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ORIGINAL PAPER

Ethics of the Electrified Mind: Defining Issues and Perspectives on the Principled Use of Brain Stimulation in Medical Research and Clinical Care

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Abstract In recent years, non-pharmacologic approaches to modifying human neural activity have gained increasing attention. One of these approaches is brain stimulation, which involves either the direct application of electrical current to structures in the nervous system or the indirect application of current by means of electromagnetic induction. Interventions that manipulate the brain have generally been regarded as having both the potential to alleviate devastating brain-related conditions and the capacity to create unforeseen and unwanted consequences. Hence, although brain stimulation techniques offer considerable benefits to society, they also raise a number of ethical concerns. In this paper we will address various dilemmas related to brain stimulation in the context of clinical practice and biomedical research. We will survey current work involving deep brain stimulation, transcranial magnetic stimulation and transcranial direct current stimulation. We will reflect upon relevant similarities and differences between them, and consider some potentially problematic issues that may arise within the framework of established principles of medical ethics: nonmaleficence and beneficence, autonomy, and justice.

Keywords Neuroethics · Medical ethics · Brain stimulation · Deep brain stimulation · Transcranial direct current stimulation · Transcranial magnetic stimulation

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Introduction

In recent years, non-pharmacologic approaches to modifying human neural activity have gained increasing attention. One of these approaches is brain stimulation, which involves either the direct application of electrical current to structures in the nervous system or the indirect application of current by means of electromagnetic induction. Deep brain stimulation (DBS) has been discussed widely in the medical, scientific, and ethical literature, and is currently being employed as a therapy. In addition, less invasive techniques for stimulating the brain, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are being explored increasingly as investigative and therapeutic techniques (Fig. 1). In this paper we will specifically address these three techniques. Although there are other widely used techniques for stimulating the central nervous system (such as vagus nerve stimulation), we will focus our attention on those technologies for which there has been a large and growing literature demonstrating their ability to manipulate cognition. This is especially true of TMS and tDCS. We are also interested in discussing techniques that have been debated prominently in the neuroethical literature, as is the case with DBS.

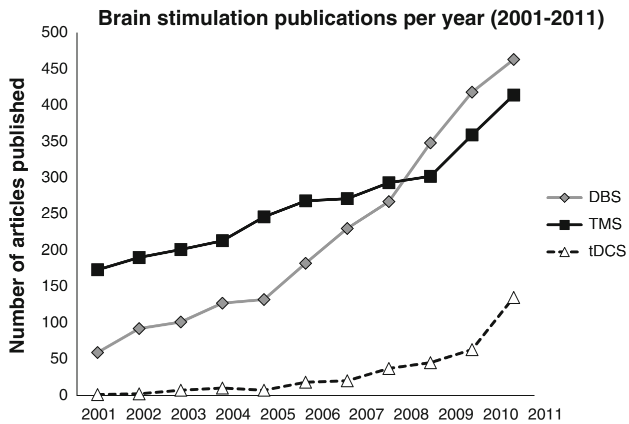

Fig. 1 Published papers related to brain stimulation (2001–2011). Data were acquired by searching pubmed.gov for articles using "deep brain stimulation OR DBS" "transcranial magnetic stimulation OR TMS," or "transcranial direct current stimulation OR tDCS" in the title and by publication date (2001–2011). All searches were conducted on December 8th, 2012

Even though the technology required to perform human brain stimulation has existed for a number of years, it is only recently that the enormous potential of these approaches in cognitive neuroscience, neuropsychology, psychiatry, and neurology has been more fully realized (Wagner et al. 2007). Compared to other therapeutic interventions, brain stimulation has a number of real and theoretical advantages that prompt us to consider how it is being used in the present and how it should be used in the future. In some instances brain stimulation has already proven to be effective in treating disorders that are difficult to manage using more conventional therapies (e.g. DBS and TMS for medication-refractory depression). Also because brain stimulation is more focally targeted than most pharmacologic therapies, it theoretically circumvents many of the undesired side effects of other treatments and can potentially be tailored to meet the needs of individual patients (Fregni and Pascual-Leone 2007). In addition, in some circumstances, brain stimulation has been shown to be more cost-effective than typical pharmaceutical interventions (Valldeoriola et al. 2007; Valldeoriola 2011). In the case of TMS and tDCS, the ability to induce persistent modulation of human cortical excitability and function in a minimally invasive and painless way is a clear advantage over more invasive techniques. Moreover, for certain techniques—most notably tDCS—practical aspects such as device size, cost, and ease of use make it plausible that brain stimulation could someday be implemented in environments with limited resources, such as in developing countries. Finally, these techniques may now be moving beyond laboratories and clinics, and have started (or at least have been envisioned) to play a role in the cognitive enhancement of healthy individuals.

While brain stimulation techniques offer considerable benefits to society as treatments for a variety of debilitating neurologic and psychiatric conditions, they also raise a number of concerns. Naturally, the implementation of new medical technologies introduces questions regarding their use and potential abuse. In this way the ethical issues that arise with brain stimulation are similar to those raised by any other treatment. However, technologies such as brain stimulation that specifically have the capacity to alter cognitive abilities and patterns of thought also merit special consideration, since they may raise unique concerns related to personhood and identity. In this paper we will address various issues related to brain stimulation in the clinical setting, focusing on interventions that modulate cognition. We will survey current work involving DBS, TMS and tDCS, reflect upon relevant similarities and differences between them, and consider some potentially problematic issues that may arise within the framework of established principles of medical ethics.

Overview of Brain Stimulation Techniques

DBS is an invasive technique that stimulates brain structures that lie deeper than the cerebral cortex, including but not limited to the basal ganglia, thalamus, and deep portions of the cingulate gyrus. The DBS system consists of: (1) a lead, (2) an extension, and (3) the implanted pulse generator (neurostimulator), which is placed below the skin. The lead, a thin electrode, is inserted through a small opening in the skull and implanted in the brain, with its tip positioned within the targeted brain area. The extension, an insulated wire, is passed under the skin of the head, neck and shoulder, connecting the lead to the neurostimulator (UNC School of Medicine 2012). The neurostimulator (sometimes called a 'brain pacemaker') delivers a constant high frequency stimulus to the tip of the lead, and is usually implanted under the patient's clavicle or abdomen (Lozano et al. 2002; UNC School of Medicine 2012). To date, the precise mechanism of action of DBS remains unclear (Ponce and Lozano 2010); however it is thought that the stimulation induced by this system may interrupt specific circuits in the brain that are overactive in different disease states.

TMS is a minimally invasive technique that allows for both neurostimulation and neuromodulation (Wagner et al. 2007). It involves an electromagnet, which generates a rapid time-varying magnetic field in a coil of wire, that when held to the head of a subject creates magnetic pulses that penetrate the scalp and the skull, inducing a small localized electrical current parallel to the plane of the coil in the brain. This induced current is sufficient to depolarize neuronal membranes and generate action potentials (Hamilton et al. 2011). Depending on the frequency, intensity, and temporal pattern of stimulation, TMS can be employed to focally induce either excitatory or inhibitory cortical activity. Single-pulse TMS has long been used as a neurophysiologic tool to assess and briefly modulate cortical excitability, and has also been used to assess the integrity of central neural pathways in the brain and spinal cord. Closely paired pulses of TMS—administered either within the same hemisphere or bihemispherically—have also been used to explore cortical excitability. In contrast to the very transient effects of these techniques, repetitive TMS (rTMS) employs longer trains of pulses, which can induce neurophysiologic and behavioural effects that can outlast the period of stimulation (Pascual-Leone et al. 1999a). It is thought that the mechanisms that drive these persistent post-stimulation rTMS effects are analogous to those seen in animal models of long-term potentiation (LTP) and long-term depression (LTD) (Korchounov and Ziemann 2011; Pascual-Leone et al. 1999b). Our discussion of the real and theoretical concerns associated with TMS will focus on treatments involving rTMS, since other approaches have not been associated with persistent changes in brain activity or behavior.

tDCS is a minimally invasive technique that differs from TMS in that it only allows for neuromodulation and not neurostimulation (Wagner et al. 2007). The technique involves applying a weak direct current (1–2 mA) to the scalp via electrodes (an anode and a cathode), which deliver current to underlying tissues, including the brain. Only a portion of the applied current enters the skull (Priori et al. 2009). tDCS differs qualitatively from TMS because the current applied to the brain is insufficient to induce the rapid shift in neuronal membrane potentials required to produce action potentials (Nitsche et al. 2008). Rather, it is believed that tDCS modulates cerebral activity by inducing incremental shifts of cortical excitability (Nitsche and Paulus 2001; Nitsche et al. 2005, 2008). TDCS can have prolonged effects, lasting from minutes to hours depending on the intensity, polarity and duration of stimulation applied (Priori 2003). These effects have been attributed to neuronal changes that affect synaptic connectivity, including synthesis of specific proteins and modification of intracellular cAMP and calcium levels (Nitsche et al. 2008). Like TMS, it has also been suggested that tDCS induces neuroplastic changes that are physiologically similar to LTP and LTD (Nitsche et al. 2003).

Comparison of Brain Stimulation Techniques

There are clear differences between DBS, TMS, and tDCS that inform the contexts in which they have been and can be used. Perhaps the most obvious of these differences is that DBS is an invasive technology, in that it involves surgical implantation of an electrode (or electrodes in the case of bilateral DBS) within the brain parenchyma. DBS is therefore associated with surgical risks such as bleeding or infection. Patients with DBS sometimes require further surgeries in cases where the batteries of the neurostimulator are depleted or malfunctioning (Blomstedt and Hariz 2005; Merkel et al. 2007). By contrast, TMS and tDCS are applied externally (that is, they are placed in direct contact with the head or in close proximity to it), and do not involve insertion of mechanical hardware into brain tissue. TMS and tDCS are often classified as non-invasive to emphasize their external nature. In this piece we refer to these two technologies as "minimally invasive", in part to underscore the notion that they impose exogenous magnetic fields or electrical currents upon the brain, and can thus be considered at least somewhat invasive (George et al. 2009). While the fact that TMS and tDCS do not require brain surgery is clearly an advantage, one difference and potential drawback related to the minimally invasive nature of these technologies is that they are much more limited in their ability to affect brain structures deeper than the cortex. The fact that these techniques target very different sites in the brain leads to broad differences in the disease processes for which invasive and minimally invasive stimulation techniques are being explored. In addition, the spatial resolution of DBS is thought to be superior to that of minimally invasive stimulation techniques, especially tDCS (Nitsche et al. 2008), allowing for anatomic structures to be targeted precisely, which in turn yields specific clinical benefits and minimizes stimulation side effects (Ponce and Lozano 2010). One practical consideration is that compared to DBS minimally invasive brain stimulation techniques are inexpensive, since they do not involve the costs and potential liabilities associated with surgery. Finally, while TMS and tDCS can be employed in a variety of ways to pursue basic studies of physiology and behavior, diagnostic procedures, and therapeutic interventions (Pascual-Leone and Wagner 2007), DBS is generally only employed as a treatment because of the risks and expense involved.

Comparison of TMS to tDCS reveals a number of relevant differences. As noted above, TMS is capable of stimulating neuronal action potentials, whereas tDCS is only capable of incrementally modulating the activity of neurons. Another difference is that single pulses or short trains of TMS can be delivered with great temporal precision, which potentially affords much greater temporal resolution than tDCS (Priori et al. 2009). While this is a meaningful advantage for many cognitive neuroscience studies, the temporal precision of TMS is perhaps less relevant to treatment studies, wherein long trains of rTMS are often employed. Another potential disadvantage of tDCS in comparison with TMS is its relatively low spatial resolution. However one can change the size of the electrodes to achieve a better spatial resolution with tDCS (Nitsche et al. 2007), and investigators have recently developed "high-definition" tDCS (HD-tDCS) systems designed to deliver more focal stimulation (Datta et al. 2008). Nonetheless, conventional tDCS may theoretically be preferable in cases where stimulation of a more distributed network of cortical sites is desirable. Extending this notion, a theoretical advantage of tDCS is that by virtue of having two possible sites of concurrent stimulation on the scalp (an anode and a cathode) this technique may be especially useful in cases of unilateral injury, where "behavioural effects occur not only through dysfunction at the damaged site, but also from overinhibition arising from the contralateral healthy side of the brain" (Priori et al. 2009). Sham (placebo) tDCS can be administered readily and is difficult to distinguish from actual stimulation (Brunoni et al. 2012b; Gandiga et al. 2006). Moreover tDCS stimulators can be pre-programmed to deliver sham or real tDCS in a masked manner, so as to enable double-blinded experimental designs (Nitsche et al. 2008). Sham TMS studies are more difficult to execute, insofar as scalp sensations, facial muscle twitches, and noise generated by the coil make it difficult to conceal whether or not real stimulation has been applied (Priori et al. 2009).

Although TMS may be a more spatially and temporally precise instrument than tDCS, there are a number of practical considerations that make tDCS attractive as well. For instance, tDCS is highly portable (it fits inside a briefcase and is battery powered) compared to TMS. In addition, subjects undergoing tDCS have more freedom to move their heads during the course of stimulation compared to subjects receiving TMS, which allows tDCS to be used more readily with existing behavioral tasks and therapies (Hamilton et al. 2011; Priori et al. 2009). Administration of TMS carries a small risk of inducing seizures, which has never been reported with tDCS (Rossi et al. 2009). Importantly, the cost of a tDCS unit is approximately an order of magnitude less than a TMS machine paired with neuronavigational equipment and software. All of these characteristics give tDCS a greater potential to be used in areas lacking resources or with poor infrastructure (such as developing countries) (Brunoni et al. 2012b). These practical advantages also predispose tDCS to use outside the clinical setting, potentially as a "do-it-yourself" technique. This brings with it a host of ethical issues, which we will touch upon in the discussion section.

Better Living Through Electricity: the Therapeutic Promise of Brain Stimulation

A growing number of studies speak to the beneficial effects of brain stimulation in treating a variety of conditions affecting the nervous system. DBS is supported by the most evidence, as it has been in clinical use the longest out of the three technologies. The US Food and Drug Association (FDA) has approved DBS as a treatment for essential tremor (1997), Parkinson's disease (2002) and dystonia (2003). Psychiatric applications of DBS are also moving from experimental to clinical use (Synofzik and Schlaepfer 2011), and DBS is currently being explored as a treatment for depression (Anderson et al. 2012; Mayberg et al. 2005), Tourette's syndrome (Kuhn et al. 2009), Alzheimer's disease (AD) (Laxton et al. 2010), anorexia (Wu et al. 2012), and alcoholism (Heldmann et al. 2012).

TMS (specifically repetitive TMS, or rTMS) was given FDA approval in 2008 as a treatment for medication refractory depression.[1] There is also ongoing research into its potential therapeutic benefits for a variety of other neurologic and psychiatric conditions, including but not limited to motor dysfunction (Groppa et al. 2012), obsessive compulsive disorder (OCD) (Wu et al. 2010), Alzheimer's disease (Haffen et al. 2012), hallucinations in schizophrenia (Guller et al. 2012), and pain disorders (Sampson et al. 2011).

Despite its benign side-effect profile, tDCS has not yet received approval from the FDA for any clinical indication. However, promising data indicate that it may eventually prove effective in treating major depressive disorder (Brunoni et al. 2012a, 2013), motor and cognitive deficits after stroke (Schlaug et al. 2008), working memory deficits (Fregni et al. 2005), and memory loss in patients with Alzheimer's disease and Parkinson's disease (Boggio et al. 2006). Moreover, it has been hypothesized that tDCS could be helpful for the treatment of a variety of other conditions, such as anorexia nervosa (Hecht 2010). Given the invasiveness, risks, and costs associated with DBS, it seems likely that less invasive techniques such as TMS and tDCS will eventually be more widely used in clinical settings.

The Ethical Challenges of Brain Stimulation

The notion of therapeutically altering brain function has always raised both hopes and fears, and different interventions that accomplish this goal have always come with both promises and perils. Neurotechnologies such as brain stimulation bring to the forefront a variety of challenges that are "relatively novel and emerge primarily because of the very special status of the brain in human life" (Farah 2010; cf. Glannon 2007; Racine 2010). Direct manipulation of the brain, for instance, has generally been regarded as an intervention with both the potential to cure

[1] Even though TMS has FDA approval, its "clinical effect sizes are modest and the ultimate clinical significance remains unclear and is still controversial" (George et al. 2009).

devastating brain-related conditions and the capacity to create unforeseen and unwanted consequences including radical changes in the complex perceptions, thoughts, motivations, and behaviors that confer upon us our humanity and our personhood (Bell et al. 2009; Farah and Wolpe 2004; Hamilton et al. 2011; Heinrichs 2012).

Considering the potentially vulnerable status of many patients with brain disorders, the lack of extensive data about effectiveness of these relatively new stimulation technologies, the increasing exploration of these techniques for a variety of neurologic and psychiatric indications, and the potential for their use in the absence of professional oversight (specifically in the case of tDCS), we believe that the community of clinicians and investigators employing brain stimulation in the context of clinical research and care needs to take closer stock of the ethical concerns associated with these emerging technologies, and should also identify a framework of principles that can be employed to inform both clinical and research decision-making (Bell et al. 2009; Heinrichs 2012; Priori et al. 2009; Synofzik and Schlaepfer 2011). In this paper, which focuses on the use of brain stimulation in clinical practice and biomedical research, we will consider the ethical issues of brain stimulation within the context of well-established principles of medical ethics: nonmaleficence and beneficence, autonomy, and justice (Beauchamp and Childress 2001). Here is it important to emphasize that we are focusing on issues that could arise from either current or proposed therapeutic applications of brain stimulation, rather than basic science investigations that employ these technologies. However, we will also touch upon some basic studies of physiology and cognition, insofar as they suggest that neurologic functions can be manipulated and enhanced in ways that may someday be relevant to patients.

"First, Do No Harm": Nonmaleficence and Beneficence in Brain Stimulation

The notions of acting in the interests of a patient (beneficence) and avoiding harm (nonmaleficence) are central principles of bioethics that have guided the practice of medicine since antiquity. Therefore, while these two concepts are certainly important to brain stimulation techniques, they are in no way unique to them; we can draw on current practices in clinical and research ethics to inform and guide the appropriate use of brain stimulation. In clinical practice, beneficence and nonmaleficence are often addressed in tandem, when a conversation takes place between a clinician and patient in which the risks and benefits of a particular therapeutic intervention are discussed. In the clinical setting, where the techniques have already been subjected to controlled clinical trials and been given approval by government bodies for specific medical indications (e.g. FDA approval of DBS for Parkinson's Disease), the immediate benefits and risks likely to be faced by the patients are relatively easy to predict and discuss based on existing data. This is less clear in the clinical research setting, where therapies are still experimental and where only limited evidence regarding either the benefits or the risks to patients may be available. Most investigators currently conduct research within the guidelines established by regulatory bodies in their institutions or by the Declaration of Helsinki (World Medical Association General Assembly 2001), both of which emphasize that in biomedical research the benefits to a human subject and to society should exceed the risk imposed on the individual. Nonetheless, the onus is on researchers to be frank about the fact that benefits are not certain and that risks, in some cases, are not completely known.

With respect to known risks, each brain stimulation technique has its own unique safety profile. Like in all clinical practices, it is important for physicians and others administering therapies to thoroughly discuss safety issues with patients related to these technologies. DBS, for example, is considered to be a largely reversible technique in spite of its invasive features, because it is thought that the therapy does not leave permanent lesions (Ponce and Lozano 2010). Nonetheless, considering the risks and side effects associated with the surgery (i.e. hemorrhage, infection, fracture, misplacement, or migration of the lead) (Merkel et al. 2007), and the relative lack of long-term data with this relatively new technique, this notion of reversibility is debatable. Indeed, given the potential risk associated with surgical implantation of DBS electrodes, it has generally been employed as a treatment of last resort for patients who are refractory to other forms of therapy. By contrast, TMS and tDCS are regarded as relatively safe, although not entirely without risks. Single pulses of TMS are considered very safe, and this approach has been used extensively to investigate various aspects of human neurophysiology. On the other hand, repetitive TMS (rTMS) has been associated with a small risk of inducing seizures, although rigorous safety guidelines have been established to avoid this adverse event (Rossi et al. 2009; Wassermann 1998). The most common side effect of TMS is mild and transient headaches. TDCS has not shown any serious side effects, except for some tingling or itching under the electrodes, and infrequent nausea, fatigue, and headache (Nitsche et al. 2008; Poreisz et al. 2007), and in rare cases skin lesions (Palm et al. 2008). However, safety for tDCS has not been extensively investigated in persons with skull defects or neuropsychiatric disorders (Brunoni et al. 2012b), so caution should be exercised with these groups of patients. Naturally, an important point to take into consideration is whether brain stimulation leads to long-term changes in brain function. In non-clinical research, the changes in brain activity induced by stimulation are believed to be transient, whereas in the clinical setting the goal is often to achieve effects that persist well beyond the stimulation period. The possibility that these therapies might induce permanent changes in the brain raises theoretical concerns that there may be unintended neural consequences of stimulation.

When considering technologies that can potentially alter neurologic function, cognition, and behavior, the notion of unintended consequences takes on special significance. Brains are delicately balanced, intricately connected, and highly ordered systems; it is difficult, if not impossible, to predict all the likely consequences of brain stimulation. Years from now we may discover that repeated stimulation of a specific brain area has a beneficial effect on one cognitive domain, but a deleterious effect on others. For example, there have been cases in which the placement of DBS successfully treated patients' motor deficits but also exacerbated cognitive problems, depression, or (hypo)mania (Temel et al. 2006). There have also been cases in which patients, despite improvement in motor function, experience difficulties adapting to the expectations associated with being restored to a normal level of function (Gilbert 2012). Numerous studies in cognitive neuroscience have employed TMS to focally suppress activity, creating "virtual lesions" for investigative purposes (Pascual-Leone et al. 1999a). This implies that TMS, in addition to having the capacity to induce beneficial effects on cognition and behavior, could theoretically have the potential to induce unintentional deleterious effects on neurologic function. In the case of tDCS the position and polarity of electrodes is crucial, and there is evidence that unintentional electrode misplacement or reversal of polarity can cause at least transient impairment of specific cognitive functions (Cohen Kadosh et al. 2010) or induce maladaptive behavioral changes (Fumagalli et al. 2010). The potential issue of unintended consequences due to brain stimulation finds clear parallels with the unintended side effects of medications. However, we believe that the targeted nature of brain stimulation increases the likelihood that the side effects of these techniques will be cognitive and behavioral in nature, and that for this reason these approaches merit special consideration. Insofar as brain function instantiates the perceptual and cognitive experiences that comprise identity, personality, and self, one very real possibility is that these technologies may affect these vital human abilities in unpredictable and undesired ways, as we will discuss below.

Finally, directly linked to the idea of risks and benefits is the notion of the so-called "double effect." That is, there are situations in which we accept the deleterious effects of a treatment in light of other beneficial effects (e.g. medications that alleviate pain but also shorten the lives of terminally ill patients). In the case of brain stimulation, there may be scenarios in which known changes in neurologic function are deemed to be acceptable in light of specific potential benefits. This raises difficult questions, including how much of a bad or questionable effect do we tolerate for the sake of a desirable effect? How does one weigh different mental abilities or neurological functions against each other? Who prioritizes these abilities? Is it, for instance, appropriate to change a person such that he or she is worse at mathematical reasoning but better with respect to verbal fluency? What about decreasing empathy for the sake of increasing working memory? While it is largely speculative whether brain stimulation is likely to lead to these kinds of cognitive trade-offs, it is worth considering potential consequences such as these before we see them emerge in treated patient populations. Will there be certain cognitive domains that should be inviolable with respect to manipulation?

Although we cannot answer all of these questions, we can start to address them in common sense ways. The issue of unintended consequences demands that researchers and clinicians pay careful attention to their subjects or patients to detect any possible unexpected deleterious effects of stimulation. This may require more careful scrutiny of a variety of neurologic and cognitive domains aside from those that are being intentionally experimentally or therapeutically manipulated. Publication of safety data and responsible reporting of unexpected outcomes are also essential for defining the landscape of risks and benefits associated with these technologies. As these risks and benefits of brain stimulation become more completely known, issues of double effect will need to be addressed on an individual study-by-study basis since the trade-off of risks to benefits will be dependent on the nature of each investigation. In such instances, investigators must be willing to work closely with regulatory bodies (e.g. Institutional Review Boards or the U.S. Food and Drug Administration), who are charged with safeguarding the interests of subjects and patients with respect to medical interventions.

Autonomy: Searching for Self in the Stimulated Brain

Direct manipulation of the brain—of which brain stimulation techniques are just one example—can lead to changes that extend beyond modification of specific cognitive abilities and behaviors. If permanent and significant changes in physiology are induced by these interventions, they could affect the motives and other general dispositions that underlie behavior (Bublitz and Merkel 2009). Thus, brain stimulation could theoretically be regarded as an intervention that circumvents the normal capacities of individuals in order to alter those capacities, in a sense "imposing itself over [ourselves]" (Levy 2007). This poses a challenge when thinking about the principle of respect for autonomy. Here, we would like to touch upon two interrelated issues of autonomy: informed consent and personhood.

Informed-Consent, Decision-Making Capacity and Withdrawal

The notion that a patient or subject should only be subjected to an intervention if he or she is well-informed, willing to participate, and free from coercion is fundamental to the ethical conduct of medical research and clinical practice, and finds its foundations in the principle of respect for autonomy. Several issues arise with respect to informed consent as it relates to brain stimulation. The fact that many therapeutic applications of brain stimulation remain experimental underscores the duty to fully inform individuals of the potential risks of these techniques, as discussed above. In addition, as it is the case of DBS, most of the therapeutic applications are only offered for treatment-refractory patients, which could mean that patients are already in vulnerable states in which they might feel that they have no viable options but to consent. Another issue that makes informed consent potentially problematic is that many proposed and currently employed therapeutic applications of brain stimulation are geared towards individuals with either psychiatric disorders or cognitive impairment. This further underscores the need to establish, on an individual basis, whether persons are capable of providing appropriate consent. Extending this notion further, an assessment of the ethical implications of these techniques must also take into consideration whether the cognitive and behavioral effects of stimulation themselves alter the ability of individuals to provide or withdraw consent (Heinrichs 2012; Schmitz-Luhn et al. 2012). Finally, a set of concerns relates to whether the wider use of these technologies may eventually introduce either explicit or implicit coercive pressure for individuals to undergo brain stimulation to treat real or perceived cognitive or psychological impairments (Hamilton et al. 2011). While the issue of coercion is not unique to brain stimulation, we should nonetheless be mindful that in our competitive fast-paced society, more widespread implementation of techniques that can potentially enhance mental activity may eventually lead to direct or indirect pressure on individuals to make use of them.

The notion of capacity is of central concern in any discussion of informed consent (Klaming and Haselager 2010). In the context of clinical care and medical research, capacity can be defined by four key abilities: communication, understanding, appreciation, and rationalization/reasoning (Appelbaum and Grisso 1998). An individual must be able to not only understand the information presented to them but also be able to apply the information to their own personal situation and rationally explain the reason for the decision that they made. A separate, but related concept is mental competence, which is a legal status that must be demonstrated in order to start, continue, or stop any clinical or experimental manipulation that entails intervening on an individual's body or mind.[2] With these definitions in mind, clinicians and investigators employing brain stimulation techniques must be cognizant that for individuals with certain conditions, particularly psychiatric disorders, the determination of medical decision-making capacity may be quite complicated (Bell et al. 2009; Cabrera 2011; Schmitz-Luhn et al. 2012; Synofzik and Schlaepfer 2011). One reason for this is that individuals' treatment preferences[3] (Synofzik and Schlaepfer 2011) and decision-making capacities (Cabrera 2011) are strongly influenced by mood and affect, which are in turn affected in these types of conditions. Another reason is that the potential psychiatric side effects of brain stimulation itself, such as mood changes or elevated anxiety, may be more prevalent or pronounced in psychiatric patients. Thus, depending on the conditions for which these techniques are used, additional efforts may be required in order to accurately assess capacity, provide information, and acquire consent in a manner that is appropriate to the abilities and needs of patients and subjects. While this determination can at times be complicated, evidence suggests that providing clinicians with adequate knowledge of the key components of capacity increases the reliability of their assessments (Marsden et al. 2000). Moreover, in the broader field of medicine, structured clinical interviews and other formal assessment instruments have proven helpful in making such determinations (Dunn et al. 2006). In some cases capacity may be further informed by evaluation of cognitive abilities and psychological states (see Appelbaum 2007 for a brief review of assessment). In short, for many current and future practitioners of brain stimulation, assessment of capacity may represent a new clinical skill set that will need to be acquired.

Identity/Personhood

Our sense of individual identity and our understanding of ourselves as distinct persons derive largely from our ability to experience psychological continuity and persistence through time as the same beings. Importantly, it has been

[2] The foundational document of research ethics, the Nuremberg Code, begins the first of its ten requirements with: "the voluntary consent of the human subject is absolutely essential".

[3] For instance, treatment-resistant patients might feel desperate to find a cure.

argued that neural interventions have the capacity to alter these experiences so profoundly that they may impact the experience of personhood (Farah and Wolpe 2004). This has been a major topic in the discussion of ethical issues surrounding DBS in particular (Heinrichs 2012; Jotterand and Giordano 2011; Klaming and Haselager 2010; Lipsman and Glannon 2012; Mathews 2011; Schmitz-Luhn et al. 2012; Witt et al. 2011), and is also a theoretical concern for other brain stimulation techniques.

There are certainly limits to what would be reasonable concerns regarding brain stimulation and personhood. For instance, it would be difficult to argue that the individuals who receive brain stimulation are abruptly transformed into wholly different persons by their experience. This is because these techniques generally do not fundamentally disrupt the continuity and persistence of mental experience. Moreover, practitioners of these techniques—perhaps more so those who administer TMS and tDCS than DBS—can reasonably assert that, while brain stimulation can potentially alter the neural states and experiences of its recipients, these interventions do not affect the personhood or identity of individuals more than psychopharmacological treatment or behavioral and cognitive therapies, all of which are generally accepted by the public. The main questions for brain stimulation related to personhood are therefore more along the lines of whether or not these technologies alter aspects of selfhood in more subtle but nonetheless worrisome ways. While this concern remains largely theoretical at this point, an issue as important as this will require more comprehensive assessment of cognitive outcomes in studies that employ these techniques as well as comparative studies with other brain intervention technologies. Here we will discuss two specific concerns, one related to the short-term, reversible effects of brain stimulation, and a second concern related to its enduring effects.

The putative reversibility of brain stimulation raises an intriguing question that relates both to personhood and to informed consent: under which condition—stimulation on or off—should an individual be approached regarding continuation or cessation of treatment? Stated another way, it may be unclear whether a person whose cognition and affective capacities have been temporarily changed by brain stimulation is fully entitled to make decisions on behalf of the person they are when their brain is not being stimulated. Some patients might have preferences while under the influence of stimulation that do not reflect their values in the absence of stimulation. In some cases, it is possible that brain stimulation treatments may affect cognition so profoundly that persons who previously were not considered to have been competent medical decision-makers and advocates for themselves might be more intellectually capable of decision-making after stimulation. Are there limits on a treated individual's ability to make decisions on behalf of his or her less capable future self, or vice versa? On the other hand, one could also make the countervailing argument that the diseases for which stimulation may be used as a therapy may have already altered patients' initial cognitive and affective functions. Extending this reasoning, it could potentially be argued that therapeutic interventions, including brain stimulation, allow patients to make decisions in a state that is more akin to their pre-morbid, and perhaps preferred, selves. Regarding the decision-making rights of the treated self versus the untreated self, some insights can be gleaned from the field of psychiatry, wherein patients who are being treated pharmacologically for mental conditions are generally allowed to guide their decision-making in both the treated condition and the untreated condition, provided they are deemed to have the capacity to do so in both states. There are, however, situations in which patients' ability to control their treatment are curtailed, for instance when it is deemed that by refusing treatment, the mental states and behaviors of these individuals put either themselves or others in imminent danger.

While the cognitive and psychological effects induced by TMS, tDCS, and DBS are generally thought of as being reversible, there is evidence that suggests that prolonged or repeated stimulation can lead to lasting changes in neural function. Extending this notion, persistent changes in neural activity may manifest in long-lasting alterations of elements of a person's perception, cognition, motivations, and behavior that touch upon the fundamental nature of who they are. In many cases these changes in self will be desired by the individuals receiving stimulation, and may be the main objective of their treatment. Indeed, just as some patients taking psychoactive medications report that they feel more like their "authentic selves" while on treatment than off (Kramer 1994), some persons receiving stimulation may find their stimulated state to be more in accordance with their notion of themselves (or with their notion of who they would like to be). On the other hand, as we touched upon in our discussion of risks and benefits, the limitless complexities of the brain and our limited experience with brain stimulation make it entirely plausible that extensive use of these technologies could lead to changes that are unanticipated, undesired, or both, such as significant changes in our personalities and concepts of who we are. We may already have examples of such cases with respect to invasive brain stimulation, and as more data is gathered from minimally invasive stimulation we will begin to develop a clearer sense of whether this is also a realistic concern with these technologies.

Arguments connected to identity and personhood do not translate readily into concrete, practical, and systematic criteria for guiding research and clinical decision-making

(Synofzik and Schlaepfer 2011). Nonetheless, they are important for persons in the field of brain stimulation to consider, as they could have far-reaching consequences for subjects, patients, and caregivers, as well as the social environments in which persons living in 'altered states' interact (Baylis 2011). These concerns should prompt more research into the significance and long-term impact of brain stimulation on the components of mental experience that contribute to identity and personhood, as well as identification of the conditions, stimulation parameters, and patient populations wherein fundamental changes in mental experience are most likely to occur. In this way practitioners of brain stimulation could provide anticipatory guidance to allow stimulation recipients to make informed decisions about desired and undesired changes in being.

Justice: Fairness and Equity in Brain Stimulation

The concept of justice encompasses the idea the benefits should not be unfairly denied to individuals without good reason and also the notion that specific groups of individuals should not by unduly burdened (Sims 2010). In research and clinical settings these ideas find their application in the equitable distribution of medical resources, technologies, and research priorities. Because DBS, TMS, and tDCS vary widely with respect to cost, equipment needs, and administrator expertise, the three technologies need to be considered separately with respect to distributive justice. DBS is by far the most resource-intensive brain stimulation technique as it involves the cost of the implanted electrode system, the labor of a skilled neurosurgeon and clinical staff, and the cost of brief hospitalization. The resource requirements associated with both TMS and tDCS are significantly less, although there a considerable difference in cost and equipment needs between these two minimally invasive techniques as well. As noted above, compared to tDCS, TMS involves components (e.g. a stimulation unit and possibly a neuronavigational system) that are larger, heavier, and require a constant power supply. Thus, compared to both DBS and TMS, tDCS is inexpensive, portable, requires the least additional resources, and requires the least specific training in order to implement. These properties may eventually facilitate the widespread use of this technology, insofar as tDCS could be used in places with limited resources or where the medical or technological infrastructure is not sufficient to maintain the other two techniques (Pascual-Leone et al. 2011).

Therapeutic brain stimulation is currently delivered in an inequitable manner. At least in the US, the high cost of DBS limits its implementation largely to patients with health insurance, while many patients who receive TMS for depression must possess the means to pay for treatment out of pocket. However, while distributive justice is certainly an important ethical issue that pertains to brain stimulation, we assert that this issue is not unique to these techniques. It is the rule rather than the exception that when innovative technologies are introduced into the public sphere they are at first the almost exclusive purview of a privileged group of individuals. This is certainly the case in the medical field, where persons with resources—whether those resources be personal wealth or the right kind of medical insurance—have nearly unfettered access to advanced medical treatments, while individuals without access do not. Thus, inequity with respect to brain stimulation simply serves as another instance of the "widening gap between rich and poor with respect to almost all aspects of life" (Hamilton et al. 2011). Importantly, we do not mean to imply that efforts to enhance fairness with respect to brain stimulation are either misguided or futile. Rather, our point is that inequity in the administration of brain stimulation is reflective of a larger issue of distributive justice that is endemic to medicine in the industrialized world.

Discussion

We have tried to make the case that, although not all the ethical issues brought forward by brain stimulation are unique to these techniques, there are certain aspects that indeed require special attention. Moreover, while we do not assert that all ethical issues play the same role for DBS, TMS, and tDCS, the basic idea of stimulating the brain—be it electrically or magnetically, invasively or minimally invasively—implies commonalities among the three techniques. We do not need to reinvent the wheel for assessing the ethical aspects of every clinical and research area to be explored for each one of these techniques, but we also do not want to overgeneralize and overlook their differences.

We have also emphasized issues that brain stimulation techniques engender related to the foundational principles of medical ethics: beneficence and nonmaleficence, autonomy and justice. Insofar as most proposed therapeutic applications of brain stimulation are still only in the experimental or in some cases conceptual stage, these 'early days' for the field are an opportune time for clinicians and investigators to reflect on their fiduciary responsibilities with respect to patients and subjects undergoing brain stimulation. The clinician-patient relationship defines a bond of trust that is of paramount importance in the practice of medicine, including therapeutic brain stimulation. One issue that could threaten that relationship is the fact that many clinical practitioners of these techniques are themselves investigators, setting the stage for a possible conflict of interest between the best interests of patients and the desire to demonstrate the efficacy of brain stimulation techniques. Faced with strong professional incentives to demonstrate positive results, and faced with patient populations who are highly motivated to pursue treatments they hope will help them, clinicians and investigators must strive to maintain both transparency and equipoise with respect to the benefits and risks of treatment, and work to communicate these, as free from bias as possible, to potential patients and subjects. Thus leadership from practitioners and researchers is required in this burgeoning field in order to create and maintain standards of ethical conduct for research with human subjects.

To summarize the issues we have touched upon in this paper we want to make three basic points:

(1) The therapeutic use of brain stimulation can be guided by the same framework of ethical principles that inform other fields of medical research and treatment, including beneficence, nonmaleficence, autonomy, and justice.
(2) Issues in brain stimulation related to nonmaleficence, beneficence, and distributive justice are relatively well informed by ethical thinking in other areas of medicine. As the body of research evidence and clinical experience related to brain stimulation continues to expand, we anticipate that treatment parameters will be continually refined to optimize the benefits, minimize the risks, and determine which techniques are most effective for specific clinical indications.
(3) Autonomy is a particularly thorny issue with respect to brain stimulation because we are dealing with treatments that can potentially change aspects of subjects and patients that relate to their identity and personhood. Thus far the literature has focused mainly on DBS and potential changes to identity, but TMS or tDCS could theoretically induce similar changes despite their minimally invasive characteristics. Some lessons regarding how to deal with challenges connected to autonomy and brain stimulation techniques can be gleaned from the field of psychiatry. However, additional answers will need to come from cognitive neuroscience, as we explore how our brains instantiate our thoughts, and how our thoughts instantiate our identities as rational actors with autonomy and agency.

In closing, we would like to point out two foreseeable future ethical challenges related to brain stimulation. The first of these is the slippery slope of clinical necessity. At issue is the concern that practitioners of brain stimulation may someday be pressured to ‘treat’ cognitive or psychological states that many would consider to be part of the spectrum of normal human ability rather than pathology. In such cases, the boundaries between treatment of disease and enhancement of normal cognition could easily be blurred. The notion that therapies initially developed to treat pathological brain states could be directed toward more cosmetic applications is neither far-fetched nor far off in the future. For the sake of comparison, consider underachieving students who get treated with Ritalin when it is not clear they meet the criteria for attention deficit disorder or the individual who feels ‘down in the dumps’ and is prescribed a small dose of an antidepressant for symptoms that do not meet the clinical criteria for major depression. There is nothing that speaks against the possibility that brain stimulation will be any different. Given the invasive nature and cost associated with DBS, it is easier to envision individuals obtaining TMS or tDCS for the purposes of cognitive or emotional enhancement. However, there are circumstances under which individuals may be motivated to use DBS for reasons other than its clinical indications, such as cases in which patients have experienced “morphine-like” feelings associated with stimulation (Morgan et al. 2006). Given that there are DBS systems that allow patients to control when they are stimulated, these cases raise questions regarding who should be able to exercise control over implanted brain stimulators, and whether there is a potential for intentional misuse.

A second, foreseeable issue that is closely tied to the notion of cosmetic neural enhancement is the potential for self-treatment by the public. Currently, this issue might be only limited to tDCS, given the equipment and costs associated with the TMS and DBS. Simply put, building a tDCS device is not rocket science, and a rudimentary system can be put together with less than $100 and a basic understanding of electronics. Consequently, there are currently individuals who are actively engaged in self-experimentation and self-treatment using home-made tDCS units. This effort is fostered by so-called “do-it-yourself” and “biohackers” movements (http://brmlab.cz/project/brain_hacking/tdcs), and by a number of publically accessible websites and videos that provide the schematics for building a tDCS unit as well as testimonials from individuals that have tried these home-made devices on themselves. While self-experimentation with a home-made brain stimulator may sound to some like eccentric behaviour, the notion of magnetically or electrically enhancing cognitive abilities is one that may have broad appeal to an increasingly technology-dependent public. In a recent survey of an unselected group of 1,000 respondents, we found that 87 % would be willing to use minimally invasive brain stimulation to enhance their intellectual ability or performance at work or school (Hamilton, personal communication), reinforcing the idea that people could use tDCS for “nonresearch and nontherapeutic objectives” (Brunoni et al. 2012b). Insofar as brain stimulation techniques may also have benefits in boosting mood or improving sleep, it is possible to envision situations in which individuals could use stimulation as a means of self-medication before going to a qualified medical doctor, akin to self-treatment with over-the-counter medications.

The notion of healthy persons stimulating themselves for the sake of cognitive self-enhancement raises fascinating questions with respect to autonomy and the fiduciary responsibilities of practitioners of brain stimulation. Modern Western society tends to recognize the primacy of autonomy, leaning heavily towards persons being free to do as they wish with their minds and bodies, provided they do not harm others in doing so. Since no permanent adverse effects of either TMS or tDCS have been conclusively demonstrated, one could easily make the argument that individuals should be allowed to stimulate their brains should they desire to do so. However, with so much still unknown about the neural mechanisms and long-term effects of brain stimulation, the notion of unregulated public usage may be worrisome to some practitioners who currently administer these techniques. To that end, the community of clinicians and researchers in this field may someday feel obligated, for the sake of public safety, to inform and advise non-professionals with respect to self-administration of minimally invasive brain stimulation. In this situation, the principle of nonmaleficence ("first do no harm") takes on special significance, and it would be worthwhile for the community of practitioners and investigators working with these technologies to consider whether guidelines for public use—based on data and expert experience—would be appropriate. Thus, in addition to developing and refining best practices of medical research and clinical care, ethical leadership with respect to the use of minimally invasive brain stimulation may also eventually call for proactive steps to be taken in both public education and public policy.

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