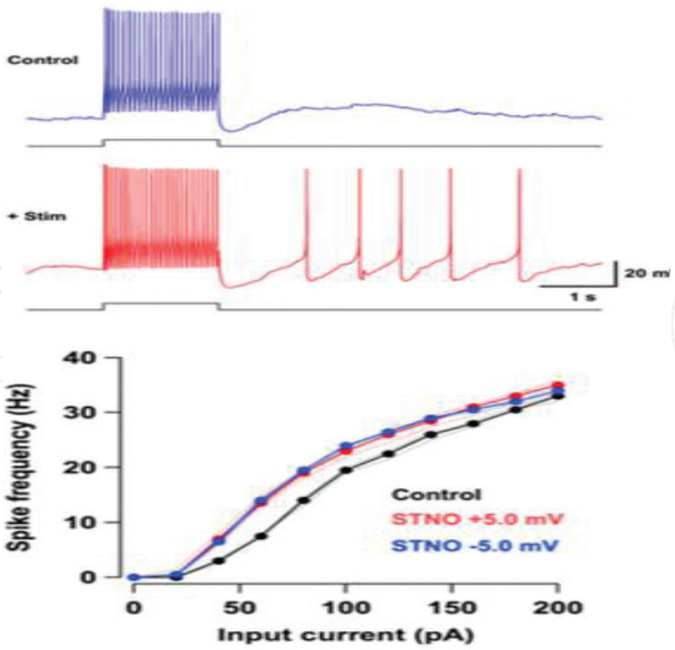

Figure 8. Spintronic particle writing to single neuron. Top: neuro-modulation in vital mouse brain slice (red) when spintronic nano-oscillator (STNO) particle is triggered by RF signal. Bottom: neuronal frequency changes in as a function of applied RF pulse.

dopants dramatically reduces the magnetic field strength required to alter capacitance [28]. Therefore, a composite of magnetic particles and liquid crystals (as discussed above) might be able to convert a changing externally applied magnetic field into local electrical stimulation.

6.4. Spintronic particles

As discussed above, spintronic particles have been used to convert low-frequency electrical currents into high-frequency radio-frequency emissions. Our group successfully reversed this process, to convert applied radio-frequency (RF) radiation into low-frequency electrical currents that were able to affect the firing frequency of a single neuron (**Figure 8**) [35]. An attractive potential application of this technology is that the efficiency of conversion of the RF radiation exhibits frequency dependence that is also a function of the ambient magnetic field. This mechanism would permit spintronic devices to be addressed with micron-level spatial resolution.

7. Conclusion

Magnetic neuroparticle solutions to brain-machine interface were predicted a long time ago and are under development today. As shown above, animal data show that nontoxic magnetic particles could be noninvasively directed to specific locations in the brain under real-time imaging guidance. Particles could be placed with high spatial resolution in focal regions for specific clinical indications (addiction, Parkinson's disease). Alternatively, the particles could be globally spread in the brain and selectively addressed for local stimulation and/

or readout with appropriate RF or magnetic tuning. Many of the particles listed above (e.g., magnetoelectric, electret-based particles) can both read and write electrically and therefore potentially fit the bill for high-speed bidirectionality. Building on the work of deep-brain stimulation, one might expect that the focal stimulation of specific brain nuclei would be the first clinical target for noninvasive or minimally invasive bidirectional BMI. The high temporal and spatial resolution of voltage-sensitive contrast media would likely shed additional light on large-scale brain processes (e.g., attractors [44]) that would be useful in building more eloquent BMIs. System architectures for reading from and writing to the brain would be similar to conventional MRI systems, preferably with the ability to rapidly turn off the static magnetic field in order to manipulate the magnetic particles with high flexibility [12]. Once the particles were placed in the appropriate location, stimulation could be implemented with a wearable coil. Readout with voltage-sensitive contrast media could be performed with conventional MRI systems.

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