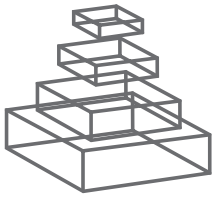
frontiers
RESEARCH TOPICS

THE DEVELOPMENT OF DEEP BRAIN STIMULATION FOR NEUROLOGICAL AND PSYCHIATRIC DISORDERS: CLINICAL, SOCIETAL AND ETHICAL ISSUES

Hosted by
Thomas E. Schlaepfer and Chiara Saviane

frontiers in
INTEGRATIVE NEUROSCIENCE



frontiers

Cover image provided by Ibbl sarl, Lausanne CH

ISSN 1664-8714
ISBN 978-2-88919-040-9
DOI 10.3389/978-2-88919-040-9

ABOUT FRONTIERS

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

FRONTIERS JOURNAL SERIES

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing.
All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

DEDICATION TO QUALITY

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.
By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

WHAT ARE FRONTIERS RESEARCH TOPICS?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area!
Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

THE DEVELOPMENT OF DEEP BRAIN STIMULATION FOR NEUROLOGICAL AND PSYCHIATRIC DISORDERS: CLINICAL, SOCIETAL AND ETHICAL ISSUES

Hosted By
Thomas E. Schlaepfer, University Hospital of Bonn, Germany
Chiara Saviane, SISSA, Italy

To date more than eighty thousand patients worldwide have received deep brain stimulation (DBS), mainly in order to alleviate symptoms of treatment-resistant disorders such as tremor associated with Parkinson's disease, essential tremor, chronic pain, epilepsy, obsessive compulsive disorder, major depression and Tourette syndrome. The number of indications for neurological and psychiatric conditions using this technology is rapidly increasing, raising important societal and ethical issues that cannot be dealt with by scientists and clinicians on their own, but need discussions among all possible stakeholders on questions such as: what are the comprehensive risks and benefits of this technology? what is the real impact on patients' life, in terms of health, quality of life and personal identity?

This Research Topic provides an overview of potentials and limitations of deep brain stimulation as used to treat neurological and psychiatric conditions, bringing together Mini Reviews, Perspectives and Opinion papers from key stakeholders interested in the development and social impact of this technology. It is also a continuation of the debate that started among scientists, clinicians, patients, sociologists, journalists, philosophers and other experts during the "brains in dialogue on deep brain stimulation" workshop that was organized in September 2010 in Warsaw, Poland, by the FP7 project bid – brains in dialogue (www.neuromedia.eu) coordinated by the Interdisciplinary Laboratory of SISSA (Trieste, Italy).

Table of Contents

frontiers in
INTEGRATIVE NEUROSCIENCE

MINI REVIEW ARTICLE
published: 18 August 2011
doi: 10.3389/fnint.2011.00042

Origin and evolution of deep brain stimulation

Vittorio A. Sironi*

Research Institute on the History of Biomedical Thought, University of Milano Bicocca, Milan, Italy

Edited by:
Thomas E. Schlaepfer, University Hospital of Bonn, Germany

Reviewed by:
Edward Shorter, University of Toronto, Canada
Patric Blomstedt, University Hospital of Umeå, Sweden

***Correspondence:**
Vittorio A. Sironi, Facoltà di Medicina e Chirurgia, Centro Studi sulla Storia del Pensiero Biomedico, Università di Milano Bicocca, Villa Serena, Via Pergolesi 33, 20900 Monza, MB, Italia.
e-mail: vittorio.sironi@unimib.it

This paper briefly describes how the electrical stimulation, used since antiquity to modulate the nervous system, has been a fundamental tool of neurophysiologic investigation in the second half of the eighteenth century and was subsequently used by the early twentieth century, even for therapeutic purposes. In mid-twentieth century the advent of stereotactic procedures has allowed the drift from lesional to stimulating technique of deep nuclei of the brain for therapeutic purposes. In this way, deep brain stimulation (DBS) was born, that, over the last two decades, has led to positive results for the treatment of medically refractory Parkinson's disease, essential tremor, and dystonia. In recent years, the indications for therapeutic use of DBS have been extended to epilepsy, Tourette's syndrome, psychiatric diseases (depression, obsessive–compulsive disorder), some kinds of headache, eating disorders, and the minimally conscious state. The potentials of the DBS for therapeutic use are fascinating, but there are still many unresolved technical and ethical problems, concerning the identification of the targets for each disease, the selection of the patients and the evaluation of the results.

Keywords: deep brain stimulation, history, cerebral localization, neuronal devices, bioethics, stereotactic neurosurgery

INTRODUCTION

Since ancient times, electrical stimulation has been used to modulate the nervous system and to treat some neurological disorders (Rossi, 2003). Scribonius Largo, physician of the Roman emperor Claudius, in his text "Compositiones medicamentorum" (46 AD) suggested the application of electric ray (*Torpedo torpedo* and *Torpedo nobiliana*) on the cranial surface as a remedy for the headache. These fishes are known for being capable of producing an electric discharge and their scientific name comes from the Latin "torpere," to be stiffened or paralyzed (but also to be numb, insensitive), referring to the effect on someone who handles them (Debru, 2006). Electric fishes were later used for the treatment of seizures, depression, and pain until the eighteenth century (Kellaway, 1946; Schwalb and Hamani, 2008).

In the early ninetieth century Giovanni Aldini (1762–1834), nephew of the discoverer of animal electricity Luigi Galvani (1727–1798) and professor of Physics at the University of Bologna, performed electrical stimulations on the exposed human cerebral cortex of recently decapitated prisoners. In 1804, Aldini reported that cortical stimulation evoked horrible facial grimaces. This finding led him to conclude that the cortical surface could be electrically stimulated; supporting that electricity could have therapeutic effects in the treatment of many neuropsychiatric disorders (Aldini, 1804; Boling et al., 2002; Parent, 2004). Aldini's experimentations and hypotheses led to direct research into two strands that would later developed during the ninetieth and twentieth century: on the one hand the use of brain stimulation for neurophysiologic investigation (initially on animals and then on humans) to understand the functioning of the brain, on the other hand the use of the techniques of brain stimulation for therapeutic purposes.

NEUROPHYSIOLOGIC BRAIN STIMULATION

Concerning neurophysiologic research, in 1809 Luigi Rolando (1773–1831) first used galvanic current to stimulate the cortical cortex of animals (Rolando, 1809), highlighting the functions of brain areas, while in 1870 Gustav Fritsch (1838–1927) and Eduard Hitzing (1838–1907) showed that electrical stimulation of specific cortical areas evoked muscle contractions in dogs (Fritsch and Hitzing, 1870). In 1872 David Ferrier (1843–1924) identified monkey's cerebral cortex points whose stimulation was related to specific movements of the animal (Ferrier, 1873; Gross, 2007). In 1874 the American physician Robert Bartholow (1831–1904) was the first to report findings from studies of electrical stimulation of the cerebral cortex in an awake human (Bartholow, 1874). In 1882 the Italian neuropsychiatrist Ezio Sciamanna (1850–1905) performed a series of systematic experiments of electrical stimulation on a trepanned patient who had a traumatic brain injury (Sciamanna, 1882; Zago et al., 2008). In 1883 the Italo-Argentine surgeon Alberto Alberti (1856–1913) conducted an experiment lasting more than 8 months of cerebral stimulation in a woman in whom an eroding tumor of the skull allowed easy access to the dura mater surface, like in Bartholow's case (Alberti, 1886). Unfortunately, the contribution of these researches in determining the motor topography of the human brain nonetheless remained poorly exploited except to confirm the electrical excitability of the cortex and demonstrate the contralateral cortical hemispheric representation of motor functions (Zago et al., 2008).

More precise and systematic observations on the topography of the brain had been made in 1887 by the British surgeon Victor Horsley (1857–1916) (Vilensky and Gilman, 2002), but we should wait for until 1950 – when fundamental studies of the neurosurgeon Wilder Penfield (1891–1976) were published – before the

brain stimulation of the human cortex could give a real accurate representation of the human brain functions, including motor and somatosensory areas (cortical homunculus; Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950).

THERAPEUTIC BRAIN STIMULATION

Electroshock, introduced by Ugo Cerletti (1877–1963) in 1938 was the first modern example of therapeutic application of brain stimulation for the treatment of severe psychosis (Cerletti, 1940; Kalinowsky, 1986). The application of an electric current on the skull evoked an epileptic seizure that "roughly" remodeled the neural connections, providing a clinical improvement to the patients. Despite opposing opinions about this technique, this method had a more solid foundation rather than the dubious experiments of electrical brain stimulation for the treatment of schizophrenia and other mental illness conducted at Tulane University in the 1960s (Baumeister, 2000).

Brain stimulation for pain control, used as early as 1950 with good effects through temporary electrodes implanted into brain regions, after a first experimental phase, found its explanation in the "gate control theory" developed by Melzach and Wall in 1962 (Rezai and Lozano, 2002). These previous studies were the basis that led to the development of new techniques of neurostimulation: transcranial magnetic stimulation, cortical brain stimulation, and deep brain stimulation (DBS).

Transcranial magnetic stimulation produces a magnetic field to modulate the excitability of the brain cortex. Unlike electroshock, it can stimulate only a specific area (selectivity) through an eight-shaped magnet and it does not involve loss of memory and/or seizures. It is mainly used for the treatment of psychiatric diseases, as obsessive–compulsive disorder and depression, and recently in one case of minimally conscious state (Wassermann et al., 2008; Piccione et al., 2011).

Cortical brain stimulation involves the application of chronic low-frequency electrical pulses on the motor cortex through intra- or extra-dural implantation of one or more electrodes connected to a generator with a battery located in the chest. It is particularly used for the treatment of some forms of Parkinson's disease, epilepsy, and dyskinesia, but also for the pain control and in patients afflicted with stroke (Pagni et al., 2005; Harvey and Nudo, 2007).

Deep brain stimulation is a surgical procedure that allows implanting microelectrodes precisely in some brain areas through a combination of stereotactic and neuroimaging techniques. A subcutaneous external pacemaker lets these electrodes send electrical impulses to the brain.

Deep brain stimulation is an evolution of functional stereotactic neurosurgery techniques, initially used to produce selective lesions of specific deep brain structures (thalamic and cerebellar nuclei). Thus, a new balance of damaged neural circuits could be found, removing the tremor in patients suffered from medically refractory Parkinson's disease and motor disorders of dyskinesias.

In 1947 Ernst Spiegel and Henry Wycis, modifying the original apparatus of Clarke and Horsley (1906), produced the first human stereotactic frame that using pneumoencephalogram allowed to determine Cartesian coordinates of structures around ventricles (basal ganglia) for identifying the precise localization of the targets that had to be destroyed by radiofrequency (Spiegel et al., 1947; Zonenshyn and Rezai, 2005). Intra-operative electrical stimulation of these structures was systematically used for the exploration and the localization of the deep cerebral nuclei and for confirming target (Guiot et al., 1961; Gildenberg, 2005). These observations led to suggest that these stimulations of deep cerebral nuclei could be used not only as a method for diagnostic purposes but also as a therapeutic method itself. Thus, the evolution from lesional to stimulating functional neurosurgery was determined (Porta and Sironi, 2009).

DEEP BRAIN STIMULATION

The origins of this technique are linked to the discovery of the effects of electrical stimulation of the deep brain areas, conducted during the stereotactic lesional functional neurosurgery to identify the correct position of coagulant electrodes for the treatment of dyskinetic disorders and tremor in Parkinson's disease (Schwalb and Hamani, 2008). Thanks to the spread of stereotactic method, various studies demonstrated that, while "low-frequency stimulation" (5–10 Hz) could enhance tremor and other correlated symptoms, "high-frequency stimulation" (50–100 Hz) resulted in a reduction of symptoms (Albe Fessard et al., 1963; Blomstedt and Hariz, 2010). The pioneers of DBS were Delgado et al. (1952), Bekthereva et al. (1963), Sem-Jacobsen (1965), and Cooper (1978). Deep electrical stimulation of brain structures was originally introduced as a therapeutic option to treat behavioral disorders or chronic pain.

In 1952, the Spanish neuroscientist José M. Delgado, basing on his experience of deep neurophysiologic electrical stimulation in animals, first described the technique of implantation of intracranial electrodes in humans, indicating the importance of this method for diagnosis and its possible therapeutic role in patients with mental disorders (Delgado et al., 1952). Over the next two decades, he implanted radio-equipped electrode arrays that he called "stimoceivers," in cats, monkeys, chimpanzees, gibbons, bulls, and even humans, and he showed that he could control subjects' mind and bodies with the push of a button. His experiments on animals were often very "theatrical." For example, in 1963 he demonstrated the possibility to stop a bull from charging in response to a radio-signal of one electrode implanted in the brain of animal. However, the critics contended that the stimulation did not quell the bull's aggressive instinct, as Delgado suggested, but rather forced it to turn to the left (Horgan, 2005).

At that time, he implanted electrodes in 25 human subjects, most of them schizophrenics and epileptics. In 1969 he described his brain stimulation researches and discussed critical aspects and ethic implications in the book *Physical Control of the Mind: Toward a Psychocivilized Society*, where he showed the tremendous opportunities but also the great risks derived from neurotechnology (Delgado, 1969).

The first to use chronic depth stimulation as a therapy in motor disorders was Natalia Petrovna Bekthereva, neuroscientist at the Institute of Experimental Medicine and the Academy of Medical Sciences in Leningrad. In 1963 she published a work on the use of multiple electrodes implanted in sub-cortical structures

for the treatment of hyperkinetic disorders (Bekthereva et al., 1963). However, since her papers were written in Russian, her works were not well known around the world. In her "therapeutic electro-stimulation," as she named this method, she used "electric stimulation with high-rate pulses of suprathreshold current," achieving excellent results (Bekthereva et al., 1975).

The Norwegian neurophysiologist and psychiatrist Carl Wilhelm Sem-Jacobsen initially used depth electrodes implanted for recording and stimulation in patients with epilepsy and psychiatric disorders. He successfully implanted multiple electrodes in the thalamus to stimulate the targets in order to identify the best lesional site in Parkinson's disease. These electrodes were often left into the patient's brain for several months, without any side effects. As he wrote: "these electrodes could then be used, following stimulation responses, to make incremental staged lesions in the target area" (Sem-Jacobsen, 1965, 1966; Blomstedt and Hariz, 2010).

By the early 1970s, there were some reports of chronic DBS system implanted in the thalamus for the treatment of chronic pain (Hosobuchi et al., 1973; Mazars et al., 1974), and isolated experiences in the patients with persistent vegetative state (Hasserl et al., 1969; Sturm et al., 1979).

The experience of the American neurosurgeon Irving S. Cooper in placing electrodes over the cerebellum and into the deep thalamic nuclei for central palsy, spasticity and epilepsy was more extensive and continuous. In 1977 he reported its excellent results from chronic cerebellar stimulation in over 200 patients (Cooper, 1978).

The lack of correlation of opinion of efficacy between the patients and clinicians led Cooper and other scientists to perform double-blind studies on cerebellar stimulation for spasticity. The results of these studies did not try to show a real efficacy of this procedure (Schwalb and Hamani, 2008).

After the introduction of L-dopa in the late 1960s, there was a sharp decline of the surgical treatment of Parkinson's diseases and the ablative procedures continued, only targeting ventral intermediate nucleus (Vim) and globus pallidus. DBS progressed as a technique through its use in psychiatric and pain control surgery.

Despite the sharp decline of surgery for Parkinson's disease given the use of L-dopa, many groups continued to perform thalamotomy for tremor of various etiologies (Schwalb and Lozano, 2004). The positive effect of thalamic stimulation on tremor was well known (due to the diagnostic neurostimulation maneuver done prior to coagulation to be sure of being in the right target), but the idea to use chronic stimulation as a therapeutic method did not emerge until Benabid's preliminary report in 1987 on stimulation of the Vim nucleus (Benabid et al., 1987).

PRESENT AND FUTURE OF DEEP BRAIN STIMULATION

In 1991, both Benabid and Blond and Sigfried groups reported their results on thalamic DBSs for tremor (Benabid et al., 1991; Blond and Siegfrid, 1991). Subsequent studies found that the DBS of thalamus was safer than thalamotomy and especially bilateral thalamotomy. Likewise, the stimulation of globus pallidus was demonstrated safer than pallidotomy, originally proposed by Laitinen for medically refractory Parkinson's disease in the early 1990s (Laitinen et al., 1992). The major safety of the DBS of these areas led a gradual abandonment of lesional techniques. In 1994 Pollak's group began to stimulate a new target, involved in Parkinson's disease: the sub-thalamic nucleus of Luys (STN; Pollak et al., 1993). In particular, the DBS of this area has been found to be effective for bradykinesia, tremor, and rigidity. Moreover, the stimulation of SNT and globus pallidus was explored for the treatment of both generalized and segmental dystonia (Yu and Neimat, 2008).

In addition to movement disorders, DBS was also mostly used and explored for treatment of chronic pain, subsequently approved by US Food and Drug Administration in 1989.

Concerning the future of DBS for movement disorders, although multiple studies demonstrated its efficacy, many questions still require answers. In deed, as above reported, DBS has been showed to be effective in patients with medically refractory Parkinson's disease in both motor function and quality of life, but it is unclear what the effect of these techniques are on non-motor aspects of this pathology. Furthermore, we should exactly know when a patient could be considered as drug unresponsive and whether a early DBS could slow the progression of the disease. Concerning dystonia, a rigorous trial was conducted on the efficacy of DBS of globus pallidus for primary dystonia, but the report of DBS for secondary dystonia consists of small case series. On contrary, the efficacy of stimulation of SNT is still clearly defined for this disorder (Holloway et al., 2006; Benabid, 2007; Schwalb and Hamani, 2008).

BDS in the treatment of refractory epilepsy has gotten the attention from epileptologists due to its well-documented success in treating movement disorders. Early results of the SANTE trial should lay the foundation for widespread implementation of DBS for epilepsy targeting the anterior thalamic nucleus. Other hopeful target seems to be the caudate nucleus, the sub-thalamic nucleus, the cerebellum, the centro-median nucleus of the thalamus, and the hippocampus, even if the results are non-conclusive (Halpner et al., 2008; Lega et al., 2010).

Recently, the indication of the use of DBS has been extended to new diseases, so new interesting perspectives for future therapies seem to be opened. Bilateral thalamic stimulation has been used for the treatment of refractory Tourette syndrome, a complex pathology characterized by multiple motor tics and one or more phonic/vocal tics lasting longer than 1 year. The first results are positives with improved clinical features (Porta et al., 2010). DBS has been also indicated for the treatment of serious psychiatric disorders, such as refractory depression and obsessive–compulsive disorder. In addition to psychiatric diseases, DBS has also been suggested as a potential therapy for obesity, eating disorders, and drug resistant hypertension (Mayberg et al., 2005; Lipsman et al., 2007).

Although DBS for pain has been largely abandoned, the group of Milan has explored DBS of the posterior hypothalamus for cluster headache (Franzini et al., 2003; Leone et al., 2005). Moreover, a recent study has re-explored DBS for the minimally consciousness state after severe traumatic brain injury (Schiff et al., 2007).

CONCLUSION

Since the introduction of DBS, almost 20 years ago, there has been an immense resurgence of interest in the neurosurgical technique for the treatment of more neurological and psychiatric disorders. The reversible nature of stimulation technique is an

attractive feature and clinical conditions that were not believed to be surgically tractable are now being considered suitable for DBS therapy.

The success of DBS in the treatment of refractory Parkinson disease is evident, while for the other motor disorders (primary tremor, dyskinesias, medically refractory Tourette's syndrome) good results are waited. The major psychiatric diseases (refractory depression, obsessive–compulsive disorder), cluster headache, epilepsy, eating disorders (obesity), and drug resistant hypertension are the new field where the DBS seems to have interesting therapeutic possibilities.

The potentials of this neurotechnique are fascinating, but many questions still remain unanswered. Several technical and ethical problems have to be still solved. What are the optimal targets for each disease? What other neurological and psychic disorders can DBS be applied to? What should be the criteria for selecting candidates? Only when they are or are considered as? For some diseases should DBS be used regardless of pharmacological therapy? Could an early use of DBS change the natural history of some kinds of disease? In addition, an objective and statistically valid assessment of long-term results and of possible technique-related complications is still central.

Ethical problems are not less important than clinical ones. In the selection of patients, it is fundamental to the involvement of family members, in addition to their direct involvement with the informed consent. The procedure must be supported by interdisciplinary teams of neurosurgeons, neuroscientists, psychiatrist, psychologist, and other health professionals who can help assess patients' suitability for DBS and continuously monitoring them over time.

The DBS is not a modern form of psychosurgery and for this reason – technical and ethical – mistakes, that historically characterized this terrible chapter of history of neuroscience, should be avoided (Kringelbach and Aziz, 2010). While psychosurgery was a lesional unselective and irreversible manipulation of a brain area (e.g., the lobotomy proposed by Egas Moniz since 1935 and its subsequent variants), the primary goal of DBS is to rebalance the damaged neuronal circuits through a electrical selective and reversible manipulation (stimulation) of targeted brain structures, whose alteration may determine, along with neurological deficits, also behavioral problems (e.g., Tourette's syndrome). Concerning the "psychiatric" indications (refractory depression and obsessive–compulsive disorder), the evidences of organic alterations underlying these events provide an adequate explanation for the fact that the rebalancing of specific neurophysiologic substrates through the DBS can improve these behavioral disorders, harmonizing the physical and psychological expressions of these subjects.

REFERENCES

Albe Fessard, D., Arfel, G., Guiot, G., Derome, P., Dela, H., Korn, H., Hertzog, E., Vourch, G., and Aleonard, P. (1963). Characteristic electric activities of some cerebral structures in man. *Ann. Chir.* 17, 1185–1214.

Alberti, A. (1886). *Contribucion al studio de las localisationes cerebrales y a la patogénesis de la epilepsia*. Buenos Aires: Biedma.

Aldini, J. (1804). *Essai théorique et expérimental sur le galvanisme, avec une série d'expériences faites devant des commissaires de l'Institut nationale de France, et en divers amphithéâtres anatomiques de Londres*. Paris: Fournier Fils.

Bartholow, R. (1874). Experimental investigations into the functions of the human brain. *Am. J. Med. Sci.* 134, 305–313.

Baumeister, A. A. (2000). The Tulane electrical brain stimulation program. A historical case study in medical ethics. *J. Hist. Neurosci.* 9, 262–278.

Bekthereva, N. P., Bondarchuck, A. N., Smirnov, V. M., Meliutcheva, L. A., and Shandurina, A. N. (1975). Method of electrostimulation of the deep brain structures in treatment of some chronic diseases. *Confin. Neurol.* 37, 136–140.

Bekthereva, N. P., Grachev, K. V., Orlova, A. N., and Iatsuk, S. L. (1963). Utilisation of multiple electrodes implanted in the subcortical structure of the human brain for the treatment of hyperkinesis. *Zh. Nevropatol. Psikhiatr. Im. S S Korsakova* 63, 3–8.

Benabid, A. L. (2007). What the future holds for deep brain stimulation. *Expert Rev. Med. Devices* 6, 895–903.

Benabid, A. L., Pollak, P., Gervason, C., Hoffmann, D., Gao, D. M., Hommel, M., Perret, J. E., and de Rougemont, J. (1991). Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 337, 403–406.

Benabid, A. L., Pollak, P., Louveau, A., Henry, S., and de Rougemont, J. (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson's disease. *Appl. Neurophysiol.* 50, 344–346.

Blomstedt, P., and Hariz, M. I. (2010). Deep brain stimulation for movement disorders before DBS for movement disorders. *Parkinsonism Relat. Disord.* 16, 429-433

Blond, S., and Siegfrid, J. (1991). Thalamic stimulation for the treatment of tremor and other movement disorders. *Acta Neurochir. Suppl.* 52, 109–111.

Boling, W., Olivier, A., and Fabinyi, G. (2002). Historical contributions to the modern understanding of function in the central area. *Neurosurgery* 50, 1296–1310.

Clarke, R. H., and Horsley, V. (1906). On a method of investigating the deep ganglia and tracts of the central nervous system (cerebellum). *Br. Med. J.* 2, 1799–1800.

Cerletti, U. (1940). L'elettroshock. *Riv. Sper. Freniatr. Med. Leg. Alien. Ment.* I, 209–310.

Cooper, I. S. (1978). *Cerebellar Stimulation in Man*. New York: Raven Press.

Debru, A. (2006). The power of torpedo fish as a pathological model to the understanding of nervous transmission in antiquity. *C. R. Seances Soc. Biol. Fil.* 329, 298–302.

Delgado, J. (1969). *Physical Control of the Mind. Toward a Psychocivilized Society*. New York: Harper and Row.

Delgado, J., Hamlin, H., and Chapman, W. (1952). Technique of intracranial electrode implacement for recording and stimulation and its possible therapeutic value in psychotic patients. *Confin. Neurol.* 12, 315–319.

Ferrier, D. (1873). Experimental researches in cerebral physiology and pathology. *West Riding Lunatic Asylum Med. Rep.* 3, 30–96.

Franzini, A., Ferroli, P., and Leone, M., and Broggi, G. (2003). Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. *Neurosurgery* 52, 1095–1099; discussion 1099–1101.

Fritsch, G. T., and Hitzing, E. (1870). Über die elektrische Erregbarkeit des Grosshirns. *Arch. Anat. Physiol.* 37, 300–302.

Gildenberg, P. L. (2005). Evolution of neuromodulation. *Stereotact. Funct. Neurosurg.* 83, 71–79.

Gross, C. G. (2007). The discovery of motor cortex and ist background. *J. Hist. Neurosci.* 16, 320–321.

Guiot, G., Hardy, J., and Alabe-Fessard, D. (1961). Delimitation precise des structures sous-corticales et indentification de noyuax thalamiques chez l'homme par l'electrophysiologie stereotaxique. *Neurochirurgia (Stuttg.)* 5, 1–18.

Halpner, C. H., Samadani, U., Litt, B., Jaggi, J. L., and Baltuch, G. H. (2008). Deep brain stimulation for epilepsy. *Neurotherapeutics* 5, 59–67.

Harvey, R. L., and Nudo, R. J. (2007). Cortical brain stimulation: a potential therapeutic agent for upper limb motor recovery following stroke. *Top. Stroke Rehabil.* 14, 54–67.

Hasserl, R., Dalle Ore, G. D., Bricolo, A., Dieckmann, G., and Dolce, G. (1969). EEG and clinical arousal induced by bilateral long-term stimulation of pallidal systems in traumatic vigil coma. *Electroencephalogr. Clin. Neurophysiol.* 27, 689–690.

Holloway, K. L., Baron, M. S., Brown, R., Cifu, D. X., Carne, W., and Ramakrishnan, V. (2006). Deep brain stimulation for dystonia: a meta-analysis. *Neuromodulation* 9, 253–261.

Horgan, J. (2005). The forgotten era of brain chips. *Sci. Am.* 293, 66–73.

Hosobuchi, Y., Adams, J. E., and Rutkin, B. (1973). Chronic thalamic stimulation for the control of facial anesthesia dolorosa. *Arch. Neurol.* 29, 158–161.

Kalinowsky, L. B. (1986). History of convulsive therapy. *Ann. N. Y. Acad. Sci.* 462, 1–4.

Kellaway, P. (1946). The part played by the electrical fish in the early history of bioelectricity and electrotherapy. *Bull. Hist. Med.* 20, 112–137.

Kringelbach, M. I., and Aziz, T. Z. (2010). Deep brain stimulation. Avoiding the errors of psychosurgery. *JAMA* 301, 1705–1707.

Laitinen, L. V., Bergenheim, A. T., and Hariz, M. I. (1992). Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J. Neurosurg.* 76, 53–61.

Lega, B. C., Halpern, C. H., Jaggi, J. J., and Baltuch, G. H. (2010). Deep brain stimulation in the treatment of refractory epilepsy: update on current data and future directions. *Neurobiol. Dis.* 38, 354–360.

Leone, M., Franzini, A., Felisati, G., Mea, E., Curone, M., Tullo, V., Broggi, G., and Bussone, G. (2005). Deep brain stimulation and cluster headache. *Neurol. Sci.* 26(Suppl. 2), s138–s139.

Lipsman, N., Neimat, J. S., and Lozano, A. M. (2007). Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery* 61, 1–11; discussion 11–13.

Mayberg, H. S., Lozano, A. M., Voom, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M., and Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–660.

Mazars, G., Merienne, L., and Cioloca, C. (1974). Traitement de certains types de doulers par des stimulateurs thalamiques implantes. *Neurochirurgie* 20, 117–124.

Pagni, C. A., Altibrandi, M. G., Bentivoglio, A., Caruso, G., Cioni, B., Fiorella, C., Insola, A., Lavano, A., Maina, R., Mazzone, P., Signorelli, C. D., Sturiale, C., Valzania, F., Zeme, S., and Zenga, F. (2005). Extradural motor cortex stimulation (EMCS) for Parkinson's disease. History and first results by the study group of the Italian neurosurgical society. *Acta Neurochir. Suppl.* 93B, 113–119.

Parent, A. (2004). Giovanni Aldini: from animal electricity to human brain stimulation. *Can. J. Neurol. Sci.* 31, 576–584.

Penfield, W., and Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studies by electrical stimulation. *Brain* 60, 389–443.

Penfield, W., and Rasmussen, T. (1950). *The Cerebral Cortex of Man. A Clinical Study of Localisation of Function.* New York: MacMillan.

Piccione, F., Cavinato, M., Manganotti, P., Formaggio, E., Storti, S. F., Battistin, L., Cagnin, A., Tonin, P., and Dam, M. (2011). Behavioral and neurophysiological effects of repetitive transcranial magnetic stimulation on the minimally conscious state: a case study. *Neurorehabil. Neural Repair* 25, 98–102.

Pollak, P., Benabid, A. L., Gross, C., Gao, D. M., Laurent, A., Benazzouz, A., Hoffmann, D., Gentil, M., and Perret, J. (1993). Effets de la stimulation du noyau sousthalamique dans la maladie de Parkinson. *Rev. Neurol.* 149, 175–176.

Porta, M., Brambilla, A., Capanna, A. E., Servello, D., Sassi, M., Rickards, H., and Robertson, M. M. (2010). Thalamic deep brain stimulation for treatment-refractory tourette syndrome. Two-year outcome. *Neurology* 73, 1375–1380.

Porta, M., and Sironi, V. A. (2009). *Il cervello irriverente. Storia della malattia dei mille tic.* Roma-Bari: Laterza, 136–143.

Rezai, A. R., and Lozano, A. M. (2002). "Deep brain stimulation for chronic pain," in *Surgical Management of Pain*, ed. K. J. Burchiel (New York: Thieme), 565–576.

Rolando, L. (1809). *Saggio sopra la struttura del cervello dell'uomo e degli animali e sopra le funzioni del sistema nervoso.* Sassari: Stamperia Privilegiata.

Rossi, U. (2003). "The history of electrical stimulation of the nervous system for the control of pain," in *Electrical Stimulation and the Relief of Pain*, ed. B. A. Simpson (Amsterdam: Elsevier B.V.), 5–16.

Schiff, N. D., Giacino, J. T., Klamar, K., Victor, J. D., Baker, K., Gerber, M., Fritz, B., Eisenberg, B., Biondi, T., O'Connor, J., Kobylarz, E. J., Farris, S., Machado, A., McCagg, C., Plum, F., Fins, J. J., and Rezai, A. R. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 448, 600–6003.

Schwalb, J. M., and Hamani, C. (2008). The history and future of deep brain stimulation. *Neurotherapeutics* 5, 3–13.

Schwalb, J. M., and Lozano, A. M. (2004). Surgical management of tremor. *Neurosurger. Q.* 14, 60–68.

Sciamanna, E. (1882). Fenomeni prodotti dall'applicazione della corrente elettrica sulla dura madre e modificazione del polso cerebrale. Ricerche sperimentali sull'uomo. Atti della R. Accademia dei Lincei. Memorie della Classe di scienze Fisiche. *Matematiche e Naturali* 13, 25–42.

Sem-Jacobsen, C. W. (1965). Depth electrographic stimulation and treatment of patient with Parkinson's disease including neurosurgical technique. *Acta Neurol. Scand. Suppl.* 13, 365–377.

Sem-Jacobsen, C. W. (1966). Dept-electrographic observations relate to Parkinson's disease. Recording and electrical stimulation in the area around the third ventricle. *J. Neurosurg.* 24, 388–402.

Spiegel, E. A., Wycis, H. T., Marks, M., and Lee, A. S. (1947). Stereotactic apparatus for operation on the human brain. *Science* 106, 349–350.

Sturm, V., Kuhner, A., Schmitt, H. P., Assmus, H., and Stock, G. (1979), Chronic electrical stimulation of the thalamic unspecific activating system in a patient with coma due to midbrain and upper brain stem infarction. *Acta Neurochir.* 47, 235–244.

Vilensky, J. A., and Gilman, S. (2002). Horsley was the first to use electrical stimulation of the human cerebral cortex intraoperatively. *Surg. Neurol.* 58, 425–426.

Wassermann, E. M., Epstein, C. M., Ziemann, U., Walsh, V., Paus, T., and Lisanby, S. H. (2008). *Oxford Handbook of i Stimulation.* New York: Oxford University Press.

Yu, H., and Neimat, I. S. (2008). The treatment of movement disorders by neural deep brain stimulation. *Neurotherapeutics* 5, 26–36.

Zago, S., Ferrucci, R., Fregni, F., and Priori, A. (2008). Bartholow, Sciamanna, Alberti: pioneers in the electrical stimulation of the exposed human cerebral cortex. *Hist. Neurosci.* 5, 521–528.

Zonenshyn, M., and Rezai, A. (2005). "Stereotactic surgery," in *Principles of Neurosurgery*, eds S. S. Rengachary and R. G. Ellenbogen (Edinburg: Elsevier), 785–817.

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 26 January 2011; accepted: 02 August 2011; published online: 18 August 2011.

Citation: Sironi VA (2011) Origin and evolution of deep brain stimulation. Front. Integr. Neurosci. ***5****:42. doi: 10.3389/fnint.2011.00042*

frontiers in
INTEGRATIVE NEUROSCIENCE

MINI REVIEW ARTICLE
published: 25 January 2012
doi: 10.3389/fnint.2012.00002

Deep brain stimulation for movement disorders

Gilberto Pizzolato[1] and Tomasz Mandat[2,3]*

[1] Neurology Clinic, Department of Medical Sciences, University of Trieste, Trieste, Italy
[2] Department of Neurosurgery, Maria Sklodowska-Curie Memorial Oncology Center-Institute, Warszawa, Poland
[3] Department of Neurosurgery, Institute of Psychiatry and Neurology, Warszawa, Poland

Edited by:
Chiara Saviane, Scuola Internazionale Superiore di Studi Avanzati, Italy

Reviewed by:
Romulo Fuentes Flores, Edmond and Lily Safra International Institute of Neuroscience of Natal, Brazil
Carlo Colosimo, Sapienza University of Rome, Italy
Lars Wojtecki, University Duesseldorf, Germany

***Correspondence:**
Tomasz Mandat, Klinika Nowotworów Układu Nerwowego, Centrum Onkologii – Instytut, ul. Roentgena 5, 02-781 Warszawa, Poland.
e-mail: tomaszmandat@yahoo.com

Stereotactic technique and the introduction of deep brain stimulation (DBS) can be considered two milestones in the field of surgical neuromodulation. At present the role of DBS in the treatment of clinically and epidemiologically relevant movement disorders is widely accepted and DBS procedures are performed in many clinical centers worldwide. Here we review the current state of the art of DBS treatment for the most common movement disorders: Parkinson's disease, essential tremor, and dystonia. In this review, we give a brief description of the candidate patient selection criteria, the different anatomical targets for each of these condition, and the expected outcomes as well as possible side effects.

Keywords: DBS, movement disorders, Parkinson's disease, dystonia, essential tremor

INTRODUCTION

Movement disorders encompass a number of neurological diseases affecting the ability to control movement. Movement is in command of several interacting brain structures, including the motor cortex, the cerebellum, and the basal ganglia (BG). The BG comprises a group of interconnected deep brain nuclei [caudate and putamen (C–P), Globus pallidus (GP), substantia nigra (SN), subthalamic nucleus (STN)] that, through their connections with the thalamus and the cortex, primarily influence the involuntary components of the movement and muscle tone. Disruption of this complex circuitry within the BG causes the most frequent movement disorders, such as Parkinson's disease (PD), essential tremor (ET), and dystonia (Alexander et al., 1990). The treatment of these disorders with the deep brain stimulation (DBS) technique is the topic of the present review, which describes the current clinical use and approval of DBS indications.

Already in the 1950s, some early studies evaluated the possible therapeutic benefits of chronic stimulation of the subcortical structure in psychotic patients (Hariz et al., 2010). Nevertheless, modern DBS was first clinically used in the treatment of movement disorders. Several reviews provide a comprehensive account of the symptoms/syndromes that might be the target of this treatment, its clinical efficacy, as well as its possible complications and side effects (Skidmore et al., 2006; Wichmann and Delong, 2006; Collins et al., 2010). The DBS surgical treatment of movement disorders has its foundations in two seminal papers by the "Grenoble Group" of Benabid et al. (1987) describing the combined (thalamotomy and stimulation) stereotactic surgery of the ventral intermediate (VIM) nucleus of the thalamus and, in 1993, DBS of the STN for PD patients (Pollak et al., 1993). Modern DBS followed ablative stereotaxy that was performed for most of the twentieth century for medically refractory severe movement disorders, mostly PD and ET, with selective destruction of parts of the GP or of the thalamus (Schwalb and Hamani, 2008). Although the procedure was largely effective in relieving the symptoms, it was irreversible, and in some cases side effects were actually encountered. As a result, in the 1970s, following the advent of the highly effective levodopa treatment for PD, ablative surgery was largely abandoned. However, after the initial enthusiasm for the medical treatment of PD, it was apparent that long-term levodopa therapy had significant drug-induced complications (the so-called "long-term levodopa syndrome") mainly consisting in involuntary movements (dyskinesias) and motor fluctuations, which could have a severe disabling effect in a significant percentage of levodopa-treated PD patients. In addition, among the classic symptomatologic triad of PD – bradykinesia, rigidity, and resting tremor – this latter symptom is always less responsive to levodopa treatment (Fishman, 2008). Therefore, many clinical centers took advantage of the fact that DBS technology is less invasive than stereotactic surgery, and is also reversible and adjustable, more suitable for an increasing number of medically treated PD patients with disabling dyskinesias/motor fluctuations and/or medically refractory tremor (Collins et al., 2010).

The DBS technique uses continuous high-frequency stimulation of specific brain regions through chronically implanted electrodes, connected to a pulse generator, similar to a cardiac pacemaker, that is telemetrically programmable. Electrodes are implanted into the target brain area by using a stereotactic surgical procedure with electrophysiological recordings. Clinically, the effects of DBS mimic those produced by lesioning the target structure (Schwalb and Hamani, 2008). However – at the cellular or pathway level – the actions of high-frequency DBS that mediate its clinical efficacy are not fully understood. Indeed, recent evidence suggests that DBS has more complex mechanisms of action than

the pure functional inactivation of the target region. For instance, high-frequency stimulation of the most used target structures for DBS in PD and ET, i.e., the STN and the internal part of the GP (GPi), not only produces both inhibitory and excitatory effects on local neurons, but has also a modulatory influence on the afferent inputs to the target nucleus and on the efferent outputs (McIntyre et al., 2004). In any case, the ultimate effect of modulating the network activity within the BG can be viewed as the takeover on hyperactive elements or structures of the cortico-BG-thalamocortical complex circuit (Gradinaru et al., 2009; Kopell et al., 2009; McIntyre and Hahn, 2010).

PARKINSON'S DISEASE

Parkinson's disease is the second most common neurodegenerative disease. Its complex multifactorial etiology might comprise, from recent genetic and epidemiological studies, genetic susceptibility factors, and environmental risk factors. PD is a progressive disease with age-dependent increasing prevalence (from 1 to 3% in the population aged over 65 years; Wirdefeldt et al., 2011). Loss of SN pars compacta (SNc) dopaminergic neurons projecting to the C–P is considered the neuropathologic hallmark of PD. The consequent reduced dopaminergic input is considered the cause of the motor manifestations of the disease (bradykinesia, rigidity, resting tremor, and postural instability) and the reason for the remarkable clinical success of dopamine replacement therapy. However, it has become increasingly apparent that the neuropathological changes of PD (mostly alpha-synuclein pathology) extend far beyond the nigro-striatal system, affecting also the olfactory bulbs, and the autonomic nervous system, many structures of the lower brainstem, the limbic system, as well as the mesocortical and neocortical regions. Most of the extra-nigral pathological alterations are considered responsible of the non-motor symptoms of the disease, such as hyposmia, autonomic dysfunctions, sleep disorders, depression, and cognitive impairments (Braak et al., 2003).

Nevertheless, with regard to DBS treatment in PD, the main focus is on the progressive degeneration of the nigro-striatal dopaminergic projections and the appearance of disabling side effects, i.e., motor fluctuations and dyskinesias, in a large percentage of PD patients on long-term dopaminergic therapy (Schrag and Quinn, 2000). Because such complications are often poorly managed by oral therapy, it is estimated that more than 10% of PD patients could benefit from DBS treatment. The selection of candidate patients for DBS has strict inclusion/exclusion criteria. The best candidates are PD patients with severe motor symptoms in the off-medication condition that continues to indicate a substantial benefit from levodopa therapy, despite the disabling drug-induced motor complications. Main exclusion criteria are the presence of symptoms suggesting an atypical parkinsonian syndrome that usually does not respond to levodopa therapy, or the presence of neuropsychiatric (depression) or cognitive alterations (Bronstein et al., 2011).

There are four possible target sites for the placement of the stimulating electrodes: although stimulation of the VIM thalamic nucleus has a clear effect on tremor, DBS of the STN, or GPi has a broader influence on all parkinsonian symptoms and represents, nowadays, the treatment of choice in most PD patients. A more recent, still experimental, target is the pedunculopontine nucleus (PPN) that may be appropriate for patients with gait freezing (Stefani et al., 2007; Wilcox et al., 2011). Because most patients undergoing the DBS procedure have bilateral symptoms, both right and left STN or GPi are usually implanted for maximal benefit. Any parkinsonian symptom that can improve with levodopa can also improve with DBS. Three recent randomized controlled studies in patients with PD reported that STN DBS plus best medical therapy was more effective than best medical therapy alone in improving motor function and quality of life, but was also associated with an increased risk of serious adverse events (Deuschl et al., 2006; Weaver et al., 2009; Williams et al., 2010). After neurostimulation, the clinical response is more stable during the day, with significant lessening of the "off" periods that are so frequent and disabling in PD patients. Furthermore, DBS reduces levodopa-induced dyskinesias. In the case of STN DBS, this effect could be mostly ascribed to the reduction in medication dose, possible when the stimulation is active. GPi stimulation patients experience a reduction in dyskinesias without any levodopa dose reduction (Weaver et al., 2009; Follett et al., 2010). In addition, reduction of dopaminergic therapy after STN DBS may help in reducing some psychiatric symptoms, like visual hallucinations and impulse control abnormalities, which are frequent behavioral complications in the treatment with dopamine agonists (Lulé et al., 2012).

Complications related to surgery are primarily intracerebral hemorrhage (less than 2% in most centers) and infection (in about 4% of the cases; Kleiner-Fisman et al., 2006). STN DBS can worsen speech and gait in some patients, requiring an adjustment of stimulation parameters. A recent study reported that depression worsened with STN DBS but was improved with GPi DBS (Follett et al., 2010). There are several reports that describe neuropsychiatric symptoms following STN DBS in PD patients. However, such symptoms were generally transient and mild if managed appropriately (Volkmann et al., 2010). With these possible complications in mind, we can say that DBS offers important symptomatic benefits in cognitively intact PD patients with moderate disability who still maintain a therapeutic response to levodopa. Medium- and long-term studies have provided evidence that stimulation-induced motor improvement was still evident at 5–8 years' follow-up (Fasano et al., 2010; Moro et al., 2010). However, DBS does not modify the progression of the underlying PD pathology, so, after years, patients can still develop disabling levodopa-resistant symptoms, like gait disturbances and cognitive impairment.

ESSENTIAL TREMOR

Essential tremor is one of the most common movement disorders with prevalence that varies depending on age, raising up to 5% in the population over 60. The typical postural and action tremor is most often located in the upper limbs; less frequently it affects the head, the tongue, and the lower limbs. Even though the quality of life is impaired by tremor in more than 70% of patients, only 10% are medically treated. In addition, only 50% of treated patients show a good response to therapy (Lyons et al., 2003). In the middle of the twentieth century the ventrolateral thalamus became the main surgical target for parkinsonian and various other types of tremor, including ET. After the introduction, in the early 60s, of micro recording during stereotactic surgery, it became apparent

that small lesions of the VIM could suppress tremor. Afterward, unilateral stereotactic VIM lesioning was a frequent procedure in many clinical centers worldwide and resulted in a permanent significant contralateral improvement of the most common types of tremor. However, the very satisfactory results in controlling ET and other types of tremors (significant reduction of limb tremor in 80–90% of patients with ET) obtained thanks to the thalamotomy, were accompanied by a relatively high complication rate, especially if the procedure was performed bilaterally. In fact, almost 30% of patients who underwent the ablative procedure bilaterally experienced permanent speech and cognitive deficits. Introduction of DBS of the thalamic VIM nucleus in ET treatment helped to reduce complication rate with remaining high efficacy. Therefore, VIM DBS is viewed as the target therapy for these patients with a debilitating ET. Although the exact etiology and pathophysiology of ET is still unknown, it is believed that high-frequency stimulation of the VIM nucleus may block the abnormal oscillatory activity within the interconnected regions, including the cerebellum and the motor cortex (Dostrovsky and Lozano, 2002).

The main exclusion criteria of DBS treatment for ET include altered cognition and the presence of an untreated or disabling psychiatric illness. Patients with ET are considered good DBS candidate if they were also refractory to an adequate trial of accepted oral medications (Katz et al., 2011). The most frequent stimulation-induced side effects are paresthesias, followed by dysarthria and pain, symptoms that are reversible when the stimulation is turned off. Furthermore, gait/balance may worsen following DBS for medication refractory ET (Hwynn et al., 2011). The high initial efficacy of VIM DBS declines over time (Schuurman et al., 2008). However, most patients experience a good response for several years.

DYSTONIA

Dystonia is a movement disorder that presents with sustained, uncontrolled, often painful muscle contractions causing repetitive movements and abnormal postures. Depending on the localization, dystonia is divided into focal (affecting a single body region), segmental (two or more adjacent areas), or generalized (involving the legs, or one leg and the trunk, plus at least one other area of the body). Depending on etiology, dystonia might be primary (idiopathic) or secondary to a known structural lesion of the brain, like perinatal hypoxia, infections, stroke, and trauma. Idiopathic dystonia in adults is most commonly a focal/segmental disease, like cervical dystonia (the most common form), blepharospasm, or writer's cramp, whereas in children and young adults the generalized inherited forms are more common. There are multiple forms of inheritable dystonia, with the DYT-1 gene mutation, responsible for early-onset generalized dystonia, as the most frequent form (Albanese et al., 2011). Medical therapy is very effective in a very limited subset of dystonia patients (20–40%). In addition, doses of drug(s) required for therapy often produce intolerable side effects. Dystonia is still one of the most important indications for botulinum toxin (BT) therapy that selectively blocks the cholinergic innervation of the muscles. BT can be used to treat focal dystonias and also the most relevant target muscles in segmental and generalized dystonias. Combinations of BT therapy with all other treatment options, including DBS, are possible.

Patients with dystonia who might be evaluated for DBS treatment should have symptoms that cause significant disability, despite maximally tolerated medical treatment. The factors that influence the selection of patients with various types of dystonia for treatment with DBS have been recently reviewed by Bronte-Stewart et al. (2011). Patients candidate to surgery should undergo DBS treatment before the onset of orthopedic deformities that may impede functional benefit even if dystonia is ameliorated by DBS. The exact pathophysiological mechanisms of dystonia are not completely understood and the best brain target for DBS in dystonic patients has not been quite identified yet. However, a lot of evidence indicates that the interplay between the BG and cerebellar circuits has a major role. In particular, the GPi has been proven to show an abnormal firing activity in dystonia, and GPi is the usual target of DBS for such patients. On the other hand, previous studies on STN stimulation in dystonia gave contrasting results (Detante et al., 2004; Sun et al., 2007). In a 3-year follow-up study, the beneficial effects of bilateral GPi stimulation in young patients with identified DYT-1 mutation reached 90% (Coubes et al., 2000). Positive effects of DBS on dystonia scales, quality of life, and pain reduction have been confirmed in different studies also in adults with primary generalized dystonia and in heterogeneous groups comprising patients with secondary or focal disease (Vidailhet et al., 2005; Kupsch et al., 2006; Andrews et al., 2010). Dynamic movements are the first that respond to DBS, whereas improvement of persistent dystonic posture could be observed after months or years (Welter et al., 2010). Because improvement may take months to occur, the evaluation of the efficacy of DBS treatment is more challenging than in patients with PD or ET. Another difference with the DBS system in PD is that the optimal frequency and amplitude stimulation settings needed for DBS in many dystonia patients are higher than for GPi DBS in PD, and much higher than for STN DBS in PD patients.

PERSPECTIVES ON EVOLUTION OF DEEP BRAIN STIMULATION

Currently, the DBS technique uses electrodes of 1.3 mm in diameter integrating four contacts of 1.5 mm length each, connected to an internal pulse generator. Minimizing the hardware dimensions remains one of the goals of DBS development, to allow the implantation of the internal pulse generator in the scalp or within the skull. Minimizing the size of the hardware would also allow implanting multiple electrodes to multiple anatomical targets of the brain more precisely and effectively. Further development of DBS will probably depend on the use of multiple electrodes with "closed-loop" systems that include macro recordings and stimulation. The influence of local monitoring of neurotransmitter activity might impact on the patterns of stimulation, particularly with regard to the interactions between stimulation and medications. Moreover, since the introduction of the DBS technique the lifespan of the battery has increased twice, but programming the stimulation today is performed via telemetry that requires several time consuming visits before the best therapeutic effect can be reached. In the future, development of "closed-loop" DBS systems and neuroimaging modalities might allow the performance of effective and safe programming through remote access, such as the telephone or the Net (Andrews, 2010; Shah et al., 2010).

The role of DBS for PD, ET, and dystonia is a well-established treatment option, currently approved for use in the United States (DBS for drug refractory primary dystonia received in 2003 the FDA approval as humanitarian use device – HUD), Canada, Europe, and Australia. As the indications for DBS broaden to include other neurological and psychiatric conditions, the number of DBS implants worldwide is expected to grow in the next years. In 2009, treatment with DBS of obsessive compulsive disorder (OCD) was approved by FDA as HUD and received the CE mark approval. In 2010, the CE mark for DBS treatment of Epilepsy refractory to medical treatment was also granted. On-going clinical trials with DBS in the treatment of mood disorders, tremor in multiple sclerosis, pain and cluster headache, hypertension, minimally conscious state, obesity, memory impairment, aggressiveness, drug addiction, and other CNS disorders will increase the number of indications for DBS in the future (Lyons, 2011). However, the fact that FDA allowed DBS to be used in dystonia or OCD under an humanitarian device exemption (HDE) application, thereby without the need for a randomized clinical trial of sufficient size to demonstrate statistically significant benefit without undue harm, has spurred impassioned debate on the regulatory and ethical issues linked to the clinical use of DBS (Fins et al., 2011). These issues likely will become even more urgent as the number of indications for DBS treatment will increase.

REFERENCES

Albanese, A., Asmus, F., Bhatia, K. P., Elia, A. E., Elibol, B., Filippini, G., Gasser, T., Krauss, J. K., Nardocci, N., Newton, A., and Valls-Solé, J. (2011). EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur. J. Neurol.* 18, 5–18.

Alexander, G. E., Crutcher, M. D., and DeLong, M. R. (1990). Basal ganglia–thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog. Brain Res.* 85, 119–146.

Andrews, C., Aviles-Olmos, I., Hariz, M., and Foltynie, T. (2010). Which patients with dystonia benefit from deep brain stimulation? A metaregression of individual patient outcomes. *J. Neurol. Neurosurg. Psychiatr.* 81, 1383–1389.

Andrews, R. J. (2010). Neuromodulation advances in the next decade. *Ann. N. Y. Acad. Sci.* 1199, 212–220.

Benabid, A. L., Pollak, P., Louveau, A., Henry, S., and de Rougemont, J. (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl. Neurophysiol.* 50, 344–346.

Braak, H., Del Tredici, K., Rub, U., de Vos, R. A., Jansen Steur, E. N., and Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* 24, 197–211.

Bronstein, J. M., Tagliati, M., Alterman, R. L., Lozano, A. M., Volkmann, J., Stefani, A., Horak, F. B., Okun, M. S., Foote, K. D., Krack, P., Pahwa, R., Henderson, J. M., Hariz, M. I., Bakay, R. A., Rezai, A., Marks, W. J. Jr., Moro, E., Vitek, J. L., Weaver, F. M., Gross, R. E., and DeLong, M. R. (2011). Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch. Neurol.* 68, 165–171.

Bronte-Stewart, H., Taira, T., Valldeoriola, F., Merello, M., Marks, W. J. Jr., Albanese, A., Bressman, S., and Moro, E. (2011). Inclusion and exclusion criteria for DBS in dystonia. *Mov. Disord.* 26(Suppl. 1), S5–S16.

Collins, K. L., Lehmann, E., and Patil, P. G. (2010). Deep brain stimulation for movement disorders. *Neurobiol. Dis.* 38, 338–345.

Coubes, P., Roubertie, A., Vayssiere, N., Hemm, S., and Echenne, B. (2000). Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. *Lancet* 355, 2220–2221.

Detante, O., Vercueil, L., Krack, P., Chabardes, S., Benabid, A. L., and Pollak, P. (2004). Off-period dystonia in Parkinson's disease but not generalized dystonia is improved by high-frequency stimulation of the subthalamic nucleus. *Adv. Neurol.* 94, 309–314.

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., Daniels, C., Deutschländer, A., Dillmann, U., Eisner, W., Gruber, D., Hamel, W., Herzog, J., Hilker, R., Klebe, S., Kloss, M., Koy, J., Krause, M., Kupsch, A., Lorenz, D., Lorenzl, S., Mehdorn, H. M., Moringlane, J. R., Oertel, W., Pinsker, M. O., Reichmann, H., Reuss, A., Schneider, G. H., Schnitzler, A., Steude, U., Sturm, V., Timmermann, L., Tronnier, V., Trottenberg, T., Wojtecki, L., Wolf, E., Poewe, W., Voges, J., and German Parkinson Study Group. (2006). Neurostimulation section. A randomized trial of deep-brain stimulation for Parkinson's disease. *N. Engl. J. Med.* 31, 896–908.

Dostrovsky, J. O., and Lozano, A. M. (2002). Mechanisms of deep brain stimulation. *Mov. Disord.* 17(Suppl. 3), S63–S68.

Fasano, A., Romito, L. M., Daniele, A., Piano, C., Zinno, M., Bentivoglio, A. R., and Albanese, A. (2010). Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 133, 2664–2676.

Fins, J. J., Mayberg, H. S., Nuttin, B., Kubu, C. S., Galert, T., Sturm, V., Stoppenbrink, K., Merkel, R., and Schlaepfer, T. E. (2011). Misuse of the FDA's humanitarian device exemption in deep brain stimulation for obsessive-compulsive disorder. *Health Aff. (Millwood)* 30, 302–311.

Fishman, P. S. (2008). Paradoxical aspects of parkinsonian tremor. *Mov. Disord.* 23, 168–173.

Follett, K. A., Weaver, F. M., Stern, M., Hur, K., Harris, C. L., Luo, P., Marks, W. J. Jr., Rothlind, J., Sagher, O., Moy, C., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E. C., Duda, J. E., Holloway, K., Samii, A., Horn, S., Bronstein, J. M., Stoner, G., Starr, P. A., Simpson, R., Baltuch, G., De Salles, A., Huang, G. D., Reda, D. J., and CSP 468 Study Group. (2010). Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N. Engl. J. Med.* 362, 2077–2091.

Gradinaru, V., Mogri, M., Thompson, K. R., Henderson, J. M., and Deisseroth, K. (2009). Optical deconstruction of parkinsonian neural circuitry. *Science* 324, 354–359.

Hariz, M. I., Blomstedt, P., and Zrinzo, L. (2010). Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg. Focus* 29, E1.

Hwynn, N., Hass, C. J., Zeilman, P., Romrell, J., Dai, Y., Wu, S. S., Foote, K. D., Subramony, S. H., Oyama, G., Velez-Lago, F., Fernandez, H. H., Resnick, A. S., Malaty, I. A., and Okun, M. S. (2011). Steady or not following thalamic deep brain stimulation for essential tremor. *J. Neurol.* 258, 1643–1648.

Katz, M., Kilbane, C., Rosengard, J., Alterman, R. L., and Tagliati, M. (2011). Referring patients for deep brain stimulation: an improving practice. *Arch. Neurol.* 68, 1027–1032.

Kleiner-Fisman, G., Herzog, J., Fisman, D. N., Tamma, F., Lyons, K. E., Pahwa, R., Lang, A. E., and Deuschl, G. (2006). Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov. Disord.* 21(Suppl. 14), S290–S304.

Kopell, B. H., Molnar, G. F., and Hiner, B. (2009). "Movement disorders: anatomy and physiology relevant to deep brain stimulation," in *Neuromodulation*, Vol. 2, eds E. Krames, P. H. Peckham, and A. H. Rezai (London: Elsevier), 529–538.

Kupsch, A., Benecke, R., Müller, J., Trottenberg, T., Schneider, G. H., Poewe, W., Eisner, W., Wolters, A., Müller, J. U., Deuschl, G., Pinsker, M. O., Skogseid, I. M., Roeste, G. K., Vollmer-Haase, J., Brentrup, A., Krause, M., Tronnier, V., Schnitzler, A., Voges, J., Nikkhah, G., Vesper, J., Naumann, M., Volkmann, J., and Deep-Brain Stimulation for Dystonia Study Group. (2006). Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N. Engl. J. Med.* 355, 1978–1990.

Lulé, D., Heimrath, J., Pinkhardt, E. H., Ludolph, A. C., Uttner, I., and Kassubek, J. (2012). Deep brain stimulation and behavioural changes: is comedication the most important factor? *Neurodegener. Dis.* 9, 18–24.

Lyons, K. E., Pahwa, R., Comella, C. L., Eisa, M. S., Elble, R. J., Fahn, S., Jankovic, J., Juncos, J. L., Koller, W. C., Ondo, W. G., Sethi, K. D., Stern, M. B., Tanner, C. M., Tintner, R., and Watts, R. L. (2003). Benefits and risks of pharmacological treatments for essential tremor. *Drug Saf.* 26, 461–481.

Lyons, M. K. (2011). Deep brain stimulation: current and future clinical applications. *Mayo Clin. Proc.* 86, 662–672.

McIntyre, C. C., and Hahn, P. J. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol. Dis.* 38, 329–337.

McIntyre, C. C., Savasta, M., Walter, B. L., and Vitek, J. L. (2004). How does deep brain stimulation work? Present understanding and future questions. *J. Clin. Neurophysiol.* 1, 40–50.

Moro, E., Lozano, A. M., Pollak, P., Agid, Y., Rehncrona, S., Volkmann, J., Kulisevsky, J., Obeso, J. A., Albanese, A., Hariz, M. I., Quinn, N. P., Speelman, J. D., Benabid, A. L., Fraix, V., Mendes, A., Welter, M. L., Houeto, J. L., Cornu, P., Dormont, D., Tornqvist, A. L., Ekberg, R., Schnitzler, A., Timmermann, L., Wojtecki, L., Gironell, A., Rodriguez-Oroz, M. C., Guridi, J., Bentivoglio, A. R., Contarino, M. F., Romito, L., Scerrati, M., Janssens, M., and Lang, A. E. (2010). Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov. Disord.* 25, 578–586.

Pollak, P., Benabid, A. L., Gross, C., Gao, D. M., Laurent, A., Benazzouz, A., Hoffmann, D., Gentil, M., and Perret, J. (1993). Effects of the stimulation of the subthalamic nucleus in Parkinson disease. *Rev. Neurol. (Paris)* 149, 175–176.

Schrag, A., and Quinn, N. (2000). Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. *Brain* 123, 2297–2305.

Schuurman, P. R., Bosch, D. A., Merkus, M. P., and Speelman, J. D. (2008). Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. *Mov. Disord.* 23, 1146–1153.

Schwalb, J. M., and Hamani, C. (2008). The history and future of deep brain stimulation. *Neurotherapeutics* 5, 3–13.

Shah, R. S., Chang, S. Y., Min, H. K., Cho, Z. H., Blaha, C. D., and Lee, K. H. (2010). Deep brain stimulation: technology at the cutting edge. *J. Clin. Neurol.* 6, 167–182.

Skidmore, F. M., Rodriguez, R. L., Fernandez, H. H., Goodman, W. K., Foote, K. D., and Okun, M. S. (2006). Lessons learned in deep brain stimulation for movement and neuropsychiatric disorders. *CNS Spectr.* 11, 521–536.

Stefani, A., Lozano, A. M., Peppe, A., Stanzione, P., Galati, S., Tropepi, D., Pierantozzi, M., Brusa, L., Scarnati, E., and Mazzone, P. (2007). Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain* 130, 1596–1607.

Sun, B., Chen, S., Zhan, S., Le, W., and Krahl, S. (2007). Subthalamic nucleus stimulation for primary dystonia and tardive dystonia. *Acta Neurochir. Suppl.* 97, 207–214.

Vidailhet, M., Vercueil, L., Houeto, J. L., Krystkowiak, P., Benabid, A. L., Cornu, P., Lagrange, C., Tézenas du Montcel, S., Dormont, D., Grand, S., Blond, S., Detante, O., Pillon, B., Ardouin, C., Agid, Y., Destée, A., Pollak, P., and French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group. (2005). Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N. Engl. J. Med.* 352, 459–467.

Volkmann, J., Daniels, C., and Witt, K. (2010). Neuropsychiatric effects of subthalamic neurostimulation in Parkinson disease. *Nat. Rev. Neurol.* 6, 487–498.

Weaver, F. M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W. J. Jr., Rothlind, J., Sagher, O., Reda, D., Moy, C. S., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E. C., Duda, J. E., Holloway, K., Samii, A., Horn, S., Bronstein, J., Stoner, G., Heemskerk, J., Huang, G. D., and CSP 468 Study Group. (2009). Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 301, 63–73.

Welter, M. L., Grabli, D., and Vidailhet, M. (2010). Deep brain stimulation for hyperkinetics disorders: dystonia, tardive dyskinesia, and tics. *Curr. Opin. Neurol.* 23, 420–425.

Wichmann, T., and Delong, M. R. (2006). Deep brain stimulation for neurologic and neuropsychiatric disorders. *Neuron* 52, 197–204.

Wilcox, R. A., Cole, M. H., Wong, D., Coyne, T., Silburn, P., and Kerr, G. (2011). Pedunculopontine nucleus deep brain stimulation produces sustained improvement in primary progressive freezing of gait. *J. Neurol. Neurosurg. Psychiatr.* 82, 1256–1259.

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., Scott, R., Ives, N., Rick, C., Daniels, J., Patel, S., Wheatley, K., and PD SURG Collaborative Group. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol.* 9, 581–591.

Wirdefeldt, K., Adami, H. O., Cole, P., Trichopoulos, D., and Mandel, J. (2011). Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur. J. Epidemiol.* 26(Suppl. 1), S1–S58.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 05 November 2011; accepted: 09 January 2012; published online: 25 January 2012.

Citation: Pizzolato G and Mandat T (2012) Deep brain stimulation for movement disorders. Front. Integr. Neurosci. ***6****:2. doi: 10.3389/fnint.2012.00002*

frontiers in
INTEGRATIVE NEUROSCIENCE

GENERAL COMMENTARY
published: 23 February 2012
doi: 10.3389/fnint.2012.00006

Deep brain stimulation for movement disorders – a history of success and challenges to conquer

Lars Wojtecki[1,2]*, Carlo Colosimo[3] and Romulo Fuentes[4]

[1] Center for Movement Disorders and Neuromodulation, Department of Neurology, Medical Faculty, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany
[2] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany
[3] Department of Neurology and Psychiatry, "Sapienza" University, Rome, Italy
[4] Edmond and Lily Safra International Institute of Neuroscience of Natal, Natal, Brazil
*Correspondence: wojtecki@uni-duesseldorf.de

A commentary on

Deep brain stimulation for movement disorders
by Pizzolato, G., and Mandat, T. (2012). Front. Integr. Neurosci. 6:2. doi: 10.3389/fnint.2012.00002

Up to date, tens of thousands patients have undergone implantation of deep brain stimulation electrodes – mainly for the treatment of Parkinson's disease, Essential Tremor, and Idiopathic Dystonia. Pizzolato and Mandat (2012) give a short and comprehensive review on the current status of deep brain stimulation for these movement disorders. For this special issue "The development of deep brain stimulation for neurological and psychiatric disorders: clinical, societal, and ethical issues" the reviews of Pizzolato and Mandat (2012) and of Sarem-Aslani and Mullett (2011) give an overview of the state of the art and currently approved indications for this therapy. There is no doubt, that especially in the field of movement disorders, deep brain stimulation is a history of great success in neurological therapy and a most valuable tool for research.

However, especially in the light of other articles of this special issue that deal, e.g., with ethical issues, modulation of affect, cognition, and behavior, or possible changes of personality by deep brain stimulation, there remain some major challenges and questions for the future. We will have to conquer these challenges in order to understand and improve the technique – to finally transfer it to a successful therapy for other disorders especially in the neuro-psychiatric domain.

These challenges are:

(1) To understand the natural history of the diseases and the underlying functional networks and circuits to select the best targets for neuromodulation.
Beneficial motor effects of DBS are well described, e.g., there is class one evidence for the usefulness of DBS for Parkinson's disease (Deuschl et al., 2006; Weaver et al., 2009; Williams et al., 2010). However, to determine the real value in improving quality of life we have to gain more insight into the dynamics of the diseases. What is the right time point for implantation? Current data suggest that despite stable long terms effects on motor fluctuations in PD, we might miss the right time window in elderly patients as DBS will not manage to improve axial motor symptoms (Fasano et al., 2010b). On the other hand, prospective studies to examine the benefits of earlier implantation are still on the way. Furthermore, the interactions of disease state, operation, and implantation on cognitive side effects are not fully understood. Although there are many publications that show "on/off" effects on cognitive measurements, some data suggest that the implantation *per se* – and not the stimulation – might be the main cause of the decline in executive function (Okun et al., 2012). In line with this discussion we have to further study the right stimulation targets for to gain the best outcome. For example, GPI stimulation recognizes a renaissance, as it might be a cognitive safer target for some patients. In order to efficiently access and modulate the neural networks, many findings point into the direction that fiber tracts rather than nuclei might be the right target of choice – not only in PD, but also in thalamic stimulation for essential tremor: some findings suggest that differential stimulation of fiber tracts can be crucial for modulation of distinct symptoms like tremor versus ataxia (Fasano et al., 2010a).

(2) To disentangle the mechanisms of action of deep brain stimulation.
The discussion about the effects of stimulating different fiber pathways leads to the point were we need a refined understanding of the connections and relationship between the different neural circuits involved in the desired output behavior. When it comes to STN stimulation, stimulation of afferents from cortical areas might be the main mechanism – as studies that used the optogenetic method suggest (Gradinaru et al., 2009). Additionally, volume of tissue activated studies, other functional imaging, microelectrode multi-site recordings, local field potential-, EEG-, and magnetoencephalographic studies, alone or combined, might provide guides to understand the stimulation effects on local and long range neuronal networks.

(3) To improve stimulation techniques
On the basis of a better understanding of the mechanisms underlying DBS, we have to tailor new stimulation techniques. New programming options as interleaving (Wojtecki et al., 2011) and constant current devices (Okun et al., 2012) are on the market now. Furthermore, new electrodes with improved variability of stimulation

direction will be helpful. Finally, as a result of disentangling the neuronal network codes (e.g., beta and high frequency oscillations in PD), closed-loop devices (Rouse et al., 2011), that could provide stimulation "on demand," will hopefully be a major step forward to improve these therapies.

(4) To learn from the history of DBS in movement disorders.

Especially when discussing modulation of complex behavior in patients with DBS and when we aim to increase the usage and indication of the technique, we have to learn from the lessons of the past. What was the reason for success of DBS in movement disorders? We think that there are four main points: determining the right patients with a distinct diagnosis for therapy, a detailed knowledge of the involved neural circuits, good designed and ethical clinical studies, and interdisciplinary cooperation between specialists (e.g., neurology, neurosurgery). On this basis, the future will be open for more indications and better understanding.

REFERENCES

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., Daniels, C., Deutschländer, A., Dillmann, U., Eisner, W., Gruber, D., Hamel, W., Herzog, J., Hilker, R., Klebe, S., Kloss, M., Koy, J., Krause, M., Kupsch, A., Lorenz, D., Lorenzl, S., Mehdorn, H. M., Moringlane, J. R., Oertel, W., Pinsker, M. O., Reichmann, H., Reuss, A., Schneider, G. H., Schnitzler, A., Steude, U., Sturm, V., Timmermann, L., Tronnier, V., Trottenberg, T., Wojtecki, L., Wolf, E., Poewe, W., Voges, J., and German Parkinson Study Group, Neurostimulation Section. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *N. Engl. J. Med.* 355, 896–908.

Fasano, A., Herzog, J., Raethjen, J., Rose, F. E. M., Muthuraman, M., Volkmann, J., Falk, D., Elble, R., and Deuschl, G. (2010a). Gait ataxia in essential tremor is differentially modulated by thalamic stimulation. *Brain* 133, 3635–3648.

Fasano, A., Romito, L. M., Daniele, A., Piano, C., Zinno, M., Bentivoglio, A. R., and Albanese, A. (2010b). Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 133, 2664–2676.

Gradinaru, V., Mogri, M., Thompson, K. R., Henderson, J. M., and Deisseroth, K. (2009). Optical deconstruction of parkinsonian neural circuitry. *Science* 324, 354–359.

Okun, M. S., Gallo, B. V., Mandybur, G., Jagid, J., Foote, K. D., Revilla, F. J., Alterman, R., Jankovic, J., Simpson, R., Junn, F., Verhagen, L., Arle, J. E., Ford, B., Goodman, R. R., Stewart, R. M., Horn, S., Baltuch, G. H., Kopell, B. H., Marshall, F., Peichel, D., Pahwa, R., Lyons, K. E., Tröster, A. I., Vitek, J. L., Tagliati, M., and for the SJM DBS Study Group. (2012). Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol.* 11, 140–149.

Pizzolato, G., and Mandat, T. (2012). Deep brain stimulation for movement disorders. *Front. Integr. Neurosci.* 6:2. doi: 10.3389/fnint.2012.00002

Rouse, A. G., Stanslaski, S. R., Cong, P., Jensen, R. M., Afshar, P., Ullestad, D., Gupta, R., Molnar, G. F., Moran, D. W., and Denison, T. J. (2011). A chronic generalized bi-directional brain-machine interface. *J. Neural Eng.* 8, 036018. doi: 10.1088/1741-2560/8/3/036018

Sarem-Aslani, A., and Mullett, K. (2011). Industrial perspective on deep brain stimulation: history, current state, and future developments. *Front. Integr. Neurosci.* 5:46. doi: 10.3389/fnint.2011.00046

Weaver, F. M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W. J., Rothlind, J., Sagher, O., Reda, D., Moy, C. S., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E. C., Duda, J. E., Holloway, K., Samii, A., Horn, S., Bronstein, J., Stoner, G., Heemskerk, J., Huang, G. D., and CSP 468 Study Group. (2009). Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 301, 63–73.

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., Scott, R., Ives, N., Rick, C., Daniels, J., Patel, S., Wheatley, K., and PD SURG Collaborative Group. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol.* 9, 581–591.

Wojtecki, L., Vesper, J., and Schnitzler, A. (2011). Interleaving programming of subthalamic deep brain stimulation to reduce side effects with good motor outcome in a patient with Parkinson's disease. *Parkinsonism Relat. Disord.* 17, 293–294.

Received: 30 January 2012; accepted: 08 February 2012; published online: 23 February 2012.

Citation: Wojtecki L, Colosimo C and Fuentes R (2012) Deep brain stimulation for movement disorders – a history of success and challenges to conquer. Front. Integr. Neurosci. ***6****:6. doi: 10.3389/fnint.2012.00006*

frontiers in
INTEGRATIVE NEUROSCIENCE

MINI REVIEW ARTICLE
published: 24 June 2011
doi: 10.3389/fnint.2011.00029

Modulating affect, cognition, and behavior – prospects of deep brain stimulation for treatment-resistant psychiatric disorders

Thomas E. Schlaepfer[1,2]*, Bettina Bewernick[1], Sarah Kayser[1] and Diane Lenz[1]

[1] *Brain Stimulation Group, Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany*
[2] *Department of Psychiatry and Behavioral Science, The Johns Hopkins University, Baltimore, MD, USA*

Edited by:
Chiara Saviane, Scuola Internazionale Superiore di Studi Avanzati, Italy

Reviewed by:
Nir Lipsman, University of Toronto – University Health Network, Canada
Bruno Millet, Rennes 1 University, France

***Correspondence:**
Thomas E. Schlaepfer, Department of Psychiatry, University Hospital, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany.
e-mail: schlaepf@jhmi.edu

Most patients suffering from psychiatric disorders respond to combinations of psycho- and psychopharmacotherapy; however there are patients who profit little if anything even after many years of treatment. Since about a decade different modalities of targeted neuromodulation – among them most prominently – deep brain stimulation (DBS) – are being actively researched as putative approaches to very treatment-resistant forms of those disorders. Recently, promising pilot data have been reported both for major depression (MD) and obsessive–compulsive disorder (OCD). Given the fact that patients included in DBS studies had been treated unsuccessfully for many years with conventional treatment methods, renders these findings remarkable. Remarkable is the fact, that in case of the long-term studies underway for MD, patients show a stable response. This gives hope to a substantial percentage of therapy–resistant psychiatric patients requiring new therapy approaches. There are no fundamental ethic objections to its use in psychiatric disorders, but until substantial clinical data is available, mandatory standards are needed. DBS is a unique and very promising method for the treatment of therapy–resistant psychiatric patients. The method allows manipulating pathological neuronal networks in a very precise way.

Keywords: major depression, obsessive–compulsive disorder, deep brain stimulation

INTRODUCTION

PRINCIPLE, SAFETY, AND ADVANTAGES OF DBS

Different modalities of neuromodulation such as repetitive transcranial magnetic stimulation (Schlaepfer et al., 2003; George, 2010), vagus nerve stimulation (Kosel and Schlaepfer, 2003; Schlaepfer et al., 2008b), and magnetic seizure therapy (Lisanby et al., 2001; Kayser et al., 2010) have been proposed and systematically studied in psychiatric different disorders (Schlaepfer et al., 2010). Both clinically and scientifically the most promising method of neuromodulation might be deep brain stimulation (DBS). DBS refers to the stereotaxic placement of unilateral or bilateral electrodes connected to a permanently implanted neurostimulator (Schlaepfer and Lieb, 2005b). The exact neurobiological mechanisms by which DBS exerts effects on brain tissue are not yet fully understood (Hardesty and Sackeim, 2007). Various mechanisms have been discussed, on the neuronal level, excitatory and inhibitory processes might play a role (McIntyre et al., 2004). Most probably, DBS leads to a functional lesion of the surrounding tissue. Today, it is unknown which part of the neuron (e.g., cell body, axon) is primarily modulated by DBS. Certainly, the stimulation volume is not a fixed area around the electrode and the effect on neuronal tissue is variable. Stimulation parameters (frequency, amplitude, pulse width, duration) also clearly have an impact on the effect (Ranck, 1975). With commonly used parameters, a relatively large volume of neural tissue is influenced (Kringelbach et al., 2007).

Side effects in DBS are either related to the operation itself (e.g., bleeding, local infections at the chest) or to the stimulation (e.g., elevation of mood, anxiety, motor slowing). Fortunately, the safety of the stereotactic operation technique has been extremely improved in the last years with the help of neuroimaging. Bleeding rate of DBS surgeries are between 0.2 and 5% (Kosel et al., 2007; Kühn et al., 2007). On the other hand, DBS has many advantages over traditional therapy methods: clinical effects can be achieved without irreversible lesioning, stereotactic operation is the most minimal neurosurgical method and electrodes can be completely removed if necessary. Brain activity can be changed in a direct, controlled manner. Furthermore, DBS offers the opportunity to continuously adjust stimulation variables for each patient in order to optimize therapy. The patient can turn off stimulation immediately if side effects occur. DBS is the only neurosurgical method that allows blinded studies for therapy control. In comparison to antidepressant medication, nor side effects such as extrapyramidal effects, weight gain, that substantially effect compliance and patient's quality of life, are reported. Also no long-time side effects as in antidepressant treatments (Geddes et al., 2003; Furukawa et al., 2007) have been reported. Nonetheless, DBS can be associated with side effects due to stimulation that are transient and can be counteracted by a change in stimulation parameters (see **Table 1**). But until it has been proven that DBS has the same clinical effect as pharmacotherapy, the latter together with psychotherapy must be the first treatment choice.

Table 1 | Possible side effects of DBS in OCD or depression.

Negative effects of DBS	Positive effects of DBS
For example, bleeding or local infections at the chest caused by the operation itself	Clinical effects can be achieved without irreversible lesioning
For example, elevation of mood, anxiety, motor slowing caused by the stimulation	Electrodes can be completely removed if necessary
	Brain activity can be changed in a direct, controlled manner
	Opportunity to continuously adjust stimulation variables for each patient individually
	The patient can turn off stimulation immediately if side effects occur
	Allows blinded studies for therapy control
	No extrapyramidal effects
	No weight gain
	No long-time side effects as in antidepressant treatments are reported

Thus, DBS could become an exciting method in the treatment of depression and obsessive–compulsive disorder (OCD) and offers unique possibilities to gain more insight into the underlying neurobiology of psychiatric disorders.

FIRST EFFICACY RESULTS IN OCD AND DEPRESSION

The main focus of studies on the underlying neurobiology of major depression (MD) has focused on the description of biological differences between patients and healthy subjects such as alterations of monoaminergic or endocrine systems. The relative importance of the various biological changes has not been elucidated; correlation with specific symptoms of the disease has rarely been attempted. Psychotropic drugs work by altering neurochemistry to a large extent in widespread regions of the brain, many of which may be unrelated to depression.

In contrast to some neurological disorders, the pathological interplay of several brain regions contributes to the behavioral, emotional, and cognitive symptoms of psychiatric disorders. Metabolic studies suggest that different symptoms are mediated by different brain regions (Berton and Nestler, 2006; Yurgelun-Todd et al., 2007; Krishnan and Nestler, 2008) A convincing network-model of depression integrating biochemical, electrophysiological, imaging, and animal studies, has been described by Mayberg (1997). According to this model, depression results from a dysregulation of limbic–cortical connections: pathological changes in dorsal brain regions (including the dorsolateral prefrontal cortex, inferior parietal cortex, and striatum) were associated with cognitive symptoms (e.g., apathy, anhedonia, hopelessness, deficits in attention, and executive function), changes in ventral areas (hypothalamic–pituitary–adrenal axis, Insula, subgenual cingulate, and brainstem) contribute to the vegetative and somatic aspects of depression (e.g., sleep disturbance, appetite, endocrine dysregulation). This model underlines the role of the rostral cingulate cortex in regulating the network (Mayberg, 1997). The involvement of further regions in depression is discussed: the hippocampus contributes to memory deficits, the nucleus accumbens was associated with anhedonia and lack of motivation, the amygdala plays a role in the processing of aversive stimuli and avoidance (Berton and Nestler, 2006).

Obsessive–compulsive disorder is characterized by obsessions (anxiety-provoking thoughts) and compulsions (repeated, time-consuming behaviors; Stein, 2002). As in most psychiatric disorders, a complex interplay of genetic factors, neurotransmitter changes and psychosocial characteristics contribute to the development of this disease. Changes in dopamine and serotonin have been reported (Stein, 2002). Dysfunctions in a network connecting the cortex and basal ganglia are supposed to underlie OCD. Imaging data demonstrated changes in orbitofrontal cortex, anterior cingulate cortex and caudate nucleus in OCD (Baxter, 1990). Emerging evidence suggests that different alternations of the OCD circuitry subserve different symptom subtypes (Kopell and Greenberg, 2008). It has been hypothesized that an over activation of the direct pathway of the cortico-striatal–pallidal–thalamic–cortical loop leads to intrusive thoughts (Baxter et al., 2001).

These novel conceptualizations of both OCD and MD, brought about mainly by advances in functional neuroimaging but also electrophysiological and molecular studies and their synthesis have paved the road to hypothesis-guided studies on targeted reversible neuromodulation with DBS in these disorders.

The subgenual cingulate cortex (Brodmann Area cg25) has probably dysfunctional connections to the dorsal and ventral compartments of the emotion regulation circuit in depression (Mayberg, 1997). The subgenual cingulate cortex modulates negative mood states (Mayberg et al., 2005b). It has been involved in acute sadness and in antidepressive treatment effects (Mayberg et al., 2005a; Lozano et al., 2008). The rostral part of the cingulate cortex seems to play a key role in modulating the network of depression (Mayberg, 1997).

Mayberg et al. (2005b) could demonstrate, that 2 months after surgery, 5/6 patients met the response criterion [baseline score in the Hamilton Depression Rating Scale (HDRS) minus 50%], after 6 months, four patients showed sustained response. Different neuropsychological parameters that were impaired at baseline were significantly improved. A reduction in the pathological hyperactivity in this region has also been demonstrated using positron emission tomography (PET) in this study. During the blinded sham stimulation phase ($n = 1$), the patient's condition worsened considerably. No adverse events due to stimulation were observed (Mayberg et al., 2005b).

Malone et al. (2009) investigated the use of DBS at the ventral capsule/ventral striatum (VC/VS). The VC/VS was targeted, because former studies targeting the VC/VS in OCD patients (Nuttin et al., 1999; Greenberg et al., 2006) showed improvement not only for OCD symptoms but also for depressive symptoms. This finding was supported by the fact that the VS has complex architecture and includes structures such as the bed nucleus of the stria terminalis and the nucleus accumbens, which are regions believed to be involved with stress-related and reward–motivation components of depression (Forray and Gysling, 2004; Epstein et al., 2006). Once stimulation was titrated to therapeutic benefit and the absence of adverse effects, patients received significant improvements in depressive symptoms measured by the HDRS.

Responder rates of 40% at 6 months ($n = 15$) and 53.3% at last follow-up (mean last follow-up of 23.5 ± 14.9 months) receiving continuous DBS stimulation are referred. Remission rates were reported 20% at 6 months and 40% at last follow-up with the HDRS. So the results of this study suggest that DBS of the VC/VS could also provide benefit in highly treatment-refractory patients with depression. However, since the larger contacts of the VC/VS leads have twice the surface area of standard leads used in other DBS applications, more frequent battery replacements or rather implanting recharging batteries should be considered (Malone et al., 2009).

We selected the Nucleus Accumbens as target for DBS because of its prominent role in the reward system. The Nucleus accumbens is known to act as motivational gateway between systems involved in motor control and limbic systems in charge of emotion processing; especially the ventral striatum is uniquely located to modulate other regions of the brain (Schlaepfer et al., 2008a). By targeting one site in a network of brain regions implicated in processing of affective stimuli, it was possible to manipulate anhedonia in particular. It could be demonstrated that modulation of this structure was associated with changes in the symptoms of anhedonia and mood in three depressed patients. Stimulation current correlated negatively with anhedonia ratings. Normalization of brain metabolism in fronto-striatal networks as result of stimulation was also observed (Schlaepfer et al., 2008a). It is notable, that no side effects due to stimulation were observed. Results from a total of nine patients in this study show acute as well as long-term antidepressant effects of DBS at this target have been published recently, demonstrating a responder rate of 50% (Bewernick et al., 2010).

The habenula has been proposed recently as target for DBS in depression (Sartorius and Henn, 2007). Animal data and imaging studies have shown, that this regions controls serotonergic fibers from the dorsal raphe nuclei and noradrenergic fibers from the locus coeruleus (Winter et al., 2011). The authors hypothesize that over activation of the habenula is related to depression and recently reported on the course of depression after DBS to the habenula in a case report (Sartorius et al., 2010).

Another putative target site for MD has been proposed very recently, the medial forebrain bundle (Coenen et al., 2011). Magnetic resonance diffusion tensor imaging (DTI) can visualize distinct functional circuits in the living human brain on the basis of the anisotropy of the brain tissue. This technique has been applied to an analysis of the different DBS sites for MD and lead to the hypothesis-guided development of yet another site with hypothetically greater efficacy and even less unwanted effects. Pilot studies assessing clinical efficacy are underway.

Single-case studies in OCD patients with comorbid depression have shown antidepressant effects: bilateral stimulation of the ventral nucleus caudatus in combination with Nucleus Accumbens for OCD led to remission of depression (HDRS_17 < 7) after 6 month. No neuropsychological deterioration was reported (Aouizerate et al., 2004).

It was supposed that dysregulation of the connection between unspecific thalamic system and orbitofrontal cortex plays an important role in the development of depression (Jiménez et al., 2005). Therefore, bilateral stimulation of the lower thalamus stem was performed one depressed patient and led to remission (HDRS $42 \rightarrow 10$). The effect remained stable for 24 months. During blinded discontinuation of stimulation, the patient's condition aggravated (Jiménez et al., 2005).

In OCD, there have been proposed different targets according to the underlying pathological network. The orbitofrontal cortex and the anterior cingulate cortex are part of the OCD circuit. Unfortunately, these regions are very large and not well circumscribed in relation to this disease. Thus the size of cortex region that needs to be modulated would be too large (Lipsman et al., 2007). In most studies, the anterior limb of the internal capsule was the target for either unilateral or bilateral stimulation (Anderson and Ahmed, 2003; Gabriels et al., 2003; Nuttin et al., 1999; Nuttin et al., 2003; Sturm et al., 2003). All studies reported on promising results ranging from response to complete remission. In terms of side effects, some studies reported on induced, directly stimulation related symptoms of hypomania which all ceased completely after reduction of stimulation intensity.

The Nucleus thalamicus – zona incerta has been studied at three patients with Parkinson's disease and comorbid OCD (Mallet et al., 2002; Fontaine et al., 2004). Both studies reported considerable amelioration of OCD symptoms. The subthalamic nucleus was stimulated in a study (Malone et al., 2009), this group included 16 patients and received significant lower symptoms of OCD. In a recent OCD study targeting the subthalamic nucleus, OCD symptoms were significantly reduced after the 3-months double-blind stimulation phase compared to the double-blind sham stimulation phase (Mallet et al., 2008). Both studies refer to possible associated risk of serious adverse events (Mallet et al., 2008; Malone et al., 2009). The Nucleus Accumbens and Nucleus Caudatus were target in one case study with comorbid depression (s above). This patient achieved remission status (Aouizerate et al., 2004). Unilateral stimulation of the NAcc in a well-designed, controlled study lead to somewhat less impressive but significant improvements results in 10 patients (Huff et al., 2010). The stimulation of the VC/VS led to a significant improvement in 50% of the patients (Greenberg et al., 2006). Side effects related to the stimulation were transient hypomania and increased anxiety, which could be counteracted by parameter change (Greenberg et al., 2006).

Recently results of bilateral DBS to the Nucleus Accumbens in OCD with an open 8-month treatment phase, followed by a double-blind crossover phase with randomly assigned 2-week periods of active or sham stimulation, ending with an open 12-month maintenance phase have been published (Denys et al., 2010). Nine of the 16 patients were classified as responders, indicating that bilateral stimulation of the nucleus accumbens may be an effective and safe treatment in patients with highly refractory OCD.

In summary, promising effects for different targets have been demonstrated, but as worldwide sample sizes are small, it is too early to select one favorable target if there is any. As OCD is a heterogeneous disease, there might be different optimal targets for different symptom clusters.

ETHICAL ISSUES

Introducing a new invasive therapeutic approach requires evaluation according to high ethical standards. The high mortality,

low quality of life, and the social burden of inadequately treated serious psychiatric illness favor the use of DBS for treatment-resistant patients. The potential benefit to the understanding of pathological principles in mental disorders is evident (Schlaepfer and Lieb, 2005a; Fuchs, 2006; Ford, 2007; Synofzik and Schlaepfer, 2008, 2010).

Fundamental ethical concerns are generally applicable to all clinical interventions (e.g., pharmacotherapy, psychotherapy) including DBS in neurological disorders. Foremost, are patients able to give conformed consent? It has been demonstrated that depressed patients show few impairments in decision-making capacity related to clinical treatment research (Appelbaum et al., 1999). Another concern is, how far human nature may ethically be manipulated (Fuchs, 2006). Long-term effects of DBS cannot be evaluated yet, but in comparison to pharmacotherapy, brain stimulation is a more specific and reversible intervention. No harmful effects are reported so far. More problematic is the danger of misuse, such as for mind control or for over-enhancement of normal (healthy) cognitive function ("brain doping"; Fuchs, 2006; Ford, 2007). As clinical researchers in psychiatry, our aim is to help patients to lead a normal life, including normal cognitive function and personal autonomy.

More practical ethical concerns are the availability of alternative treatment methods (e.g., pharmacotherapy, ECT, psychotherapy). Taking to account that DBS is used only with treatment-resistant patients, who have already shown no benefit with other treatment approaches currently available, the apparent reversibility of DBS and its robust potential benefits, as described by prior pilot studies, are strong ethical arguments for considering DBS treatment for resistant psychiatric disorders (Synofzik and Schlaepfer, 2008, 2010).

However, there are also some notable risks with DBS, particularly intracerebral bleeding and wound infection and its efficacy is not yet formally and extensively established in controlled trials. Therefore, until the DBS treatment method is scientifically validated; obligatory standards for patient inclusion and exclusion criteria as well as the selection of targets are needed. Partly this has been already described by Rabins et al. (2009), recommending 16 key points for guiding research and protecting the safety and rights of research subjects, as well as Nuttin et al. (2002) advocating certain minimum requirements for using DBS in psychiatric conditions. Whereas we question the suggestion of Nuttin et al. (2002) to form a separate committee with only distant access to the individual patient or no direct involvement to the study for reviewing patient selection. It is our belief, that despite any committee review – might it be as thorough and exhaustive as possible – the clinical responsibility remains with the patient's clinicians and cannot be shared by review committees. So from our point of view further research regarding obligatory standards in DBS is needed.

Another possible event to consider is the risk of selective publishing of results. This is by no means unique to DBS, but this area is particularly vulnerable to bias because of an excessive reliance on single-patient case reports (Schlaepfer and Fins, 2010). Until cohort studies are routinely performed, the possibility will remain that only positive results will be published at the expense of negative data that might also have important implications. Balanced publishing of results is even more important taking to account, that patients and public understanding of the risks and benefits of DBS is strongly shaped by media (Racine et al., 2007).

DISCUSSION

A substantial percentage of therapy–resistant psychiatric patients require new therapy approaches. DBS offers the possibility to manipulate pathological neuronal networks in a very precise way. First studies showed very promising effects in depression and OCD. There are no fundamental ethic objections to its use in psychiatric disorders, but until substantial clinical data is available, mandatory standards are needed for patient and target selection, quality of research center, and study protocol. It is very important to point out that in the actual stage of research; DBS for psychiatric diseases is clinical research on therapeutics. The benefit of this method has to be proven first, until DBS will be available for many patients. Before, much more information about the therapeutic effect, individual predictors of response, possible short and long-time side effects, and neuroethical issues have to be gained.

Deep brain stimulation is a unique and very promising method for the treatment of therapy–resistant psychiatric patients. Nonetheless, the duration of the battery limits the choice of stimulation parameters, increases the risk of infection, and raises treatment costs. Rechargeable batteries are currently being introduced to the field. Actual technology allows mainly continuous stimulation with little possibility for dynamic adjustment. A particular advantage of DBS is, that it allows recording signals from the stimulating electrodes (Cohen et al., 2009a,b,c) and combining these data with functional neuroimaging in order to map the spatiotemporal unfolding of DBS-elicited whole brain activity will lead to a much broader knowledge on functional and dysfunctional circuits processing affective stimuli revealing fundamental mechanisms of brain function.

REFERENCES

Anderson, D., and Ahmed, A. (2003). Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. Case report. *J. Neurosurg.* 98, 1104–1108.

Aouizerate, B., Cuny, E., Martin-Guehl, C., Guehl, D., Amieva, H., Benazzouz, A., Fabrigoule, C., Allard, M., Rougier, A., Bioulac, B., Tignol, J., and Burbaud, P. (2004). Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. *J. Neurosurg.* 101, 574–575.

Appelbaum, P. S., Grisso, T., Frank, E., O'Donnell, S., and Kupfer, D. J. (1999). Competence of depressed patients for consent to research. *Am. J. Psychiatry* 156, 1380–1384.

Baxter, L. R. (1990). Brain imaging as a tool in establishing a theory of brain pathology in obsessive compulsive disorder. *J. Clin. Psychiatry* 51(Suppl.), 22–25; discussion 26.

Baxter, L. R. J., Clark, E. C., Iqbal, M., and Ackermann, R. F. (2001). "Cortical-subcortical systems in the mediation of OCD: modeling the brain´s mediation of a classic "neurosis"," in *Frontal-Subcortical Circuits in Psychiatric and Neurological Disorders,* eds D. G. Lichter and J. L. Cummings (New York: Guilford Press), 207–230.

Berton, O., and Nestler, E. J. (2006). New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.* 7, 137–151.

Bewernick, B. H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., Lemke, M., Cooper-Mahkorn, D., Cohen, M. X., Brockmann, H., Lenartz, D., Sturm, V., and

Schlaepfer, T. E. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol. Psychiatry* 67, 110–116.

Coenen, V. A., Schlaepfer, T. E., Maedler, B., and Panksepp, J. (2011). Cross-species affective functions of the medial forebrain bundle-implications for the treatment of affective pain and depression in humans. *Neurosci. Biobehav. Rev.* doi: 10.1016/j.neubiorev.2010.12.009

Cohen, M. X., Axmacher, N., Lenartz, D., Elger, C. E., Sturm, V., and Schlaepfer, T. E. (2009a). Good vibrations: cross-frequency coupling in the human nucleus accumbens during reward processing. *J. Cogn. Neurosci.* 21, 875–889.

Cohen, M. X., Axmacher, N., Lenartz, D., Elger, C. E., Sturm, V., and Schlaepfer, T. E. (2009b). Neuroelectric signatures of reward learning and decision-making in the human nucleus accumbens. *Neuropsychopharmacology* 34, 1649–1658.

Cohen, M. X., Axmacher, N., Lenartz, D., Elger, C. E., Sturm, V., and Schlaepfer, T. E. (2009c). Nuclei accumbens phase synchrony predicts decision-making reversals following negative feedback. *J. Neurosci.* 29, 7591–7598.

Denys, D., Mantione, M., Figee, M., van den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A., and Schuurman, R. (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch. Gen. Psychiatry* 67, 1061–1068.

Epstein, J., Pan, H., Kocsis, J. H., Yang, Y., Butler, T., Chusid, J., Hochberg, H., Murrough, J., Strohmayer, E., Stern, E., and Silbersweig, D. A. (2006). Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *Am. J. Psychiatry* 163, 1784–1790.

Fontaine, D., Mattei, V., Borg, M., von Langsdorff, D., Magnie, M. N., Chanalet, S., Robert, P., and Paquis, P. (2004). Effect of subthalamic nucleus stimulation on obsessive-compulsive disorder in a patient with Parkinson disease. Case report. *J. Neurosurg.* 100, 1084–1086.

Ford, P. J. (2007). Neurosurgical implants: clinical protocol considerations. *Camb. Q. Healthc. Ethics* 16, 308–311.

Forray, M. I., and Gysling, K. (2004). Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis. *Brain Res. Brain Res. Rev.* 47, 145–160.

Fuchs, T. (2006). Ethical issues in neuroscience. *Curr Opin Psychiatry* 19, 600–607.

Furukawa, T. A., Cipriani, A., Barbui, C., and Geddes, J. R. (2007). Long-term treatment of depression with antidepressants: a systematic narrative review. *Can. J. Psychiatry* 52, 545–552.

Gabriels, L., Cosyns, P., Nuttin, B., Demeulemeester, H., and Gybels, J. (2003). Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatr. Scand.* 107, 275–282.

Geddes, J. R., Carney, S. M., Davies, C., Furukawa, T. A., Kupfer, D. J., Frank, E., and Goodwin, G. M. (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 361, 653–661.

George, M. S. (2010). Transcranial magnetic stimulation for the treatment of depression. *Expert Rev. Neurother.* 10, 1761–1772.

Greenberg, B. D., Malone, D. A., Friehs, G. M., Rezai, A. R., Kubu, C. S., Malloy, P. F., Salloway, S. P., Okun, M. S., Goodman, W. K., and Rasmussen, S. A. (2006). Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* 31, 2384–2393.

Hardesty, D. E., and Sackeim, H. A. (2007). Deep brain stimulation in movement and psychiatric disorders. *Biol. Psychiatry* 61, 831–835.

Huff, W., Lenartz, D., Schormann, M., Lee, S. H., Kuhn, J., Koulousakis, A., Mai, J., Daumann, J., Maarouf, M., Klosterkotter, J., and Sturm, V. (2010). Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: outcomes after one year. *Clin. Neurol. Neurosurg.* 112, 137–143.

Jiménez, F., Velasco, F., Salin-Pascual, R., Hernández, J. A., Velasco, M., Criales, J. L., and Nicolini, H. (2005). A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *J. Neurosurg.* 57, 585–593.

Kayser, S., Bewernick, B. H., Grubert, C., Hadrysiewicz, B. L., Axmacher, N., and Schlaepfer, T. E. (2010). Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. *J. Psychiatr. Res.* 45, 569–576.

Kopell, B. H., and Greenberg, B. D. (2008). Anatomy and physiology of the basal ganglia: implications for DBS in psychiatry. *Neurosci. Biobehav. Rev.* 32, 408–422.

Kosel, M., and Schlaepfer, T. E. (2003). Beyond the treatment of epilepsy: new applications of vagus nerve stimulation (VNS) in psychiatry. *CNS Spectr.* 8, 515–521.

Kosel, M., Sturm, V., Frick, C., Lenartz, D., Zeidler, G., Brodesser, D., and Schlaepfer, T. E. (2007). Mood improvement after deep brain stimulation of the internal globus pallidus for tardive dyskinesia in a patient suffering from major depression. *J. Psychiatr. Res.* 41, 801–803.

Kringelbach, M. L., Jenkinson, N., Owen, S. L., and Aziz, T. Z. (2007). Translational principles of deep brain stimulation. *Nat. Rev. Neurosci.* 8, 623–635.

Krishnan, V., and Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature* 455, 894–902.

Kühn, J., Huff, W., Lee, S.-H., Lenartz, D., Sturm, V., and Klosterkötter, J. (2007). Tiefenhirnstimulation bei psychiatrischen Erkrankungen. *Fortschr. Neurol. Psychiatr.* 75, 447–457.

Lipsman, N., Neimat, J. S., and Lozano, A. M. (2007). Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery* 61, 1–11; discussion 11–13.

Lisanby, S. H., Schlaepfer, T. E., Fisch, H. U., and Sackeim, H. A. (2001). Magnetic seizure therapy of major depression. *Arch. Gen. Psychiatry* 58, 303–305.

Lozano, A. M., Mayberg, H. S., Giacobbe, P., Hamani, C., Craddock, R. C., and Kennedy, S. H. (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol. Psychiatry* 64, 461–467.

Mallet, L., Mesnage, V., Houeto, J. L., Pelissolo, A., Yelnik, J., Behar, C., Gargiulo, M., Welter, M. L., Bonnet, A. M., Pillon, B., Cornu, P., Dormont, D., Pidoux, B., Allilaire, J. F., and Agid, Y. (2002). Compulsions, Parkinson's disease, and stimulation. *Lancet* 360, 1302–1304.

Mallet, L., Polosan, M., Jaafari, N., Baup, N., Welter, M. L., Fontaine, D., du Montcel, S. T., Yelnik, J., Chereau, I., Arbus, C., Raoul, S., Aouizerate, B., Damier, P., Chabardes, S., Czernecki, V., Ardouin, C., Krebs, M. O., Bardinet, E., Chaynes, P., Burbaud, P., Cornu, P., Derost, P., Bougerol, T., Bataille, B., Mattei, V., Dormont, D., Devaux, B., Verin, M., Houeto, J. L., Pollak, P., Benabid, A. L., Agid, Y., Krack, P., Millet, B., and Pelissolo, A. (2008). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *N. Engl. J. Med.* 359, 2121–2134.

Malone, D. A. Jr., Dougherty, D. D., Rezai, A. R., Carpenter, L. L., Friehs, G. M., Eskandar, E. N., Rauch, S. L., Rasmussen, S. A., Machado, A. G., Kubu, C. S., Tyrka, A. R., Price, L. H., Stypulkowski, P. H., Giftakis, J. E., Rise, M. T., Malloy, P. F., Salloway, S. P., and Greenberg, B. D. (2009). Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol. Psychiatry.* 65, 267–275.

Mayberg, H., Lozano, A., Voon, V., McNeely, H., Seminowicz, D., Hamani, C., Schwalb, J., and Kennedy, S. (2005a). Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–660.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M., and Kennedy, S. H. (2005b). Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–660.

Mayberg, H. S. (1997). Limbic-cortical dysregulation: a proposed model of depression. *J. Neuropsychiatry Clin. Neurosci.* 9, 471–481.

McIntyre, C. C., Savasta, M., Kerkerian-Le Goff, L., and Vitek, J. L. (2004). Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin. Neurophysiol.* 115, 1239–1248.

Nuttin, B., Cosyns, P., Demeulemeester, H., Gybels, J., and Meyerson, B. (1999). Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 354, 1526.

Nuttin, B., Gybels, J., Cosyns, P., Gabriels, L., Meyerson, B., Andreewitch, S., Rasmussen, S., Greenberg, B., Friehs, G., Rezai, A. R., Montgomery, E., Malone, D., and Fins, J. J. (2002). Deep brain stimulation for psychiatric disorders. *Neurosurgery* 51, 519.

Nuttin, B. J., Gabriels, L. A., Cosyns, P. R., Meyerson, B. A., Andreewitch, S., Sunaert, S. G., Maes, A. F., Dupont, P. J., Gybels, J. M., Gielen, F., and Demeulemeester, H. G. (2003). Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery* 52, 1263–1272; discussion 1272–1274.

Rabins, P., Appleby, B., Brandt, J., DeLong, M., Dunn, L., Gabriëls, L., Greenberg, B., Haber, S., Holtzheimer, P., Mari, Z., Mayberg, H., McCann, E., Mink, S., Rasmussen, S., Schlaepfer, T., Vawter, D., Vitek, J., Walkup, J., and Mathews, D. (2009). Deep Brain Stimulation for Disorders of Mood, Behavior and Thought: Scientific and Ethical Issues. *Arch. Gen. Psychiatry* 66, 931–937.

Racine, E., Waldman, S., Palmour, N., Risse, D., and Illes, J. (2007). "Currents of hope": neurostimulation techniques in U.S. and U.K. print media. *Camb. Q. Healthc. Ethics* 16, 312–316.

Ranck, J. B. Jr. (1975). Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.* 98, 417–440.

Sartorius, A., and Henn, F. A. (2007). Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Med. Hypotheses* 69, 1305–1308.

Sartorius, A., Kiening, K. L., Kirsch, P., von Gall, C. C., Haberkorn, U., Unterberg, A. W., Henn, F. A., and Meyer-Lindenberg, A. (2010). Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biol. Psychiatry* 67, e9–e11.

Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., Joe, A. Y., Kreft, M., Lenartz, D., and Sturm, V. (2008a). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33, 368–377.

Schlaepfer, T. E., Frick, C., Zobel, A., Maier, W., Heuser, I., Bajbouj, M., O'Keane, V., Corcoran, C., Adolfsson, R., Trimble, M., Rau, H., Hoff, H. J., Padberg, F., Muller-Siecheneder, F., Audenaert, K., Van den Abbeele, D., Stanga, Z., and Hasdemir, M. (2008b). Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol. Med.* 38, 651–661.

Schlaepfer, T. E., and Fins, J. J. (2010). Deep brain stimulation and the neuroethics of responsible publishing: when one is not enough. *JAMA* 303, 775–776.

Schlaepfer, T. E., George, M. S., Mayberg, H., and WFSBP Task Force on Brain Stimulation. (2010). WFSBP guidelines on brain stimulation treatments in psychiatry. *World J. Biol. Psychiatry* 11, 2–18.

Schlaepfer, T. E., Kosel, M., and Nemeroff, C. B. (2003). Efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of affective disorders. *Neuropsychopharmacology* 28, 201–205.

Schlaepfer, T. E., and Lieb, K. (2005a). Deep brain stimulation for treatment of refractory depression. *Lancet* 366, 1420–1422.

Schlaepfer, T. E., and Lieb, K. (2005b). Deep brain stimulation for treatment refractory depression. *Lancet* 366, 1420–1422.

Stein, D. J. (2002). Obsessive-compulsive disorder. *Lancet* 360, 397–405.

Sturm, V., Lenartz, D., Koulousakis, A., Treuer, H., Herholz, K., Klein, J. C., and Klosterkotter, J. (2003). The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J. Chem. Neuroanat.* 26, 293–299.

Synofzik, M., and Schlaepfer, T. (2010). Electrodes in the brain – ethical criteria for research and treatment with deep brain stimulation for neuropsychiatric disorders. *Brain Stimul.* 4, 7–16.

Synofzik, M., and Schlaepfer, T. E. (2008). Stimulating personality: ethical criteria for deep brain stimulation in psychiatric patients and for enhancement purposes. *Biotechnol. J.* 3, 1511–1520.

Winter, C., Vollmayr, B., Djodari-Irani, A., Klein, J., and Sartorius, A. (2011). Pharmacological inhibition of the lateral habenula improves depressive-like behavior in an animal model of treatment resistant depression. *Behav. Brain Res.* 216, 463–465.

Yurgelun-Todd, D. A., Sava, S., and Dahlgren, M. K. (2007). Mood disorders. *Neuroimaging Clin. N. Am.* 17, 511–521, ix.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 January 2011; accepted: 14 June 2011; published online: 24 June 2011.

Citation: Schlaepfer TE, Bewernick B, Kayser S and Lenz D (2011) Modulating affect, cognition, and behavior – prospects of deep brain stimulation for treatment-resistant psychiatric disorders. Front. Integr. Neurosci. ***5****:29. doi: 10.3389/fnint.2011.00029*

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 06 June 2011
doi: 10.3389/fnint.2011.00022

The need for a proper definition of a "treatment refractoriness" in Tourette syndrome

Mauro Porta, Marco Sassi*, Claudia Menghetti and Domenico Servello

Functional Neurosurgical Unit, IRCCS Galeazzi, Milano, Italy
**Correspondence: dr.sassi@yahoo.it*

Gilles de la Tourette syndrome (TS) is a complex neuropsychological disorder usually characterized by both phonic and motor tics (Robertson, 2000; Porta et al., 2009a,b). The prevalence of TS reaches 50 per 10,000 in the general population (Leckman, 2002). Nevertheless, it is generally considered a "rare disease": this is probably because of all the patients affected with TS only a minority suffers from a severe clinical picture. The syndrome demonstrates approximately a 10-fold higher incidence in children than in adults (Leckman, 2002), with a prevalence of up to 299 per 10,000 in children of age 13–14 years (Mason, 1998), while the onset of tics occurs at a mean age of 5–7 years (Freeman, 2000; Leckman, 2002). Especially because of this last issue, patients who are diagnosed with TS are often socially impaired. Even though the various degrees of severity of clinical manifestations of TS in certain cases allow a normal social functioning, when there is a social impairment this is often caused by tic manifestations. Tics are usually perceived as inappropriate, mimicking complex behaviors often of sexual nature. On the other hand, there is a widespread lack of information about TS so that people are unprepared to deal with these patients or to consider their behaviors as part of a disease. Moreover, behavioral comorbidities such as attention deficit-hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), and depression can further complicate the picture, and patients may be socially hindered because of both tics and behavioral abnormalities. Considering the complexity of such a variable clinical symptomatology in TS, the Tourette Syndrome Classification Study Group has introduced in their classification the subdivision between Definite Tourette Syndrome in which videotapes record the very clinical manifestations of the disease, and Tourette Syndrome by history, in which reliable caregivers (a family member or a close friend) documents and describes the clinical features of the disease (Tourette Study Group, 1993).

A further difficulty in defining the specific clinical picture for the patient is that tics may change during the course of illness and new tics can issue (Du, 2010; Liao, 2010; Worbe, 2010). The development of diagnostic instruments that try to bypass the timing of the different clinical manifestations, such as the Diagnostic Confidence Index (Robertson, 1999), demonstrate the need for a sound description of such an ever-changing clinical picture.

As previously said, in a significant number of cases TS patients present also behavioral comorbidities. OCD is documented in up to 50% of patients in published experiences in Literature (Freeman, 2000; Robertson, 2000), while in our experience obsessive traits of personality can be demonstrated in up to 85% of patients. ADHD is present in up to 60% of patients in our series and in patients series presented in literature (Freeman, 2000; Robertson, 2000). Anxiety is documented in up to 40% of patients in literature data (Freeman, 2000; Robertson, 2000) while in our experience it presents in 50% of patients, while learning difficulties during school age present in 30% of TS patients both in our experience and in literature data (Freeman, 2000; Robertson, 2000). Some patients demonstrate a high grade of impairment in their social and working life (Neuner et al., 2009; Conelea, 2010; Du, 2010; Eddy et al., 2010, 2011).

Considering that a significant percentage of these patients may show a certain degree of improvement up to a complete disappearance of all clinical manifestations by the major age, deep brain stimulation (DBS) has classically been indicated for those patients failing to show a significant amelioration of symptoms during adulthood (Mink, 2006). On the other hand, it is during developmental age that clinical stigmata of the disorder cause the most of the damage, severely, and permanently altering the social functioning of the patient, in some cases to an extent in which even after regression of symptoms the return to a normal social life is impossible. Moreover, DBS for TS seems to have significant incidence of complications and thus its indication must be evaluated adequately before proceeding (Servello, 2010). Conversely, drug treatment has been used when treating a young patient with a significant social impairment, but again, important adverse event may issue (Bestha, 2010).

Drug therapies involve antipsychotic medications that have been shown to be weighted by significant adverse effects that may persist during adulthood to a point that recently the need for more strict treatment guidelines has been required (Panagiotopoulos, 2010; Pringsheim and Pearce, 2010).

Considering the experiences presented in international literature, a structured protocol for drug therapies is usually not cited, and reports describe "maximum dose of established treatments" (Kuhn, 2007), "an inadequate response to at least two dopamine blockers or catecholamine depletors" (Maciunas, 2007), "failure of best treatment by medication (antipsychotics), or intolerance after a minimum of 6 months of treatment" (Welter, 2008).

Indication to treatment be it invasive or conservative should be considered on the basis of a definition of refractoriness to treatments proposed in the previous "step" of the algorithm.

Our guideline is that patients need to be observed in order to document (1) the most impairing feature of that specific TS picture – this also helps when determining the appropriate target for DBS, and (2) the evolution of the clinical picture – and thus the need for an invasive treatment on the basis of the severity of clinical manifestations and the need for specific medications on the basis of clinical manifestations. At our Institution (IRCCS Galeazzi, Milan, Italy) patients are followed with at least 2 years

of psychological therapy, and must show unsatisfying results (i.e., inadequate clinical response and/or side effects) with at least two drugs belonging to these categories: (1) traditional and/or innovative antipsychotics, (2) catecolamine depletors, (3) SSRI.

When considering DBS, our main goal (Servello, 2008) is to put the patient's quality of life at the base of a therapeutic algorithm involving DBS.

Results of the DBS choice for these patients are at best still experimental, and thus a definitive indication to treatment still has to be defined (Hariz and Robertson, 2010).

Ackermans (2008) reports different nuclei targeted with DBS for intractable TS: (1) the medial portion of the thalamus, at the cross point of centromedian nucleus (CM) with ventralis oralis pars intermedia (Voi); (2) the medial portion of thalamus, CM – parafascicularis (Pf); (3) the globus pallidus pars interna (GPi), posteroventrolateral part; (4) the GPi, anteromedial part; and (5) the nucleus accumbens (NAc) and anterior limb of internal capsule (IC).

A complete evaluation of the patient's quality of life must include the main complain of the patient and thus treatment should aim at treating that particular comorbidity or tic, and thus DBS target has to be tailored to the specific patient's clinical manifestation (Sassi, 2010).

REFERENCES

Ackermans, L., Temel, Y., and Visser-Vandewalle, V. (2008). Deep brain stimulation in Tourette's syndrome. *Neurotherapeutics* 5, 339–344.

Bestha, D. P., Jeevarakshagan, S., and Madaan, V. (2010). Management of tics and Tourette's disorder: an update. *Expert Opin. Pharmacother.* 11, 1813–1822.

Conelea, C. A., Woods, D. W., Zinner, S. H., Budman, C., Murphy, T., Scahill, L. D., Compton, S. N., and Walkup, J. (2010). Exploring the impact of chronic tic disorders on youth: results from the Tourette syndrome impact survey. *Child Psychiatry Hum. Dev.* 42, 219–242.

Du, J. C., Chiu, T. F., Lee, K. M., Wu, H. L., Yang, Y. C., Hsu, S. Y., Sun, C. S., Hwang, B., and Leckman, J. F. (2010). Tourette syndrome in children: an updated review. *Pediatr. Neonatol.* 51, 255–264.

Eddy, C. M., Cavanna, A. E., Gulisano, M., Agodi, A., Barchitta, M., Calì, P., Robertson, M. M., and Rizzo, R. (2010). Clinical correlates of quality of life in Tourette syndrome. *Mov. Disord.* 26, 735–738.

Eddy, C. M., Rizzo, R., Gulisano, M., Agodi, A., Barchitta, M., Calì, P., Robertson, M. M., and Cavanna, A. E. (2011). Quality of life in young people with Tourette syndrome: a controlled study. *J. Neurol.* 258, 291–301.

Freeman, R. D., Fast, D. K., Burd, L., Kerbeshian, J., Robertson, M. M., and Sandor, P. (2000). An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Dev. Med. Child Neurol.* 42, 436–447.

Hariz, M. I., and Robertson, M. M. (2010). Gilles de la Tourette syndrome and deep brain stimulation. *Eur. J. Neurosci.* 32, 1128–1134.

Kuhn, J., Lenartz, D., Mai, J. K., Huff, W., Lee, S. H., Koulousakis, A., Klosterkoetter, J., and Sturm, V. (2007). Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome . *J. Neurol.* 254, 963–965.

Leckman, J. F. (2002). Tourette's syndrome. *Lancet* 360, 1577–1586.

Liao, I. H., and Sharp, F. R. (2010). Tourette syndrome: gene expression as a tool to discover drug targets. *Chemotherapeutics* 7, 302–306.

Maciunas, R. J., Maddux, B. N., Riley, D. E., Whitney, C. M., Schoenberg, M. R., Ogrocki, P. J., Albert, J. M., and Gould, D. J. (2007). Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. *J. Neurosurg.* 107, 1004–1014.

Mason, A., Banerjee, S., Eapen, V., Zeitlin, H., and Robertson, M. M. (1998). The prevalence of Tourette syndrome in a mainstream school population. *Dev. Med. Child Neurol.* 40, 292–296.

Mink, J. W., Walkup, J., Frey, K. A., Como, P., Cath, D., Delong, M. R., Erenberg, G., Jankovic, J., Juncos, J., Leckman, J. F., Swerdlow, N., Visser-Vandewalle, V., Vitek, J. L., and Tourette Syndrome Association, Inc. (2006). Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. *Mov. Disord.* 21, 1831–1838.

Neuner, I., Podoll, K., Janouschek, H., Michel, T. M., Sheldrick, A. J., and Schneider, F. (2009). From psychosurgery to neuromodulation: deep brain stimulation for intractable Tourette syndrome. *World J. Biol. Psychiatry* 10(Pt 2), 366–376.

Panagiotopoulos, C., Ronsley, R., Elbe, D., Davidson, J., and Smith, D. H. (2010). First do no harm: promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. *J. Can. Acad. Child Adolesc. Psychiatry* 19, 124–137.

Porta, M., Brambilla, A., Cavanna, A. E., Servello, D., Sassi, M., Rickards, H., and Robertson, M. M. (2009a). Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome. *Neurology* 73, 1375–1380.

Porta, M., Servello, D., Sassi, M., Brambilla, A., Defendi, S., Priori, A., and Robertson, M. (2009b). Issues related to deep brain stimulation for treatment-refractory Tourette's syndrome. *Eur. Neurol.* 62, 264–273.

Pringsheim, T., and Pearce, M. (2010). Complications of antipsychotic therapy in children with tourette syndrome. *Pediatr. Neurol.* 43, 17–20.

Robertson, M. M. (2000). Tourette syndrome, associated conditions and the complexities of treatment. *Brain* 123, 425–462.

Robertson, M. M., Banerjee, S., Kurlan, R., Cohen, D. J., Leckman, J. F., McMahon, W., Pauls, D. L., Sandor, P., and Van de Wetering, B. J. (1999). The Tourette syndrome diagnostic confidence index: development and clinical associations. *Neurology* 53, 2108–2112.

Sassi, M., Porta, M., and Servello, D. (2010). Deep brain stimulation therapy for treatment-refractory Tourette's syndrome: a review. *Acta Neurochir. (Wien)* 153, 639–645.

Servello, D., Porta, M., Sassi, M., Brambilla, A., and Robertson, M. M. (2008). Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. *J. Neurol. Neurosurg. Psychiatr.* 79, 136–142.

Servello, D., Sassi, M., Gaeta, M., Ricci, C., and Porta, M. (2010). Tourette syndrome (TS) bears a higher rate of inflammatory complications at the implanted hardware in deep brain stimulation (DBS). *Acta Neurochir. (Wien)* 153, 629–632.

Tourette Study Group. (1993). Definitions and classification of tic disorders. The Tourette syndrome classification study group. *Arch. Neurol.* 50, 1013–1016.

Welter, M. L., Mallet, L., Houeto, J. L., Karachi, C., Czernecki, V., Cornu, P., Navarro, S., Pidoux, B., Dormont, D., Bardinet, E., Yelnik, J., Damier, P., and Agid, Y. (2008). Internal pallidal and thalamic stimulation in patients with Tourette syndrome. *Arch. Neurol.* 65, 952–957.

Worbe, Y., Mallet, L., Golmard, J. L., Béhar, C., Durif, F., Jalenques, I., Damier, P., Derkinderen, P., Pollak, P., Anheim, M., Broussolle, E., Xie, J., Mesnage, V., Mondon, K., Viallet, F., Jedynak, P., Ben Djebara, M., Schüpbach, M., Pelissolo, A., Vidailhet, M., Agid, Y., Houeto, J. L., and Hartmann, A. (2010). Repetitive behaviours in patients with Gilles de la Tourette syndrome: tics, compulsions, or both? *PLoS ONE* 5, e12959. doi: 10.1371/journal.pone.0012959

Received: 30 December 2010; accepted: 09 May 2011; published online: 06 June 2011.

Citation: Porta M, Sassi M, Menghetti C and Servello D (2011) The need for a proper definition of a "treatment refractoriness" in Tourette syndrome. Front. Integr. Neurosci. 5:22. doi: 10.3389/fnint.2011.00022

frontiers in
INTEGRATIVE NEUROSCIENCE

PERSPECTIVE ARTICLE
published: 02 May 2011
doi: 10.3389/fnint.2011.00008

Balancing the brain: resting state networks and deep brain stimulation

Morten L. Kringelbach[1,2,3]*, Alexander L. Green[3] and Tipu Z. Aziz[2,3]

[1] *Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK*
[2] *Centre for Functionally Integrative Neuroscience, University of Aarhus, Aarhus, Denmark*
[3] *Nuffield Department of Surgery, John Radcliffe Hospital, Oxford, UK*

Edited by:
Chiara Saviane, Scuola Internazionale Superiore di Studi Avanzati, Italy

Reviewed by:
Hiroki Toda, The Tazuke Kofukai Medical Research Institute Kitano Hospital, Japan
Jens Kuhn, University of Cologne, Germany

****Correspondence:***
Morten L. Kringelbach, Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford OX3 7JX, UK.
e-mail: morten.kringelbach@psych.ox.ac.uk

Over the last three decades, large numbers of patients with otherwise treatment-resistant disorders have been helped by deep brain stimulation (DBS), yet a full scientific understanding of the underlying neural mechanisms is still missing. We have previously proposed that efficacious DBS works by restoring the balance of the brain's resting state networks. Here, we extend this proposal by reviewing how detailed investigations of the highly coherent functional and structural brain networks in health and disease (such as Parkinson's) have the potential not only to increase our understanding of fundamental brain function but of how best to modulate the balance. In particular, some of the newly identified hubs and connectors within and between resting state networks could become important new targets for DBS, including potentially in neuropsychiatric disorders. At the same time, it is of essence to consider the ethical implications of this perspective.

Keywords: resting state networks, oscillations, spontaneous activity, affective disorders, movement disorders

INTRODUCTION

Over the last couple of decades, deep brain stimulation (DBS) has shown remarkable clinical efficacy and safety in helping with otherwise treatment-resistant problems such as movement disorders and chronic pain (Kringelbach et al., 2007b; Deniau et al., 2010). The underlying principles and neural mechanisms of DBS are not yet fully understood but translational research has shown that DBS directly changes brain activity in a controlled manner (McIntyre and Hahn, 2010) and that, in principle, the resulting effects are reversible (Perlmutter and Mink, 2006). Many chronic brain disorders are linked to disturbances in finely balanced oscillatory brain networks, and we have previously proposed that an important principle by which DBS might work is to help restore the balance of resting state networks (Kringelbach et al., 2010). Thus the identification and understanding of the structural and functional architecture of these neural networks have the potential to direct novel targets and treatments with DBS.

The purpose of this perspective is to review the current state-of-the-art in characterizing the structural and functional architecture of the brain with a view to how this can best be modulated through DBS. We will focus on the analysis of the spontaneous brain activity that give rise to the intrinsic dynamics of the brain, which can be measured as spatially and temporally segregated networks (Deco et al., 2011). Some of this activity can be measured with functional neuroimaging as spontaneous fluctuations in blood oxygen level-dependent (BOLD) functional MRI (fMRI) signal. These intrinsic measures are stable across sessions and participants, and remarkably quick to acquire over only a matter of minutes (Greicius, 2008), which opens up for their use in even severely impaired patient groups. The functional activity is linked to structural brain connectivity which can now be measured *in vivo*, and which to some extent constrain the functional networks (Bullmore and Sporns, 2009). The resulting brain networks are remarkable stable in healthy individuals but have been shown to break down in various brain disorders. This in turn opens up for the discovery of the function of the hubs and connectors that are controlling the activity within and between brain networks. We argue that a better understanding of the detailed breakdown of the sub-components of the resting state networks in brain disorders opens for a principled way to discover novel targets with DBS.

INTRINSIC NETWORK DYNAMICS

Over the last few years the focus of modern neuroimaging has started to shift from the study of extrinsic to intrinsic brain activity (Biswal et al., 2010). This change has been brought about by the realization that while the vast majority of neuroimaging studies have been devoted to studying task-related changes in brain activity, the additional energy associated with this activity is remarkable low, often less than 5% (Raichle and Mintun, 2006). Instead, the majority of brain energy consumption is devoted to intrinsic brain activity.

This intrinsic brain activity was mapped during the rest period in cognitive studies where researchers found a network of brain regions with remarkably high rates of change in metabolic markers such as cerebral blood flow, oxygen extraction and BOLD fMRI (Lou et al., 1999). This network of brain regions was termed the Default Mode Network where the main regions in the network showed the largest deactivations during extrinsic cognitive tasks (Raichle and Mintun, 2006). While the network was initially thought to subserve internal modes of cognition such as representations of self (Buckner et al., 2008), this view is challenged by the persistence of the default mode network during light anesthesia in humans (Greicius et al., 2008) and monkeys (Vincent et al., 2006), as well as during early stages of sleep (Fukunaga et al., 2006).

Other strands of research have focused on measuring the temporal correlation of spontaneous low-frequency BOLD signal fluctuations (Biswal et al., 1995). The measurement of these spontaneous fluctuations across various brain regions in the absence of an overt task has identified multiple functional resting state networks including the default mode network (Lowe et al., 1998; Greicius et al., 2003). Sophisticated independent component analyses of resting state patterns have identified at least seven networks which stay coherent over several minutes (Damoiseaux et al., 2006). Based on their brain components, these networks have been classified in (1) primary input–output networks (including sensorimotor, visual, auditory regions), (2) higher integrative networks (including attention, language, default mode, and executive regions; Beckmann et al., 2005), and (3) cortico-subcortical networks (including structures as the thalamus, basal ganglia, and cerebellum; Fox and Raichle, 2007). Interestingly, regions of the default mode network will remain tightly coherent but tend to show negative correlations with task-positive regions in the other networks.

The intrinsic activity of the human brain must be closely related to the large-scale anatomical connectivity between brain regions. Techniques such diffusion spectrum imaging and graph theory have revealed that the human brain exhibits a special kind of topology known as small-world architecture (Watts and Strogatz, 1998), which is characterized by high levels of local clustering among neighboring nodes (Hagmann et al., 2007; Bullmore and Sporns, 2009). Some nodes have higher connectivity in comparison with other nodes and are called hubs (He et al., 2009). The default mode network mostly consists of hubs, and in particular the precuneus and posterior cingulate cortex have been proposed to form the structural core (Hagmann et al., 2008). In general, structural and functional connectivity are linked, with the former predicting the latter (Honey et al., 2007). However, strong functional connectivity can exist between regions with no direct structural connection but that indirect connections and inter-regional distance to some extent can account for this (Honey et al., 2009).

This opens up the question of why these resting state networks exist in the first place. A long line of research has shown that the brain is primarily concerned with creating predictions optimizing input–output, which are then compared and updated accordingly (Friston, 2005). A potential explanation of the brain dynamics at rest has therefore been proposed to be linked to this constant state of exploration (Deco et al., 2011). The dynamics of the resting state networks could represent a metastable state; i.e., a state which persists for an extended period of time away from the natural equilibrium state. The brain is constantly exploring the potential functional network configurations, which over longer time windows will come to reflect the anatomical connectivity but over shorter time scales may be considerably more varied according to the impact of environmental demands. Computational models have shown how the important parameters in this process include local and global dynamics, noise, and signal transmission delay (Deco et al., 2009).

What has become clear is that neither the general neural dynamics, the structural connectivity, or the functional resting state networks are fully formed at birth but are being shaped during development (Fransson et al., 2007). As a result, important differences exist between infants, children, and adults (Gao et al., 2009; Supekar et al., 2010; Fan et al., 2011). The maturational processes must be driven foremost by extrinsic, environmental demands (Power et al., 2010) but also by intrinsic changes such as white matter maturation reshaping structural connectivity (Hagmann et al., 2010). It has been proposed that the epigenetic influences on shaping the neural dynamics of the resting state networks are at least as important as genetic factors, and can have a lasting impact on a number of important variables influencing quality of life, especially during the first 18 months (Parsons et al., 2010). One major variable of quality of life is overall hedonic tone, i.e., the likelihood of enjoying life and not suffering from anhedonia in mental disorders such as depression and anxiety. We have previously speculated that the default mode network may have an important role in shaping our overall well-being (Kringelbach and Berridge, 2009) (see **Figure 1**).

BALANCING RESTING STATE NETWORKS IN DISEASE

In general, resting state networks have been found to undergo significant, if sometimes only temporary changes in chronic brain disorders such as neuropsychiatric disorders (Greicius, 2008; Broyd et al., 2009). The causes of these perturbations are currently not well understood but it is clear that successful treatments somehow rebalance resting state networks. In disorders with no known pathology such as depression and anxiety, the subsequent rebalancing can occur spontaneously, or through carefully targeted interventions of either a cognitive nature (Teasdale et al., 2000) or even through more invasive methods such as DBS (Bewernick et al., 2010).

In pathological disorders with known pathologies like Parkinson's disease (PD) or chronic pain, spontaneous rebalancing is much less common and treatments often relies on heavily on understanding the system through the appropriate translational methods. In the case of PD, significant progress has been made through a number of animal models including the highly successful 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model in higher primates (Langston et al., 1983). This model has helped identify a number of efficacious DBS targets such as the subthalamic nucleus (STN; Bergman et al., 1990; Aziz et al., 1991).

In PD, the loss of dopaminergic cells means that the basic oscillations between cortex and subcortical regions become unbalanced. Human studies have found there are strong increases in beta (15–30 Hz) oscillatory activity in the STN when the patients are without dopaminergic medication, while therapeutic effective STN stimulation of larger than 70 Hz has the effect of suppressing this noisy activity in the basal ganglia (Brown et al., 2004).

Careful animal and human experimentation have thus given a better understanding of some of the fundamental principles of the breakdown in PD of how brain regions oscillate and communicate (Schnitzler and Gross, 2005). DBS has in turn brought some relief for over 60,000 PD patients since the early 1990s.

On the basis of this experimentation, some conclusions can be drawn about the neural and systems level mechanisms of action of DBS. The effects of DBS are closely linked to at least three factors: (1) the stimulation parameters (including frequency, amplitude, pulse width, and duration); (2) the intrinsic physiological properties of the neural tissue which may change with disease state; and (3) the interactions between the electrode and the geometric configuration of the surrounding neural tissue and specific anatomy

of the targeted region (Kringelbach et al., 2007b). The evidence clearly shows that DBS affects multiple neural elements; foremost myelinated axons – and to a lesser degree cell bodies.

The fundamental mechanism of DBS is through stimulation-induced modulation of the activity of larger brain networks (Montgomery and Baker, 2000; Vitek, 2002; McIntyre et al., 2004; Kringelbach et al., 2007b; McIntyre and Hahn, 2010). This has been confirmed by optogenetic experiments in rodents which show that the therapeutic effects within the STN can be accounted for by direct selective stimulation of afferent axons projecting to this region (Gradinaru et al., 2009).

Despite the remarkable successes in treating PD with DBS, it is not clear at this point if the existing targets and treatments are the most efficacious. The oscillatory activity clearly reflects a variety of motor and cognitive–emotional processes but it is not clear how disease severity or extrinsic task demands affect the neural dynamics of PD (Vardy et al., 2010). Neuroimaging studies have, however, shown that the default mode network exhibits specific changes in PD (van Eimeren et al., 2009; Delaveau et al., 2010). Significant functional differences were found in the posterior cingulate cortex and precuneus, and connectivity analysis showed that the medial prefrontal cortex and rostral ventromedial caudate nucleus were functionally disconnected in PD. Some of these changes can be restored with administration of levodopa (Delaveau et al., 2010). Yet, so far DBS has not been used in any of the affected hubs of the default mode network in PD.

The large body of PD research mapping the underlying mechanisms of DBS has not yet been matched by a similar body of evidence for the emerging DBS treatment of neuropsychiatric disorders (Kopell and Greenberg, 2008). Interestingly, however, it should be noted that many of the brain structures involved in movement disorders are also implicated in affective disorders. This is for example demonstrated by how severe depression can be reversibly induced by DBS for PD (Bejjani et al., 1999; Temel et al., 2006).

From the present perspective, these transient changes are of considerable interest taken together with the demonstrated altered activity in affective disorders for many of the main hubs and connectors such as the subgenual cingulate cortex, orbitofrontal cortex, ventral pallidum, and nucleus accumbens (Giacobbe et al., 2009; Bewernick et al., 2010). These reward-related brain regions are known to modulate hedonic state and as such could be responsible for the debilitating anhedonia found in affective disorders (Kringelbach, 2005; Berridge and Kringelbach, 2008). One possible hypothesis is thus that DBS for affective disorders could work by modulating the hedonic circuitries in order to alleviate anhedonia (Kringelbach and Berridge, 2009; Kringelbach et al., 2010).

NOVEL RESEARCH AVENUES

The future of direct brain interventions will rely on having a much better understanding of the fundamental nature of intricate dynamics of the resting state networks. Most of the current evidence has come from neuroimaging techniques such as BOLD fMRI and positron emission tomography which are only indirect, correlational measures of neural activity. The dynamic nature of the short and long-term brain activity means that we will need a far more detailed understanding of underlying signals, including computational modeling (Deco et al., 2011). More temporally suitable neuroimaging methods such as magnetoencephalography (MEG) are starting to address these shortcomings (Hansen et al., 2010).

In fact, combining MEG and DBS may offer new insights into the fine-grained temporal neural dynamics of aberrant brain states, while at the same time providing novel insights into the fundamental principles as first demonstrated in 2006 (Kringelbach et al., 2007a) (see **Figure 1C**). The technical challenges of using an invasive technique with a highly sensitive method are significant but not insurmountable. One subsequent study used simultaneous MEG and local field potential (LFP) recordings from the DBS electrode to demonstrate that an image analysis method called beamforming is capable of suppressing the high-amplitude artifacts caused by the DBS wire and electrode and extracting artifact-free virtual electrode time-series (Litvak et al., 2010). Another study using DBS, LFP, and MEG found frequency-specific functional connectivity between basal ganglia and cortex in PD, suggesting

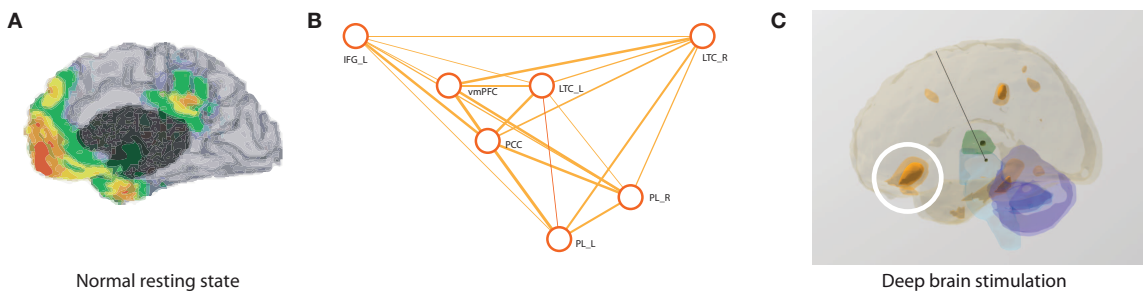


FIGURE 1 | (A) The brain's default mode network is a steady state circuit of the brain where activity increases during rest (Gusnard and Raichle, 2001). The coloring indicates brain areas with significant levels of blood flow. **(B)** In the normal brain, this brain network can be described in terms of functional connectivity graphs. More strongly connected regions (indicated by heavier orange lines) are clustered near each other while weakly correlated regions are placed further away with the line width proportional to the connection strength (Gao et al., 2009). **(C)** Deep brain stimulation causally alters brain activity and future challenges include how to best restore this default network in malignant brain disorders. We made a tentative start by using MEG to investigate how a deep brain stimulation electrode implanted in the PVG/PAG can help a wider network alleviate the suffering of chronic pain (Kringelbach et al., 2007a). The three-dimensional rendering shows the significant increases in activity in shades of orange, e.g., in regions such as the mid-anterior orbitofrontal cortex (white circle), while the other colors represent landmark brain structures: thalamus (green), cerebellum (blue), and brainstem (light blue). IFG_L, IFG_R left and right inferior frontal gyrus; LTC_L, LTC_R, left and right lateral temporal cortex; PCC, posterior cingulate cortex/retrosplenial; PL_L, PL_R, left and right parietal lobes; vmPFC, ventromedial prefrontal cortex.

that simultaneous inter-regional interactions may be segregated in the frequency domain (Hirschmann et al., 2010). Specifically, coherent activity was found in the low and high beta range in the ipsilateral sensorimotor and the premotor cortex, while coherence in the alpha range (7–12 Hz) was observed at various locations in the ipsilateral temporal lobe.

We combined DBS and MEG to obtain important new information about the underlying neural dynamics in a rare case of whole-body chronic pain (Mohseni et al., 2010). We stimulated one of the main hubs of the brain, the anterior cingulate cortex, and found the stimulation-specific alleviation of whole-body pain was modulating brain activity in a wide spread network of regions including the pre-supplementary motor area, brainstem periaqueductal gray, rostral anterior cingulate cortex, and medial prefrontal areas. Given the lack of good animal models for chronic pain, this information could be important for guiding future treatments. It could also be pertinent to our general understanding of the role of the anterior cingulate cortex in refractory depression, pain, and obsessive–compulsive disorder, and in particular why bilateral anterior cingulotomies have been found to have some beneficial effects (Steele et al., 2008).

DISCUSSION

We are only beginning to understand the neural dynamics underlying the intrinsic structural and functional brain activity (Biswal et al., 2010). It is, however, clear that specific modulation of these resting state networks in disease could bring significant benefits for future treatments of chronic brain disorders. The demonstrated clinical efficacy and safety of DBS means that this technique is an important tool for rebalancing the resting state networks (Kringelbach et al., 2010).

In this perspective article, we have reviewed the current evidence for DBS as a tool for modulation of the activity of the highly coherent functional and structural brain networks in health and disease. In particular, we have focused on how some of the hubs and connectors within and between resting state networks of the brain could become important new stimulation targets, including potentially in neuropsychiatric disorders.

Overall, DBS remains an important tool both for alleviating human suffering and for obtaining novel insights into the nature of fundamental brain function. Combining DBS with a better understanding of the intrinsic activity of the brain may come to serve as an important tool for rebalancing resting state network activity in chronic brain disorders. Yet, this promising avenue for discovering novel DBS targets must be guided by careful ethical considerations (Kringelbach and Aziz, 2009; Schlaepfer and Fins, 2010).

ACKNOWLEDGMENTS

The authors were funded by TrygFonden Charitable Foundation, Medical Research Council, Norman Collisson Foundation, and Charles Wolfson Charitable Trust.

REFERENCES

Aziz, T. Z., Peggs, D., Sambrook, M. A., and Crossman, A. R. (1991). Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Mov. Disord.* 6, 288–292.

Beckmann, C. F., DeLuca, M., Devlin, J. T., and Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 360, 1001–1013.

Bejjani, B. P., Damier, P., Arnulf, I., Thivard, L., Bonnet, A. M., Dormont, D., Cornu, P., Pidoux, B., Samson, Y., and Agid, Y. (1999). Transient acute depression induced by high-frequency deep-brain stimulation. *N. Engl. J. Med.* 340, 1476–1480.

Bergman, H., Wichmann, T., and DeLong, M. R. (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 249, 1436–1438.

Berridge, K. C., and Kringelbach, M. L. (2008). Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology (Berl.)* 199, 457–480.

Bewernick, B. H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., Lemke, M., Cooper-Mahkorn, D., Cohen, M. X., Brockmann, H., Lenartz, D., Sturm, V., and Schlaepfer, T. E. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol. Psychiatry* 67, 110–116.

Biswal, B, Yetkin, F. Z., Haughton, V. M., and Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn. Reson. Med.* 34, 537–541.

Biswal, B. B., Mennes, M., Zuo, X. N., Gohel, S., Kelly, C., Smith, S. M., Beckmann, C. F., Adelstein, J. S., Buckner, R. L., Colcombe, S., Dogonowski, A. M., Ernst, M., Fair, D., Hampson, M., Hoptman, M. J., Hyde, J. S., Kiviniemi, V. J., Kotter, R., Li, S. J., Lin, C. P., Lowe, M. J., Mackay, C., Madden, D. J., Madsen, K. H., Margulies, D. S., Mayberg, H. S., McMahon, K., Monk, C. S., Mostofsky, S. H., Nagel, B. J., Pekar, J. J., Peltier, S. J., Petersen, S. E., Riedl, V., Rombouts, S. A., Rypma, B., Schlaggar, B. L., Schmidt, S., Seidler, R. D., Siegle, G. J., Sorg, C., Teng, G. J., Veijola, J., Villringer, A., Walter, M., Wang, L., Weng, X. C., Whitfield-Gabrieli, S., Williamson, P., Windischberger, C., Zang, Y. F., Zhang, H. Y., Castellanos, F. X., and Milham, M. P. (2010). Toward discovery science of human brain function. *Proc. Natl. Acad. Sci. U.S.A.* 107, 4734–4739.

Brown, P., Mazzone, P., Oliviero, A., Altibrandi, M. G., Pilato, F., Tonali, P. A., and Di Lazzaro, V. (2004). Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. *Exp. Neurol.* 188, 480–490.

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., and Sonuga-Barke, E. J. (2009). Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci. Biobehav. Rev.* 33, 279–296.

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38.

Bullmore, E., and Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat. Rev. Neurosci.* 10, 186–198.

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., and Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proc. Natl. Acad. Sci. U.S.A.* 103, 13848–13853.

Deco, G., Jirsa, V., McIntosh, A. R., Sporns, O., and Kotter, R. (2009). Key role of coupling, delay, and noise in resting brain fluctuations. *Proc. Natl. Acad. Sci. U.S.A.* 106, 10302–10307.

Deco, G., Jirsa, V. K., and McIntosh, A. R. (2011). Emerging concepts for the dynamical organization of resting state activity in the brain. *Nat. Rev. Neurosci.* 12, 43–56.

Delaveau, P., Salgado-Pineda, P., Fossati, P., Witjas, T., Azulay, J. P., and Blin, O. (2010). Dopaminergic modulation of the default mode network in Parkinson's disease. *Eur. Neuropsychopharmacol.* 20, 784–792.

Deniau, J. M., Degos, B., Bosch, C., and Maurice, N. (2010). Deep brain stimulation mechanisms: beyond the concept of local functional inhibition. *Eur. J. Neurosci.* 32, 1080–1091.

Fan, Y., Shi, F., Smith, J. K., Lin, W., Gilmore, J. H., and Shen, D. (2011). Brain anatomical networks in early human brain development. *Neuroimage* 54, 1862–1871.

Fox, M. D., and Raichle, M. E. . (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci.* 8, 700–711.

Fransson, P., Skiold, B., Horsch, S., Nordell, A., Blennow, M., Lagercrantz, H., and Aden, U. (2007). Resting-state networks in the infant brain. *Proc. Natl. Acad. Sci. U.S.A.* 104, 15531–15536.

Friston, K. (2005). A theory of cortical responses. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 360, 815–836.

Fukunaga, M, Horovitz, S. G., van Gelderen, P., de Zwart, J. A., Jansma, J. M., Ikonomidou, V. N., Chu, R., Deckers, R. H., Leopold, D. A., and Duyn, J. H. (2006). Large amplitude,

spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. *Magn. Reson. Imaging* 24, 979–992.

Gao, W., Zhu, H., Giovanello, K. S., Smith, J. K., Shen, D., Gilmore, J. H., and Lin, W. (2009). Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proc. Natl. Acad. Sci. U.S.A.* 106, 6790–6795.

Giacobbe, P., Mayberg, H. S., and Lozano, A. M. (2009). Treatment resistant depression as a failure of brain homeostatic mechanisms: implications for deep brain stimulation. *Exp. Neurol.* 219, 44–52.

Gradinaru, V., Mogri, M., Thompson, K. R., Henderson, J. M., and Deisseroth, K. (2009). Optical deconstruction of Parkinsonian neural circuitry. *Science* 3247, 354–359.

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Curr. Opin. Neurol.* 21, 424–430.

Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpää, V., Alahuhta, S., Reiss, A. L., and Menon, V. (2008). Persistent default-mode network connectivity during light sedation. *Hum. Brain Mapp.* 29, 839–847.

Greicius, M. D., Krasnow, B., Reiss, A. L., and Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc. Natl. Acad. Sci. U.S.A.* 100, 253–258.

Gusnard, D. A., and Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* 2, 685–694.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., and Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol.* 6, e159. doi: 10.1371/journal.pbio.0060159

Hagmann, P., Kurant, M., Gigandet, X., Thiran, P., Wedeen, V. J., Meuli, R., and Thiran, J. P. (2007). Mapping human whole-brain structural networks with diffusion MRI. *PLoS ONE* 2, e597. doi: 10.1371/journal.pone.0000597

Hagmann, P., Sporns, O., Madan, N., Cammoun, L., Pienaar, R., Wedeen, V. J., Meuli, R., Thiran, J. P., and Grant, P. E. (2010). White matter maturation reshapes structural connectivity in the late developing human brain. *Proc. Natl. Acad. Sci. U.S.A.* 107, 19067–19072.

Hansen, P. C., Kringelbach, M. L., and Salmelin, R. (2010). *MEG. An Introduction to Methods*. Oxford: Oxford University Press.

He, Y., Wang, J., Wang, L., Chen, Z. J., Yan, C., Yang, H., Tang, H., Zhu, C., Gong, Q., Zang, Y., and Evans, A. C. (2009). Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PLoS ONE* 4, e5226. doi: 10.1371/journal.pone.0005226

Hirschmann, J., Ozkurt, T. E., Butz, M., Homburger, M., Elben, S., Hartmann, C. J., Vesper, J., Wojtecki, L., and Schnitzler, A. (2010). Distinct oscillatory STN-cortical loops revealed by simultaneous MEG and local field potential recordings in patients with Parkinson's disease. *Neuroimage* 55, 1159–1168.

Honey, C. J., Kotter, R., Breakspear, M., and Sporns, O. (2007). Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc. Natl. Acad. Sci. U.S.A.* 104, 10240–10245.

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., and Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proc. Natl. Acad. Sci. U.S.A.* 106, 2035–2040.

Kopell, B. H., and Greenberg, B. D. (2008). Anatomy and physiology of the basal ganglia: implications for DBS in psychiatry. *Neurosci. Biobehav. Rev.* 32, 408–422.

Kringelbach, M. L. (2005). The orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci.* 6, 691–702.

Kringelbach, M. L., and Aziz, T. Z. (2009). Deep brain stimulation: avoiding the errors of psychosurgery. *JAMA* 301, 1705–1707.

Kringelbach, M. L., and Berridge, K. C. (2009). Towards a functional neuroanatomy of pleasure and happiness. *Trends Cogn. Sci. (Regul. Ed.)* 13, 479–487.

Kringelbach, M. L., Green, A. L., Owen, S. L. F., Schweder, P. M., and Aziz, T. Z. (2010). Sing the mind electric: principles of deep brain stimulation. *Eur. J. Neurosci.* 32, 1070–1079.

Kringelbach, M. L., Jenkinson, N., Green, A. L., Owen, S. L. F., Hansen, P. C., Cornelissen, P. L., Holliday, I. E., Stein, J., and Aziz, T. Z. (2007a). Deep brain stimulation for chronic pain investigated with magnetoencephalography. *Neuroreport* 18, 223–228.

Kringelbach, M. L., Jenkinson, N., Owen, S. L. F., and Aziz, T. Z. (2007b). Translational principles of deep brain stimulation. *Nat. Rev. Neurosci.* 8, 623–635.

Langston, J. W., Ballard, P., Tetrud, J. W., and Irwin, I. (1983). Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 219, 979–980.

Litvak, V., Eusebio, A., Jha, A., Oostenveld, R., Barnes, G. R., Penny, W. D., Zrinzo, L., Hariz, M. I., Limousin, P., Friston, K. J., and Brown, P. (2010). Optimized beamforming for simultaneous MEG and intracranial local field potential recordings in deep brain stimulation patients. *Neuroimage* 50, 1578–1588.

Lou, H. C., Kjaer, T. W., Friberg, L., Wildschiodtz, G., Holm, S., and Nowak, M. (1999). A ^{15}O-H_2O PET study of meditation and the resting state of normal consciousness. *Hum. Brain Mapp.* 7, 98–105.

Lowe, M. J., Mock, B. J., and Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage* 7, 119–132.

McIntyre, C. C., and Hahn, P. J. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol. Dis.* 38, 329–337.

McIntyre, C. C., Savasta, M., Kerkerian-Le Goff, L., and Vitek, J. L. (2004). Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol.* 115, 1239–1248.

Mohseni, H. R., Kringelbach, M. L., Probert Smith, P., Parsons, C. E., Young, K. S., Hyam, J. A., Schweder, P. M., Stein, J. F., Green, A. L., and Aziz, T. Z. (2010). "Application of a null-beamformer to source localisation in MEG data of deep brain stimulation," in *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC'10,* Buenos Aires, 4120–4123.

Montgomery, E. B. Jr., and Baker, K. B. (2000). Mechanisms of deep brain stimulation and future technical developments. *Neurol. Res.* 22, 259–266.

Parsons, C. E., Young, K. S., Murray, L., Stein, A., and Kringelbach, M. L. (2010). The functional neuroanatomy of the evolving parent-infant relationship. *Prog. Neurobiol.* 91, 220–241.

Perlmutter, J. S., and Mink, J. W. (2006). Deep brain stimulation. *Annu. Rev. Neurosci.* 29, 229–257.

Power, J. D., Fair, D. A., Schlaggar, B. L., and Petersen, S. E. (2010). The development of human functional brain networks. *Neuron* 67, 735–748.

Raichle, M. E., and Mintun, M. A. (2006). Brain work and brain imaging. *Annu. Rev. Neurosci.* 29, 449–476.

Schlaepfer, T. E., and Fins, J. J. (2010). Deep brain stimulation and the neuroethics of responsible publishing. *JAMA* 303, 775–776.

Schnitzler, A., and Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nat. Rev. Neurosci.* 6, 285–296.

Steele, J. D., Christmas, D., Eljamel, M. S., and Matthews, K. (2008). Anterior cingulotomy for major depression: clinical outcome and relationship to lesion characteristics. *Biol. Psychiatry* 63, 670–677.

Supekar, K., Uddin, L. Q., Prater, K., Amin, H., Greicius, M. D., and Menon, V. (2010). Development of functional and structural connectivity within the default mode network in young children. *Neuroimage* 52, 290–301.

Teasdale, J. D., Segal, Z. V., Williams, J. M., Ridgeway, V. A., Soulsby, J. M., and Lau, M. A. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J. Consult. Clin. Psychol.* 68, 615–623.

Temel, Y., Kessels, A., Tan, S., Topdag, A., Boon, P., and Visser-Vandewalle, V. (2006). Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. *Parkinsonism Relat. Disord.* 12, 265–272.

van Eimeren, T., Monchi, O., Ballanger, B., and Strafella, A. P. (2009). Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. *Arch. Neurol.* 66, 877–883.

Vardy, A. N., van Wegen, E. E., Kwakkel, G., Berendse, H. W., Beek, P. J., and Daffertshofer, A. (2010). Slowing of M1 activity in Parkinson's disease during rest and movement – an MEG study. *Clin. Neurophysiol.* 122, 789–795.

Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., and Buckner, R. L. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. *J. Neurophysiol.* 96, 3517–3531.

Vitek, J. L. (2002). Mechanisms of deep brain stimulation: excitation or inhibition. *Mov. Disord.* 17, S69–S72.

Watts, D. J., and Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature* 393, 440–442.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 January 2011; accepted: 18 April 2011; published online: 02 May 2011. Citation: Kringelbach ML, Green AL and Aziz TZ (2011) Balancing the brain: resting state networks and deep brain stimulation. Front. Integr. Neurosci. ***5****:8. doi: 10.3389/fnint.2011.00008*

frontiers in
INTEGRATIVE NEUROSCIENCE

MINI REVIEW ARTICLE
published: 27 September 2011
doi: 10.3389/fnint.2011.00046

Industrial perspective on deep brain stimulation: history, current state, and future developments

Ali Sarem-Aslani* and Keith Mullett

Medtronic International Trading Sàrl, Tolochenaz, Switzerland

Edited by:
Thomas E. Schlaepfer, University Hospital of Bonn, Germany

Reviewed by:
Ziad Nahas, Medical University of South Carolina, US Minor Outlying Islands
Sidney Kennedy, University Health Network, Canada

****Correspondence:***
Ali Sarem-Aslani, Medtronic Europe, Earl-Bakken-Platz 1, 40670 Meerbusch, Germany.
e-mail: ali.sarem.aslani@medtronic.com

Deep brain stimulation (DBS) emerged in the late 1960s as a possible therapeutic alternative to lesioning in patients with severe, chronic, intractable pain. DBS devices in the era were based on cardiac pacing technology but were greatly modified in implementation due to the unique needs of DBS. Clinical studies in the 1970s and early 1980s have revealed a technique with modest results which did not lead to regulatory approval for the treatment of pain. In the 1980s a new application for DBS emerged in the treatment of movement disorders. Clinical trials confirmed the robustness of the therapy leading to approvals by regulatory authorities in the US and Europe for the treatment of tremor and the symptoms of Parkinson's disease. Technology based on that used for earlier clinical research in pain was improved by leveraging advances in cardiac pacing technology resulting in the sophisticated and reliable systems available today. In the 1990s scientific exploration began in the treatment of psychiatric disorders which is ongoing today. Simultaneously, studies into the treatment of epilepsy were begun which resulted in regulatory approval in Europe. Suggestions have been made to expand these scientific explorations to other central nervous system dysfunctions. Opportunity remains to improve the technology including individualized and symptom specific stimulation patterns, more physician and patient friendly programming, and possibly closed-loop systems for more situation dependent and effective therapy.

Keywords: deep brain stimulation, history, technology, pain, movement disorders, psychiatric disorders, epilepsy

INTRODUCTION

Neurostimulation is a method applied to treat various neurological disorders including chronic pain, urinary incontinence, and movement disorders. The vast experience with active implantable technology in cardiac stimulation has been evolved successfully into the development of neurostimulators and applications for chronic neurological and gastro-urological diseases. Major developments have been achieved through ongoing collaboration and partnership between academia and medical device industry. More than 80,000 patients have been treated with DBS worldwide through the end of 2010. The aim of this article is to provide an overview of the history, present status, and potential future developments of deep brain stimulation (DBS).

NOTICE

This article discusses current developments and future possibilities for DBS therapies. Three companies, Medtronic, Inc. (Minneapolis, MN, USA), St Jude Medical (St. Paul, MN, USA), and Boston Scientific (Natick, MA, USA) have developed DBS systems currently at various stages of regulatory evaluation and approval. The authors wish to emphasize that the only Medtronic DBS systems approved by regulatory authorities in Europe and the US are for the following therapies:

- Essential Tremor: CE Mark; FDA approval
- Symptoms of Parkinson's Disease (PD): CE Mark; FDA approval
- Dystonia: CE Mark; Humanitarian Device Exemption (HDE) in US
- Obsessive Compulsive Disorder (OCD): CE Mark; HDE in US
- Epilepsy: CE Mark

Refer to the product labeling packaged with Medtronic DBS products for specific indications, contraindications, warnings, precautions, adverse events summary, and patient selection. Refer to the product labeling of St Jude Medical and Boston Scientific for the specific regulatory status of these systems.

DBS HISTORY AND CURRENT STATE

With new findings on the pathophysiology and neuroanatomy of thalamocortical–basal ganglia neural circuits in neurological and psychiatric disorders, Neurosurgeons, Neurologists, and Psychiatrists have explored DBS targets in regions that correspond to traditional lesional targets. At first, DBS was considered to be "reversible lesioning." Further investigations, however, suggested that stimulation-induced modulation of brain activities may rather be the mechanism of action (Kringelbach et al., 2007). During the evolution of DBS in the treatment of pain, movement disorders, epilepsy, and psychiatric disorders, industry has worked hand-in-hand with physicians to develop these therapies.

PAIN

The first evidence of physician/industry collaboration on DBS came in 1969 when Hosobuchi approached Medtronic, Inc. to

design and build a system to stimulate the ventral posterior medial (VPM) nucleus of the thalamus in a patient with severe intractable facial pain (Hosobuchi et al., 1973). Today, DBS for pain is utilized in a small number of centers who report positive results in a highly selected patient population (Owen et al., 2007).

MOVEMENT DISORDERS

In 1987, Siegfried and Benabid independently reported suppression of severe, intractable tremor by stimulation of the ventral intermediate (Vim) nucleus of the thalamus (Benabid et al., 1987, 1991, 1993; Siegfried and Shulman, 1987). Although there were earlier reports of stimulation suppressing involuntary movements in the context of treating pain, these were the first reports of chronic DBS specifically for the treatment of movement disorders. Subsequently, Benabid collaborated with Medtronic on the development of DBS for treating patients with severe, intractable tremor which culminated in a multicenter clinical trial and regulatory approval for the therapy. In 1994, Siegfried reported improvement of multiple symptoms of PD by stimulation of the globus pallidus internal (GPi; Siegfried and Lippitz, 1994). In 1993, Benabid extended this work to stimulation of the sub-thalamic nucleus (STN) in patients with PD (Limousin et al., 1995). Clinical studies in North America and Europe resulted in regulatory approvals for these two indications (Limousin et al., 1999; The Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). Later clinical studies confirmed the early data with evidence Level 1 results (Deuschl et al., 2006; Weaver et al., 2009; Williams et al., 2010).

Deep Brain Stimulation has been explored for treating other movement disorders, most notably dystonia with stimulation in the GPi (Coubes et al., 2000; Kupsch et al., 2006; Mueller et al., 2008; Vidailhet et al., 2009). Studies are ongoing for DBS in the treatment of cervical dystonia (Krauss et al., 1999), tardive dystonia (Trottenberg et al., 2001; Gruber et al., 2009), Gilles de la Tourette syndrome (Temel and Visser-Vandewalle, 2004; Porta et al., 2009; Hariz and Robertson, 2010), and other movement disorders.

EPILEPSY

Velasco et al. (1987) reported favorable results with stimulation of the centromedian nucleus of the thalamus with DBS. In 2002, Lozano reported seizure reduction with DBS of the anterior nucleus (AN) of the thalamus (Hodaie et al., 2002). This led to a multicenter, double blind, randomized industry sponsored clinical trial of DBS of the AN in patients with refractory epilepsy which resulted in regulatory approval for the therapy in Europe. Fisher et al. (2010) concluded that bilateral DBS of the AN is useful in medically refractory partial and secondarily generalized seizures while the complication rates are modest. However, in the US, the FDA continues to review the data for risk benefit and approval for the therapy has not yet been granted. Meanwhile, Boon conducted pilot studies of amygdalohippocampal stimulation in temporal lobe epilepsy (Vonck et al., 2002; Boon et al., 2007). These studies are ongoing. A second industry sponsored clinical study is currently underway which evaluates the effect of stimulation of the seizure focus with a device capable of either surface or depth stimulation (NeuroPace, Mountain View, CA, USA).

PSYCHIATRIC DISORDERS

In 1999, Nuttin proposed stimulation of the internal capsule (IC) as an alternative to irreversible capsulotomy in the treatment of OCD opening the gateway for exploration of DBS in psychiatric disorders (Nuttin et al., 1999). Early mixed results led to a redefinition of the target as the area just ventral to the IC (ventral capsule/ventral striatum, VC/VS) and/or the nucleus accumbens (NA; Sturm et al., 2003; Denys et al., 2010; Greenberg et al., 2010). A French multicenter study explored the effects of DBS in the associative limbic part of the STN (Mallet et al., 2008). Observations that OCD patients treated with DBS in the region of the ventral striatum showed reduced depression led teams in North America and Europe to explore the use of DBS in the treatment of severely refractory depression patients (Malone et al., 2009; Bewernick et al., 2010). Studies are ongoing in North America, Europe, and elsewhere on these applications.

Other targets for the treatment of depression disorders under clinical investigation include the white matter adjacent to Brodmann Area 25 in the subgenual cingulated cortex (Cg25; Mayberg et al., 2005; Hamani et al., 2011), the ventral caudatum (Aouizerate et al., 2009), and the lateral habenula (Sartorius et al., 2010). Very recently the lateral branch of the medial forebrain bundle has been hypothesized to represent an alternative target (Coenen et al., 2010).

Deep Brain Stimulation is currently approved for the treatment of OCD by stimulation of the VC/VS through the HDE process in the US and by CE Mark in Europe. Both approvals were based on limited data and additional studies are ongoing to further clarify the benefits and limits of the therapy. Major industry sponsored trials of DBS of the VC/VS and DBS of the Cg25 in the treatment of depression are now underway. DBS for all other applications and targets in the treatment of psychiatric disorders is at an exploratory stage. The scientific community is concerned to avoid repeating the errors of a previous era of psychosurgery by proceeding carefully and in consultation with experts in ethics (Kringelbach and Aziz, 2009).

RISKS

Infection is one the most common adverse events reported at around 2.5% per year of which about one in five results in the explant of a portion of the system. Surgical complications are reported in the 3–4% range. Intracranial hemorrhage is reported at about 3%, approximately half of which are asymptomatic, a quarter are transient, and a quarter result in permanent deficit. Operative mortality is well under 1% (Voges et al., 2007). Hardware failure including lead dislodgement and fracture can also occur leading to replacement surgery.

Depression, suicidal ideations, and suicide have been reported in patients receiving DBS for movement disorders although no direct cause and effect relationship has been established (Witt et al., 2008). Patients should be assessed preoperatively for risk and monitored post-operatively for presence of these effects.

ETHICAL CONSIDERATIONS

Other potential therapeutic applications for DBS are numerous [cluster headache, dementia, addiction, gait disorders, obesity (Halpern et al., 2008), blood pressure, etc.] The ultimate goal is

to improve quality of life for patients and their caregivers. While there is strong evidence for DBS in Parkinson's disease, essential tremor, and dystonia, there is still more work needed to extend the knowledge on therapy efficacy, safety, and cost efficiency in other indications. Therefore it is crucial to conduct well designed controlled studies in line with the ethical criteria described by Lipsman et al. (2010). DBS should be used to help restore normal function and provide relief from distress and should never be used for augmentation or brain enhancement (Kringelbach and Aziz, 2009). The potential benefit should always be balanced with the potential risk for surgical or stimulation-induced adverse events.

DESIGN AND BUILD OF DEVICES

The components of implantable DBS systems include the neurostimulator, extensions, lead, and electrodes and the external components such as physician programmer, patient programmer (**Figure 1**), and a recharger for rechargeable devices.

When Hosobuchi approached Medtronic in 1969 to build a DBS system, cardiac pacing technology, the basis of the industry, utilized mercury zinc batteries housed in large devices with simple circuits. Clearly to deliver a pulse train of up to 100 pulses per second (pps) at the therapeutic voltage and pulse width required for neurostimulation demanded an alternative approach. Thus, the first DBS systems were radio frequency devices. The electrode was implanted at the appropriate brain target and cabled to a passive radio frequency receiver powered from a transmitter carried on the patient's belt. The transmitter was coupled to the implanted device with an antenna taped to the patient's skin over the implanted receiver.

Over the following two decades, improvements in power sources and circuit efficiencies in cardiac pacing were adapted for neurostimulation devices. The advent of lithium battery technology for implantable applications led to the possibility for neurostimulators to be fully implantable by the end of the 1980s, thereby reducing the dependence on the patient to care for and manage an external device. Implantable devices are programmed by a physician programmer. The programmer communicates with the electronics of the implanted device using pulse-width and/or pulse interval-modulated encoding of an inductively coupled carrier frequency.

In addition, improvements to circuit efficiency and capability have allowed for the development of dual channel devices capable of powering two four-contact leads. A new generation of devices provides increased parameter variability thus allowing the physician to tailor the stimulation to meet the topography and nature of the patient's symptoms with the aim to optimize therapeutic outcome while minimizing side effects (Wojtecki et al., 2011). A new generation of silver vanadium oxide batteries has been developed to meet these increased power requirements.

Commercial stimulators use charge-balanced stimulation resulting in zero net flow of charge to avoid deleterious effects. Different electrode configurations can be programmed for monopolar and bipolar stimulation. Based on the specific therapy application the parameters can be adjusted over a range of 0–10.5 V, 60–450 μs, and 2–250 pps (Testerman et al., 2006). Typical stimulation parameters for DBS for currently approved therapies such as movement disorders are in the range of 2–4 V (2–4 mA for a

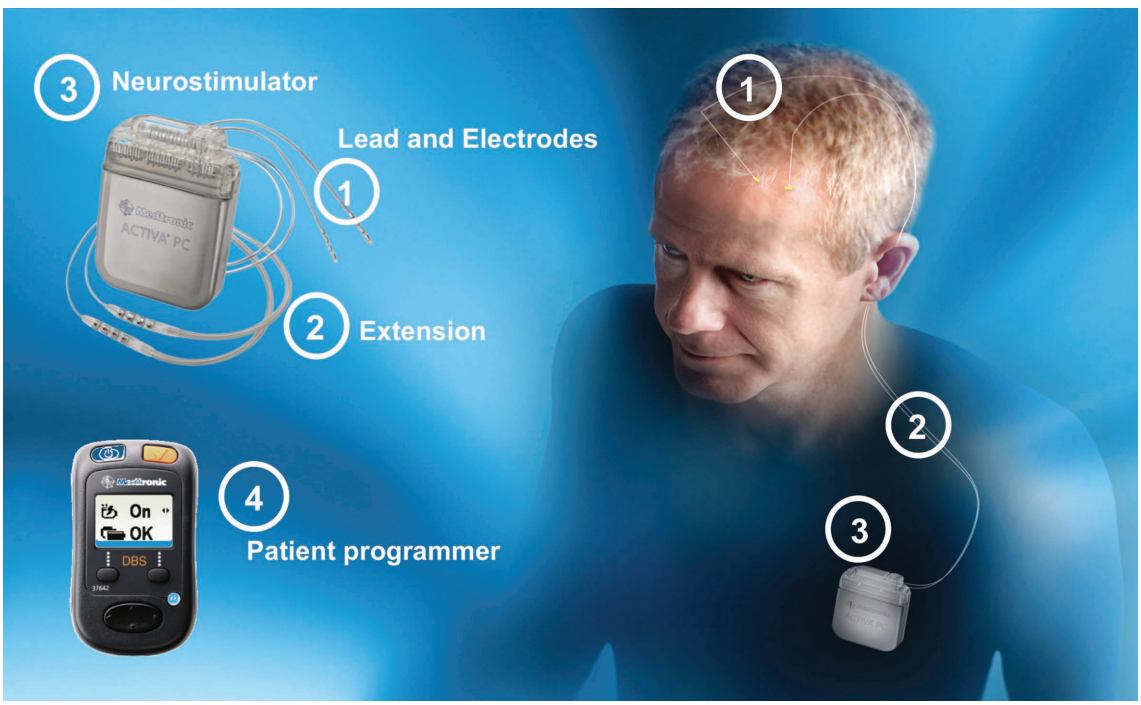


FIGURE 1 | Deep Brain Stimulator System Type Activa® PC (primary cell). The patient programmer may perform device status interrogation (e.g., power status, program group, battery status, and on/off function).

DBS electrode impedance of 1000 Ω) 90–180 μs pulse width, and 100–185 pps.

Due to the wide range of parameters in a neurostimulator, the battery life can vary considerably. For movement disorder applications, typical battery life expectation ranges from 2 to 5.5 years. For psychiatric applications, battery life may be considerably shorter due to the larger electrode surface areas and voltage levels required. The expected life can be from under 1 to 1.5 years although these numbers have been increasing as the targeting of the electrode contact has been refined.

The recent development of implantable rechargeable batteries has allowed physicians to provide DBS therapy to patients with higher energy requirements. Expected time-to-replacement is increased with the use of rechargeable DBS neurostimulators to 9 years. The aim of these developments is to improve patient comfort, reduce frequency of replacement surgeries, increase safety and efficacy, and to improve cost–benefit ratio of the therapy. However, recharging a neurostimulator requires patient cooperation and the patient's ability to comply should be considered before selecting this option.

Simultaneously, improvements have been made to the electrode systems. Today's electrodes are flexible, yet durable, and are configured to meet the anatomical requirements of the area to be stimulated. Pathological findings in the brains of eight Parkinson's disease patients treated with DBS showed only mild gliosis around the lead track. The authors concluded that chronic DBS does not cause damage to adjacent brain tissue (Haberler et al., 2000).

The description of the DBS implantation procedure would expand the scope of this article beyond its intent. However, it is important to point out that the surgery requires a multidisciplinary team. It involves several steps from mounting the stereotactic frame to implanting the DBS neurostimulator (**Figure 2**). Recent findings from a study on Parkinson's disease patients suggest that frameless implantation of DBS leads compared to frame based technique may result in comparable clinical outcome when performed by an experienced team (Brontë-Stewart et al., 2010).

FUTURE DEVELOPMENTS

The ultimate goal of new technologies and developments is to improve patient outcome, reduce clinical burden, and reduce dependency on the patient to manage the device. Any new medical device requires the balance of three key elements: unmet medical or user need, technical feasibility (including safety and reliability), and scientific verification.

Several areas to consider are:

- The ability to steer the electrical field around the electrodes will be an advantage in optimization providing some forgiveness in electrode location while still allowing the physician to optimize the therapy post-operatively.
- Exploration of alternatives to the fixed rate pulse train may improve efficacy and/or decrease potential for adaptation over time. These alternatives could include amplitude, frequency, or pulse-width modulation and intermittent stimulation.
- Many patients with chronic neurological diseases are at a point in their life where interacting with a medical device can be confusing. Making that interaction simpler and more obvious is a continuing challenge for the industry.
- MRI safe systems will provide a great advantage to the physician in the ongoing care of these patients.
- Work will continue to explore how to identify and use biomarkers, e.g., local field potentials, for closed-loop neurostimulators to provide intelligent DBS therapies (Stanslaski et al., 2009).

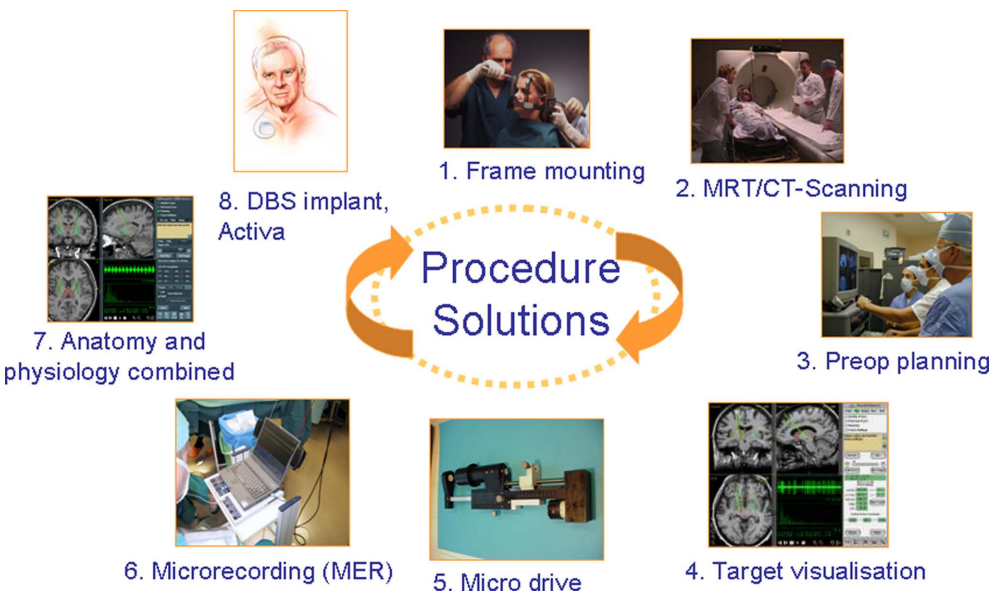


FIGURE 2 | Deep Brain Stimulator requires an multidisciplinary expert team and is a multi-step procedure involving stereotactic frame mounting (or "frameless" tools fixation); imaging, neurophysiological assessment, target verification prior to the DBS lead, and DBS system implantation.

CONCLUSION

Deep Brain Stimulation is a novel technique which has shown beneficial results in individual patients in several central nervous system disorders including pain, movement disorders, psychiatric disorders, and epilepsy. DBS therapy and product development has depended on a close collaboration between industry and physician pioneers in the fields of interest. Today DBS for the treatment of essential tremor and the symptoms of PD is approved by the regulatory authorities in the US and Europe. DBS for the treatment of dystonia, and OCD is CE Mark approved in Europe and through the HDE process in the US. DBS for the treatment of epilepsy is approved in Europe but remains unapproved in the US.

The nervous system plays a role in the control of every body function and, as a result, it is tempting to think that DBS could play a role in all medical dysfunction. Industry and physicians must be careful to select those potential applications of DBS that will bring maximum value to patients and must be committed to fully respect and comply with all applicable rules and regulations in the therapy development process and particularly in the conduct of clinical studies.

DISCLAIMER

The reader will note that the authors are associated with Medtronic, Inc. as employe and consultant. This paper contains information which discusses uses of DBS that have not been approved by regulatory agencies. Medtronic does not market its products for unapproved indications and can make no representations regarding the safety and/or efficacy of the devices if used for unapproved claims.

REFERENCES

Aouizerate, B., Cuny, E., Bardinet, E., Yelnik, J., Martin-Guehl, C., Rotge, J. Y., Rougier, A., Bioulac, B., Tignol, J., Mallet, L., Burbaud, P., and Guehl, D. (2009). Distinct striatal targets in treating obsessive-compulsive disorder and major depression. *J. Neurosurg.* 111, 775–779.

Benabid, A. L., Pollak, P., Gervason, C., Hoffmann, D., Gao, D. M., Hommel, M., Perret, J. E., and de Rougemont, J. (1991). Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 337, 403–406.

Benabid, A. L., Pollak, P., Louveau, A., Henry, S., and de Rougement, J. (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl. Neurophysiol.* 50, 344–346.

Benabid, A. L., Pollak, P., Seigneuret, E., Hoffmann, D., Gay, E., and Perret, J. (1993). Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. *Acta Neurochir. Suppl. (Wien)* 58, 39–44.

Bewernick, B. H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., Lemke, M., Cooper-Mahkorn, D., Cohen, M. X., Brockmann, H., Lenartz, D., Sturm, V., and Schlaepfer, T. E. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol. Psychiatry* 67, 110–116.

Boon, P., Vonck, K., De Herdt, V., Van Dycke, A., Goethals, M., Goossens, L., Van Zandijcke, M., De Smedt, T., Dewaele, I., Achten, R., Wadman, W., Dewaele, F., Caemaert, J., and Van Roost, D. (2007). Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia* 48, 1551–1560.

Brontë-Stewart, H., Louie, S., Batya, S., and Henderson, J. M. (2010). Clinical motor outcome of bilateral subthalamic nucleus deep-brain stimulation for Parkinson's disease using image-guided frameless stereotaxy. *Neurosurgery* 67, 1088–1093.

Coenen, V. A., Schlaepfer, T. E., Maedler, B., and Panksepp, J. (2010). Cross-species affective functions of the medial forebrain bundle-Implications for the treatment of affective pain and depression in humans. *Neurosci. Biobehav. Rev.* doi: 10.1016/j.neubiorev.2010.12.009. [Epub ahead of print].

Coubes, P., Roubertie, A., Vayssiere, N., Hemm, S., and Echenne, B. (2000). Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. *Lancet* 355, 2220–2221.

Denys, D., Mantione, M., Figee, M., van den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A., and Schuurman, R. (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch. Gen. Psychiatry* 67, 1061–1068.

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., Daniels, C., Deutschländer, A., Dillmann, U., Eisner, W., Gruber, D., Hamel, W., Herzog, J., Hilker, R., Klebe, S., Kloss, M., Koy, J., Krause, M., Kupsch, A., Lorenz, D., Lorenzl, S., Mehdorn, H. M., Moringlane, J. R., Oertel, W., Pinsker, M. O., Reichmann, H., Reuss, A., Schneider, G.-H., Schnitzler, A., Steude, U., Sturm, V., Timmermann, L., Tronnier, V., Trottenberg, T., Wojtecki, L., Wolf, E., Poewe, W., Voges, J., and German Parkinson Study Group, Neurostimulation Section. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *N. Engl. J. Med.* 355, 896–908.

Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., Bergen, D., Bakay, R., Henderson, J., French, J., Baltuch, G., Rosenfeld, W., Youkilis, A., Marks, W., Garcia, P., Barbaro, N., Fountain, N., Bazil, C., Goodman, R., McKhann, G., Babu Krishnamurthy, K., Papavassiliou, S., Epstein, C., Pollard, J., Tonder, L., Grebin, J., Coffey, R., Graves, N., and SANTE Study Group. (2010). Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51, 899–908.

Greenberg, B. D., Gabriels, L. A., Malone, D. A. Jr., Rezai, A. R., Friehs, G. M., Okun, M. S., Shapira, N. A., Foote, K. D., Cosyns, P. R., Kubu, C. S., Malloy, P. F., Salloway, S. P., Giftakis, J. E., Rise, M. T., Machado, A. G., Baker, K. B., Stypulkowski, P. H., Goodman, W. K., Rasmussen, S. A., and Nuttin, B. J. (2010). Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol. Psychiatry* 15, 64–79.

Gruber, D., Trottenberg, T., Kivi, A., Schoenecker, T., Kopp, U. A., Hoffmann, K. T., Schneider, G. H., Kühn, A. A., and Kupsch, A. (2009). Long term effects of pallidal deep brain stimulation in tardive dystonia. *Neurology* 73, 53–58.

Haberler, C., Alesch, F., Mazal, P. R., Pilz, P., Jellinger, K., Pinter, M. M., Hainfellner, J. A., and Budka, H. (2000). No tissue damage by chronic deep brain stimulation in Parkinson's disease. *Ann. Neurol.* 48, 372–376.

Halpern, C. H., Wolf, J. A., Bale, T. L., Stunkard, A. J., Danish, S. F., Grossman, M., Jaggi, J. L., Grady, M. S., and Baltuch, G. H. (2008). Deep brain stimulation in the treatment of obesity. *J. Neurosurg.* 109, 625–634.

Hamani, C., Mayberg, H., Stone, S., Laxton, A., Haber, S., and Lozano, A. M. (2011). The subcallosal cingulate gyrus in the context of major depression. *Biol. Psychiatry* 15, 301–308.

Hariz, M. I., and Robertson, M. M. (2010). Gilles de la Tourette syndrome and deep brain stimulation. *Eur. J. Neurosci.* 32, 1128–1134.

Hodaie, M., Wennberg, R. A., Dostrovsky, J. O., and Lozano, A. M. (2002). Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 43, 603–608.

Hosobuchi, Y., Adams, J. E., and Rutkin, B. (1973). Chronic thalamic stimulation for the control of facial anesthesia dolorosa. *Arch. Neurol.* 29, 158–161.

Krauss, J. K., Pohle, T., Weber, S., Ozdoba, C., and Burgunder, J. M. (1999). Bilateral stimulation of globus pallidus internus for treatment of cervical dystonia. *Lancet* 354, 837–838.

Kringelbach, M. L., and Aziz, T. Z. (2009). Deep brain stimulation: avoiding the errors of psychosurgery. *JAMA* 301, 1705–1707.

Kringelbach, M. L., Jenkinson, N., Owen, S. L. F., and Aziz, T. Z. (2007). Translational principles of deep brain stimulation. *Nat. Rev. Neurosci.* 8, 623–635.

Kupsch, A., Benecke, P., Müller, J., Trottenberg, T., Schneider, G.-H., Poewe, W., Eisner, W., Wolters, A., Müller, J.-U., Deuschl, G., Pinsker, M. O., Skogseid, I. M., Roeste, G. K., Vollmer-Haase, J., Brentrup, A., Krause, M., Tronnier, V., Schnitzler, A., Voges, J., Nikkah, G., Vesper, J., Naumann, M., Volkmann, J., and Deep-Brain Stimulation for Dystonia Study Group. (2006). Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N. Eng. J. Med.* 355, 1978–1990.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J. F., Broussolle, E., Perret, J. E., and Benabid, A. L. (1995). Effect of Parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 14, 91–95.

Limousin, P., Speelman, J. D., Gielen, F., and Janssens, M. (1999). Multicenter European study of thalamic stimulation in Parkinsonism and essential tremor. *J. Neurol. Neurosurg. Psychiatr.* 66, 289–296.

Lipsman, N., Bernstein, M., and Lozano, A. M. (2010). Criteria for the ethical conduct of psychiatric neurosurgery clinical trials. *Neurosurg. Focus* 29, E9.

Mallet, L., Polosan, M., Jaafari, N., Baup, N., Welter, M. L., Fontaine, D., du Montcel, S. T., Yelnik, J., Chéreau, I., Arbus, C., Raoul, S., Aouizerate, B., Damier, P., Chabardès, S., Czernecki, V., Ardouin, C., Krebs, M. O., Bardinet, E., Chaynes, P., Burbaud, P., Cornu, P., Derost, P., Bougerol, T., Bataille, B., Mattei, V., Dormont, D., Devaux, B., Vérin, M., Houeto, J. L., Pollak, P., Benabid, A. L., Agid, Y., Krack, P., Millet, B., Pelissolo, A., and STOC Study Group. (2008). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *N. Engl. J. Med.* 359, 2121–2134.

Malone, D. A. Jr., Dougherty, D. D., Rezai, A. R., Carpenter, L. L., Friehs, G. M., Eskandar, E. N., Rauch, S. L., Rasmussen, S. A., Machado, A. G., Kubu, C. S., Tyrka, A. R., Price, L. H., Stypulkowski, P. H., Giftakis, J. E., Rise, M. T., Malloy, P. F., Salloway, S. P., and Greenberg, B. D. (2009). Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol. Psychiatry* 65, 267–275.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M., and Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–660.

Mueller, J., Skogseid, I. M., Benecke, R., Kupsch, A., Trottenberg, T., Poewe, W., Schneider, G. H., Eisner, W., Wolters, A., Müller, J. U., Deuschl, G., Pinsker, M. O., Roeste, G. K., Vollmer-Haase, J., Brentrup, A., Krause, M., Tronnier, V., Schnitzler, A., Voges, J., Nikkhah, G., Vesper, J., Naumann, M., Volkmann, J., and Deep-Brain Stimulation for Dystonia Study Group. (2008). Pallidal deep brain stimulation improves quality of life in segmental and generalized dystonia: results from a prospective, randomized, sham-controlled trial. *Mov. Disord.* 23, 131–134.

Nuttin, B., Cosyns, P., Demeulemeester, H., Gybels, J., and Meyerson, B. (1999). Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 354, 1526.

Owen, S. L., Green, A. L., Nandi, D. D., Bittar, R. G., Wang, S., and Aziz, T. Z. (2007). Deep brain stimulation for neuropathic pain. *Acta Neurochir. Suppl.* 97, 111–116.

Porta, M., Brambilla, A., Cavanna, A. E., Servello, D., Sassi, M., Rickards, H., and Robertson, M. M. (2009). Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome. *Neurology* 73, 1375–1380.

Sartorius, A., Kiening, K. L., Kirsch, P., von Gall, C. C., Haberkorn, U., Unterberg, A. W., Henn, F. A., and Meyer-Lindenberg, A. (2010) Remission of major depression under deep brain stimulation of the lateral habenula in a therapy refractory patient. *Biol. Psychiatry* 67, e9–e11.

Siegfried, J., and Lippitz, B. (1994). Chronic electrical stimulation of the VL-VPL complex and of the pallidum in the treatment of movement disorders: personal experience since 1982. *Stereotact. Funct. Neurosurg.* 62, 71–75.

Siegfried, J., and Shulman, J. (1987). Deep brain stimulation. *Pacing Clin. Electrophysiol.* 10, 271–272.

Stanslaski, S., Cong, P., Carlson, D., Santa, W., Jensen, R., Molnar, G., Marks, W. J. Jr., Shafquat, A., and Denison, T. (2009). An implantable bi-directional brain-machine interface system for chronic neuroprosthesis research. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009, 5494–5497.

Sturm, V., Lenartz, D., Koulousakis, A., Treuer, H., Herholz, K., Klein, J. C., and Klosterkötter, J. (2003). The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J. Chem. Neuroanat.* 26, 293–299.

Temel, Y., and Visser-Vandewalle, V. (2004). Surgery in Tourette syndrome. *Mov. Disord.* 19, 3–14.

Testerman, R. L., Rise, M. T., and Stypulkowski, P. H. (2006). Electrical stimulation as a therapy for neurological disorder. *IEEE Eng. Med. Biol. Mag.* 25, 74–78.

The Deep Brain Stimulation for Parkinson's Disease Study Group. (2001). Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's Disease. *N. Engl. J. Med.* 345, 956–963.

Trottenberg, T., Paul, G., Meissner, W., Maier-Hauff, K., Taschner, C., and Kupsch, A. (2001). Pallidal and thalamic neurostimulation in severe tardive dystonia. *J. Neurol. Neurosurg. Psychiatry* 70, 557–559.

Velasco, F., Velasco, M., Ogarrio, C., and Fanghanel, G. (1987). Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. *Epilepsia* 28, 421–430.

Vidailhet, M., Yelnik, J., Lagrange, C., Fraix, V., Grabli, D., Thobois, S., Burbaud, P., Welter, M. L., Xie-Brustolin, J., Braga, M. C., Ardouin, C., Czernecki, V., Klinger, H., Chabardes, S., Seigneuret, E., Mertens, P., Cuny, E., Navarro, S., Cornu, P., Benabid, A. L., Le Bas, J. F., Dormont, D., Hermier, M., Dujardin, K., Blond, S., Krystkowiak, P., Destée, A., Bardinet, E., Agid, Y., Krack, P., Broussolle, E., Pollak, P., and French SPIDY-2 Study Group. (2009). Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. *Lancet Neurol.* 8, 709–717.

Voges, J., Hilker, R., Bötzel, K., Kiening, K. L., Kloss, M., Kupsch, A., Schnitzler, A., Schneider, G. H., Steude, U., Deuschl, G., and Pinsker, M. O. (2007). Thirty days complication rate following surgery performed for deep-brain-stimulation. *Mov. Disord.* 22, 1486–1489.

Vonck, K., Boon, P., Achten, E., De Reuck, J., and Caemaert, J. (2002). Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Ann. Neurol.* 52, 556–565.

Weaver, F. M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W. J. Jr., Rothlind, J., Sagher, O., Reda, D., Moy, C. S., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E. C., Duda, J. E., Holloway, K., Samii, A., Horn, S., Bronstein, J., Stoner, G., Heemskerk, J., Huang, G. D., and CSP 468 Study Group. (2009). Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 301, 63–73.

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., Scott, R., Ives, N., Rick, C., Daniels, J., Patel, S., Wheatley, K., and PD SURG Collaborative Group. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol.* 9, 581–591.

Witt, K., Daniels, C., Reiff, J., Krack, P., Volkmann, J., Pinsker, M. O., Krause, M., Tronnier, V., Kloss, M., Schnitzler, A., Wojtecki, L., Bötzel, K., Danek, A., Hilker, R., Sturm, V., Kupsch, A., Karner, E., and Deuschl, G. (2008). Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomized, multicentre study. *Lancet Neurol.* 7, 605–614.

Wojtecki, L., Vesper, J., and Schnitzler, A. (2011). Interleaving programming of subthalamic deep brain stimulation to reduce side effects with good motor outcome in a patient with Parkinson's disease. *Parkinsonism Relat. Disord.* 17, 293–294.

Conflict of Interest Statement: The authors are affiliated with Medtronic, Inc. as employee (Ali Sarem-Aslani) and consultant (Keith Mullett). Medtronic is a manufacturer of Deep Brain Stimulation systems.

Received: 23 February 2011; paper pending published: 20 May 2011; accepted: 16 August 2011; published online: 27 September 2011.

Citation: Sarem-Aslani A and Mullett K (2011) Industrial perspective on deep brain stimulation: history, current state, and future developments. Front. Integr. Neurosci. ***5****:46. doi: 10.3389/fnint.2011.00046*

frontiers in
INTEGRATIVE NEUROSCIENCE

PERSPECTIVE ARTICLE
published: 16 May 2011
doi: 10.3389/fnint.2011.00019

Perspective on the economic evaluation of deep brain stimulation

Emma Sarah McIntosh*

Department of Public Health, Health Economics Research Centre, University of Oxford, Oxford, UK

Edited by:
Chiara Saviane, SISSA, Italy

Reviewed by:
Pablo Martinez-Martin, Fundación Centro de Investigación de Enfermedades Neurológicas, Spain
Ivar Sonbo Kristiansen, University of Oslo, Norway

****Correspondence:***
Emma Sarah McIntosh, Department of Public Health, Health Economics Research Centre, University of Oxford, Old Road Campus, Oxford OX3 7LF, UK.
e-mail: emma.mcintosh@dphpc.ox.ac.uk

Parkinson's disease (PD) is an example of a disease area experiencing increasing use of deep brain stimulation (DBS) to treat symptoms. PD is a major cause of morbidity and has a substantial economic impact on the patients, their caregivers, the health service, and broader social and community services. The PDSURG Collaborators Group reported that DBS surgery for patients with advanced PD improves motor function and quality of life that medical therapy alone at 1 year but there are surgery related side effects in a minority (Williams et al., 2010). The aim of this paper however is to build upon the knowledge generated from evaluating DBS in PD and to provide a detailed perspective on the economic evaluation of DBS more generally with a view to providing a framework for informative design of DBS economic evaluations. This perspective will outline the key categories of resource use pertinent to DBS beyond the surgical scenario and into the broader aspects of follow-up care, adverse events, repeat procedures, social and community care, patient and carer costs, and will explore the importance of handling capital costs of DBS equipment appropriately as well as including costs occurring in the future. In addition, this perspective article will outline the importance of capturing broader aspects of "outcome" or benefits as compared to those traditional clinical measures used. The key message is the importance of employing a broad "perspective" on the measurement and valuation of costs and benefits as well as the importance of adopting the appropriate time horizon for evaluating the costs and benefits of DBS. In order to do this effectively it may be that alternative methods of economic evaluation in health care to the commonly used cost-effectiveness analysis may have to be used, such as cost-benefit analysis (McIntosh et al., 2010).

Keywords: economic evaluation, deep brain stimulation, broad perspective, time horizon, Parkinson's disease

INTRODUCTION

The aim of this paper is to outline issues pertinent to the economic evaluation of deep brain stimulation (DBS) with a view to providing a general framework for future economic evaluations of DBS technology whatever the indication. The broad economic issues around DBS technology are currently an under researched topic. This is due to the lack of evidence from large comparative studies but also due to a lack of theoretical consideration of the key range of costs and benefits associated with DBS, their long-term impact and related methodological considerations. Whilst a number of economics publications have contributed to the evidence base in this area independently on costs and health-care outcomes in the area of Parkinson's disease (PD) significant gaps remain on the "cost-effectiveness" of DBS technology more generally. At present Government funding for many health-care procedures such as DBS is often based on inaccurate costs and narrow measures of benefit. This is partly due to the complexity of costing disease treatment pathways and limited vista on the definition of benefits used. DBS is no exception to this. It is therefore important to have robust evidence on both the short and long-term costs and health-care outcomes of DBS interventions. Such information allows decision makers to prioritize funding appropriately using sound evidence.

This perspective article will begin by introducing the key cost and outcome components relevant to DBS and this will be followed by specific topics of methodological importance in the DBS area related to both costs and benefits. Finally, a discussion will be based around the key economic factors that will influence the cost-effectiveness of DBS as well as the theoretical and methodological challenges to using a broad evaluation perspective, with particular reference to the importance of measuring outcomes in the DBS area.

THE IDENTIFICATION OF RESOURCE USE DATA IN DBS

A detailed comparison of patient resource utilization and costs of all aspects of DBS surgery and its comparator is crucial in any evaluation of DBS. Ideally such data will come from a randomized controlled trial (RCT) or other rigorous design. Resource use data in DBS are typically related to the resources outlined in **Table 1**.

HOSPITAL STAY

In DBS it is predicted that the duration of hospital stay for the DBS surgery and any related subsequent events and adverse events related to the surgery such as infections will be a significant key cost driver of the total cost. It is therefore important to identify hospital stay in the economic evaluation as accurately as possible.

DBS EQUIPMENT

As outlined in **Table 1** above the different types of equipment involved in DBS are: implantable pulse generator (IPG), electrodes, extension leads, patient controller as well as the large capital items used by the surgeons, nurses, and electrophysiologists during the operation such as the stereotactic frame which keeps the head still during the DBS operation and the planning station used to identify the appropriate coordinates in the brain for targeting the electrodes. There are a number of different suppliers producing these equipments and generally the prices are similar. Due to the high cost of these pieces of equipment it is important that they be accurately annuitized as a function of lifespan and cost per use estimated based on throughput. A paper by Joint et al. (2002) estimated the hardware-related problems of DBS and noted a 20% rate of hardware-related problems in their cohort as compared to a range of 7–65% reported by other groups. The cost of the equipment may change over time for instance in DBS a new implant has been developed with a much longer battery life however the capital cost of this is more expensive and currently in the UK only few patients have been given this option. **Table 2** below gives a summary of the range of costs for the DBS equipment.

Table 1 | Resource data typical in DBS.

Stage	Resource use
Pre-operative	Clinic appointments
	Pre-operative assessment: neurology staff
Operative	Theater time: neurology staff and consumables
	DBS equipment: implantable pulse generator (IPG); electrodes; leads; extension leads; patient controller
	Planning station
	Stereotactic frame
	Robotic equipment
	Hospital stay (neurology ward)
Post-operative	Follow-up clinic appointments
	GP visits
	PD nurse appointments
	Subsequent procedures: theater time, hospital stay, equipment
	Adverse events: all operative resources outlined above; medications (e.g., antibiotics for infections)
All stages	Social and community care costs: GP visits; physiotherapy visits; nurse visits; community psychiatric care visits
All stages	Patient costs: out of pocket expenses; travel costs attending appointments; medication costs; aids and adaptations; modifications to homes; cleaner costs; gardening costs; home equipment such as special beds/shower units; Loss of Income due to time off work/inability to work
All stages	Informal carer costs: time spent caring for PD patient (value of time); loss of income due to time spent caring
All stages	Hospital stay
	Institutionalization costs
	Care home costs
	Meals on wheels
	Day centers
All stages	Medication/drugs

MEDICATION

It is the case in PD that often following DBS surgery patients become less reliant on certain forms of medication. The reduction in such a cost should be taken into consideration by the economic evaluation as a function of time. Drug prices should been calculated from the net cost used in pricing excluding VAT (For UK specific medication costs are obtained from the British National Formulary, BNF; Joint Formulary Committee, 2010. Prices should reflect the cost per individual patient dosage calculated on a daily basis and multiplied by the appropriate time period. In DBS data should also be collected on medication change over time to allow for the beneficial effects of DBS permitting a reduction in medication use. Such detailed information on drug use is important in the evaluation of DBS as it is the case that whilst the majority DBS costs are up front and occur at the time of the surgical episode it may be the case that the offset reductions in expensive drugs (e.g., Apomorphine in PD) may continue for a number of years and give rise to substantial cost savings which, if ignored, could bias the economic evaluation. In the situation where long-term data are unavailable then the use of economic modeling techniques and sensitivity analysis methods are recommended to identify the magnitude of savings.

SERIOUS ADVERSE EVENTS

In DBS in PD some of the more common serious adverse events arising following surgery include infections (often caused by breakthrough of electrodes), stroke, hemorrhage, DVT (Costs identified in Ramzi and Leeper, 2004) and fractures arising from falls following DBS (wrist, humerus, pelvic, odontoid). The main cost incurred with infections are the cost of hospital stay and antibiotic treatment but the costs increase markedly where the infection requires that the IPG and electrodes be removed and a new set inserted. Such adverse

Table 2 | Approximate costs# of DBS equipment and related planning equipment.

Item	Cost UK (2008)
Implantable pulse generator	£7,000–£8,500
Electrode	£800–£900*
Extension lead	£700–£850*
Patient controller	£600–£700
Accessory kit	£75–£100
Planning station	£60,000[1]
Stereotactic frame	£75,000[2]

#Costs provided are approximated based on averages from different suppliers and exclude VAT.
**Usual number required for DBS surgery = 2.*
[1]Life span usually 5 years (this cost does not include maintenance costs not take into account throughput).
[2]Life span usually 3 years (this cost does not include maintenance costs nor take into account throughput).
Source: personal correspondence with suppliers.

events are likely to be similar across disease areas as they are common to the technology rather than the disease hence, the costing for such adverse events may be transferable across economic evaluations.

INFORMAL CARE COSTS

The number of carers per patient and the duration of time spent caring per week should be collected where possible so that the impact of DBS on such "informal care" can be estimated. The informal costs of caring can be estimated based on a number of different assumptions for the hourly rate of caregivers (Van den berg and Ferrer-I-Cabonell, 2007; De Meijer et al., 2010). Informal care can comprise a substantial part of long-term care and often substitutes formal home and nursing home care (Van Houtven and Norton, 2004). Van Houtven and Norton (2004) show that informal care reduces formal health-care use and delays nursing home entry. Informal care can be thought of as comprising elements such as home keeping, personal care, support with mobility, administrative tasks, and socializing. In health care, unlike the available unit costs identifiable for formal care such as those outlined in **Table 2**, market prices for such informal care services often do not exist. For example the cost of informal care may not reflect the true societal value of resources attributed to this activity (Drummond et al., 2005) and as such "shadow" prices or proxy values are used (McIntosh et al., 2010). With health services becoming increasingly reliant on informal care and the associated shift in costs from the health-care sector to the community, for instance through early discharge programs, the substitution of inpatient care with ambulatory care and the move toward community care of the mentally ill – the greater the importance attached to recognizing and valuing the true cost of unpaid inputs. Provision of informal care may also result in additional costs (although perhaps not direct financial costs within the health-care sector) which should also be incorporated into the value of the unpaid input. These additional costs are shown in **Table 3**. In DBS it may be the case that the amount of informal care required by recipients is reduced with successful DBS and as such should be incorporated into the economic evaluation.

INSTITUTIONALIZATIONS AND CARE HOME COSTS

Where DBS treatment allows patients to continue staying in their own home being cared for by their carers then the avoidance of institutionalization and care home costs can be substantial. It important therefore that such costs be included in the evaluation of DBS – it may be that this gives rise to substantial savings over time.

Table 3 | Additional costs associated with informal care.

Additional "costs"	"Shadow" price*
Time spent traveling by patients, relatives, carers	Value of time
Time spent waiting for consultation, during consultation, treatment, and rehabilitation	Value of waiting time Opportunity cost of time
Leisure time lost (if time allocated to unpaid activity involves a displacement of non-working time)	Value of leisure activities forgone

**Shadow prices are proxy values where there are no identifiable market prices or values.*

PRODUCTIVITY COSTS AND DBS

Productivity costs as defined by the Washington Panel are: "…*costs associated with lost or impaired ability to work or engage in leisure activities due to morbidity and lost economic productivity due to death*" (Gold et al., 1996). Brouwer et al. (2001) propose an alternative definition of productivity costs as "Costs associated with production loss and replacement costs due to illness, disability, and death of productive persons, both paid and unpaid." For a comprehensive guide to all three methods both theoretically and practically as well as a direct comparison of the methods see Pritchard and Sculpher (2000), see also (Rice and Cooper, 1967; Koopmanschap et al., 1997). Productivity cost are pertinent to DBS as this technology may enable patients to engage in or indeed return to an economically productive life such as returning to a job or engaging in valued leisure time once again. As such any economic evaluations in the area of DBS should ensure that employment status or daily activities are measured accordingly so that the impact of DBS on such activities are captured.

KEY CONCEPTS IN COSTING METHODOLOGY USED FOR DBS EVALUATIONS

A "micro" approach to the costing of surgery and medical resources uses patient-specific data itemized by use of resources and such an approach is useful in early evaluation of new technologies where the key cost drivers have yet to be identified. The key cost drivers in DBS will ultimately be the high capital costs of the equipment which is patient-specific as well as the ward stay and follow-up procedures including adverse events and repeat implantations. It is recommended that where DBS is being evaluated for the first time in a disease area a micro-costing approach be used to identify the key cost drivers.

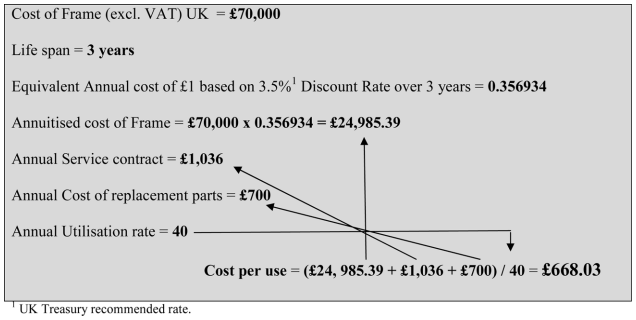
BASE YEAR

It is important to identify all costs in the same base year. This may require inflation or deflation of some items. The current discount rate for annuitization of capital items is 3.5% as recommended by HM Treasury (HM Treasury, 2003). Bearing in mind that to get to the final "total" cost figure many different variables have to be added together and different data points will have differing levels of complete data from patients hence missing data should be analyzed using appropriate techniques such as multiple imputation methods (Van Buuren et al., 1999).

EQUIVALENT ANNUAL COST (EAC) OF DBS EQUIPMENT COSTS

As outlined in earlier annuitization is an important costing method relevant to DBS as a result of the high cost items of equipment used. Capital costs tend to occur at a single point in time however, capital assets are used over time and can be sold at any time therefore the opportunity cost of capital is spread over time. As a consequence of this, the appropriate costing of capital items requires the calculation of an EAC. This EAC is therefore the capital cost apportioned into EACs as a function of expected lifespan and appropriate discount rate. In addition to this however to obtain a "unit cost per use" items of capital generally also require the inclusion of annual servicing and replacement part costs and these "annual costs" should then be divided by the annual throughput of patients using the equipment to

BOX 1 | Annuitization example of stereotactic frame used in dbs surgery.



[1] UK Treasury recommended rate.

obtain a unit cost per use. **Box 1** below provides a worked example of the annuitization of the cost of a stereotactic frame and this annuitized cost transformed into a "cost per use" as a function of annual service costs, annual replacement parts, and annual utilization rate.

HANDLING UNCERTAINTY IN DBS ECONOMIC ANALYSES

Briggs (2001) distinguishes among a number of different types of uncertainty depending upon whether the data are patient level or from decision analytic models. In stochastic analyses such as alongside clinical trials they identified four main types of uncertainty: methodological; sampling variation; extrapolation; and generalizability/transferability. For all types of uncertainty apart from extrapolation, where modeling methods are recommended, sensitivity analysis is the recommended approach to handling uncertainty. Sensitivity analysis is a method whereby various parameters in the analysis are varied in order to test the impact on the overall result. The main types of sensitivity analysis are one way; multi-way; scenario analysis, threshold analysis, and probabilistic sensitivity analysis (PSA). See Briggs (2001), Drummond et al. (2005), and Glick et al. (2007) for fuller expositions of these methods. Key parameters influencing the cost of DBS and which may make the total cost variable "sensitive" to change and therefore impact the overall result of the study include the following: source of unit costs; cost perspective; lifespan of capital items such as those outlined in **Table 2**; patient throughput; discount rate and annual service and maintenance costs. **Box 1** above outlined the importance of appropriate methodology to identify the cost per use of a stereotactic frame used in DBS. **Box 2** below now uses this to highlight the importance of sensitivity analysis on key costs in DBS based on changing the key assumptions regarding *lifespan*, *throughput*, and *annual service and maintenance costs*.

Box 1 above showed that the base cost of £668.03 per use was estimated based on the following assumptions: lifespan = 3 years; annual service cost = £1,036; annual cost of replacement parts = £700 and annual utilization rate = 40. Carrying out the sensitivity analysis outlined in **Box 2** shows that the cost per use is sensitive to changes in lifespan and throughput but less sensitive to changes in annual service and maintenance costs. This analysis shows that for the stereotactic frame cost involved in DBS, efficiency savings could be achieved by increasing its lifespan (albeit incurring some extra maintenance and service costs) and increasing the annual throughput of the Frame – this may be achieved by diversifying the frame's use to procedures other than DBS.

BOX 2 | Sensitivity analysis of DBS stereotactic frame cost assumptions.

Assumption	Costperuse(£)
Lifespan of 5 years	£430.99
Lifespan of 10 years	£253.82
Annual throughput of 20 patients	£1,336.07
Annual throughput of 80 patients	£334.02
Reducing the annual service and maintenance costs by 50%	£646.33

THE IMPORTANCE OF TIME HORIZON WHEN EVALUATING DBS TECHNOLOGIES

In the UK the National Institute for Health and Clinical Excellence (NICE) makes recommendations to the NHS on new and existing medicines, treatments, and procedures. NICE have devised the concept of a reference case which was developed by experts in the methodological aspects of economic evaluation. The reference case, based on that published by Gold et al. (1996) specifies the methods considered by the institute to be consistent with an NHS objective of maximizing health gain from limited resources. Within this reference case the time horizon recommended should be long enough to *include all relevant costs and outcomes relating to the intervention*. This is an importance issue for economic evaluation of DBS technologies as it is the case that many of the expensive equipment and hospital stay costs are very much "up front" and it is possible that the savings in terms of reduced medication and other health service costs do not occur till further in the future. Likewise additional costs incurred such as replacement IPGs and adverse events related to for example, infection, hemorrhage, and falls may not happen till later then these costs must be included in the economic evaluation to reveal the true economic picture of DBS in relation to the next best alternative treatment.

IDENTIFICATION, MEASUREMENT, AND VALUATION OF HEALTH ECONOMIC OUTCOMES IN DBS

While the majority of this paper so far has been dedicated to the identification, measurement, and valuation of resources involved in DBS another crucial element to any economic evaluation is the identification, measurement, and valuation of outcomes. Indeed, it is my opinion that this is an area under researched and of great significance to the economic research arena in this area. Investigation into the science behind outcomes valuation is not always considered by many to be the job of economists who are often heralded as "accountant" types however this is far from true. Indeed mainstream economists in many disciplines from environmental to transport and health economics have developed sound theoretical methodologies for valuing outcomes that are increasingly being used.

MEASURING HEALTH –QALYs AND BEYOND

The subject of measuring health and disease is the concern of many disciplines beyond health economics (Bowling, 1991, 1995), including public health, epidemiology, and statistics. In health economics it is widely accepted that it is theoretically possible to use numeraires such as health state utility to value outcomes (Torrance and

Sackett, 1972; Torrance, 1976; Sackett and Torrance, 1978; Torrance et al., 1982). Culyer (1989) argued for an "extra welfarist" approach to health. Unlike the traditional economic "welfarist" approach which measures everything deemed to impact upon a person's overall utility (including health) the task of measuring only changes in "health" was advocated in the "extra welfarist" approach, with the quality adjusted life year (QALY) as the instrument of choice (Williams, 1985; Culyer, 1989). As a consequence, much of the health economics literature in recent years has concentrated on issues around measuring and valuing preferences for health care in non-monetary mediums, i.e., quality of life (QOL; Drummond et al., 1987; Buckingham, 1993, 1995; Richardson, 1994). This has led to the development of health state valuation measures such as QALYs (Williams, 1985). In health economics the QALY is the common outcome measure employed by health economists alongside the many clinical outcomes measures specific to disease areas (such as the Hoehn and Yahr, 1967 and PDQ-39 Jenkinson et al., 2008 in PD) and measures of clinical effectiveness commonly used in cost-effectiveness analyses (Drummond et al., 2005). The advantage of the generic QALY is its ability to be compared across many disease areas allowing cost-utility estimates to be compared. In DBS surgery, given the global acceptance of the QALY as a generic measure of QOL (Dolan et al., 1995), with its 150 language translations, it would be recommended as a generic measure to be administered alongside disease specific measures of relevance to the particular condition. The EuroQol Group launched a new EQ-5D-5L (EQ-5D 5 level) self-complete version in 2009 with the aim of further improving the sensitivity and reducing ceiling effects of the existing EQ-5D-3 level version. This is now available in more than 40 translations. Future plans include EQ-5D-5L versions in web and tablet format (The EuroQol Group, 2011).

RISKS IN DBS

As outlined earlier, there are a number of risks associated with DBS surgery and how these are communicated effectively to patients is important. It is often the case with DBS surgery, such as in advanced PD that DBS surgery is the only remaining option once medication effects have worn off over time. In this situation, for some patients, there are little viable alternative treatments. The risks and benefits of the surgery must be explained to the patient, often using detailed patient information leaflets summarizing the available evidence on the risks, side effects, and long-term outcomes of the procedure. The University of Florida Movement Disorders Centre (MDC; Movement Disorders Centre UoF, 2011) outline the main risks occurring during the surgical procedure. One of these risks occurs when microelectrodes are inserted into the brain to determine the best target location. If a microelectrode, or alternatively the DBS lead, punctures a blood vessel it can lead to a stroke or a stroke-like syndrome which may result in weakness, numbness, sensory loss, visual difficulties, or a host of other neurological problems. Additionally, patients with cognitive dysfunction may worsen following DBS, and the surgery may affect one of many mood and cognitive circuits leading to changes such as depression, laughter, memory problems, or other psychiatric, and/or behavioral features. Additionally, there is a chance the lead may migrate, or the electrode, connecting wire, or implanted pulse generator may break and need to be replaced. Any time a foreign body is implanted into a human there is a risk for infection, both at the skin level, and in the brain. The batteries in the device will have to be changed requiring additional surgery, with the average time to battery replacement differing based on the underlying disorder, as well as the stimulation settings. As with all surgical procedures, there is a small chance of infection, and death from the procedure. To download the patient information leaflet used in the DBS in PD study (PDSURG) to see how the risks of DBS surgery were described in this context please see the PDSURG website (http://www.pdsurg.bham.ac.uk).

Clinicians have seen first-hand how DBS has provided significant improvements in QOL for patients with PD, tremor, dystonia, and other movement and basal ganglia related brain disorders. However as outlined above DBS surgery is not suitable for everyone and clinicians we will need to be able to select the best possible candidates by making assessments as to those patients who have the most favorable risk-benefit ratios and delivering that information effectively (Movement Disorders Centre UoF, 2011). Clinicians will need to better educate patients about who is a suitable candidate, and what they can expect and anticipate from the DBS surgical approach to their problems. As outlined by the MDC perhaps the biggest risk of surgery is that for patients and families the surgery will not meet *perceived expectations*. Hence it is recommended that patients have an in depth consultation with a movement disorders neurologist to outline the risks and benefits of DBS. The MDC at the University of Florida offers a mnemonic device for PD patients interested in DBS to help educate them and alter their perceptions to more closely match what is known about anticipated benefits of surgery. The future however will also bring about changes in risks and benefits as the technology evolves. For instance there will be rechargeable devices as well as devices that will work on a closed-loop circuit (meaning they will automatically turn on when needed).

THE IMPORTANCE OF BROAD OUTCOME MEASURES IN DBS

In DBS the use of QALY's as a generic measure is recommended alongside other relevant clinical measures. However a recurring theme across all disciplines attending the BIDS DBS workshop in September 2010 was the importance of broad outcome measures in DBS to measure and value attributes of importance *beyond* those of pure clinical relevance. Broader, and more complex outcomes of DBS such as happiness, dignity, personality change, depression, euphoria, social stigma and so on may not be adequately captured within clinical measures and may need to rely on broader economic measures to "value" them. If a health service such as the provision of DBS contributes positively to human wellbeing, it has economic value. Whether something contributes to an individual's wellbeing is determined by whether or not it satisfies that *individual's preferences*. The basic value judgment underlying economic valuation is that "preferences count," although this does not imply that all decisions must be made on the basis of what people want. Other factors, such as what is morally appropriate, what is ethically acceptable, and what is reasonable and practical, should be taken into account, although often such factors are less amenable to formal economic analysis. Such a concept is crucially important in the economic evaluation of DBS as there are a number of ethical, moral, social, and legal factors which all play a part in this technology (as outlined by the other papers in this special edition). One way of estimating the economic

values attached to non-marketed goods and services is to use a stated preference (SP) approach. SP approaches are based on hypothetical or constructed markets, i.e., they ask people to state what *economic value* they attach to attributes of those goods and services. SP methods in the DBS context would reply on health-care researchers devising questions about the risks and benefits involved in DBS and asking patients or members of the population to make valuations of the possible outcomes using money (willingness to pay methods) or identify trade-offs related to life expectancy (time-trade off methods) or risk of death (standard gamble methods). It is this approach which will be relevant to the broad evaluation of economic outcomes in DBS as it would permit the valuation of attributes *beyond* only health of importance to patients, as outlined above. In the area of DBS it may be that an economic SP measure may afford the measurement and valuation of a much broader range of benefits than individual clinical specific or disease specific measures are able to.

DBS AND THE CAPABILITY APPROACH

One developing approach in health economics that may be suited to such broader evaluation of DBS outcomes is the capability approach (Sen, 1993). As outlined more recently by Coast et al. (2008b) the capability approach advocates the evaluation of programs or interventions on the basis of the extent to which a person is *able* (has the capability) to function in a particular way. Given this, the capability approach offers a potentially much richer set of dimensions for evaluation. Nussbaum (2003) has drawn up a list of 10 central human capabilities comprising life, bodily health, bodily integrity, senses, imagination and thought, emotions, practical reason, affiliation, other species, play and control over one's environment. Indeed research using capabilities to develop a measure of outcome relevant to older people in the UK (ICECAP-O) looks promising as it contains attributes of direct relevance to the older population such as attachment, security, role, enjoyment, and control (Grewal et al., 2006; Coast et al., 2008a). The capabilities approach may be pertinent to DBS surgery in many areas as there are broader impacts than simply "health" *per se* with such surgery. The human capabilities outlined above such as bodily integrity, emotions, and control over one's environment can easily be linked to say the outcomes from DBS in advanced PD. Further development of such approaches will likely require the use of economic evaluation frameworks beyond cost-effectiveness and cost-utility and into the realms of cost-benefit analysis (McIntosh et al., 2010).

DISCUSSION

In providing a perspective on the economic evaluation of DBS this article has attempted to cover the key topics of specific economic relevance to DBS pertinent to all indications. These key topics include the importance of appropriate handling of DBS equipment costs, the significance of evaluating within the appropriate time horizon due to the possibility of repeat DBS procedures, adverse effects, and economic impacts upon medication use affected by DBS. In addition to this the article has outlined the importance of adopting the use of broader outcome measures to allow the true impact of the wide range of effects of DBS to be valued by patients and their carers. It may be the case that newer developments such as the ICECAP-O measure or other approaches utilizing the capabilities approach capture the value of attributes of outcomes otherwise left unvalued by other measures.

The use of DBS is gradually increasing in a number of different health-care indications. While the evidence of health benefits from trials are encouraging and there have been significant QOL increases shown in DBS patients it is crucial that economic evidence complement these data so as to show the true economic impact of the technique. Key to the estimation of cost-effectiveness in the area of DBS however are the importance of unbiased long-term costs and benefit data such that the high "up front" costs of DBS are accounted for but also included are any longer term resource use implications such as IPG replacement, adverse events, and impacts upon medication use. In addition to this are the methodological challenges involved in the valuation of a broader set of benefits than have been previously accounted for. It is the belief that for many DBS applications the estimation of such broad benefits alongside long-term cost data may be the key to revealing the true economic potential of this technology.

ACKNOWLEDGMENT

This research was funded by Parkinson's UK.

REFERENCES

Bowling, A. (1991). *Measuring Health: A Review of Quality of Life Measurement Scales*. Buckingham: Open University Press.

Bowling, A. (1995). *Measuring Disease*. Buckingham: Open University Press.

Briggs, A. H. (2001). "Handling uncertainty in economic evaluation and presenting the results," in *Economic Evaluation in Health Care: Merging Theory with Practice*, eds M. F. Drummond and A. McGuire (Oxford: Oxford University Press), 172–214.

Brouwer, W., Rutten, F., and Koopmanschap, M. A. (2001). "Costing in economic evaluations," in *Economic Evalaution in Health Care: Merging Theory with Practice*, eds M. F. Drummond and A. McGuire (Oxford: Oxford University Press), 68–93.

Buckingham, K. (1993). A note on HYE (Healthy Years Equivalents). *J. Health Econ.* 12, 301–309.

Buckingham, K. (1995). Economics, health and health economics – HYEs versus QALYs-a response. *J. Health Econ.* 14, 397–398.

Coast, J., Flynn, T., Natarajan, L., Sproston, K., Lewis, J., and Jea, L. J. (2008a). Valuing the ICECAP capability index for older people. *Soc. Sci. Med.* 67, 874–882.

Coast, J., Smith, R., and Lorgelly, P. (2008b). Should the capability approach be applied in health economics? *Health Econ.* 17, 667–670.

Culyer, A. J. (1989). The normative economics of health care finance and provision. *Oxf. Rev. Econ. Pol.* 5, 34–58.

De Meijer, C., Brouwer, W., Koopmanschap, M., Van den berg, B., and Van Exel, J. (2010). The value of informal care – a further investigation of the feasibility of contingent valuation in informal caregivers. *Health Econ.* 19, 755–771.

Dolan, P., Gudex, C., Kind, P., and Williams, A. (1995). *A Social Tariff for EuroQol: Results from a UK General Population Survey*. York: University of York.

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B., and Stoddart, G. L. (2005). *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press.

Drummond, M. F., Stoddard, G. L., and Torrance, W. (1987). *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press.

Glick, H., Doshi, J. A., Sonnad, S. S., and Polsky, D. (2007). *Economic Evaluation in Clinical Trials*. Oxford: Oxford University Press.

Gold, M. R., Siegel, J. E., Russell, L. B., and Weinstein, M. C. (1996). *Cost-effectiveness in Health and Medicine*. New York: Oxford University Press.

Grewal, I., Lewis, J., Flynn, T., Brown, J., Bond, J., and Coast, J. (2006). Developing attributes for a generic quality of life measure for older people: preferences or capabilities? *Soc. Sci. Med.* 62, 1891–1901.

HM Treasury (2003). *The Green Book: Appraisal and Evaluation in Central Government*, London: TSO, UK.

Hoehn, M., and Yahr, M. (1967). Parkinsonism: onset, progression and mortality. *Neurology* 17, 427–442.

Jenkinson, C., Fitzpatrick, R., Peto, V., Harris, R., and Saunders, P. (2008). *The Parkinson's Disease Questionnaire PDQ-39 User Manual*. Oxford: University of Oxford.

Joint Formulary Committee. (2010) *British National Formulary*, 60 Edn. London: British Medical Association and Royal Pharmaceutical Society.

Joint, C., Nandi, D., Parkin, S., Gregory, R., and Aziz, T. (2002). Hardware-related problems of deep brain stimulation in 100 consecutive electrodes. *Mov. Disord.* 17(Suppl. 3), S175–S180.

Koopmanschap, M. A., Rutten, F., van Ineveld, B. M., and van Roijen, L. (1997). The friction cost method for measuring indirect costs of disease. *J. Health Econ.* 6, 253–259.

McIntosh, E., Clarke, P., Frew, E., and Louviere, J. J. (2010). *Applied Methods of Cost Benefit Analysis in Health Care*. Oxford: Oxford University Press.

Movement Disorders Centre UoF. (2011). Movement Disorders Centre (MDC).

Nussbaum, M. (2003). Capabilities as fundamental entitlements: Sen and social justice. *Fem. Econ.* 9, 33–59.

Pritchard, C., and Sculpher, M. (2000). *Productivity Costs: Principles and Practice in Economic Evaluation*. London: Office of Health Economics.

Ramzi, D. W., and Leeper, K. V. (2004). DVT and pulmonary embolism: Part II. Treatment and prevention. *Am. Fam. Physician* 69, 2841–2848.

Rice, D. P., and Cooper, B. S. (1967). The economic value of human life. *Am. J. Public Health* 57, 1954–1966.

Richardson, J. (1994). Cost utility analysis – what should be measured? *Soc. Sci. Med.* 39, 7–21.

Sackett, D. L., and Torrance, G. W. (1978). The utility of different health states as perceived by the general public. *J. Chronic Dis.* 31, 697–704.

Sen, A. (1993). "Capability and well-being," in *The Quality of Life*, eds M. Nussbaum and A. sen (Oxford: Clarendon Press), 30–53.

The EuroQol Group. (2011). *EQ-5D Home Page*. Available at: www.euroqol.org

Torrance, G. W. (1976). Social preferences for health states: an empirical evaluation of three measurement techniques. *Socioecon. Plan. Sci.* 10, 128–136.

Torrance, G. W., Boyle, M. H., and Horwood, S. P. (1982). Application of multiattribute utility theory to measure social preferences for health states. *Oper. Res.* 30, 1043–1069.

Torrance, G. W., and Sackett, D. L. (1972). A utility maximising model for evaluation of health care programmes. *Health Serv. Res.* 7, 118–133.

Van Buuren, S., Boshuizen, H. C., and Knook, D. L. (1999). Multiple imputation of missing blood pressure covariates in survival analysis. *Stat. Med.* 18, 681–694.

Van den berg, B., and Ferrer-I-Cabonell, A. (2007). Monetary valuation of informal care: the well-being valuation method. *Health Econ.* 16, 1227–1244.

Van Houtven, C. N., and Norton, E. C. (2004). Informal care and health care use of older adults. *J. Health Econ.* 23, 1159–1180.

Williams, A. (1985). Economics of coronary artery bypass grafting. *Br Med J* 291, 326–329.

Williams, A., Gill, S., varma, T., Jenkinson, C., Quinn, N., mitchell, R., Scott, R., Ives, N., Rick, C., Daniels, J., Patel, S., Wheatley, K., and PD SURG Collaborative Group. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's Disease (PDSURG Trial): a randomised, open-label trial. *Lancet Neurol.* 9, 581–591.

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 11 January 2011; accepted: 04 May 2011; published online: 16 May 2011. Citation: McIntosh ES (2011) Perspective on the economic evaluation of deep brain stimulation. Front. Integr. Neurosci. ***5****:19. doi: 10.3389/fnint.2011.00019*

frontiers in
INTEGRATIVE NEUROSCIENCE

PERSPECTIVE ARTICLE
published: 10 May 2011
doi: 10.3389/fnint.2011.00016

Deep brain stimulation in the media: over-optimistic portrayals call for a new strategy involving journalists and scientists in ethical debates

Frédéric Gilbert[1] and Daniela Ovadia[2,3]*

[1] *Ethics and Bionics/Nanomedicine, Australian Centre of Excellence for Electromaterials Science, Faculty of Arts, University of Tasmania, Launceston, Australia*
[2] *Zoe Agency for Science Information, Milan, Italy*
[3] *Department of Cognitive Neuropsychology, Niguarda Ca' Granda Hospital, Milan, Italy*

Edited by:
Chiara Saviane, Scuola Internazionale Superiore di Studi Avanzati, Italy

Reviewed by:
Emily Bell, Institut de recherches cliniques de Montreal, Canada
Julie M. Robillard, University of British Columbia, Canada

***Correspondence:**
Daniela Ovadia, Agenzia Zoe – Informazione medica e scientifica, Via Perosi, 3, 20146 Milano, Italy.
e-mail: dovadia@agenziazoe.it

Deep brain stimulation (DBS) is optimistically portrayed in contemporary media. This already happened with psychosurgery during the first half of the twentieth century. The tendency of popular media to hype the benefits of DBS therapies, without equally highlighting risks, fosters public expectations also due to the lack of ethical analysis in the scientific literature. Media are not expected (and often not prepared) to raise the ethical issues which remain unaddressed by the scientific community. To obtain a more objective portrayal of DBS in the media, a deeper collaboration between the science community and journalists, and particularly specialized ones, must be promoted. Access to databases and articles, directly or through science media centers, has also been proven effective in increasing the quality of reporting. This article has three main objectives. Firstly, to explore the past media coverage of leukotomy, and to examine its widespread acceptance and the neglect of ethical issues in its depiction. Secondly, to describe how current enthusiastic coverage of DBS causes excessive optimism and neglect of ethical issues in patients. Thirdly, to discuss communication models and strategies to enhance media and science responsibility.

Keywords: deep brain stimulation, science journalism, mass media, neurosurgery, neuroethics

INTRODUCTION

As a treatment for psychiatric disorders, neurosurgical interventions, such as prefrontal leukotomy, were performed in the mid-twentieth century on many tens of thousands of patients (Gostin, 1980, 1982; Mashour et al., 2005). This therapeutic approach, later called "psychosurgery," was hailed by the media enthusiastically, despite a lack of scientific evidence of its effectiveness and without an evaluation of the ethical issues involved. Medical research is propelled, in part, by public needs and sometimes by public expectation. Researchers have an interest in promoting their research also in the popular press, and this can stimulate public interest in new therapies without adequate information. This is particularly troubling in the case of the new neuromedical discoveries with deep ethical implications.

The current experimental expansion of deep brain stimulation (DBS) applications, from the control of motor disorders to psychiatric conditions (Bell et al., 2009; Clausen, 2010; Schlaepfer and Fins, 2010) raises the legitimate worry that DBS treatments might also gain popularity in the media before a full evaluation of issues related to ethics and effectiveness is undertaken. This worry can, in part, be motivated by three factors. First, although distinct from classic psychosurgery (Synofzik and Schlaepfer, 2008; Schlaepfer et al., 2010), DBS is an invasive treatment that can generate several postoperative complications and side effects, such as cognitive, behavioral, psychiatric, and psychosocial impairments (Clausen, 2010). Second, the ethical discourse is often ignored in the scientific literature (Bell et al., 2010), which is characterized by a selection bias favoring the publication of positive results (Schlaepfer and Fins, 2010). Finally, DBS in psychiatry raises additional ethical questions because its mechanism of action is not yet clear, even for movement disorders (Benabid et al., 2005; Kringelbach et al., 2007), the hypotheses being either synaptic inhibition or depolarization blockade (Dostrovsky et al., 2000; Perlmutter et al., 2002; Vitek, 2002).

In the first section this paper examines media coverage of surgical brain therapies for psychiatric disorders, in particular prefrontal leukotomy. In the second section, it explores current, enthusiastic media portrayals of DBS, and how these might encourage a false assumption that all ethical issues have been fully discussed. In the third section, it addresses the primary sources of DBS information used by science journalists and the roles of scientific experts, peer-reviewed journals and the media in evaluating and shaping ethical issues raised by the development and expansion of DBS. In particular it suggests embracing a novel strategy to produce ethical consensus about controversial issues such as DBS.

LESSONS FROM THE PAST

Deep brain stimulation is not the first surgical treatment for psychiatric disorders to be depicted in the popular media. Between 1935 and 1960, in Europe and the United States, prefrontal leukotomy (widely called "lobotomy" in journalistic accounts) was accepted uncritically by a large part of the scientific community. Consequently it was presented by the media as a "miracle cure" for

disruptive behaviors. In 1949, the Nobel Prize for Physiology or Medicine was awarded to the Portuguese neurologist Egas Moniz, "for his discovery of the therapeutic value of leukotomy in certain psychoses" (Nobel Foundation, 1949). This prestigious prize demonstrated the wide acceptance by the scientific community at the time, and most probably encouraged the public to see prefrontal leukotomy as a safe procedure.

In their paper on the portrayal of lobotomy in the American popular press, Diefenbach et al. (1999) concluded that the acceptance of lobotomy benefited from optimistic media coverage, especially in the 1930s and 1940s. It was proposed that unbalanced popular press coverage was an important factor in stimulating interest in lobotomy: "It was generally known that many patients were referred [ ] as a result of all the publicity" wrote Valenstein (1986) in his history of psychosurgery. Walter Freeman, an American physician who had strong relationships with journalists from widely read newspapers and magazines, played an important role in advertising the procedure (El-Hai, 2005). Diefenbach et al. (1999) described how competition between media professional to break dramatic stories combined with fame-seeking by representatives of the medical community (or with research interests in some fields) created a relationship which served both the media and the physicians, but not necessarily the public interest.

In a study on psychosurgery in Sweden between 1944 and 1958, Ogren noted that pioneering early experiments of prefrontal lobotomy, performed by neurosurgeons in collaboration with psychiatrists in Stockholm in 1944, were followed by a rapid implementation of the new surgical approach (Ogren et al., 2000). In 1946 and 1947, the two state mental hospitals, Umedalen and Sidsjön, introduced prefrontal lobotomy on a large scale. Prefrontal lobotomy was characterized, in certain city hospitals, by an initially high rate of postoperative mortality that reached more than 15%. Nonetheless, in a comparative media study Ogren found that most of the articles on lobotomy in the Swedish and American media were positive or neutral toward psychosurgery, whilst negative articles were less frequent. Neutral articles were more common in Swedish media (43%) whilst less common in American media (19%). Articles that were highly negative toward lobotomy were more often found in the American press (32%) than in the Swedish (14%). This difference was due to the lack, in the Swedish society of the time, of a small but strong opposition to this procedure that was present in the American scientific community. There was also a tradition of investigative journalism that pushed some American writers to examine patients' postoperative outcomes (Ogren, 2007).

More balanced reports started to appear in American press in 1945, in parallel with the appearance of scientific studies that quantified dramatic side effects associated with the therapy. Following this more balanced reporting, the use of the procedure declined. This was also, in part, due to the introduction of chlorpromazine, the first drug for mental illness, which raised new hopes for psychiatric patients (Pressman, 1998).

Low-income patients with low-educational attainment were the first victims of media enthusiasm for lobotomy (Valenstein, 1986). Part of the explanation was the higher burden of psychiatric illness for patients and families in a poor social environment.

It is important to recognize that contemporary public perceptions of the efficacy of DBS in psychiatric disorders may parallel earlier enthusiasm for surgical interventions in psychiatry, since the media had already made a connection between psychosurgeries and DBS (Fins, 2003).

OVERLY OPTIMISTIC MEDIA PORTRAYAL AND NEGLECT OF ETHICS

Past and present DBS media reports, without or with only a passing attention to ethics, offer fertile ground for hype in both scientific journals and the popular press. For example, following the publication of "Memory Enhancement Induced by Hypothalamic/Fornix Deep Brain Stimulation" (Hamani et al., 2008), there was a wave of positive reporting concerning the use of DBS for memory enhancement, with a particular focus on Alzheimer's patients, without scrutiny of either the vulnerable nature of these patients or the merely accidental or serendipitous nature of this discovery (initially the study was conducted to treat severe obesity). For instance, the scientifically respected and influential *Nature* announced the findings in an optimistic news article entitled "Brain electrodes can improve learning" (Abbott, 2008) and suggested the possible application for people with Alzheimer's disease without any concern for the ethics related to this population of patients. This enthusiastic media shock wave was instantly replicated on an international scale. Indeed, *BBC News* popularized the same results by publishing an article positively entitled "Deep stimulation 'boosts memory'" (Coombes, 2008), while articles appeared in *The Telegraph* and *The Independent* titled respectively "Discovery could make Alzheimer's a memory" (Clout, 2008) and "Scientists discover way to reverse loss of memory" (Laurence, 2008). None of these articles discussed or mentioned the opportunity of using DBS for memory enhancement in a vulnerable population such as Alzheimer's patients, although they all referred to this neurodegenerative disorder as a pathology potentially treatable with DBS.

By praising medical and scientific innovation without paying attention to ethical issues, the media risk to turn ethical neglect into de facto ethical approval, thereby promoting public acceptance of DBS. Other important questions raised by DBS applications (i.e., criteria for the selection of patients, acute, and chronic side effects, DBS use in pediatrics, benefits to patients, and quality of life) are absent in popular media, also due to the fact that they are not properly discussed in scientific literature (Clausen, 2010; Racine et al., 2010).

Regrettably, this type of optimistic coverage of DBS is not only limited to mass media. As Schlaepfer and Fins (2010) report, several DBS single-case studies have been published which highlight the secondary effects of research (such as memory enhancement) even when the primary goals (such as treating obesity) have not been achieved; as was the case in the Hamani et al. (2008) paper, referred to earlier. Even if selective publishing bias is not unique to research on DBS (Chien, 2004; Nature Neurosci, 2004; Lau et al., 2008; Schlaepfer and Fins, 2010), by focusing on the positive outcomes of DBS, both the scientific literature and the popular media neglect common ethical issues (risk–benefit ratio, informed consent, inclusion–exclusion, side effects, patient's autonomy, etc.).

In a seminal study, Racine et al. (2007) reviewed 235 articles on neurostimulation techniques in the print news media in the U.K. and the U.S. They reported that 51% were optimistic depictions, whilst only 4% emphasized the risks. Among the articles reviewed, 29% contained a "personal twist," including first person narratives and descriptions of "miracle stories of patients cured of Parkinson's disease, dystonia, and Tourette's syndrome" (Racine et al., 2010). Diem et al. (1996) and Schneiderman (2005) have pointed out that patients educate themselves and build their hopes from uncritical sources, such as television and the internet. In that sense, the media have an influential place in patient education, comprehension, and understanding of health issues.

From the point of view of the lay reader or potential psychiatric patient who goes through an informed consent process, the use of an easily optimistic depiction – both in the medical literature and in the popular media – can be far more influential than some of the austere and subtle explanations found in specialized ethics journals. Bell et al. (2009), in an insightful study using healthcare providers, report that enthusiastic media portrayals of DBS influence patients' hopes and expectations. They concluded that healthcare providers view media portrayals of DBS as "playing a key role in establishing expectations for DBS patients and for the public in general." Media portrayals of DBS can lead to a false assumption that ethical issues have been discussed which affects patients' expectations.

Ford (2009) suggests that overly optimistic reports about new neurosurgical innovations generate an "educational vulnerability" for patients. He affirms that very often when patients consider neurosurgical techniques they have already been preconditioned by overly optimistic portrayals of novel brain interventions, and this compromises informed consent. This is similar to what Bell et al. (2009) report in their study of healthcare provider perspectives.

Even if DBS is both scientifically valid and reasonably safe, patients' lack of appreciation of the risks and the potential consequences of the procedure raises significant ethical challenges. Moreover, whilst potential DBS patients may be legally competent, they may not be able to make meaningfully autonomous decisions regarding their participation in any proposed DBS treatment. This is not only because of the burden of their own illness, but also a consequence of the impression created by enthusiastic media accounts often coupled with the non-neutral attitude of the surgeon. Given the lack of common official ethical guidelines for patient selection in DBS trials amongst countries, it is difficult to prevent unethical applications of this technique on competent but fragile subjects.

Informed consent is an important mechanism for respecting patient autonomy, but in order to reach this ambitious goal, the effect of exposure to unbalanced media reports must also be considered. DBS providers have the responsibility of designing a process for obtaining a fully informed consent, while avoiding the exploitation of unrealistic hopes. Addressing the lack of awareness of the ethical and social challenges of DBS is a duty and a responsibility not only of the popular media. Most of the neurosurgical literature focuses mainly on technical details and only superficially addresses fundamental questions about patient selection and inclusion criteria, informed consent and resource allocation.

ETHICAL DEBATE AND MEDIA CONSTRAINTS

When analyzing media coverage of DBS, it is important to examine the process of selection of what becomes "news," and evaluate the primary sources of information on this topic: peer-reviewed publications and experts. This is confirmed by a study by Racine et al. (2010) which reports that 42% of the quotations about DBS published in articles in the popular press come from a scientist with a public sector affiliation and 14% come from physicians and other healthcare providers.

The role of science journalism, especially in covering ethical topics, has been discussed in depth in recent years. In a recent *Nature* editorial "Science Journalism, too close for comfort," Boyce Rensberger, past director of the Knight Science Journalism Fellowship program at the Massachusetts Institute of Technology, argued that science journalists need to stay as close as possible to the researchers producing science, but still need to keep a healthy distance. Tracing a brief history of the evolution of science journalism in the Internet era – from the role of "cheerleaders" of scientists to the role of "watchdog" – he affirms that: "If science journalists are to regain relevance to society [ ] they must learn enough science to analyze and interpret the findings – including the motives of the funders. And, as if that were not enough, they must also anticipate the social impacts of potential new technologies while there is still time to make a difference" (Rensberger, 2009).

Anticipating the social impacts of promising new DBS therapies obviously requires a discussion about ethics. Such discussion is just starting in the scientific community, and with some reluctance: "Neuroscientists have reasons for their reluctance to wade into ethics. The questions raised are likely to be open-ended, and their arrival in the world outside the laboratory may be some way off" stated a *Nature* Editorial (2006) entitled "Neuroethics Needed," which focused in particular on functional MRI. Now, how can science journalists identify and discuss, in a meaningful and satisfactory way, the ethical issues raised by a new DBS therapy when even the experts in the field and the scientific literature tend not to discuss them?

The answer is not easy, and lies at least in part in the search for new ways of cooperation, particularly between the scientific community and the media, which face these kinds of difficulties, not only when dealing with DBS and neuroscience, but throughout the whole spectrum of issues related to research and health. A recent statement published under the auspices of the International Society of Pharmacovigilance, for instance, highlighted the importance of such an approach: "New ways to cooperate with the media as professional equals must be explored to help the provision of balanced, comprehensible, trustworthy, and interesting safety information to the public on a regular basis, apart from specific announcements or reports of problems or crises" (Erice Statement, 2010).

Media are expected to play an informative and argumentative role – in particular, to conduct wide debate of social issues regarding DBS. In the current over-optimistic portrayal, media typically do not question the assumptions under which the medical literature reports DBS results. Ethics may be difficult to implement when dominant scientific news is based on DBS efficacy rather that safety. In addition, promises of a cure – with or without exaggeration, are useful to attract public attention in a news world in which every article needs to compete in order to be noticed. The issue, well

known inside the journalistic profession, is reflected in a recent headline in the *British Medical Journal*: "Health Journalism: two clicks away from Britney Spears?" (Coombes, 2009).

Although a variety of critiques have been leveled at mass media portrayals of DBS (Racine et al., 2007; Ford, 2009), it is very difficult to create a context in which such portrayals can be questioned by all parties – the media, science experts, and the public. Several experts in neuroethics have stressed the importance of a novel approach, capable of moving from the current widespread top-down approach – from the scientists to the general public through the "translation" by the media – to a multidirectional model of discussion that encourages open dialog and the mutual enrichment of all parties. In particular, Racine et al. (2009) argue that: "Such a scheme recognizes both that science is part of culture and that societies are increasingly multicultural. The distinction between expert and lay conceptions becomes a continuum, in which each interacts with the other. Given calls for increased public dialog, sustained relationships with the media and growing interdisciplinary dialog with colleagues in the humanities and social science are also needed. This scheme will also enable public advocacy for neuroscience [ ] and will firmly situate science communication within a robust framework."

Public deliberation has already been used in several contexts related to health and ethics. It was adopted, for instance, to explore public concerns and desires about the development of biobanks (O'Doherty and Burgess, 2009) and the adoption of new health technologies (Milewa, 2006). Applying this logic to the communication of neuroscience research, Illes et al. (2010) focus on the need for scientists to listen to the public and the public's interest in learning about science, in order to promote an approach capable of reflecting "the values of trust, reciprocity and transparency by engaging non-experts and acknowledging that they have a right to be involved in the conduct of science." Illes et al. (2010) note, however, that this "calls for enhanced training of neuroscientists and a willingness to engage in less conventional approaches. Empirical research throughout the process of public engagement is an integral part of this training."

DISCUSSION

By presenting exclusively positive data, the media tend to describe and explain DBS outcomes without reference to ethical debates. Despite the immature state of DBS as a treatment for psychiatric conditions, patients rely on information about DBS from media portrayals. This may encourage the use of DBS as a treatment for more and more psychiatric conditions in which there are good theoretical grounds justifying the surgery but the evidence is still weak and preliminary. The ethical issues related to DBS are usually debated by scientists and experts only after specific concerns have been raised, as it happened in Canada after the discovery of the potential effects of DBS on memory (Hamani et al., 2008). What was presented as a possible treatment that could be offered to all patients has become the subject of a study by Laxton et al. (2010) on six Alzheimer's patients which in phase 1 proved the safety of the procedure and is currently evaluating its long-term efficacy.

Unbalanced media reports can convey to the general public, and to potential patients, the idea that DBS represents a default option for the treatment of all refractory psychiatric diseases. As noted in the first section, this happened in the past with other surgical treatments for behavioral disorders that have a heavy social impact. In the absence of public debate on the complex ethical aspects of the widespread use of DBS, enthusiastic media accounts might result in an unjustified promotion of these therapies (Schlaepfer and Fins, 2010). The need for more responsible reporting, both from popular media and from neuroscientists and neurosurgeons, calls not only for better research on this topic but also for the promotion of initiatives favoring a multidirectional model of discussion among all parties – science experts, the public and the media. This amounts to a "cultural" shift that openly acknowledges and rewards public outreach, whilst supporting the development of neuroscience communication experts, as well as empirical research into neuroscience communication (Racine et al., 2010).

In an environment in which the media are not expected (and often not prepared) to raise the ethical issues which remain unaddressed by the scientific community, the challenge is to rethink and reinvent communication strategies to improve the role of the media. This improved role requires the members of the press to act as watchdogs of science and to highlight the gap often existing between the goals of science and the needs of society. This goal could be achieved by promoting continuing education and training within the journalistic profession, with the help of the scientific community, which should start considering journalists as "professional equals" (Erice Statement, 2010). In order to achieve more effective communication by researchers, and to help journalists in their background research on ethical issues related to science, a number of approaches have proved effective. These include: free access for journalists to medical literature databases and official sources of information, peer review within the profession and science media centers designed to put scientists in touch with journalists in a context promoting cooperation and reciprocal trust (Schwitzer, 2008; Editorial Lancet, 2009; Kirby, 2011).

In a case-study published on *Science Communication*, Smith et al. (2010) evaluate the impact that a cancer media center had on the quality of cancer news in the United States. They conclude that in order to spread the use of good preventive practices, providing the community of journalists and the general audience with good informative materials about cancer prevention is not enough, and has to be coupled with the search for a "clear articulation of shared goals."

The search for an alliance between all the stakeholders characterizes the experience of the British Science Media Centre (SMC). According to its director Fox (2009), combining the provision of good information materials with the organization of regular meetings and debates between the media and the science community improved the quality of reporting, especially on issues related to ethics. This goal was achieved by putting a great effort in helping specialized reporters: "[ ] The support we give to specialist correspondents has undoubtedly helped to strengthen their hand by ensuring that they get the best science stories in advance of non-specialists in the newsroom. The SMC has continued to champion specialist reporters both within the scientific community and in all our dealings with news editors. It is our strong view that they are the best allies of science in the media [ ]" (p. 125).

The role of the media is crucial if a society wants to involve citizens in relevant decisions about their health. The partnership between science, research, and the media is needed if crucial health issues such as those related to the use of DBS are to be put on the public agenda appropriately. The public and furthermore the patients, need clear and accurate information. Until now, the provision of such clear and accurate information was mostly the responsibility of reporters and editors. The time has come for scientific publishers, scientists and health care workers to contribute to this difficult task, especially in issues, like DBS, that have important ethical and social implications.

ACKNOWLEDGMENTS

This research was partly found by the Australian Centre of Excellence for Electromaterials Science (ACES). Thanks to Fabio Turone and Eliza Goddard for reviewing the text. Thanks to anonymous reviewers for comments.

REFERENCES

Abbott, A. (2008). *Brain Electrodes Can Improve Learning*. Nature News, January 29. Available at: http://www.nature.com/news/2008/080129/full/news.2008.538.html

Bell, E., Mathieu, G., and Racine, E. (2009). Preparing the ethical future of deep brain stimulation. *Surg. Neurol.* 72, 6.

Bell, E., Maxwell, B., McAndrews, M. P., Sadikot, A., and Racine, E. (2010). Hope and patient's expectations in deep brain stimulation: healthcare providers' perspectives and approaches. *J. Clin. Ethics* 21, 112–124.

Benabid, A. L., Wallace, B., Mitrofanis, J., Xia, R., Piallat, B., Chabardes, S., and Berger, F. (2005). A putative generalized model of the effects and mechanism of action of high frequency electrical stimulation of the central nervous system. *Acta Neurol. Belg.* 105, 149–157.

Chien, K. R. (2004). Stem cells: lost in translation. *Nature* 428, 607–608.

Clausen, J. (2010). Ethical brain stimulation – neuroethics of deep brain stimulation in research and clinical practice. *Eur. J. Neurosci.* 32, 1152–1162.

Clout, L. (2008). *Discovery Could Make Alzheimer's a Memory*. The Daily Telegraph, January 30. Available at: http://www.telegraph.co.uk/news/uknews/1577009/Discovery-could-make-Alzheimers-a-memory.html

Coombes, R. (2009). Health journalism: two clicks away from Britney Spears? *Br. Med. J.* 338, b570.

Coombes. (2008). *Deep Stimulation "Boosts Memory"*. BBC News, January 30. Available at: http://news.bbc.co.uk/2/hi/health/7213972.stm

Diefenbach, G. J., Diefenbach, D., Baumeister, A., and West, M. (1999). Portrayal of lobotomy in the popular press: 1935–1960. *J. Hist. Neurosci.* 8, 60–69.

Diem, S. J., Lantos, J. D., and Tulsky, J. A. (1996). Cardiopulmonary resuscitation on television, miracles and misinformation. *N. Engl. J. Med.* 334, 1578–1582.

Dostrovsky, J. O., Levy, R., Wu, J. P., Hutchison, W. D., Tasker, R. R., and Lozano, A. M. (2000). Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *J. Neurophysiol.* 84, 570–574.

Editorial. (2004). The promise of stem cells. *Nat. Neurosci.* 7, 1013.

Editorial. (2006). Neuroethics needed. *Nature* 441, 907.

Editorial. (2009). Does the media support or sabotage health? *Lancet* 373, 604.

El-Hai, J. (2005). *The Lobotomist: A Maverick Medical Genius and His Tragic Quest to Rid the World of Mental Illness*. Hoboken, NJ: John Wiley and Son.

Erice Statement. (2010). Erice Statement 2009: communication, medicines and patient safety. *Br. J. Clin. Pharmacol.* 69, 207–208.

Fins, J. (2003). From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of neuropsychiatric research. *Neurosurg. Clin. N. Am.* 14, 303–319.

Ford, P. J. (2009). Vulnerable brains: research ethics and neurosurgical patients. *J. Law Med. Ethics* 37, 1, 73–83.

Fox, F. (2009). "Science communication and ethics. Trying to get it right: the Science Media Center – a case study," *Communicating Biological Sciences – Ethical and Metaphorical Dimensions*, eds B. Nerlich, R. Elliott, and B. Larson (Farnham: Ashgate Publishing Limited), 109–128.

Gostin, L. O. (1980). Ethical consideration of psychosurgery: the unhappy legacy of the pre-frontal lobotomy. *J. Med. Ethics* 6, 3, 149–154.

Gostin, L. O. (1982). Psychosurgery: a hazardous and unestablished treatment? A case for the importation of American legal safeguards to Great Britain. *J. Soc. Welfare Law* 83–95.

Hamani, C., McAndrew, M. P., Cohn, M., Oh, M., Zumsteg, D., Shapiro, C. M., Wennberg, R. A., and Lozano, A. (2008). Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Ann. Neurol.* 63, 1, 119–123.

Illes, J., Moser, M. A., McCormick, J. B., Racine, E., Blakeslee, S., Caplan, A., Check Hayden, E., Ingram, J., Lohwater, T., McKnight, P., Nicholson, C., Phillips, A., Sauvé, K. D., Snell, E., and Weiss, S. (2010). Neurotalk: improving the communication of neuroscience research. *Nat. Rev. Neurosci.* 11, 61–69.

Kirby, T. (2011). Science media centres go global. *Lancet* 377, 285.

Kringelbach, M. L., Jenkinson, N., Owen, S. L., and Aziz, T. Z. (2007). Translational principles of deep brain stimulation. *Nat. Rev. Neurosci.* 8, 623–635.

Lau, D., Ogbogu, U., Taylor, B., Stafinski, T., Menon, D., and Caulfield, T. (2008). Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell* 3, 591–594.

Laurence, J. (2008). *Scientists Discover way to Reverse Loss of Memory*. The Independent, January 30. Available at: http://www.independent.co.uk/news/science/scientists-discover-way-to-reverse-loss-of-memory-775586.html

Laxton, A. W., Tang-Wai, D. F, McAndrews, M. P., Zumsteg, D., Wennberg, R., Keren, R., Wherrett, J., Naglie, G., Hamani, C., Smith, G. S., and Lozano, A. M. (2010). A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann. Neurol.* 68, 521–534.

Mashour, G. A., Walker, E. E., and Martuza, R. L. (2005). Psychosurgery: past, present, and future. *Brain Res. Rev.* 48, 409–419.

Milewa, T. (2006). Health technology adoption and the politics of governance in the UK. *Soc. Sci. Med.* 63, 3102–3112.

Nobel Foundation. (1949). *The Nobel Prize in Physiology or Medicine 1949*. Available at: http://nobelprize.org/nobel_prizes/medicine/laureates/1949/index.html

O'Doherty, K. C., and Burgess, M. M. (2009). Engaging the public on Biobanks: outcomes of the BC biobank deliberation. *Public Health Genomics* 12, 203–215.

Ogren, K. (2007). *Psychosurgery in Sweden 1944–1958: The Practice, The Professional and Media Discourse*. Sweden: Umeå University. Available at: http://urn.kb.se/resolve?urn=urn:nbn:se:umu:diva-1084

Ogren, K., Sjöström, S., and Bengtsson, N. O. (2000). The unknown history of lobotomy. *Lakartidningen* 97, 3395–3398.

Perlmutter, J. S., Mink, J. W., Bastian, A. J., Zackowski, K., Hershey, T., Miyawaki, E., Koller, W., and Videen, T. O. (2002). Blood flow responses to deep brain stimulation of thalamus. *Neurology* 58, 1388–1394.

Pressman, J. D. (1998). *The Last Resort: Psychosurgery and the Limits of Medicine*. Cambridge: Cambridge University Press.

Racine, E., Bar-Ilan, O., and Illes, J. (2009). fMRI in the public eye. *Nat. Rev. Neurosci.* 6, 159–164.

Racine, E., Waldmag, S., Rosenbergi, J., and Illes, J. (2010). Contemporary neuroscience in the media. *Soc. Sci. Med.* 71, 725–733.

Racine, E., Waldman, S., Palour, N., Risse, D., and Illes, J. (2007). "Currents of hope": neurostimulation techniques in U.S. and U.K. print media. *Camb. Q. Healthc. Ethics* 16, 312–316.

Rensberger, B. (2009). Science journalism: too close for comfort. *Nature* 459, 1055–1056.

Schlaepfer, T. E., and Fins, J. (2010). Deep brain stimulation and the neuroethics of responsible publishing, when one is not enough. *JAMA* 303, 775–776.

Schlaepfer, T. E., Lisanby, S. H., and Pallanti, S. (2010). Separating hope from hype: some ethical implications of the development of deep brain stimulation in psychiatric research and treatment. *CNS Spectr.* 15, 285–287.

Schneiderman, L. (2005). The perils of hope. *Camb. Q. Healthc. Ethics* 14, 235–239.

Schwitzer, G. (2008). How do US journalists cover treatments, tests, products, and procedures? An evaluation of 500 stories. *PLoS Med.* 5, e95. doi: 10.1371/journal.pmed.0050095

Smith, K. C., Singer, R. F., and Kromm, E. E. (2010). Getting cancer research into the news: a communication case study centered on one U.S. Comprehensive Cancer Center. *Sci. Commun.* 32, 202–231.

Synofzik, M., and Schlaepfer, T. E. (2008). Stimulating personality: ethical criteria for deep brain stimulation in psychiatric patients and for enhancement purposes. *Biotechnol. J.* 3, 1511–1520.

Valenstein, E. S. (1986). *Great Desperate Cures: The Rise and Decline of Psychosurgery and Other Radical Treatment for Mental Illness.* New York: Basic Books.

Vitek, J. L. (2002). Mechanisms of deep brain stimulation: excitation or inhibition. *Mov. Disord.* 17, S69–S72.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 03 January 2011; accepted: 26 April 2011; published online: 10 May 2011. Citation: Gilbert F and Ovadia D (2011) Deep brain stimulation in the media: over-optimistic portrayals call for a new strategy involving journalists and scientists in ethical debates. Front. Integr. Neurosci. ***5****:16. doi: 10.3389/fnint.2011.00016*

frontiers in
INTEGRATIVE NEUROSCIENCE

MINI REVIEW ARTICLE
published: 09 May 2011
doi: 10.3389/fnint.2011.00017

Ethical issues in deep brain stimulation

Maartje Schermer*

Department of Medical Ethics and Philosophy, Erasmus University Medical Center, Rotterdam, Netherlands

Edited by:
Chiara Saviane, Scuola Internazionale Superiore di Studi Avanzati, Italy

Reviewed by:
Eric Racine, Institut de recherches cliniques de Montréal, Canada
Walter Glannon, University of Calgary, Canada

***Correspondence:**
Maartje Schermer, Department of Medical Ethics and Philosophy, Erasmus University Medical Center, AE 340, PO Box 2040, 3000 CA Rotterdam, Netherlands.
e-mail: m.schermer@erasmusmc.nl

Deep brain stimulation (DBS) is currently used to treat neurological disorders like Parkinson's disease, essential tremor, and dystonia, and is explored as an experimental treatment for psychiatric disorders like major depression and obsessive compulsive disorder. This mini review discusses ethical issues in DBS treatment and research, as they have been discussed in the medical and ethical literature. With regard to DBS treatment, the most important issues are balancing risks and benefits and ensuring respect for the autonomous wish of the patient. This implies special attention to patient selection, psycho-social impact of treatment, effects on personal identity, and treatment of children. Moreover, it implies a careful informed consent process in which unrealistic expectations of patients and their families are addressed and in which special attention is given to competence. In the context of research, the fundamental ethical challenge is to promote high-quality scientific research in the interest of future patients, while at the same time safeguarding the rights and interests of vulnerable research subjects. Several guidelines have been proposed to ensure this. One of the preconditions to further development of responsible and transparent research practices is the establishment of a comprehensive registry.

Keywords: medical ethics, bioethics, neuroethics, deep brain stimulation, neuromodulation, research ethics, psychosurgery, neuro-psychiatric disorders

INTRODUCTION

Deep brain stimulation (DBS) is currently used to treat neurological disorders like Parkinson's disease (PD), essential tremor and dystonia, and is explored as an experimental treatment for psychiatric disorders like major depression (MD) and obsessive compulsive disorder (OCD).

Since DBS involves brain surgery and modulation of brain-states, it may invoke reminiscences of unethical neurosurgical practices from the past. For instance, it may remind one of the lobotomies performed by Moniz and Freeman or of the Tulane electrical stimulation program by Heath. Images from works of popular fiction, such as *One Flew Over the Cuckoo's Nest* or *The Manchurian Candidate*, in which interventions in the brain are used to manipulate or otherwise abuse people, may also come to mind. Such images may influence the public perception of DBS and related ethical issues. There are, however, clear differences between past forms of neurosurgery and current DBS, which make the comparison go awry. Most importantly, operation techniques such as MRI-guided stereotactic surgery have improved and the intervention is therefore much safer. Moreover, the effects of DBS are mostly reversible – the stimulation can be turned off if it is not effective or causes too many adverse effects. Unlike some of the controversial neurosurgical interventions in the past, DBS is performed only in otherwise treatment-resistant patients, and only with informed consent from the patient (Synofzik and Schlaepfer, 2008).

Still, DBS raises some important ethical issues, both in the context of treatment and in that of research. These issues have been discussed in the medical as well as bioethical community, and researchers from both fields have often collaborated in identifying and discussing ethical issues. This contribution will give an overview of these discussions, based on a review of the relevant medical and ethical literature.

ETHICAL ISSUES IN TREATMENT OF NEUROLOGICAL DISORDERS

An ethical assessment of DBS treatment can depart from – and be structured by – the four basic principles of medical ethics: non-maleficence, beneficence, justice and respect for autonomy, and the additional principles of subsidiarity and proportionality (**Table 1**).

BALANCING BENEFICENCE AND NON-MALEFICENCE

The first important ethical question is whether DBS is beneficial and does not harm the patient. In other words: are the expected risks and side-effects proportional to the expected benefits? This must be assessed both at a group-level and at the level of individual patients. At the group-level, this means that the available evidence regarding effectiveness, risks, and side effects of DBS for various conditions, in various target areas, and for various patient-populations must be assessed.

For disorders like PD, dystonia, and essential tremor DBS has been proven to be effective.

The risks and complications associated with DBS surgery include hemorrhage (1.3–4%), infection (2.8–6.1%), lead migration, misplacement or breakage (5.1%), and even death (0.4%; Clausen, 2010). Side effects depend partly on the stimulation target and include effects on cognition, behavior and psyche, including speech disturbances (10.8–33%), memory impairment (1.1–20%), aggression (2%), (hypo)mania (2–28%), hypersexuality (0.8%), depression (1.5–25%), and increased suicide risk (Clausen, 2010).

Table 1 | Deep brain stimulation and the basic principles of medical ethics.

Ethical principle	Issues pertinent to DBS treatment
Non-maleficence, *"first, do no harm"*	• Risks • Side effects (physical and mental) • Change in personal identity? • Effects on developing brain?
Beneficence, *"do well"*	• Effectiveness • Need for psycho-social care
Proportionality and subsidiarity, *"risks and benefits in proportion,"* *"choose least burdensome alternative"*	• Patient selection: Risks proportional to benefits? Refractory to other treatments?
Justice, *"treat like cases alike"*	• Rationing and prioritizing
Respect for autonomy, *"respect patients' well-informed choices"*	• Informed consent • Desperation and unrealistic expectations • Competence to consent • Use in minors

The principle of subsidiarity implies that DBS should only be used when other less risky or burdensome treatment options have been exhausted.

PATIENT SELECTION

In order to secure a favorable risk–benefit ratio for individual patients, careful patient selection is necessary. Patients need to stand a good chance to benefit from the procedure, have severe functional impairments and be refractory to other, less invasive or less burdensome, treatments. Also, candidates should be physically, cognitively, and emotionally capable of tolerating surgery and participating in postoperative care (Bell et al., 2009). This is best assessed in a multidisciplinary team (Kubu and Ford, 2007). Progress in DBS research may provide new insights that justify an expansion of indications for DBS. For example, it may prove to be beneficial for PD patients to start DBS treatment earlier in the disease process, because this may have a neuroprotective effect, or because it may prevent psycho-social problems related to advanced PD. In essential tremor, on the other hand, earlier intervention may not be beneficial because tolerance may develop.

GOOD CARE

With regard to the side effects of DBS it is increasingly recognized that these include not only physical or psychiatric symptoms. The psycho-social impact of the DBS treatment and the effects on overall quality of life should be included as well. Several studies have found that sometimes "the doctor is happy, the patient less so" (Agid et al., 2006), and DBS has been described as "a unique form of biographical disruption" (Gisquet, 2008). It was found that quality of life on aspects such as emotional well-being, social support, and interpersonal relationships may actually decrease after surgery, even when physical symptoms improve. These findings may be partly due to unrealistic expectations of patient. This emphasizes the need for good pre-operation counseling and the provision of clear and honest information in the informed consent process. Moreover, these findings point to the unsettling effects of successful treatment. Paradoxically, regained functioning may upset established social and relational patterns. Many patients have difficulties with psycho-social adjustment after surgery, especially with regard to their marital relationships, self-perception, and work. After surgery, a period of adaptation is necessary for both patients and their families. This requires professional psycho-social preparation and follow-up support (Schüpbach et al., 2006).

CHANGES IN PERSONAL IDENTITY – A SPECIAL KIND OF SIDE EFFECT?

A special and frequently mentioned concern regarding the side effects of DBS is that changes in behavior, mood, or cognition caused by DBS might result in changes in "personal identity." The ethical discussion on this point is complicated by the lack of clear and undisputed definitions of central concepts such as personality, self, identity, and authenticity (Merkel et al., 2007). A useful distinction can be made between numerical identity and narrative identity (Schermer, 2009a; Schechtman, 2010). The first refers to continuity of the same person over time, defined by bodily criteria (like DNA), or psychological criteria such as (autobiographical) memory or a set of core-characteristics. A change in numerical identity would mean that someone literally became someone else. If DBS would cause changes in mood, cognition, or behavior that would affect numerical identity (e.g., by completely wiping out or changing biographical memory), they would indeed be problematic since they would put people out of existence and create new people. This is not the case, however.

The relevant notion of personal identity is therefore narrative identity, which involves the person's self-conception, his biography, values, and roles as well as his psychological characteristics and style. It is the answer to the question "who am I?" A person's personality, defined by the DSM as "the enduring patterns of perceiving, relating to, and thinking about the environment and oneself that are exhibited in a wide range of social and personal contexts," is thus part of his narrative identity. Mood, cognitions and behavior are also part of one's personal narrative.

Changes in narrative personal identity are not necessarily ethically problematic in themselves – that is, apart from possible harmful consequences for others. People always change in many respects throughout their lives; personal identities are not static but develop over time. Disorders such as PD or dystonia can have a profound impact on the development of a person's identity, as can their (successful) treatment. Some of the changes that DBS can bring about in personality, cognition, behavior, or mood may actually be sought by the patient and be the goal of treatment, for example mood improvement in depression, or tic-reduction in Tourette's syndrome. Other changes may not be intended but can still be welcomed by the patient, for example an elevated mood or increased libido. The same changes can, however, be evaluated differently by different patients. The relevant ethical point is therefore whether or not the patient himself perceives the changes in his personality, mood, behavior, or cognition brought about by DBS as disruptive of his personal narrative identity (Schermer, 2009a; Synofzik and Schlaepfer, 2008).

Moreover, the acute, rapid changes that DBS can bring about, can disrupt the normal, "narrative flow of life" and it may take time and effort of the patient to pick up and continue his life story (Schechtman, 2010). This may well account for the adjustment problems discussed above. Finally, if changes in personality and behavior negatively affect others, this may raise the problem of responsibility (see Schermer, 2009b).

JUSTICE

Little has been written on the issue of justice with regard to DBS treatment. DBS is an expensive form of treatment, although it has been argued that DBS may turn out to be cost effective in the longer run as compared to alternative treatment options (Bell et al., 2009). In the face of scarcity of resources, it may be necessary to prioritize between (groups of) patients. From a perspective of justice, ideally, priority should be given to those who are most seriously impaired and who will benefit the most from the intervention. Priority setting becomes more difficult when "chance to benefit" and "seriousness of impairment" do not go together. Anyway, one should be careful not to exclude patients who might benefit from the procedure on grounds not related to expected benefit, for example because of their age.

AUTONOMY AND CONSENT

Patients undergoing DBS must give their voluntary and fully informed consent to this procedure, just like for any other medical intervention. In practice this may be problematic for a number of reasons. First, some patients may be desperate because of their hopeless situation, suffering as they are from a serious, progressive, and treatment-refractory disease. They may feel they have no other option but to consent to the proposed treatment. However, this is not a unique situation for DBS and the fact that there are no other treatment options left does not imply that consent is not voluntary. Second, patients' hopes and expectations of DBS may have been raised to unrealistic levels by enthusiastic media reports (Bell et al., 2010). Balanced and realistic information is therefore needed, not only regarding risks and side effects of the procedure but also regarding the expected benefits and the limitations of this treatment. It must be clear to patients, for example, that DBS will not cure their PD and will not stop its progression.

Another important consideration is the patient's competence to consent to treatment. Competence can be challenged by the primary neurological disorder, or by co-morbidity like cognitive impairments or depression. It can however also be affected by DBS itself (Glannon, 2009).

Deep brain stimulation can, for example, induce a (hypo)manic state in patients and there are case reports of such patients who subsequently refuse adaptation of the stimulator settings because they are not aware of their disturbed mental state. These patients may harm themselves or others, for example by excessive gambling or reckless driving. Here, assessment of competence to decide is crucial to determine whether or not the treatment team may change the settings or discontinue treatment without the patient's consent. If an incompetent patient inflicts severe harm on himself or others, it is ethically justified to intervene, under conditions of proportionality and subsidiarity. Because the effects of DBS are reversible, adjustment of settings or discontinuation of stimulation can restore the patient's competence. In this way, the patient can be enabled to make his own autonomous decisions considering the further course of action. Fortunately, dramatic dilemma-situation as in the case report by Leentjens et al. (2004) – where a PD patient had to choose between being either completely bed-ridden but competent, or physically improved but manic – seem to be rare.

SPECIAL GROUPS: CHILDREN

Deep brain stimulation treatment in children or adolescents, e.g., for dystonias or tic disorders, warrants extra ethical attention. First, because children are incompetent to decide for themselves about risks and benefits and are therefore more vulnerable to abuse. While this is no reason to exclude them from beneficial treatment – parents can act as representatives and make decisions in the best interest of their child – it necessitates an extra careful assessment of the risk–benefit ratio. Second, research on DBS in children is scarce. Only 35 children have been treated for dystonia and so there is little evidence regarding benefits and risks in children especially regarding long term effects on the developing brain (Lipsman et al., 2010). DBS treatment for neurological disorders in children should therefore be regarded as experimental and should only be performed by highly specialized teams and within well-designed and independently reviewed research protocols.

A special case that generates significant controversy concerns DBS treatment for treatment-refractory Tourette's syndrome. Because the majority of Tourette's patients have meaningful clinical improvement in adolescence or early adulthood, it is very questionable whether the immediate benefits that DBS may give these children in the short term, will eventually outweigh the risks in the longer run. Moreover, evidence of effectiveness of DBS is very limited, even in adult Tourette's patients (Sassi et al., 2010). A consensus seems to be developing that only in extreme cases where tics cause spinal cord injury or myelopathy DBS may be considered as last-resort treatment in children (Lipsman et al., 2010).

ETHICAL ISSUES IN INVESTIGATIONAL TREATMENT FOR PSYCHIATRIC DISORDERS

Many new indications for DBS are currently investigated, among which many psychiatric disorders such as MD, OCD, and addiction. For clinical research involving human subjects the fundamental ethical challenge is to promote high-quality scientific research in the interest of (future) patients, while at the same time safeguarding the rights and interests of vulnerable research subjects. In the United States and Europe, national and international regulations apply to scientific research with human subjects and Institutional Review Boards (IRBs) or local ethics committees oversee their observance. With regard to DBS research in psychiatric disorders a number of ethical requirements have been specified and guidelines have been proposed by experts from the field (Nuttin et al., 2002; Kuhn et al., 2009; Rabins et al., 2009). The ethical principles underlying these guidelines are respect for autonomy and protection of research subjects, benefit for future patients, quality of research, and transparency (**Table 2**).

RESEARCH ETHICS GUIDELINES

Important and generally agreed upon recommendations are that research with DBS for psychiatric disorders should only be performed in expert centers, with experienced multidisciplinary

Table 2 | Ethical guidelines for DBS research (based on: Nuttin et al., 2002; Kuhn et al., 2009; Rabins et al., 2009; Clausen, 2010; Schlaepfer and Fins, 2010).

Ethical principles	Requirements
Protection of research subject	• Performed by expert multidisciplinary teams • Strict inclusion criteria (including severity and refractoriness) • Informed consent • Long term follow up • IRB oversight • Goal to improve patient's life (no law enforcement, enhancement, or political purposes)
Autonomy of research subject	• Competence assessment • Informed consent; special attention to therapeutic misconception, hope, and despair • No Financial barriers to withdraw
Quality of research	• Only at expert centers • Independently reviewed protocols, hypothesis driven • IRB oversight • Comprehensive outcome measures (including QoL, psycho-social impact) • Long term follow up
Transparency	• Comprehensive registry (both trial and single-case) • Disclosure potential conflict of interest
Benefit to future patients	• Include all experimental treatment in trial • Comprehensive registry (both trial and single-case) • Comparative studies
Special protection vulnerable groups	• Inclusion limited to competent adult subjects

teams. An IRB should review the research protocol and monitor the research-process. The research goals should include finding the appropriate anatomic sites and stimulation parameter, and comparing safety and efficacy of DBS with established treatments. Patient selection should be conducted carefully, and only severely afflicted and otherwise treatment-refractory patient should be included. Informed consent should be obtained, making sure the patient is competent and has realistic expectations and is not drive by sheer desperation and unrealistic hopes. According to Rabins et al. (2009) only adults and no children should be included. In general, experimental treatment should only be performed within the context of an established, duly constituted and independently reviewed research protocol. This will protect research subjects, as well as ensure that the experimental treatment will add to our scientific understanding of DBS and thus be potentially beneficial to future patients. Because of the importance of creating a sound evidence base and in order to prevent publication bias the creation of an independent registry has been proposed, both for trials and single-case studies (Rabins et al., 2009; Schlaepfer and Fins, 2010).

Long term follow up by a multidisciplinary team is ethically required both to ensure the well-being of the research subjects as for the benefit of future patients. This follow up should include safety and efficacy but also quality of life and psycho-social effects; follow up should also take into account information provided by a person close to the patient (Kuhn et al., 2009).

CONFLICTS OF INTEREST STATEMENT

One ethical issue that has great salience in DBS research concerns the role of the industry. As Fins and Schiff (2010: 125) state: "clinical research in DBS presents a unique nexus of science and commerce in which market forces influence the contours of discovery, a small cadre of investigators is dependent upon an even smaller number of manufacturers for its tools of inquiry, and conflicts of interest complicate research." Although companies may sincerely take the interests of patients at heart they also have a – legitimate – interest in making a profit. These two interests do not always coincide and the commercial motive may hamper free and innovative research, especially when researchers also have conflicting roles (e.g., both company-advisor and principal investigator). Disclosure of potential conflict of interest is important, but insufficient, since it does not resolve the underlying conflict of interest itself. This issue has been underexposed in the ethical discussion up till now but warrants serious attention from researchers, companies, and regulators.

DISCUSSION

Deep brain stimulation is an established treatment in neurology and is emerging as experimental treatment in the field of psychiatry. Over the past years, bioethicists and philosophers have been working in close cooperation with clinicians and researchers to identify and discuss the most important ethical issues in both clinical practice and research. There is a growing corpus of literature available that addresses these issues. The most pressing issues to be explored in further bioethical research are the psycho-social and identity-effects of DBS, its use in children, and the further development of responsible and transparent research practices.

REFERENCES

Agid, Y., Schüpbach, M., Gargiulo, M., Mallet, L., Houeto, J. L., Behar, C., Maltête, D., Mesnage, V., and Welter, M. L. (2006). Neurosurgery in Parkinson's patients: the doctor is happy, the patient less so? *J. Neural Transm.* 70, 409–414.

Bell, E., Mathieu, G., and Racine, E. (2009). Preparing the ethical future of deep brain stimulation. *Surg. Neurol.* 72, 577–586.

Bell, E., Maxwell, B., McAndrews, M. P., Sadikot, A., and Racine, E. (2010). Hope and patients' expectations in deep brain stimulation: healthcare providers' perspectives and approaches. *J. Clin. Ethics* 21, 112–124.

Clausen, J. (2010). Ethical brain stimulation – neuroethics of deep brain stimulation in research and clinical practice. *Eur. J. Neurosci.* 32, 1152–1162.

Fins, J. J., and Schiff, N. D. (2010). Conflicts of interest in deep brain stimulation research and the ethics of transparency. *J. Clin. Ethics* 21, 125–132.

Gisquet, E. (2008). Cerebral implants and Parkinson's disease: a unique form of biographical disruption? *Soc. Sci. Med.* 67, 1847–1851.

Glannon, W. (2009). Stimulating brains, altering minds. *J. Med. Ethics* 35, 289–292.

Kubu, C. S., and Ford, P. J. (2007). Ethics in the clinical application of neural implants. *Camb. Q. Healthc. Ethics* 16, 317–321.

Kuhn, J., Gaebel, W., Klosterkoetter, J., and Woopen, C. (2009). Deep brain stimulation as a new therapeutic approach in therapy-resistant mental disorders: ethical aspects of investigational treatment. *Eur. Arch. Psychiatry Clin. Neurosci.* 259, S135–S141.

Leentjens, A. F., Visser-Vandewalle, V., Temel, Y., and Verhey, F. R. (2004). Manipulation of mental competence: an ethical problem in a case of electric stimulation of the subthalamic nucleus for severe Parkinson's disease. *Ned. Tijdschr. Geneeskd.* 148, 1394–1398.

Lipsman, N., Ellis, M., and Lozano, A. M. (2010). Current and future indications for deep brain stimulation in pediatric populations. *Neurosurg. Focus* 29, E2.

Nuttin, B., Gründler, T. O., Lenartz, D., Sturm, V., Klosterkötter, J., and Huff, W. (2002). Deep brain stimulation for psychiatric disorders. *Neurosurgery* 51, 519.

Rabins, P., Appleby, B. S., Brandt, J., DeLong, M. R., Dunn, L. B., Gabriëls, L., Greenberg, B. D., Haber, S. N., Holtzheimer, P. E. III, Mari, Z., Mayberg, H. S., McCann, E., Mink, S. P., Rasmussen, S., Schlaepfer, T. E., Vawter, D. E., Vitek, J. L., Walkup, J., and Mathews, D. J. (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior and thought. *Arch. Gen. Psychiatry* 66, 931–937.

Merkel, R., Boer, G., Fegert, J., Galert, T., Hartmann, D., Nuttin, B., and Rosahl, S. (2007). *Intervening in the Brain. Changing Psyche and Society*. Berlin: Springer.

Sassi, M., Porta, M., and Servello, D. (2010). Deep brain stimulation therapy for treatment refractory Tourette's syndrome. *Acta Neurochir. (Wein)* 153, 639–645.

Schechtman, M. (2010). Philosophical reflections on narrative and deep brain stimulation. *J. Clin. Ethics* 21, 133–139.

Schermer, M. (2009a). Changes in the self: the need for conceptual next to empirical research. *Am. J. Bioeth.* 9, 45–47.

Schermer, M. (2009b). The mind and the machine. On the conceptual and moral implications of brain-machine interaction. *Nanoethics* 3, 217–230.

Schlaepfer, T. E., and Fins, J. J. (2010). Deep brain stimulation and the ethics of responsible publishing. *JAMA* 303, 775–776.

Schüpbach, M., Gargiulo, M., Welter, M. L., Mallet, L., Béhar, C., Houeto, J. L., Maltête, D., Mesnage, V., and Agid, Y. (2006). Neurosurgery in Parkinson's disease. A distressed mind in a repaired body? *Neurology* 66, 1811–1816.

Synofzik, M., and Schlaepfer, T. E. (2008). Stimulating personality: ethical criteria for deep brain stimulation in psychiatric patients for enhancement purposes. *Biotechnol. J.* 3, 1511–1520.

Conflict of Interest Statement: The research for this mini review was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

Received: 14 December 2010; accepted: 26 April 2011; published online: 09 May 2011.

Citation: Schermer M (2011) Ethical issues in deep brain stimulation. Front. Integr. Neurosci. ***5****:17. doi: 10.3389/fnint.2011.00017*

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 29 April 2011
doi: 10.3389/fnint.2011.00007

Informed consent in deep brain stimulation – ethical considerations in a stress field of pride and prejudice

Tobias Skuban[1]*, Katja Hardenacke[1], Christiane Woopen[2] and Jens Kuhn[1]

[1] *Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany*
[2] *Research Unit Ethics, Institute for the History of Medicine and Medical Ethics, University of Cologne, Cologne, Germany*
**Correspondence: tobias.skuban@uk-koeln.de*

The story of psychosurgery is one of great visions, groundbreaking ideas, and heroic acts; similarly it is a story of a great rise, a deep fall, and a cautious resurrection. For a long time, psychosurgery mainly had an experimental character and was dominated by anecdotal reports. In the aftermath of Fulton and Jabobsen's presentation of their results of a series of neurosurgical experiments performed with primates (Kopell and Rezai, 2003) during the International Neurological Congress in London in 1935, a considerable amount of ethically as well as scientifically doubtful surgical interventions were carried out in humans, occasionally even by medically uneducated personnel (Feldman and Goodrich, 2001). In this context one might paradigmatically mention prefrontal lobotomies, which virtually were advertised as magic bullet for all sorts of psychiatric diseases mainly in the 1940s and 1950s (Feldman et al., 2001; Kopell and Rezai, 2003; Mashour et al., 2005). Issues of informed consent frequently were neglected (Feldman and Goodrich, 2001; Pippard, 2001; Huys et al., 2010), critical side effects of the operation were concealed in many cases (Feldman and Goodrich, 2001) and the procedure even was offered to patients considered as criminally insane in exchange for their freedom (Lowinger, 1987). It was not long after Egas Moniz shared the Nobel Prize for medicine "for his discovery of the therapeutic value of prefrontal leucotomies in certain psychoses" in 1949 (Anonymous, 1949) when the public opinion of psychosurgery changed and questionable practices were unmasked (Heller et al., 2006).

Prompted by growing public criticism, a lack of a sufficient theoretical foundation, the uncertainty of its therapeutic value and severe side effects, the Department of Health, Education, and Welfare (Public Health Service) released strict restrictions regarding the usage of leucotomy in 1978 (Department of Health, Education, and Welfare, 1978); back then, many other nations already had prohibited this technique. While in the aftermath of the approval of chlorpromazine as first medicament for the treatment of psychiatric diseases in 1954 psychopharmacological therapy progressively began to revolutionize the psychiatric world, surgical methods for the treatment of psychiatric diseases involving gross damage of brain tissue were abandoned. However, encouraged by former success with invasive methods and supported by a growing knowledge regarding neuroanatomy and neural circuits underlying psychiatric and neurological diseases, novel and innovative surgical techniques came up. By now the somewhat prestressed term "psychosurgery" gave way to the broader idea of "neuromodulation," which summarizes not only invasive methods like deep brain stimulation (DBS) and vagus nerve stimulation, but also non-invasive techniques such as transcranial magnetic stimulation.

The ambivalent history of psychosurgery in mind, it is utterly comprehensible that even a reversible though (minimally) invasive technique like DBS reactivates ancient fears. Furthermore, with the observation of psychiatric side effects following DBS of the subthalamic nucleus in patients suffering from Parkinson's disease in the late 1990s (Bejjani et al., 1999; Hariz et al., 2010; Kuhn et al., 2010) psychiatric diseases came in the focus of DBS. Particularly since this amelioration of possible indications of DBS, the to some extent disreputable inheritance of psychosurgery has been brought up frequently.

However, DBS has not only proven to be an effective tool for the therapy of movement disorders such as Parkinson's disease, essential tremor, and dystonia, but it also has been successfully applied for the treatment of various psychiatric disorders such as obsessive-compulsion disorder (OCD), depression, Gilles-de-la-Tourette Syndrome, alcoholism, minimal conscious states, and Alzheimer's dementia. (Freund et al., 2009; Kuhn et al., 2010; Laxton et al., 2010).

A considerable amount of ethical skepticism culminates in the question of whether and how patients suffering from occasionally debilitating psychiatric diseases are capable of giving fully and freely their informed consent to a partly experimental procedure like DBS; we use the term "experimental" with precaution, but it should be kept in mind that there still is a considerable need for further research especially on its long-term therapeutic value with respect to its usage in psychiatric disorders (Hall and Carter, 2011).

Particularly patients with Alzheimer's disease may be limited in certain cognitive dimensions and this restriction could endanger their ability to completely understand all the implications connected with DBS. Beyond that, cognitive impairment is a common finding in patients with depression which could be linked to a dysfunction of the prefrontal cortex in interaction with subcortical regions (Clark et al., 2009); this dysfunction may result in deficits of attention, perception, concentration, and memory, hereby leading to a significant ambivalence of the patient. Moreover, patients suffering from substance abuse frequently are impaired with respect to tasks that involve highly goal-directed behavior; just recently it has been hypothesized that this deficit may be a result of a dysfunctional hypocretin system in the lateral thalamus (Boutrel et al., 2010). Due to this psychiatric condition, these patients might be constricted in their free decision making process.

Furthermore, many questions regarding DBS are still unanswered yet, for which reason it frequently is considered as a last resort when other therapeutic strategies could not be of substantial help. In this situation the desperate hope for ultimate relief may unduly affect a patient's ability to give his

or her consent (Glannon, 2010): this aspect exemplarily is emphasized by the fact that OCD patients have to suffer up to 8 h a day from typical symptoms of their disease to be accepted as possible candidates for DBS (Glannon, 2010). Additionally, the media's perception of DBS and its therapeutic potential tend to be euphoric and occasionally too optimistic. Contrariwise, psychosurgery's frightful history not infrequently is picked out as the central theme of novels and movies (cp. "One Flew Over the Cocoo's Nest," 1975 or "Shutter Island," 2010), which might be a source of inadequate fright for patients and their family members.

We go along with Lang and Widner's (2002) suggestion that "surgery should never be offered to a patient until [a] realistic understanding is fully established." Beauchamp and Childress (2001) and Berg et al. (2001) found that informed consent implies three basic requests: (1) all medically relevant information about diagnosis and prognosis of a patient's disease, the therapy, its potential risks and alternative therapies must be disclosed. (2) The patient should have the mental capacity to understand his or her situation and the presented information. (3) The patient must not be coerced or compelled, but autonomously decides about a treatment on the basis of the information disclosed. Regarding what has been discussed above, a patient and his or her family members might be prejudiced and influenced in many ways considering DBS. In addition, due to the underlying psychiatric disease, the patient might lack the mental capacity to fully comprehend his or her condition. Considering all this, envisaging DBS bears the risk that a patient's autonomy, i.e., his or her capacity to determine freely what action should be taken, if any, might be endangered. The concept of autonomy is closely connected to personal uniqueness (Breden and Vollmann, 2004) – so what if this uniqueness is affected by disease and possibly by prejudice as well? Even though this challenge is not unique to DBS or even to DBS in psychiatric diseases, the specific history of DBS, the complex connotations of a patient suffering from a psychiatric illness and potentially existing prejudice of the patient or his or her relatives, urgently call for detailed ethical examinations, highly skilled physicians, and more specific instruments for the assessment of a patient's capacity.

The MacArthur Competence Assessment Tool-Treatment (MacCAT-T) currently is regarded as psychiatry's gold standard for the determination of a patient's decision making competence. However, it has been reasonably criticized: the underlying construct of "competence" evaluated by the MacCAT-T is dominated by cognitive criteria, whereas emotional and biographical factors and a patient's values are ignored, although these dimensions might be of substantial importance during a decision making process (Breden and Vollmann, 2004). No alternative tool has been developed so far, so there is a high and urgent need for further endeavor in the design of proper assessment tools, which should include an extension of the cognition-based construct of competence proposed by the MacCAT-T.

REFERENCES

Anonymous. (1949). News and views. Nobel Prize for physiology and medicine for 1949. *Nature* 4179, 947.

Beauchamp, T., and Childress, J. (2001). *Principles of Biomedical Ethics*, 5th Edn. Oxford: Oxford University Press.

Bejjani, B. P., Damier, P., Arnulf, I., Thivard, L., Bonnet, A. M., Dormont, D., Cornu, P., Pidoux, B., Samson, Y., and Agid, Y. (1999). Transient acute depression induced by high-frequency deep-brain stimulation. *N. Engl. J. Med.* 340, 1476–1480.

Berg, J. W., Appelbaum, P. S., Lidz, C. W., and Parker, L. S. (2001). *Informed Consent: Legal Theory and Clinical Practice*, 2nd Edn. New York: Oxford University Press.

Boutrel, B., Cannella, N., and De Lecea, L. (2010). The role of hypocretin in driving arousal and goal-oriented behaviors. *Brain Res.* 1314, 103–111.

Breden, T. M., and Vollmann, J. (2004). The cognitive based approach of capacity assessment in psychiatry: a philosophical critique of the MacCAT-T. *Health Care Anal.* 12, 273–283; discussion 265–272.

Clark, L., Chamberlain, S. R., and Sahakian, B. J. (2009). Neurocognitive mechanisms in depression: implications for treatment. *Annu. Rev. Neurosci.* 32, 57–74.

Department of Health, Education, and Welfare. (1978). Determination of Secretary Regarding Recommendation on Psychosurgery of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Fed. Regist.* 43, 221.

Feldman, R. P., Alterman, R. L., and Goodrich, J. T. (2001). Contemporary psychosurgery and a look to the future. *J. Neurosurg.* 95, 944–956.

Feldman, R. P., and Goodrich, J. T. (2001). Psychosurgery: a historical overview. *Neurosurgery* 48, 647–657; discussion 657–649.

Freund, H. J., Kuhn, J., Lenartz, D., Mai, J. K., Schnell, T., Klosterkötter, J., and Sturm, V. (2009). Cognitive functions in a patient with Parkinson-dementia syndrome undergoing deep brain stimulation. *Arch. Neurol.* 66, 781–785.

Glannon, W. (2010). Consent to deep brain stimulation for neurological and psychiatric disorders. *J. Clin. Ethics* 21, 104–111.

Hall, W., and Carter, A. (2011). Is deep brain stimulation a prospective "cure" for addiction? *F1000 Med. Rep.* 3, 4.

Hariz, M. I., Blomstedt, P., and Zrinzo, L. (2010). Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg. Focus* 29, E1.

Heller, A. C., Amar, A. P., Liu, C. Y., and Apuzzo, M. L. (2006). Surgery of the mind and mood: a mosaic of issues in time and evolution. *Neurosurgery* 59, 720–733; discussion 733–729.

Huys, D., Möller, M., Kim, E. H., Huff, W., Klosterkötter, J., Timmermann, L., Woopen, C., and Kuhn, J. (2010). Historische Grundlagen der Tiefen Hirnstimulation bei psychiatrischen Erkrankungen. Nervenarzt (in press).

Kopell, B. H., and Rezai, A. R. (2003). Psychiatric neurosurgery: a historical perspective. *Neurosurg. Clin. N. Am.* 14, 181-197, vii.

Kuhn, J., Grundler, T. O., Lenartz, D., Sturm, V., Klosterkötter, J., and Huff, W. (2010). Deep brain stimulation for psychiatric disorders. *Dtsch Arztebl Int* 107, 105–113.

Lang, A. E., and Widner, H. (2002). Deep brain stimulation for Parkinson's disease: patient selection and evaluation. *Mov. Disord.* 17 Suppl 3, 94–101.

Laxton, A. W., Tang-Wai, D. F., McAndrews, M. P., Zumsteg, D., Wennberg, R., Keren, R., Wherrett, J., Naglie, G., Hamani, C., Smith, G. S., and Lozano, A. M. (2010). A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann. Neurol.* 68, 521–534.

Lowinger, P. (1987). Two comments on psychosurgery. *N. Engl. J. Med.* 316, 114–115.

Mashour, G. A., Walker, E. E., and Martuza, R. L. (2005). Psychosurgery: past, present, and future. *Brain Res. Brain Res. Rev.* 48, 409–419.

Pippard, J. S. (2001). Leucotomy: a qualified defence of "then". *QJM* 94, 451.

Received: 31 December 2010; accepted: 18 April 2011; published online: 29 April 2011.

*Citation: Skuban T, Hardenacke K, Woopen C and Kuhn J (2011) Informed consent in deep brain stimulation – ethical considerations in a stress field of pride and prejudice. Front. Integr. Neurosci. **5**:7. doi: 10.3389/fnint.2011.00007*

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 06 May 2011
doi: 10.3389/fnint.2011.00014

DBS makes you feel good! – why some of the ethical objections to the use of DBS for neuropsychiatric disorders and enhancement are not convincing

Anna Pacholczyk*

Institute for Science, Ethics and Innovation, School of Law, University of Manchester, Manchester, UK

**Correspondence: anna.pacholczyk@postgrad.manchester.ac.uk*

Deep brain stimulation (DBS) offers the potential to relieve some symptoms of movement disorders such as Parkinson's disease and dystonia. Recently, the applications of DBS have been extended to treatment-resistant mental health problems such as depression (Rabins et al., 2009). The successful application of DBS requires stimulation settings to be individually adjusted and the process of finding optimal settings can be lengthy. But what exactly are optimal settings?

Consider a hypothetical case of Philip, a 34-year-old patient with a history of severe depression who undergoes a successful implantation of stimulation electrodes. Depending on the parameters of stimulation, Philip is not clinically depressed but his symptoms drop only to a sub-clinical level (setting 1), he reaches an average level of well-being (setting 2), becomes very cheerful and energetic and takes advantage of it, trying to, as he says, "make up for the lost time" (setting 3), feels even better but a frequent ecstatic state makes him appear to misjudge some situations and he seems to have an incomplete awareness that he may be doing so (setting 4), becomes manic to the extent that he is rendered legally incompetent to make treatment decisions (setting 5).

There have been attempts to construct the concepts of disability and disease as a deviation from normal or species-typical functioning (e.g., Sabin and Daniels, 1994). If health is understood as an absence of disease and the goal of a medical intervention is to promote health thus defined, a transition from a diseased state to either a sub-clinical (setting 1) or average state of well-being (setting 2) achieves the goal equally well. However, the "normality view" faces well-known problems and the treatment/enhancement distinction is itself problematic enough not to serve as a good normative guide (Harris, 2007; Synofzik, 2009). It is unlikely that medical professionals would be satisfied by merely bringing a patient to a sub-clinical state if there is a more effective (after accounting for side-effects) intervention available. And for good reason – at the heart of medical intervention is the concern for the patient's well-being. The effectiveness of DBS for reducing the symptoms as assessed by clinical rating scales is admittedly important, but as Synofzik and Schlaepfer (2008) correctly point out, those improvements have to translate into the patient's improved ability to pursue and achieve their personal goals – goals that are connected to the patient's conception of a good life.

Some consider changes in personality to be among the risks of the DBS procedure (Glannon, 2009). This criticism is problematic even in the case of treatment for movement disorders, as not all side-effects are necessarily unwanted or undesirable, but becomes inapplicable when looking at treatment for neuropsychiatric conditions, since the goal of the intervention is exactly to change some cognitive and affective aspects of personality. Also, the aim of the treatment is not necessarily to rediscover the "real" patient hidden under the symptoms of a disorder. Rather, its aim is to improve patients' quality of life, given their own idea of what that means. Consequently, legally competent patients are not obliged to live up to or agree with the ideas of authenticity or rationality held by their doctors.

Medical professionals may be hesitant to utilize their skills for what they see as enhancement, but this apparent presumption against enhancement seems to be unjustified. Although we may have good reasons to prioritize interventions that improve the lives of those with generally worse health, medical professionals justifiably also use their expertise for medical interventions that have little to do with restoring health. The obvious examples of socially valued enhancements provided by medical professionals are vaccinations (Harris, 2007) and contraception – the goal of the former is to enhance the immune system, while that of the latter is to disrupt the reproductive function, which in turn enhances people's control over their lives. Medical professionals also perform interventions that are of no medical benefit to the subjects of the intervention (for example, blood donation or live organ donation). Thus, there is nothing in principle wrong with doctors using their expertise to provide an enhancing intervention other than treatment. The questions we should be asking instead are about appropriate consent procedures, issues of prioritization, some ethical quandaries arising from the application of DBS and the limits of legitimate power of the physician in the setting characterized by high power inequalities, exacerbated by the fact that a patient cannot simply go to a different health care provider.

Currently, the medical professional may say "we can provide you with the possibility of leading a good life, but not with what you think is necessary for a very good life." However, the presumption should surely be to provide the benefit that the patient seeks, and so the burden of giving reasons against this course of action rests on those who would deny this potential benefit. Legitimate concerns such as those related to limited financial resources (which could be offset if the patient is willing to pay for extra services) or the time constraints of the limited number of DBS specialists have to be weighed against other good moral reasons to perform the enhancing procedure. Some of the variables in this moral calculus may be different in the case of enhancement for non-patients (for example, we have to add a costly and invasive surgical procedure and follow-up), but the principle is the same. Since DBS practitioners are most commonly also researchers and members of

the scientific community, good reasons in favor of the procedure include, for example, the gains in scientific and medical knowledge about DBS and the brain. If DBS can bring benefit, there have to be really good reasons to deny it.

Although the use of DBS in non-clinical populations is not intrinsically unethical, this scenario seems, at least *prima facie*, to differ from the clinical uses of DBS in the predicted benefit to the subject and the acceptability of risks. Let us have a closer look. In relation to the use of psychopharmacological agents in non-therapeutic context, Synofzik (2009) proposed that the ethically justified decision of whether to provide and/or recommend a potentially enhancing agent should rest on the assessment of predicted risks and benefits and the respect for autonomy of the subject. His approach has the advantage of accounting not only for the moral weight of the predicted benefits of an intervention (especially when benefits outweigh the risks), but also for the fact that we often (and justifiably so) do what is not in our medical interest or otherwise narrowly construed self-interest in order to live according to our values – and for the importance of respecting choices of those with the capacity to make them, even if we find them surprising or difficult to explain.

Synofzik and Schlaepfer (2008) argued that although there is nothing in principle wrong with DBS for enhancement in non-clinical subjects, DBS is not ready for non-therapeutic application. They point out, for example, that there are no systematic studies of DBS effectiveness with non-clinical populations, making the evidence-based benefit assessment difficult. However, although there have been reports of at least one patient who chooses a setting depending on how she wants to feel (Russo, 2007), there also are no systematic studies of an non-therapeutic use of DBS for clinical populations – but this fact need not be a definitive argument against the permissibility of using DBS in those cases. What seems crucial here is rather the fact that the risks associated with surgery have already been taken, and so the risk/benefit ratio is more favorable in those cases – in other words, "trying it out" seems to be not as risky.

It is worth noting that at present it is highly unlikely that the public will queue to undergo DBS for non-therapeutic purposes – for many the benefits are too uncertain and the invasiveness of the procedure and associated risks and inconveniences too discouraging to even entertain the possibility of undergoing DBS. Those few that want to undergo DBS may do it for reasons that include, but are not limited to, the expectation of benefits. When the expectation of benefits is the main reason, this may be due to misunderstanding about effectiveness and risks of the procedure; this can be however addressed by providing appropriate information and the role of the specialist is of a crucial importance. Potential subjects do not have the obligation to "argue their case" or convince the physician, but they need to display sufficient awareness of the risks and benefits so that the requirements of informed consent are met.

However, there may also be those who are aware of the risks and the speculative nature of benefits but still want to undergo the procedure (e.g., for various reasons to do with pushing the boundaries of science and medicine). What should be done in such cases? Synofzik (2009) suggest that there may be cases where predicted risks outweigh predicted benefits, in which a physician has a good reason to discourage the use of an intervention on medical grounds but may still have a good moral reason to provide it; and to do so on the basis of subjects' widely constructed interest and the respect for their autonomy. So there may be cases, when despite medical risks outweighing the benefits (including cases where risks are possible to estimate with a higher degree of certainty than benefits) it may be ethically permissible to provide DBS solely on the basis of considering the subject's interests, albeit interests that go beyond the simply medical. This first step of the assessment will likely be followed by considering reasons for and against the procedure independent of the first step (funding, the potential to gain knowledge that could be transferred to the clinical setting, progress of science, etc.).

We may understand the sentiment of doctors who want to focus on relieving suffering, but we have to remember that the treatment/enhancement distinction that seems so obvious and apparent in the medical setting is much more difficult to construct as an ethically relevant one. The prospect of non-therapeutic use of DBS, and neuroenhancement in general, raises important questions about the societal implications of neurotechnologies. Among others, it restates old questions about the role and purpose of the medical profession and the role that doctors should play in managing access to medical technologies: those that aim at alleviating suffering and those that more generally promote well-being. At present, a limited number of specialists have control over the application of DBS. With this power, however, comes responsibility. Given that the ethics of the neuroenhancing application of DBS is less straightforward than it might have appeared at first sight, this responsibility includes, at the very least, a careful ethical assessment of requests for DBS for non-clinical use.

ACKNOWLEDGMENTS

I am grateful for the support from the Wellcome Strategic Programme "The Human Body – Its Scope, Limits, and Future." I would also like to thank John Coggon, John Harris, and Tom Lardner for their comments.

REFERENCES

Glannon, W. (2009). Stimulating brains, altering minds. *J. Med. Ethics* 35, 289–292.

Harris, J. (2007). *Enhancing Evolution*. Princeton: Princeton University Press.

Rabins, P., Appleby, B., Brandt, J., DeLong, M. R., Dunn, L. B., Gabriëls, L., Greenberg, B. D., Haber, S. N., Holtzheimer, P. E., Mari, Z., Mayberg, H. S., McCann, E., Mink, S. P., Rasmussen, S., Schlaepfer, T. E., Vawter, D. E., Vitek, J. L., Walkup, J., and Mathews, D. J. H. (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior and thought. *Arch. Gen. Psychiatry* 66, 931–937.

Russo, F. (2007). How to change a personality. *Time* 169, 101.

Sabin, J. E., and Daniels, N. (1994). Determining "medical necessity" in mental health practice. *Hastings Cent. Rep.* 24, 5–13.

Synofzik, M. (2009). Ethically justified, clinically applicable criteria for physician decision-making in psychopharmacological enhancement. *Neuroethics* 2, 89–102.

Synofzik, M., and Schlaepfer, T. E. (2008). Stimulating personality: ethical criteria for deep brain stimulation in psychiatric patients and for enhancement purposes. *Biotechnol. J.* 3, 1511–1520.

Received: 08 January 2011; accepted: 18 April 2011; published online: 06 May 2011.

Citation: Pacholczyk A (2011) DBS makes you feel good! – why some of the ethical objections to the use of DBS for neuropsychiatric disorders and enhancement are not convincing. Front. Integr. Neurosci. 5:14. doi: 10.3389/fnint.2011.00014

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 23 May 2011
doi: 10.3389/fnint.2011.00021

Authenticity, depression, and deep brain stimulation

Veronica Johansson[1,2]*, Martin Garwicz[1,3], Martin Kanje[1,4], Jens Schouenborg[1,3], Anders Tingström[1,5] and Ulf Görman[1,2]

[1] *Department of Experimental Medical Science, Neuronano Research Center, Lund University, Lund, Sweden*
[2] *Ethics Unit, Centre for Theology and Religious Studies, Lund University, Lund, Sweden*
[3] *Neurophysiology Unit, Department of Experimental Medical Science, Lund University, Lund, Sweden*
[4] *Department of Biology, Lund University, Lund, Sweden*
[5] *Molecular Psychiatry Unit, Department of Clinical Sciences, Lund University, Lund, Sweden*
**Correspondence: veronica.johansson@med.lu.se*

In 2005 the journal Neuron published Mayberg et al.'s (2005) pioneering study on deep brain stimulation (DBS) targeting treatment-refractory major depressive disorder (MDD). Since then a handful of studies, in total encompassing little over 50 patients, have been published (Aouizerate et al., 2005; Jimenez et al., 2005; Mayberg et al., 2005; Kuhn et al., 2007; Lozano et al., 2008; Neimat et al., 2008; Schlaepfer et al., 2008; Malone et al., 2009; Bewernick et al., 2010; Sartorius et al., 2010) and larger trials are underway (Bell et al., 2009). A common ethical concern voiced when DBS is used for a psychiatric disorder such as MDD is that the stimulation specifically targets cognition, mood, and behavior; elements which are closely linked to the patient's personality. Obviously, this holds true also for other antidepressants such as psychotherapy and medication. Apart from that these standard therapies have been of no avail for the patients considered for MDD DBS, one could still ask whether their potential to alter cognition, mood, and behavior, differ - with regard to ethical concerns - from that of DBS. Further, the relevant ethical concern is arguably not what functions the stimulation are *intended* to alter, as in psychiatric indications, but rather what functions that *could* be altered by DBS. Unintended alterations of cognition, mood and behaviour could occur as a consequence of both psychiatric and motoric DBS. Thus, potential alterations of personality seem, apart from the historical stigma connected with the former, to be relevant for most DBS indications. A lot of work remains to be done before a comprehensive analysis of these concerns could be presented. Our contribution is to introduce one question relevant to the intersection of DBS, MDD, and the notion(s) of authenticity.

At the heart of the notion of "authenticity" is the idea, with the words of the late British philosopher Bernard Williams, "that some things are in some real sense really you, or express what you are, and others aren't." This idea have not only attracted and been elaborated by philosophers (for further orientation, see Taylor, 1995 or Golomb, 1995), it also appears in our everyday lives. Expressions like "Mary wasn't really herself today" or, "Eric finally showed his true face," points to the notion that not all which we think, feel, or act on express who we really are. Thus, the notion of authenticity can both provide new perspectives to philosophical concerns regarding MDD and DBS, and in addition captures intuitions and beliefs held by many patients (Kramer, 1996; Bolt and Maartje, 2009). In contemporary analytical philosophy, authenticity has usually been employed in discussions on autonomy (Waddell Ekstrom, 1993, 2005), or in theories on "the Self" (Schechtman, 1996, 2004). In addition, authenticity has surfaced in bioethical discussions on issues like sex changes, human enhancement, and treatment of psychiatric disorders. A full account of these diverse interpretations cannot be given here (for instance, solely accounts of the self range from ideas that there are no such thing to ideas of the self as an immortal soul); hence this article is limited to introducing a few key features and their implications.

First one needs to address what the US philosopher Marya Schechtman describes as the characterization question, namely the set of characteristics that makes me the person I am; or, when applied to authenticity, the set of characteristics defining a person's "true self." One answer is suggested by the US philosopher Charles Guignon in the book "On being authentic." He describes this set of characteristics as "the constellation of feelings, needs, desires, capacities, aptitudes, dispositions, and creative abilities that make the person a unique individual" (Guignon, 2004). Guignon's suggestion bears some resemblance to the definition of personality traits according to the DSM-IV of the APA as "enduring patterns of perceiving, relating to, and thinking about the environment and oneself that are exhibited in a wide range of social and personal contexts." The emphasis of "enduring patters" touches on another important feature regarding the true self; does the true self consist of enduring patterns, or is it "constantly shifting and reacting and altering" (Williams, 2002)? However, two other common features of the notion of authenticity diverge from the definition of personality traits according to the DSM.

First, beside the descriptive content the notion of authenticity usually entails a normative claim. To be authentic, it does not suffice to identify the characteristics of one's true self. In addition, the defining set of characteristics must shine through or be expressed in the person's way of living; reflecting on undertakings such as relationships, professional life, and hobbies. Thus, we fail to be authentic when we fail to express some part of our defining characteristics (Guignon, 2004; Schechtman, 2004). Second, these characteristics are often more or less explicitly described as "natural" disposition; implying that this set of inclinations and traits are bestowed on each individual by nature. When these two features combine, authenticity urges the person to live in accordance with this given nature; that which "we are" has a privileged position. Thus, on this view diversions from a person's given nature are morally problematic. Noteworthy, the moral claim of authenticity does not oppose all kinds of alterations of a person; only the changes which distance a person from his or her true selves. Nor is a complete change in personality required for the change to be morally significant; or the rather major changes alluded to within

psychiatry when talking about personality changes. For being morally significant, it suffices if any of the characteristics that make up your true self is altered.

Given the belief that it would be morally problematic to diverge from who we really are, how could different interpretations of this belief shape our views on MDD and DBS? We will start by introducing one main question, and then briefly sketch some other considerations. Sometimes it seems to be taken for granted that new technology, especially invasive electrodes altering brain function, threaten human values such as dignity, autonomy, quality of life, or a flourishing individual life (these specific examples of "threats" are found in Kuhn et al., 2009); instead of also examining to what extent these techniques could benefit or strengthen these values. Though, we will build an argument regarding authenticity which indicates that the latter may just as well be the case. The group of patients considered for DBS are those suffering from severe, often chronic forms of depression where all standard therapies have failed. Thus, this is our subject matter. So what could be said of these patients? In its severe forms, MDD causes physical symptoms, cognitive impairment, and a diminished emotional reactivity and motivation (Malhi and Bartlett, 2000; SBU, 2004). Thus, the depression greatly impairs the afflicted person's quality of life (Sobocki et al., 2007); it influences personal relationships, work ability, the ability to pursue one's interests etc. (Malhi and Bartlett, 2000; SBU, 2004). Further, beside the well known risk of suicide – one in six of the patients severely affected by MDD take their own life (Malhi and Bartlett, 2000) – there are indications that MDD can cause permanent structural changes in various brain regions, for example hippocampus, amygdala, and prefrontal cortex, as well as an increased likelihood to develop coronary artery disease and type 2 diabetes (WHO, 2001; Kramer, 2005; Krishnan and Nestler, 2008). Nor could these patients, despite common romanticized view of MDD, be considered to benefit from their depressions by increased creativity, thoughtfulness, or by being more insightful (Elliott, 1999, 2003). There might be less severe forms of MDD were such claims could hold some validity, but for this fraction of patients the opposite applies (Kramer, 2005; Ghaemi, 2007).

As previously noted, according to the normative thesis of authenticity we are less authentic if we fail to express some part of our defining characteristics. Conversely, to be fully authentic we must express our true selves in our daily lives, such as relationships, professional life, and hobbies. Considering the impact of MDD described above, it seems obvious that the depression prevents the patients from being and living authentic; i.e., the alterations caused by the depression distance (albeit to what degree varies from case to case) a person from his or her true selves and are thus morally problematic. Accordingly, a successful outcome of DBS could be viewed as a form of liberation since a hindrance for the patient to be and live authentic is eliminated when the depression is vanquished or significantly reduced. Some examples could be an improved health or quality of life, or the ability to return to work, as many of Mayberg's patients managed to do (Egan, 2006); or establishing a relationship. If so, then the DBS treatment would be in accordance with, even promoting, the moral imperative of authenticity. The closer we get to an ideal DBS treatment; with set criteria for patient selection; optimal brain targets identified; and a new generation of electrodes which are more tissue friendly, minute, with precise and directed stimulation fields, and preferably designed to match the intended brain target, the likelihood of this outcome increases (something which in turn may open up for usage in less severe forms of MDD).

Much work lay ahead in identifying and examine other issues where authenticity could provide insights to the ethical implications of DBS for MDD. One fundamental question is whether the depression is a part of, or perceived to be a part of, the patient's personality or not? If the former is the case it would, restricted to an authenticity perspective only, follow that treating the depression is morally problematic – if the alteration distance a person from his or her true self. More importantly, the patient's view on this issue might influence whether he or she will consider DBS, hence empirical studies of this, and similar, questions is warranted. Another issue addresses authenticity, personality changes, and desired treatment outcomes. In a recent article on DBS (Müller and Christen, 2011), it was suggested that the aim of an ethically acceptable treatment, at least *prima facie*, should be to restore the personality to its premorbid state. Though this suggestion might have an intuitive appeal, and could be defended given a static view of the self, it does seem problematic at a closer look. Most of the patients with MDD considered for DBS have lived with the disorder for years or even decades. Considering the severe impact of the disorder; the depression, as well as the treatment, is not likely to leave the patients unchanged. For instance, at the "brains in dialog on DBS" workshop in Warsaw a participating Parkinson patient gave a telling account of such changes. She described that she after the DBS operation experienced "a third version of me," in comparison to the version of her prior to Parkinson's Disease and the version affected by the disease but prior to the effective symptom relief provided by DBS. Another angle to this question is provided by an observation made by American psychiatrist Peter Kramer in his book "Listening to Prozac." Some of his (previously) depressed patients claimed that, at long last, taking Prozac made them experience their true selves for the first time, even though they, until then, had had another disposition (Kramer, 1996). These accounts point to the problems in assuming that there is such a thing as a premorbid, implicitly authentic, personality to be restored, or, in determining which "version" of the self that is authentic. However, if this is the case does it then make sense to talk about authenticity at all?

We suggest that it does. The concept of authenticity as such provides a means to entangle both philosophical and generally held intuitions regarding normative claims connected to personality changes. A superficial understanding of the concept and its normative implications; for instance, that alterations of cognition, mood, and behavior due to the disorder would be more authentic than comparable alterations caused by the treatment; or that the moral demand of authenticity require that the patient is restored to a premorbid state which obviously is gone forever, could lead us astray. Likewise, the concept is not bound to a dated belief of an authentic self which is given by nature and unchanged by time. Instead, we suggest that the concept of authenticity could be used to capture and analyze the intuition that some alterations of cognition, mood and behavior are ethically objectionable, whereas others are

unproblematic or even desirable. The concept of authenticity can illuminate ethical concerns regarding changes of a patient's fundamental defining characteristics; how these characteristics vary from patient to patient; and, over the lifespan of a single patient.

ACKNOWLEDGMENTS

We want to thank Prof. Dan Egonsson, Mats Lindström, and Frits Gåvertsson as well as the participants in the research seminars in ethics, and medical ethics, for valuable comments on earlier drafts. This research project was sponsored by a Linné grant, project number 60012701, from the Swedish Research Council and The Knut and Alice Wallenberg Foundation, project number: KAW 2004.0119.

REFERENCES

American Psychiatric Association (APA). (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edn, Washington, DC: American Psychiatric Association.

Aouizerate, B., Martin-Guehl, C., Cuny, E., Guehl, D., Amieva, H., Benazzouz, A., Fabrigoule, C., Bioulac, B., Tignol, J., and Burbaud, P. (2005). Deep brain stimulation for OCD and major depression. *Am. J. Psychiatry* 162, 2192.

Bell, E., Mathieu, G., and Racine, E. (2009). Preparing the ethical future of deep brain stimulation. *Surg. Neurol.* 72, 577–586.

Bewernick, B. H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., Lemke, M., Cooper-Mahkorn, D., Cohen, M. X., Brockmann, H., Lenartz, D., Sturm, V., and Schlaepfer, T. E. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol. Psychiatry* 67, 110–117.

Bolt, I., and Maartje, S. (2009). Psychopharmaceutical enhancers: enhancing identity? *Neuroethics* 2, 103–111.

Egan, D. (2006). T*he New Lobotomy? 'Deep brain stimulation' Tested at UBC as Depression Cure*. The Tyee: A Feisty One. Available at: http://thetyee.ca/News/2006/10/26/DBS/

Elliott, C. (1999). *A Philosophical Disease: Bioethics, Culture, and Identity*. New York: Routledge.

Elliott, C. (2003). *Better Than Well: American Medicine Meets the American Dream*. New York: W.W. Norton.

Ghaemi, S. N. (2007). *The Concepts of Psychiatry: A Pluralistic Approach to the Mind and Mental Illness*. Baltimore: Johns Hopkins University Press.

Golomb, J. (1995). *Problems of Modern European Thought: In Search of Authenticity*. New York: Routledge

Guignon, C. B. (2004). *On Being Authentic*. New York: Routledge.

Jimenez, F., Velasco, F., Salin-Pascual, R., Hernández, J. A., Velasco, M., Criales, J. L., and Nicolini, H. (2005). A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery* 57, 585–593; discussion 585–593.

Kramer, P. D. (1996). *Lyssna till Prozac*. Falun: Bokförlaget Natur och Kultur.

Kramer, P. D. (2005). *Against Depression*. New York: Viking.

Krishnan, V., and Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature* 455, 894–902.

Kuhn, J., Gaebel, W., Klosterkoetter, J., and Woopen, C. (2009). Deep brain stimulation as a new therapeutic approach in therapy-resistant mental disorders: ethical aspects of investigational treatment. *Eur. Arch. Psychiatry Clin. Neurosci.* 259, 135–141.

Kuhn, J., Lenartz, D., Huff, W., Lee, S., Koulousakis, A., Klosterkoetter, J., and Sturm, V. (2007). Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? *J. Neurol. Neurosurg. Psychiatr.* 78, 1152–1153.

Lozano, A. M., Mayberg, H. S., Giacobbe, P., Hamani, C., Craddock, R. C., and Kennedy, S. H. (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol. Psychiatry* 64, 461–467.

Malhi, G. S., and Bartlett, J. R. (2000). Depression: a role for neurosurgery?. *Br. J. Neurosurg.* 14, 415–422.

Malone, D. A., and Dougherty, D. D., Rezai, A. R., Carpenter, L. L., Friehs, G. M., Eskandar, E. N., Rauch, S. L., Rasmussen, S. A., Machado, A. G., Kubu, C. S., Tyrka, A. R., Price, L. H., Stypulkowski, P. H., Giftakis, J. E., Rise, M. T., Malloy, P. F., Salloway, S. P., and Greenberg, B. D. (2009). Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol. Psychiatry* 65, 267–276.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M., and Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–660.

Müller, S., and Christen, M. (2011). Deep brain stimulation in Parkinsonian patients – ethical evaluation of cognitive, affective, and behavioral sequelae. *AJOB Neurosci.* 2, 3–13.

Neimat, J. S., and Hamani, C., Giacobbe, P., Merskey, H., Kennedy, S. H., Mayberg, H. S., and Lozano, A. M. (2008). Neural stimulation successfully treats depression in patients with prior ablative cingulotomy. *Am. J. Psychiatry* 165, 687–693.

Sartorius, A., Kiening, K. L., Kirsch, P., von Gall, C. C., Haberkorn, U., Unterberg, A. W., Henn, F. A., and Meyer-Lindenberg, A. (2010). Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biol. Psychiatry* 67, e9–e11.

SBU. (2004). *Behandling av depressionssjukdomar: En systematisk litteraturöversikt, Volym 1–3*. SBU-rapport nr 166/1–3, Stockholm: SBU.

Schechtman, M. (1996). *The Constitution of Selves*. Ithaca: Cornell University Press.

Schechtman, M. (2004). Self-expression and self-control. *Ratio* 17, 409–427.

Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., Joe, A. Y., Kreft, M., Lenartz, D., and Sturm, V. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33, 368–377.

Sobocki, P., Lekander, I., Borgström, F., Ström, O., and Runeson, B. (2007). The economic burden of depression in Sweden from 1997 to 2005. *Eur. Psychiatry* 22, 146–152.

Taylor, C. (1995). *The Ethics of Authenticity*. Cambridge, MA: Harvard University Press.

Waddell Ekstrom, L. (1993). A coherence theory of autonomy. *Philos. Phenomenol. Res.* 53, 599–616.

Waddell Ekstrom, L. (2005). Alienation, autonomy, and the self. *Midwest Stud. Philos.* 29, 45–67.

WHO. (2001). *The World Health Report 2001 – Mental Health: New Understanding, New Hope*. Available at: http://www.who.int/whr/2001/en/index.html

Williams, B. A. O. (2002). *Truth and Truthfulness: An Essay in Genealogy*. Princeton, NJ: Princeton University Press.

Received: 24 January 2011; accepted: 09 May 2011; published online: 23 May 2011.

*Citation: Johansson V, Garwicz M, Kanje M, Schouenborg J, Tingström A and Görman U (2011) Authenticity, depression, and deep brain stimulation. Front. Integr. Neurosci. **5**:21. doi: 10.3389/fnint.2011.00021*

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 02 May 2011
doi: 10.3389/fnint.2011.00009

Pediatric deep brain stimulation: a cautionary approach

Farah Focquaert*

Department of Philosophy and Moral Sciences, Bioethics Institute Ghent, Ghent University, Ghent, Belgium
**Correspondence: farah.focquaert@ugent.be*

Today, deep brain stimulation (DBS) is performed to treat dystonia in children as young as 7 years of age (Roubertie et al., 2000). For a variety of reasons, timely intervention in childhood dystonia is important: (1) to prevent irreversible damage, (2) to obtain optimal treatment outcomes, since severity and duration of the disease are negative prognostic factors for successful DBS treatment, and (3) to prevent long-term social costs due to social isolation (Isaias et al., 2008; Mehrkens et al., 2009; Clausen, 2010). Individual cases of DBS for neuropsychiatric disorders in adolescents have been published over the last 3 years (e.g., Shaded et al., 2007). Considering the investigational nature of DBS for psychiatric disorders, this is unsettling to say the least.

A group of experts recently proposed guidelines for the use of DBS for disorders of mood, behavior and thought (Rabins et al., 2009). Due to the investigational nature of DBS for psychiatric disorders, they defend the position that, at present, DBS for mood, behavior and thought disorders should be reserved for adults. However, they also put forward that "if DBS is found to be safe and effective for adults, then it might be appropriate to investigate its benefits for a younger population with severe, treatment-refractory symptoms" (p. 933). Their opinion is quite different from the statement made by another group of experts on the use of DBS for Tourette syndrome (TS) in children (Mink et al., 2006). They argue that patients should be at least 25 years old, with rare potential exceptions involving younger patients. Bloch and Leckman (2009) similarly claim that "invasive interventions for TS such as DBS and neurosurgery are strongly discouraged until well into adulthood, even for patients with impairing tics" (p. 499).

Is it ethical to categorically exclude children and adolescent patients from receiving DBS for treatment-refractory disorders such as TS? If clear scientific criteria exist why specific pediatric disorders need to be excluded, then yes. However, if no such criteria exist for a given disorder, then surely it is unethical to categorically exclude children and adolescent patients from receiving the only treatment available that could dramatically increase their quality of life. Experts that oppose the use of DBS for pediatric TS (Mink et al., 2006; Porta et al., 2009) defend their position based upon the nature of childhood TS. According to a recent review, by early adulthood, approximately three quarters of children with TS will have greatly diminished tics and more than one-third will be tic free (Bloch and Leckman, 2009). A recent follow-up study on childhood and adolescent OCD found that 60% of children and adolescents did not have a full clinical disorder at follow-up, and two-thirds of participants rated themselves as much improved (Micali et al., 2010). According to the authors, many young people adapt to their illness and can lead a fairly normal life despite their symptoms. These are indeed important findings that highlight the exceptional caution that is needed when considering pediatric DBS for disorders that may spontaneously disappear or become subclinical over time. However, do they warrant the categorical exclusion of child patients? As Mink et al. (2006) themselves put forward: "Remission of tics may occur in the third decade of life in up to 50% of patients, but to date, there are no prognostic features that predict which patients will have a remission in their symptoms" (p.1832), and according to experts, the situation remains the same today. Which means that we do not possess clear scientific criteria to warrant the categorical exclusion of all child patients.

Children with severe treatment-refractory diseases are an extremely vulnerable group, and they should not be exposed to an invasive intervention like DBS unless successful treatment outcomes have been established in adults. However, if treatment success for neurological or psychiatric disorders is established in adults, and provided no clear scientific criteria exist to categorically exclude minors, then children and adolescents can be involved in small-scale, early-phase studies provided these are done in research centers. Children with treatment-refractory disorders should not be categorically excluded from receiving DBS treatment, and this holds for any disorder for which treatment success has been established in adults and for which no clear scientific criteria exist that warrant their exclusion. Moreover, it is crucial that the decision-making process is a shared process between the child patient, the medical experts and the parents or parental guardians to maximally protect the vulnerable child patient. The decision-making process should involve a dual consent procedure with parents giving informed consent and children giving explicit assent. Medical experts should not start treatment in those cases where the only benefit to incur would be relief of caregiver burden. Unless clear scientific data can show that a child patient would benefit by receiving DBS treatment and would be harmed if not given treatment (e.g., cases of severe childhood dystonia), DBS treatment should not be performed if the child patient dissents. If successful, timely DBS treatment for dystonia benefits both the child patient (by preventing irreversible harm and long-term social costs due to social isolation, and providing optimal treatment outcomes) and the caregiver. Hence, we have strong reasons to consider DBS treatment in a timely fashion, and potentially even in those cases where the child patient dissents. This is not so for certain other disorders. If DBS treatment is performed for childhood TS or OCD that might have spontaneously remitted or become subclinical with time, then the dissenting child patient is harmed because an unnecessary invasive procedure was forced upon him/her, and the only benefit that occurred is a third-party benefit (i.e., caregiver relief). In fact, treatment compliance is a patient selection requirement according to the Italian DBS group treating TS (Porta et al., 2009). Indeed, it is crucial that the decision-making procedure is a shared process between child patients, medical experts and parents: (a) to ensure

the best possible care and support during the treatment process, (b) to preserve family intimacy, and (c) to stimulate children's development of autonomy.

REFERENCES

Bloch, M. H., and Leckman, J. F. (2009). Clinical course of Tourette syndrome. *J. Psychosom. Res.* 67, 497–501.

Clausen, J. (2010). Ethical brain stimulation – neuroethics of deep brain stimulation in research and clinical practice. *Eur. J. Neurosci.* 32, 1152–1162.

Isaias, I. U., Alterman, R. L., and Tagliati, M. (2008). Outcome predictors of pallidal stimulation in patients with primary dystonia: the role of disease duration. *Brain* 131, 1895–1902.

Mehrkens, J. H., Boetzel, K., Steude, U., Zeitler, K., Schnitzler, A., Sturm, V., and Voges, J. (2009). Long-term efficacy and safety of chronic globus pallidus internus stimulation in different types of primary dystonia. *Stereotact. Funct. Neurosurg.* 87, 8–17.

Micali, N., Heyman, I., Perez, M., Hilton, K., Nakatani, E., Turner, C., and Mataix-Cols, D. (2010). Long-term outcomes of obsessive compulsive disorder: follow-up of 142 children and adolescents. *Br. J. Psychiatry* 197, 128–134.

Mink, J. W., Walkup, J., Frey, K. A., Como, P., Cath, D., DeLong, M. R., Erenberg, G., Jankovic, J., Juncos, J., Leckman, J. F., Swerdlow, N., Visser-Vandewalle, V., Vitek, J. L., and the Tourette Syndrome Association, Inc. (2006). Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. *Mov. Disord* 21, 1831–1838.

Porta, M., Servello, D., Sassi, M., Brambilla, A., Defendi, S., Priori, A., and Robertson, M. (2009). Issues related to deep brain stimulation for treatment-refractory Tourette's syndrome. *Eur. Neurol.* 62, 264–273.

Rabins, P., Appleby, B. S., Brandt, J., DeLong, M. R., Dunn, L. B., Gabriëls, L., Greenberg, B. D., Haber, S. N., Holtzheimer, P. E. III, Mari, Z., Mayberg, H. S., McCann, E., Mink, S. P., Rasmussen, S., Schlaepfer, T. E., Vawter, D. E., Vitek, J. L., Walkup, J., and Mathews, D. J. (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior, and thought. *Arch. Gen. Psychiatry* 66, 931–937.

Roubertie, A., Echenne, B., Cif, L., Vayssiere, N., Hemm, S., and Coubes, P. (2000). Treatment of early-onset dystonia: update and a new perspective. *Childs Nerv. Syst.* 16, 334–340.

Shaded, J., Poysky, C., Kenney, C., Simpson, R., and Jankovic, J. (2007). GPi deep brain stimulation for Tourette improves tics and psychiatric comorbidities. *Neurology* 68, 159–162.

Received: 03 January 2011; accepted: 18 April 2011; published online: 02 May 2011.

Citation: Focquaert F (2011) Pediatric deep brain stimulation: a cautionary approach. Front. Integr. Neurosci. ***5****:9. doi: 10.3389/fnint.2011.00009*

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 09 May 2011
doi: 10.3389/fnint.2011.00012

Must family/carers look after strangers? Post-DBS identity changes and related conflicts of interest

Robin Mackenzie*

Kent Law School, Eliot College, University of Kent, Canterbury, Kent, UK

**Correspondence: r.mackenzie@kent.ac.uk*

Deep brain stimulation (DBS), a favored treatment option for Parkinson's disease and treatment resistant depression, restores disrupted brain mechanisms to default states and is likely to extend to mental and movement disorders and neurodegenerative conditions. All are associated with gradual cognitive, affective and/or behavioral changes. DBS confronts family/carers with emotionally, physically, and mentally trying challenges, as successful symptomatic relief may be accompanied by instantaneous apparent identity changes. Patients become restored to a previous state, "normal" or species-typical in ways they have never been, or placed in an enhanced state of subjective well-being. They are likely to feel like a new person, both to themselves and to others. How clinicians conceptualize patients' post-DBS personality changes has profound ethical implications not only for the patient but also for their family/carers. These amplify existing conflicts of interests.

Some involve patients, family/carers, and healthcare authorities. Family/carers looking after patients with neurodegenerative conditions, mood disorders, and brain injuries in the home conserve healthcare resources at considerable personal cost. They are increasingly subject to coercive expectations of affection and day-to-day care for the aging and infirm as demographic changes foster devolution of care from hospitals to homes. These resource-driven policies tend to be couched in terms of the rhetoric of patient choice, e.g., deinstitutionalization of neurorehabilitation and hospice services on the grounds that most of us wish to die at home. Family/carers are placed in an invidious position as they are expected to function almost as ancillary members of clinical teams in terms of providing care, yet lack the authority, training, remuneration, and legal safeguards accorded clinicians.

The potential of DBS to provide symptomatic relief could spare healthcare budgets and family/carers' personal resources. Devolution from hospitals to homes depends upon family/carers providing day-to-day care, monitoring patients' conditions and taking momentous decisions, like assessing decision-making competence and capacity after the cognitive, affective, and behavioral changes DBS is likely to treat. As increasing proportions of the population will suffer from chronic conditions, or be involved in looking after the seriously impaired at home, the financial, and clinical implications of successful DBS treatment are immense. Patients, family/carers and society at large could reap significant benefits from symptomatic relief leading to returns to paid employment, increased social participation, and release from carer burden. Yet these benefits must be balanced against the risks of conflicts of interest arising from the impact of post-DBS personality changes on family/carers.

Both sudden and gradual personality/identity changes stress family/carers. Conditions like stroke and traumatic brain injury can cause sudden identity alterations, while gradual changes characterize neurodegenerative conditions. Family/carers experience poorer mental and physical health and more stress where patients' personalities have changed. They report more resilience when there has been cognitive but not affective change so affectionate relations are preserved. Caring for someone where love and affection continue is understandably easier than providing services for someone who may look the same, but feels and behaves like a stranger (Mackenzie and Sakel, 2011). Clinical strategies emphasize constructing narratives providing continuities of identity, as where neurorehabilitative goal-setting supports recovery of self and capacities after sudden changes, or narratives connecting past memories and present events preserve fading self-concepts in dementia. Family/carers who adhere to these stories are more able to continue to provide care on the basis of affection for those who still feel like their loved ones, despite clinically induced changes. Narratives provide a context of continuous meaning for patients' personality changes which allow for grief for the loss of capacities, but continuity of caring (Ylvisaker et al., 2008).

Post-DBS personality changes are different. Patients may not behave or feel like familiar damaged or diseased loved ones, but like healthy strangers with claims on family/carers' time, affection, and assets. While cognitive and behavioral incapacities characterize patients with stroke, brain injury, and dementia, affectionate mutuality often continues, so that family/carers feel that the relationship is maintained despite misfortune. Yet conditions where patients maintain their cognitive abilities, but lose their capacities for empathy, insight into their own behavior and considering others' interests, as in "acquired sociopathy" associated with behavioral variant frontotemporal dementia, are notorious for placing the maximum burden on carers (Mackenzie and Sakel, 2011). Thus, family/carers of DBS patients are likely to be faced with significant stresses associated with being linked to those who look like their loved ones, but may behave quite differently, value very different things, and be unconstrained by past ties of affection.

Family/carers are likely to feel guilty and conflicted if they prefer patients who were previously suffering from serious clinical symptoms, yet remained affectionate, to the same patients in their post-DBS state where DBS results in altered personalities, values, and choices over ways of life. Grieving for the lost person's presence may feel unethical in that serious symptoms have been alleviated, but, where the healthy person feels like a stranger, their claims on family/carers' time, affection, and assets may feel inappropriate and unjustified. Unanticipated breakdowns of relationships, dispersal of familial assets and inordinate stress on family/carers are likely outcomes, which should be addressed carefully in pre-DBS informed consent procedures. This is particularly

crucial as competent patients whose values change post-DBS could repudiate advance decisions made pre-DBS.

Deep brain stimulation effects' reversibility also provokes unique ethical dilemmas. Neuromodulatory stimuli may be turned on or off and up or down. Using DBS to map connections between neural mechanisms, specific brain locations, subjective experiences and ways of behaving may provide evidence allowing for choice over where settings should be to ensure desired personality traits post-DBS. Accompanying disruptions are inevitable in diagnostic categories and conceptions of what constitutes normality, neurodiversity, and neurodysfunction. Clinicians may become able to use DBS to create tailor-made personalities for patients. After taxonomic upheavals, an increased range of personality traits are likely to become accepted as neurodiverse rather than neurodysfunctional. This all impacts on clinicians' ethical responsibilities, as it may be possible to provide DBS in ways which are clinically equivalent, but have varied outcomes in terms of patients' personality and behavioral changes. How choices amongst settings determining this should be made, and by whom, is unclear.

Patients are likely to choose settings enabling them to feel "better than well," whereas family/carers may prefer personality traits more like their familiar loved ones'. Should either be clinically preferable, it should prevail. Yet no ethical guidelines exist for choosing between clinically equivalent settings. Eschewing extreme settings may be deplored as coerced normalization and there are no clear grounds for considering specific settings as guaranteeing more authentic patient identities. Conflicts are inevitable over which settings should be chosen to enable which personality characteristics (Mackenzie, 2011). Boundaries between neurodiversity and neurodysfunction are likely to be bitterly contested.

Should symptomatic relief be accompanied by altered personality traits leading to relationship breakdown and dispersal of family assets, family/carers may want some say in choices over treatment outcomes. Yet as clinicians' duty of care is to patients alone, where post-DBS personality traits are clinically equivalent, patients should be accorded autonomous choice. Clinicians would retain a duty to ensure that patients were informed of the risks and options accompanying their choices. As patients' risk preferences are likely to alter with DBS treatment, questions arise over which of a range of possible states should be accepted as a basis for autonomous choices. Should the choice over settings of the patient in a risk-averse, risk-neutral, or risk-seeking state be accepted? As conditions treated by DBS involve cognitive, affective, and behavioral alterations, patients' pre-treatment states cannot be seen as more authentic than any of a range of clinically equivalent post-treatment states of being.

Clinicians may feel an ethical obligation to redress such conflicts of interest by including family/carers in the informed consent procedures, or suggesting they obtain legal advice on protecting familial assets pre-DBS. Yet clinicians also need to protect their patients. They should monitor refusals of DBS treatment and assess how autonomous patients' choices over post-DBS settings are in relation to undue influence or coercion. Family/carers may attempt to manipulate patients to refuse DBS or to choose settings which preserve affectionate bonds and family assets. Where patients eligible for DBS are incompetent, family/carers may be tempted to influence discussions over whether DBS is in patients' best interests, or to institutionalize them prematurely. Access to outside interference with DBS mechanisms and settings may need to be restricted, as may the range of settings able to be chosen.

This opinion has sketched out some conflicts of interest which may arise between healthcare authorities, clinicians, patients, and family/carers post-DBS treatment. Yet the promise of DBS to transform the well-being of all parties is commensurately immense. In the light of these factors, as well as others which space constraints prevent my mentioning, there is an urgent need for ethical guidelines on DBS.

REFERENCES

Mackenzie, R. (2011). Who should hold the remote for the new me? Cognitive, affective and behavioural side-effects of DBS and authentic choices over future personalities. *AJOB Neurosci.* 2, 18–19.

Mackenzie, R., and Sakel, M. (2011). "Neuroscience of cruelty as brain damage: legal framings of capacity and ethical issues in the neurorehabilitation of MND and bvFTD," in *Law and Neuroscience*, ed. M. Freeman (Oxford: Oxford University Press), 285–307.

Ylvisaker, M., Mcpherson, K., Kayes, N., and Pellett, E. (2008). Metaphoric identity mapping: facilitating goal setting and engagement in rehabilitation after traumatic brain injury. *Neuropsychol. Rehabil.* 18, 713–741.

Received: 31 January 2011; accepted: 18 April 2011; published online: 09 May 2011.

Citation: Mackenzie R (2011) Must family/carers look after strangers? Post-DBS identity changes and related conflicts of interest. Front. Integr. Neurosci. ***5****:12. doi: 10.3389/fnint.2011.00012*

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 05 May 2011
doi: 10.3389/fnint.2011.00013

Single cases promote knowledge transfer in the field of DBS

***Markus Christen*[1]* and Sabine Müller*[2]**

[1] *Institute of Biomedical Ethics, University of Zurich, Zürich, Switzerland*
[2] *Division of Mind and Brain Research, Department of Psychiatry and Psychotherapy, Charité – Universitaetsmedizin Berlin, Berlin, Germany*
**Correspondence: christen@ethik.uzh.ch*

The development and clinical application of deep brain stimulation (DBS) is based on the cooperation of various disciplines in order to address its neuroscientific, neurological, psychological, technological, and ethical challenges (Benabid et al., 2009). Safeguarding the quality of this interdisciplinary cooperation requires that novel issues (e.g., on adverse events) are raised timely in the scientific community and are communicated across disciplinary borders. In this opinion, we describe the development of the complexity of DBS research and assess knowledge transfer in terms of citations that transcend disciplinary borders. Our argument is based on an extended, ongoing meta-analysis of scientific journal papers on DBS in the nucleus subthalamicus (STN); a literature body that comprises more than 550 case reports, outcome studies, and review papers (Müller and Christen, 2011). Because STN–DBS, beginning in the early 1990s, is the most common DBS application, lessons learned in STN–DBS are important for evaluating clinical, societal, and ethical issues of novel DBS applications that emerge in psychiatry and other fields.

The complexity of DBS research is illustrated by the various issues that are discussed in the DBS literature. Our meta-analysis revealed a broad range of issues that can be grouped into four classes (see **Figure 1A**):

1. Understanding therapeutic effects: motor effects of DBS, effects on medication, and comparison with medication-based therapy, research about the physiological mechanisms of DBS.
2. Medical intervention issues: surgery-related issues (e.g., hemorrhage risks) and patient management (e.g., patient selection).
3. Affective, behavioral, and cognitive side effects of DBS: sequelae on behavior, cognition, mood, language, and quality of life.
4. Other issues: cost-benefit studies, technological issues (e.g., battery life), effects of DBS on autonomous functions, sensory systems, emotion recognition, sleep, and body weight.

For investigating how and when the discussion in the scientific communication about those issues has developed, the analysis of conference posters is preferable to the analysis of journal papers, since posters are published faster, have a lower publication threshold, and are more thematically focused. The International Congress of Parkinson's Disease and Movement Disorders (since 1990 biannually, since 2004 annually) maps very accurately the research on DBS applications for movement disorders. Since the amount of DBS journal papers has significantly increased after 2000 – indicating a transition from a "pioneer phase" to an "application phase" (Müller and Christen, 2011), we compare the posters published on the 2002 (175 DBS posters out of 1,183) and 2010 (124 DBS posters out of 1,067) conferences. Thus we cover a time span in which the scientific debate on DBS issues already was established. A content analysis of the posters presented in 2002 reveals a dominance of issues about understanding the therapeutic effects of DBS. However, the thematic spectrum was impressively wide and broadened further in 2010, where in particular the fractions of posters about patient management and about behavioral and cognitive side effects have increased.

One way to investigate knowledge transfer between different disciplines that cooperate for developing new therapies is an impact analysis, i.e., a comparison of the number of publications with the number of citations of those publications in different disciplinary fields (Christen, 2008). In the Thomson Reuters Web of Knowledge database (the broadest academic citation indexing and search service), each publication is related to one or several subject categories based on the journal in which it has been published. These subject categories are pooled to "disciplinary clusters," whereas the pooling is adapted to the type of problem and the number of citations obtained. By way of example, if 50% of the publications of a specified literature body are attributed to one cluster, whereas only 10% of all citations generated by this literature body are attributed to the same cluster, a publication–citation-transfer between this cluster and other clusters has happened.

For the impact analysis, we have compared six disciplinary clusters of three subsets of publications from our DBS literature body (see below) with the set of publications that cite these publications. The impact analysis shows that the subject category "clinical neurology" covered the most citations (and publications), and thus became a separate cluster, whereas the other disciplinary clusters (Neuroscience, Biology, Psychiatry/Psychology, Medicine, Social/Technical Sciences and Humanities) were formed by several subject categories with thematic similarities. Subject categories of technical and social sciences or humanities obtained only a few citations and were therefore pooled in one large cluster. It has to be noted that journals for social sciences and humanities are covered insufficiently by the Web of Knowledge database. Therefore the impact analysis underestimates the impact of the DBS literature in these disciplines.

The following publication-subsets from our STN–DBS literature body (~550 publications) have been chosen for the impact analysis: 40 Case Reports on adverse events after STN–DBS; 44 Outcome Studies that achieve high "relevance ratings" (i.e., they have been regularly analyzed by the DBS-review-papers that form the third set); 23 "high quality" Review Papers that used a standard meta-analysis methodology or were based at least on a systematic

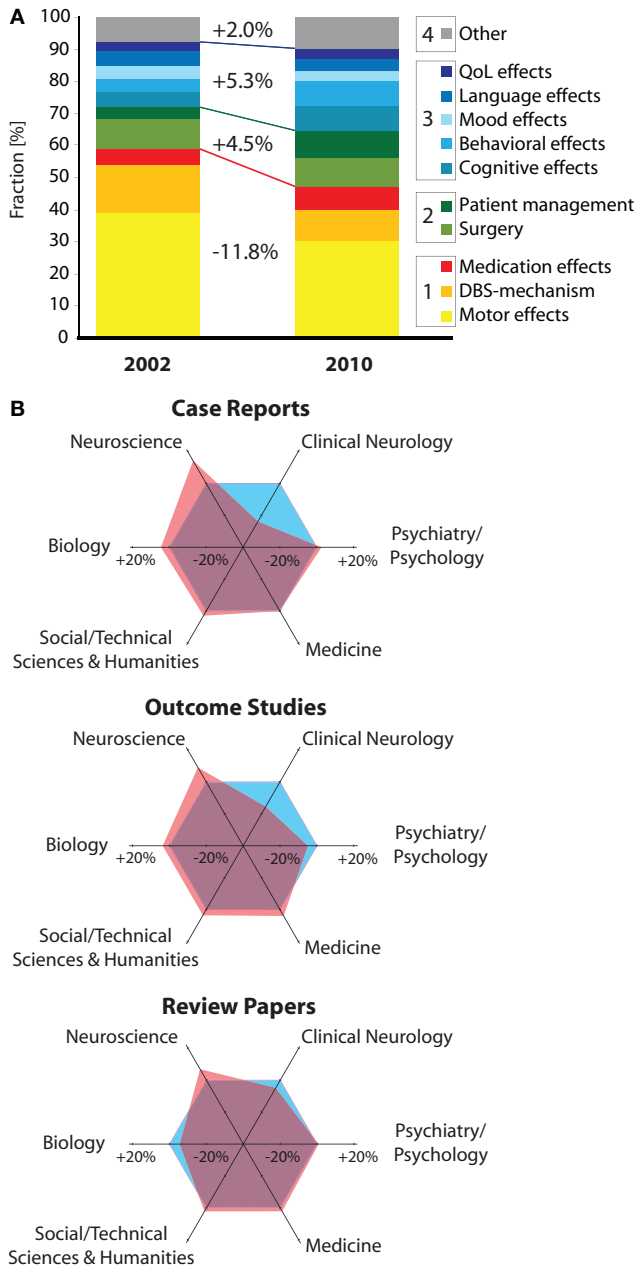


FIGURE 1 | (A) Change of the relative weight of issues discussed in the DBS community based on an analysis of the posters published in 2002 and 2010 on the International Congress of Parkinson's Disease and Movement Disorders. The issues are grouped into four classes: 1. Understanding therapeutic effects, 2. Medical intervention issues, 3. Affective, behavioral, and cognitive side effects of DBS, 4. Other issues. **(B)** Impact analysis for three types of DBS literature: case reports, outcome studies, and review papers. The blue hexagon is the reference (percentage of publications equals percentage of citations in each cluster), whereas the red polygon shows the actual fraction of citations minus the fraction of publications for each disciplinary cluster.

examination of outcome studies (i.e., no narrative reviews). **Figure 1B** shows the results of the impact analysis for each type in a spider diagram that displays the citation fraction minus the publication fraction for each cluster in percent. The blue hexagon is the reference (i.e., the fraction of citations minus the fraction of publications equals zero), whereas the red area shows the actual differences of the fractions of citations minus publications. In all three cases, the cluster "Clinical Neurology" was the main source of publication–citation-transfers. However, the "overall transfer" – i.e., the sum of all positive (or all negative) transfers between all clusters – differ markedly between the three types of publications: Whereas in the case reports 23.8% of all citations were generated outside their disciplinary origin, only 10.9% of citations generated by review papers left their disciplinary origin (outcome studies: 20.5%). The cluster "Neuroscience" was the main transfer target. In absolute numbers, only few citations (Case Reports: 2.9%, Outcome Studies: 3.7%, Review Papers: 2.0%) were generated from the cluster "Social/Technical Sciences and Humanities."

In summary, two lessons can be learned: First, the DBS community indeed recognized the complexity associated with this novel therapeutic approach and adapted its focus to emerging issues. Second, not high quality review papers, but reports on complex, single cases spearheaded the interdisciplinary knowledge transfer. Therefore the discussion about clinical, societal, and ethical issues of DBS should not rely on the assumption that the DBS community underestimates the complexity of DBS. Further research should focus on the question how reports on paradigmatic cases diffuse into different disciplines in order to understand the communication processes that accompany the development of novel, stimulation-based therapies for psychiatric and other diseases.

REFERENCES

Benabid, A. L., Chabardes, S., Mitrofanis, J., and Pollak, P. (2009). Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol.* 8, 67–81.

Christen, M. (2008). Varieties of publication patterns in neuroscience at the cognitive turn. *J. Hist. Neurosci.* 17, 207–225.

Müller, S., and Christen, M. (2011). Deep brain stimulation in Parkinsonian patients – ethical evaluation of cognitive, affective and behavioral sequelae. *AJOB Neurosci.* 2, 3–13.

Received: 12 January 2011; accepted: 18 April 2011; published online: 05 May 2011.

Citation: Christen M and Müller S (2011) Single cases promote knowledge transfer in the field of DBS. Front. Integr. Neurosci. 5:13. doi: 10.3389/fnint.2011.00013

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 02 May 2011
doi: 10.3389/fnint.2011.00011

Opting for DBS: the role of patients' associations between scientific and humanistic knowledge

Lucilla Bossi*

Parkinson Italia, Milan, Italy

**Correspondence: lucilla.bossi@fastwebnet.it*

The movement which, in the years between the late 1980s and the early 1990s of the past century, led to the establishment of the first patients' associations in Italy was initially based on the patients' need for adequate medical information. In those days, upon leaving the neurologist's office with a diagnosis of Parkinson's disease (PD), you were stuck with the feeling of having received a really bad piece of news while – at the same time – not having the tools necessary to fully understand such diagnosis and its impact on your life. The adjustment to the new situation, which still nowadays can take many years, then was made even harder by the difficulty of gathering the information needed to understand what this illness really was and what its causes, its progression and outcomes were.

However, today a doubt is creeping among the associations: that they are going from one extreme to the other. As a matter of fact, it is a common occurrence to discover that too much information has been made available to the patients. Among the most common signs of information overload is the patients' fear and overreaction to the prospected future course of the condition: therefore, they quite often end up assuming the "omnipotent" illusion that the more they know about the disease, the easier it will be to be in control of it.

Considering that nowadays the information to the patients is taken for granted, it may be worth finding out if there are other kinds of knowledge the associations could take care of that might prove to be useful in order to improve the patient's quality of life. From this perspective the associations could be of real service if they broadened their mission to include a humanistic knowledge attentive not only to the physical needs of the suffering human beings but also to the emotional, intellectual, and spiritual ones. Such knowledge could be of great help to the people with Parkinson's, supporting them in critical situations such as the agonizing decision making process leading to the resolution to undergo deep brain stimulation (DBS) or drop the idea. The simple possibility of brain surgery evokes ghastly pictures of devastating lobotomies which leave the patient in the grip of anxiety and distress. And desperately alone. For however close and loving his/her family may be, however caring his friends and competent his doctors, the head that 1 day will have to be screwed into the stereotactic helmet is the patient's one. As his/her is the brain that all life long will depend for "normal" functioning on a constant electric charge. Moreover, the association offers the candidate an invaluable opportunity for the operation: getting in touch with other patients who have already undergone DBS or plan to do so. Thanks to the association, the patient gets acquainted with a wide range of human situations and individual reactions, while finding some relief from anxiety and attaining a more serene outlook.

This function of the associations could be implemented if, to help their members, they could offer them, besides well trained wholehearted volunteers, the help of a philosophical counselor. This is a new professional figure – drawing his knowledge from the more than 2500-year-old western philosophy – which has existed for some time now in more than a few Italian hospitals. The difference between a philosophical counselor and a psychologist lies herein: while psychotherapy addresses the patients unease from the point of view of his personal story and situation, philosophical counseling helps the patients to adjust to circumstances which, even though striking individually, are universal (i.e., depending on the human condition as such).

In my capacity as President of Parkinson Italia – a Federation of 23 patients' associations – I think that the availability of a qualified philosophical counselor, both as a group leader and for individual sessions would make a remarkable shift in the associations' role: from simple information provider to a place of warm reception and inner growth.

In the context of a wider understanding of the meaning of suffering it is worth noticing that according to ancient wisdom, disease is not only a setback but an opportunity as well, fostering meaningful insights into our inner world and taking stock of our life. A long disease gives us time to inquire ourselves in depth about many issues that otherwise would have remained buried deeply in our unconscious. Then the disease becomes a descent in the innermost depths of the soul. And it is just when suffering grows unbearable and we feel that we can not hold on for one more single second that the quantum leap takes place and suddenly the consciousness opens to a new perception of the world. But unfortunately our culture is one of appearance and consumerism, while experiencing the sacred is considered an embarrassing occurrence. But human beings do need spiritual nourishment especially if they are about to pass through "the narrow doors" of experience. And among the many "tight spots" trough which the disease forces us, brain surgery is possibly one of the narrowest and of the most crowded with unanswered questions.

One would expect from a patient restored to a better life at least some contentment. On the contrary there are more than a few people with Parkinson's who, after a completely successful DBS which greatly improved their motor symptoms, instead of being happy develop a depression or other psychiatric conditions.

It is clear that the above problem is deeply hidden and neurologists, neurosurgeons, and psychiatrists look for a solution in a specific malfunctioning area of the brain. Even in a perspective that does not reduce the psyche to a simple epiphenomenon of brain activity, one must admit that the fact is unsettling and raises many questions. How is it possible that infirmity

could be regretted by a person to whom DBS gave back the priceless good of autonomy? What unimaginable and possibly perverse secondary gains could hide in such a distressing disease? What secret reward could be worth the agony of advanced Parkinson's.

However it must be remembered that recently it has been supposed that some of the psychiatric problems following surgery could be related to the sudden reduction of the dopaminergic drugs that usually takes place in the follow up.

It remains that there is no certainty at all and that such questions are not easily answered.

It is a dangerous ground where both humanistic and scientific knowledge are tightly interwoven together with ethics; however the resulting pattern is still blurred and indistinct.

As for me, treated by DBS with extraordinary results, the feeling is that we are just at the very beginning but, at the same time, that we are bound to reach most encouraging goals. As I used to say at the time of my operation: "It may-not be a cure, but it certainly feels much like one."

Received: 07 January 2011; accepted: 18 April 2011; published online: 02 May 2011.
*Citation: Bossi L (2011) Opting for DBS: the role of patients' associations between scientific and humanistic knowledge. Front. Integr. Neurosci. **5**:11. doi: 10.3389/fnint.2011.00011*

frontiers in
INTEGRATIVE NEUROSCIENCE

OPINION ARTICLE
published: 04 May 2011
doi: 10.3389/fnint.2011.00010

What is "narrative bioethics"

Helmut Dubiel*

Institute of Sociology, University of Giessen, Giessen, Germany
**Correspondence: helmut.dubiel@sowi-giessen.de*

It was not me who coined the term "narrative bioethics." I discovered the term in the title of a dissertation, written by a young theologian, Katrin Bentele, which dealt with ethical dilemmas in doing research on Parkinson (Bentele, 2007). She concluded her dissertation with a quotation out of my book, which has the title, in English, "Deep in the brain" (Dubiel, 2009). This book, in which I described my experience with living with Parkinson and with deep brain stimulation, turned out to be – compared to the books I had published previously – a real bestseller.

What struck me in particular was that, from the moment of its appearance, this slim book of mine was praised as a decisive contribution in the field of narrative bioethics. The above mentioned Katrin Bentele went so far to quote 10 pages out of my book, calling it social scientific discipline "avant la lettre."

The first question I want to raise is how the ethical, political, and cultural implications and consequences of the new high-risk technologies differ from other technologies of the past century, like nuclear energy or nano-technology. To my impression, no other technology has raised even prior to its final implementation a comparable mix of apocalyptic anxieties and chiliastic hopes.

Bioethicians are not motivated – like many of their critics seem to suppose – by a naive form of technophobia, inspired by irrational ideologies. Nor do they indulge in a blind appraisal for anything that is technically new, irrespective of the purposes it serves. The ethical evaluation of a new surgery technique, a new pill or a new treatment usually starts with general principles or norms, which are sharpened (or specified) in a dialectical interplay with individual case studies. Thus they pretend to arrive at bioethical positions, which are "thick" and "thin" at the same time. They are "thick" in the sense of having absorbed a lot of empirical context–knowledge; they are "thin" in the sense of having been inspired by the most abstract set of cognitive and ethical principles. Some bioethicians are convinced to have discovered a scheme of judgment, which is no longer affected or distorted by empirical contingencies or too high levels of theoretical abstraction. This kind of (over-) generalized principles are also called the "the first order principles," such as truthfulness, justice, fairness, universability (Kant's "Categorical Imperative"), "divine-command." These "first order principles" will soon prove to be too abstract for constructing the foundations of an applied ethics like bioethics. In this case you have to construe an elaborated set of "second order principles." Examples for "second order principles" taken out of the context of bioethics are:

- Respect for the self determination of people affected by a disease which is or will be curable or at least treatable within the life-span of the affected;
- Strict avoidance of any further damage;
- Care for all affected in the philosophical sense of "justice";
- Professional ethics like pledge of secrecy in the case of medical doctors, therapists and priests.

But even this far more complex approach does not withstand critique. The "second order principles" mentioned above remain vague and indeterminate. The so-called "first order principles" are by no means neutral phenomena, the existence of which could be proven with means of clinical purity. The only way of taking account of social phenomena is by means of communication. The person who is entangled in ethical dilemmas and the bioethicist who is theoretically interested in ethical problems do have to talk to each other. This is the first and most essential relation, which the two parties have to enter. We have to keep in our mind, however, that the project of a narrative bioethics is not in competition with traditional forms of ethical justification. The necessity of an alternative ethical concept results from the blind spots of an ethics based on principles alone.

One can assume that members of former generations have made similar experiences. But the sociologist contradicts this widely held belief forcefully. We sociologists hold onto the conviction that the narrability of suffering has emerged in history. Physical pain in all its dimensions is a product of that kind of modernization, which we sociologists call "individualization." In this new sociological discourse "individualization" means the breaking away of existential railings, the dissolution of traditional, mostly religiously shaped patterns of life, which used to protect us from despair and give us hope and consolation. In contrast to other areas of life, love, and erotic pleasure, where the existential balance sheet is definitely positive, the balance in the case of illness, solitude and fear of death is clearly negative. The culturally shaped coping strategies with death, dying, and illness are melting away.

So the necessity came into the modern world to be able of making sense of one's own life, in particular when leaving or entering the stage of life. We are, as it was wonderfully put by Katrin Bentele, exposed to the contingencies of life without any protection.

Crises in the sense of breakdown of collective or individual identities are managed with similar means. My identity has to be protected against external threats of its integrity by means of increased "reflexive efforts." "Reflexive efforts" basically mean telling stories – stories which are told and retold on different levels and contexts – this means the stories of the nation's history, its triumphs, its guilts, the stories of the family, the stories which parents tell their children when putting them to bed. These stories demonstrate that human beings have identity not as an immutable possession. But more as a provisional result of permanent reflexive efforts, which last as long as our lives.

Helmut Plessner, a German philosopher born in the early twentieth century, introduced the famous distinction between "having a body" and "being in a body." This distinction corresponds to the older

German distinction of *Körper* and *Leib* (Plessner, 1928). The difference between "having a body" (*Körper*) and "being in a body" (*Leib*) can be illustrated with the way with which infants experience their body. Experiencing the body in the sense of *Leiberfahrung* (physical experience) forms the basis of personal identity.

The reflection of people in distress prefigures the line along which the experience of physical suffering can become the raw material of bioethical reflection. I call this constellation of pain and identity paradoxical, because it is just the medical intervention into the integrity of our body which directs our attention to this complex constellation.

The body is checked, measured, and evaluated by the medical profession. It is evident that these interventions affect persons differently; the doctors are interested in the body only as mechanic system, whereas the patient can take this role only for a short time.

I am neither a philosopher nor a theologian, but only a sociologist, an expert only for the penultimate matters. But even people like me can be aware of the fact that each of us entered one stage of life and will leave it on another. Now, finally, we have found the close link between our capacity to reflect on our bodies in distress and the capacity to talk, to tell, and listen to stories. "Hermeneutics" as the art of reading texts paradoxically starts to work in view of ruptures in the text, which block its understanding. Experiencing a severe disease is a similar rupture in the lifecycle. The only chance which remains for the sick person consists in keeping aware of this rupture, as long as he or she is able to. This may be the only way to recover in a deep existential sense in regaining the existential sovereignty, which he or she has lost with the experience of his or her vulnerability. In our times a sick person is compelled to make one's own sense of his life and his mortality. This ability of making one's own sense on birth and death is necessary, because being born and dying is due to the successes of biotechnology, no more a simple act which is accepted by its mere suddenness. Since entering and leaving the stage of life has become a process which is stretched and compressed in a peculiar way, because pregnancy and parenthood are discoupled and the former status of the dead person is differentiated in person in a coma, persons partially in coma, and persons with no vital signs of the heart or the brain. Thus life and death have developed not only into an ethical, but also in a political question.

I can think, talk, and formulate thoughts as I speak just like before. In the recent past I have tried – with some success – to secure the positive stocks of my life rather than lament what I am no longer able to have or to do. Thus, I have begun to reconcile myself with my pacemaker. It gives me energy and mobility. I can accept it now because I more often take the liberty of turning it off. Then I feel as if nothing has ever happened before.

Coming to the end, only that person, who has lived a good life, will be able to stand the outlook of imminent death in a calm and relaxed manner. It was a good life, if the person can feel like an author, who has inscribed traces in the texture of civil society, which cannot be overlooked and will be remembered. A life has gained significance beyond its mere zoological dimension when it can be told as a story. The collective life of a civil society is a texture of told and yet untold stories, a mosaic of biographies. Biography is a strange genre, because its constitutive features – the beginning and the end of a life – are concealed to the respective person. The preconditions and consequences of all the important decisions in life are too complex for the individuals involved to be fully aware of them. On the contrary, one of the prerequisites for happiness is realizing life's open-endedness and having an inkling that beyond the next mountain range, around the next bend in the road, lies an unknown land.

REFERENCES

Bentele, K. (2007). *Ethische Aspekte der Regenerativen Medizin. Das Beispiel Morbus Parkinson*. Berlin: LIT Verlag

Dubiel, H. (2009). *Deep Within the Brain: Living with Parkinson's Disease*. New York: Europa editions.

Plessner, H. (1928). *Die Stufen des Organischen und der Mensch. Einleitung in die Philosophische Anthropologie*. Berlin: de Gruyter.

Received: 07 January 2011; accepted: 18 April 2011; published online: 04 May 2011.

*Citation: Dubiel H (2011) What is "narrative bioethics" Front. Integr. Neurosci. **5**:10. doi: 10.3389/fnint.2011.00010*