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Neuromodulation with electromagnetic stimulation for seizure suppression: From electrode to magnetic coil

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Running title: Seizure suppression with magnetic coil

Abstract

Non-invasive brain tissue stimulation with a magnetic coil provides several irreplaceable advantages over that with an implanted electrode, in altering neural activities under pathological situations. We reviewed clinical cases that utilized time-varying magnetic fields for the treatment of epilepsy, and the safety issues related to this practice. Animal models have been developed to foster understanding of the cellular/molecular mechanisms underlying magnetic control of epileptic activity. These mechanisms include (but are not limited to) (1) direct membrane polarization by the magnetic field, (2) depolarization blockade by the deactivation of ion channels, (3) alteration in synaptic transmission, and (4) interruption of ephaptic interaction and cellular synchronization. Clinical translation of this technology could be improved through the advancement of magnetic design, optimization of stimulation protocols, and evaluation of the long-term safety. Cellular and molecular studies focusing on the mechanisms of magnetic stimulation are of great value in facilitating this translation.

Keywords: epilepsy; magnetic stimulation; animal models; cellular mechanisms

Abbreviations

4-AP: 4-aminopyridine

CD_{50}: Convulsant dose

DBS: Deep Brain Stimulation

EcoG: Electrocorticography

EEG: Electroencephalography

ELF-MF: Extremely low frequency magnetic fields

GABA: Gamma-Aminobutyric acid

HFS: High Frequency Stimulation

KA: Kainic acid

LD_{50}: Lethal dose

LTD: Long-term depression

LTP: Long-term potential

MEG: Magnetoencephalography

MRI: Magnetic resonance imaging

NMDAR: N-methyl-D-aspartate receptor

PTZ: Pentylenetetrazol

REM: Rapid eye movement

tDCS: Transcranial direct-current stimulation

TES: Transcranial electrical stimulation

TLE: temporal lobe epilepsy

TMS: Transcranial magnetic stimulation

rTMS: Repetitive transcranial magnetic stimulation

SMF: Static magnetic field

Epilepsy is one of the most widespread and devastating neurological disorders, with a lifetime prevalence of 7.60 per 1,000 people (Fiest et al., 2017). The disease is characterized by abnormal neural activity in the brain, which ultimately leads to spontaneous recurrent seizures. In the U.S. alone, the annual epilepsy-related medical expenses are close to $15.5 billion (NIH), with yearly epilepsy-specific healthcare costs ranging up to $19,749 per patient (Begley and Durgin, 2015). Despite significant advances made in new pharmacological development (Kaur et al., 2016), traditional anti-epileptic drugs demonstrate limited specificity in targeting particular groups of cells and epileptic neural circuitry. One-third of patients continue to experience pharmacologically intractable seizures (Kwan and Brodie, 2000, Laxer et al., 2014) and may have to consider a variety of surgical options, such as resectional surgery (*e.g.* temporal lobectomy, cortical excision, lesionectomy) and disconnection surgery (*e.g.* corpus callosotomy and functional hemispherotomy). These surgeries are irreversible, and are often associated with many neurological deficits such as memory, speech, motor, and visual impairments (Josephson et al., 2013).

1. Electric stimulation for seizure control

Electric activation of neurons has been reported for more than two centuries, dating back to the discovery by Luigi Galvani in 1780 (Galvani, 1791), who accidently found that muscle from a deceased frog would twitch upon touch with a charged metal scalpel. The event sparked the appreciation of electricity in relation to animation — or life. At present, electric stimulation of neurons in the central and peripheral nervous systems has been successful in controlling neural network activity (Selimbeyoglu and Parvizi, 2010), regulating synaptic transmission (Nowak and Bullier, 1998), alleviating memory loss (Esmaeilpour et al., 2017) and blocking pain (Coderre et al., 1993, Rodrigo et al., 2017). Electric currents have also been clinically used to modulate or suppress seizure activity, as a reversible and adjustable alternative to surgical removal of epileptic foci. One successful therapy is vagus nerve stimulation (Morris and Mueller, 1999, Yuan and Silberstein, 2016, Oliveira et al., 2017).

Deep bran stimulation (DBS)

Electric currents delivered via deeply implanted electrodes, or deep bran stimulation (DBS), have been effective in alleviating seizures in humans. In this practice, many discrete brain structures have been target areas, including the locus coeruleus (Faber and Vladyka, 1983), centromedian nucleus (Velasco et al., 2000), anterior nucleus of the thalamus (Kerrigan et al., 2004, Salanova et al., 2015), cerebellum (Cooper, 1973, Cooper et al., 1973), and other predetermined epileptic foci (Morrell and Group, 2011, Sun and Morrell, 2014). It is generally

believed that the effects of an electric field on neuronal tissue are caused by the establishment of a transmembrane potential (Esselle and Stuchly, 1994, Schnabel and Struijk, 2001, McIntyre et al., 2004, Ye et al., 2007, Lu et al., 2008). In addition, other field-induced mechanisms, such as K^+ release (Shin and Carlen, 2008, Sutton et al., 2013), depolarization blockage (Gluckman et al., 1996, Lian et al., 2003), inactivation of voltage-gated currents (Shin et al., 2007), altered synaptic transmission (Chiken and Nambu, 2014), or altered field coupling among neurons (Ghai et al., 2000), are believed to be involved in the modification of neural network activity. A more detailed discussion is also presented in section 5.

Despite the significant improvement and clinical promise of electrical stimulation for seizure control with directly implanted electrodes, its implementation comes with some technical and biological limitations, mainly invasiveness and poor bio-compatibility.

DBS cannot avoid the risks of major surgery including hemorrhage (1–2%) and infection (3–5%) (Doshi, 2011, Bjerknes et al., 2014). Other complications include lead migration (1.60%) and electrode fracture (1.46%) (Jitkritsadakul et al., 2017). The complication rate is dependent on the experience of the surgical team.

A primary concern in DBS device design is biocompatibility of the implanted electrodes (Polikov et al., 2005). Therapeutic effects can be largely altered by inflammatory and immune responses due to the direct contact between the tissue and stimulating electrode (Kim et al., 2004, Liu et al., 2017). The formation of glial scarring around individual electrodes (Polikov et al., 2005, Grill et al., 2009) can block electric currents produced by the electrode, which causes a change (or even loss) of the resultant neural response. Electrodes implanted into the primary visual cortex of macaque monkeys lost effectiveness within a few months, even though each electrode had reliably elicited a visual percept (phosphene) shortly after implantation (Davis et al., 2012). There is some recent exploration into new electrode designs and implantation techniques to minimize tissue response and promote long-term stability of the implants (Liu et al., 2017, Luan et al., 2017).

When DBS patients are examined by Magnetic Resonance Imaging (MRI), excess heat can be produced at the stimulating electrode tip due to the interaction between the MRI-generated radio-frequency waves and the conductive leads (Angelone et al., 2004), which can result in neurological damage (Rezai et al., 2004). In examination of possible alternatives to the customary platinum-iridium electrodes, carbon nanotube yarns have demonstrated improved biocompatibility and decreased MRI distortion (Jiang et al., 2013, Guo et al., 2015).

Transcranial direct current stimulation (tDCS)

tDCS, a noninvasive method that modulates cortical excitability, was developed in the last 20 years for the treatment of epilepsy. tDCS is applied using two electrodes (anode and cathode) positioned on the cranium to deliver a weak electric current and alter cortical excitability. Cortical excitability decreases under cathodal stimulation (Nitsche and Paulus, 2000), a principle used for suppressing epileptiform discharges and seizures in basic and clinical studies of epilepsy (Fregni et al., 2006c, Varga et al., 2011, Yook et al., 2011, Auvichayapat et al., 2013, San-Juan et al., 2017, San-Juan et al., 2018). tDCS is generally considered safe in clinical practice (Matsumoto and Ugawa, 2017). tDCS experimental protocols have resulted in only minor side effects, including mild headache and itching at the site of electrode placement (Fregni et al., 2005) (Fregni et al., 2006a), but no obvious adverse effects such as cognitive impairment (Fregni et al., 2006a).

New methods have been developed in recent years to further improve the efficiency of neural control by tDCS. Voroslakos et al. developed an "intersectional short pulse" method to increase the intensity of the electric current injected into the brain, and to keep the sensation on the scalp surface relatively low (Voroslakos et al., 2018). Grossman et al. used temporally interfering electric fields to stimulate neurons throughout a region where interference between the multiple fields establishes an electric field envelope (Grossman et al., 2017). The researchers demonstrated that temporally interfering stimulation facilitated the targeting of deep neurons in living mice without stimulating overlying cortical cells. Using a rodent model of generalized epilepsy, Berenyi et al. developed a closed-loop system to provide on-demand stimulation, which avoided detrimental side effects of continuous stimulation (Berenyi et al., 2012). These works have significantly improved the temporal and spatial resolution of tDCS.

2. Magnetic stimulation as an alternative method in neural modulation

While electric currents delivered by tissue-contacting electrodes have provided a physical mechanism to modulate neuronal activity, electric currents can also be generated via magneto-electric induction with magnetic coils (Maccabee et al., 1991, Maccabee et al., 1993, Ye et al., 2010, Ye et al., 2011, Ye and Steiger, 2015). Magnetic stimulation on excitable biological tissues was first reported in the early 20th century by Jacques d'Arsonval (1896) and Silvanus P. Thompson (1910) with their pioneer work on human visual sensations. Effects of a time-varying magnetic field are generally believed to be caused by its induced electric field and the establishment of a transmembrane potential (Ye et al., 2007) (Pashut et al., 2014). In comparison to electrical stimulation, magnetic stimulation offers advantages in biocompatibility and consistency.

While electrodes require direct contact with biological tissue, magnetic stimulation may stimulate neural tissue without requiring surgery for coil implantation. The magnetic field can penetrate biological tissue without much attenuation, thereby maintaining its intensity and stimulation consistency.

More importantly, magnetic stimulation can prevent the direct contact between an electrode and neural tissue, eliminating numerous problems that arise at the brain-electrode interface. For example, issues including charge transfer, electrode surface modification, and corrosion are reduced through coil-based stimulation (Polikov et al., 2005, Cogan, 2008, Koivuniemi et al., 2011). The coils are capable of stimulating specific nuclei with decreased disruption of surrounding regions. By avoiding direct contact with brain tissue, these coils greatly enhance biocompatibility and MRI compatibility (Golestanirad et al., 2018, Zaeimbashi et al., 2018).

Coils may still be implanted if focal stimulation is required. The coils are insulated with a soft biocompatible material, which attenuates the cortical tissue response to implantation (Saxena et al., 2013, Canales et al., 2015, Lee et al., 2016) while increasing stimulation intensity to the target tissue. Regulating the spatial orientation of miniature-sized implantable coils allows the induced electric fields to be specifically designed to activate particular groups of neurons while simultaneously avoiding others (Bonmassar et al., 2012, Lee and Fried, 2014). In the cortex, this could include the ability to activate vertically oriented pyramidal neurons without activating horizontally oriented passing axons (Lee et al., 2016). Encapsulation of the miniature coils could prevent many adverse effects and the diminishing of coil performance over time, as occurs with electrodes (Lee et al., 2016).

3. Epilepsy treatment with magnetic field and its safety

Reports on epilepsy treatment with magnetic field emerged in the 1990s (Anninos et al., 1991, Anninos et al., 1999). It was reported that magnetic field caused attenuation in seizure frequency and alteration in the circadian occurrence of seizure (Sandyk and Anninos, 1992b). The authors proposed that magnetic fields alter the functions of the pineal gland, which is a magnetosensitive organ that "transduces" environmental information of the light-dark cycle and earth's magnetic field into an endocrine message. This message, mediated via circadian release of melatonin, attenuates seizure activity. In a case report, external magnetic field was applied to seizure foci (Sandyk and Anninos, 1992a). This was done by emitting back the same intensity and frequency of magnetic field defined by the magnetoencephalography (MEG) from the patient. The method was successful in mitigating seizure activity in over 150 patients with

various forms of epilepsy. Similarly, it was found that external magnetic stimulation applied in the frontal, occipital, and temporal lobes resulted in rapid attenuation of the MEG activity of epileptic patients (Anninos et al., 2003).

At present, repetitive transcranial magnetic stimulation (rTMS) is amongst emerging options for seizure treatment. Overall, case reports demonstrate reduction of seizure frequency and/or epileptic discharges after rTMS applications. Menkes and Gruenthal investigated the impact of slow-frequency rTMS in a patient with medically refractory partial seizures due to focal cortical dysplasia (Menkes and Gruenthal, 2000). rTMS led to a 70% decrease in the frequency of seizures and a 77% reduction in the occurrence of interictal spikes. In another study, rTMS was delivered to the vertex with a round coil, at an intensity 5% below motor threshold (Brasil-Neto et al., 2004). This led to a 22.8% decrease in the mean daily number of seizures in patients. Kinoshita et al. evaluated the effects of rTMS on seizure frequency in adults with medically intractable extratemporal lobe epilepsy (Kinoshita et al., 2005). After low-frequency rTMS for one week, the frequency of all seizure types, complex partial seizures, and simple partial seizures was reduced by 19.1, 35.9, and 7.4%, respectively. Liu et al. reported that transcranial magnetic stimulation (TMS) decreased seizure frequency for refractory focal status epilepticus in the intensive care unit (ICU) (Liu et al., 2013). In a randomized double-blinded study, rTMS significantly decreased the number of seizures in the active compared with the sham rTMS group for patients with refractory epilepsy and malformations of cortical development (Fregni et al., 2006b). Likewise, low-frequency high intensity rTMS (90% resting motor threshold) delivered into the epileptogenic zone had a significant antiepileptic effect on patients with refractory partial seizures (Sun et al., 2012). A recent meta-analysis revealed a 30% average rate of 50% seizure reduction when low-frequency rTMS was used in the treatment of drug-resistant epilepsy (Cooper et al., 2018). This is consistent with previous analysis that identified a 34% reduction in seizure frequency after rTMS treatment (Hsu et al., 2011).

In general, rTMS is a safe practice with some side effects. Liu et al. reported that rTMS was safe and did not interfere with the functioning of ICU equipment (Liu et al., 2013). In a systematic review, Pereira et al. summarized 46 studies with epileptic subjects undergoing rTMS. Among these subjects, 18.3% reported adverse events. The majority of the adverse effects were mild, with headache or dizziness being most common. The authors calculated a 2.9% per subject seizure risk (Pereira et al., 2016). It appears that in about 2% of the studies, rTMS could induce seizures, especially when rTMS was implemented in relatively high frequency (Rossi et al., 2009). A recent systematic review of available data indicates that risk

from TMS/theta-burst stimulation is small in children and is similar to that in adults (Allen et al., 2017).

4. Basic research that investigates magnetic control of epilepsy

Although clinical and experimental results show that magnetic stimulation, including rTMS, is effective and relatively safe in the treatment of epilepsy, the characteristics of the magnetic field are empirical in these studies. Most of the explorations were case reports and randomized trails, which showed high dependency on individual parameters. Animal models were developed to provide better control of these parameters in basic lab research, and to provide in-depth study of the neurological mechanisms underlying magnetic control of seizure.

Interactions between inhibitory and excitatory elements shape neural network activity (Ziburkus et al., 2006). Alteration of this balance is believed to be the underlying mechanism of epileptogenesis (Epsztein et al., 2006, Derchansky et al., 2008, Lasztoczi et al., 2009, Huberfeld et al., 2011). Therefore, animal models of epilepsy were developed mainly by disrupting this balance. Current animal model work focuses on investigating the possibility of magnetic intervention in restoring the excitation/inhibition balance. A few studies have started to delineate the neurological mechanisms of its action.

Magnetic fields may suppress seizure by altering the inhibitory network. Sung et al. found that magnetic field exposure decreases an animals' convulsion susceptibility to bicuculline (an antagonist of $GABA_A$ receptors) (Sung et al., 2003). Mice were exposed to either a placebo, or 20 G of extremely low frequency magnetic fields (ELF-MF) for 24 hours. Bicuculline was administered intraperitoneally at various doses and the seizure onset time and duration were measured. In addition, lethal dose (LD_{50}) and convulsant dose (CD_{50}) of the clonic and tonic convulsions were measured. The mice subjected to ELF-MFs showed moderately higher CD_{50}, LD_{50}, and induction time on the bicuculline-induced seizure. In another investigation, Kistsen et al. studied the anticonvulsive effects of different modes of impulse magnetic field on the picrotoxin (a non-competitive channel blocker of $GABA_A$ receptors) seizure model, with the animals exposed to a big ring coil (Kistsen et al., 2016). In the study, picrotoxin was injected at a dose of 2.5 mg/kg subcutaneously after either rTMS or a placebo. Exposure to rTMS caused a decrease in the number of seizures and a reduction in the convulsive readiness of the brain, which was quantified by the latent period of myoclonuses during the picrotoxin test. These works suggest that magnetic stimulation may alter the convulsion susceptibility through a GABAergic mechanism.

Magnetic fields may suppress seizure by altering the excitatory network. Sung et al. studied the effects of magnetic field exposure on the convulsant and lethal doses of NMDA-

induced seizures in animals (Sung et al., 2003). Subjection to magnetic field was followed by a significant increase in glutamate and decrease in GABA levels in this seizure model. Yet, this elevation in glutamate concentration did not precipitate an increase in convulsion response. Pentylenetetrazol (PTZ) increases calcium and sodium influx to the cell, both of which depolarize the neuron. After intraperitoneal administration (60 mg/kg) of PTZ, mice were exposed to a 50 Hz, 2 G (0.2 mT) magnetic field in glass cages for 1 hour. This magnetic field did not demonstrate a significant effect on the average number of PTZ-induced seizures, seizure latency, total seizure duration, or mortality (Keskil et al., 2001). In another work, magnetic stimulation was applied to a rat kainate (a glutamate receptor agonist) status epilepticus model. Bursts of high-frequency rTMS, together with a low dose of lorazepam, suppressed seizures (Gersner et al., 2016a). Therefore, the minimal effect of magnetic field on the excitatory network could be promoted in conjunction with pharmacologic approaches.

Magnetic fields may suppress seizure by altering cellular properties. Repeated stimulation of the amygdala can prompt afterdischarges and motor seizure (Chen et al., 2016). Potschka et al. found that chronic exposure of rats to a 50-Hz, 100-μT magnetic field exerted weak inhibitory effects on some seizure parameters in amygdala kindled rats (Potschka et al., 1998). In another study, application of rTMS during amygdala kindling prevented seizures. A cellular mechanistic study revealed that rTMS administration inhibited kindling-induced changes in the electrophysiological properties of hippocampal CA1 pyramidal neurons (Shojaei et al., 2014).

Magnetic fields may suppress seizure by altering synaptic activity. Varro et al. studied the effects of extremely low frequency electromagnetic field (ELF-EMF) on living rats. Animals were then sacrificed and the brain slices were examined (WhB or “Whole body group”). The authors compared this to a group to rats who were not exposed to magnetic field while they were living, but rather their brain slices were exposed to the ELF-EMF (”slice group”). Interestingly, the development of seizure-like activity was promoted in the WhB group. In contrast, seizure activity was inhibited in the slice group (Varro et al., 2009). The authors concluded that ELF-EMF exposure exerts significant effects on synaptic activity, which depended on the specific spatial parameters and constancy of EMF.

These animal model investigations provide a link between bench studies and clinical practice. Outcomes from such systemic level works beg for in-depth analysis of cellular and molecular studies on the biological effects of magnetic fields.

5. Possible cellular mechanisms underlying magnetic field stimulation

Electric fields that are induced by the magnetic stimulation have been found to control many aspects of neuronal behavior, which set the foundation for the magnetic control of seizure. However, in comparison to the large body of literature studying the cellular basis of seizure control with direct electric stimulation, studies with magnetic field as an inhibitory stimulus are rare. There are several possible molecular/cellular mechanisms by which magnetic fields could affect network activity, and potentially suppress seizure, namely (A) direct alteration of neuronal excitability, (B) alteration of ion channel functions, (C) alteration of synaptic transmission, (D) interruption of ephaptic effects, and so on.

(A) Direct alteration of neuronal excitability by induced membrane polarization

Evidence supports the direct membrane polarization of individual neurons by magnetically-induced currents in neuronal tissue. In vivo and in vitro studies from TMS revealed that low frequency stimulation decreases neural activity, while high frequency stimulation excites neural circuitry (Dayan et al., 2013, Parkin et al., 2015). Application of rTMS conserved normal neuronal firing of CA1 pyramidal neurons induced by kindling and prevented hyperexcitability in these cells (Shojaei et al., 2014, Moradi Chameh et al., 2015). Micro-magnetic stimulation, using a small coil, has been successful in the local activation of neurons *in vitro* (Bonmassar et al., 2012) and *in vivo* (Park et al., 2013), offering potential advantages over electric field and TMS due to enhanced spatial selectivity in neural control. Lee et al. described a new micro-coil design to activate cortical neurons and drive behavioral responses (Lee et al., 2016).

Computational work on the effects of magnetic stimulation on neurons provides valuable, quantitative insight and supporting evidence for the direct polarization of the cell membrane by the magnetic field. Using analytical methods, we calculated the induced membrane potential for a spherical cell (Ye et al., 2007) and internal organelles (Ye et al., 2010). Other works focused on axonal responses to the fields (Schnabel and Struijk, 2001) (Esselle and Stuchly, 1994, Ye et al., 2011), or axons located at the center of a nerve bundle (Nagarajan and Durand, 1995). Numerical simulation allows for the insertion of ion channels into modeled cells, which provide a close-to real morphological representation of the cell. Using this method, it was found that magnetic stimulation depolarized the soma of central nervous system neurons, followed by initiation of an action potential in the initial segment of the axon (Pashut et al., 2014). Goodwin and Butson modeled cortical neurons subject to external TMS, and found that the sites of neural activation are coil orientation dependent (Goodwin and Butson, 2015). This finding is consistent with previous animal studies, which indicated that the effects of magnetic field on synaptic activity are influenced by spatial parameters (Varro et al., 2009).

(B) Control of neuronal activity and network excitability via alteration of ion channels

Change in neuronal excitability is associated with the modulation of ionic channels under magnetic stimulation. Specifically, modifications in the electrophysiological properties of Na^+-channels, A-type K^+ channels, and Ca^{2+} channels are associated with altered neural excitability in rTMS (Tan et al., 2013). Computational simulation suggests that magnetic stimulation could adjust sodium channel currents and field excitatory postsynaptic potentials in rat hippocampal CA1 neurons (Zheng et al., 2017).

Modification in ionic homogeneity could be an interesting strategy for seizure blockage through the electromagnetic field. In support of this notion, it was found that high frequency (140 Hz) electric stimulation of hippocampal slices induced an increase in the extracellular potassium concentration and blocked neuronal depolarization (Lian et al., 2003). Bikson et al. (2001) found that during high frequency stimulation (HFS), the increase in extracellular potassium concentration ($[K^+]_e$) coincided with suppressed epileptiform activity. Likewise, HFS or elevated K^+ depresses neuronal activity in the rat entopeduncular nucleus (Shin et al., 2007). It is hypothesized that direct magnetic stimulation can suppress seizures via an increase in $[K^+]_e$, leading to an inactivation of voltage-dependent ion channels and depolarization blockade.

(C) Control of neural activity via alteration in synaptic transmission

Magnetic field could alter synaptic transmission via its induced electric field, including long- term and short-term modulation. Magnetic field generated by a circular coil (50Hz, 100 mT) increased long term potential (LTP) induction in the hippocampal area of rats (Komaki et al., 2014). In addition, 100 Hz pulsed sinusoidal magnetic field can also modulate LTP in the hippocampus (Dong et al., 2018), likely due to a NMDAR-dependent mechanism (Tokay et al., 2009).

Research on the effects of magnetic field on short term synaptic plasticity is rare. However, one can make speculations from works of electric field stimulation. Short-term depression of synaptic transmission was observed during high frequency electric stimulation in the globus pallidus in rats (Rav-Acha et al., 2005) and in primates (Erez et al., 2009). Depression of synaptic transmission by HFS could be due to the fact that HFS-induced release of inhibitory GABA molecules is more prominent than the excitatory neurotransmitter (Feuerstein et al., 2011). Alternatively, it could be due to axonal and/or synaptic failure, which suppress the synaptic transfer of firing rate oscillations, synchrony, and rate-coded information during high frequency DBS (Rosenbaum et al., 2014). DBS-induced short term depression is a major therapeutic mechanism of DBS for Parkinson's disease. It was found that stimulation can

decouple pre- and post-synaptic spiking patterns and suppress pallidal β oscillations in Parkinson's patients (Rosenbaum et al., 2014).

(D) Interruption of ephaptic coupling

Neurons affect each other via local electric fields, a phenomenon called ephaptic coupling. The functional significance of ephaptic coupling was largely ignored until the 1960s, when an inhibitory function of mauthner cells in goldfish was discovered (Furukawa and Furshpan, 1963). Via ephaptic interaction, these cells control 40-80 interneurons (Faber and Korn, 1983). Ephaptic interactions play a critical role in non-synaptic epileptogenesis (Haas and Jefferys, 1984, Richardson and O'Reilly, 1995). Communication among cells via ephaptic coupling could facilitate synchronized activity, epileptic-like neuronal bursting (Dudek et al., 1998), and neuron-glia communication (Amzica and Steriade, 2000). As such, interruption of ephaptic interaction between neurons, using external electric stimulation, has been proposed as a key neuronal mechanism for seizure suppression (Ghai et al., 2000). Similarly, by interrupting ephaptic coupling mechanisms in epileptogenesis, magnetic field could also de-synchronize neuronal firing and suppress seizure via its induced electric field.

(E) Other mechanisms

The impact of magnetic field is not only limited to neurons and their activation/deactivation. Magnetic fields can also enhance adult neural stem and progenitor cell proliferation (Cullen and Young, 2016). In addition, magnetic fields may effect microglia, which can modulate normal neuronal activity. Low intensity, high frequency rTMS following ischemic injury or demyelination activates microglia (Fang et al., 2010, Raus et al., 2013). On the other hand, high intensity, high frequency rTMS applied to injured spinal cord decreased microglial activation (Kim et al., 2013). In another study, high intensity, low frequency rTMS did not significantly change microglial number in the motor cortex or hippocampus of healthy rats (Liebetanz et al., 2003). The various results and limited number of studies assessing the effects of TMS on microglia suggest the need for further research in this area.

6. Translational Considerations

Several practical strategies could potentially improve the transition into more clinically relevant contexts. It is premature to completely replace current pharmacological treatments with magnetic stimulation in seizure treatment. Rather, a combination of the two could be expected to yield more efficient seizure suppression. For example, bursts of high-frequency rTMS, together with lorazepam, suppresses seizures in a rat kainate status epilepticus model (Gersner et al., 2016a), with the combined methods more effective than rTMS alone. In another example,

static magnetic field (SMF) is more effective in decreasing audiogenic seizure severity when administrated with the anticonvulsant phenytoin (McLean et al., 2003) (McLean et al., 2008). The combined methods can potentially reduce the required dose of the anticonvulsant medicine (and, therefore, the likelihood of medication-induced side effects). Future research should address issues that could potentially improve the outcomes of the complementary therapies.

As a replacement for electric stimulation with invasive electrodes, magnetic stimulation must also overcome some of the limitations that occur with electric stimulation. For example, specific stimulation of certain cell types is not easily addressed. Nevertheless, delicate design of the coil can provide a desired electric field distribution that significantly improves specificity of the target. It is possible to construct customized coils to fit the needs of specific requirements and animal models (Tang et al., 2016). While conventional rTMS stimulators activate only superficial cortical areas, it is possible to reach deep epileptic foci, such as in temporal lobe epilepsy (TLE), by using specially designed H-coils (Gersner et al., 2016b). Furthermore, mini-coils can be covered in biocompatible material and positioned inside the animals, closer to the distinct target (Lee et al., 2016).

The ultimate goal of epilepsy therapies is to control seizure while minimizing side effects. A closed-loop system that can automatically detect seizure activity, optimize stimulus input, and apply current to the coil would be an ideal system for precise, low cost, and efficient seizure control with magnetic field. Successful examples of closed-loop control systems for seizure control have emerged from transcranial electrical stimulation (TES) studies (Berenyi et al., 2012, Kozak and Berenyi, 2017). The closed-loop approach also generated promising results in optogenetic inhibition of epilepsy (Krook-Magnuson et al., 2013), in which EEG has been used to predict and trigger optogenetic inhibition of excitatory principal cells, or to activate a subpopulation of GABAergic cells. For rTMS control of seizure, EEG has been used to guide rTMS in a rat kainic acid （KA) epilepsy model. In this study, the idea of closed-loop control emerged but had not been fully developed. EEG was continuously viewed by an operator who identified each seizure onset (Rotenberg et al., 2008).

The above-mentioned, successful closed-loop examples in TES and optogenetic studies could shine some lights on closed-loop seizure control with magnetic fields. This control diagram could be constructed to form a therapeutic loop. First, seizure signal must be reliably measured through electrophysiological recording, such as electrocorticography (EcoG), electroencephalography (EEG), and single unit recording. Other physiological parameters can also be measured to improved seizure prediction, such as blood flow, blood oxygenation, metabolism (Schwartz, 2007, Zhao et al., 2011, Patel et al., 2013), and heart rate (Lockman et

al., 2011). Features of these recordings will then be extracted with computational tools. Previous work done in these areas could be readily adapted into an innovative closed-loop system for seizure control with magnetic field. The above mentioned novel coil design will ultimately provide more specific stimulation, which will be seamlessly integrated into a system that contains hardware and software design for accurate temporal prediction and stimulation.

Concluding remarks

Despite the promising clinical potential for magnetic treatment of epilepsy, significant progress is still necessary. This includes the advancement of magnetic design, optimization of stimulation protocols, and evaluation of the long-term safety of these approaches so that the technique can become more translatable for clinical use in humans. Basic laboratory research that focuses on the mechanisms of magnetic field stimulation at the molecular, cellular, and network levels are of great value in facilitating this translation. We are optimistic that these challenges are not insurmountable, and that magnetic stimulation can become a reliable, practical method for epilepsy treatment with the continued close collaboration of clinicians, neuroscientists, engineers, and regulators.

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