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The Ethics of Expanding Applications of Deep Brain Stimulation

Markus Christen & Sabine Müller

Abstract

This chapter outlines the key characteristics of deep brain stimulation (DBS) as an exemplary case of a neuromodulation intervention and compares it with ablative techniques. Ethical aspects are then discussed along patient-centered aspects of DBS (patient decision making and patient eligibility; dealing with unintended side effects; patient selection and justice) as well as infrastructure-related aspects (research dynamics in the field of DBS; novel DBS indications; intervention quality issues; infrastructure capacity issues).

Keywords: Deep Brain Stimulation; Neuromodulation; Ablation; Parkinson's Disease; Depression; Obsessive-compulsive disorder; Dementia; Informed Consent

1. Introduction

Deep brain stimulation (DBS) is a neuromodulation technique for movement disorders and other indications (see also Info-Box 1 "Neuromodulation"). The roots of DBS can be traced to developments from the early 1950s (Hariz et al., 2010). However, DBS of subcortical structures like the ventral intermediate part of the Thalamus, the *globus pallidus internus* and the *nucleus subthalamicus* (STN) for addressing, e.g., specific symptoms of Parkinson's disease (PD) emerged in the 1980s (Siegfried, 1986; Benabid et al., 1987). In recent years, both the application of DBS as well as its appreciation in the literature has grown remarkably, in particular since 2000 (Müller & Christen, 2011). Global estimations of the number of patients who received DBS exceed 100,000; several thousand patients per year are newly implanted (Christen et al., 2014a). These numbers are expected to increase, as DBS is investigated for various other neurological and psychiatric diseases, including some with a high prevalence (in particular treatment-resistant depression and dementia). This expansion of applications shows the growing importance of DBS as a potential therapeutic approach for various diseases.

These expanding applications of DBS give rise to several important ethical questions that will be outlined in this chapter as follows: In Section 2, we discuss the intervention as such, exemplified by its most common indication, PD, and we outline the challenges of patients who may be candidates for DBS in weighing the risks and benefits of the intervention. We call this the "decision problem". Section 3 provides information on experiences with expanding indications thus far. Section 4 discusses the ethical issues related to DBS. Two info boxes provide additional information: box 1 about neuromodulation in general, box 2 about ablative techniques, i.e., the historical forerunner of DBS and potential alternative in some cases.

BOX 1: Neuromodulation

Neuromodulation is among the fastest-growing areas of medicine, involving many diverse specialties and impacting hundreds of thousands of patients with numerous disorders worldwide. It can briefly be described as the science of how electrical and chemical interventions can modulate nervous system function (Krames et al., 2009). The field of neuromodulation covers a wide range of mostly chronic conditions such as epilepsy, blindness or other eye conditions, gastric mobility, headaches, deafness, movement disorders, occipital and peripheral neuralgias, chronic pain, psychiatric and neurobehavioral disorders, spasticity, stroke, traumatic brain injury and others. Instruments for neuromodulation include electrical stimulators, sensory prostheses like cochlear implants, and implantable infusion pumps. Given the economic importance of this field – the global market volume is estimated to equal $3.65 billion US (http://www.marketsandmarkets.com/Market-Reports/neurostimulation-devices-market-921.html) – and the fact that it addresses a population of roughly 14 million patients in the United States alone (Krames et al., 2009), it is very likely that such techniques will extend into various medical fields that address neurological and psychiatric disorders.

Neuromodulation interventions are characterized by three conditions (Holsheimer, 2003): First, the intervention is applied repeatedly or constantly; a "one shot" lesion does not count as neuromodulation. Second, the intervention causes *local* changes in neuronal processes (unlike medication) that does, however, not exclude the possibility of effects on the whole brain activity. Third, the clinical effects can be influenced by modulating the intervening process for the benefit of the patient to improve the therapeutic effect of the intervention or counteract sequelae – sometimes,

this involves balancing of the two intentions such as maximizing motor control and minimizing affective sequelae. Often, reversibility is also mentioned as a defining feature of neuromodulation. However, due to neuroplasticity, this assumption can be reasonably questioned, as the intervention may lead to long-lasting changes in the neuronal network (Udupa et al. 2016).

DBS is a paradigmatic type, but not the most widely used form of neuromodulation. More common are sensory prostheses for counteracting deafness and blindness (mostly cochlear implants; ≫300,000 patients) and spinal cord stimulations as therapy for several forms of chronic pain (≫100,000 patients). Another common technology is vagus nerve stimulation as a therapy for epilepsy and depression (>65,000 patients; references for the estimations are included in Christen, 2016). Among those very common neuromodulation interventions, cochlear implants in particular have been a subject of much ethical debate.

2. Deep Brain Stimulation – the intervention exemplified for Parkinson's disease

DBS intervenes into a neuronal network in the brain by chronic electrical stimulation (Benabid et al. 2009): One or (in most cases) two quadripolar electrodes are stereotactically implanted into specific targets deep in the brain. The electrodes are connected to a pulse generator (usually placed under the skin in the subclavicular or abdominal area) that chronically applies electrical current. The precise effects of the electrical field on the local neural tissue are not yet clear. High-frequency DBS (usually ~130 Hz) has been considered as a method that creates temporary functional lesions by inhibiting the targeted area with electrical current. However, it yields a mostly unpredictable, mixed pattern of inhibition of cell somata and activation of axons that can

result in opposite effects. Furthermore, within the target area, multiple neurons with different biochemical characteristics are addressed in the same way. For example, DBS inhibits simultaneously activating glutamatergic projection neurons and inhibiting GABAergic interneurons, the net effect of inhibition is reduced (Sturm, 2013).

As DBS involves surgical intervention into the brain, it usually becomes an option for a patient when medication or other therapeutic approaches are no longer sufficient to control the symptoms or have unbearable side effects. DBS is a complex intervention that requires a close relationship between the patient and medical specialists of several disciplines. This relationship starts with the process of patient selection and ideally should last during the lifetime supervision of the stimulation system. The necessary long-lasting commitment between the patient and medical experts distinguishes DBS (and other neuromodulation techniques) from "classical" neurosurgical procedures. Furthermore, many new technological developments such as closed-loop systems are currently experimentally investigated (McIntyre et al., 2015), leading to the question of how innovation in collaboration with the device-manufacturing industry can be secured; e.g., to counteract publication bias in case of unsuccessful trials, to cover the economic risk of experimental devices or to lower the regulatory burden associated with introducing new systems into the market (Ineichen et al., 2014).

Because the most common indication for DBS is Parkinson's disease (PD), we outline the intervention using this example. Whereas medication-based therapies (levodopa, dopamine receptor agonists) address the PD induced shortage of dopamine that causes an imbalance in the neuronal network for movement generation and control, DBS directly intervenes into a node of the neural

network itself. The beneficial effects of DBS on motor functions are well established (e.g., Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Wider et al., 2008). But the intervention can also cause unintended cognitive, affective and behavioral side effects (Videnovic & Metman, 2008; Volkmann et al., 2010; Witt et al., 2008). The DBS research community has recognized the complexity associated with this therapeutic approach and has begun to dedicate its attention to emerging issues, whereby reports on complex, single cases have incited discussions with more interdisciplinary stakeholders (Christen & Müller, 2011). In particular, the target STN is critically discussed (Moro, 2009).

The evaluation of unintended sequelae is complex, as they may result from three causes: from surgery, stimulation, or drug reduction after the intervention. Furthermore, in the case of PD, one has to take into account that similar effects may result both from disease progression as well as from medication therapy. An additional complicating factor is the potential negative sequelae that accompany the therapeutic benefits of dopaminergic medication. For example, even though dopamine agonists may alleviate symptoms of PD better than levodopa for some patients, deficits in impulse control are more likely if a patient is treated using dopamine receptor agonists instead of levodopa (Ambermoon et al., 2011). Paradoxical side effects that manifest as affective and social problems, especially in relationships and work, may occur in spite of a good clinical outcome for the movement disorder (such as alleviating motor symptoms of PD) (Schüpbach et al., 2006). For example, some patients do not want to return to work, although they could, because their attitudes towards work and leisure time have been changed following DBS. This may lead to conflicting outcome interpretations, e.g. when the patient's accompanying side effects

from treatment are negative, but the clinical effects are positive (the so-called "satisfaction paradox"; Agid et al., 2006), when the changes are evaluated positively by the patient, but negatively by other people, in particular if these changes involve increased energy, novelty seeking, risk-taking, or changes in sexual drive (see for an overview: Müller & Christen, 2011). Furthermore, ethnic and cultural factors in assessing the degree of aberrant behavior can be expected, for example in the case of hypersexuality (where no standard diagnostic criteria exist what counts as "excessive sexuality") or pathological gambling (e.g., because patients are less willing to admit their problems due to the absence of legalized gambling in some eastern Asian countries) (Chiang et al., 2012). For investigating psychosocial aspects of DBS, a third-party perspective (e.g. by close relatives, caregivers) is necessary. However, few studies have investigated a third-party perspective on DBS patients so far (Christen et al., 2012). A possible explanation for behavioral, affective or social adaption problems has been conceptualized as the "burden of normality" (Gilbert, 2012; Wilson et al., 2001). For some patients, fighting against the disease has been the sense of their lives, which is lost after the successful therapy. Some patients also have severe problems to take on responsibility again and to abandon the patient role. The decision to undergo DBS poses a complex "decision problem" for a patient that is eligible for this intervention. Nevertheless, a psychosocial focus alone is insufficient, because some of the observed effects are clearly stimulation-caused and can be influenced by appropriate selection of the stimulation parameters (Saleh and Fontaine, 2015).

Generally, eligible patients are those who are diagnosed with idiopathic PD and whose symptoms previously responded well to L-dopa or apomorphine, who are in good general and cognitive health, and whose medication-based therapies are no longer successful (e.g. due to on-off-

phenomena, motor fluctuations, or wearing-off phenomena). Furthermore, the patients must be able to undergo a long operation which is partly under full anesthesia. With respect to medical eligibility, there is a consensus on exclusion criteria (e.g., non-idiopathic PD or severe cognitive and psychiatric impairment of the patient) (Hilker et al., 2009; Okun et al., 2010) such that DBS is suitable only for a subgroup of PD patients. Little research is devoted to determining the fraction of PD patients eligible for DBS. The referring clinicians seem to underestimate the number of suitable patients (Oyama et al., 2012), and they refer fewer women than men (Setiavan et al., 2006). A reasonable guess is that 10-20 % of PD patients may qualify for DBS (Christen & Müller, 2012), i.e. a substantial number of patients face the challenge of deciding whether DBS is appropriate for them or not.

The patients that qualify for DBS have to weigh benefits and risks of the intervention, as well as the alternatives. Given the burden of normality problem and the satisfaction paradox, there is a need for communication with patients, their families, and caregivers long before surgery is performed. This is necessary both to anticipate problems that might occur, and to give patients and their entourage the necessary time to prepare for the changes that are to be expected in their lives (Schüpbach & Agid, 2008). Thus, decision making with respect to DBS cannot be reduced to the mere assessment procedure in DBS centers. Rather, in the course of standard treatment of PD, the possibility of DBS may be raised either by the patient or the general neurologist.

Current research on decision making with respect to DBS has focused on improving the ability of general neurologists to identify appropriate candidates for this procedure. This led to various

electronic decision tools that assist neurologists in determining which PD patients should be referred for DBS consideration (Moro et al., 2009; Wächter et al., 2011). These tools, however, are not intended to be used by the patient; they have only an indirect effect in providing information about whether the patient is eligible or not from a medical point-of-view.

With respect to DBS in general, the private practice neurologist is the decisive entry point both with respect to patient information and referral (Christen et al., 2014a), but the patients also rely in their decision making on information emerging from support groups, media, other patients, or the general practitioner. A recent survey found that the quantity of realistic expectations of patients and family members significantly correlated with a positive evaluation of DBS, whereas doubts as well as unrealistic expectations of family members correlated with a negative attitude (Südmeyer et al., 2012). Furthermore, it is known that in medical interventions that are characterized by scientific uncertainty regarding their benefits and harms, the communication of the physician is influenced both by individual differences in physicians' tolerance of uncertainty as well as physicians' beliefs about their patients' tolerance for uncertainty (Portnoy, 2013). This demonstrates the importance of appropriate information for a realistic assessment of DBS by the patient.

3. The broadening of DBS indications

In recent years, the spectrum of indications for DBS has been broadened in two ways: First, there is a trend to apply DBS in earlier stages of disease. Second, DBS is being extended to a very broad spectrum of neurological and psychiatric diseases.

With respect to the first trend, the results of the so-called EARLYSTIM study (Schüpbach et al., 2013) suggest that an early DBS intervention can be beneficial for Parkinsonian patients with early motor complications. There are, however, also specific challenges of STN-DBS at an earlier stage of PD such as the inclusion of patients who later evolve to atypical parkinsonism and the risk of a floor effect (which arises when a data-gathering instrument has a lower limit to the data values it can reliably specify) for the benefit from DBS (Mestre et al., 2014). Nevertheless, it is likely that the EARLYSTIM study will lead to an adaptation of the criteria published in the consensus statements (e.g., Hilker et al., 2009), so that the criterion that the medical therapy is no longer successful might be skipped. The number of patients who are referred to DBS centers would be higher, if the patients were referred earlier (Charles, 2012; Deuschl et al., 2013; Schüpbach et al., 2007/2013), because younger patients as well as patients in an earlier disease stages could fulfill less rigorous exclusion criteria. Indeed, earlier referral seems to be a trend in various centers (Okun et al., 2010).

Second, there is a trend to expand the indications for DBS. To date, DBS has been approved only for PD, essential tremor, dystonia, epilepsy, and obsessive-compulsive disorder. However, current DBS research includes refractory depression (Morishita et al., 2014), Tourette syndrome (Andrade & Visser-Vandewalle, 2016), dementia (Mirzadeh et al., 2016), minimally conscious state (Schiff et al., 2007), severe obesity (Dupré et al., 2015), aggressive disorder (Franzini et al., 2013), drug addiction (Müller UJ et al., 2013), anorexia nervosa (Müller S et al., 2015), and schizophrenia (Salgado-López et al., 2016; Corripio et al., 2016).

Rigorous evidence-based comparison of the efficacy of these new DBS applications is not yet possible due to methodological hurdles and publication bias in the DBS literature (Schläpfer & Fins, 2010). Publication bias in the psychiatric neurosurgery literature is a fundamental problem that compromises the systematic evaluation and comparison of the different procedures, and therefore also the ethical evaluation, which critically depends on objective information of evidence-based risk-benefit ratios (Müller, forthcoming). Furthermore, most psychiatric DBS studies are methodologically weak. Lack of statistical power is a major concern in these studies, because they have very small patient numbers, most with fewer than ten patients. Furthermore, most studies are neither placebo-controlled nor double-blinded (Müller, forthcoming). Observer bias in reporting results also presents a methodological concern, as the evaluation of treatment outcomes has not yet been conducted by independent parties who were not involved in patient selection, surgery, or follow-up (Pepper et al., 2015). Therefore, the following efficacy data of DBS for three psychiatric indications should be regarded with caution.

Obsessive-compulsive disorder (OCD): Kohl et al. (2014) analyzed 25 papers comprising 109 DBS patients and 5 targets (NAcc, VC/VS, ITP, STN, and ALIC) and found response rates ranging from 45.5% to 100%. Pepper et al. (2015) compared DBS and ablative neurosurgery that included more or less homogeneous anatomical areas to ensure a fair comparison. Their analysis included 10 studies with a total of 108 patients, who were treated with anterior capsulotomy, and 10 studies with a total of 62 patients, who underwent DBS with the targets VC/VS and NAcc. The response rate of DBS patients was 52%, and of the anterior cingulotomy patients 62% (response = improvement of Y-BOCS score ≥ 35%) (Pepper et al., 2015).

Major depression: Morishita et al. (2014) reviewed data from 22 papers comprising 188 DBS patients and 6 targets (NAcc, VC/VS, SCC, lateral habenula, ITP, and slMFB). Very recently, an additional target, namely the ALIC, has been tested in 25 patients (Bergfeld et al., 2016). The reported response rates ranged from 29 to 92%. However, the failure of two multicenter, randomized, controlled, prospective studies evaluating the efficacy of VC/VS DBS and SCC DBS (Dougherty et al., 2015; Cavuoto, 2013) raises questions about the efficacy of DBS for depression.

Anorexia nervosa: We have reviewed six papers comprising 18 patients and three targets (NAcc, SCC, and VC/VS) (Müller et al., 2015). Remission in terms of normalized body mass index occurred in 61% of patients, and psychiatric comorbidities improved in 88.9% of the patients as well. However, Sun et al. (2015) have recently published less favorable results in which only 20% (3/15) of their patients treated with NAcc DBS showed improvements in symptoms. The other 80% underwent anterior capsulotomy, which improved eating behavior and psychiatric symptoms in all patients (Sun et al. 2015).

Adverse effects of DBS in those indications include surgery-related, device-related, and stimulation-related effects. Regarding the first category, serious adverse events during or shortly after surgery included intracerebral hemorrhages, which in one case, resulted in a temporary hemiparesis (Kohl et al., 2014; Morishita et al., 2014; Pepper et al., 2015); intraoperative seizure; intraoperative panic attack; and cardiac air embolus (Lipsman et al., 2013a). In several cases, wound infections or inflammation occurred (Kohl et al., 2014; Pepper et al., 2015). Regarding the second category, several device-related adverse effects have been reported, namely breaks of

electrodes, stimulating leads or extension wires requiring replacement (Kohl et al., 2014; Pepper et al., 2015). Finally, many patients suffered from stimulation-induced adverse effects, particularly from depression, anxiety, worsening of OCD, suicidality, panic attacks, fatigue, hypomania, increased libido, and problems at home. In some cases, these adverse effects were caused either by a change of stimulation parameters or by battery depletion, and were reversible by respective adjustments (Kohl et al., 2014; Morishita et al., 2014). Interestingly, patients suffering from anorexia nervosa had a particularly high rate of severe complications, namely an epileptic seizure during electrode programming, further weight loss, pancreatitis, hypophosphataemia, hypokalaemia, a refeeding delirium, cardiological disturbances, and worsening of mood (Lipsman et al., 2013a).

BOX 2: Ablation Techniques

Ablative techniques are used for both movement disorders and psychiatric disorders. Although the effects of ablative techniques are irreversible, they can be an appropriate alternative for patients for whom DBS is not an option, be it for medical reasons, because of the treatment costs, or because of personal preferences. Two expert panels have affirmed stereotactic ablative procedures as important alternatives for appropriately selected patients (for Parkinson's disease: Bronstein et al., 2011; for psychiatric disorders: Nuttin et al., 2014).

Ablation creates brain lesions by destroying localized brain tissue. Different techniques are used: thermal or radiofrequency ablation, which require craniotomy, as well as Gamma Knife radiosurgery and magnetic resonance-guided focused ultrasound (MRgFUS), which are non-invasive. Gamma Knife radiosurgery is a very precise method for creating confined brain lesions and is mainly used for treating brain tumors and brain arteriovenous malformations, but is also used for

treating neurological and psychiatric disorders such as Parkinsonism, essential tremor, trigeminal neuralgia, intractable tumor pain, some forms of epilepsy, and psychiatric illness (Friehs et al., 2007). MRgFUS has recently been introduced into the field (Lipsman et al., 2014). It has been tested in four patients with chronic and medication-resistant essential tremor (Lipsman et al., 2013b) and in four OCD patients (Na et al., 2015). MRgFUS might also become an alternative therapy approach for major depression, too (Na et al., 2015; Lipsman et al., 2013b).

Both DBS and ablative neurosurgical procedures, if used for psychiatric indications, belong to psychiatric neurosurgery. Psychiatric neurosurgery is defined as neurosurgery for treating psychiatric disorders that do not have identified structural brain anomalies, such as brain tumors or epileptogenic tissue. Nonetheless, psychiatric neurosurgery is based on the assumption that certain dysfunctional brain areas or structures play a crucial role in psychiatric disorders, and that lesioning or deactivating them can alleviate psychiatric symptoms.

Early psychiatric neurosurgery procedures such as lobotomy became discredited in the 1970s because they had been widely abused and had caused many severe complications (Valenstein, 1986; Chodakiewitz et al., 2015). After a nearly 30-year hiatus, in the late 1990s psychiatric neurosurgery experienced a revival. Today, modern ablative psychiatric neurosurgery is much more precise and safer than its historical predecessors. Anterior capsulotomy and cingulotomy are used today. The main indication is obsessive-compulsive disorder. Further indications for contemporary ablative microsurgical procedures include anxiety disorder, major depression, anorexia nervosa, drug addiction, hyperaggressivity, and schizophrenia (Müller, forthcoming).

4. Ethical Issues

The ethical literature on DBS is well-developed (overview in Christen 2015). Taking the principles of biomedical ethics (Beauchamp & Childress 2013) as a framework, issues of beneficence and nonmaleficence, autonomy and justice have been intensively discussed (for discussion about the validity and scope of this approach, see Christen et al. 2014b; Müller 2014).

Regarding beneficence and nonmaleficence, several ethicists have discussed the problem that the benefit of psychiatric DBS is probably overestimated due to publication bias (Schläpfer & Fins, 2010; Gilbert & Dodds, 2013). Furthermore, several authors have called for better regulation of the disclosure of conflicts of interests (Schermer, 2011), and have criticized the misuse of the humanitarian device exemption in stimulation for obsessive-compulsive disorder (Fins et al., 2011).

Autonomy, and in particular the capacity to consent in patients that may undergo a DBS intervention, is much discussed. For example, to what extent is a patient with a pathological brain condition able to provide informed consent for a therapeutic intervention that intends to change this condition, if the brain condition affects the capacity to consent? A second problem with respect to autonomy is the ethical relevance and practical handling of conflicting outcome evaluations of DBS interventions that address pathological brain states among the stakeholders involved (patient, relatives, medical experts; see Section 2). This problem is likely to increase when psychiatric conditions are targeted through DBS. Another ethical feature of DBS interventions concerns the principles of beneficence and nonmaleficence. As these interventions target

areas of the brain, which are relevant for emotions and behavior, they may have unwanted behavioral consequences, which could even include violations of the rights of third parties, e.g., if the interventions make the patient hypersexual or extremely aggressive (Müller et al., 2014). Ethical issues related to justice finally often relate to a fair assignment process for patients, and cost issues. For example, ethicists have critically discussed the enrollment criteria of DBS studies (Bell et al., 2009) and the need for the equitable distribution of treatment options (Goldberg, 2012). Several ethicists have investigated the influence of economic interests that drive the development of DBS (Erickson-Davis 2012; Christen et al. 2014a). However, this part of the ethical debate is less-well developed, as only few studies address issues like cost-effectiveness, infrastructure-development and the like in the field of neuromodulation.

This brief overview outlines the many questions associated with DBS interventions. We suggest that many of them will become more relevant when the whole field is evaluated from a health quality research point-of-view. In a recent study (Christen et al., 2014a), we have outlined patient-centered aspects of DBS (patient decision making and patient eligibility; dealing with unintended side effects; patient selection and justice) as well as infrastructure-related aspects (research dynamics in the field of DBS; novel DBS indications that require new ways of patient assignment structures, especially in psychiatry; intervention quality issues; infrastructure capacity issues), demonstrating a broad spectrum of open questions in that respect. To date, no integrative study on health service research in neuromodulation that integrates several factors – e.g., combining patient-centric and infrastructure-related issues – has been done. This is of particular relevance as psychiatric conditions like addiction, depression or eating disorders are targeted for DBS interventions. Questions include: Who would be the gatekeepers in these conditions, and

how can adequate patient information and patient referral be guaranteed? It is likely that the referral practice will differ compared to movement disorders, because these conditions have different gatekeepers. For example, patients suffering from addiction usually have regular contacts with social workers, who may be skeptical about biological disease models and biomedical interventions for changing behavior.

Also the decision making process of potential DBS patients is a major research topic within medical ethics, in particular with respect to the informed consent of a patient. Certainly, as DBS involves risks of both clinical and ethical relevance (Glannon, 2010), there is an obligation on the part of physicians to obtain fully informed consent from patients undergoing the procedure. A key ethical orientation in this discussion is the principle of autonomy (Beauchamp & Childress, 2013) that involves various facets like the foundation of autonomy in philosophical theories, the concept of autonomy in law, or the capacities for performing autonomy and the assessment of them in a concrete decision problem, for example in the case of dementia (see for an overview: Donnelly, 2010; Tauber, 2005). In that respect, some scholars emphasize the notion of a "relational" understanding of autonomy, arguing that decision making should consider not only the individual perspectives of patients, but also those of their families, and members of the health care team, as well as the perspectives that emerge from the interactions among them (Epstein & Street, 2011). It has furthermore been suggested that a strong focus on the decision situation itself is problematic, especially when combined with a tendency to stress the importance of patients' independence in choosing (Entwistle et al., 2010). This could distract attention from other important aspects of and challenges to autonomy in health care. In contrast, a relational understanding of autonomy attempts to explain both the positive and negative implications of social

relationships for individuals' autonomy. Furthermore, many health care practices can affect autonomy by virtue of their effects not only on patients' treatment preferences and choices, but also on their self-identities, self-evaluations and capabilities for autonomy. A relational understanding of autonomy de-emphasizes independence and facilitates well-nuanced distinctions between forms of clinical communication that support or undermine patients' autonomy. Individuals usually rely on others to help them think and feel their way through difficult decisions, so the concept of "shared minds" (Epstein & Street, 2011) may be a suitable approach for framing the ethical problem in DBS decision making by patients. This approach intends to understand why, when, and how individuals involve trusted others in sharing information, deliberation, and decision making through the sharing of thoughts, feelings, perceptions, meanings, and intentions among two or more people.

One particularly important issue in DBS decision making is unrealistic expectations of personal benefits or risks by the patient. This is a major issue in experimental DBS research involving novel indications, where research participants may not appreciate important differences between research and treatment – a problem usually framed as "therapeutic misconception" (e.g., Henderson et al., 2007). Indeed, experimental research in DBS, e.g. for treatment resistant depression, demonstrate that unrealistic expectations may be a key motivation for study participants (Rabins et al., 2009). A recent study, however, found that participants of such studies did not express a set of motivations or influencing factors that suggested compromised decision-making capacity or diminished voluntariness of decision making, and that the trials that were studied utilized sufficiently robust informed consent processes (Christopher et al., 2012). The issue of therapeutic misconception is of less relevance in DBS in movement disorders, as the intervention in these

cases is no longer considered experimental, but the problem of unrealistic expectations remains. Although the study of Südmeyer et al. (2012) indicates that only a minority of patients had unrealistically high expectations for therapy, these results are nevertheless in some tension with the earlier mentioned phenomenon of a "satisfaction paradox" (Agid et al., 2006) after intervention (Christen et al., 2014a). The study of Südmeyer et al. (2012) also found that patients deciding on DBS often mention unrealistically high risk of intraoperative complications and stimulation-induced worsening of symptoms that do not match with the known complication rates of the intervention. This may partly explain why only 28% of patients that have been identified in a large European multi-center-study as eligible for DBS actually decided to undergo the surgery (Wächter et al., 2011). Südmeyer et al. suggest that these opinions of patients and their relatives with respect to expectations and risks are formed well-before the eligibility assessment.

The ethical issues of decision making in DBS do not only concern the individual decision. In our study (Christen & Müller, 2012), we found indications that the referral practice in Switzerland for DBS interventions may be too conservative, i.e., some patients do not get the optimal treatment, which would is ethically problematic– this may also be the case in other countries (Christen et al., 2014a). However, this point needs further backing by more solid data. In particular, investigation is needed to determine whether this finding results from a justified skepticism regarding possible adverse effects of DBS by the patients, the close relatives, and the general neurologists, or whether it reflects lack of knowledge or prejudice in the referring stakeholders and/or patients. Certainly, not only factors like skepticism or risk aversion determine the referring practice, as the DBS centers themselves perform a sophisticated selection procedure based on medical and psychological factors. Nevertheless, those factors are relevant before the potential DBS

patient actually goes to the center for a detailed assessment. An analysis of this problem is complex, as the willingness to undergo such an intervention strongly depends on the quality of the information that is available in the decision making process, but also on the capabilities of the patient, within his environment, to deal with this information. The fact that DBS is increasingly investigated for other indications – in particular psychiatric ones, where the decision problem may be even more complex – underscores the need for a thorough analysis of the current patient decision making process with respect to DBS.

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Abbreviations

ALIC: anterior limb of the internal capsule

Cg25: Brodmann area 25 in the subgenual cingulate cortex

DBS: deep brain stimulation

ITP: inferior thalamic peduncule

MR: magnetic resonance

MRgFUS: magnetic resonance-guided focused ultrasound

MRI: magnetic resonance imaging

NAcc: nucleus accumbens

OCD: obsessive-compulsive disorder

SCC: subgenual cingulate cortex

slMFB: superolateral medial forebrain bundle

STN: nucleus subthalamicus

VC/VS: ventral capsula/ventral striatum

Y-BOCS: Yale-Brown Obsessive Compulsive Scale

Notes on Contributors

Markus Christen (PhD, M. Sc.) is a Senior Research Fellow at the Centre for Ethics of the University of Zurich and member of the Ethics Advisory Board of the Human Brain Project. Recent publication: Christen M (2015): The Ethics of Neuromodulation-Induced Behavior Changes. Habilitation in the Field of Biomedical Ethics. Medical Faculty of the University of Zurich.

Sabine Müller (PhD M.Sc.) is Assistant Professor for Neurophilosophy and Medical Ethics at the Department for Psychiatry and Psychotherapy of the Charité – Universitätsmedizin Berlin. She is principle investigator of the international research project "Psychiatric neurosurgery – ethical, legal and ethical issues".

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