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Deep brain stimulation as a new therapeutic approach in therapy-resistant mental disorders: ethical aspects of investigational treatment

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Abstract Deep brain stimulation (DBS) is an established treatment option for some movement disorders, in particular Parkinson's disease. Only recently, a number of promising studies with small samples of patients have been published in which impressive therapeutic outcomes achieved by DBS in otherwise treatment-resistant obsessive–compulsive disorder, major depression, and Tourette's syndrome were reported. It seems probable that the investigational approach to treat mental disorders by DBS will increase substantially. Neurosurgical interventions in psychiatric patients raise ethical considerations not only based on the disreputable experiences of the era of psychosurgery. Therefore, it is necessary to implement transparent and well-defined regulations for the protection of the patients as well as appropriate support for therapeutic research. The current article aims to provide a synopsis of the DBS approach in mental disorders and the hitherto existing criteria for research. It suggests some additional requirements for ethically justifiable therapeutic research employing DBS in psychiatric patients.

Keywords Deep brain stimulation · Neuroethics · Mental disorders · Major depression · Obsessive–compulsive disorder · Tourette's syndrome

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Introduction

After its introduction more than 20 years ago, the deep brain stimulation (DBS) today is established as an option to treat Parkinson's disease and essential tremor. Use of DBS for movement-related disorders has been approved by the US Food and Drug Administration (FDA) and has been used in more than 35,000 patients worldwide [7]. The improvement in symptoms of many patients has captured the attention of the general public, and neuroscientists are now introducing DBS for psychiatric disorders. Successful treatments of small samples suffering from otherwise treatment-refractory obsessive–compulsive disorder (OCD), major depression (MD) or Tourette's Syndrome (TS) make an increased use of DBS for the treatment of mental disorders in the future appear probable. Even now, the effectiveness of DBS for the treatment of addiction and schizophrenia is being discussed.

Having in mind the disreputable history of psychosurgery throughout the mid 20th century, discussions of neurosurgical interventions in psychiatric diseases must be approached with caution. Besides Gottlieb Burckhardt, psychosurgery was first introduced by Egas Moniz [19] who was awarded the Nobel Prize in 1949 for developing surgical methods that disrupted afferent/efferent pathways of the frontal lobe. This frontal lobotomy was not only based on very little clinical evidence, but even abuses of

this technique occurred: less appropriate patients were selected and non-surgeons began performing lobotomies. Some 4,000 of these psychosurgical procedures were performed or supervised by Walter Freeman, a psychiatrist who performed transorbital lobotomy with an icepick and with minimal surgical technique.

It is important to appreciate the difference between the scientifically guided procedures of today and the empirical psychosurgery methods that existed about 50 years ago. DBS offers several advantages over traditional lesioning surgery. As the most important one, DBS is a reversible and adaptable procedure without causing irreversible brain lesions. The stimulator can be turned off or on, and the stimulation can be adjusted. Finally, there is the possibility to remove the intracranial electrode completely and nearly without damage to the stimulated region. The adaptability of the procedure allows researchers to manipulate the settings of the stimulating electrode, and to perform sham stimulations to measure the placebo effects. In terms of research, such a technological development is invaluable and was previously unavailable with lesioning operations.

However, despite these advantages, DBS is not an entirely innocuous operation. Even seemingly simple components of the procedure can have serious consequences if the surgeon does not have the appropriate expertise, and the implications of the procedure are not yet examined in their full range, including possible cognitive and psychosocial consequences.

DBS of mental disorders—a short overview

DBS and OCD

The first mental disorder to be experimentally treated by DBS was OCD. In 1999, in a pilot study, Nuttin et al. [20] reported encouraging results in three of four OCD patients after implantation of electrodes in the anterior limbs of the internal capsule and the neighboring nucleus accumbens. Last year, four different research groups reviewed 26 patients with OCD, in which a similar DBS approach was used [4]. With bilateral DBS, more than one-third of the patients achieved remission, and about two-thirds were living more independently and with a better social standing. Based largely on these findings, in February 2009, the FDA approved a special device from Medtronic Inc. (Minneapolis, MN, USA) under the Humanitarian Device Exemption (HDE) program for chronic and severe OCD [29]. This type of limited approval applies to treatments for relatively rare conditions after Institutional Review Board (IRB) approval, and it marks the first approval of DBS for a psychiatric condition. In Cologne, the efficacy of unilateral (only right hand sided) DBS of the nucleus accumbens in OCD has been under investigation in a randomized, sham controlled clinical trial since 2002. The 1-year effects of the unilateral approach were nearly comparable with previous studies employing bilateral stimulation of the internal capsule in treatment-resistant OCD [5]. Recently, Mallet et al. [11] presented preliminary findings showing that even the stimulation of the subthalamic nucleus, the usually targeted structure in Parkinson's disease, can reduce the symptoms of severe forms of OCD. Remarkably, this approach was associated with a substantial risk of serious adverse events.

DBS and TS

Since the first case report of successful treatment of TS with DBS of the thalamus was published in 1999 [31], several other groups have used this target in a limited number of TS patients. Maciunas et al. [10], e.g., investigated the efficacy of thalamic stimulation in five adult TS patients with a double-blind crossover study design. A statistically significant improvement was observed at the end of the 4-week double-blind period, although two patients did not respond to DBS. The largest study of thalamic DBS consisted of a sample of 18 patients [27], in which all patients were responders and tic reduction rates between 31 and 95% could be achieved. But other subcortical nuclei were also used as targets for DBS and proved the efficacy of this approach. Based on imaging data which show a prominent role of the ventral striatum, the nucleus accumbens with the neighboring part of the internal capsule was stimulated in patients with TS resulting in clinical improvement [8]. However, the most optimal target area for DBS in refractory TS is still to be identified.

DBS and MD

Reports about distinct mood changes in DBS-treated Parkinson's disease patients suggested that DBS can be used to treat affective disorders. First data from psychiatric patients were confirmed in an open study of six treatment-resistant patients with major depression [13]. Mayberg and collaborators [9] implanted DBS bilaterally in the white matter fibers connecting to Brodman area 25 in the subgenual cingulate gyrus and achieved remission in four of six patients who had not responded to drugs, psychotherapy, or electroconvulsive therapy. This group showed a correlation of their clinical findings with changes in the activity in depression-relevant brain regions. In a more recent study, 12 out of 20 severely depressed patients undergoing DBS targeting the subcallosal cingulate gyrus had significant improvements in their symptoms, effectively going into remission for 1 year. Another promising target structure of stimulation for depression is the ventral

capsule and the neighboring ventral striatum, including the nucleus accumbens. Malone et al. [12] used a similar approach for the stimulation of OCD and improved depression in 8 of 15 patients significantly. Schlaepfer et al. [25] implanted electrodes in the shell and core regions of the nucleus accumbens in three patients and also achieved promising results (see Fig. 1).

Mechanism of action

For DBS, the underlying precise mode of action is still unknown. DBS induces an electrical field in the brain tissue that attenuates exponentially with the distance from the electrode. Because DBS in some diseases achieves effects that are remarkably similar to lesioning, the simplified proposed mechanism was a functional neuronal blockade. In this context theories ranged from synaptic inhibition and depolarization blockade to release of inhibitory neurotransmitters [2]. However, recent research has identified an excitatory response to high-frequency stimulation [15]. In any case, the complex effects of DBS depend on the stimulus settings: For example, the amplitude and temporal characteristics of the stimulation, physiological properties of individual cells, the geometry of the stimulus field, and the underlying disease. With regard to the mechanism of action, an important factor is the distance from the electrode of the neural element to be modulated. At high currents, nearby elements may be blocked, and distant elements may not receive sufficient stimulation, but elements in an intermediate region will be activated. Gray matter and neurons respectively have different responsiveness as do myelinated and unmyelinated fibers. Therefore, the effects of DBS in the context of therapeutic DBS differ across the target points [23]. However, the most likely explanation of DBS-efficacy is a stimulation-induced modulation of impaired network activity, may be by enhancing rhythmic and synchronous inhibition within and between afferent structures [14].

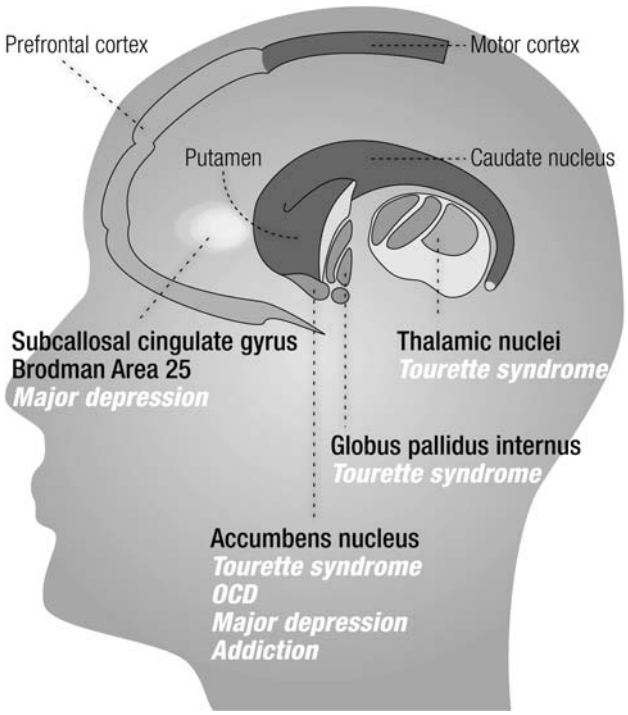

Fig. 1 Schematic representation of different anatomical structures used as targets for deep brain stimulation in mental disorders

Ethical aspects

Regarding the present state-of-the-art of DBS in patients with mental disorders, ethical aspects are first of all related to research, which is especially complex in psychiatric patients. Furthermore, the ethical aspects of DBS as a possible future standard therapy are to be dealt with early enough. Last but not least, there are overarching philosophical questions concerning the underlying general concepts of health and disease, quality of life, our understanding of what is "personality" [28], and a flourishing individual life. These aspects may be threatened by new techniques like DBS and have to be reconsidered because of new insights into their neural foundations. This already points to the necessity of an interdisciplinary approach to evaluate the benefits and risks, and more generally the implications of DBS in psychiatric patients. Here, we focus on some ethical aspects with regard to research for therapeutic purposes including individual treatment attempts outside of controlled clinical trials.

DBS for psychiatric patients is not a standard therapeutic method. Therefore, every application of DBS in a psychiatric patient somehow enters into the experimental domain and has to be justified by a thorough in depth-analysis of possible benefits, risks, and burdens. The protection of the vulnerable patient by respecting fundamental ethical principles, like dignity, autonomy, and beneficence requires some criteria and procedural rules to safeguard them, but they shall not exclude the patient from therapeutic progress and participation in research. Miller and Fins [17] framed this conception on a more general level: "… research ethics inescapably involves balancing the competing moral objectives of promoting valuable science and protecting subjects… ".

Some helpful recommendations were already put forward by the OCD–DBS collaborative group in 2002 as 12 minimum requirements for studies aimed at investigating the use of DBS to treat patients with psychiatric illnesses. Furthermore, the Tourette's Syndrome Association developed recommendations to guide the early use and potential clinical trials of DBS in tic disorders [18]. The first

recommendations include, e.g., the involvement of an ethics committee that will have ongoing oversight of the project, and a patient assessment committee. There have to be defined criteria for severity, chronicity, disability, and treatment-refractoriness. Only patients with decision-making capacity should be included, and there should be a psychiatric follow-up. The investigative team has to include specialists from functional neurosurgery and psychiatry in close collaboration, who must disclose conflicts of interest. The procedure should never be performed for political, law enforcement or social purposes, but only to improve the patients' lives [16, 21]. Mink et al. [18] focus on comprehensive pre- and postoperative assessments, on the use of the same terminology and methodology at different investigation centers, and on rigorous and well-defined study protocols.

Here, we consider some additional aspects that should be regarded as essential for every investigational treatment of psychiatric patients with DBS that could complement the recommendations already at hand. Table 1 lists our proposed requirements for the therapeutic research in the field of DBS in patients with mental disorders.

First of all, there have to be well-proven reasons for the choice of the implantation area and the stimulation parameters for the particular mental disorder—regardless of whether the intervention is a clinical study or an

Table 1 Requirements for therapeutic research in the field of deep brain stimulation in patients with mental disorders

Criterion	Pragmatical function	Ethical function
Hitherto proposed requirements [18, 21]		
Ethics committee/institutional review board	Approval of the protocol	Quality of research
	Ongoing oversight	Protection of the patient
Patient assessment committee	Evaluation of each patient as candidate for inclusion according to defined criteria	Quality of research Protection of the patient
	Monitoring the adequacy of the consent process	Autonomy
Defined criteria for severity, chronicity, disability, treatment-refractoriness	Definition of inclusion criteria	Quality of research
Patient has decision-making capacity	Informed consent by the patient himself	Autonomy
Clinical research center	Conducting and supervising patient selection, surgical treatment, device programming, follow-up	Quality of research
Collaboration between functional neurosurgical team and team of psychiatrists	Guarantee of extensive experience in DBS and the psychiatric condition under investigation	Quality of research
Disclosure of potential conflicts of interest by the investigators	Transparency with regard to possible misuse	Protection of the patient
Purpose to improve patients' lives; no political, law enforcement or social purposes	Prevention of misuse	Protection of the patient
Standardized nomenclature, assessment protocols, outcome instruments	Comparability of research results	Quality of research
Additionally proposed requirements		
Scientific preclarification	Definition of target area and stimulation parameters	Quality of research Protection of the patient
Multidisciplinary long-term follow-up (study/case-advisory panel)	Comprehensive evaluation with inclusion of psychosocial, ethical and legal expertise	Quality of research Protection of the patient and his family
Disease selection	Thoughtful progress	Quality of research Protection of the patient
Patient selection according to the impact on patient's life	Focusing individual quality of life	Quality of research Protection of the patient Autonomy
Inclusion of a near-by person	Caring and monitoring	Quality of research Protection of the patient and his family

individual treatment attempt. All previously gained scientific results and experiences, e.g., from neuroimaging and repetitive transcranial magnetic stimulation, have to be taken into account to develop an elaborated hypothesis for the intended device location and the mechanism of effect [24]. There has to be as much preliminary clarification as necessary of these factors as a proper scientific foundation for the surgical intervention and the whole study design (criterion of scientific preclarification). But we have to accept that unlike movement disorders most of the psychiatric disorders do not have good translational animal models for this purpose. Nevertheless, a potential effect of DBS for selective mental disorders, e.g., addiction, was underscored by the application of DBS in some translational animal models [6, 30].

Having in mind the unforeseeable emotional, cognitive, and behavioral consequences of DBS when interfering in neuronal networks that are not yet completely understood, and regarding the psychosocial effects that are known from patients with Parkinson's disease [26], there should be a multidisciplinary long-term follow-up in every study or treatment attempt. This should include ethical, legal, and psychosocial competence which could be brought together with the neurosurgical, neuropsychological, and psychiatric specialists in study- or case-advisory panels from the beginning.

Let us postulate that there are well-developed scientific hypotheses for DBS, for the area to be stimulated, and the stimulation parameter in several psychiatric disorders, respectively. Then it may be argued that there are reasons to prefer some diseases over others in doing research. This refers to the criterion of disease selection. Regarding the complexity of the intervention, the disease to be preferred in research should be severe. There should be no alternatives to heal it in another and less intrusive way. Furthermore, there should be little hope for spontaneous healing; otherwise, there is the possibility of false positive effects. And last but not least, the disorder should be preferred which interferes with the patient's ability to consent as little as possible. This aspect is obviously in conflict with the first requirement for a severe psychiatric disorder. The more severe a disorder, the more probable it is that the patient cannot provide informed consent. Firstly, the patient may not properly understand the nature, risks, and the implications of DBS. Secondly, the patient may tend to consent to almost everything regardless of possible risks because of the back-breaking suffering the patient wants to overcome. But the argument about informed consent can entail unjust consequences. If it is strongly applied, patients with an impairment of providing consent would never have a chance to participate in research for therapeutic purposes. If there was sufficient evidence for possible benefits in patients with persistent vegetative state [32] or severe dementia, for example, it would be ethically dubious to exclude them categorically from therapeutic research. Additional or substitutional consent by a representative according to the alleged interest of the patient is a feasible approach here, but further discussions are necessary on this topic.

Once there are good reasons for choosing a specific disorder for research, there have to be appropriate criteria for patient selection among all those who suffer from this disease. Usually, therapy-resistance to all available standard therapies (e.g., psychopharmacotherapy, behavioral or cognitive therapy, electroconvulsive therapy) is seen as the ethically indispensible inclusion criterion [1]. There is a deep intuition that an invasive procedure such as DBS should only be tested when nothing else can be beneficial any more. DBS is then an ultima-ratio therapy. But this widespread conviction is not as evident and intangible as it seems to be at the first sight. It is conceivable that DBS works in earlier stages, might even be neuroprotective, but fails in later stages of the disease [3]. The criterion of therapy-refractoriness excludes the possibility to study if patients can benefit from DBS in earlier stages of mental disorders, so that progression of the disease may be delayed (as is conceivable for dementia) or even stopped, time consuming psychotherapies might be avoided, and social as well as occupational consequences could be diminished. The ethically decisive criterion for the severity of a disorder is its impact on the life of the patient in all dimensions, whereas the severity of symptoms is only a subsidiary indicator-criterion. If there are sufficient reasons pointing to a possible benefit for DBS in earlier stages of the disease and the patient can give informed consent, there is no paramount reason to exclude these patients categorically from research for possible medical progress. It even may be seen as a matter of justice.

Another aspect for patient selection is the psychosocial situation. A patient with a severe psychiatric disorder usually is unemployed. The more important it becomes to know which daily-life activities the patient prefers and is still able to carry out. Are there family and friends? Is there a nearby person who knows the patient very well and who attends to the patient regularly? The latter can be seen as a crucial point. Such a person can care for the patient and monitor the patient [22]. If this person is well informed—and this should be a prerequisite anyway—this person can detect peculiar clinical signs as hints for unwanted side effects or for the necessity to adapt the stimulation parameters. Preliminary experiences from our own research project concerning ethical, legal, and social aspects of DBS in neurological and psychiatric patients (ELSA-DBS) funded by the German Federal Ministry of Education and Research support this claim.

Conclusion

Even when the FDA approved DBS for OCD patients under the HDE program, DBS is still an investigational therapeutic approach in severe mental disorders. Nevertheless, it has to be assumed that the indications for DBS and frequency of its therapeutic application in psychiatry will increase substantially. Therefore, it is important to learn ethical lessons from the historical experiences with psychosurgery, and to implement transparent and well-defined regulations for the protection of the patients as well as appropriate support for therapeutic research. In addition to some pilot recommendations [18, 21], the following aspects should be imperative: a solid scientifically founded hypothesis for the efficacy of DBS based on strong experimental support for choosing therapeutic target regions should be an indispensible starting point for every treatment attempt. Furthermore, the methodological design of any clinical study using DBS should fulfill ambitious scientific and ethical standards. Patients must be closely monitored in the long-term in multidisciplinary collaboration. A person close to the patient should be integrated in the follow-up. For the time being, those mental disorders should be investigated first which are severe, chronic, and without promising therapeutical alternatives. These criteria might interfere with the ethically important claim for informed consent by the patient, but such consent should be strived for vigorously and complemented by an additional or substitutional consent by a person close to the patient or a caregiver. Patients for DBS studies thus have to be carefully selected. As long as there is no evidence for neuroprotective effects or greater efficacy of DBS in early stages of mental disorders, it should be restricted to therapy-resistance of the later stages.

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