Ethical Considerations

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Abstract

Since its first applications in humans, DBS has triggered a plethora of ethical questions and concerns and stimulated extensive ethical debates as to its significance and desirability. The main ethical goal is to guide and support responsible decision-making in clinical DBS treatment, as well as related medical research, and to raise awareness about salient ethical issues.

Traditional medical ethics consists of the three basic principles of respect for autonomy, beneficence/nonmaleficence and justice. In the context of DBS, these principles require specific attention as to what exactly it means to "respect autonomy," to safeguard beneficence and nonmaleficence, and to live up to the requirements of justice. Taking the risks and side effects of DBS into account and comparing this treatment to possible alternative treatments is crucial. Given the increasing interest in applying DBS to psychiatric disorders, research ethical questions have been put on the agenda. The status of the brain also gave rise to the expression of profound ethical concerns, particularly regarding potential changes in patients' personal identity. However, different understandings of this very concept lead to diverging evaluations of the ethical value of potentially identity-modifying techniques. Independent ethical substudies or integral add-on projects in DBS research can advance systematic ethical thought regarding ongoing research endeavors and upcoming new applications.

Introduction

Deep brain stimulation (DBS) is an accepted therapy for neurological and psychiatric disorders, including Parkinson's disease, essential tremor, dystonia, as well as epilepsy and obsessive compulsive disorder (OCD). It is increasingly studied as a potential therapeutic intervention for a series of other disorders, including depression, anorexia nervosa, Gilles de la Tourette syndrome (TS), and addiction (Holtzheimer and Mayberg 2011; Temel et al. 2012).

DBS has been welcomed as an effective treatment modality for otherwise refractory patients, and the number of patients with movement disorder who receive the surgery is increasing.

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Y. Temel et al. (eds.), *Fundamentals and Clinics of Deep Brain Stimulation*,
https://doi.org/10.1007/978-3-030-36346-8_10

However, since its first applications in humans, DBS has also triggered a plethora of ethical questions and concerns and stimulated extensive ethical debates as to the significance and desirability of deep brain stimulation.

With invasive brain modulation, something special seems to have entered the medical arena. As the Nuffield Council on Bioethics (2013) aptly put it, our brain has a special status that distinguishes it from other organs. "Its healthy functioning plays a central role in the operation of our bodies, our capacities for autonomous agency, our conceptions of ourselves and our relationships with others—and thus in our abilities to lead fulfilling lives." As a consequence, neurointerventions trigger and raise ethical questions that are not also triggered by other biomedical technologies. In particular, ethical questions have been raised that target the way in which DBS, and potentially other neuromodulation techniques, could influence people's identities, their sense of agency, and who they are as a person (e.g., Baylis 2015; Bell et al. 2009; Clausen 2010; Galert 2015; Glannon 2009; Nuffield Council on Bioethics 2013; Schechtman 2010; Schermer 2011; Synofzik 2015b; Witt et al. 2013). Therefore, conditions that can be linked to brain functioning pose a particular challenge. On the one hand, any diseases or disturbances of the brain are likely to directly and aversively affect, almost by definition, also our personal identities and sense of selves. This emphasizes the need for effective remedies and puts particular pressure on the search for therapeutic applications. However, on the other hand, special caution is needed as well. For brain interventions, it is often particularly unclear what the effects and possible side effects are and how they do affect not only target conditions but also other traits and even the identity or personality of patients.

Against this background, and right from its emergence, DBS has triggered a plethora of ethical questions and concerns and stimulated extensive ethical debates as to its significance and desirability. The main ethical goal is to guide and support responsible decision-making in clinical treatment, as well as in medical research, and to raise awareness about salient ethical issues. It is important to note that ethical issues or aspects do not only refer to potential problems or threats but also cover potential advantages and benefits.

Traditional medical ethics consists of the three basic principles of respect for autonomy, beneficence/nonmaleficence, and justice. In the context of DBS, these principle require specific attention as to what it means exactly to "respect autonomy" and to safeguard beneficence and nonmaleficence and how to live up to the requirements of justice (Beauchamp and Childress 2009; Bell et al. 2009; Clausen 2010; Synofzik and Schlaepfer 2008). Taking the risks and side effects of DBS into account and comparing this treatment to possible alternative treatments, such as psychotherapy, pharmacological treatment, and other forms of neuromodulation is crucial. Given the increasing interest in applying DBS to psychiatric disorders, and the numerous investigations and experimental treatments taking place in this area, research ethical questions have been put on the agenda (Fins et al. 2011; Holtzheimer and Mayberg 2011; Synofzik 2015a).

Medical Ethics in DBS

The ethics of medical treatments can be well based on the four medical ethical principles, as defined and described by Beauchamp and Childress (2009). These cover respect for autonomy, beneficence, nonmaleficence, and justice. Many consider the principle of nonmaleficence, "first, don't do harm," to be the most important one. Not only do many medical procedures have positive effects, but their use may also be accompanied by side effects that may burden or even harm patients. In practice, this means that possible risks and benefits must be weighed against each other and that medical treatments are only justified in case the benefits outweigh the foreseeable risks and burdens for individual patients. The principle of "respect for autonomy" refers to the ethical requirement that competent patients have and should be granted the right to self-determination. That is, after being adequately informed, it is up to the patients whether or not to accept a certain therapy or engage in any medical

procedure. That is, they may also refuse, even if this were against doctors' sincere conviction or even against patients' own medical interests (Emanuel and Emanuel 1992). "Justice," finally, refers to the social aspect of DBS, referring to requirements of fair patient selection, equal access to care facilities, and the just distribution of financial and other resources, particularly in situations of scarcity. The following will explore what these ethical requirements imply in the context of DBS, how they could be fulfilled, and also which specific challenges physicians and others providing care might face.

Respect for Autonomy

Individuals have rights of bodily and mental integrity, which entails that others may not intervene in their bodies or the functioning of their minds without their informed and well-considered consent (Bell et al. 2009; Clausen 2010). For competent patients, this right for self-determination means that doctors may start treatments only after they have informed them about their health conditions, reasonable prospects, and any treatment options, pointing out possible benefits and expected effects, as well as potential risks and side effects. It is the doctors who indicate treatments in their patients and who decide whether or not DBS could be an appropriate treatment for the condition at hand (cf. below issues regarding justice in DBS). Still in the end, it is always the patients who decide whether or not to undergo this (or any) treatment. Particularly if serious side effects are expected or feared, patients might prefer to not engage in intensive treatments like DBS but rather stick to other treatment modalities, even if these are less effective. This right to self-determination holds regarding initial surgery and also regarding the handling of all kinds of problems or complications that might develop along the trajectory and any further decisions that have to be taken later in the trajectory. This presupposes, of course, that doctors provide encompassing information that remains comprehensible also to their lay patients, covering medical procedures and requirements, expected benefits, and also possible side effects. Clinicians should also ensure that patients understand any information provided well. In the context of DBS, this might even entail that clinicians put unbalanced media reports, positive or negative, into perspective, as these might easily influence patients' perception and give rise to exaggerated hopes, as well as unfounded fears (Gilbert and Ovadia 2011; Johansson et al. 2013). In certain cases, the requirement of respect for autonomy may also require that doctors estimate the decision-making capacities of their patients (Glannon 2010). While this does not need to be a particular point of concern in the context of movement disorders, which currently are the most important indication for DBS, this issue might gain exceptional importance if DBS will be also applied for the treatment of severe and treatment-resistant neuropsychiatric conditions in the near future.

So far, from an ethical point of view, DBS for severe cases of predefined diseases is not different from the ethical treatment of other severe diseases. Still, one has to realize that once a decision in favor of DBS has been made, there are some relevant differences compared to, for example, psychopharmacological treatment with regard to the requirement of respect for autonomy. In case of conservative psychopharmacological treatments, patients retain autonomy during the treatment phase. They can always, even if they have given their initial consent, divert from the advice given by their doctors and either not take the drug at all or change the frequency of intake above or below advised levels (Leentjens et al. 2016). Patients might want to do so because they do not dare to answer back to their doctor, to reduce side effects that are experienced as more severe than expected, or maybe even to evoke hedonistic effects that might result from dopamine agonists. All this, however, is different in case of treatment by stimulation. For the settings of the stimulator, patients are largely dependent on their doctors. They have no or only very limited possibilities to adapt the settings themselves. Patients can experience this as a relief and be happy that doctors take control and responsibility. However, they might also experience this as a limitation of their

possibilities to decide for themselves and to adapt their medical treatment on a direct and timely basis. While there might be relevant medical reasons for this situation, clinicians should realize that device dependency entails a continuous reduction of the autonomy of their patients to determine their daily proceedings. In this sense, the situation of device dependency is particularly demanding for doctors and patients alike such that DBS puts particular demands on a good doctor–patient relationship. Patients must report particularly honestly about all kinds of troubles and side effects they experience, doctors have special responsibilities to continuously inform about their patients' well-being, and treatment facilities must support long-term professional relationships.

Beneficence and Nonmaleficence

Most treatments do not only have the aimed at effects but also know undesired side effects. The principles of beneficence and nonmaleficence require that, from the outset, it must be ensured that the expected effects outweigh any foreseeable side effects. This requires knowledge about the kind and probable severity of possible side effects and also of the individual situation of patients who might experience side effects differently. As a consequence, it has been argued that invasive and burdensome procedures such as DBS should only be suggested to patients if less intensive treatment options are not, or no longer, sufficiently effective (Kuhn et al. 2009). In addition, the probable medical effects must be sufficiently well known, and the physical, cognitive, and emotional situation of individual patients should be such that one may reasonably be expected to successfully go through surgery and participate in aftercare (Bell et al. 2009; Pollak 2013). In case individual patients turn out to not fully live up to all selection criteria; for example, due to beginning cognitive impairments, they must be either excluded, or, in some well-defined exceptions, special arrangements and safeguards must be in place (Kubu and Ford 2017). Against this background, careful patient selection is crucial for ethical surgery and stimulation, and it is preferably multidisciplinary teams that take final decisions on who should be offered DBS and who is not eligible (Kubu and Ford 2017).

In this sense and from the perspective of beneficence and nonmaleficence, DBS treatment is not necessarily different from other invasive and potentially risky medical treatments. Nonetheless, a number of effects and side effects seem to be unique for DBS treatment. It appeared that some patients, who were successfully treated for a movement disorder, experienced significant drawbacks in their social and familial lives and developed stimulation-dependent mental health difficulties or even a psychiatric disorder (Glannon 2009; Müller and Christen 2011; Schüpbach 2006; Volkmann et al. 2010). To a certain extent, disturbing behavioral and mental symptoms that follow otherwise successful DBS treatment can be considered signs of the so-called "burden of normality" (Gilbert 2012). That is, the movement-disorder or the obsessive-compulsive behaviors were such severe that over the years they rendered typical family life, social contacts, or employments unfeasible. The healing, almost all of a sudden, rendered it not only possible but also necessary that patients and family members adapt to the requirements of a "typical" life. This, however, can put significant burdens on those concerned. Patients might fail to know what to do with their newly won time once their movement disorder has disappeared and they just can walk or once their need for compulsive rituals has receded. In so far as this phenomenon is foreseeable, the principles of beneficence and nonmaleficence require that patients and families are both prepared and informed beforehand and are provided with adequate aftercare, that is, care that not only covers the medical features of DBS but also takes into account wider psychological, familial, and social aspects.

In addition to the burden of normality, stimulation-driven and -modifiable neuropsychiatric effects like (hypo-)mania, impulsivity, hypersexuality, and excessive euphoria have been observed, particularly in the early days of DBS. To date, because of increased knowledge about the anatomical targets of DBS, this is far less common. Still, the very occurrence of such

side effects underlines the special status of the brain, as emphasized by the Nuffield Council on Bioethics (2013), and as such they show that (and how) questions regarding the weighing of risks and benefits can be particularly complex. If a patient can be successfully treated for a movement disorder but as a consequence experiences severe neuropsychiatric side effects, a serious ethical dilemma emerges where different spheres of well-being have to be compared. This might render it impossible to "merely" weigh risks and benefits. Instead, it will be necessary to determine what is most desirable in a given situation and hence what should even count as "beneficence" and what as "maleficence". In such situations, patients are required to make up their minds and define what is most valuable for them under the given circumstances with the given possibilities and complications. Doctors, in turn, are required to respect what patients turn out to consider more beneficial or less harmful. A frequently cited and discussed Dutch case gained notoriety in this sense (Leentjens et al. 2004). This case showed the mentioned dilemma in an extraordinary hard but clear way. The patient had a severe form of Parkinson's disease rendering him bedridden, but after undergoing DBS treatment he regained good mobility. Still 3 years later, he had been admitted to a psychiatric ward involuntarily. As a side effect of the stimulation, the patient showed chaotic, megalomaniac, and manic behavior, leading to serious familial and financial troubles and depriving the patient of decision-making capacities. It appeared that this behavior did not respond to "typical" psychiatric treatment but did respond to changes in stimulation settings. Adaptation of the stimulation ceased the manic behavior and restored decision-making capacity but also reverted the original severe motoric symptoms making him bedridden. In this specific case, no satisfactory window between the two extremes seemed feasible. As a result, the patient had to be admitted either to a nursing home because of his serious PD or to a psychiatric ward because of his uncontrollable mania, which rendered him insane and a danger to both himself and others. From an ethical perspective, this situation is particularly challenging because it is not clear what should count as a greater benefit or a lesser harm. Both options are troublesome, albeit for different reasons, and not making a choice at all is both impossible and irresponsible. Rather than trying to do good and avoid harm, the patient—with the stimulation turned off—and the doctors must make up their minds and reflect on the question what should count as good, or better, and what is bad, or worse. In a certain sense, the patient also has to make up his mind on who to be as a person and how to live in the years to come (Bransen 2000; Taylor 1985). In the end, this patient preferred turning on the stimulation, having movement rather than full mental capacities, and being admitted to the psychiatric ward. For the clinicians, this meant that "doing good" entailed not only healing the movement disorder but also actively taking away the patient's decision-making capacity. In an attempt to attenuate this mental harm, arrangement had been made to periodically turn off the stimulation and restore the patient's decision-making capacity such that the initial preference could be reviewed. The ethical dilemma between mental and physical well-being as discussed in this case does also show that and why ethics is not necessarily about the most ethical option but about coherent and comprehensible argumentation and deliberation.

Justice

Justice in medical care contexts entails that all patients get offered treatment according to the same criteria, taking into account any economic limitations and the possibilities of highly specialized care centers to actually provide the care needed, as well as any long-term aftercare (Bell et al. 2009). This might mean that, at times, specific groups of patients must and should be prioritized when indicating DBS as the appropriate means of treatment. As a consequence, careful patient selection is of ethical importance also when it comes to determining the fairness of the implementation of the procedure. In this context, it appears to be most fair to prioritize those patients with the most severe symptoms and for

whom the chance of recovery is highest. Apparently, these two requirements do not always need to go hand in hand. Even then, however, patients should only be prioritized for DBS on the basis of medical criteria and not on the basis of criteria relating to age, economic wealth, or social status. Justice also requires that the continuity of treatment and follow-up care must be safeguarded once the DBS procedure has been started and the device has been implanted (Bell et al. 2009; Kubu and Ford 2017; Leentjens et al. 2016). Patients, however, might be dependent on a rather limited number of treatment centers and practitioners or doctors, particularly in case conditions get treated that are rather infrequent. This puts particular and ongoing responsibilities upon institutions that do offer DBS for the treatment of rare or new indications.

DBS for Psychiatric Conditions

From the treatment of movement disorders, insights were gained into side effects affecting the mood, thought, and behavior of patients. Together with results from emerging imaging techniques, these findings have led to the exploration of DBS as a treatment option for patients with disorders in these domains (Clair et al. 2018; Clausen 2010; Holtzheimer and Mayberg 2011). By today, DBS has been approved as a treatment modality for OCD and is under investigation for a large number of psychiatric conditions, including depression, addiction, eating disorders, Tourette syndrome, and aggression. Given that DBS in psychiatric contexts, with an exception for OCD, is investigational at the moment, many of today's ethical discussions focus on research ethical aspects, in particular on the status of ongoing experiments and on participant protection (see next section). However, several authors also point toward a series of ethical issues that are likely to arise once DBS is shown to be safe and effective for mental health disorders and will be part of regular treatment algorithms. (Glannon 2010; Kuhn et al. 2009; Rabins et al. 2009; Synofzik and Schlaepfer 2008). To a certain extent, these are the same medical ethical requirements as in the context of movement disorders, discussed above. In order to be ethically justified, DBS must be more beneficial or less risky and harmful than accepted alternatives of psychotherapy, psychopharmacology, or even ablative surgery. It must be based on patients' informed consent to the treatment, and also the typical standards of justice are to be fulfilled. Although being formally similar, mental health conditions are also considered to pose particular challenges in these regards.

Given its invasive and intensive character, DBS is typically considered as a last-resort treatment applicable only for the most severe cases of otherwise treatment-resistant populations. However, while most patients retain decision-making capacity throughout the course of also mental health conditions, patients can be more likely to lack or have diminished decision-making capacities in case their psychiatric condition is particularly severe and enduring, for instance in the case of depression (Glannon 2008). Similar problems could hold in case of patients with Alzheimer's dementia. By now, DBS in Alzheimer's dementia has been applied in research contexts only, and its benefit has not been shown yet. However, as soon as the condition is sufficiently severe that no other means of symptom delay or alleviation are effective any longer, patients are highly likely to no longer be cognitively able to decide about engagement in DBS treatment (Siegel et al. 2017). Informed consent could also be structurally challenged if addiction or substance abuse disorder were to be treated by DBS. Severely addicted patients might continuously oscillate between conditions of intoxication or withdrawal, potentially eliminating periods of full decision-making capacity that would allow for thinking through the pros and cons of DBS treatment (Carter et al. 2011; Pisapia et al. 2013). Against this background, decision-making capacity can be a general point of concern when it comes to decisions about the initiation of a DBS procedure. In addition, there are indications that for psychiatric conditions, it may take weeks or even months until first responses occur, if at all, and stimulation settings are optimal. As a consequence, patients need

capacities to not only make initial treatment decision but also to keep autonomously engaged for extended periods of time (Beeker et al. 2017). Against this background, the ethical requirement of respect for autonomy can be particularly challenging if DBS is extended to psychiatric disorders. Moreover, in order to safeguard that DBS is beneficial and does not disproportionally harm patients, the effects of treatment should be compared not only to the burden of the initial disease but also to the impact that alternative treatments had and still have on patients. Against the background of the treatment for depression, Johansson et al. (2013) showed how particularly complex this comparison can be. On the one hand, they show that DBS is less destructive than ablative surgery; it affects smaller areas of brain tissue, and the stimulation is adjustable and also reversible after the operation. As regards time and space, it is also more specific than psychopharmacology because it targets only well-described areas of the brain, whereas drugs spread out throughout the whole brain. On the other hand, the implants are rather expensive; they require access to highly specialized medical centers, a likely problem for patients from remote areas; and they depend on long-term, potentially lifelong, follow-up, which is highly burdensome for patients. DBS also knows a series of complications and side effects related to both surgery and stimulation, and it should be acknowledged that still much is unknown about how DBS works and what the risks of long-term harm are. All this renders it highly difficult to determine what should count as a reasonable balancing of benefits and burdens and how the various implications are to be weighed. To this end, ethical scrutiny, taking into the account the specificities of respective target diseases, as well as the situation of individual patients, will be of utmost importance.

For example, in patients suffering from anorexia nervosa (AN), it will be important to note that these patients do not only suffer from a mental disorder, but as a direct consequence, they also do have severe physical problems, and the extreme thinness of their bodies might render DBS surgery much more risky than in other patient groups (Müller et al. 2015; Park et al. 2017).

In addition to these medical ethical aspects of respect for autonomy and risk-benefit balances, in the context of mental health disorders, more might be at stake. Affecting people's thoughts, mood, and behavior, these disorders are always also closely related to one's identity or who one experiences oneself as a person. In the context of movement disorders, effects of DBS on a person's emotions or feelings have been described as unintended, and often undesirable, side effects and gave raise to critical appraisals of the therapy (Müller and Christen 2011; Schüpbach 2006). However, in the context of psychiatry, changes in personal identity or experiences of selfhood are not necessarily unintended side effects but could also be part of the intended treatment goal. Improvements in mood are aimed for in the treatment of depression, a different body image is desired in the treatment of anorexia nervosa, and new forms of behavior are looked for in the treatment of OCD. In so far as DBS could indeed bring about or contribute to such changes, previous concerns might hold no longer, and DBS could be perceived as an aid rather than a threat for personal identity and autonomy. This situation, however, gives rise to further questions and concerns. Improving mood, thought, or behavior directly and via stimulation might constitute a situation in which psychological development or personal effort to achieve such (desired) changes is no longer needed and in which active personal involvement can be bypassed. As opposed to traditional psychotherapeutic methods that depend on patients' cooperation, active efforts, and their contribution as an agent, stimulation-induced direct changes to self and identity could track passivity. Thereby, however, they could disable patients' agency and undermine their autonomy over the course of the treatment and while their identity is about to change. One question that arises is whether later identities or behaviors are more or less desirable than original states. Quite another question, however, concerns the passivity entailed that runs the risk of rendering direct means of identity change ethically dubious because they would undermine rather than rely on or support people's autonomy (Focquaert and Schermer 2015). So far, these questions have not

received full attention. However, as psychiatric disorders become more mainstream as indication for DBS treatment and research, the moral salience of the very means should come under ethical scrutiny.

Research Ethics in DBS

To date, the only accepted psychiatric indication for DBS is OCD. While in the US DBS for OCD is approved under a "Humanitarian Device Exemption" only, for Europe full EC approval is given. As a consequence, most current applications of DBS for psychiatric disorders are investigational. This situation comes with a series of specific ethical challenges, and activities in this regard ideally live up to research ethical requirements. Several internationally established guidelines on medical research with human beings, most prominently the Helsinki Declaration of the World Medical Association (WMA) (2013) and the Guideline for Good Clinical Practices of the ICH (2016), determine a normative framework for doing research with human participants. The essence and core focus of medical research are to gain knowledge and to serve the interests of future patients. On that route, doing research might endanger today's participants. In order to safeguard participant protection, medical ethical principles have been extended to the requirements of medical research with human beings. In order to be ethical, research must be based on the informed consent of participants, entail a favorable risk-benefit balance, and safeguard fair subject selection. For their daily practice, this asks researchers to ensure that their studies have scientific or social value and are scientifically valid, that they pay proper attention to any vulnerable participants, that their studies reduce risks and increase benefits as far as feasible, that they ensure that protocols are independently reviewed, and that participants are adequately informed and give their free and voluntary consent (Emanuel et al. 2000). DBS research, particularly for new indications, however, faces a set of challenges that are not easily covered by "typical" medical research ethics (Nuffield Council on Bioethics 2013). First, the research often takes place in the context of so-called experimental treatment rather than following a scientifically designed setup and methodology, and second, when DBS is on trial, the situation is often one of high uncertainty about possible outcomes, great despair among potential participants, and particular incertitude about the comparative risks and benefits.

The Grey Area of Experimental Treatment

DBS for mental health conditions is often applied as last-resort experimental treatment for single patients with serious symptoms who have failed or ceased to respond to available treatments. While individual patients might indeed have been helped and offered a relief for their suffering, and also important medical insights have been gained from these practices, from the perspective of both scientific interest and research ethics, experimental treatment constitutes a grey area and is therefore highly challenging. It is unlike regular research with human beings because it has no scientific research design, is not independently reviewed, or is not necessarily reported in scientific publications, Moreover, it is also unlike regular treatment because it is not evidence based and does not follow any treatment protocol. Therefore, it is unclear whether, and if so how, single case studies and reports, case series, and small-scale clinical trials could reliably increase our knowledge, and it is also unclear whether patients remain adequately protected. Against this background, the Nuffield Council on Bioethics (2013) calls for "clear and specific ethical guidance on how clinicians and investigators should navigate this difficult boundary in a way that is responsible, without stifling inventiveness." International societies in neurosurgery are actually encouraging researchers to make a start with the setup of well-designed randomized controlled trails and hence avoid the mentioned grey area (Nuttin et al. 2014). However, this may not always be feasible because even in highly specialized centers often only very low numbers of eligible patients are

available. Therefore, experimental treatment with DBS in mental health conditions is likely to stay. This requires responsible dealing within an area in which neither medical nor research ethical requirements hold neatly. For official trials, registration and publication of results are obligatory. In order to avoid biased publication of only positive findings, similar requirements have been suggested also for the context of investigational DBS. The danger of publication bias could, and should, be avoided by the setup of central case registers for new indications in which all patients, as well as any outcome of each single experimental treatment, get registered (Synofzik 2015a). Moreover, it is crucial to establish responsible publication practices (Schlaepfer and Fins 2010). Experimental treatments should always be reported as such, that is, as a single-case or a small-case series rather than as being a full-fledged research project. This can avoid the over-interpretation of findings. Moreover, it is crucial to avoid ad hoc publishing, that is, to only make results public in case they are positive and point out a therapeutic benefit while nothing gets published in case of adverse findings. Biased publishing of results does not only contribute to undue hypes regarding upcoming treatment modalities (Gilbert and Ovadia 2011), but it also puts future patients and participants at unnecessary risks when negative experiences are kept back. In order to make sure that lessons can be learned, researchers have the responsibility to also report and critically discuss unfavorable findings (e.g., as done by Smeets et al. 2018), and journals have the responsibility to, in principle, accept such outcomes for publication.

Challenged Participant Protection in DBS Research

Current encouragements to set up proper RCTs also in the context of psychiatric DBS may lead to a reduction of experimental treatments. Obviously, typical ethical requirements for clinical research do also hold in the context of DBS (Clausen 2010; Emanuel et al. 2000). For a series of reasons, however, these ideals might be challenged, particularly if DBS gets investigated in the context of new indications and for further groups of patients. Concerns have been uttered with regard to the feasibility of each of the three requirements of informed consent, favorable risk-benefit balance, and fair subject selection, as well regarding inherent dilemmas between different ethical requirements (Nuffield Council on Bioethics 2013). DBS research is considered particularly challenging, and specialized ethical criteria are proposed that should allow researchers to meet named challenges (Kuhn et al. 2009; Lipsman et al. 2010; Nuttin et al. 2014; Rabins et al. 2009).

Regarding informed consent, uncertainty about possible research outcomes is often great such that researchers might not be able to inform potential participants reasonably well about possible risks, burdens, or side effects. They might inform about own uncertainties but still have to leave participants in greater uncertainty than is the case in most other medical research. Another aspect that might undermine participants' informed consent consists in the fact that patients who are considered eligible for being invited to research projects are those with the most severe and hitherto untreatable symptoms. This situation might render patients highly desperate, willing to accept whatever comes on their way as a possible relief but also undermining their capacity to make a well-considered decision. In addition, typically there are only a few centers and professionals who are involved in experimental DBS treatment for possible new indications. This might render participants highly dependent on the researcher who is also their therapists, challenging free and voluntary decision-making. Situations of severe symptoms and great despair might also facilitate the danger of the so-called therapeutic misconception in which patients believe that whatever is offered to them entails a therapeutic benefit rather than understanding the experimental character of an innovative treatment procedure or a research study (Appelbaum et al. 1987). A final challenge for informed consent stems from the very conditions that form the current focus of DBS investigations. Neuropsychiatric conditions, particularly in their severe forms, might undermine the

decision-making capacity of research candidates. Against these multifaceted challenges, the requirement of voluntary and informed consent might be particularly difficult to fulfill.

For related reasons, proportionate balancing of risks and benefits can also be a rather delicate endeavor. Particularly in case only preliminary data from limited pilot studies are available, it is hard to make clear claims about expected benefits. However, risks of invasive surgery are always given, and it is also known that stimulation often brings about a series of side effects that concern cognition, daily life, and overall quality of life. A further complication to adequately weight possible risks and benefits consists in the fact that DBS has to be compared to totally different treatment options such as psychotherapy, psychopharmacology, or even ablative surgery. The respective effects and side effects of these alternatives might be hardly comparable, rendering it unclear what should count as a greater risk or burden and what is more safe or convenient: the long-term involvement required by DBS or the once-in-a-lifetime invasion of ablative surgery; the spatially rather specific approach of DBS or the broad and general impact of psychopharmacology; the direct brain modulation achieved by DBS or the behavior change and indirect brain modulation entailed in psychotherapy?

Fair participant selection has gained special attention in the last years, and consensus seems to exist that only long-term treatment refractory patients should be invited who are adult (Rabins et al. 2009) and who do have decision-making capacity (Nuttin et al. 2014). Others, however, have argued in favor of research for more early phase research because of potential neuroprotective effects, for example, in Parkinson's disease (Schermer 2011), or in order to prevent severe and lasting psycho-social and educational problems in, for example, adolescent patients with severe symptoms of Tourette's syndrome (TS) (Smeets et al. 2018).

In order to develop ethical criteria that can do justice to these research ethical complications and in order to specify possible solutions to the various conditions investigated today, suggestions have been made as to include ethical add-ons or ethic substudies into whatever research studies that investigate the effects and the potential of DBS treatment in various psychiatric disorders (Nuttin et al. 2014) and thereby to determine whether special safeguards for participant protection are needed, which these are, and how they could best be implemented. By today, such an ethical substudy has been carried out in the context of a DBS trial for anorexia nervosa and has resulted in the formulation of the "Gold Standard Framework," which identifies specific requirements for the ethical setup of studies in this context and determines criteria for justifiable inclusion of participants with anorexia (Park et al. 2017, 2018). This framework takes, among others, into account the often deadly course of the disease, the young age of many patients, the ego-dystonic character of the condition, and the bad physical shape of patients' bodies. Specified ethical research criteria taking into account the specificities of their respective condition have also been formulated for DBS investigations in addiction (Carter et al. 2011), depression (Christopher and Dunn 2015; Dunn et al. 2011; Johansson et al. 2013), Alzheimer's dementia (Siegel et al. 2017), and adolescent TS patients (Smeets et al. 2018).

Personal Identity and DBS

As emphasized above, the brain is considered a special organ because it is the biological substrate of our sense of selves, our agency, and our personal identity. It is against this background that case studies on neuropsychiatric effects (Leentjens et al. 2004), as well as extended patient reports and interview studies with stimulated patients (De Haan et al. 2013; Gilbert 2018; Schüpbach 2006; Voigt 2018), gained great significance in ethical discussions on the desirability and justifiability of direct and invasive interventions in the brain. If DBS for a movement disorder not only modulates the functioning of a patient's brain and his/her movement capacities but also influences the patient's personal identity or modifies who he/she is as a person, the procedure might come to stand on ethically shaky

grounds (Baylis 2013; Gilbert et al. 2017; Glannon 2009; Kraemer 2013; Witt et al. 2013). In an important sense, this objection is different from the previously discussed dilemma between the benefit of a successfully treated target disease, for example, Parkinson's disease, and the harm and burden of a newly acquired mental health problem, for example, mania or impulsivity. Instead, the situation would be one in which people come to experience themselves as strangers or parts of their body as alien to themselves. Thereby, patients would lose their true selves, would no longer act authentically, and instead would exhibit a device-steered behavior.

Certain aspects of these questions have been discussed in contexts that preceded DBS. A changed body image, for example, has also been reported in the early years of pacemakers and implantable cardioversion defibrillators (ICDs), and also the impact of psychopharmacological treatment has been critically discussed because of the wider impact of such agents, for example, the usage of fluoxetine (Prozac®) for the treatment of depression or of methylphenidate (Ritalin®) for the treatment of ADHD in children (Kramer 1993; Singh 2013). These discussions, however, showed that not only were changes in these wider regard real and meaningful to patients but also that they were incomplete rather than encompassing; that is, they concerned specific parts or aspects of the subject patients but did not generate new persons with entirely different identities.

In an early interview study with Parkinson's disease patients after DBS, Schüpbach (2006) reported that 19 out of 29 patients announced that they would not recognize themselves as the same person, and a significant portion of these patients experienced this situation as problematic. More recently, Gilbert and coworkers confirmed this finding and pointed out that many PD patients after surgery have significant feelings of self-estrangement, which oftentimes are considered troublesome (Gilbert 2018; Gilbert et al. 2017). From an ethical point of view, it is important to analyze what these findings on self-estrangement and changes in patients' personhood mean. Are DBS-induced changes in self-perception or personal identity ethically problematic almost by definition, and do they constitute a reason to meet the procedure with skepticism? (Gilbert et al. 2018) Or are these changes, whenever they do occur, comparable with other major life events that also could change people's identity but that people have to learn to live with? In this context, it is also important to note that some patients do not have such experiences, that some patients do not characterize these experiences as overly troublesome, and that some patients even evaluate changes to their selves or identity as explicitly positive. The latter holds, for example, for patients with Parkinson's disease, who sometimes report relief and even joy or happiness after having regained movement capacities, announcing that DBS allows them to become again the active and grown-up person who they had been before their disease (Pacholczyk 2011; Voigt 2018). In addition, this can hold for OCD patients who occasionally reported that it was the disease that oppressed their "real identity" and that it is due to DBS that now again they can be who they "really are" (De Haan et al. 2013). Against this background, it would become important to safeguard that concerns about personal identity do not prevent the application of the therapy and the advantages and benefits it can have for certain other patients (Müller et al. 2017).

First-hand views and experiences of patients are an important source of insight for ethical reflection (Snoek et al. 2019). Still, an "ethical opinion poll" among patients or research participants might not suffice for sound ethical decision-making (Salloch et al. 2014). For normative deliberation and adequate ethical reflection, it is also important to have a clear understanding of the concepts underlying the discussion. In this sense, Schechtman (2010) discussed a differentiated meaning of personal identity and applied this to the context of DBS. She drew a difference between so-called numerical identity and narrative identity. Numerical identity concerns the continuity of a person over time, physiologically and psychologically. A change in numerical identity would entail the development of a new person, psychologically unrelated to the previous one and also without relevant autobiographical memories of one's former self. This would indeed

constitute a significant ethical problem for, at least, two reasons. The earlier person would actively be annihilated—and would also have no vote in the "ethical opinion poll"—and one would bring—all of a sudden—people into existence who apparently do not have personal memories, histories, relationships, or any meaningful social environment. However, even the most serious cases and the most skeptical and troubled patients did not go that far. Quite the contrary, changes reported and estrangements experienced explicitly refer to and make a comparison with one's experiences of self and body, but also one's social relationships and other aspects of life before and after surgery and stimulation. Changes hence do not target patients' numerical identity, yet they can significantly affect their narrative identity, i.e., the way in which they give meaning to and make sense of their lives and their experiences. In that sense, DBS appears comparable to other major events or intensive procedures that entail or lead to adaptations in a person's identity. Everybody will have to adapt her social role and personal identity during life, for better or worse, once or even several times, because of major "life events." People become parents, get a chronic disease, survive a serious accident, climb or fall down a career ladder, or loose a dear person to death. Even though these events require people to adapt their narrative identity, it is not for this reason that they would be condemned. Likewise, changes of one's narrative identity due to DBS do not render the procedure ethically problematic by default. Instead, it will be important to investigate how individual patients are affected in this sense, how they experience any changes to their identity, and how well they manage to adapt or cope in the contexts of their daily lives.

The ethical debate on personal identity teaches us at least three important lessons. First, the success of any DBS treatment does not solely depend on improved brain physiology and symptom relief but also on the wider effects on patients' self-perception and social life. Second, for the procedure's desirability, it is crucial to determine how individual patients experience any changes to their identity, how well they feel able to adapt to any new or altered aspects, and how they perceive the comparative value of the "healed body" or the "healed mind"—if any (Gilbert et al. 2017). Third, given current insights into these features, clinicians have the responsibility to prepare patients, and family members, right from the start for such concomitant challenges, and these prospects should become part of any informed consent procedure. Moreover, treatment centers should ensure that any aftercare goes beyond purely medical issues and does also cover help and support for the patient's psychological continuity and well-being (Gilbert 2018).

Conclusion and Outlooks

DBS treatment can and should live up to established medical ethical requirements and ensure that the patients' autonomy is respected, that patients' well-being is pursued while they are not being harmed, and that treatments are offered in a just way whereby solely medical reasons play a role in patient selection. While being established in the context of movement disorders, DBS is still under investigation for a range of psychiatric disorders. This research faces a series of fundamental challenges that require special attention from a research ethical point of view. Often, DBS is investigated in the context of experimental treatment rather than of proper research studies. This may impede general knowledge gain, lead to publication bias, and endanger patient safety. As remedies, it will be increasingly important to establish international collaboration between specialized treatment centers, which may render research studies more feasible. Central trial registers could create a reliable overview of all experiments and findings in this area, both positive and negative. The trial register for Tourette patients treated with DBS is a good example in this regard (Martinez-Ramirez et al. 2018). In addition, independent ethical substudies (Park et al. 2017) or integral add-on projects (Nuttin et al. 2014) can advance systematic ethical thought regarding ongoing research endeavors and upcoming new applications (Johansson et al. 2014). In addition, it will be crucial to develop ethical reflection in the

context of the new stimulation features of so-called next-generation DBS (Goering et al. 2017).

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