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Target Article

Deep Brain Stimulation in Parkinsonian Patients—Ethical Evaluation of Cognitive, Affective, and Behavioral Sequelae

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an important therapeutic advancement for the treatment of Parkinson's disease (PD). Its beneficial effects on motor functions are well established, but its cognitive, affective, and behavioral sequelae come increasingly into the focus of the medical and ethical discussion. In order to evaluate whether these side effects may counteract the beneficial effects of STN DBS on the patient's quality of life, we classify them along the dimensions "measurement complexity" and "weighted life-impact." Based on this analysis, we discuss their ethical impact and propose guidelines for the clinical setting of STN DBS.

Keywords: deep brain stimulation, neuroethics, Parkinson's disease, personality changes, side effects, subthalamic nucleus

Currently, ethical issues of deep brain stimulation (DBS) are broadly discussed by medical ethicists, but most contributions deal with psychiatric patients (e.g., Rabins et al. 2009; Synofzik and Schlaepfer 2008), whereas only a few analyze ethical issues of DBS for Parkinson's disease (PD) patients (Ford and Hendersen 2006; Fins 2009; Bell et al. 2009). This imbalance of ethical concern not only contrasts with the sheer number of patients suffering from PD or from other movement disorders who underwent DBS (~75,000[1]) compared to about 100 to 200 psychiatric DBS patients (Kuhn et al. 2010), but it also disregards the entanglement of motor functions, cognition, mood, and behavior affected by PD and the fact that both pharmaceutical and neurosurgical treatments address more than just motor functions.

In this paper we discuss ethical problems of deep brain stimulation for parkinsonian patients. In doing so, we consider in particular the difficulties of identifying affective, behavioral, and social sequelae of DBS and of differentiating between disease-related and therapy-induced effects. First, we describe PD and DBS, especially DBS of the subthalamic nucleus (STN DBS), as the STN has become the preferred target. Second, we present results from a review of the clinical literature on main and side effects of STN DBS. Third, we develop an analysis scheme that evaluates side effects of therapy along the dimensions "measurement complexity" and "relative life impact." This analysis scheme is applied to STN DBS in the fourth part. In the fifth part we evaluate these results with regard to the principles of biomedical ethics. Finally, we formulate recommendations for further research and the clinical use of STN DBS.

PARKINSON'S DISEASE AND ITS TREATMENT

PD patients suffer from chronic neurodegenerative disorder with severe motor dysfunctions (tremor, rigor, and dyskinesia) (Lang and Lozano 1998). Traditionally regarded as a movement disorder, PD is increasingly recognized as a disease with cognitive, affective, and behavioral symptoms (Pillon et al. 2003; Tröster and Woods 2003). Histopathologically, PD is characterized by the progressive degeneration of dopamine producing cells of the nigrostriatum. This causes imbalanced activity in a network of subcortical structures, including the globus pallidus internus (GPi), the nucleus subthalamicus (STN), and the ventral intermediate part of the thalamus (Vim). This mechanism is held responsible for the cardinal PD symptoms, e.g., hypokinesia and

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1. This number is a recent estimation by Medtronic, the leading supplier of DBS stimulators, in spring 2010 based on their own sales and the assessment of competitor sales (Regina Strasser, Key Account Manager Medtronic Switzerland, July 12, 2010).

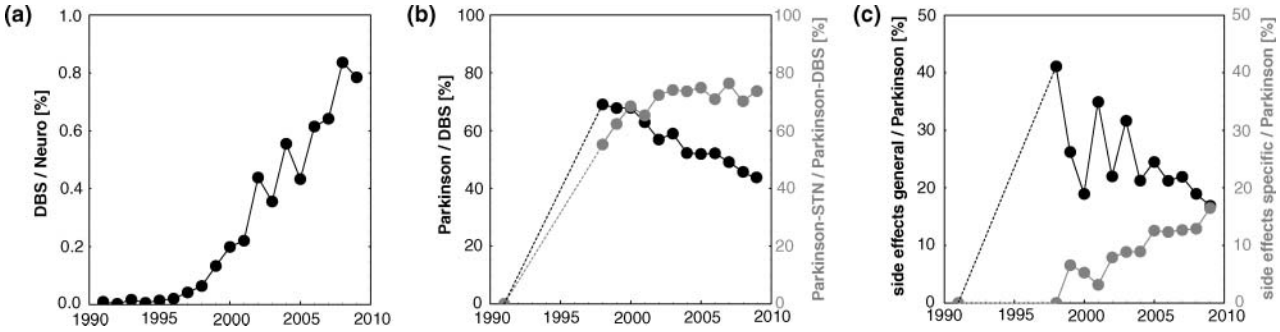

Figure 1. Bibliometric analysis of the significance of STN DBS and the investigation of its nonintended effects in the neuroscientific literature on an annual basis. (a) Fraction of DBS literature relative to neuroscience literature, indicating a relative increase in DBS publication activity. (b) Fraction of Parkinson-DBS literature relative to the DBS literature (black), indicating a relative decrease of Parkinson-DBS publication activity within the DBS literature, and fraction of the Parkinson-STN-DBS literature relative to the Parkinson-DBS literature (gray), indicating the increased importance of the STN as a target in the Parkinson-DBS literature. (c) Fraction of Parkinson-DBS literature mentioning generalized side effects relative to Parkinson-DBS literature (black) and fraction of Parkinson-DBS literature mentioning specific side effects relative to Parkinson-DBS literature (gray), indicating a more detailed investigation of side effects in recent years. Dashed lines indicate years that have been excluded from the analysis due to an insufficient number of publications. [Methodological remarks: The analysis was performed on April 15, 2010, in the SCI expanded database (database description http://images.isiknowledge.com/WOK46/help/WOS/h_database.html). For each year, the number of publications containing the Boolean expressions of the following keywords and/or word stems has been evaluated: Set *Neuro*: neuro* OR neural OR brain* OR amygdala OR cerebellum OR cortical OR cortex OR hippocampus. Set *DBS* (within the set *Neuro*): „deep brain stimulation." Set *Parkinson* (within the set *DBS*): Parkinson. Set *Parkinson-STN* (within the set *Parkinson*): "subthalamic nucleus" OR STN. Set *side effects general* (within the set *Parkinson*): "side effect" OR "side effects" OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR sequela* OR complication* OR "mood change" OR "mood changes" OR "clinical outcome" OR safety OR "quality of life." Set *side effects specified* (within the set *Parkinson*): (aggressi* OR anhedonia OR anxiety OR apathy OR delirium OR depressi* OR disinhibition OR hallucinat* OR hypersexual* OR hypoman* OR "limbic effect" OR mania OR psychosis OR suicide OR "transient confusion") NOT *side effects general*.]

rigidity (Albin et al. 1989; Obeso et al. 2000). As the damaged dopaminergic cells are part of the reward processing system (Pagonabarraga et al. 2007), psychiatric symptoms are common in PD patients. According to Kulisevsky and colleagues (2008), 87% out of 1,351 PD patients without dementia reported at least one psychiatric symptom; most frequently are depression (70%), anxiety (69%), apathy (48%), irritability (47%), and executive impairment (41%).

All known treatments for PD are only symptomatic and do not stop disease progression. Neurosurgery was the first treatment option for PD and other movement disorders and dates back to the late 19th century (Fields and Tröster 2000). Due to the introduction of levodopa in 1968, surgical approaches were abandoned almost completely. Levodopa and other dopamine agonists reduce firing rates in the GPi and the STN and thus alleviate motor symptoms (Santiago and Factor 2003). But many patients develop "motor fluctuations": They alternate between "on" periods, in which moving is relatively easy, and "off" periods, in which movements become difficult. Another form of motor fluctuation is dyskinesia (choreiform movement). Furthermore, the chronic and pulsatile administration of dopamine can cause "hedonistic homeostatic dysregulation" with impulse control disorder, such as pathological gambling, addiction to levodopa, and hypersexuality (Voon et al. 2006).

These shortcomings of pharmacotherapy of PD, as well as advances in stereotaxis, radiology, and theoretical knowledge about basal ganglia functions, led to a renaissance of surgical approaches since the 1980s, in particular of thalamotomy (Guridi et al. 1993) and pallidotomy (Laitinen et al. 1992). In the late 1980s, two groups (in Grenoble and Zurich) independently developed chronic electrical deep brain stimulation as an alternative for ablative surgery (Benabid et al. 1987; Blond and Siegfried 1991). The rationale for this novel approach was its adjustability and reversibility. A bibliometric analysis reveals a strong increase of the fraction of DBS literature compared to the neuroscience literature in the last decade (see Figure 1a).

DBS surgery is performed stereotactically in patients selected after a standardized assessment procedure (Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease, CAPSIT-PD; see Defer et al. 1999). It involves confirmation of the target site using imaging methods (ventriculography, computed tomography [CT], or magnetic resonance imaging [MRI]) and electrophysiology methods (intraoperative stimulation or microelectrode recording), and (mostly bilateral) implementation of quadripolar electrodes for chronic stimulation. In a second intervention, a pulse generator is placed under the skin in the subclavicular area and connected by a subcutaneous

lead with the electrodes (Dowsey-Limousin and Pollak 2001). A few days after surgery, the stimulation is switched on, and its parameters (frequency, pulse width, and amplitude) are adjusted.

DBS for treatment of PD is applied to different targets: GPi, STN, and Vim. Thalamic DBS (Vim) mainly improves contralateral tremor and is therefore restricted to patients with severe isolated tremor (Dowsey-Limousin and Pollak 2001). Both GPi and STN DBS improve off-motor periods and dyskinesias; the latter has a more constant effect against off-motor phases, permits a reduction of medication, and requires lower stimulation amplitude (Dowsey-Limousin and Pollak 2001). These advantages make STN the preferred target (see Figure 1b), although the incidence of adverse events after STN DBS is higher than after GPi DBS (Temel et al. 2006; Hariz et al. 2008; Voon et al. 2006). Several lines of evidence (positron emission tomography [PET] studies in PD patients with STN DBS, lesion experiments with rats and monkeys, and clinical observations) indicate that the STN modulates sensorimotor, limbic, and cognitive functions (Funkiewiez et al. 2003). This is reflected in the anatomical organization of STN consisting of a somatomotor (dorsolateral) part, a limbic (medial) part, and an associative (ventromedial) part. With the current DBS technique it is very unlikely to influence selectively the motor part of such a small target without affecting its associative and limbic parts. This makes the emergence of unintended cognitive or affective side effects plausible (Temel et al. 2005, 406).

In the sections that follow, we examine the STN DBS literature and discuss some findings. We focus on the most recent studies, meta-analyses, reviews, and case reports on adverse effects published since the advent of STN DBS.

OVERVIEW OF STN DBS EFFECTS

Intended and nonintended effects of STN DBS may result from three causes: from surgery, stimulation, or drug reduction. A recent meta-analysis (Kleiner-Fishman et al. 2006) found that the overall cumulative incidence of adverse events directly related to surgery was about 11%. Intracranial hemorrhage occurred in 3.9% and infection in 1.6% of the cases. In addition to these common neurosurgical risks, DBS involves specific risks; e.g., in 4.4% of the cases portions of the device (e.g., the electrodes) had to be replaced.

Several studies that compared STN DBS and the best medical therapy have confirmed that STN DBS is efficient to treat levodopa-related motor complications in advanced PD (Hamani et al. 2005; Deuschl et al. 2006; Weaver et al. 2009). Furthermore, STN DBS allows for a significant drug reduction for most patients, and consequently it reduces medication-induced side effects (evaluated with UPDRS section IV) effectively and sustainably.

Also, neuropsychological side effects of STN DBS are discussed in the clinical literature. Already in 1995, Limousin and colleagues reported transient confusion and hallucinations in the first patient and neuropsychological impairment caused by a thalamic infarction in the second of their first three STN DBS patients. Since then, we have identified about 300 outcome studies. Adverse effects are increasingly studied, as our bibliometric analysis shows. But their prevalence and relevance are evaluated quite differently: Although some studies are rather critical (e.g., Saint-Cyr and Trépanier 2000; Hariz et al. 2008), others consider STN DBS as safe with respect to neuropsychological and psychiatric effects (e.g., Castelli et al. 2006; Heo et al. 2008). Several papers even report enhanced affective and cognitive functioning (e.g., Ardouin et al. 1999; Schneider et al. 2003). Some papers argue that motor benefits usually outweigh adverse events, which is reflected by a significant increase of the quality of life (e.g., Lagrange et al. 2002; Witt et al. 2008). These different evaluations are reflected in about 50 reviews and meta-analyses. Their authors criticized that almost all outcome studies have important shortcomings, i.e., small sample sizes, lack of standardized evaluation, lack of control groups, lack of randomization and blinding, test–retest problems, etc., which make their comparison problematic. Finally, an impressive amount of case reports emerged in the last 15 years: About 40 studies (published before January 2010) report incidences of aggression, delusion, depression, suicides, hallucinations, hypersexuality, hypomania, mania, or pseudobulbar crying.

Anecdotal reports about personality changes provided support to several studies investigating changes of behavior and socio-moral attitudes after stimulation. The results are heterogeneous. Houeto and colleagues (2002) have evaluated 24 Parkinson's disease patients retrospectively for adjustment disorders (social adjustment scale), psychiatric disorders, and personality changes (IOWA scale of personality changes). They found that social adjustment was moderately or severely impaired in 62.5% of the patients. Personality traits were improved in 35%, unchanged in 30%, and aggravated in 35%. But a recent retrospective study of the same research group (Houeto et al. 2006) with 20 rigorously selected patients regarding psychiatric criteria came to contrary results: The patients' personality traits were unmodified, and scores for social adjustment remained stable. Schüpbach and colleagues (2006) documented subtle personality changes in unstructured interviews: They found that several patients were logorrheic, irritable, and impatient, and expressed their opinions more freely.

A few studies investigated the social lives of the patients. Perozzo and colleagues (2001), Houeto and colleagues (2002), and Schüpbach and colleagues (2006) found modified familiar relations and often deteriorations of conjugal relationships. Of the couples, 12.5% were divorced within 2 years after the operation. The marital conflicts emerged after STN DBS either because the patients gained autonomy and rejected their spouses, or because the spouses expected more personal responsibility of the patients, whereas those did not want to give up the patient's role. Several studies also concluded that professional activity worsened after STN DBS more often than it improved (Schüpbach et al. 2006; Gisquet 2008)—either because the patients did not feel able to work or because they gave priority to leisure activities.

However, similar problems can emerge in the natural history of PD (e.g., prevalence of generalized anxiety disorder or social phobia in PD patients: 40%, according to Richard and Kurlan 2002) as well as under medication therapy (e.g., prevalence of medication-induced mania 1.5%, according to Molho 2002). Such effects also include unintended cures of psychiatric disorders caused either by PD or by medication. For example, Witt and colleagues (2008) found a much higher incidence of psychoses in the control group (11.1%) than in the DBS group (6.7%). Pathological gambling, known as part of the dopamine dysregulation syndrome (Dodd et al. 2005), sometimes disappears after DBS (Ardouin et al. 2006; Bandini et al. 2007). However, probably not DBS itself but the subsequent drug reduction is the cause of this positive side effect.

ETHICAL ISSUES ASSOCIATED WITH A SCHEME-BASED EVALUATION OF SIDE EFFECTS

Unintended side effects are important issues for ethical evaluations of novel therapies. But ethical evaluations are faced with two fundamental methodological difficulties: First, some side effects are difficult to measure and to quantify, which exacerbates the determination of the incidence of certain side effects. Second, the impact of some side effects on the patient's life is hard to determine, especially in comparison with the impact of the disease's natural progression, which complicates the evaluation of their severity. Therefore, the ethical assessment of novel therapeutic interventions has to reflect methodological difficulties. Consequently, we introduce an analytic scheme that classifies therapy side effects along two gradual, qualitatively described dimensions: (1) measurement complexity of the side effect, and (2) relative life impact of the side effect (life impact of the side effect weighted by its incidence in the natural disease history).

1. *The dimension "measurement complexity" of a side effect* describes the adequacy and precision of available tests for its determination. The measurement complexity is small if the measurement object is well defined and if the measurement procedure is clearly formalized. Examples are some neuropsychological tests, e.g., the Finger Tapping Test or the Hopkins Verbal Learning Test. The measurement complexity is high if the measurement object is complex or only roughly defined, and/or the measurement procedure is not formalized and requires experience-based judgments of specialists. Examples are depression (e.g., evaluated with the Beck Depression Inventory) or alterations in the quality of life (e.g., measured by the Parkinson Disease Quality of Life questionnaire). Side effects with high measurement complexity may also be subtle, subjective, or dependent on real-life situations so that clinical tests cannot assess them. They may be reported by the patients, by their families, or as anecdotal reports by clinicians. At best they may be captured by unstructured interviews.

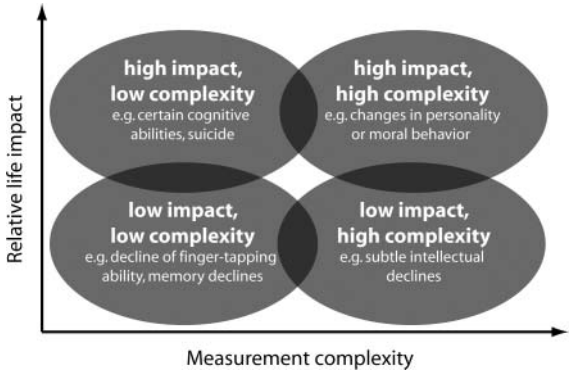

Figure 2. Classification of side effects of STN DBS along the dimensions "measurement complexity" and "relative life impact"; highlighted are four clusters of side effects.

2. *The dimension "relative life impact" of a side effect* describes its importance for the patient's life weighted by its altered incidence because of the therapy. This weighting is crucial because some effects may occur under therapy as well as in the natural disease history. Thus, a side effect has a high relative life impact if its importance for the patient's life is high and its incidence under therapy is significantly higher than without therapy. The relative life impact of a side effect is small if either its impact on the patient's life is small or its incidence under therapy is not significantly higher than in the natural disease history.

The usage of this analysis scheme shapes the ethical analysis: The reflection of the dimension "measurement complexity" implies a higher ethical sensibility for complex side effects. Considering their "relative life impact" reflects not only the fact that side effects of interventions are ethically relevant but also the consequences of not intervening. This leads to four clusters of side effects that represent ideal types (Figure 2).

The scheme should not be misunderstood as an objective and general classification of the salience of side effects. Whether certain side effects can be tolerated or compensated or whether they cause suffering or are disabling depends strongly on the individual patient's attitudes and life situation (professional activity, social situation, psychological condition, and plans for the future). Furthermore, several effects with small life impact may cumulate to an effect with a high life impact. Finally, changes in average scores and caseness (the number of persons having a condition before and after therapy) do not always go hand in hand (Voon et al. 2006). For these reasons, the attribution of life-impact scores to specific side effects should be done individually for each patient. The classification scheme may serve as a tool in the patient briefing and in shared-decision making.

Another methodological caveat has to be mentioned: The clinical literature reflects a growing sensibility toward nonmotor effects of STN DBS and describes them more and more specifically (see Figure 1c). But the roughly 50 reviews

and meta-analyses addressing cognitive, affective, and behavioral sequelae of STN DBS reveal rather big differences between the prevalence of "severe psychiatric events" reported in the different studies. One reason for that is that earlier studies did not use sufficiently sensitive tests to identify affective disturbances (Meagher et al. 2008). We assume that the inconsistent findings result from a high measurement complexity of some side effects and problems of weighing their life impact.

In the following, we classify the published findings of cognitive, affective, and behavioral sequelae of STN DBS according to the analysis scheme described earlier in order to prepare the ethical evaluation of STN DBS.

Cluster 1 side effects, which are relatively easy to measure but do not have a high relative life impact, have been the subject of many studies and several meta-studies. Small cognitive declines belong to this cluster. Cognitive impairments after STN DBS were observed in 41% of the patients (Temel et al. 2006: meta-analysis of 82 studies published until June 2004 with 1,398 patients). Standard neuropsychiatric tests verified significant, although small, declines in executive functions and verbal learning and memory. Moderate changes were proven only in semantic and phonemic verbal fluency (Parsons et al. 2006: meta-analysis of 28 articles published between 1990 and 2006 with 612 patients). These findings were confirmed in prospective, controlled studies (Smeding et al. 2006; Witt et al. 2008). As PD progression also affects cognitive functions, it is not surprising that patients generally do not evaluate them as decisive for their quality of life (Witt et al. 2008).

Cluster 2 side effects are relatively easy to measure and have a high relative life impact. The paradigmatic example of a cluster 2 side effect is suicide. Suicides after successful DBS have been reported in various studies with highly variable outcomes: Berney and colleagues (2002) found transiently suicidal tendencies in 12.5% (24 patients). Houeto and colleagues (2002) reported 3.6% suicides (28 patients), Burkhard and colleagues (2004) 4.3% (140 patients), Funkiewiez and colleagues (2004) 5.2% suicide attempts plus 1.3% suicides (77 patients), Smeding and colleagues (2006) 1% suicide attempts (99 patients), Witt and colleagues (2008) 1.3% suicides (78 patients), and Soulas and colleagues (2008) 1% committed and 2% attempted suicides (200 patients). A meta-analysis by Voon and colleagues (2008) (5,311 patients) reported a suicide rate of 0.45% plus a suicide attempt rate of 0.90%. The suicide rate in the general population is about 0.8%, whereas the suicide rate of PD patients is approximately 10 times lower than the age-, gender-, and country-adjusted World Health Organization (WHO) expected suicide rates in the general population (Voon 2008). Thus, the suicide (attempt) rate after STN DBS has high ethical relevance.

Cluster 3 side effects are comparatively hard to measure, while their relative life impact compared to disease progression is relatively small. This cluster comprises subtle intellectual declines, which can be compensated by the patients, as well as more serious declines, whose incidence after DBS does not differ significantly from their incidence in the natural disease history. An example is apathy, which often occurs after stimulation, but also in the natural disease history. Assumedly, increased apathy after STN DBS is no effect of stimulation but rather of drug reduction, because STN stimulation is probably less effective than a dopaminergic treatment to control the parkinsonian apathetic state (Funkiewitz et al. 2004; Schneider et al. 2003; Witt et al. 2006; Voon et al. 2006).

Depression is a phenomenon with high measurement complexity, as clinical tests for its diagnosis and measurement require psychiatric experience. Additionally, there is an ongoing debate on whether these tests measure the phenomenon adequately (Rickards 2006). Its weighted life impact is unclear, because depression is a symptom of PD (prevalence: 40–50%, according to Cummings 1992). Although a direct comparison showed a significantly higher incidence of depression in the DBS group (6.7%) than in the control group (0%) (Witt et al. 2008), other studies claim an antidepressant effect of STN DBS (Schneider et al. 2003; Witt et al. 2006; Houeto et al. 2006). Depression after DBS may be most commonly secondary to dopaminergic withdrawal symptoms and/or premorbid vulnerabilities (Voon et al. 2006, S306). Furthermore, depression caused by STN DBS usually resolves under pharmacological treatment (Temel et al. 2006). Therefore, its weighted life impact may be relatively small.

Cluster 4 side effects are comparatively hard to measure, whereas their relative life impact is high. Examples are subtle intellectual problems that are overlooked in neuropsychological tests but have a great impact on the ability to work, namely, difficulties in ordering complex actions and thoughts, anticipating and planning, problems with attention, and distractibility (Schüpbach et al. 2006). Also neurobehavioral and psychiatric side effects with a significantly higher incidence after DBS than in the normal disease history belong to cluster 4. For example, hypomania has been reported in 4% to 15% of patients, and emotional reactivity even in 75% (Voon et al. 2006). But the reliability and generality of the most neurobehavioral outcome studies are limited because of small sample sizes and the absence of control groups. According to Voon and colleagues (2006), only 2 of 30 neuropsychological STN DBS studies had adequate power to detect large effects and none to detect small or medium effects. These methodological problems are amplified for cluster 4 effects. To detect and quantify personality alterations, changes of the socio-moral attitude, or hypersexuality is a methodological challenge.

Cognitive, affective, and behavioral side effects of STN DBS related to cluster 4 are not predictable, and sometimes seem to be paradoxical. Affective and social problems, especially in partnership and work, often occur in spite of a good clinical outcome (see, for example, Sensi et al. 2004; Romito et al. 2002; Herzog et al. 2003; Houeto et al. 2002; Krause et al. 2001; Brentrup et al. 2004; Houeto et al. 2002; Schüpbach et al. 2006; Perozzo et al. 2001; Houeto et al. 2002; Gisquet 2008). Sometimes the changes are evaluated positively by the patients, but negatively by their social surrounding. That is true especially for an increased energy,

novelty seeking, risk willingness, and sexual drive, as well as for decreased social conformance. In most cases, negative affective sequelae such as depression, decreased moral competence, mania, kleptomania, and emotional hyperreactivity are transient or can be managed through the adaptation of the stimulation parameters, so that a good outcome can be reached. But in some cases, the affective changes after STN DBS persist even after deactivation of the stimulation. That is valid especially for decreased frontal cognitive abilities (verbal fluency and memory). Gisquet (2008) concludes that DBS is a unique form of biographical disruption of which neither patients nor physicians measure the impact.

BIOETHICAL EVALUATION OF STN DBS-RELATED SIDE EFFECTS

After having classified STN DBS-related side effects according to our analysis scheme, we evaluate them with regard to the principles of biomedical ethics (Beauchamp and Childress 2009).

Risk-Benefit Considerations

With regard to the principles of *beneficence* and *nonmaleficence*, the question is whether the risk of a specific side effect of STN DBS may counteract its mostly achievable benefits on motor functions. In general, a risk-benefit assessment for cluster 1 side effects (e.g., small declines of executive functions and verbal learning and memory) yields a positive evaluation. Nevertheless, cluster 1 side effects may be intolerable for some patients, especially for patients suffering from dementia, who usually suffer more from stimulation-induced cognitive declines. Therefore, most hospitals exclude patients suffering from dementia from STN DBS. A risk of small cognitive declines may also be intolerable for patients for whom their cognitive abilities are very important, maybe because of their professional activity or their personal values.

A risk-benefit assessment for cluster 2 side effects—especially for the elevated suicide risk—is of high ethical relevance and justifies assessment and follow-up of patients, in particular regarding postoperative depression. The awareness of this risk has produced stricter patient selection procedures in many hospitals: Patients at high risk for suicide, especially those with an anamnesis of non-Parkinsonism-related depression, are often excluded from DBS. However, it is not clear whether stricter selection criteria are the best way to prevent post-DBS suicides. An alternative could be to allow STN DBS also for risk cases, but to make long-term follow-up and possibly psychiatric intervention mandatory for those patients.

Cluster 3 and cluster 4 side effects are entangled with measurement problems so that their ethical analysis is more complicated. First, the differentiation of therapy-induced and disease-related effects may be unclear (e.g., in case of apathy, depression or intellectual declines). Second, these effects are neither well defined nor consistently reported in the scientific literature. Third, their frequency is unknown.

For these reasons, disclosure and informed consent should include specifications regarding these methodological difficulties, especially for cluster 4 side effects, which are characterized by measurement problems and a high relative life impact. The most difficult ethical problem of STN DBS is posed by the fact that it may cause not only alterations of mood and intellectual capacities, but real personality changes (as understood in psychiatry). The current data indicates that each of the "Big Five" (i.e., the five basic personality traits: extraversion, neuroticism, agreeableness, conscientiousness, openness to experience; see Costa and McCrae 1992) has been influenced by STN DBS in some patients. Given the high ethical valence of the concept of personality, the first intuition could be that STN DBS is generally unethical. But the mere occurrence of personality alterations is no argument against this therapy. As we have already seen, Parkinson's disease itself often deeply affects the personality. In many cases, this disease makes patients depressive, apathetic, rigorous, anhedonic, or compulsive; some even become pathological gamblers. Thus, the abnegation of effective cures of disease-caused personality changes will conserve pathological personality traits even if the patients consider them as alien and suffer considerably from them. Therefore, not only interventions into the brain but also their abnegation can be ethically problematic (Müller 2007). Furthermore, it is frequently unclear why the patients' personality at the moment of the decision about DBS should be saved. Generally, it is not clear why the current personality at any point of time should be morally distinguished. Taking into account that at that moment of the decision about DBS, the patient's personality has already been altered by the neuropsychiatric disease and that these changes are mostly unwanted, there is no reason to conserve the personality at that special moment.

One might object that only personality changes caused by intentional technical interventions into the brain are ethically unacceptable. But this argument implies that naturally occurring personality changes (e.g., resulting from neurological disorders, brain traumata, brain cancer, or strokes) have to be accepted, even if they cause severe suffering and even if the "former person" (the person before the brain trauma, cancer or stroke) would have disliked or even condemned the later personality. This position may be a legitimate personal opinion, but is not convincing in general because it is dogmatic (Müller 2007).

Another common position accepts medical interventions that aim at restoring the patient to the condition s/he was in prior to naturally occurring personality changes. This position differs between an "original" personality and a personality changed by disease, trauma, or—possibly—degeneration. According to that position, therapies that restore the original personality are ethically acceptable; not acceptable are therapies that accept or even aim at a post-therapeutic personality that differs considerably from both the original and the disease-altered personality. Although this argument is intuitive and looks sensible at the first glance, it faces at least two problems: first the difficult distinction between therapy and enhancement, and second the

problem of the determination of the "original" personality. The latter issue is especially relevant for patients suffering from chronic neuropsychiatric disorders that cause subtle, lingering alterations rather than sudden, radical changes and that do not have a clear starting point. Nevertheless, the prima facie principle is to accept DBS-caused personality changes that restore the personality to its premorbid state. But this principle should not be applied for cases in which the original personality was not "good" (however "good" is defined with regard to personalities) or in which DBS could "improve" the personality. By way of example, a patient who was dysphoric during his whole life (but not clinically depressed) became severely depressed by the Parkinson's disease. Now DBS offers two different stimulation parameters that cure both his motor symptoms and the severe depression. But the first parameters would restore his dysphoric state, whereas the second one would change his mood to a level that is normal for most people but not for him. According to the position that accepts only therapeutic interventions that restore the original personality, the second option would be unethical.

Therefore, the ethically decisive question is not *whether* DBS can alter the personality or not, but whether it does so *in a good or bad way* (Müller 2007; Synofzik and Schläpfer 2008). But this is indeed a difficult ethical question, because a consensus on criteria for good personality traits is hard to find, since the evaluation of personality properties strongly depends on culture and on individual evaluations. Nevertheless, psychiatry cannot avoid evaluating personality properties, because it aims at changing certain negatively evaluated traits. And at least a minimal consensus in this question is not utopian.

Competence for Medical Decision Making

According to Beauchamp and Childress, the principle of *autonomy* implies that patients have the right to choose between different medical therapy options, taking into account risks and benefits as well as their personal situation and individual values. To enable an autonomous decision the procedure of informed consent has been developed. This procedure has become the gold standard in medical decision making in almost every part of medicine (Müller and Walter 2010). But in surgery, the high degree of "culpability" and responsibility is accompanied by an almost "old-world paternalistic discretion"; this can have implications for the informed-consent process (Fins 2008). However, in neurosurgery the respect of the patient's autonomy and the procedure of informed consent are especially important: Since surgical interventions into the brain generally bear not only somatic risks, but also risks of cognitive and affective changes, the evaluation of risks and benefits is an extremely individual issue.

The issue of patients' autonomy with regard to STN DBS is tricky: On the one hand, STN DBS can increase the ability to be an autonomous agent by enhancing mobility, independence of care, and ability to work, and by reducing depression, anxiety, or obsessive compulsive disorder. On the other hand, STN DBS can decrease the ability to be an autonomous agent by inducing mania, depression, or apathy or reducing moral competence. Furthermore, STN DBS may decrease *experienced* autonomy, since some patients feel remote-controlled by the physicians, feel a sense of impotence and passivity regarding their clinical condition, or suffer from self-alienation (Perozzo et al. 2001; Gisquet 2008).

Cluster 4 side effects may pose ethical dilemmas, as the following case (Leentjens et al. 2004) illustrates: A 62-year-old parkinsonian patient had become manic through STN DBS. After 3 years of mania in which he became financially ruined, he finally was hospitalized in psychiatry. The mania could be "switched on and off" by switching stimulation on or off. Unfortunately, it was not possible to control the mania by medication, because the drugs were either not effective or not tolerated because of severe side effects. Therefore, the patient and his physicians were confronted with a dilemma: With stimulation off, the patient was mentally competent and had insight and capacity to judge but was physically so impaired that he was bedridden. With stimulation on, he was manic and could not live independently. Before letting the patient decide whether he wanted the stimulation on or off, it was necessary to decide in which state the patient should be when he made this decision: on or off stimulation? The hospital's ethics committee advised that the patient should make a decision about stimulation while he was in the off state—probably following the intuition that this was his more "natural" state. The patient decided—while he was in the off state—to continue stimulation, although he knew that on stimulation he had to live within a psychiatric institution.

This example demonstrates a typical problem of cluster 4 side effects: For patients, it is very difficult to weigh the potential of a decrease in cognition and change in personality as complications of an intervention. Evaluating a patient's capacity to make therapeutic decisions becomes especially difficult when the potential risks involve psychological impairment or cognitive loss (Ford and Henderson 2006, 216 and 220). Therefore, the treating physicians have the duty to evaluate the patient's ability to give informed consent carefully and to counsel their patients very responsibly.

An optimal counseling process and safeguards in the patient selection criteria to exclude patients at risk can avoid ethical problems in many cases. But since no definite tests exist to predict for an individual patient whether DBS will induce mania or reduce the ability to act as an autonomous agent and to give informed consent, the risk of ethical dilemmas remains. In the case reported by Leentjens et al. (2004), a conflict has occurred between medical paternalism and patient autonomy with regard to the question of who should control the settings of the internal device. If a stimulation-induced mania occurs, the patient would be evaluated as not competent by psychiatrists, and then the treating physicians would be allowed to adapt the stimulation parameters according to their medical judgment. To reduce the risk of such conflicts, we propose to implement advance directives for the case of losing (temporarily) the decisional competence. An advance directive probably could settle the issue,

as long as it does not stipulate decisions resulting in the patient's behavior posing a risk to him-/herself or to others. Even if the patient is judgmentally able, if he or she decides for a therapy that might put him-/herself or other persons at unreasonable risk, then the physician is not allowed to comply with the patient's decision. This is valid for the stimulation parameters as well as for the dosage of potent psychiatric drugs; both must be determined neither by patients against medical prescription nor by physicians against the patient's will.

Patient Selection Considerations

Questions of *justice* are raised by patient selection criteria. On the one hand, safeguards make sense to exclude patients at risk, especially those with a history of depression, mania, and anxiety disorder. On the other hand, strict selection criteria might unfairly exclude patients who could profit from the therapy and would be able to handle the surgery and the stimulation (Ford and Henderson 2006, 222).

ETHICAL RECOMMENDATIONS

Based on the reviewed studies and the ethical analysis, we propose a catalog of measures for the clinical practice of DBS, especially for counseling, patient selection, surgery, and postoperative care.

As our literature review has shown, the DBS community is indeed sensible for side effects of STN DBS. Additionally to existing guidelines (e.g., CAPSIT-PD; Defer et al. 1999), we recommend focusing on the following issues:

In order to support the patients to make the best therapeutic decision, a manual including the state of the art on all treatment options on grounds of evidence-based medicine should be created that provides this information in an understandable way. Especially the risks and the expected benefits should be described, in particular the incidence of side effects, including those with high measurement complexity. In order to help the patients to make an informed decision, the manual should contain general considerations about the impact of certain side effects and about the imperative to evaluate possible side effects with regard to the individual situation and to personal attitudes. Furthermore, the manual should provide addresses of support groups.

The patient manual should contain an appendix (which is continually updated in the internet and in printed copies) that provides data about how local outcomes compare with national ones (Fins 2009). Important are comparative data of single centers about the morbidity, and about incidence of surgical complications (e.g., intracranial hemorrhage and infection) and of their consequences (e.g., paralysis, speech problems, required replacement of the electrodes). Furthermore, single-center data about the neuropsychological outcome, quality of life. and functional return should be compared with national data. All these data should be measured with standardized procedures, be collected consecutively, and be analyzed statistically.

The patients should be supported in evaluating the risks and the expectable benefits with regard to their individual situation (professional activity, social situation, psychological condition, and plans for the future) and personal values. The counseling of the patient about all risks of STN DBS should include considerations on the difficulty of predicting and evaluating possible side effects. It should include the risk of partnership and professional problems. The counseling necessitates a balance of optimism with reality (Ford and Henderson 2006, 215). Since DBS is often used as a last-resort procedure, expectations and desperation may create substantial challenges for free and informed consent (Bell et al. 2009). Information about less invasive alternatives to DBS should also be provided in order to foster voluntary choice (Fins 2009).

Patients should be selected who are physically, cognitively, and emotionally capable of tolerating surgery and participating in their own postoperative care (Bell et al. 2009). Assessments of the decision-making capacity and its implication for informed consent should involve an interdisciplinary team including psychiatrists, psychologists, and ethicists (Fins 2009). The safeguards should balance the principles of nonmaleficence and justice: On the one hand, patients at risk, especially those with a history of depression, mania, and anxiety disorder, should be excluded from DBS in order to protect them from severe side effects. On the other hand, the selection criteria should not be too rigid lest they exclude patients who would profit from the therapy and would be able to handle the surgery and the stimulation (Ford and Henderson 2006). DBS surgery should be performed only in a limited number of centers in order to increase the number of cases per center. If necessary, also experienced neurosurgeons should learn new techniques from colleagues who are experts in this technique (see also Fins et al. 2006; Fins 2008; Lieberman et al. 2008).

At least some centers should also offer DBS in targets other than the STN and ablative surgery. Although STN DBS has become the standard intervention for medication refractory PD, the two other stimulation targets may be more appropriate in specific cases (Plaha et al. 2006): the GPi in the case of disabling motor fluctuations, and the Vim in the case of therapy-resistant disabling tremor (Temel et al. 2006, 269). Furthermore, ablative procedures may be more adequate for individual patients (Blomstedt and Hariz 2006), for example, for patients who would not accept a device in their brain or who would not be compliant in the long period of stimulation adaptation. Therefore, for these alternatives both clinical research and maintenance of clinical experience should not be completely abandoned.

The adaptation of the stimulation parameters should not only optimize motor functions, but additionally aim at saving or restoring the patient's autonomy and compatibility with his or her surroundings. Especially, stimulation parameters that induce mania, loss of control over sexual drive, drug abuse, and criminal behavior must not be selected, even if the patient requires them. Advance directions should be established to deal with such adverse events.

CONCLUSION AND RECOMMENDATION FOR FURTHER RESEARCH

Research on the causes of cognitive, affective, behavioral, and social side effects of STN DBS should be intensified (Bell et al. 2009). In particular, this concerns research on the electrophysiological properties of the basal ganglia-thalamocortical circuits and the functional parts of the STN and their possibly different thresholds of electrical stimulation (Temel et al. 2005, 407). But also the *technique* of DBS should be refined in order to minimize negative side effects. A hopeful candidate is the research on desynchronized DBS (developed by Peter Tass and colleagues in Jülich, Germany) (Popovych et al. 2005), which seems to have less side effects. Finally, research on positive and negative effects of DBS of the different targets should be intensified in order to find alternatives to STN DBS especially for patients who are at risk for affective sequelae. This includes research for identifying risk predictors for cognitive or emotional declines after STN DBS (Smeding et al. 2006; Temel et al. 2006; Voon et al. 2006) and for better methods for assessing phenomena of high measurement complexity.

In order to support the decision making of patients, independent, evidence-based information about benefits and risks of the therapy options is required. We propose the development of a "living database" that contains the consecutive, standardized outcomes of all DBS treatments of a multitude of neurosurgical centers. This database should be available online and be continuously updated. An independent organization, optimally a patient organization, should organize the database; it should be supported scientifically and financed by public resources. ■

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