Neuromodulation
in Psychiatry

Edited by
Clement Hamani
Paul Holtzheimer
Andres M Lozano
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CHAPTER 1

History of invasive brain stimulation in psychiatry: Lessons for the current practice of neuromodulation

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The basic problem of psychosurgery is psychiatric. Therefore, the initiative in considering surgical treatment must be taken by the psychiatrist. As soon as he is sure that conservative treatment by every available method cannot cure the patient, he should consult the neurosurgeon. Psychosurgery will remain experimental for years. Therefore, its use should be concentrated and restricted to psychosurgical research units having strong and intimate affiliation with scientists from many disciplines.

Lauri V. Laitinen, 'Ethical Aspects of Psychiatric Surgery', 1977 [1]

The International Neuromodulation Society defines neuromodulation as the alteration of nerve activity through the delivery of electrical or electromagnetic stimulation, chemical agents or light (optogenetics) to targeted sites of the central or peripheral nervous system. The aim of neuromodulation is to modulate (aka normalize) pathological nerve function. Some examples of various means to provide 'neuromodulation' to treat various illnesses and symptoms are functional electrical stimulation, spinal cord stimulation, peripheral nerve stimulation, intrathecal drug delivery systems, occipital nerve stimulation, motor cortex stimulation, repetitive transcranial magnetic stimulation, sacral nerve stimulation, transcranial direct current stimulation, vagus nerve stimulation and deep brain stimulation (DBS).

Thus, it appears that electricity has been and still is the main agent used to provide 'neuromodulation', starting in antiquity with the electrical fish and gaining a momentum with the so-called 'electrotherapy' in the 18th and 19th centuries when electrotherapy was used for the 'treatment' of a variety of illnesses, including epilepsy, paralysis, chorea, deafness, blindness, rheumatism, glandular enlargement and also for artificial respiration and resuscitation [2].

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According to the web site of the International Neuromodulation Society (http://www.neuromodulation.com/brief-history-of-neuromodulation consulted on 14 January 2014), 'The modern era of neuromodulation began in the early 1960s, first with deep brain stimulation which was soon followed (in 1967) by spinal cord stimulation, both for otherwise intractable pain'. In the opinion of this author, this is a rather selective way of writing history! In fact, the modern era of neuromodulation began at least a decade before 'the early 1960s' and it was not 'for otherwise intractable pain'. It is true that the *main* application of deep brain stimulation in the late 1960s and 1970s was for the treatment of chronic pain, and it is true that Medtronic trademarked the term 'DBS' with respect to chronic subcortical stimulation for pain in the mid-1970s [3]. However, scholar sources show that the history of deep brain stimulation before it was called 'DBS', that is, the history of *electrical stimulation of subcortical structures delivered through chronically implanted electrodes*, started in the early 1950s soon after the introduction of the method of human stereotactic surgery. It is also evident that subcortical brain stimulation was not initially intended to treat pain but rather was applied in psychiatry and to modify behaviour. In order to be able to fully grasp the 'lessons learned for current practice', as is suggested by the title of this chapter, one has to understand how DBS unfolded historically and why do we today need, in the first place, to 'learn lessons' from the 'history of neuromodulation in psychiatry'.

In the contemporary discourse about the history of DBS, there is a commonly held belief that DBS was initiated for surgical treatment of movement disorders in 1987 [4], and entered the realm of psychiatry first in 1999 [5, 6]. Indeed, it was the paper by Veerle Vandewalle *et al.* on DBS for Tourette syndrome published in *The Lancet* in February 1999 [5], and the publication of Nuttin *et al.* on DBS for obsessive–compulsive disorder (OCD), also in *The Lancet* in October 1999 [6], that heralded the most recent era of DBS in psychiatry. As the field of psychiatric neuromodulation has literally exploded in the last decade, at least judging by the number of publications in the field, with new psychiatric applications of DBS on an ever-increasing number of brain targets [7], perhaps a sober look at past experience in this field may provide some clues about what is to be expected and what can go wrong in this specific area of psychiatric neuromodulation, aka *psychiatric surgery*.

The main aim of this chapter is thus to review the historical applications and trials of DBS in the realm of psychiatry and behaviour, and to summarize what lessons, if any, can be learned from these previous practices.

The birth, rise and fall of the 20th-century psychiatric DBS

Human stereotactic neurosurgery was initially and purposely devised with the intent to avoid the devastating side effects of the crude frontal lobotomy by allowing to perform anatomically focused tiny lesions in psychiatric patients. Thus, in the same way, as human stereotactic *ablative* surgery was applied at its inception in 1947 in the psychiatric domain [8], human subcortical brain stimulation was also first proposed in the realm of psychiatry: in 1952, neurophysiologist and neurobehaviourist José Delgado and his colleagues [9] described a technique of electrode implantation for chronic recording and stimulation to evaluate 'its possible therapeutic value in psychotic patients'. The following year, the Mayo Clinic organized a symposium on 'intracerebral electrography'. The proceedings of that meeting were published and included a paper on 'Neurosurgical and neurologic applications of depth electrography', where one could read: 'An observation that may have some practical significance was that several of our psychotic patients seem to improve and become more accessible in the course of stimulation studies lasting several days' [10]. The authors thought that a likely explanation for this effect 'was that the local stimulation was having a therapeutic effect comparable to that of electroshock' and concluded that '… this aspect of localized stimulation studies requires further investigation since it may lead to a most specific, less damaging, and more therapeutically effective electrostimulation technic than can be achieved by the relatively crude extracranial stimulation methods in use at present' [10]. One of the authors in this paper was Carl Wilhelm Sem-Jacobsen, a Norwegian neurophysiologist and neuropsychiatrist who was a fellow at the Mayo Clinic and who continued to work with chronic subcortical stimulation for psychiatric illness when he returned to Norway (see further next).

Also in the early 1950s, a team at Tulane University in New Orleans, led by psychiatrist Robert Heath, had started chronic depth electrode stimulation, including stimulation of the 'septal area' in schizophrenic and other psychotic patients [11].

Furthermore, already in 1961, Daniel Sheer, Professor of psychology at the University of Houston, edited a book entitled *Electrical Stimulation of the Brain – An Interdisciplinary Survey of Neurobehavioral Integrative Systems* [12]. As the title indicates the main focus of electrical stimulation was on neurobehaviour and the authors of the chapters of that book discussed the use of subcortical recording and stimulation in epilepsy, obesity, aggressive behaviour and other neurological and behavioural conditions. Hence, from its very beginning, the technique of chronic stimulation of deep brain structures was intended and applied for behavioural and psychiatric studies and occasionally in the treatment of mental disorders.

What went wrong?

Studying the literature on old psychiatric DBS from the mid-1950s to the 1970s, it appears that DBS was used more for exploration and modification of behaviour, and less for the treatment of true psychiatric illness: those scarce publications detailing the few attempts to treat psychiatric illnesses with DBS were authored mainly by neurosurgeons, whereas the non-neurosurgeons were more prolific publishers on DBS mainly as a means to study and alter personality. To give few examples: in 1972, Mexican neurosurgeon Escobedo *et al.* [13] implanted quadripolar electrodes bilaterally in the head of the caudate nucleus in two patients with epilepsy, mental retardation and destructive aggressive behaviour, and described vegetative, motor and behavioural responses to stimulation. In 1979, West-German neurosurgeon Gert Dieckmann [14] performed unilateral stimulation of the non-dominant thalamus using a quadripolar Medtronic 'deep brain stimulation electrode' to treat a woman with phobia. The electrode contacts extended over 12 mm and were aimed at the parafascicular and rostral intralaminar areas. Stimulation was delivered intermittently at a low frequency (5 Hz) and resulted in disappearance of the phobias, while attempts at stimulation with 50 Hz 'was experienced as being very disagreeable'. A possible reason for the scarcity of neurosurgical papers on psychiatric DBS as a treatment of psychiatric illness during the 1960s and 1970s was that during that period, which saw the demise of the previously popular lobotomy, focused stereotactic ablative procedures (anterior capsulotomy and cingulotomy) were gaining momentum and were the preferred surgical method to treat psychiatric illness, since the DBS hardware and technology of that period were quite cumbersome and not user-friendly.

On the other hand, there is a wealth of publications on DBS from the 1950s through the 1970s, authored by very few psychiatrists and neurophysiologists, in which DBS was not mainly a tool to treat psychiatric disease, but rather to study the brain and to alter human behaviour, as stated earlier. The scholar literature reveals three main workers, a neurophysiologist, a psychiatrist and a neurophysiologist-psychiatrist, who, independently of each other, devoted much of their career to study the effect of DBS in humans and sometimes to promote its use for aims beyond psychiatric disease.

José Delgado, a Spanish neurophysiologist and neurobehaviourist who moved from Spain to Yale University in 1950 and worked there with Fulton, is probably best known for a motion picture showing a bull whose charge in the arena could be stopped through remote brain stimulation. Delgado worked extensively with chronic subcortical stimulation in rats, goats and monkeys and then in humans. In a lecture delivered in 1965 titled *Evolution of Physical Control of the Brain*, he reported: 'Monkeys may learn to press a lever in order to stimulate by radio the brain of another aggressive animal and in this way to avoid his attack'. Heterostimulation in monkey colonies demonstrates the possibility of 'instrumental control of social behaviour' [15]. He concluded, 'Autonomic and somatic functions, individual and social behaviour, emotional and mental reactions may be evoked, maintained, modified, or inhibited, both in animals and in man, by electrical stimulation of specific cerebral structures. Physical control of many brain functions is a demonstrated fact…' [15]. Delgado's enthusiasm for this new technology and its possible effects on behaviour led him to publish in 1969 a book titled *Physical Control of the Mind: Towards a Psychocivilized Society* [16]. This book's title provoked a storm of critic and Delgado was compelled to negate the impression that mind control could be achieved by electrodes wired into people's brain. He emphasized that the technique of 'Electrical Stimulation of the Brain (ESB)', as he called it, was meant as a research tool to study and understand the human mind. Delgado then developed a technique of subcortical stimulation using chronically implanted electrodes connected to a subcutaneous receiver implanted in the scalp that he labelled 'Stimoceiver', which could be remotely controlled by radio waves. This technique of 'radio communication with the brain' was developed by Delgado explicitly for use in psychiatric patients [16–18], although there are no testimonies in the scholar literature to its results in 'real' patients. Anecdotically, Harvard physician turned writer Michael Crichton described in his semi-fictive and famous book *The Terminal Man* first published in 1972 [19] a patient whose personality and behaviour were changed by stimulation through several electrodes implanted in various parts of his brain initially for control of epilepsy, but who also suffered from psychosis. Some of the stimulation effects experienced by the hero of this novel bear strange resemblance to the DBS experiments conducted on real people by another psychiatrist, Robert Heath, at Tulane University in New Orleans.

Robert Heath was a psychiatrist at Tulane University, New Orleans. He implanted a multitude of electrodes in several subcortical nuclei and pathways to study the effect of stimulation on behaviour and probably pioneered the concept of electrical 'self-stimulation'[20]. Heath started a program of DBS to treat schizophrenia as well as pain and epilepsy in the early 1950s [21]. There were no benefits in schizophrenic patients, but Heath made the interesting observation that some patients described the experience of self-stimulation as 'pleasant', 'jovial' or 'euphoric'. In these patients, the electrodes were located in the septal area [21, 22]. This pleasurable response obtained from the 'septal area' came to dominate Heath's further research on DBS applications. He reported relief from physical pain by stimulation of 'this pleasure-yielding area of the brain' and extended studies of this brain area during sexual arousal and orgasm [21–23].

In 1972, Moan and Heath [24] described the use of septal stimulation to induce heterosexual behaviour in a homosexual man. The individual was shown a pornographic video, then a female prostitute was introduced to him in the laboratory and following stimulation to his septal area, the individual and the woman had a sexual intercourse culminating in the subject's orgasm and description of the experience as 'pleasurable'. The authors wrote that during these sessions the individual 'stimulated himself to a point that he was experiencing an almost overwhelming euphoria and elation, and had to be disconnected, despite his vigorous protests' [24]. Two electrodes, each with six contacts, had been implanted in this individual and the paper contains two figures from the Atlas of Schaltenbrand and Bailey depicting their location: one electrode lay in the 'septal area' (close to the nucleus accumbens) and the other in the region of the centromedian nucleus of the thalamus. Heath pursued similar and other experiments through the 1970s and received sponsorship from the US military who were interested in his experiments. Incidentally, and interestingly, in an article published in *Nature* on 12 November 2013, titled 'Implant aims to track brain signals in real time. Device that zaps neurons and monitors electrochemical changes could reveal secrets of deep-brain stimulation therapy', Helen Shen wrote: 'The results come at a time of great excitement in the DBS field. More recently, the US government's Defense Advanced Research Projects Agency (DARPA) announced a 5-year, US$70-million initiative to support development of the next generation of therapeutic brain-stimulating technologies' (http://www.nature.com/news/implant-aims-to-track-brain-signals-in-real-time-1.14153) (accessed 14 January, 2014).

One of Heath's last publications in the 1970s was 'Modulation of emotion with a brain pacemaker. Treatment for intractable psychiatric illness' [25] featuring an illustration showing the commonly used DBS system at the time consisting of a pulse sender with an antenna placed above the skin of the pectoral area where the receiver was implanted (the Xtrel Medtronic system). 'Modulation of emotion' by DBS, an issue widely criticized in the 1970s [22], re-emerged 30 years later from the pen of another psychiatrist Luc Mallet from Paris who published a paper titled: 'La stimulation cérébrale profonde: un outil pour la modulation thérapeutique du comportement et des emotions' (Deep brain stimulation: a tool for therapeutic modulation of behavior and emotions) [26].

The third main proponent of DBS in psychiatry during the 1950–1970s was the Norwegian physiologist-psychiatrist mentioned earlier, Carl Wilhelm Sem-Jacobsen who was a fellow at the Mayo Clinic in the early 1950s [10]. In 1963, he published an article about depth-electrographic observations in psychotic patients [27] in which he stated: 'electrical stimulation in some regions of the ventro-medial part of the frontal lobe resulted in a temporary improvement to complete freedom from symptoms'. The specific aim of his studies was 'to use chronic implanted electrodes in the target area in an attempt to improve the leucotomy operation' [28]. In 1972, he reported that 213 patients had been treated with his 'depth-electrographic stereotactic neurosurgical technique'; of these, 123 patients were suffering from mental disorders [28]. Sem-Jacobsen's technique using chronically implanted electrodes aimed merely to study brain activity and perform intermittent chronic stimulation of various brain targets before subsequent lesioning.

DBS in psychiatry and behaviour never gained momentum, and, similarly to lobotomy, became increasingly discredited and abandoned. In the 20 years between the paper of Dieckmann published in 1979 on DBS in a patient with phobia [14], and the first paper of the 'new' DBS era about DBS in OCD in 1999 [6], one cannot find a single paper on DBS in psychiatry. In fact, it was the misuse of this technique for dubious indications in the 1960–1970s, especially at the hands of the Heath and the Tulane team [21], that contributed to its demise.

In that respect, it is interesting to note that, already in 1977, Finnish neurosurgeon Laitinen commented on the questionable ethics of one of Heath's papers [23]. Laitinen wrote: 'There is no doubt that in this study all standards of ethics had been ignored. The ethical responsibility of the editors who accept reports of this kind for publication should also be discussed' [1]. Laitinen was not against the use of DBS as a therapeutic tool in psychosurgery; in that same paper he wrote, 'After implantation of chronic electrodes, long-term depth recordings and repeated electrical stimulations enable the psychosurgeon to accumulate knowledge about the pathophysiology of the brain and to improve the treatment of the patient in question. It may even be possible to treat the patient with repeated electrical stimulation without macroscopic destruction of brain tissue' [1], and Laitinen proposed a 'model of controlled trial', whereby eligible patients are randomized to receive either the best available conservative therapy or stereotactic surgery and stated, 'Psychosurgery will remain an experimental therapy for years. Therefore its use should be concentrated and restricted to psychosurgical research units having strong and intimate affiliation with scientists from many disciplines' [1]. Neurosurgeon Laitinen's public suggestion to set up a randomized trial of stereotactic psychosurgery versus 'best available conservative therapy' fell on deaf ears at that time, probably because psychosurgery altogether was already doomed and psychiatrists were no longer interested. In any case, this is a historical testimony that it was in fact a pioneer neurosurgeon who was first to suggest a scientific approach to psychosurgery, which contradicts the often repeated contemporary claims that neurosurgeons of the past were those responsible of the 'errors of the past' or were those who were 'acting alone' [29].

In 2000, Heath's experiments were analysed in depth by psychologist Baumeister in a paper titled 'The Tulane Electrical Brain Stimulation Program a historical case study in medical ethics', published in the *Journal of the History of the Neurosciences* [21]. Baumeister reviewed three decades of DBS work performed at Tulane University and concluded by this verdict: '… the Tulane electrical brain stimulation experiments had neither a scientific nor a clinical justification… The conclusion is that these experiments were dubious and precarious by yesterday's standards']21].

The contemporary discourse on psychiatric neuromodulation

Contemporary DBS started in 1987 in the surgical treatment of movement disorders [4]. Since the turn of the century, and ongoing, the field of psychiatric neuromodulation by DBS is witnessing a frenetic activity, whereby DBS is being tried in no less than nine brain targets for Gilles de la Tourette, eight brain targets for OCD and seven brain targets for depression [7, 30], and the search for the ideal target(s) for these conditions is still ongoing, and none of the psychiatric indications in none of the brain targets for DBS is as yet considered as 'established' (Figure 1.1). The number of published papers about psychiatric DBS probably exceeds even the number of operated patients. In parallel, a plethora of publications by ethicists, psychologists, neurologists, psychiatrists, sociologists, philosophers and others have suddenly started to appear dealing with ethics, reviews, guidelines and so forth for conduct of DBS in mental illness. Many of these articles have kept repeating the obvious mantra that the novel era of DBS in psychiatry should not repeat 'the errors of the past', should 'avoid the abuses of that earlier era' [29] and should

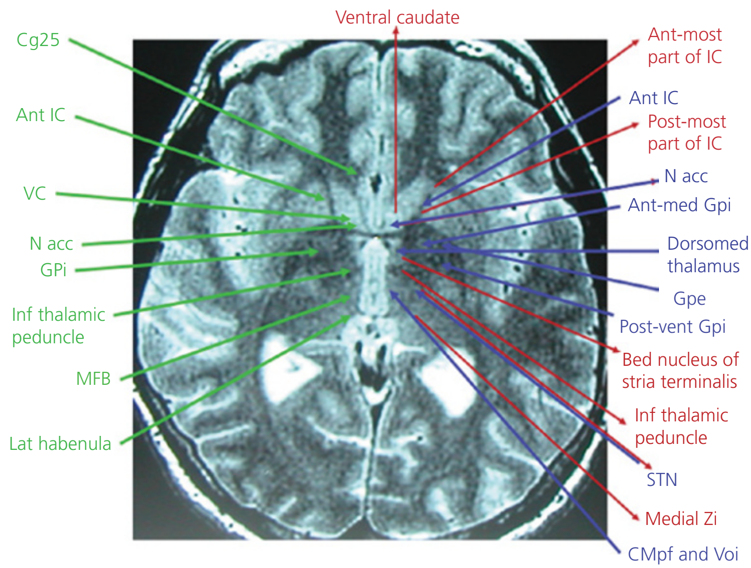

Figure 1.1 Published brain targets submitted to DBS for depression (green) OCD (red), and Tourette (blue). Some targets are overlapping between these three conditions. Note: Not all targets are visible on this axial slice at the level of anterior–posterior commissural plane. Ant-med, anteromedial; Ant-most, anteriormost; Cg25, Cingulum area 25; CMPf, centre median parafascicular nucleus of thalamus; Dorsomed, dorsomedial; GPe, globus pallidus externus; GPi, globus pallidus internus; IC, internal capsule; Inf, inferior; Lat, lateral; MFB, medial forebrain bundle; N acc, Nucleus accumbens; Post-most, posteriormost; Post-vent, posteroventral; STN, subthalamic nucleus; VC, ventral caudate; Voi, nucleus ventralis oralis internus of thalamus; Zi, zona incerta. (*See insert for color representation of the figure*.)

be multidisciplinary. One publication from 2006 stated outright that 'It is ethically untenable for this work to proceed by neurosurgeons in isolation without psychiatrists determining the diagnosis and suitability of patients for treatment'[29]. This latest statement, implying that neurosurgeons have been or are conducting surgery for psychiatric illness 'in isolation' from psychiatrists, merits a few comments.

1 'Abuses of that earlier era' [29] alludes mainly to the unrestricted lobotomies practised by Walter Freeman, who was a neurologist not a neurosurgeon; in fact, 'his' neurosurgeon, James Watts, abandoned him because of Freeman's all too liberal indications for lobotomy [31, 32].
2 In the modern era, it was indeed a neurosurgeon, Alim-Louis Benabid, the father of contemporary DBS, who was the first to take the initiative to seek ethical review on the use of DBS in psychiatry by asking 'the French commission to consider the ethics of using neurostimulation on OCD patients'[33].
3 A search of PubMed using the search words 'ethics' and 'deep brain stimulation' reveals that the first article ever dealing with the ethics of DBS was published in 1980 and authored by three neurosurgeons [34]. That article, titled 'Indications and ethical considerations of deep brain stimulation', was published 7 years before the start of the modern DBS era; at that time, DBS was mostly used to treat chronic pain.
4 After that paper from 1980, the next publication dealing with ethics of DBS did not appear until the year 2000 [35] discussing DBS in impaired consciousness. Then, it was in 2003 that the first paper discussing ethics

of DBS in psychiatry was published [36]. Hence, it was first when modern DBS moved from neurology and movement disorders towards psychiatry and behaviour, that ethics of modern DBS became a matter of concern, which implies that between 1987 and 1999, when modern DBS was used only for Parkinson's, tremor and dystonia, there did not seem to be any ethical considerations worth discussing and publishing.

5 The September 2009 issue of the *Archives of General Psychiatry* featured an article titled 'Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior and thoughts' [37]. This article summarized a 2-day conference that was convened to examine scientific and ethical issues in the application of DBS in psychiatry in order to 'establish consensus among participants about the design of future clinical trials of DBS for disorders of mood, behaviour and thought' and to 'develop standards for the protection of human subjects participating in such studies'. None of the 30 participants at the meeting, 19 of whom are authors of the article, was a neurosurgeon.

Twenty-first century DBS: a tool for enhancement and social control?

Today DBS is perceived as reversible, and because stereotactic ablative surgery for psychiatric illness suffered and still suffers from the legacy of the lobotomy era, DBS is considered as a more 'legitimate' and acceptable tool for surgical treatment of psychiatric illnesses. This neuromodulation technique has opened further avenues for its applications in other behavioural disorders such as substance addiction and eating disorders, and in cognition.

Recently, notwithstanding the fact that no psychiatric neuromodulation procedure is as yet 'established' despite 15 years of intense activity in the field, DBS is witnessing a qualitatively different and potentially alarming jump, whereby DBS is being discussed for purposes beyond disease: for cognitive enhancement of healthy people and as a means to 'treat' antisocial behaviour: a survey of North American neurosurgeons published in 2011 revealed that more than 50% of those who answered the survey saw no ethical issue in using DBS to provide surgical memory enhancement to healthy people who request it [38]. Furthermore, in February 2012, *Brain* published an uncommented article titled 'Functional and clinical neuroanatomy of morality' [39], in which the authors wrote that 'understanding the dysfunctional brain structures underlying abnormal moral behaviour can lead to specific treatments nowadays using deep brain stimulation or other new non-invasive neuromodulation techniques'. Then, the authors assert 'evidence that subcortical structures intervene in morality' and suggest that 'deep brain stimulation might be used in…pathological antisocial behavior or violence…' and for 'shaping individual morality'. This proposal of a possible use of DBS for such indications, even if the authors acknowledge that this 'raises intriguing ethical issues that should prompt the development of treatment guidelines' is not without provoking a strong sense of déjà vu.

Lessons learned for current practice

When asked in 1972 about what can be learned from the experience of the French Revolution, Mr. Zhou En Lai, China's prime minister between 1949 and 1976, replied: 'It is too early to tell'. Similarly, and in light of the above, it is perhaps still too early today to grasp the 'Lessons learned for Current Practice' from the history of neuromodulation in psychiatry. Besides, what is exactly the 'current practice' of 'neuromodulation in psychiatry' to start with?

According to WHO, psychiatric illness is by far much more prevalent in the world, and carries a much higher burden, than Parkinson's disease (PD) and other movement disorders. Also, it is a fact that the number of clinically active psychiatrists worldwide very highly exceeds the number of clinically active functional neurosurgeons. So how come that in the last 14 years since the introduction of DBS in psychiatry, so very few patients have received this neuromodulative therapy? Is the very rare use of DBS in psychiatry due to the lessons drawn from the practices of the past? Be it as it may, eventual 'lessons learned' from past history play in fact a minor role in the paucity of patients operated. Psychiatrists active in the field of psychiatric DBS, judging by names on publications, can be counted on the fingers of both hands. They are a microscopic minority compared with the number of neurologists active in the field of neurological DBS. There are, in absolute and relative terms, almost infinitely more functional neurosurgeons interested in psychiatric DBS than there are interested psychiatrists. In fact, most psychiatrists, including biological psychiatrists, seem to have very poor idea as to what DBS entails, to the extent that the Chair of the 'Task Force on Brain Stimulation' of the World Federation of Societies of Biological Psychiatry had to literally specify in a guidelines publication in *The World Journal of Biological Psychiatry* in 2010 that 'the term deep brain stimulation refers to methods where electrodes are implanted deep in the brain under the dura' [40].

The criteria for patient selection for DBS in PD and other movement disorders have been for a long time, and still are in most centres, the severity, chronicity and refractoriness of the symptoms. These same selection criteria do indeed apply for the many more available patients who suffer from depression or OCD. Yet, very few patients are referred/recruited for surgery. Unlike in PD patients, where the L-DOPA test usually predicts the outcome of DBS, there are no predictive tests for the outcome of DBS in OCD and depression. Unlike tremor patients, for example, in whom it is established in which brain target(s) DBS should be located to be efficient, we are still far from sure which brain areas are best to target with DBS for depression and OCD. As of today, there is a total of 10–12 different brain targets, the indications for which are overlapping between OCD, depression and Tourette syndrome, such that the same brain target may be used for any of these three illnesses. So, unlike DBS for PD, especially DBS in the STN, it is evident that DBS in psychiatry has not had a breakthrough yet, in any brain target and for any indication. Hence, we do not have today a 'current practice' of DBS in psychiatry. What we have are case reports, very small series and ongoing trials. One of these completed trials on DBS in ventral striatum–ventral capsule versus sham stimulation in 30 patients with major depression showed that DBS was not better than sham stimulation at 4 months blinded follow up, and in the open-phase stimulation at 8–12 months only 21% of patients were 'responders' [41]. In another double-blind trial of STN DBS for OCD, published in 2008, the results were mitigated by the frequency of side effects and the follow up after surgery was 3 months [42], and so far no publication has been made available about the fate of this cohort of patients at longer follow up. These publications using 'evidence-based' methodology are not something that will convince psychiatrists to start referring patients with severe OCD or depression for DBS on a mass scale. Even in trials, one of the problems is the low recruitment of eligible patients, the difficulty to program stimulation parameters in psychiatric patients, the compliance of patients with the trials if it involves sham stimulation, the necessary length of follow up, the lack of disease-specific evaluation tools pertaining to the quality of life and social (re)integration of patients, and many other issues, so in summary one cannot claim that there is any current 'practice' of DBS in psychiatry.

In fact, the main lessons of past historical experience of psychiatric neuromodulation are that there are now about 15 different publications providing ethical guidelines for the conduct of psychiatric DBS, starting with the first published in 2003 [43] and the last just published online [44]. These publications from partly overlapping authors and centres share the same fundamental main ethical requirements for the conduct of DBS in psychiatry. The main guidelines from these publications are summarized as follows, and they are discussed and commented in light of previous historical as well as contemporary practices:

a DBS in any brain target tried so far, and for any psychiatric or behavioural disorder, still remains at an investigational stage.

Interestingly, when FDA approved DBS for OCD as a humanitarian device exemption (HDE) in 2011, that decision was questioned and criticized as a 'misuse' of the HDE by the very pioneers of DBS for OCD, surgeons, psychiatrists and ethicists [45].

b Researchers are encouraged to design randomized controlled trials, based on scientific rationale for DBS in various psychiatric diseases and various brain targets.

Here it is of interest to reiterate what was stated earlier in this chapter that, already in 1977, Laitinen had proposed a similar approach for stereotactic ablative psychosurgery but apparently nobody was interested at that time [1].

c An experienced multidisciplinary team is mandatory for the safe and ethical conduct of any psychiatric neurosurgery.

As shown previously, published guidelines about 'Scientific and ethical issues related to DBS for disorders of mood, behaviour and thought' by 19 authors and co-authors [37] included all disciplines (neurology, psychiatry, ethics, etc.) except neurosurgeons. So much for modern multidisciplinarity! Besides, the multidisciplinarity that is so important today in all functional neurosurgeries did also exist in the previous era of lesional stereotactic surgery. The father of cingulotomy, neurosurgeon Thomas Ballantine from Massachusetts General Hospital in Boston, was praised by neuroethicist Joe Fins in a paper in 2003, in which Fins wrote about the role of Ballantine in promoting a multidisciplinary approach to stereotactic psychosurgery, whereby 'decisions to operate were to be made in conjunction with a psychiatrist, who would also make psychiatric follow-up available, and patients and family were to be informed of potential risks and benefits' [36].

d Severity, chronicity and refractoriness of patients submitted to DBS must be documented.

e There should be proper consent procedures that respect patient's capacity and autonomy.

f Evaluation should rely on validated and multifaceted scales and tools preoperatively as well as at long term after surgery.

g There should be a comprehensive reporting of all effects and side effects for *all* patients submitted to DBS.

With respect to this last guideline, it appears that even in contemporary practice, multidisciplinarity in psychiatric DBS and ethical awareness may still not be enough to ensure a truly ethical and honest conduct of DBS in psychiatry. There has been at least one example where a DBS trial failed to live up to this fundamental rule, that is, that all patients included in that trial should be accounted for [46]: Two of the very first patients operated upon with DBS for OCD, one of whom was included in the first trial ever performed in DBS for OCD, were never reported, neither in the pioneer paper describing the first four patients, published in *Lancet* in October 1999 [6], nor in subsequent publications, despite the very rigorous ethical standards advocated in the ethical guidelines published by that same group in 2002 [43]. The first mention ever about the existence of these two missing patients is to be found in a paper by Greenberg *et al.* in 2010 [47] in which one laconic sentence reads: 'Two patients operated in Stockholm had no clear benefit'.

Be it as it may with respect to 'lessons' learned or not learned, and as has been discussed earlier, the real issues facing psychiatric neuromodulation with DBS are that very few psychiatrists are interested in DBS. One reason may be that no DBS procedure for any psychiatric illness in any of the multitude of brain targets tried so far has shown a breakthrough during the 15 years of trials of DBS in psychiatry. For a comparison, it did not take 15 years, or 10 or even 5 years before STN DBS or pallidal DBS was endorsed by virtually the whole world community of movement disorders neurologists as a surgical treatment for PD. In the opinion of this author, successful treatment of chronic complicated severe psychiatric illness such as depression or OCD, by modulating pathological brain circuitries with DBS, leading to an improvement that will allow chronic, refractory and severely ill patients to reintegrate society and lead a normal life, is unfortunately still very far away. The technique of DBS involves implantation of hardware in generally young patients, with the need to deliver high energy stimulation, with the need for frequent visits to hospital, with the need of frequent changes of battery over life time, with a cumulative risks of hardware infection and with possible rebound of symptoms in patients who do well when the battery is depleted or when it has to be explanted, aside from many other issues well described recently by the Okun team in Florida [48]. Hence, this technique may perhaps not be ideal in patients with OCD or depression, unless any of the ongoing trials of DBS in OCD or depression shows a real unequivocal and long-term breakthrough in terms of safety and efficacy.

One wonders whether one main 'lesson' of historical psychiatric surgery praxis is that stereotactic lesional surgery (capsulotomy and cingulotomy) has been unnecessarily and unjustly too much denigrated so that almost nobody uses it or even discusses it today, despite its more or less documented long-term efficacy [49–51]. Also the corollary 'lesson' is that DBS is presented today not only as promising (it has been labelled constantly as 'promising' during the last 15 years), but also as safe, reversible, adjustable, adaptable and non-destructive, so much so that it is not even being considered as a surgical treatment: a title published in *The Harvard Mental Health Letter* reads, 'Treating obsessive–compulsive disorder. Options include medication, psychotherapy, surgery, and deep brain stimulation'. [52]. So at Harvard, DBS for OCD is different from 'surgery'!

With this in mind, the commentary of Rhode Island neurologist Joseph H. Friedman from 2004 is worth to meditate about: 'Now that DBS means that psychosurgery is reversible, we no longer have to worry about permanent harm. On the other hand, now that psychosurgery could be readily available, potentially for a large number of conditions, we have a lot more to worry about' [53].

Conclusions

In the last 15 years, neuromodulation, using mainly the technique of DBS, is being increasingly trialled as a potential treatment for various psychiatric and behavioural disorders. The contemporary ethical discourse on psychiatric neuromodulation insists on avoiding the 'abuses' and 'errors' of the past without stating explicitly what is meant by abuses and errors of the past. The modern literature insists on the need for multidisciplinarity and strict ethical conduct in psychiatric surgery, as if ethics and multidisciplinarity were unknown in the past. A study of the historical scholar literature shows that the use of DBS in psychiatry is almost as old as human stereotactic surgery itself, and that principles of ethics and multidisciplinarity did indeed exist, but they were simply ignored by some workers in this field.

Therefore, it is important that those involved in the field of neuromodulation for psychiatric illness properly acknowledge history and keep in mind the following: (i) While it is certainly 'untenable that neurosurgeons act alone' [29], the scholar literature shows that 'acting alone' was not at all restricted to neurosurgeons. (ii) Multidisciplinarity in psychosurgery is not new. It has been the rule, not the exception, in the stereotactic lesional era of psychosurgery. (iii) Multidisciplinarity, per se, is not a guarantee against the excesses or the malpractice of psychosurgery, and proper moral or ethical values are not necessarily better or worse within one particular medical profession, as compared with another. (iv) 'Lessons learned for current practice' will not be learned fully before acknowledging that 'neuromodulation in psychiatry' can also become 'neuromanipulation' and that DBS is not the only and holy surgical approach available for the treatment of severe refractory psychiatric illnesses such as OCD and depression.

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The author dedicates this chapter to the memory of a pioneer neurosurgeon 'of the past', Lauri Laitinen, who insisted on, and advocated, the ethical, multidisciplinary, scientific and evidence-based conduct of stereotactic psychosurgery.

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CHAPTER 2

Ethics of neuromodulation in psychiatry

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Introduction

Neuropsychiatric conditions pose profound moral dilemmas within the health care system. Many individuals suffering from severe psychiatric illnesses do not receive treatments that respond to their clinical needs and many others suffer from the pervasive stigma attached to mental illness [1]. Given the marginalization of patients with psychiatric illness, neurosurgeons, neurologists, psychologists and psychiatrists have an ethical obligation to assist this population by pursuing novel therapeutic interventions. Neuromodulation, especially through deep brain stimulation (DBS), offers just this opportunity for patients with refractory conditions that do not respond to conventional pharmacological therapies or psychotherapy [2]. The most promising areas of research for DBS as a novel therapeutic are for patients with severe depression and obsessive–compulsive disorder (OCD), suggesting that it could become a standard therapy for these two conditions [3].

The ethical principles governing the use of neuromodulation in psychiatry will seek to protect this underserved and vulnerable population from harm and support research that enhances its welfare. These commitments draw upon the basic tenets of research and clinical ethics, as electrical stimulation of the brain for psychiatric disorders straddles both the therapeutic and investigational divide, as well as the emerging domain of *neuroethics* with its inherent concerns, which hind upon mind and personhood, about interventions in the brain.

We will begin this consideration with a brief historical recapitulation of the ethical issues that attended antecedent periods of research and practice involving psychosurgery and then move into the modern era of neuromodulation for neuropsychiatric disorders.

A brief history

While neuromodulation continues to grow as an established science holding great therapeutic promise for individuals with psychiatric conditions, it follows a history of treatment for psychiatric illnesses riddled with controversy. Some of these ethical issues arose in the mid-20th century with the development of ablative surgery and electrical stimulation in the brain. Briefly examining the legacy of psychosurgery provides a cautionary note for our consideration of neuromodulation in modern psychiatric practice and research [4].

Electricity has played a role in treating and understanding neuropsychiatric illnesses since the 19th century. Early experiments in animals used electricity as a means of understanding epilepsy, and neurosurgeons Harvey Cushing and Wilder Penfield continued such explorations during the first half of the century

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[5]. By 1947, neurosurgery had advanced with the significant development of how to localize the brain in three dimensions with the advent of stereotactic neurosurgery. This facilitated the placement of electrodes on targets deep in the brain without open craniotomies but by their passage through burr holes [6].

While these developments in the electrical stimulation of the brain are an important part of the history leading to DBS and neuromodulation, they were neither the only one nor the most controversial. Instead, it was the ablative lineage of psychosurgery that destroyed tissue in the service of health that most shaped public perceptions of any form of intervention in the brain. Initially welcomed as a treatment of refractory psychoses and for the shell shock of returning veterans from World War II, psychosurgery would eventually be perceived with disdain and outrage with which it was zealously promoted by its adherents [4, 7].

But make no mistake about it, psychosurgery constituted a major therapeutic breakthrough. Before the Portuguese Egas Moniz pioneered the lobotomy as an effective therapy for severe mental illness in 1935, physicians could only manage patients with psychoses by committing them to mental institutions that deprived patients of their freedom, their community and dignity. When Moniz subsequently won the Nobel Prize for his contribution to medicine and physiology in 1949, the award partially signified the public perception that this therapeutic option had great clinical utility. Contemporaries commenting on novel and experimental therapeutics, such as Cornell's psychiatry chair Oskar Diethelm, argued that physicians should acknowledge the uncertainty surrounding such intervention and to safeguard patients from harm [8].

This admonition, however, did not translate to the work of those who followed Moniz and who pursued dangerous, irreversible procedures with little scientific proof of its efficacy [4]. Indeed, Walter Freeman's disturbing crusade performing frontal lobotomies using an ice pick, without training as a neurosurgeon, as well as the advent of major tranquilizers in the early 1950s, led to the rapid decline of ablative procedures by mid-decade [9].

The work of Jose M.R. Delgado, beginning in the 1950s, continued at the basic and applied level in studies geared to understand neurophysiology. Delgado advanced work in the electrical stimulation of the brain, designing a brain implant, what he called a 'stimoceiver' that he controlled with a remote control. He famously implanted the electrode into the caudate nucleus of a Spanish fighting bull and demonstrated an ability to stem the animal's aggressive charges [10]. His work became controversial because it aroused fears of mind control by third parties who would use the stimoceiver. Delgado courted further controversy because he advocated these technologies to 'psychocivilize society', an objective that was perceived as necessary by some during the tumultuous 1960s [11]. Although many feared how these technologies could threaten civil liberties, Delgado imagined that their use would quell aggression and promote liberty and autonomy within a more civil community [4, 11].

The worry that interventions such as Delgado's and other forms of psychosurgery would be used for behavioural control pervaded the public's distrust for such measures. Some experts argued for the use of psychosurgery to control violence within American cities, basing this recommendation on the correlation between brain disorders such as epilepsy and violent behaviours and, despite reports suggesting evidence to the contrary, many assumed that American prisons commonly used psychosurgery to control its inmates, although this was not the case [12]. Artistic works such as Michael Crichton's *The Terminal Man* fuelled the worry that law enforcement might use electrical stimulation to treat violent individuals [4, 13]. In response to the public's growing objection to psychosurgery, as well as the emergence of a bioethics movement during this same period, the

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued a report on psychosurgery [14]. This report was one of many others, including one from the Hastings Center that explored the ethical dimensions of psychosurgery at that time [4, 12].

In 1977, the National Commission published its report on psychosurgery – defined to include both electric stimulation and ablative surgery. The report acknowledged the therapeutic efficacy of certain surgical procedures such as cingulotomy and concluded that, with rigid regulatory structures in place, clinicians could study and utilize psychosurgery for therapeutic purposes, not as a form of social control [4]. In advocating for strict regulation of psychotherapy, the National Commission suggested that institutional review boards (IRBs) comprised of experts in neurology, neurosurgery, psychiatry and psychology assess the safety, efficacy and utility of any psychotherapeutic procedure performed on an individual [4, 14].

This recommendation entailed concerns for acquiring adequate informed and voluntary consent from those participating in such research. The report excluded a variety of individuals – children, mentally ill, prisoners and people the courts deemed incompetent or who clinicians deemed incapacitated – from participating in psychosurgery. While this provision respected the vulnerability of many populations whose researchers might otherwise exploit (a safeguard steeped in the then recent exposure of scandals such as the Tuskegee syphilis study) [15], it also denied patients with psychiatric conditions that may influence their decision-making capacity the opportunity of participating in research of interest to them [4].

History with a difference

Although the National Commission's report on psychosurgery may have foreshadowed many normative commitments relevant to neuromodulation in psychiatry, it was forgotten until one of us (JJF) brought it back into the current literature on neuromodulation [4]. This omission is striking given that many modern clinicians, researchers and neuroethicists also possess a balanced enthusiasm for psychiatric neurosurgery [9]. So why was the report lost to history? It would seem that until the modern era of neuromodulation, it was easier to see the excesses of these interventions in isolation without due appreciation of their therapeutic potential. There was no need to have a balanced view of the harms if the putative benefits were unappreciated. But once the potential for these therapies is realized, differences between past and present, ablative and neuromodulatory approaches become salient [4, 16].

First, neuromodulation, unlike surgery, is reversible. Whether electroconvulsive therapy, transcranial magnetic stimulation or deep-brain stimulation, an individual can switch the source of stimulation on or off and even can remove the electrodes without great risk [4, 17, 18]. Second, while some classical psychosurgery procedures (such as lobotomy) lacked experimental evidence demonstrating their therapeutic success, a number of research studies have begun to demonstrate its safety and efficacy in the treatment of psychiatric or neurological illnesses or injuries [19–21]. Third, unlike past psychosurgeries performed without stringent selection criteria, modern DSM nosology and proper longitudinal regard for side effects, current studies must now meet rigorous specifications and interdisciplinary teams must perform long-term follow ups [22]. Finally, a vast neuroethical cannon has accompanied its development and encouraged a culture that responds to both the 'promise and perils' of technological interventions in the brain [7, 23]. With these differences in mind, it is possible to revive the National Commission's tempered endorsement of psychosurgery and reflect upon some of the more fundamental ethical concerns.

Any form of intervention in the brain raises philosophical concerns about free will, autonomy and personal identity, in turn, bearing on the more practical need for the best ways of obtaining voluntary, informed consent [5, 9, 24]. Given the complexities of the brain itself, technologies that probe this organ often complicate existing boundaries between research and therapy and make proportionality assessments all the more difficult. These ethical issues point to a need for a regulatory climate that allows clinician-investigators to use these devices to advance the basic scientific understanding of the brain itself while also developing meaningful therapies for patients with psychiatric illnesses. Moreover, these ethical concerns raise the possibility for adopting the focus of palliative care: using neuromodulation to alleviate suffering associated with psychiatric illness. This chapter will discuss each of these elements in turn.

Autonomy and the self

Part of what made psychosurgery so contentious, as we have seen, was that it entailed the act of operating on the brain. As a *Lancet* editorial written in 1972 explained, to enter the brain 'surgically carries a peculiar penumbra of sacrilege' [25]. The act of intervening in the brain through neuromodulation continues to worry many individuals today because it raises a unique series of ethical questions dealing with subjective experience and autonomy [5]. The brain is, indeed, an exceptional organ that is integral to lived experience and to the formation of an individual's sense of self. Any intervention that involves the brain's structure or function implicates brain states and personhood. Electrical stimulation of the brain has the possibility to alter, albeit reversibly, an individual's actions, thoughts and thus personality leading to great concerns over the use of technologies such as DBS. But neuromodulation neither appears to fundamentally undermine any of the 'capacities constitutive for personhood', including self-consciousness, free will, episodic memory, dispositions, preferences and so on [3], nor differs in its effects of mind from those of drugs, illness and even education.

A naturalistic understanding of the self can allay concerns about the device's potential to alter personal identity in troubling ways. Such a view does not understand the person, or self, as a non-physical entity, but instead as a 'biological–cognitive representational system' with the capacity to construct a subjective experience [22]. This account eschews dualism, and conceptualizes personality as the manifestation of complex interactions between more basic sensorimotor and higher level emotional processes. Neuromodulation, in this view, can induce changes in personality on multiple levels and to varying degrees. When used as a therapy for psychiatric illness, for example, the goal of neuromodulation is precisely to alter basic sensorimotor and higher level emotional processes that have been altered by illness and to induce constructive changes in mood and behaviour in the service of normative improvement. [22].

One aspect of introducing positive alterations to personality is its ability to restore autonomy. Philosophers have long recognized that autonomy entails both the ability to act and agency over the 'conscious and unconscious mental states that move one to act' [26]. A neurological injury or psychiatric illness may cause an individual to experience a loss of autonomy, lacking control over his or her thoughts or actions [27]. Neuromodulation through its intercession may paradoxically promote autonomy by 'restoring the neural functions mediating the relevant mental and physical capacities', allowing an individual to regain control over his or her own actions; in the case of a psychiatric condition such as OCD, electrical stimulation may reduce the frequency of repetitive behaviours and enable an individual to act as he or she chooses [26].