Progress in neuromodulation of the brain

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Review article

Progress in neuromodulation of the brain: A role for magnetic nanoparticles?

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ABSTRACT

The field of neuromodulation is developing rapidly. Current techniques, however, are still limited as they i) either depend on permanent implants, ii) require invasive procedures, iii) are not cell-type specific, iv) involve slow pharmacokinetics or v) have a restricted penetration depth making it difficult to stimulate regions deep within the brain. Refinements into the different fields of neuromodulation are thus needed. In this review, we will provide background information on the different techniques of neuromodulation discussing their latest refinements and future potentials including the implementation of nanoparticles (NPs). In particular we will highlight the usage of magnetic nanoparticles (MNPs) as transducers in advanced neuromodulation. When exposed to an alternating magnetic field (AMF), certain MNPs can generate heat through hysteresis. This MNP heating has been promising in the field of cancer therapy and has recently been introduced as a method for remote and wireless neuromodulation. This indicates that MNPs may aid in the exploration of brain functions via neuromodulation and may eventually be applied for treatment of neuropsychiatric disorders. We will address the materials chemistry of MNPs, their biomedical applications, their delivery into the brain, their mechanisms of stimulation with emphasis on MNP heating and their remote control in living tissue. The final section compares and discusses the parameters used for MNP heating in brain cancer treatment and neuromodulation. Concluding, using MNPs for nanomaterial-mediated neuromodulation seem promising in a variety of techniques and could be applied for different neuropsychiatric disorders when more extensively investigated.

1. Introduction

Neurological disorders are of huge impact in society. More than 90.000 disability adjusted life years (DALYs) are estimated for neurological disorders in the year 2015 increasing to a number of 100.000 DALYs in 2030 (WHO, 2017). A larger part of these disorders includes both mental as well as neurodegenerative disorders. One example is Parkinson's disease (PD), increasing in incidence mainly due to the increase in human life expectancy (Schrag et al., 2000; van de Vijver et al., 2001; Totaro et al., 2005, Havulinna et al., 2008; Hirsch et al., 2016). The prevalence and thus disability due to PD has more than doubled from 1990 to 2015, with an estimation of 6.2 million people currently having PD worldwide. This number is expected to grow exponentially in the next decades (Dorsey and Bloem, 2018) causing a

Abbreviations: AD, Alzheimer's disease; aDBS, adaptive deep brain stimulation; AMF, alternating magnetic field; *C. elegans*, *Caenorhabditis elegans*; CED, convection-enhanced delivery; CNO, clozapine N-oxide; DBS, deep brain stimulation; DREADD, designer receptors exclusively activated by designer drugs; EAS, electric acoustic stimulation; ET, essential tremor; FUS, focused ultrasound; GBM, glioblastoma multiforme; GPCRs, G-protein coupled receptors; HEK, human embryonic kidney; HIFU, high-intensity focused ultrasound; MHT, magnetic hyperthermia; MNPs, magnetic nanoparticles; NHP, non-human primates; NIR, near-infrared; PD, Parkinson's disease; PEG, polyethylene glycol; RF, radio-frequency; (r)lPG, (rechargable) implantable pulse generator; SAR, specific absorption rate; SLP, specific loss power; STN, subthalamic nucleus; tFUS, transcranial focused ultrasound; (d)TMS, (deep) transcranial magnetic stimulation; TRPV(1), transient receptor potential vanilloid (Type 1); UCNPs, upconversion nanoparticles; US, ultrasound; VTA, ventral tegmental area

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substantial socio-economic burden for our society. For management of these disorders, we are in need of adequate treatment options. Unfortunately, up to now, preventive and drug-based therapies have shown limited progress and are not delivering the breakthroughs that the medical field needs to confront the challenges associated with population ageing (Temel and Jahanshahi, 2015). Mainly improving the blood-brain barrier (BBB) permeability remains a challenge for drug-based therapies.

Contrary to this, the field of neuromodulation is progressing rapidly to continuously improve existing treatment strategies and to deliver new ones. In recent years, the application of transcranial magnetic stimulation (TMS), electric acoustic stimulation (EAS) and deep brain stimulation (DBS) have increased substantially in the clinics with focused ultrasound (FUS) as a newly emerging approach.

The clinical efficacy of DBS has been demonstrated in a number of disorders involving the basal ganglia and several neuropsychiatric disorders. The therapeutic concept of DBS is based on electrical stimulation through chronically implanted unilateral or bilateral electrodes into a specific subcortical structure in the brain. For PD, dystonia, Tourette's Syndrome and partial and generalized seizures, DBS has proven to be effective (Ackermans et al., 2011, Odekerken et al., 2013; Schuepbach et al., 2013, Janssen et al., 2014, Dowd et al., 2017). Recently, new indications for DBS have emerged such as Alzheimer disease (AD) and intractable obesity (Whiting et al., 2013), needing greater follow up to show their effects.

Despite the proven clinical efficacy of DBS in the aforementioned indications, we lack a comprehensive understanding of the underlying mechanisms mediating these effects nor have we identified the exact distinct neural circuits underlying mental and behavioral sign and symptoms expressed in people diagnosed with the most prevalent mental and neurodegenerative disorders including depression, OCD, psychosis, dementia etc.

Current hypotheses about the key mechanisms involved in the effect of DBS are diverse. The 'inhibition hypothesis' suggests that local neuronal elements are inhibited upon stimulation, showing similar effects as lesion therapy. This hypothesis fits well into the 'firing rate model' of movements disorders in which stimulating an overactive brain region inhibits the firing rate (Lafreniere-Roula et al., 2010). The 'excitation hypothesis' suggest that DBS can also excite local neuronal elements, mainly axons, antidromically. This causes the activation of regions along efferent pathways (Deniau et al., 2010; Reese et al., 2011). Another hypothesis is 'the disruption hypothesis', proposing that the information flowing through the stimulated brain region is blocked upon DBS and thereby pathological activity is interrupted (Chiken and Nambu, 2013). This can both be inhibitory or excitatory depending on the stimulated neural elements.

Although the underlying mechanisms of electrical DBS remain to be elucidated it is known to operate on a macroscale, lacking cell-type specificity. For this reason, its therapeutic effect will depend on the composition of neural elements in the targeted region causing interference with both pathological and physiological neural activities. This occasionally gives rise to side effects in a number of patients receiving DBS. For example, PD patients treated with DBS have reported speech deterioration as well as changes in mood, sleep and behavior which in turn range from new onset to worsening of pre-existing syndromes (Tan et al., 2011, Kurtis et al., 2017; Mucke et al., 2018).

Another drawback of the current technique of DBS is that it requires the implantation of a relatively large, wired system which entails the risk of bleeding and infection peri- and postoperative. As a result, many patients are reluctant to undergo DBS when surgery is warranted (Kim et al., 2016). The first challenge thus addresses clinician and patient demands to develop new, wireless avenues for DBS technology. A second challenge addresses the continuous stimulation paradigm of current DBS which need improvements. New advancements are made introducing intermittent or adaptive DBS (aDBS) working with a closed-loop system (Herron et al., 2017). This closed-loop system is created to measure and analyze biomarkers reflecting the patient's condition and to adapt its stimulation parameters accordingly improving treatment efficacy. Furthermore, this closed-loop systems benefit from less power consumption and therefore have a longer battery life. For PD, recent research has shown positive results when using aDBS of the subthalamic nucleus (STN) with LFPs in PD patients (Arlotti et al., 2018). A commercially available closed-loop system called responsive neuromodulation (RNS) has shown good results in patients suffering from refractory epilepsy (Sun and Morrell, 2014). RNS includes an implanted neurostimulator that continuously records the electrocardiogram at the seizure focus and delivers brief pulses when abnormal electrographic activity is detected.

Another refinement for continuous stimulation is called coordinated reset (CR) DBS. In this method, brief high-frequency pulse trains are given through the different contacts of the stimulation electrode in treatment blocks for a few consecutive days resulting in desynchronizing effects lasting beyond cessation of the stimulus. In a non-human primate model of parkinsonism, CR DBS of the STN for 5 consecutive days resulted in acute motor improvements and, in contrast to traditional DBS, showed benefits persisting up to two weeks after stimulation (Wang et al., 2016). Moreover, the usage of rechargeable implantable pulse generators (rIPG) has made its entrance into the field and has been proven effective and applicable in OCD patients. These rIPGs have a longevity of nine years in contrast to the non-rechargeable IPGs showing a mean longevity of 9 months (De Vloo et al., 2017). Evaluation of the recharging process has been done with patients receiving CR DBS for PD, essential tremor (ET) and dystonia and was experienced as feasible with a low number of adverse events even in the elderly patients (Jakobs et al., 2018).

Despite these recent refinements, there remains a need for new advanced neuromodulation techniques in which the information transfer between the neuromodulation technique and the evoked neuronal signals can be performed more delicately. This ideally will only cause the modulation of pathological neural activity, leaving physiological neural activity in close vicinity unaltered, thereby minimalizing the possibility of side-effects. Here, we will discuss different advanced neuromodulation techniques of the brain and analyse their clinical potential. In particular, we will review relevant preclinical and clinical literature with emphasis on the usage of MNPs for neuromodulation and evaluate the progress of our current understanding.

2. Search strategy

To describe and evaluate advanced techniques of neuromodulation of the brain and their latest refinements, we performed an extensive literature search. The literature for this review was identified by a PubMed search where the following keywords were queried either individually or combined: 'deep brain stimulation', 'adaptive deep brain stimulation (aDBS), closed-loop deep brain stimulation (closed-loop DBS), coordinated reset (CR) DBS, 'neuromodulation', 'optogenetics', 'DREADD', 'focused ultrasound' 'neuropsychiatric disorders', 'neurodegenerative disorders' and 'neurosensory disorders' with an additional search on 'nanoparticles (NP)', 'magnetic nanoparticles (MNP), 'iron oxide nanoparticles', 'alternating magnetic field', 'magnetic hyperthermia', 'hysteresis', 'MNP heating' and 'magnetothermal deep brain stimulation'. Relevant articles were chosen from review papers, original research articles and book chapters. Articles of interest within the reference lists of selected articles were also considered. The search was limited to studies published in English.

3. Neuromodulation of the brain, new insights

There are several advanced neuromodulation techniques besides electrical stimulation, such as optogenetics, Designer Receptors Exclusively Activated by Designer Drugs (DREADD), ultrasonic neuromodulation and magnetic neuronal control (Fig. 1). Each of these

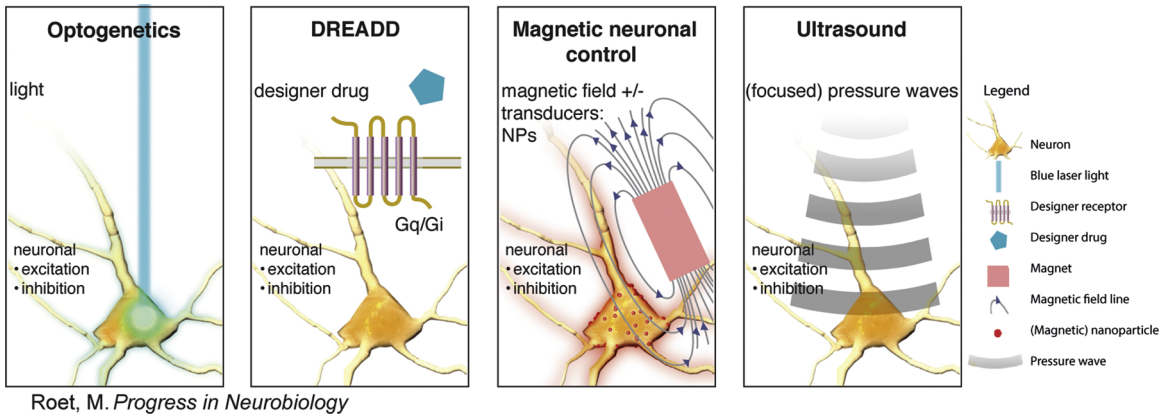

Fig. 1. Advanced techniques of neuromodulation, its modulation source and neuronal effect.
This figure illustrates advanced techniques of neuromodulation. In optogenetics, genetically modified neurons expressing specific opsins, can be either excited or inhibited by visible light. With the DREADD technique, designer drugs can activate specific neurons expressing DREADDs-genetically engineered GPCRs. Ultrasonic neuromodulation offers a non-invasive way to stimulate or suppress neuronal activity by using focused ultrasound. Magnetic neuronal control, allows for remote and wireless activation of neural cells with or without transducers such as MNPs to convert magnetic fields into different stimuli.

techniques has its own unique method of modulation and has broaden our insight into general neuronal function, numerous neural circuits underlying specific behavioral and pathological firing patterns responsible for various diseases. These advanced forms of neuromodulation might bring us closer to a more refined, clinically applicable technique of neuromodulation. Each technique, and its latest insights, is described in more detail below.

3.1. Optogenetics

In optogenetics, neurons are genetically modified to express microbial light-sensitive proteins termed 'opsins', which can be activated by visible light causing neuronal excitation or inhibition depending on the specific opsin. There are three classes of opsins, namely: the bacteriorhodopsins, the halorhodopsins and the channel-rhodopsins. Bacteriorhodopsins pump protons out of the cell causing hyperpolarization when inserted into a neuron and subsequently lead to neuronal inhibition. Inserted halorhodopsins cause hyperpolarization of neurons and neuronal inhibition by pumping negatively charged chloride ions into the cell. Channel-rhodopsins can either excite or inhibit neural systems when inserted into a neuron by allowing positively charged ions to flow into the cell or by chloride conduction, respectively (Deisseroth, 2015). Early in its development, this groundbreaking method of neuromodulation has already demonstrated its ability to control the activity of specific mammalian neuronal populations with these engineered light switches (Boyden et al., 2005). Shortly after, the modulation of a defined group of neurons in the hypothalamus, a structure deep in the brain, has been shown in freely moving mice (Adamantidis et al., 2007). This research succeeded to show a causal relationship between frequent-dependent activity of these defined neurons and changes in the sleep-wake cycle as a behavioral outcome. Neuromodulation through optogenetics has continued to make remarkable progress over the past decade in animal models, illuminating the role of defined neural cell populations and their connectivity in healthy and disease-related states (Deisseroth, 2015). Recently, implantable wireless optogenetic devices have been developed, allowing for untethered complex behavioral research in rodents. For instance, wireless optogenetic activation experiments in mice demonstrated both central and peripheral neural activation. One research group was able to design fully internal miniature light-emitting implants with a minimum size of 10 mm^3. These implants are wirelessly powered through a resonant cavity, activating a micro-LED embedded in the construct with electromagnetic energy coupling (Montgomery et al., 2015). Other research demonstrated fully implantable soft optoelectronic devices. For peripheral nerves, a soft stretchable film with an incorporated LED was used and for stimulation of the spinal cord stretchable filaments which are able to be inserted into the epidural space were designed. Their research states that in order to minimize the constructs, a dynamically moving antenna coupling radio-frequency (RF) radiation is needed (Park et al., 2015).

However, scaling up wireless optogenetic stimulation for the use in larger rodents or potentially even humans will remain a challenge since the amount of power required for RF-powered wireless optogenetic interfaces is considerably large. The need for an implanted light delivery device and the viral introduction of invertebrate genes, however, remain as the major challenges for clinical application of optogenetics. Furthermore, visible light needed to drive the inserted opsins is scattered and absorbed by neural tissue, thereby impeding its penetration into deep brain regions in the absence of an invasive probe. These features hinder clinical application of optogenetics for neuromodulation in movement and neuropsychiatric disorders although recent translational efforts are underway. A recent study investigated a different approach of wireless optogenetics using NPs to serve as optogenetic actuators of transcranial near-infrared (NIR) light to stimulate neurons. In their experiments, upconversion NPs (UCNPs) were able to convert NIR light into blue or green light with enough intensity to activate corresponding opsins in the surroundings of these UCNPs. Their results show that in transgenic mice expressing ChR2 in the ventral tegmental area (VTA), in vivo neuronal activation is possible after the injection of UNCPs into the VTA and placing a NIR light probe 2 mm above the skull 4 weeks later. Furthermore, they demonstrated that neuronal silencing is also possible when using UCNPs that emit green light upon NIR light emission in transgenic mice expressing Arch in the hippocampus (Chen et al., 2018). These findings might be another different step towards wireless optogenetics, keeping in mind that the emission intensity of these particles decreased with an increase of the distance between the NIR light and UNCPs. Long distances might therefore pose a challenge. In non-human primates (NHP), the first optogenetics study showed the activation of neurons in the primary motor cortex upon optical stimulation (Han et al., 2009). Successive studies showed that optogenetics in NHP can also serve as a tool to modulate specific behavior, such as choice behavior when modulating dopamine activity and inducing saccadic dysmetria when stimulating cerebellar Purkinje cells (Stauffer et al., 2016, El-Shamayleh et al., 2017). In recent years, different disease models in transgenic primates have been added, which create opportunities to explore new optogenetic therapies (Liu et al., 2016). In the field of ophthalmology, optogenetics is taking its first step into the clinics with a clinical trial in which researchers try to restore vision in completely blind patients by

placing channelrhodopsin-2 into retinal ganglion cells (Schmidt, 2017).

3.2. Chemogenetics with DREADD

In chemogenetics, specific neurons are virally transduced to express DREADDs-genetically engineered G-protein coupled receptors (GPCRs) with high affinity to designer drugs, allowing for modulation of cellular functions through systemic administration of the drug. Clozapine N-oxide (CNO), is the most commonly used designer drug and is a pharmacologically inert metabolite of the antipsychotic drug clozapine (Armbruster et al., 2007; Roth, 2016). Following initial discovery in yeast, both excitatory and inhibitory DREADDs have been demonstrated. For enhancing neuronal firing, the Gq-DREADDs hM1Dq, hM3Dq and hM5Dq have been developed of which hM1Dq has been used the most. These DREADDs enhance neuronal activity by increasing intracellular calcium concentrations. The first study investigating the modulation of neurons via hM1Dq demonstrated the activation of hippocampal neurons after CNO administration in hM1Dq-expressing mice (Alexander et al., 2009). To inhibited neuronal activity, Gi-DREADDs hM2Di, hM4Di, and KORD are being used. Both hM4Di and KORD inhibited neuronal activity via hyperpolarization of the cell and synaptic silencing. HM4Di is the mostly used inhibitory DREADD and the first study investigating its property showed neuronal silencing when incorporated into hippocampal neurons (Armbruster et al., 2007). Furthermore, the DREADD GsD has been used to modulate plasticity via an increase in cAMP and the DREADD Rq(R165 L) is used to enhance β-arrestin specific signaling (Roth, 2016). Chemogenetics enables genetically-precise control of cellular activity in both superficial and deep brain regions and is less invasive compared to optogenetics. Its temporal precision, however, is limited by the pharmacokinetics of the designer drugs (Guettier et al., 2009, Gomez et al., 2017). Nevertheless, this promising approach has led to the discovery of several behavioral circuits in rodents, including associative learning, memory and reward guided behavior. Moreover, it has been applied to various animal models of human disease, thereby enhancing its translational application (Urban and Roth, 2015; Roth, 2016; Whissell et al., 2016). In a chronic model of focal neocortical epilepsy in rats, it has been shown that virally introduced hM4Di into the seizure focus attenuates seizure frequency upon intraperitoneal CNO application. These results are promising as a possible intervention for intractable focal epilepsy (Katzel et al., 2014). Akin to opsins, DREADDs have recently been expressed in NHPs. Research done in rhesus monkeys demonstrated a repeatable disruption in relative reward value when the functional connection between two different brain regions, namely the orbitofrontal and rhinal cortices, was temporarily disrupted by inhibitory DREADD modulation (Eldridge et al., 2016).

Just recently, however, researchers have shown that not CNO but clozapine binds to DREADD. This finding might have implications for the interpretation of observed effects in previous research that used this technique. Based on the previous findings, it has been suggested that DREADD is an inaccurate name since the receptors are not activated by a designer drug nor are they exclusive. For future research, it has been proposed that scientists may simply apply clozapine as the actuator of this technique, keeping in mind to use proper controls. Clozapine is already an approved drug; nonetheless, due to its high affinity to various other receptors, scientists should use it at a low dose and carefully evaluate possible off-target effects (Gomez et al., 2017).

Altogether, this technique seems promising, but still requires either the use of viral DREADD introduction or genetically engineered animals. Furthermore, its temporal precision is limited by slow pharmacokinetics. One advancement for DREADD could be the implementation of NPs as a safer alternative for gene delivery than viruses. Previous research has already shown cellular siRNA delivery with gold NPs and nanocarriers (Kakizawa et al., 2006, Elbakry et al., 2009). This approach could simplify DREADD for clinical applications since now lentiviral delivery is one of its drawbacks.

3.3. Ultrasonic neuromodulation

Ultrasound (US) is acoustic energy in the form of sound pressure waves at very high frequencies not audible to the human ear. It has been shown that these sound pressure waves can interact with biological tissue, making US a well-known biomedical imaging modality. US can penetrate through the skull and be focused at specific regions deep within the brain without losing its signal. Focused ultrasound (FUS) can produce thermal and non-thermal effects depending on various parameters such as its frequency, intensity and exposure time. High-intensity FUS (HIFU) produces thermal effects on targeted tissue resulting in tissue ablation. A recently conducted randomized controlled clinical trial amongst patients suffering from ET showed that MRI-guided FUS lesioning of the thalamus resulted in an improvement in hand-tremor scores (Elias et al., 2016). HIFU has also been widely investigated as a form of cancer therapy including prostate, breast, liver, kidney, pancreatic cancer and bone malignancies showing mixed results (Hsiao et al., 2016). Recently a study investigated whether adding MNPs to HIFU could enhance the thermal effects showing promising results (Devarakonda et al., 2017). In contrary to HIFU, low-intensity FUS has shown to be able to stimulate neuronal circuits by non-thermal (mechanical) effects without causing any neuronal damage. The first *in vivo* experiments demonstrated that transcranial pulsed US to the motor cortex in anaesthetized mice could evoke motor behavior (Tufail et al., 2010). The following years, different brain circuits in various species have been modulated using transcranial FUS (tFUS), as reviewed in more detail elsewhere (Fini and Tyler, 2017). In NHP, low-intensity FUS was able to modulate visuomotor behavior due to the disruption of information processing across the frontal eye fields (Deffieux et al., 2013). Also human applications of ultrasonic neuromodulation have already been investigated. In healthy volunteers it is shown that tFUS is able to produce changes in sensory-evoked brain activity. In these experiments, healthy volunteers were given median nerve stimulation while recording these sensory evoked brain oscillations. Subsequently tFUS was given, which caused suppression of the evoked somatosensory potentials (Legon et al., 2014). Other research showed that when stimulating the primary somatosensory cortex (S1) in healthy volunteers, a transient tactile sensation on the contralateral side of the stimulated hemisphere could be observed. Simultaneously EEG recordings showed sonication specific potentials in the S1 (Lee et al., 2015a, b). When stimulating the visual cortex with tFUS in healthy volunteers, a visual sensation could be evoked. Furthermore, their results show that not only the sonicated brain area, but also other regions involved in visual processing were activated, demonstrated by simultaneously acquisition of blood-oxygenation-level-dependent functional MRI (Lee et al., 2016).

Ultrasonic neuromodulation is a promising technique since its application does not require the use of exogenous agents. However, the underlying mechanisms of FUS induced neuromodulation are still unclear. One hypothesis is that the mechanical force of FUS activates mechanosensitive ion channels embedded within cell membranes (Tyler, 2012). The applied pressure waves may stretch or deform the cellular membrane altering the state of mechanosensitive ion channels embedded within these membranes leading to transmembrane currents and consecutive neural activity. Recent research elucidated that FUS is indeed capable of modulating sodium and potassium mechanosensitive ion channels expressed in Xenopus oocytes resulting in transmembrane currents (Kubanek et al., 2016). Another research group introducing a technique called 'sonogenetics' showed that low pressure US is capable of inducing specific behavior in the *Caenorhabditis elegans* (C. elegans) by misexpressing a pore-forming subunit of the mechanotransduction channel TRP-4 (Ibsen et al., 2015). All these observations together make ultrasonic neuromodulation an interesting non-invasive technique for future clinical application and we believe this field of neuromodulation will grow rapidly within the upcoming years. Future advancements in spatial resolution is expected to further improve this technique. One interesting finding is the combination of FUS with drug

carrying NPs as is recently investigated in rats. In this research, ultrasound-gated NPs that encapsulated Propofol were given intravascular and released their drug due to a conformation change of the NPs by FUS (Airan et al., 2017). This enables a more targeting drug release. Additionally, FUS seems to be a promising method of delivering NPs to brain targets due to the possibility of BBB disruption on its own (Liu et al., 2011; Chu et al., 2016). Combining these two modalities could make the delivery of MNPs into the brain less invasive.

3.4. Magnetic neuronal control

Magnetic neuronal control is a recently discovered technique, which may hold promise as a clinical neuronal modulation approach since it does not require implantation of invasive electrodes or optical devices, it can penetrate into the brain and has a lower response latency than that achieved with drug delivery. Magnetic fields with magnitudes in millitesla range are able to penetrate into the brain without attenuation of the signal or given side effects because of the negligible magnetic susceptibility and low conductivity of biological tissue (Young et al., 1980). Several research groups are investigating magnetic neuronal control by activating ion channels on membranes using purely the magnetic field itself or by the usage of transducers responding to this magnetic field such as MNPs. The latter can be subdivided into either magnetothermal activation, magnetomechanical activation and magnetoelectric activation. All will be discussed in detail.

3.4.1. Transcranial magnetic stimulation (TMS)

TMS is a technique used for neuromodulation in which an electric current generated in a copper wire coil induces a non-invasive magnetic field able to penetrate thought the skull into brain regions directly below the coil. This magnetic field subsequently induces another electric current in the underlying brain region capable of inducing neuromodulation. Since the magnetic field strongly decays with distance, TMS is mainly limited to cortical stimulation. Depending on the given stimulation protocol, TMS can induce immediate effects through stimulation and disruption and after-effects through neuroplastic changes when multiple consecutive magnetic pulses are given called 'repetitive TMS' (rTMS). A general belief is that low frequency rTMS causes long-term depression (LTD) in the underlying brain region while high-frequency rTMS causes long-term potentiation (LTP) (Klomjai et al., 2015). Nowadays, rTMS for major depression disorder is FDA approved and other disorder such as stroke and OCD are investigated in research context (Demitrack and Thase, 2009; Avenanti et al., 2012, Elbeh et al., 2016).

One disadvantage of rTMS is its variability between individuals generating a bimodal pattern of response with responders and non-responders to a certain given TMS protocol (Fitzgerald et al., 2016). In some patients low-frequency rTMS has an inhibitory effect while in other patients it has an excitatory effect and vice versa. As a consequence, the responds to rTMS therapy is very patient-specific and applying multiple rTMS protocols might be necessary (Eldaief et al., 2011).

To be less stressful and time consuming for the patient, shortening the time of a TMS protocol is desired. For this reason, theta-burst (iTBS) and accelerated rTMS protocols have been established. rTMS protocols last 30–45 minutes, while iTBS paradigms require 1–3 min. In iTBS, short trains of stimuli at a high frequency are repeated in intervals of 200 ms. In the THREE-D study, 3 min iTBS has shown to have equal effects to 37,5 min of high frequency rTMS (Han et al., 2018). In accelerated rTMS protocols, multiple rTMS session are given within one day. Research has shown that accelerated rTMS given for depression can shorten the days of treatment in 'fast responding' patients, however other patients still need the extra days of treatment to show the same decline in BDI-II Scores (Holtzheimer et al., 2010).

One recent advantage in TMS is the introduction of deep TMS (dTMS). DTMS uses so called 'H' coils providing a magnetic field which penetrates deeper into the brain but automatically also generates a bigger field spread making the signal less specific. For this reason different 'H' coils are designed for different disorders. For Alzheimer disease, findings suggest some improvements in the Alzheimer's disease assessment scale-cognitive subscale when treated with dTMS (Coppi et al., 2016). A possible refinement of this technique could be the combination of TMS with MNPs to enhance or transduce the signal. Combining these two approaches might lead to the stimulation of more defined brain regions deeper in the brain.

3.4.2. Magnetic stimulation using transducers

Combining magnetic neuromodulation with transducers converting or enhancing the magnetic signal has recently been done through different techniques. Magnetothermal activation uses AMFs to induce MNP heating through hysteresis and triggers heat-sensitive cation channels from the Transient Receptor Potential Vanilloid (TRPV) family causing depolarization and action potential firing (Huang et al., 2010, Stanley et al., 2012; Chen et al., 2015, Munshi et al., 2017). Magnetomechanical activation uses the force exerted by iron-containing particles or proteins tethered to the cell membrane in the presence of magnetic fields to trigger pressure sensitive receptors that convert this signal into neural modulation (Stanley et al., 2015). Magnetoelectric activation uses magnetoelectric NPs composed of a magnetostrictive core and a piezoelectric shell to generate local electric fields when exposed to an external magnetic field (Guduru et al., 2015; Chen et al., 2016a, b, c). In contrast to standard DBS and TMS, adding these transducers allows to operate on a nanoscale, increasing its precision and region or cellular specific targeting.

The first study to establish remote neuronal control of cell function, leveraged RF AMFs and MNP heating to activate the capsaicin receptor TRPV1, which resulted in the calcium influx into human embryonic kidney (HEK) 293 cells. The authors also showed that the MNP heating triggered behavioral responses in C. elegans (Huang et al., 2010). Other researchers investigating magnetic cellular activation demonstrated that modified TRPV1 receptors with extracellular antibody-coated iron oxide NPs could regulate protein production *in vivo* when exposed to a magnetic field. This work also indicated that a fusion of an iron-binding protein ferritin to TRPV enables control of calcium influx *in vitro* when exposed to a magnetic field (Stanley et al., 2012). Based on these findings, several groups went on to investigate TRPV-ferritin fusion constructs in the context of magnetic manipulation of cellular function in behaving rodents (Stanley et al., 2015, Stanley et al., 2016; Wheeler et al., 2016). The mechanisms of neural modulation in these studies, however, remain poorly understood since ferritin is weakly paramagnetic and thereby the physical ability of this protein to activate TRPV by either thermal or mechanical stimuli appears unlikely (Meister, 2016). Yet, a recently published biophysical study proposes that changes in the magnetic entropy of the ferritine particle can generate heat through a magnetocaloric effect and consequently activate the TRPV channel (Duret et al., 2019). Nonetheless, several questions remain, including what the extent of excitation is, and which cell types are affected.

Magnetothermal activation in the mammalian brain was recently demonstrated by AMF induced bulk heating of MNP solution injected into the VTA of anaesthetized mice expressing TRPV1 following viral delivery (Chen et al., 2015). Hysteretic heating of MNPs in the presence of AMF activates TRPV1, which causes calcium ion influx into heat-sensitized cells and yields membrane depolarization and neural excitation. The latter suggests that such an approach could be a potential candidate for neuromodulation. As such, the first application of magnetothermal activation to control behavior of awake freely moving mice has been recently demonstrated (Munshi et al., 2017). This work showed that magnetothermal stimulation of motor cortex evoked locomotor activity and stimulation of different parts of the striatum induced rotation or freezing-of-gate. The same research group recently showed MNP induced neuronal silencing. Hippocampal neurons were

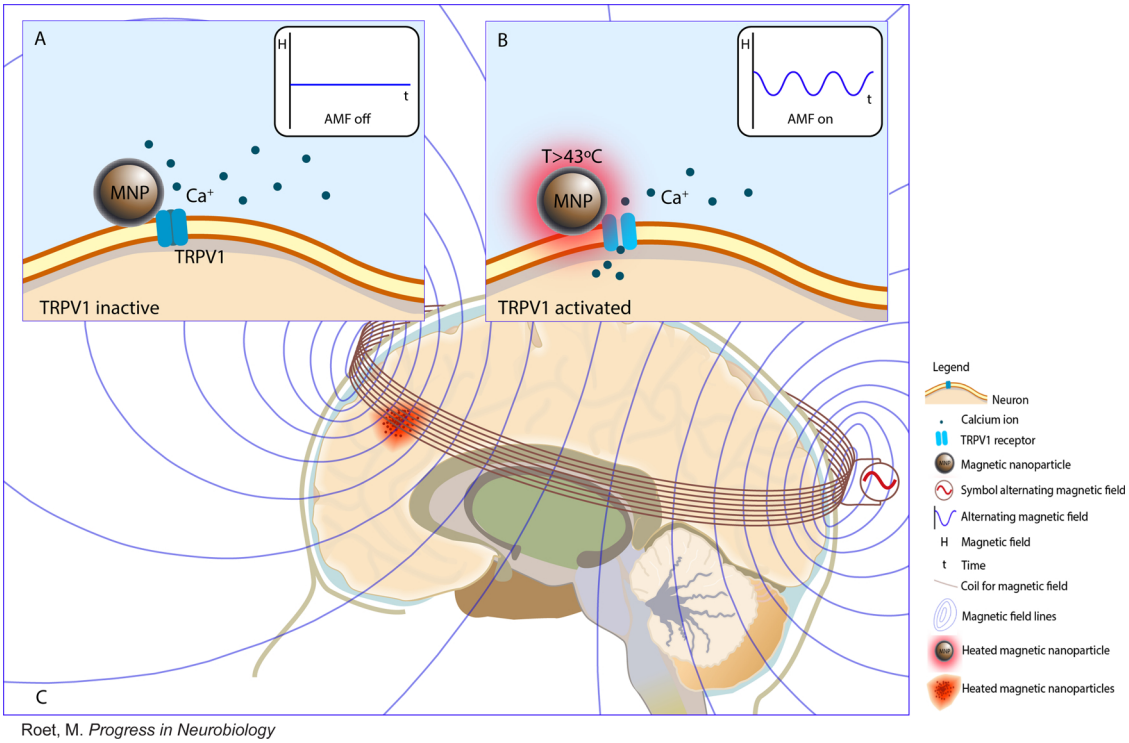

Fig. 2. A schematic view of magnetothermal DBS in the human brain.
In part A, a MNP surrounds a neuronal cell close to its cell membrane. No external AMF is applied, therefor the TRPV1 receptor remains closed. In part B, the external AMF is turned on leading to MNP heating adjacent to the neuronal cell and TRPV1 receptor. This heat signal opens the TRPV1 receptor causing a calcium influx and subsequent activation of the neuronal cell. Part C illustrates a magnetic coil surrounding the human head, which is needed to generate an AMF to activate the MNPs in a particular brain region. MNP heating is shown by the red dots.

transfected with the chloride channel Anoctamin 1 (TMEM16A) and spontaneous firing was suppressed using MNP induced heating opening this inhibitory channel (Munshi et al., 2018).

The studies discussed above employed genetic tools to achieve TRPV1 expression in the given brain areas in mice. This ion channel is endogenously expressed in neurons in the mammalian central nervous system (CNS), which suggests that it can be a promising target for future investigations for delivery of magnetic neuronal control (Marinelli et al., 2005, Starowicz et al., 2008; Sun et al., 2013, Terzian et al., 2014; Nam et al., 2015).

To develop magnetic neuronal control for biomedical applications, leveraging endogenously expressed receptors of physical stimuli may provide a convenient approach. The use of MNP heating and TRPV1 may offer a route to clinical applications with a clear mechanism of stimulation and without genetically engineered TRPV-ferritin fusion constructs (Fig. 2: Schematic view of magnetothermal DBS in human). Another approach would be the usage of magnetoelectric particles. They have the potential to improve upon resolution and cell-type specificity of traditional electrical DBS since they also work on a nano-scale and could potentially be targeted to specific cells.

MNPs have already shown promising results in a variety of biomedical applications, ranging from cancer hyperthermia to magnetic resonance imaging, and wireless neuromodulation may be another intriguing possibility.

4. Magnetic nanoparticles

4.1. Biomedical applications

MNPs can be used in a wide range of biomedical applications since they have several beneficial characteristics. Firstly, MNPs contain paramagnetic properties making them good candidates as contrast agents in imaging. For MRI, the MNPs can alter the relaxation mechanism of protons resulting in sharper images (Lee et al., 2015a, b). For fluorescence imaging quantum dot nanocrystals are used as fluorophores emitting light when excited by long wavelengths as thoroughly reviewed elsewhere (Utkin, 2018). Secondly, MNPs can be targeted toward specific tissue by the appliance of an external magnetic field or by coating the NPs with targeting moieties (Steichen et al., 2013). Thirdly, MNPs can be coated with therapeutic agents enhancing drug bioavailability while keeping the drug dose low (Latorre et al., 2014). Fourthly, MNPs can serve as transducers producing and or converting incoming stimuli. Hyperthermia is one of these examples being used in cancer therapy and to transiently increase BBB permeability (Wankhede et al., 2012, Wegscheid et al., 2014; Tabatabaei et al., 2015; Wang and Guo, 2016). Furthermore, magnetomechanical destruction and heat transfer beneficial in cryosurgery can be accomplished by MNPs (Yu et al., 2014; Wang and Guo, 2016). Combining multiple characteristics within the same particle to enable both imaging, diagnostic and therapy purposes is desired, and this concept is reviewed in more detail elsewhere (Gobbo et al., 2015).

Several decades of research in nanomaterials have delivered a diversity of particles with different compositions, structures, properties, and functions (Kateb et al., 2011; Chen et al., 2016a, b, c). MNPs constitute a class of NPs composed of magnetic materials. Some MNPs can undergo hysteretic power loss in externally applied AMF resulting in heat dissipation. Depending on the thermal dosage released by the MNPs, this remote-controlled heating can be used for tumor therapy that induces apoptosis of malignant cells or for neuronal activation as discussed above (Maier-Hauff et al., 2011, Chen et al., 2015). Combined with their utility for imaging and drug delivery, MNPs constitute a promising platform for nanotheranostics. With the new concept of magnetic neuronal control using MNPs, MNP heating for the purpose of neuromodulation might become a next step in nanotheranostics.

4.2. Materials chemistry

MNPs are crystal structures with their linear dimensions in the order of 100th of nm or less (Mody et al., 2010). For the purpose of MNP heating in AMFs, their inorganic core needs to be composed of a magnetic material and their chemistry needs to be optimized to maximize heat dissipation under specific AMF conditions (Chen et al., 2016a, b, c). The commonly used MNPs consist of the magnetite phase (Fe_3O_4) of iron-oxide (Silva et al., 2011). The common methods of MNP synthesis are chemical coprecipitation, thermal decomposition, and microemulsion. In chemical coprecipitation, a mixture of Fe^{2+} and Fe^{3+} ions are submitted to hydrolysis forming magnetite precipitates. The particle-size depends on the ratio of different ions and the temperature during hydrolysis (Petcharoena and Sirivat, 2012; Verma et al., 2014). Thermal decomposition is a process in which organometallic iron precursors are decomposed under high temperatures of up to 473 K. The advantages of this method compared to coprecipitation include superior control over chemical composition, size, and shape of the MNPs. The solvent in which the MNPs are synthesized greatly influences the consistency of magnetic properties of the particles, and optimizing the solvent's redox activity is important for appropriate magnetic phases with desirable magnetic properties (Chen et al., 2016a, b, c). Another approach of producing uniform size-controlled NPs is microemulsion. In this method Fe^{2+} salts are oxidized in a microemulsion in which the controlled temperature and added surfactant concentration determines the particle size. However, large amounts of solvent are necessary to synthesize substantial amounts of MNPs, which makes this process challenging to scale (Lee et al., 2005; Lu et al., 2007, Laurent et al., 2008; Verma et al., 2014, Wegscheid et al., 2014).

4.3. Particle coating

Besides an iron-oxide core, MNPs need a surface coating of a biocompatible material to ensure their solubility in aqueous physiological solutions, to minimize their potential cytotoxicity, and to enhance their biocompatibility. Iron oxide can give iron-mediated radical formation and oxidative stress in the brain if not coated, so adding coating is essential (Petters et al., 2014). However, it must be noted that coating can also limit characteristics of the particles such as heating, therefore choosing the right surface coating is critical. Various *in vitro* and *in vivo* studies have applied a variety of coatings including dextran, carboxydextran, glycosaminoglycan, *N*-(a-trimethyl ammonioacetyl)-didodecyl-D-glutamate chloride, and polyethylene glycol (PEG) (Laurent et al., 2008, Silva et al., 2011). For human studies, however, only aminosilane-coated MNPs have been used to date (Maier-Hauff et al., 2007, Maier-Hauff et al., 2011). It is also important to consider possible coating effects on the particle's pharmacokinetics and biodistribution. Table 1 summarizes different types of MNP coating material for studies using magnetic hyperthermia. To induce target delivery of MNPs to specific cells, MNPs can be decorated with targeting moieties such as short peptides, binding proteins, and antibodies (Wankhede et al., 2012, Shah et al., 2014; Wegscheid et al., 2014, Yin, Shah et al., 2014; Munshi et al., 2017). These target moieties will recognize the cells of interest and only stimulate the neuronal cells in close vicinity due to a small span of signal transduction. While the majority of targeting strategies have been explored in the context of tumor therapies, similar approaches may permit targeting of specific neurons deep in the brain for neuromodulation (Gobbo et al., 2015).

5. MNPs in the central nervous system

5.1. Delivery

In order to reach specific neurons in the brain, MNPs either need to cross the BBB or should be delivered directly into the brain via invasive means. Crossing the BBB remains a challenge for systemic delivery of MNPs and other substances due to its selective nature. For this reason, either direct intratumoral delivery or convection-enhanced delivery (CED) has been used in clinical applications of MNPs (Hadjipanayis et al., 2010, Maier-Hauff et al., 2011). Although these methods allow for the delivery of high concentrations of MNPs or other therapeutic substances into the brain, they are invasive and carry a potential risk of hemorrhage and infection. Many ways to cross the BBB has been researched including intra-carotid arterial infusion of hyperosmotic solutions, the lipidization of small molecules and receptor mediated transport, all being inappropriate for nanoparticle transport (Pardridge, 2007). Photodynamic therapy has also been investigated to increase BBB permeability resulting into several studies showing a high accumulation of a photosensitizer into glial tumors (Stummer et al., 2000), but only scarcely detectable amounts in intact BBB of the rat (Madsen et al., 2006). Notable, it was recently shown that MNP heating in brain capillaries can transiently increase BBB permeability without causing inflammation or neurovascular damage (Tabatabaei et al., 2015). It seems that this technique offers promise as an approach to deliver MNPs or other substances directly into the brain with minimal invasiveness. Focused ultrasound in the presence of microbubbles provides another way to transiently increase BBB permeability (Chu et al., 2016). However, in the context of magnetic hyperthermia tumor therapy or magnetothermal neuromodulation, increasing the BBB permeability may not be sufficient and magnetic field gradients may be necessary to aid transport of MNPs across the disrupted BBB (Liu et al., 2010). Another way to transiently open the BBB has been demonstrated in patients suffering from malignant glial tumors. In this study, dTMS was able to increase the BBB permeability for contrast agents in 10 out of 15 patients. Increased BBB permeability was found not only directly in the tumor region but also peritumoral, in the ipsilateral and contralateral hemisphere (Vazana et al., 2016). This method could be combined with the administration of NPs and might be a promising application for the future.

5.2. Biodistribution, uptake and clearing

What happens with MNPs once they are in the CNS? A rodent study showed that intratumoral instillation of aminosilane-coated MNPs led to the formation of stable deposits, which allowed for repeated magnetic field treatments (Jordan et al., 2006). For the purpose of neuromodulation, it has been shown that in mice NPs are distributed in extracellular spaces close to cell membranes and synaptic clefts, with a small fraction taken up by microglia and neuronal axons (Chen et al., 2018). In multiple mice studies NPs seem to minimally disperse within one month after injection (Chen et al., 2015, Chen et al., 2018). Several other research groups have demonstrated that activated microglia *in vitro* can display macrophagic properties and internalize MNPs primarily into vesicles, albeit the fate of MNPs following macrophagic internalization remains to be investigated (Rogers and Basu, 2005; Ribot et al., 2007). Furthermore, research showed that coating MNPs with PEG prevented non-specific cellular MNP uptake when incubated in human plasma (Schottler et al., 2016). A group investigating magnetoelectric NPs in human astrocytes and peripheral blood mononuclear cells showed that there is no significant toxicity of these particles when analyzed with a Cell Proliferation Assay Kit (XTT) (Guduru et al., 2015). Post mortem analysis of patients treated with magnetic hyperthermia for glioblastoma multiforme (GBM), the most aggressive malignant form of brain cancer, revealed that the majority of MNPs were aggregated in areas of necrosis within the tumor and largely distributed around the site of instillation. The MNPs at the border of the aggregates were internalized mainly by macrophages (95%) and only a few by tumor cells (5%) (van Landeghem et al., 2009). The larger clinical trials investigating MNP heating for GBM did not explicitly report the location of the MNPs after a certain exposure time (Maier-Hauff et al., 2011). Further research is warranted to investigate the long-term effects and clearance of MNPs.

Table 1
This table shows different articles investigating MNP heating in either GBM therapy, cellular or neuronal modulation. It states the composition of the MNPs, the AMF parameters used and the amount of energy produced by their MNPs in their experiments.

Study		MNP core	$Ø_{core}$ (nm)	Coating	MNP conc. (mg/ml)	Iron weight administrated	**Genetic Construct**
Jordan Maier-Hauff et al 2006	*In vivo*	Iron oxide	3 15	Carboxydextran Aminosilane	NI NI	1.80 mol/L 2.00 mol/L	–
Maier-Hauff et al., 2007	*In vivo*	Iron oxide	15	Aminosilane	NI	112 mg/ml	–
Maier-Hauff et al., 2011	*In vivo*	Magnetite	12	Aminosilane	NI	112 mg/ml	–
Silva et al., 2011 review	*In vivo*	Magnetite, Maghemite	1-35	TMAG/DLPC/ DOPE/CMC/ Carboxydextran/Dextran/ Aminosilane	NI	$2.00E^{-7}$-20 mg/ml	–
		Magnetite	12-15	Aminosilane	NI	1.12-112 mg/ml	–
Shah et al., 2014	*In vitro*	Zn-doped iron oxide	15.40	Au-coated + ATAP	$5.00E^{-3}$-0.02	NI	–
Yin et al., 2014	*In vitro*	Zn-doped iron oxide	22.92 ± 3-.70	MNP-PEI/miRNA/ PEI complexes	0.01	NI	–
Pralle et al 2010	*In vitro* *In vivo*	Magnetite Magnetite	6 6	– Polyethylene glycol (PEG)-phospholipid	** **	NI	–
Stanley et al., 2012	*In vivo*	Iron oxide	20-25	Anti-His	8	NI	TRPV1His
Stanley et al., 2015	*In vivo*	Ferritin	–	–	–	100 mg/ml iron dextran intraperitoneal	GFP-TRPV1/ GFP-ferritin
Chen et al., 2015	*In vivo*	Iron oxide	22	(Polyethylene glycol) PEG	100	NI	–
Stanley et al., 2016	*In vivo*	–	–	–	–	–	GFP–TRPV1/ GFP–ferritin, GFP–TRPV1mutant/GFP–ferritin
Pralle et al 2017	*In vivo*	Co-ferrite core, (MN-ferrite shell)	10.25 ± 1	PMA (poly -isobutylene -maleic anhydride), NeutrAvidin coupled to antibodies	1	NI	–
Pralle et al 2018	*In vitro*	Co-Mn-ferrite core	10.25 ± 1	PMA (poly -isobutylene -maleic anhydride), NeutrAvidin coupled to antibodies	10	NI	–

Study	**Subject**	**Function**	**Injected volume (ml)**	**Magnetic field frequency (kHz)**	**Magnetic field amplitude (kA/m)**	**Stimulation paradigm**	**SLP/ SAR (W/g)**	**Temperature (°C)**
Jordan Maier-Hauff et al 2006	GBM cells injected in rats	HT for GBM	$2.00E^{-2}$	100	0-18	kA/m gradually increased to desired level for 10 min and sustained for 30 min	0-35*	Max: 39 Max: 43-47
Maier-Hauff et al., 2007	Human	HT for GBM	0.25/ml tumor	100	2.5-18	60 min	2-35*	Med: 44.60 Max: 49.50
Maier-Hauff et al., 2011	Human	HT for GBM	0.28/ml tumor	100	2-15	60 min	2-30*	Med: 51.20 Max: 82

Table 1 (*continued*)

Study	Subject	Function	Injected volume (ml)	Magnetic field frequency (kHz)	Magnetic field amplitude (kA/m)	Stimulation paradigm	SLP/ SAR (W/g)	Temperature (°C)
Silva et al., 2011 review	Gliomas in mice or rat	HT for GBM	0.1-0.4	88.90-150	11-30.60	20-60 min	96-286	39-47
	Human	HT for GBM	0.25-0.28 ml/ml tumor	15-18	100	60 min	NI	49.60-65.60
Shah et al., 2014	GBM cells, metastatic breast cancer cells	Peptide therapeutics and HT	NI	300	5	45 min	NI	NI
Yin et al., 2014	GBM cells	HT for GBM	NI	225	5	0-60 min	341	44.10
Pralle et al 2010	Hippocampal neurons	Remote control neurons	NI	40000	0.67-1	45 sec	2.51	Max: 43
	C. elegans	Worm retraction	NI	40000	0.67	17 sec	2.51	Bulk: 34
Stanley et al., 2012	PC-12 cells injected in mice	Remote regulation of gene expression	$5.00E^{-2}$	465	3.99	30 min	0.63	NI
Stanley et al., 2015	MSC cells injected in mice	Remote regulation of gene expression	0.05 iron dextran intraperitoneal	465	23.13 or 25.53	60 min	NI	NI
Chen et al., 2015	Mice injected with TRPV1 lentivirus	Control of cellular signaling in non-excitable and electro-active cells	$2.50E^{-3}$	500	15	10 seconds field pulses with 50 seconds rest interval 20 min	660 +/- 50	Med: 43 Max: 45
Stanley et al., 2016	Cre mice	Activation or inhibition of glucose-sensing neurons	4.00^{E-3} iron dextran into lateral ventricle	465	18.35, 21.54 or 24.73	30 min	NI	NI
Pralle et al 2017	Mice injected with TRPV1 AAV virus	Remote control neurons, behavioral output	6.00^{E-4}	570	7.5	Four one-min field applications within a 15-min trial	450 ***	0.1 to 0.5 °C/s, membrane bound: 0.1 to 1.0 °C/s
Pralle et al 2018	Hippo-campal neurons	Remote control neurons, Ca^{2+} imaging and AP firing pattern	0.2	412.5	28.87 +/- 1.03	5 seconds intervals	553 +/- 10	3 °C in 5 seconds

NI: Not indicated in paper. -: Not applicable. * Not indicated in paper, values deducted from 'Description and characterization of the novel hyperthermia-and thermoablation-system MFH®300 F for clinical magnetic fluid hyperthermia. Uwe Gneveckow,a) Andreas Jordan,b) and Regina Scholz c). ** Hippocampal cells incubated in 10 nM nanoparticle solution for 1 min. C. Elegans incubated in 1 nM nanoparticle solution for 1 min. *** Measured at 500 kHz and 15 kA/m.

6. MNP heating and its applications in the biomedicine and neuroscience

6.1. Thermal dosage

MNPs dissipate heat when exposed to an AMF (Maier-Hauff et al., 2007, Nair et al., 2010; Maier-Hauff et al., 2011, Silva et al., 2011; Wankhede et al., 2012, Lee Titsworth et al., 2014; Rivet et al., 2014, Schaub et al., 2014; Verma et al., 2014, Wegscheid et al., 2014; Dan et al., 2015, Tabatabaei et al., 2015). Prolonged local rise in temperature above the normal body temperature is applied in cancer therapy to induce apoptosis in malignant cells. When applied in conjunction with standard treatments, MHT using MNPs enhances the overall survival rate of patients following diagnosis of first tumor recurrence of GBM (Maier-Hauff et al., 2011). Applied AMF parameters can be adjusted in order to decrease the thermal dosage delivered by MNPs, thereby making the heating signal suitable for neuromodulation without inducing cell damage. Importantly, when a MNP solution was employed for magnetothermal neural excitation in the VTA, only the neurons within a 200 µm border experienced local heating and no significant damage was observed following repeated cycles of AMF exposure (Chen et al., 2015).

MNP heating originates from hysteresis when the particles are exposed to an AMF with a given field frequency and amplitude. The amount of heat released by a MNP during one cycle of an AMF equals the area of its hysteresis loop. The amount of heat produced by MNPs in a given AMF depends on their properties, such as the magnetic anisotropy, the saturation magnetization, its volume, and the magnetic interactions between the particles. The MNP heating efficiency can be quantified either by the specific loss power (SLP), which refers to the power achievable per gram of iron in the MNPs at a given AMF, or by the specific absorption rate (SAR), which refers to the amount of energy converted into heat per time and mass. Both metrics are expressed in watts per gram. Table 1 summarizes studies that used MNP heating for either GBM therapy, cellular or neuronal modulation, showing SLP and SAR for particular MNPs and AMF parameters used.

6.2. Treatment of brain cancer

In clinical trials for the treatment of recurrent GBM, an aqueous MNPs dispersion is instilled within the tumor using neuronavigation. Postoperatively, the patient is placed in the alternating magnetic field applicator MFH 300 F causing an AMF and subsequent MNP heating within the tumor. Results from Maier-Hauff et al show that the intratumoral median temperature following AMF varied between 39–51.2℃ with a maximum intratumoral temperature of 82℃ (Maier-Hauff et al., 2007, Maier-Hauff et al., 2011). The maximal duration of hyperthermia lasted for 60 min per session, which was enough to produce a cytotoxic effect in the tumor cells. Hyperthermia treatment consisted of six semi-weekly treatment sessions, combined with stereotactic radiotherapy. In a rat model of GBM, 40 min of AMF was already sufficient to cause this cytotoxic effect (Jordan et al., 2006). Comparisons between treatment paradigms are summarized in Table 1.

6.3. The path towards neuromodulation

The application of MNP heating for cellular activation and neuromodulation requires a lower thermal dosage and median increase in temperature, as compared to hyperthermia used for GBM treatment (Table 1). As a consequence, optimization strategies for MNP properties and AMF parameters differ between the two applications. In the study by Chen et al., 2015, the combination of high MNP SLPs and short 10 s AMF stimulation pulses enabled a rapid raise in median temperature up to 43℃ with a maximum increase to 45℃.During the 50 s rest epochs, the tissue cooled back down to 37℃. This short intermittent exposure to AMF induced neural activation and prevented the harmful heating of cells by prolonged AMF exposure, thereby avoiding cytotoxicity (Table 1). In the study of Munshi et al. (2017), the combination of high MNP SLPs and three to four one-minute stimulation epochs during a 10–15 min experiment enabled control of motor behavior in mice while avoiding brain tissue damage. Their results show that magnetothermal stimulation of the motor cortex elicited running. Magnetothermal stimulation of the striatum caused rotation around the body axis, while stimulation of the ridge between dorsal and ventral striatum caused freezing of gait. Furthermore, their findings demonstrate short latencies between starting or terminating the AMF stimulation and the observed behavior (Munshi et al., 2017). These reports show that a short intermittent AMF stimulation induces well dosed and temporarily precise MNP heating, which is the key to safe and effective magnetic neuromodulation.

7. Adverse effects of MNP heating

Adverse effects of MNP heating are subject of vigorous investigation. Clinical research for MHT in GBM treatment indicated that adverse effects, such as swelling of the brain and rise of intracranial pressure, could be avoided by very slow injection of the magnetic fluid (Maier-Hauff et al., 2007). In these studies, moderate adverse effects included sweating (50%), a general sensation of warmth in the treated area (47.0%), headaches during hyperthermia (13,8%), focal convulsions (22.7%), motor disturbances (21.2%), and perifocal edema (9%). Focal convulsions stemmed primarily from a pre-existing hemiparesis. Only 2% of the patients who experienced motor disturbances or focal convulsions had developed these side effects during MHT. Despite worsening of pre-existing hemiparesis, none of the side effects persisted in the long term, and their physiological origins remain unclear (Maier-Hauff et al., 2011).

Another adverse effect of increased temperature could be the aggregation of the MNPs. A study investigating citrate-coated-iron- oxide MNPs, observed accelerated aggregation of the particles following hyperthermia *in vitro*. This clustering of MNPs can change their magnetic properties and cause occlusion when administered into a blood vessel (Wegscheid et al., 2014). This could have great disadvantageous clinical consequences, therefore preventing this is utterly important. Surface chemistry plays a significant role in avoiding MNP aggregation so a carefully designed surface passivation is essential for clinical efficacy of MNPs.

The effects of magnetic hyperthermia on the viability of healthy neurons greatly differ among different MNP studies. For MHT on healthy rat astrocytes, it has been found that stimulating for 2 consecutive hours led to decreased astrocyte viability, even at physiological temperatures (Schaub et al., 2014). Another study found that 2 h exposure of healthy chick embryonic cortical neurons to hyperthermia did not yield any negative effects (Rivet et al., 2014). Intermittent magnetothermal stimulation of healthy neurons in the VTA of mice showed no difference in neuronal or glial density between stimulated and non-stimulated groups (Chen et al., 2015). Therefore, the effects of magnetic hyperthermia on neuronal viability depend for a large part on MNPs composition, magnetic field stimulation paradigms, the interval of increased temperature, the maximum increased temperature reached, and the type of tissue stimulated. These results highlight the importance of conducting studies that directly compare neuronal viability outcomes using the same magnetic stimulation paradigms.

Another area lacking experimental investigation is the long-term effect of MNP heating on microvasculature. It is plausible that the nearby microvasculature adapts to repetitive exposure of heat and, therefore, should be taken into consideration.

Due to the dearth of studies and lack of consistency between MNP chemistries, AMF parameters, as well as exposure paradigms, toxicological data concerning hyperthermia with MNPs remain inconclusive (Table 1) (Nano et al., 2012, Wankhede et al., 2012). Some evidence point in the direction of astrocytic mitochondrial stress and

attachment defects after nanoparticle administration *in vitro* (Au et al., 2007). In patients treated with MNP heating for GBM, key parameters for iron metabolism were determined before and after the administration of MNPs, showing no indication of iron release from intratumoral deposits or iron being metabolized (Maier-Hauff et al., 2011). Nonetheless, the long-term toxicological effects of MNPs located in the CNS and their clearance require further investigation, in which different magnetic stimulation parameters should be taken into account as well.

8. Future challenges for MNP induced neuromodulation

Magnetic coils suitable for cancer hyperthermia and magnetothermal neuromodulation in rodents can be engineered to efficiently generate appropriate AMF conditions over small experimental volumes (Attaluri et al., 2015; Kossatz et al., 2015; Christiansen et al., 2017; Munshi et al., 2017). Scaling AMF coils to volumes necessary for neuromodulation or tumor therapy in deep brain regions of human patients present a formidable challenge, as the power requirements to achieve comparable AMF conditions increase substantially. Despite these challenges, recent engineering efforts build upon techniques in the field of power electronics to pave the way toward development of scaling approaches for AMF coils (Lacroix et al., 2008; Christiansen et al., 2017). The next step for this neuromodulation approach could be the implementation of magnetic neuronal control into different animal models mimicking human diseases such as PD and upscaling the size to non-human primates. For instance, MNPs injected into the STN expressing TRPV1 of 6-OHDA rats, a rat model of PD, could possible revert Parkinson's-like behavior such as circling motor abnormalities upon stimulation. Another robust experiment could be the injection of MNPs into the VTA of rodents expressing TRPV1 to modulate both rewarding and aversive drug-dependent behavior.

A different approach for MNP induced neuromodulation could be by the usage of dTMS. dTMS is able to penetrate slightly deeper into the brain than TMS, however deep brain regions such as the STN can still not be reached. One possibility could be to combine dTMS with the usage of MNPs. The magnetic field might not be strong enough to modulate the tissue on its own but added MNPs might be able to detect the magnetic signal, transducing it into a strong enough signal for neuromodulation. The challenge here remains making MNPs that respond to low field frequencies or a TMS device working at field frequencies in the kHz range. So far, the MNPs discussed above are activated by field frequencies in the kHz range while dTMS for MDD works at a frequency of 18 Hz (Tendler et al., 2016).

Other forms of neuromodulation such as optogenetics and DREADD can incorporate the usage of MNPs for a more wireless approach and to incorporate genes virus free making it more clinically applicable.

To get MNPs and or drugs into a desired brain region, FUS or dTMS seem to be a promising candidates. Both are capable of transiently increasing BBB permeability and future research combining these techniques with targeting neuromodulation using moieties need to prove its feasibility.

9. Conclusion

Current techniques of neuromodulation are limited as they require permanent implants, are invasive, lack cell-type specificity, have limited penetration depth into different brain regions, or rely on slow pharmacokinetics. Refinements are needed and are slowly making their entrance into the field. DBS is a neuromodulation technique already widely used in the clinics but interferes with both pathological and physiological neural activity due to its lack in cell-specificity causing unwanted side-effects in some patients. At the moment mostly continuous stimulation is given, but promising improvements like aDBS and CR DBS are now being investigated. For optogenetics, the limitation is the need of visible light through an invasive probe to drive neurons. Nonetheless, refinements are on the way using other actuators like NPs to convert the light signal and overcome invasive light probes. Also, small, fully implantable, optoelectronic devices converting RF radiation into visible light are now being researched. Chemogenetics, still requires DREADD introduction via viral components or genetic engineering and is mostly limited in temporal precision due to slow pharmacokinetics of the administered drug. Since the actuator of DREADD is now assumed to be clozapine instead of CNO, previous study results need to be interpreted with caution. Nanoparticle-based gene delivery could circumvent the need of viruses in DREADD, making it more convenient for clinical applications. Ultrasonic neuromodulation seems a promising technique not needing permanent implants and being less invasive than the aforementioned techniques. These sound pressure waves can penetrate the skull and interact with deep brain structures without losing its signal, making it an interesting candidate for clinical neuromodulation purposes. Furthermore, it can disrupt the BBB, making it an interesting candidate to deliver NPs and or NP encapsulated drugs into the brain. Magnetic neuronal control is another promising technique since it also does not require the implantation of invasive electrodes or optical devices. With this method, stimulation of deep brain regions is possible because of the negligible magnetic susceptibility and low conductivity of biological tissue. In addition, this technique has a faster response rate than that achieved with drug delivery.

Subsequently, we discussed the application of MNPs for nanomaterial-mediated neuromodulation in more detail and compared this application method to the current use of these particles in treating recurrent GBM. The application of MNPs as transducers of magnetic field into thermal, electrical, mechanical or chemical stimuli offers a possibility to remotely and wirelessly modulate specific groups of cells in arbitrarily deep regions of the brain. The application of AMF pulses in magnetothermal stimulation only cause a short and modest temperature increase, which modulates cells whilst avoiding cytotoxicity due to prolonged exposure. Further research should implement this new technique in various animal models of signs and symptoms as expressed in mental, neuropsychiatric, neurosensory and neurodegenerative disorders in order to restore physiological brain functions and to define the therapeutic value of magnetothermal DBS in these disorders.

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Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and (if provided by the authors) Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.pneurobio.2019.03.002.

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