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Neuroethics of Neuromodulation: An Update

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Abstract

This article reviews neuroethics issues that arise with the development, translation, and use of technologies for neuromodulation. Three electronic databases (PubMed, Embase, and PhilPapers) were searched for relevant articles published between 1/1/16 – 6/26/18. We focus on pressing ethical issues related to the use of deep brain stimulation (DBS), adaptive DBS (aDBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and associated technologies. The neuroethics issues we address include privacy, continued access to devices, device removal, do-it-yourself neurostimulation, neuroenhancement, media coverage, changes in personal identity and agency, informed consent, and neuromodulation in minors. This review should be of assistance to a variety of stakeholders, including neurotechnology developers, as they make important decisions that will drive these neurotechnologies.

Keywords

Neuroscience; Neurotechnology; DBS; Ethics; Enhancement; Registry

Introduction

The goal of this article is to review recent developments in the ethics of neuromodulation and to suggest considerations for future reflection about these issues. This review should be of assistance to neurotechnology developers, researchers, clinicians, policy makers, and patient participants and their families as they make important decisions regarding the development and use of these technologies. We focus on pressing ethical questions that arise with electrical and magnetic stimulation of the brain using conventional deep brain

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Disclosures

The authors declare no conflict of interest.

Papers of particular interest, published within the past two years, have been highlighted as:

- of special interest

stimulation (DBS), adaptive DBS (aDBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and associated technologies (See Table 1).

Registries and Privacy

Data sharing will greatly facilitate clinical and research advancements, such as statistically significant comparisons of the clinical effectiveness of various DBS and aDBS lead implantation sites. In 2012, cooperation among an international body of stakeholders led to the creation of a registry and database for DBS in Tourette's syndrome. It stores several types of data, including: demographic data, pre-operative clinical scales, surgical data, device parameters, follow-up assessment and scales, and adverse events[1]. As the registry and database develop, stakeholders emphasize ensuring data quality, data uniformity, accessibility, and transparency[1]. A similar database exists for DBS in neurodegenerative diseases more generally[2], and another has been proposed for DBS in Parkinson's disease specifically[3].

Commenting on future challenges, Deeb et al. write, "More consistent and extensive data collection is needed to improve clinical outcome assessments, lead locations, programming parameters and adverse event reporting"[4]. The more comprehensive and detailed shared data about patients and research participants are, the more valuable they are for advancing neurotechnologies. However, this also makes it more likely that participants may be deidentified. De-identification is particularly concerning for brain implant trials with a small number of subjects or clinicians using novel implantation sites. Major topics of ongoing discussion regarding data sharing of neuromodulation devices also include protection against misuse and unauthorized access, compliance with HIPAA and other privacy norms, and who should be able to use the data and how (e.g., law enforcement, educational institutions, employers, insurance companies)[5].

The development of neuromodulation technologies such as aDBS also raises concerns about inferring an individual's mental state from brain activity data. In research on aDBS for obsessive-compulsive disorder (OCD) and depression, for example, there are ongoing efforts to identify brain markers of anxiety and sadness, respectively. These possibilities have led to special privacy concerns. Ongoing debate centers on various attempts to justify a right to mental or brain privacy and how to protect this right[6] [7] [8].

Continued Access

Some argue that for patients who benefit from neuromodulation in a research study, continued access to device functionality following the study is an ethically desirable aim. Defenses of a substantive ethical *obligation* to provide continued access take a variety of forms, appealing to the principle of non-maleficence[9], to compensation for the risks of research participation[10], and to "a limited duty of care" on the part of researchers[11]. Determining whether research sponsors or researchers have an ethical obligation to ensure or facilitate continued access to those participants who benefit requires balancing the vulnerability and burden placed on participants versus the feasibility of achieving continued access without disrupting the ultimate goals of these trials: to develop interventions that

benefit the patient population[11]. In practice, subjects who benefit from emerging neuromodulation technologies often encounter significant barriers to continued access due to the reluctance of insurance companies to cover experimental treatments. Identifying potential solutions to this problem requires engagement on the part of relevant stakeholders: patients, their families, researchers, sponsors, device manufacturers, and insurance companies. Sustained dialogue and research are needed to determine the strength of obligations related to continued access and upon whom those obligations fall.

Explantation

At the end of an invasive neuromodulation study, is there an ethical obligation to remove (explant) the device? Generally, research protocols offer explantation at the end of a study but do not cover the cost. If the participant would like the device removed, researchers will typically contact the participant's health insurance provider. If the participant does not have insurance or the insurance will not cover the cost, then it is up to the participant to pay for explantation. Further research to examine the potential harms and benefits of device removal against those of keeping the device in place but turned off at the end of the study is necessary. This research will help answer whether sponsors, researchers, device manufacturers, or others have an ethical obligation to cover or assist in covering the cost of removing these devices.

Some have raised concerns about the possibility of *forced explantation* against the wishes of the subject. It has recently been asked whether such an intervention is ethically justified in extreme cases, such as one in which a subject attempted suicide[12]. While researchers in the case argued for explantation, the subject refused. Do the wishes of a subject with sufficient decision-making capacity necessarily overrule the judgment of researchers even in cases like these? If so, are there ways to nonetheless address or accommodate the objections of researchers? Related considerations arise in cases of *family* disagreement with a subject's preference to continue device use[13].

Do-It-Yourself Neurostimulation and Neuroenhancement

tDCS has been suggested to have many potential applications: cognitive enhancement of concentration and memory, athletic competition, and influence on moral decision-making[14]. The emergence of a robust "do-it-yourself" movement in which consumers self-administer tDCS gives these potential effects added ethical salience. Regulatory bodies have generally been slow in responding to the marketing of tDCS for non-medical use[14]. These developments renew perennial questions about the desirability of different types of enhancement and the inequities they may create between those who have the resources to access these technologies and those who do not. They also raise novel issues about how medical communities and governments ought to balance their duty to protect the health and safety of individuals with individual liberty rights in the context of emerging neurotechnologies.

While evidence suggests that current tDCS, TMS, and DBS technologies cannot effectively enhance individuals' levels of moral concern for others, some have suggested that invasive

neuromodulation devices could theoretically be used for indirect moral enhancement through the modulation of “emotional, volitional, or motivational” states involved in moral decision-making[15]. Particular applications of moral enhancement are already under discussion: for example, the speculative possibility of using neuromodular interventions that heighten empathy and diminish impulsivity to prevent recidivism in those who commit violent crimes[16]. As the feasibility of such applications come more clearly into view, stakeholders must come together to address the potentially far-reaching ethical, social, and policy questions they raise.

Media Coverage

Public perception of neuromodulation devices and techniques is heavily shaped by how the media covers this complex subject. Gilbert and Ovadia note that the media generally raises few ethical considerations about DBS, and the majority of media articles consistently describes DBS in an overly-optimistic tone[17]. Racine and colleagues examined features of print media coverage about invasive and noninvasive neurostimulation techniques in the UK and US between 1995 and 2004[18]. This study found that 51% of 235 articles had an optimistic tone, highlighting the benefits of neuromodulation; 31% were considered balanced because they highlighted both benefits and risks; 14% were neutral, not featuring benefits or risks; 4% were critical.

In a more recent study, researchers analyzed 517 media articles on psychiatric neurosurgery published in the United States, Canada, Germany, and Spain between 1960 and 2015[19]. The study found DBS to be the main type of intervention addressed by the media, with depression being the most frequently reported mental disorder followed by OCD. This study observed that the tone of the articles became increasingly positive over the years, and only a minority of articles from each country/region mentioned risks associated with these procedures: Spain (3%), Canada/US (13%), Germany (28%). Informed consent and justice (7%–10% of articles) were the key ethical considerations raised in North America, while just 5% of articles from Spain raised ethical concerns. Germany’s media took a more cautious stance about psychiatric neurosurgery, citing concerns about identity, mind and social control, and enhancement while mentioning risks as a disadvantage of neurosurgeries in 28% of articles.

Some argue that the scientific community has a responsibility to address these issues first as the media gather data and perspectives from researchers[20]. Yet, even if researchers carefully explain the limitations of their work, it is difficult to control how the media covers these developments. Misleading media coverage may create exaggerated expectations of what emerging neurotechnologies can achieve and promote mistrust towards science when the public realizes that these tools have not reached their purported potential. These issues raise an important question: do researchers have an ethical responsibility to educate the public about the potential and limitations of the neurotechnologies they are developing and to attempt to correct inaccurate media coverage? Schlaepfer and Fins[21] state that the field of neuromodulation is at great risk of selective reporting due to dependence on single-patient cases and reluctance to report negative results. The challenge for clinicians is that the public

has unrealistically high expectations due to receiving partial facts about potential benefits, side effects, and risks [22].

Personal Identity and Agency

Concerns about the association of DBS with changes in personality has led to a proliferation of empirical and normative-theoretical work on its effects on identity, as well as the related concepts of agency and authenticity (understood as an individual's identification with her own traits, states, and life conditions). The most recent Proceedings of the Annual DBS Think Tank affirms the continuing importance of inquiry into these topics[3].

The last few years have seen the publication of empirical studies of DBS patients' attitudes on these issues. Klein et al. report interviews with subjects who had previously participated in clinical trials of DBS for either OCD or depression[24]. They focus on relationships with others, informed consent, and degree of patient control over device function. Gilbert et al. focus on patient self-perceptions of authenticity[25]. They report feelings of *non*authenticity ("self-estrangement") in a substantial number of patients. Self-estrangement (lack of identification with some aspect of oneself) in this context consists of either a self-perceived lack of control over emotional states or actions, considerable overestimation by the patient of their own abilities, or both. Gilbert et al.'s study has generated a significant critical response literature focused on this understanding of self-estrangement and related methodological questions [26] [27]. de Haan et al. report on similar themes in their own patient population, in particular how patients employ the idea of "becoming a different person" as a result of DBS[28]. de Haan et al. argue that patients deploy this idea in a number of incompatible ways such that its clinical significance is unclear. Importantly, this study also reports no feelings of self-estrangement on subjects' part due to device implantation and function. Because these results seem at odds with those of Gilbert et al. mentioned above, further theoretical and empirical work will be required to resolve this tension. More generally, a recent literature review found only relatively limited evidence that DBS affects identity, agency, authenticity, and related aspects of the individual. The authors conclude that additional empirical work is therefore needed to inform normative theorizing about these topics in neuroethics [29].

Informed Consent

Candidates for DBS and aDBS typically have severe, treatment-resistant forms of their condition and have exhausted many other therapeutic options[30]. This makes such subjects especially vulnerable where consent is concerned for various reasons. Patients who are the target of neuromodulatory interventions are often in a state of desperation due to the failure of other treatment options and thus may see neurosurgery as their last hope; this desperation may lead them to overestimate potential benefits and minimize or ignore some potential risks[20] [21]. Furthermore, invasive neuromodulation tools often target conditions that may involve some degree of cognitive impairment [31]. Ethical reflection on consent issues posed by these technologies often focus on their use for specific conditions involving such symptoms. Some recent analyses consider DBS for major depressive disorder[30], Parkinson's disease[32], anorexia nervosa[10], Alzheimer's disease[9], and severe pain[33].

While it is undoubtedly important to consider how an individual's condition may affect capacity for informed consent, empirical work cautions strongly against inferring impaired decisional capacity from a subject's diagnosis. In one study, 80% of subjects with schizophrenia were found to have capacity for informed consent to a research study, and instances of impairment sufficient to undermine capacity were not attributed to symptoms unique to schizophrenia[34]. While subjects with schizophrenia do on average demonstrate a higher degree of decisional impairment than neurotypical subjects, it is also the case that "many patients with schizophrenia score in the same range as comparison subjects"[35]. It is therefore crucial to assess individual capacity in potential research participants rather than assuming impairment on the basis of group membership.

The presence of a condition associated with decisional impairment may justify the employment of greater safeguards to ensure appropriately informed consent. One such safeguard could be to use or develop validated decision aids to assist with subject comprehension of study information[36]. Another potential safeguard for research participants who may have transient decision-making capacity is to have the research participants identify a subject advocate at the time of enrollment. If at any point during the study the subject is deemed to lack sufficient decisional capacity, the subject advocate would serve as a surrogate decision-maker, and may even decide whether to withdraw the participant from the study[37]. Notably, in any research with participants who may lack decision-making capacity, we face the question of who is an appropriate surrogate decision-maker. This is an issue that has been discussed for years with no resolution, and state laws in the US provide little guidance on this respect in the medical research setting[38] [39]. Future research should focus on how to facilitate decision-making and establishing uniform guidelines regarding who is an appropriate surrogate decision-maker in the research context.

Neuromodulation in Minors

Research studies and clinics are commonly using neuromodulation in pediatric populations (< 18) who suffer from treatment refractory movement or psychiatric disorders. Yet Johnco and Storch[40] note the lack of a standardized definition of "refractory" when considering DBS or other neurodevices, and that the use of invasive neuromodulation in pediatric populations is in need of more thorough clinical and ethical analysis. The articles discussing pediatric DBS note concerns about the scarcity of clinical studies and data with minors, including little information about long-term effects, concerns about safety and informed consent, potential effects on agency of developing minors, and the use of neuromodulation tools to attempt to enhance healthy children[40] [41] [42] [43] [44] [45] [46] [47] [48] [49].

While most studies cite that tDCS has been found to be safe in adults, little evidence is available to prove the safety or effectiveness of electrical stimulation on a developing brain; this is particularly concerning because many of these devices are available for sale online[43] [44] [45] [46] [50] [51]. Wagner and colleagues surveyed 227 individuals about their attitudes and willingness to use tDCS to enhance a 10-year old child's cognitive abilities, finding that the majority oppose a potentially harmful intervention if it is not medically necessary. Yet 45% of respondents were inclined to consider tDCS if the child

was below average academically, socially, and/or emotionally and it would improve their well-being.

All ethical considerations specific to adults that are noted in the above sections are equally if not more salient for vulnerable populations such as children. Informed consent and agency presents a special set of challenges: who determines what is in the best interest of the child, and who gets to make the final decision about whether neuromodular interventions are used on children? Croarkin et al. note the difficulty in recruiting youth in neuromodulation studies and the lack of translational studies, resulting in little data about appropriate dosing [48]. Furthermore, some studies suggest that by age 12 children may have decision-making capacity for medical interventions and research participation and that they should play a more prominent role in these complicated decisions[52] [53].

Conclusion

Rapid advancement of neuromodulation tools require thoughtful reflection regarding their ethical and sociopolitical import. These are among the most powerful means currently available for intervening on the human brain. Their refinement through further research promises to be a great contribution to the common good. However, ensuring responsible continued development and translation of these technologies will require further neuroethics research and collaboration between scientists, ethicists, policy makers, patient-participants, and the public.

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Abbreviations

DBS	deep brain stimulation
aDBS	adaptive deep brain stimulation
rTMS	repetitive transcranial magnetic stimulation
tDCS	transcranial direct current stimulation
tES	transcranial electrical stimulation
ADHD	attention-deficit hyperactivity disorder.

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Table 1.

Neuroethics of Neuromodulation: Included and Excluded Articles

Database	Search Terms	Total articles	Relevant results including duplicates	Relevant articles
PubMed	brain AND ethic* AND (implants OR implant OR stimulat* OR device)	224	89	122
Embase	brain AND ethic* AND (implants OR implant OR stimulat* OR device)	619	88	
PhilPapers	ethic* + (brain implant neuromod* stimulat*) brain neuro (simulat implant implants device)	25 12	21 4	
		880	202	

Table 1. Three electronic databases (PubMed, Embase, and PhilPapers) were searched for relevant articles published between 1/1/16 – 6/26/18 using the keywords: ethic*, brain, stimulat*, implant, brain implant, neuro, and device. Article titles and abstracts were screened for relevancy and those articles with content about at least one ethical topic related to a neuromodulation device or technique were input into Excel spreadsheets. Our search returned 880 total articles of which 202 were of interest based on titles and abstracts. 120 articles were excluded as duplicates or not relevant after reviewing full text; ultimately, 122 articles were determined to be relevant and included in our review.