Deep Brain Stimulation in Parkinsonian patients –
Ethical evaluation of stimulation-induced personality alterations

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Abstract (110 words)

Deep brain stimulation of the subthalamic nucleus (STN DBS) has become an important option for treatment-resistant Parkinson’s disease. Although the beneficial effects of STN DBS on motor functions have been well described, complex affective and behavioral sequelae moved only recently in the focus of the medical and ethical discussion. We classify potential side-effects of STN DBS found in the scientific literature along the dimensions measurement complexity and individual life-impact, identifying side-effects of high ethical impact where compelling data is missing. Based on this analysis, we discuss the ethical consequences of complex side-effects resulting from STN DBS and outline guidelines that should be integrated in the therapeutic setting of STN DBS.

Key words: Deep Brain Stimulation, Parkinson’s disease, subthalamic nucleus, side-effects, personality changes, neuroethics.

Text: 7368 words (excluding references)
Introduction: Parkinson’s disease

Parkinsonian patients are suffering from a chronic neuropsychiatric disorder with severe motor dysfunctions (tremor, rigor and dyskinesia) as well as cognitive, affective and behavioral symptoms. Histopathologically, Parkinson’s disease (PD) is characterized by the selective, chronic and progressive degeneration of the dopamine producing cells of the nigrostriatum. This causes a continuous hyperactivity of the nucleus subthalamicus (STN) and hence an increased activity of the basal ganglia output nuclei which, consequently, excessively inhibit their targets. This mechanism is held responsible for the cardinal PD symptoms such as hypokinesia and rigidity (Temel et al. 2005, 394).

Furthermore, Parkinson’s disease is associated with a wide range of cognitive and psychiatric symptoms which can be even more challenging than its motor manifestations. Neuropsychiatric symptoms are an integral part of PD, as the damaged dopaminergic cells of the nigrostriatum are part of the reward processing system (Pagonabarraga et al. 2007). According to a study of Kulisevsky et al. (2008) with 1,351 PD patients without dementia, 87% of the patients reported at least one psychiatric symptom. The most common were depression (70%), anxiety (69%), apathy (48%), irritability (47%), and executive impairment (41%). Besides that, symptoms of impulse control disorder, such as pathological gambling, addiction to levodopa, or hypersexuality have been reported. This is important for an ethical analysis of neuropsychiatric side-effects of PD treatments, as one has to take into account that some of them may also show up in the natural history of the disease.

All known treatments of PD are only symptomatic and do not prevent disease progression. The standard treatment is drug-based using levodopa and other medications. These dopamine agonists reduce firing rates in the internal globus pallidus and STN and thus alleviate motor symptoms (Schneider et al. 2003, 296). Some patients develop variability in their response to treatment, so-called motor fluctuations. In one form, a person can move with relative ease during an ‘on’ period, whereas during an ‘off’ period the person has difficulties with movement. Another form of motor fluctuation is dyskinesia (choreiform movement) (National Parkinson Foundation 2008).

When wearing off and dyskinesia cannot be managed with adjustments of medication anymore, or when drugs are no more effective or cause significant side-effects, surgical treatment may be considered. The first surgical procedures developed were brain lesion procedures (thalamotomy and pallidotomy), which have been abandoned because of their irreversible character (National Parkinson Foundation 2008). As an alternative, chronic stereotactic deep brain stimulation (DBS) has been developed since the late 1980thies, which has the same clinical effects compared to a lesion with respect to the motor functions, but the additional advantages of adjustability and reversibility (Temel et al. 2005, 394).

Generally, DBS has gained much interest in the neuroscientific literature (Fig. 1). A bibliometric analysis performed by us based on SCI expanded reveals a strong increase of publications on this topic since the late 1990thies normalized with the general publication activity within neuroscience (set “Neuro”):1 In 2008, the numbers quadrupled compared to 2000. Furthermore, DBS is considered increasingly as therapeutic option for several neuropsychiatric diseases: Whereas in 1998, 69% of the publications on DBS mentioned the term “Parkinson”, this number decreased to 46% in 2008. In the meantime “Subthalamic nucleus” resp. STN became a predominant term within the Parkinson-DBS literature, indicating the relevance of this target for DBS. In addition, the analysis prevails an increase in a more detailed investigation of side effects. Whereas the general discussion concerning side effects of DBS (estimated
by the appearance of terms like “side effects” etc.) reached its maximum around 2000, the number of papers that mention specific side effects increased only recently. In the following, we focus our analysis only on the application of STN DBS for Parkinson’s disease, neglecting other DBS applications (e.g. for depression, obsessive compulsion disorder, etc.).

FIGURE 1

**Fig. 1:** Bibliometric analysis of the significance of STN DBS and the investigation of its non-intended effects in the neuroscientific literature on an annual basis. a) Increase of DBS-literature relative to the publication activity in neuroscience. b) Fraction of Parkinson-DBS-literature relative to the DBS-literature (black) and fraction of the Parkinson-STN-DBS-literature relative to the Parkinson-DBS-literature (grey). c) Fraction of Parkinson-DBS-literature mentioning generalized side-effects relative to Parkinson-DBS-literature (black) and fraction of Parkinson-DBS-literature mentioning specified side-effects relative to Parkinson-DBS-literature (grey). Dashed lines indicate years that have been excluded from the analysis due to the very low number of publications. For the detailed descriptions of our methodology we refer to endnote 1.

Deep Brain Stimulation of the subthalamic nucleus (STN DBS)

DBS surgery involves placing a thin metal electrode (diameter of ~1 mm) into one of several possible brain targets. This electrode receives its input from a pulse generator, which is implanted under the skin in the chest (analogue to a heart pacemaker). The stimulation system is fully implanted, whereas the stimulation parameters (frequency, pulse width, and amplitude) can be adjusted by a physician using a programming computer (Woods et al. 2002).

For PD therapy using DBS, there are three possible targets for the placement of stimulating electrodes: the Globus Pallidus internus (GPi), the subthalamic nucleus (STN), and the ventro-intermediate nucleus (Vim) in the thalamus. Thalamic stimulation (Vim) is only effective for tremor, whereas stimulation of the GPi or STN may benefit also rigidity (muscle stiffness), bradykinesia (slowdown of movements), and gait problems (National Parkinson Foundation 2008). Because stimulation of the STN has become a standard procedure for PD therapy (which is also supported by our bibliometric analysis) and the stimulation of the Vim and of the GPi seem not to produce behavioral changes compared to stimulation of the STN (Temel et al. 2006, 268), we focus our analysis on STN DBS. In the following, we first outline the functional role of STN, second we describe the surgical procedure, and third, we present the main therapeutic effects of STN DBS.

**Functional role of STN**

The STN is part of a widely distributed network, as it is situated on a central position of each of the five cortico-basal ganglia-thalamocortical circuits through which higher and lower regions of the brain communicate with the basal ganglia (Woods et al. 2002). These circuits involve motor, associative and limbic functions. Anatomically, the STN has three subdivisions: the somatomotor part (dorsolaterally located), the limbic part (medial), and the associative part (ventromedially) (Temel et al. 2005, 397). Several lines of evidence (PET studies in PD patients with STN DBS, lesion experiments with rats, and clinical observations) indicate that STN activity modulates sensorimotor, limbic, as well as cognitive functions (Funkiewiez et al. 2003).

This shows that the STN has a potent regulatory function in the processing of associative and limbic information towards cortical and subcortical regions. Therefore, changes in STN activity immediately result in changes in behavior, without being corrected by local compensatory mechanisms. Such a potent influence on associative, limbic and motor functions has not been
observed with other DBS targets. As the current technique of chronic stimulation and the dimensions of the electrodes, it is very unlikely to influence selectively the motor part of such a small target as the STN, without affecting its associative and limbic parts (Temel et al. 2005, 406). Therefore, it is plausible that STN stimulation can have a variety of effects with a complex phenomenology, and it is not surprising, that in almost all clinical studies improvement of motor disability was accompanied by unintended side-effects that will be considered in more detail in the next section.

**STN DBS surgery**

Typically, DBS operations are performed with the patient awake, using only local anesthetic and occasional sedation. The surgery is performed stereotactically: A rigid frame is attached to the patient’s head and MRI is obtained with the frame in place. The images of the brain and frame are used to calculate the position of the desired brain target and guide instruments to the target minimizing injury to the brain. Through a small skull opening, the electrodes are inserted. To maximize precision, fine microelectrodes are used to record brain cell activity in the region of the intended target to confirm that placement is correct, or to make fine adjustments in the order of 1-2 mm. The neurological status of the patient (such as strength, vision, and improvement of motor function) is monitored during the operation. Once the target site has been confirmed by microelectrode recording, the permanent electrode is inserted. It is anchored to the skull with a plastic cap, and the scalp is closed with sutures. The patient then receives a general anesthetic for the placement of the pulse generator in the chest and for positioning a connecting wire between the brain electrode and the pulse generator unit.

DBS surgery performed on the patient awake can induce posttraumatic stress disorders. Especially the drilling of the skull with only local anesthesia seems to be traumatic. Helmut Dubiel, a known sociologist at Frankfurt University, reported that during his DBS surgery he felt like a dog that undergoes an attack with a chain saw on his doghouse (Dubiel 2006, 94). Afterwards he suffered from nightmares and severe depressions. To avoid this problem, some clinicians perform the surgery when the patient is fully anesthetized.

The surgery may also have acute side-effects. The most serious potential risk of the surgical procedures is bleeding in the brain, producing a stroke. The average risk is about 2%. The effects of stroke can range from mild weakness that recovers in a few weeks or months to severe, permanent weakness, intellectual impairment, or death. The second most serious risk is infection, which is about 4%. An infection is usually not life-threatening, but it may require the removal of the entire DBS system. In most cases, a new DBS system can be re-implanted when the infection is eradicated (National Parkinson Foundation 2008).

**Therapeutic effects of STN DBS**

STN DBS does not act directly on dopamine-producing cells and does not affect brain dopamine levels (the therapeutic effect of drugs). Instead, it compensates for one of the major secondary effects of dopamine loss, the excessive and abnormally patterned electrical discharge in the STN. High STN activity (off-drug or off STN stimulation in PD patients) causes low motor activity (bradykinesia, rigidity, tremor, off dystonia), a reduction of spontaneous thoughts, impaired executive function and working memory, poor motivation, depression, anxiety, and apathy. By contrast, a low STN activity (on drug or on STN stimulation) leads to high motor activity, possibly dyskinesia, rich associations, possibly delusions and hallucinations, and enhanced mood, eventually mania or impaired emotional control. This results from the involvement of the STN in the regulation of motor, cognitive, affective, and behavioral
functions. Funkiewiez et al. (2003) found that both levodopa and STN DBS induce acute amphetamin-like psychotropic effects, in which the psychotropic effect of levodopa is higher. It is likely that the psychotropic effects are indeed specific to STN malfunction. The causal mechanisms of DBS on the neuronal level, however, are not fully understood until now, and there are at least eight possible causal mechanisms discussed in the literature (McIntyre et al. 2004).

The clinical outcome of STN DBS has been evaluated by various studies. Generally, the procedure leads to a significant improvement of motor functions in 50-60% of all cases (Schneider et al. 2003) and to a reduction of anti-parkinsonian drug use in approximately 60% of the cases (Temel et al. 2006). This positive outcome concerning the intended effects also shows up in improvements of the global Quality of Life (QoL) score, namely a significant benefit in mobility and activities of daily living (Houeto et al. 2006; Martinez-Martin et al. 2002; Smeding et al. 2006).

Benefits in mood, however, were reported inconsistently. The meta-analysis of Temel et al. (2006) found that the activities of daily living score improved by 52% in the off and by 10% in the on phase (1,398 patients). Other studies report enhanced affective processing and subjective well-being, namely depression and anxiety disorders are improved (Ardouin et al. 1999; Funkiewiez et al. 2003; Funkiewiez et al. 2004; Schneider et al. 2003; Houeto et al. 2006; Witt et al. 2006; Witt et al. 2008; Smeding et al. 2006). The review of Woods et al. (2002) lists 10 studies which assessed mood changes after DBS: Six studies documented improvements and four no significant changes. In recent times, the sensibility for negative psychic sequelae has improved. As we have shown in our bibliometric analysis, DBS-studies mentioning a vocabulary related to such sequelae were almost inexistent until the late 1990, but then started to increase to up to 6% in 2008. We will now present a deeper analysis of complex side-effects.

**Evaluation of complex side-effects of STN DBS**

The beneficial effects of STN DBS on motor functions have been well described, but its consequences on neuropsychological functions have received relatively little attention until recently (Woods et al. 2002; Temel et al. 2005, 395), although they are discussed since 1998 in the medical press (Limousin et al. 1998). According to us, the reason for this is twofold: First, one is confronted with a disease that involves a rich phenomenology in regards of cognitive and psychiatric symptoms. It is therefore difficult to distinguish therapy-induced side effects from the natural history of the disease and thus to evaluate the impact of the treatment on the life of the patient “normalized” with the impact of the disease. Second, as the target of STN DBS is involved in many different brain circuits responsible for various functions, one can expect a rich phenomenology of effects, which themselves are hard to assess.

In order to ethically evaluate the side-effects of STN DBS, we will first introduce a scheme of analysis that classifies potential side-effects along the dimensions measurement complexity and individual life-impact normalized with the natural history of the disease. We then discuss side effects found in the scientific literature along this scheme. In a third step, we relate those side-effects that we consider as the ones with the highest impact on the biography of the patients and analyse them with regard to the ethical principles beneficence, nonmaleficence, autonomy and justice. Based on the ethical analysis of STN DBS we formulate suggestions for guidelines to increase patient’s ability to give informed consent to this therapeutic option.
Investigation of complex side-effects – a scheme of analysis

Therapies may have various effects beside those directly associated with the intended goal of the therapy. In modern medicine, the assessment of such side-effects is required when introducing new therapies and also forms the basis of an ethical evaluation of these effects. However, this assessment is faced with two fundamental difficulties: First, the effects may be difficult to measure and to quantify; and second, the impact of the effects on the patient’s everyday life may be difficult to identify, especially compared to the impact of the disease’s natural progression. These problems are pronounced when therapies are investigated, which are related to diseases with psychiatric components.

The “measurement complexity” of an effect is the first dimension in our scheme of analysis. It relates to the problem to quantify effects of therapeutic interventions in experimental settings. In the following, we are not intending to define a function that relates a specific test with a continuous variable named “measurement complexity”. But we distinguish between “simple” and “complex” tests regarding the adequateness and precision of the test for the investigation of the phenomenon. As “simple” we consider neuropsychological tests like the Controlled Oral Word Association Test, the Finger Tapping Test or the Hopkins Verbal Learning Test, where both measurement object and procedure are straightforwardly defined. Such tests are typically used in DBS outcome evaluation (see for example Castelli et al. 2006). As “complex” we consider tests focusing on complex psychic phenomena like depression, or on quality of life typically investigated by questionnaires for patients and their family members. Examples for tests of complex phenomena are the Beck Depression Inventory (BDI), the Global Assessment of Functioning (GAF) or the Parkinson Disease Quality of Life questionnaire (PDQL). Also these tests are widely used in DBS outcome evaluations (see for example Diamond & Jankovic 2005).

“Life impact” of a specific effect is the second dimension in our scheme. This variable captures the importance of the effect for the patient’s everyday life “normalized” with the probability that this phenomenon also occurs during the natural history of the disease. Thus, both the importance of the effect as well as its deviation from the natural history must be high so that its “life impact” scores high. Again, we are not intending to define a function that relates a specific test with a continuous variable named “life impact”, but we claim that in this way we are able to classify the problem of evaluating the ethical impact of STN DBS along four ideal types as follows (see Fig. 2):

**FIGURE 2**

*Fig. 2: Four ideal types of problems associated to the ethical evaluation of STN DBS effects.*

- **Class 1:** There are effects that are comparatively easy to measure but have low impact on patient’s life or do no differ much between therapy and natural history of the disease. In this category fall effects which can be measured with simple neuropsychological tests, e.g. finger-tapping tests, as well as memory declines (which may be important for the patient, but does not differ much between patients who underwent stimulation and patients without DBS). Effects belonging to this class are of no specific ethical importance.

- **Class 2:** Some effects can be comparatively easily measured, and have a high impact on patient’s life. Examples are certain cognitive abilities or suicide (definitely the
highest impact). Effects of this class have a high ethical importance, but are not related to additional measurement problems.

- **Class 3:** Other effects are comparatively hard to measure, and have only a low impact on patient’s life or do no differ much between therapy and natural history of the disease. To this category belong subtle intellectual declines which can be compensated by the patient or which also often occur in the natural history of the disease. These effects concern less ethical attention.

- **Class 4:** Finally, there are effects that are comparatively hard to measure and have a high impact on patient’s life. To this class belong personality alterations caused by the therapy. These effects have a high need for discussion both in methodological and in ethical respects, especially with regard to the principles autonomy and justice.

By using this scheme, we stress that an ethical debate on the impact of therapeutic interventions like STN DBS cannot abstract from the methodological problem of defining and measuring the effects of the therapy that is ethically analyzed. We will outline this point in the ethical analysis part. In the following, we classify the published findings of side effects of STN DBS after this scheme.

Furthermore, we point out that we will use this scheme in a generalizing sense – i.e. we make general conclusions that may not necessarily apply for each individual patient. For example, effects of class 1 may result in a cumulative change of an individual patient’s well-being that scores as “high impact” compared to the natural history of the disease. This finding, however, is based on an assessment of the individual patient and not on an analysis of studies that involve many patients.

**Identifying high-impact effects**

The first clinical findings of neurobehavioral sequelae of STN DBS were published in 1998 by Limousin et al. At that time, the assessment of non-intended effects of STN DBS (i.e. effects that do not relate to motor function improvement) was mostly positive. In 2002, a review of Woods et al. which evaluated 16 papers about STN DBS provided “preliminary support for the cognitive and behavioral safety of this treatment”. The most common findings of the reviewed studies were (1) improvements in self-reported symptoms of depression and (2) a diminished verbal (lexical and categorical) fluency. Postoperative changes in global cognitive abilities, memory, attention, and frontal/executive functions were inconsistently reported and of questionable persistence and clinical significance.

Since 2001, more and more studies report on the one hand disinhibition, depression, anxiety, mania, and hypersexuality, on the other hand reduction of anxiety and obstructive compulsive disorder. Reported are also cognitive impairments: general cognitive decline, impairments in executive functioning, attention, working memory, mental speed, response inhibition, verbal memory and verbal fluency (Parsons et al. 2006). Only a minority of the clinical studies have found no or only mild negative effects on the behavioral performance (Ardouin et al. 1999; Funkiewiez et al. 2003; Jahanshahi et al. 2000; Perozzo et al. 2001; Schneider et al. 2003) and on cognitive functions (Witt et al. 2004). A meta-analysis of 82 studies published until June 2004 (1,398 patients) shows that the most commonly observed psychic sequelae are cognitive impairments (41%); the second most depression (8%), and thirdly, (hypo)mania (4%) (Temel et al. 2006). We now classify the findings along our scheme of analysis.
Class 1: Effects of class 1 which are relatively easy to measure, but do not have a high impact for the patient’s life (normalized with the natural history of the disease), have been subject of several studies and a few meta-studies. That’s no surprise at all, since these effects are comparatively easy to measure and thus to compare. Parsons et al. (2006) published a meta-analysis of 28 articles published between 1990 and 2006 about cognitive sequelae of STN DBS (612 patients). They found significant, albeit small, declines in executive functions and verbal learning and memory. Moderate changes were only reported in semantic and phonemic verbal fluency; these declines were not related to patient age, disease duration, stimulation parameters or change in medication, but were caused by STN DBS. Smeding et al. (2006) found in a prospective study with controls (99 DBS patients and 36 nonimplanted PD patients) that DBS induced an executive dysfunction, characterized by a larger decline of verbal fluency, naming speed, selective attention and verbal recall. Witt et al. (2008) found that STN DBS does not reduce overall cognition, although there is a selective decrease in frontal cognitive functions (verbal fluency and Stroop test) (123 patients, randomly assigned to STN DBS or control group).

Class 2: Effects of class 2 are relatively easy to measure, and have a high impact for the patient’s life. The effect with the highest impact certainly is suicide. Suicides after successful DBS have been reported in various studies. Berney et al. (2002) found transiently suicidal tendencies in 12.5% of the patients (in total: 24 patients). Houeto et al. (2002) report 3.6% suicides (28 patients), Burkhard et al. (2004) 4.3% (140 patients), Funkiewicz et al. (2004) 5.2% suicide attempts plus 1.3% suicides (77 patients), Smeding et al. (2006) 1% suicide attempts (99 patients), Witt et al. (2008) 1.3% suicides (78 patients), and Soulas et al. (2008) 1% committed and 2% attempted suicides (200 patients). The meta-analysis of Temel et al. (2006) found a suicide (attempt) rate of only 0.4% (1,398 patients). The decreasing suicide rates probably results from stricter indication standards for DBS in many hospitals which newly exclude patients with a previous history of (not parkinsonism-related) depression or mania. However, also the suicide prevalence reported in the meta-analysis stands in sharp contrast to the suicide rate of PD patients that is approximately 10 times lower than in the general population.

Another effect of DBS that belongs to class 2 is aggressive behavior. Sensi et al. (2004) report about a 64 year old PD patient without a history of psychiatric disease or substance abuse who underwent STN DBS. After the device was activated, the patient showed spontaneous unprovoked, aggressive outbursts, mostly verbal directed toward the medical staff. Tests showed that the behavioral disturbance was independent of the drugs, and that there was a clear correlation with the stimulation and the aggressive behavior. However, aggressive behavior after STN DBS is a rare complication: The meta-analysis of 82 studies by Temel et al. (2006) found that less than 0.5% of the patients developed aggressiveness.

Class 3: Effects of class 3 are comparatively hard to measure, and have a relatively low impact on the patient’s life. Many of them are relatively common after STN DBS, but occur often in the natural history of the disease, too. One example is apathy, which often occurs in stimulated Parkinson patients, but which seems not to be caused by stimulation, but by 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). Depression (and other psychiatric disorders) may be special case: although there exist established psychological tests for quantifying depression (e.g. the Beck Depression Inventory), there is still a debate whether these tests measure the phenomenon adequately (Rickards 2006). Furthermore, depression is relatively common after STN DBS, but also often occurs in the natural history of the disease – although depression has a high impact on patient’s life. Therefore it is necessary to compare patients treated with DBS and with drugs.
alone in order to decide, whether the phenomenon scores as “low impact” or “high impact”. Smeding et al. (2006) found that 9% of the STN patients (vs. 3% of controls) had psychiatric complications. Witt et al. (2008) found that 16.7% of the patients treated with DBS and 12.7% in the control group had severe psychiatric adverse events. In the DBS group the incidence of depressions was greater (6.7%) than in the control group (0%), whereas the incidence of psychoses was higher in the control group (11.1%) than in the DBS group (6.7%). But these results are not undisputed: Several studies claim an antidepressant effect of STN DBS (Schneider et al. 2003; Witt et al. 2006; Houeto et al. 2006) and an amelioration of anxiety (Houeto et al. 2006). Nevertheless, the meta-analysis of 82 studies by Temel et al. (2006) revealed that 8% of the patients developed a depression that usually resolved under pharmacological treatment.

Class 4: Effects of class 4 are comparatively hard to measure, and have a high impact on the patient’s live. A striking commonality of reports of these effects is that they mostly have an anecdotic character. Major changes of a patient’s personality belong to class 4. For example, Romito et al. (2002) report that 5 out of 30 PD patients treated with STN DBS developed remarkable disorders of mood or sexual behavior. Two male patients showed mania and hypersexuality a few days after the implant that lasted for some months and then gradually disappeared spontaneously. One patient developed a manic syndrome, characterised by inflated self-esteem and grandiosity, marked increase in goal-directed activities, decreased need for sleep, planning of hazardous business investments, and flights of ideas. Furthermore he began to spend much of his time writing religious poems, despite a lack of interest in religion, and he began driving his car in a reckless manner. The other patient developed inflated self-esteem, labile mood, increased sexual desire and non-customary sexual behavior (inappropriate seductive behavior towards female medical staff). For the first time in several years he resumed work and went on a journey with his wife. He wrote a manuscript about his experience with PD and resumed his university course in astrophysics which he had abandoned 15 years previously. Herzog et al. (2003) report about a female patient who gradually developed a first episode of mania with psychotic symptoms after STN DBS. She lost normal social inhibitions, and engaged in unrestrained buying of cloths, and fell in love with two neurologists. Her judgment was impaired, and she became suspicious, hostile and paranoid. Stimulation arrest led to a rapid deterioration of her mood without any improvement in mania. With the combination of clozapine and the mood stabilizer carbamazepine the affective disorder remitted within 3 months. Houeto et al. (2002) report about two patients, who showed, after STN DBS, an abnormal sexual behavior with exhibitionism or paedophilia and leisure tourism, respectively. Witt et al. (2006) present the case of a 65-year-old architect treated with STN DBS. Before stimulation he was frequently painting; his themes were exclusively architectural. Since surgery he painted exclusively female acts, although he had never painted nudes before.  

Such anecdotic reports gave reason to systematic studies investigating complex socio-moral changes of some DBS patients. The results are heterogeneous. Houeto et al. (2002) have evaluated 24 Parkinson patients retrospectively for adjustment disorders (social adjustment scale, SAS), psychiatric disorders and personality changes (IOWA scale of personality changes). They found that social adjustment was moderately or severely impaired by 62.5% of the patients. Personality traits were improved by 35%, unchanged by 30%, and aggravated by 35%. But a recent retrospective study of the same research group (Houeto et al. 2006) came to contrary results. This time, 20 Parkinson patients were rigorously selected regarding psychiatric criteria. The authors found that the patients’ personality traits were unmodified, and scores for social adjustment remained stable. Brentrup et al. (2004), however, report that 2 out of 15 patients were socially maladjusted after STN DBS for more than one year. The average value of the personality trait ‘novelty seeking’ of these two patients rose from 1.50 to
2.25 (normal range: 2.21–3.18), whereas their ‘conscientiousness’ value decreased from 2.41 to 1.66 (normal range: 1.94–3.18). Their power of socio-moral judgment decreased on the 6-level Kohlberg scale from level 4 (adhering to social system and conscience) to level 2 (serving one’s own interests and letting others do the same) (Kohlberg 1984). This number again contrasts with the meta-analysis of 82 studies by Temel et al. (2006) that refers aggressiveness, personality changes, hypersexuality, or apathy in less than 0.5% of the cases. These notable differences probably result from methodological problems in assessing and quantifying phenomena like “personality changes”, “alteration of socio-moral judgment” or “hypersexuality”.

Subtle intellectual deteriorations may fall into this category, too. These deteriorations can be overseen in neuropsychological tests, although they may have great impact on the ability to work and on the quality of life. Schüpbach et al. (2006) found that many patients have subtle intellectual problems that become apparent only in unstructured interviews, namely difficulties in ordering complex actions and thoughts, anticipating and planning, problems with attention, and distractibility.

Of particular importance is that class-4-effects may affect strongly the social lives of the patients. Perozzo et al. (2001), Houeto et al. (2002) and Schüpbach et al. (2006) found modified familiar relations and often deteriorations of conjugal relationships. Latter found that after STN DBS marital life worsened more often than it improved. Marital problems occurred in 71% of the couples (50% were in a crisis before the operation). 12.5% were divorced within 2 years after the operation. These marital conflicts emerged either because the patients gained autonomy and rejected their spouses, or because the spouses expected more personal responsibility of the patients, whereas those stuck to the patient’s role. Several studies also concluded that professional activity worsened more often than it improved after STN DBS (Schüpbach et al. 2006; Gisquet 2008) – either because the patients did not feel able to work any more after surgery or because they gave priority to leisure activities. Schüpbach et al. (2006) documented more subtle personality changes with unstructured interviews: They found that several patients were logorrhic, irritable, and impatient, and expressed their opinions more freely. These changes also may be causal of conjugal and professional problems.

One has to be aware, that class-4-effects may include a non-intended cure of psychiatric disorders, namely of pathological gambling. Bandini et al. (2007) report about two Parkinson patients who started pathological gambling within two months of dopaminergic dosage increase. This is known as part of the so-called dopamine dysregulation syndrome (Dodd et al. 2005). Both patients were treated with STN DBS, and the dopaminergic drugs were reduced. In both cases there was a dramatic improvement of the gambling. Ardouin et al. (2006) describe seven PD patients with pathological gambling due to dopaminergic treatment, intolerant to reduction in medication. After DBS surgery, the dopaminergic treatment was reduced below the dosage of gambling onset. In all patients, pathological gambling resolved post-operatively after 18 months on average. However, probably not DBS itself, but the reduction of dopaminergic treatment that became possible because of DBS is the cause of the improvement of gambling. DBS then could induce other behavioral changes. Frank et al. (2007) compared PD patients treated with dopaminergic medication and patients treated with DBS. They found that dopaminergic medication prevents learning from negative decision outcomes; this mechanism may explain pathological gambling. In contrast, DBS patients sped up their decisions under high-conflict win-win conditions. That could be explained by an inability to self-modulate decision times as a function of conflict, caused by the STN stimulation.

This overview shows that in particular the class-4-effects of STN DBS have a high ethical impact combined with a severe measurement problem. In several cases, DBS influences the mood, some cognitive functions, and personality traits as novelty seeking, risk willingness, conscientiousness, social conformance, and moral competence. The psychic effects of STN
DBS are not predictable, and sometimes seem to be paradox. Affective and social problems (partnership and job) occur often in spite of a good clinical outcome. 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 psychic sequelae as depression, decreased moral competence, mania, kleptomania, or 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 patients, psychic changes after STN DBS are permanent and sometimes even persist 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.

**Ethical analysis of high-impact effects**

We perform our ethical analysis of the identified and classified side-effects in the framework of principlism (Beauchamp & Childress 2009). We assume thereby that the intended therapeutic effects on the motor functions can indeed be achieved by STN DBS. This assumption is plausible as STN DBS nowadays generally leads to good effects.

Thus, the question is, whether the appearance of side-effects may counteract the beneficial effects of STN DBS on the motor functions, and, if so, what does that mean for the ethical evaluation of STN DBS. The mere occurrence of unwanted psychic side-effects is no argument against this therapy: Given the fact, that Parkinson’s disease itself often deeply affects the patient’s personality, not only interventions into the brain, but also their abnegation can be ethically problematic (Müller 2007).

We first discuss effects of class 1 and 2: They have the advantage of having a low measurement complexity, i.e. their occurrence or absence can easily be identified – both by doctors and patients. For the ethical analysis this means, that their ethical valence is purely based on normative arguments and not entangled with the measurement problems. The evaluation is mostly based on the principle of nonmaleficence. Take the example of suicide: The elevated suicide risk in patients treated with STN DBS is undisputedly seen as unwanted. The awareness for this risk has led to consequences on the patient selection procedure in order to decrease this risk. Another example is cognitive decline. To prevent patients from this class-2-effect, several hospitals exclude dement patients from STN DBS, because they usually suffer worse from cognitive declines than not dement persons.

As outlined earlier, class-3-effects are ethically less important, since they are either not severe or relatively common in the natural history of the disease and not related to the therapy. One example for the latter is apathy, which often occurs in stimulated Parkinson patients, but which seems not to be caused by stimulation, but by drug reduction. But that causes at least an indirect ethical problem, since either the measurement of the effect may be inadequate, or the differentiation of therapy-induced and disease-related effects is unclear. Both makes informed consent for patients more difficult.

The most difficult ethical problems are posed by the class-4-effects. STN DBS causes (at least in some cases) complex personality changes with regard to the influential „Big Five” personality model of Lewis Goldberg. The current data indicates, that each of the five basic personality traits (extraversion, neuroticism, agreeableness, conscientiousness, openness to experience) have 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 to defend this conclusion, one would need a strong argument why personality changes are generally negative. This argument is hard to defend because a person’s personality alters anyway during lifetime, not only because of experiences, but also through biological processes such as brain disease or degeneration. One may object that only personality changes caused by technical interventions into the brain are ethically unacceptable. But this argument is based on an “is-ought equalization” and implies that naturally occurring psychic changes (e.g. by disease) have to be accepted, even when they cause severe suffering. This position may be a legitimate personal opinion, but is not convincing in general, because it is dogmatic. If this position is taken serious, modern psychiatry had to be condemned because it uses technical means to cure psychic diseases (Müller 2007).

Therefore the ethically decisive question is not whether DBS alters personality or not, but whether it does so in a good or bad way (Synofzik & Schläpfer 2008). But this is indeed a difficult ethical question, because both the measurement of the effect and its life-impact are entangled. Furthermore, a general consensus on criteria for good psychic properties is hard to find, since the evaluation of psychic properties depends on culture. Examples for culture-dependent psychic properties are homosexuality, paedophilia, and religiousness. Nevertheless, medicine, especially psychiatry, cannot avoid evaluating psychic properties, as soon as changes of psychic properties are intended – which is certainly the goal of any psychiatric therapy. To some extend, these evaluations can also be used to investigate unintended side-effects as the class-4-effects. But their high measurement complexity hinders their identification as entities that impact life and allows diverging interpretations – e.g. between the patient and his or her relatives or doctors.

Regarding the effect of STN DBS on the ability to be an autonomous agent, the evaluation is heterogeneous. On the one hand, STN DBS can increase the autonomy of PD patients because it improves their mobility, makes them independent of care, and often restores their ability to work. Furthermore, it often reduces depression, anxiety, obsessive compulsive disorder or pathological gambling, so that more autonomy can be gained. On the other hand, STN DBS can decrease the patient’s autonomy, namely if it reduces the moral competence or induces mania, depression, or apathy. Furthermore, the experienced autonomy is decreased in patients who feel telecontrolled by the physicians, feel a sense of impotence and passivity regarding their clinical condition or who suffer from self-alienation (Perozzo et al. 2001; Gisquet 2008). In general, it is difficult to predict whether STN DBS will enhance the individual patient’s autonomy or not. Therefore the patient should be informed about this dilemma in extenso. If a patient’s (experienced) autonomy is decreased through stimulation, its parameters should be adapted so that this effect does not occur. The stimulation parameters should be generally chosen so that the autonomy will become as high as possible. The autonomy also could be increased if the patient is enabled to adjust the stimulation parameters himself within a certain range.

Also the principle of justice is involved along two aspects: First, because STN DBS is an effective treatment of a severe, hindering disease, patients have the right to be treated. Even from the societal point of view, the treatment would be justified, because it reduces costs for the social system, when patients become independent of care and regain the ability to work. Second, there is a small risk that the treated patient develops an antisocial or even violent behavior. The principle of justice requires that the stimulation is adapted so that not only the patient’s beneficence, but also his compatibility with his surrounding and with the society are preserved or restored. From the principle of justice does not follow necessarily that an intervention with a high incidence of marital problems is not allowed, because a right for the con-
continuation of a partnership does not exist. But it forbids interventions which cause loss of control over sexual drive, drug abuse, and criminal behavior etc.

**Recommendations**

Based on the reviewed studies and the ethical analysis, we conclude with concrete recommendations:

- Physicians should counsel patients and their relatives extensively about the risks of class-4-effects (Gharabaghi et al. 2005, 69; Temel et al. 2006, 269), including the risk of partnership problems. They should evaluate the risks and the expected benefits together with the patient and his/her relatives. Based on an extensive review of websites of German clinics offering STN DBS we suspect, that this has not been done yet sufficiently, as these risks are barely disclosed to the patients. Patients should also be informed about alternatives to STN DBS: either DBS of the Gpi (in the case of disabling motor fluctuations) or of the Vim (in the case of therapy-resistant disabling tremor) (Temel et al. 2006, 269).

- A careful psychological and psychiatric examination should be performed before surgery (Houeto et al. 2002; Saint-Cyr & Albanese 2006). Also structured interviews with the patient and his relatives pre- and post-interventions could help to identify personality changes. Patients with high risks for psychiatric disorders should be excluded from STN DBS. Cognitive deficits and dementia should be contraindications for STN DBS (Woods et al. 2002, 120; Saint-Cyr & Albanese 2006). Predictors for the risk of cognitive or emotional decline after STN DBS have to be established (Smeding et al. 2006; Temel et al. 2006, 269).

- (Bio-)medical scientists should intensify the research on the electrophysiological properties of the basal ganglia-thalamocortical circuits and of the functional parts of the STN and their possibly different thresholds of electrical stimulation (Temel et al. 2005, 407). Furthermore, the surgical procedure to modulate only the motor part of the STN should be technically improved (Temel et al. 2005, 407). The research on desynchronised DBS (developed by Peter Tass and colleagues in Jülich, Germany) should be supported, because it probably has less side-effects. The research on psychic side-effects of STN DBS should be intensified. Devices that allow patients to modify autonomously the stimulation parameters in a certain range should be made available to patients.

- Last but not least, (medical) ethicists should develop tests for moral agency in order to document and evaluate changes of moral competency through DBS. This desideratum is tackled by the authors. And a debate should be initiated about the issue which changes of personality can be accepted or are even desirable (Gharabaghi et al. 2005, 69).

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References


1 Methodological remarks: The analysis has been performed on July 2nd 2009 in the SCI expanded database (database description see: 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 effects” OR “adverse effects” 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 hypoman* OR „limbic effect“ OR mania OR psychosis OR suicide OR „transient confusion“.