A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools

John Gardner
Department of Sociology and Communications, Brunel University London, London, UK

Abstract
Deep brain stimulation involves using a pacemaker-like device to deliver constant electrical stimulation to problematic areas within the brain. It has been used to treat over 40,000 people with Parkinson's disease and essential tremor worldwide and is currently undergoing clinical trials as a treatment for depression and obsessive–compulsive disorder. This article will provide an historical account of deep brain stimulation in order to illustrate the plurality of interests involved in the development and stabilization of deep brain stimulation technology. Using Latour's notion of immutable mobiles, this article will illustrate the importance of clinical assessment tools in shaping technological development in the era of medical device regulation. Given that such tools can serve commercial and professional interests, this article suggests that it is necessary to scrutinise their application in research contexts to ensure that they capture clinical changes that are meaningful for patients and their families. This is particularly important in relation to potentially ethically problematic therapies such as deep brain stimulation for psychiatric disorders.

Keywords
clinical assessment tools, deep brain stimulation, immutable mobiles, industry, innovation, medical device, technology

Introduction

In 2002, deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD) was granted approval by the US Food and Drug Administration (FDA). Since then, DBS, which uses a pacemaker-like device to deliver constant electrical stimulation to areas

Corresponding author:
John Gardner, Department of Sociology and Communications, Brunel University London, Kingston Lane, Uxbridge, Middlesex, London, UB8 3PH, UK.
Email: john.gardner@brunel.ac.uk

within the brain, has been used to treat over 40,000 people with PD and essential tremor worldwide. Heralded as providing 'a new life for people with Parkinson's' (Chou et al., 2012), the therapy has become the subject of considerable hope. Stories of previously housebound patients with debilitating symptoms subsequently regaining independence and self-confidence with DBS are not uncommon, and the media has tended to portray the therapy in very optimistic terms (Gilbert and Ovadia, 2011; Racine et al., 2007). The success of DBS as a treatment for PD and essential tremor has prompted investigators to explore other possible uses. Subsequently, DBS has been approved for the treatment of dystonia, and it is currently undergoing clinical trials for the treatment of obsessive–compulsive disorder (OCD) and depression. More recently, investigators have begun exploring DBS as a possible treatment for severe obesity (Taghva et al., 2012).

Most contemporary accounts of DBS therapy give the impression that it is the inevitable consequence of scientific discovery and medical progress, as if the intrinsic qualities of the DBS technology were sufficient to guarantee its consolidation as a therapy for PD. Yet DBS was originally developed as a treatment for chronic pain – a therapy not currently approved by the FDA. The history of DBS is, in fact, complex. In this article, I will explore the development and stabilisation of DBS, focusing predominantly (but not exclusively) on events within the United States. Far from being inevitable, the development of DBS therapy was shaped by professional and commercial interests, parallel developments in medicines, and medical device regulation, and was contingent upon a range of factors, such as the flexibility of the technology and the development of standardised clinical assessment tools.

The need for an examination of the development of DBS

The rapid adoption of DBS technology into therapies for a range of neurological and psychiatric conditions has attracted the attention of ethicists. While the therapeutic benefits of DBS for PD and dystonia are largely undisputed, ethicists have stressed the need for caution. The high cost and invasive nature of DBS, the difficulty of managing patients' expectations and the unknown extent of psychosocial adverse effects necessitate the formation of clear ethical guidelines (Bell et al., 2009; Schermer, 2011) and the careful monitoring of clinical outcomes (Schlaepfer and Fins, 2010). Inevitably, comparisons have been made between DBS for psychiatric disorders and the psychosurgeries of the past. Such comparisons refer to the capacity of neurosurgical therapies to threaten identity and the sense of self and suggest that the spectre of psychosurgery is a necessary reminder of the need for caution (Gillett, 2011; Kringelbach and Aziz, 2009). DBS has been implicated in the 'continuous march of technologies that invade and transform the body', bringing us closer to an era of ethically contentious intelligent design, cyborgs and mind/machine interfaces (Hester, 2007: 255). Such accounts render DBS a small but definite movement towards neurotechnologies with a potential to significantly affect that which we think of as 'human' (McGee and Maguire, 2007). Commentators have also drawn attention to the role of commercial interests in disseminating DBS technology. Fins and Schiff (2010) argue that the interplay of market forces and scientific inquiry within DBS research has resulted in potentially dangerous conflicts of interest. The medical device manufacturer Medtronic, for instance, has been accused of misusing a

regulatory exemption in order to facilitate the dissemination of their DBS technology (Fins et al., 2011).

DBS, then, is not only the source of a great deal of hope, but it is also the subject of apprehension. It exemplifies important tensions associated with biomedicine in contemporary society more generally: a conviction in technology-orientated solutions, a drive to alleviate suffering, a suspicion of commercial interests, doubts over the ability of regulatory initiatives and anxiety over a precarious future. An historical account can provide some much-needed context to the present-day challenges associated with biomedicine. As Foucault puts it, the present does not rest on 'profound intentions and immutable necessities' (Foucault, in Rabinow, 1991: 89). Rather, the concepts, artefacts, dispositions and dilemmas that characterise the present day have emerged from an entanglement of actors. An historical account of the development of DBS will illustrate how it is that commercial interests have become entwined in the technology and how it is that the technology can be so rapidly adopted into therapies for a range of conditions. Importantly, by illustrating the conjunction of circumstances that led to the emergence of DBS, an historical account can identify those aspects that warrant further scrutiny when assessing the merits of potentially ethically problematic therapies for psychiatric disorders.

Science and Technology Studies and the dynamics of technological development

As Morlacchi and Nelson (2011) point out, linear narratives of scientific discovery and medical progress are common to accounts of medical device development. As a result, many members of the biomedical community and the public maintain 'inadequate and simplified understandings of how medical practice advances' (p. 511). The effect of such accounts is to reify a distinction between the realm of science and objective knowledge production, and the domain of social and political interests, where the former (ideally) progresses untainted by the latter (Latour, 1993). Yet, as a body of work in Science and Technology Studies (STS) has shown, such a distinction is untenable. A recent example of such work is Stuart Blume's account (2010) of the development of the cochlear implant. From the late 1960s onwards, several groups were attempting to develop an implantable hearing device. These groups had differing views on how such a device should work, faced considerable hostility from their colleagues and had to compete for funding. Some were not averse to using media hype in order to secure the resources they needed, much to the disdain of other hearing specialists. Competing groups formed alliances with rival device manufacturers, one of which provided the necessary resources to gain regulatory approval. Once approved, sales of the device failed to rise, partly due to the high costs associated with its implantation. Competing companies therefore formed an additional alliance to lobby the US Government to have the device covered by Medicare. Blume's account highlights the many diverse actors involved in innovation: competing scientists and engineers, the media, industry, regulatory agencies, lobby groups, patient advocacy groups and governments. As Faulkner states, this plurality of interests, both public and private, is characteristic of medical innovation within neo-liberal economies (Faulkner, 2009: 7). Brown and Webster argue that technologies emerge from, and are an integral

part of, heterogeneous networks made up of professions and institutions, users and citizens, governments, regulatory agencies and commercial industry. Technological innovations have to work within and through these networks by resonating with pre-existing values or interests. Their capacity to do this, to be co-opted, moulded and perpetuated by various actors, determines their success. No technology 'ever speaks for itself' (Brown and Webster, 2004: 38).

Indeed, as this article will illustrate, this plurality of interests and the formation of alliances are characteristics of the development of DBS technologies. DBS has its origin in the neurostimulation techniques developed within a sub-speciality of neurosurgery: stereotactic neurosurgery (also known as functional neurosurgery). From the 1940s onwards, this speciality disseminated rapidly throughout the world, providing (or attempting to provide) therapeutic relief to patients with what were then otherwise untreatable neurological and psychiatric conditions. This period of rapid growth was characterised by what Morlacchi and Nelson (2011) refer to as 'learning in practice', an overlooked but crucial component of medical innovation. Neurosurgeons developed many of the skills, material infrastructure and knowledge that would later shape DBS as they were attempting to treat individual patients. This period of unrivalled 'learning in practice', and indeed stereotactic surgery as a speciality, almost came to an end with the development of medicines for motor disorders and psychiatric conditions and a political backlash against psychosurgery. This article will also illustrate the importance of what Morlacchi and Nelson (2011) refer to as 'technology transfer' in the development of device-based therapies. The first neurostimulators were modified cardiac pacemakers and enabled stereotactic neurosurgeons to continue accessing patients with particular neurological conditions. As this technology was transferred, alliances were formed between neurosurgeons and commercial industry, particularly with the medical device manufacturer Medtronic. This article will suggest that the material qualities of the technology facilitated its rapid dissemination. As De Laet and Mol (2000) have illustrated, flexible technologies can be disseminated more easily than the technologies that impose a particular type of usership. During the 1970s, the emerging neurostimulation technologies were adapted into therapies for a range of conditions by neurosurgeons.

The advent of medical device regulation, however, brought about an end to this era of dissemination, and Medtronic was effectively left with a very limited market for their neurostimulation technology. With regulation, the notion of 'efficacy' was redefined as something objectively verifiable: this article will argue that regulation created a distance between the point at which a patient was treated and the point at which such interventions were assessed. Overcoming this distance required the formation of new alliances involving what Latour (1987) has referred to as immutable mobiles: representations of afflicted patients that could easily be circulated between points. This article will argue, then, that in the era of medical device regulation, clinical assessment tools are an essential means of generating such immutable mobiles. Such tools are an important component in the trend towards rationalisation of medicine and healthcare that has been identified by various scholars (e.g. Hunter, 2003; Porter, 1995).

Thus, while this article will supplement previous STS research illustrating the dynamics of technological innovation and the socially embedded nature of medical

devices, it will also draw attention to the role of clinical assessment tools and outcome measures in biomedical innovation. The commercial utility of such tools in the era of device regulation is one reason why they have become prominent. This has facilitated the diffusion of particular techniques for manipulating bodies to extract data. Second, this article will illustrate that such tools direct the development of devices towards specific therapeutic applications: the development of a tool for quantifying PD encouraged Medtronic to seek regulatory approval for a specific, lucrative application of the neurostimulation technology: DBS for PD. The more recent emergence of tools for quantifying other conditions has since enabled Medtronic to seek approval for other therapeutic applications. Given the importance of clinical assessment tools in producing evidence of efficacy in the era of evidence-based medicine (EBM), and given the commercial and professional interests entwined in such tools, this article concludes by suggesting that it is necessary to scrutinise their application in clinical research contexts. This is particularly important in clinical trials for potentially ethically problematic DBS therapies for psychiatric conditions.

Material and methods

The data for this article have been gathered from a range of resources. Scientific articles from 1930 onwards, relating to electro-stimulation, neurostimulation, neuromodulation and DBS, were sourced from a range of neurosurgical, neurological, and psychiatric journals, as well as engineering and bioengineering publications. Data were also gathered from scientific articles relating to the development of clinical assessment tools for movement disorders published from the 1970s onwards. Newspaper articles, press releases, transcripts of FDA panel hearings and meetings (available online), secondary historical documents and accounts produced by engineers (Mullett, 1987; Shatin et al., 1986), Medtronic medical advisors (Coffey, 2001, 2008) and numerous clinicians, particularly the neurosurgeons Philip Gildenberg (2000, 2005, 2009) and the neurologist Adrian Upton (1986; Upton and Lazorthes, 1987) were also included. These documents were critically analysed in order to adhere to Lampland and Star's (2009) dictum that we interrogate naive 'stories of inevitable technological development' and instead identify how both DBS and standardised, clinical assessment tools emerged from, and were shaped by, an entanglement of actors. Thus, these articles were used to identify the various social actors, political and institutional pressures and biomedical developments involved in the development and stabilisation of DBS.

The development and stabilisation of DBS

Much of the recent scientific literature on DBS provides overviews of the therapy's history. As Hariz et al. (2010) point out, the common narrative of these overviews is that DBS was first developed in 1987 by a team treating patients with essential tremor and PD at Grenoble, France. However, many clinicians had been aware of the therapeutic effects of electro-stimulation of the brain, or neurostimulation, for several decades prior to this, and neurostimulation technologies had been in development since the 1960s.

The rise of and near demise of stereotactic neurosurgery

Since the 1930s, clinicians had been using electrodes to explore the function of various areas within the brain and to identify areas for ablative therapy. Ablative therapy involves the deliberate, precise destruction of particular areas within the brain that are thought to be malfunctioning. The first such procedure, the 'Montreal Procedure', was developed by the neurosurgeon Wilder Penfield in the 1930s to treat epilepsy. Patients were kept awake while a surgeon would stimulate different areas of their cerebral cortex with an electrical probe. By noting the patient's response when stimulating various regions, the surgeon hoped to locate, and subsequently destroy, the particular area implicated in the patient's seizures (Penfield, 1936). In 1947, an apparatus was developed that enabled clinicians to use this technique to explore and ablate areas deeper within the brain. The stereotactic apparatus brought about the emergence of a new neurosurgical speciality, stereotactic neurosurgery, within which the skills, equipment and knowledge were developed that would later enable DBS to emerge as a therapy.

The stereotactic apparatus delineates the brain as a three-dimensional system of Cartesian coordinates. When used in conjunction with imaging technologies, any point within a patient's central nervous system can be designated as a set of three numbers. Surgeons can then plan their procedure to carefully avoid vital areas and navigate their way to areas deep within the brain (Spiegel et al., 1947). As a result of the apparatus, the mortality rate associated with neurosurgery plummeted (from 15% to 1%) and stereotactic neurosurgery went through a period of rapid growth: within 10 years it was being practised in over 40 centres worldwide (Gildenberg, 2000).

This growth was fuelled by a large demand for ablative therapies, the only means available to provide relief from a range of otherwise untreatable neurological conditions. During the period of rapid growth, stereotactic surgery was used to treat various psychiatric disorders (psychosurgery), movement disorders and chronic pain. Following Penfield's technique and guided by the stereotactic apparatus, surgeons would use electro-stimulation to identify possible target areas deep within the brain that were thought to be implicated in the condition, and if they were satisfied with the corresponding effect on the patient, the area would be carefully destroyed. Prior to the introduction of antipsychotic medications in the mid-1950s, this and the much more crude frontal lobotomy were heralded as much-needed treatments for patients with psychiatric disorders, disorders that were considered to be a huge financial burden on society, particularly in the United States (Mashour et al., 2005). Similarly, prior to the introduction of levodopa in 1968, medicines were largely ineffective in managing the symptoms of PD, a condition that affects around 3 in every 1000 individuals. PD became the main condition treated with stereotactic surgery, with approximately 25,000 surgeries by 1968 worldwide (Gildenberg, 2000).

This large body of otherwise untreatable patients provided stereotactic neurosurgeons with a great deal of work and ample opportunity to engage in what Morlacchi and Nelson (2011) refer to as 'learning in practice'. While attempting to identify the most effective means of treating each individual patient, stereotactic neurosurgeons were able to explore the effects of stimulating areas deep within the brain. As the neurosurgeon Gildenberg (2000) puts it, stereotactic surgery brought about

a period of unrivalled empirical human experimentation … From the beginning, the philosophy was to use every insertion of an electrode into the brain as an opportunity to study neurophysiology … The information obtained in the operating room was valuable to help localise the electrode position, and the information obtained about pathophysiology was used to develop new indications and targets for stereotactic surgery. (pp. 299, 301)

Surgeons continued to hunt for more effective target areas for ablation, and in the process, they created a body of knowledge based on the effects of stimulating different areas within the brain. In patients with motor disorders, it was noted that lower frequency stimulation of particular areas could exacerbate symptoms, while higher frequencies could reduce symptoms (French et al., 1962; Mundinger, 1965). In patients with PD, the sub-thalamic nucleus (STN), now the main target for DBS, was identified as one such area:

The subthalamic nucleus was not readily activated by low frequency stimulation … but there was suppression noted when values of 120 to 300 c.p.s [cycles per second] were reached. (Nashold and Slaughter, 1969: 243)

Noting the therapeutic effect of higher frequency stimulation, some surgeons carried out chronic stimulation on their patients. Electrodes were left in situ and protruding from the skull for several weeks, enabling the surgeons to identify and lesion the optimal areas for ablation in an incremental fashion (Nashold and Slaughter, 1969; Sem-Jacobsen, 1966).

By the end of the decade, however, this era of experimentation, and indeed the stereotactic speciality as a whole, almost came to an end. After the introduction of levodopa in 1968, neurologists were reluctant to refer PD patients to neurosurgeons: the reservoir of severely affected, otherwise untreatable patients willing to undergo ablative surgery was drastically reduced. Compared to surgical treatments, levodopa was inexpensive, safe (non-invasive) and remarkably effective in reducing the severity of PD symptoms, and it quickly became the first-line treatment for diagnosed patients. Indeed, when it was first introduced, it was believed to be a panacea for PD, a therapy that would control symptoms indefinably without any major side effects (Gildenberg, 2000). Additionally, neurosurgeons were discouraged from treating psychiatric conditions by a public campaign that lumped their stereotactic procedures with the frontal lobotomy. A figurehead of the campaign, the psychiatrist Peter Breggin (1972), told the US Senate Subcommittee on Health that psychosurgery has 'no empirical or rational basis …', 'attacks and mutilates brain tissue that has nothing demonstrably wrong with it' and that it can be used to 'subject the individual to the control of others' (p. 381). Using examples of surgically treated restless housewives and hyperactive children, he argued that psychosurgery was a political tool used to placate minorities. Breggin's criticisms were taken up by US representative Cornelius Gallagher, and a commission was established to further investigate his claims. Despite the commission's findings that psychosurgery appeared to be of great benefit to individual patients, the political climate led most neurosurgeons to abandon the field (Valenstein, 1997).

Thus, by the middle of the 1970s, levodopa and a hostile political climate had brought about the near demise of stereotactic neurosurgery. A few academic centres remained

open in the United States and Europe to provide relief to the small number of patients with chronic, untreatable pain and those with movement disorders that would not respond to the new levodopa medications. The skills, knowledge and equipment that had been developed during the 'era of experimentation' were maintained in these few centres. It was within these centres that DBS therapy would have its genesis. The particular material infrastructure (such as the stereotactic apparatus) and the knowledge base of these centres, the exploratory ethic of the clinicians working within them, and, as we will see, technological developments in cardiac pacemaking led to the development of the first neurostimulators.

The birth of the neurostimulator

During the period of 'unrivalled experimentation', neurosurgeons had noted the therapeutic effects of high-frequency neurostimulation. Electro-stimulation was not a therapy on its own, however. The lack of sufficient technology is no doubt a reason for this: electrodes had to be externalised, protruding from the head in order to link with a power source, which at the time were large, cumbersome and certainly not implantable. As Morlacchi and Nelson (2011) point out, new medical therapies often arise from the transfer of technological artefacts from one sector into another. This was certainly the case with neurostimulation therapies. In the early 1960s, the then-fledgling medical device manufacturer Medtronic introduced the first, commercially available cardiac pacemaker. These small, mobile power sources quickly disseminated throughout the United States, fuelling the company's rapid growth, and by 1975, Medtronic's annual turnover was over US$100 million. From this success came the components and finance required to produce neurostimulation technologies: in effect, the development of the neurostimulator piggybacked on the success of the cardiac pacemaker.

The adaptability of cardiac pacemaker technology was first demonstrated by neurosurgeons attempting to treat chronic, intractable pain in the late 1960s. Although medicines had become the first-line treatment for psychiatric disorders and PD, drug-based therapies for various forms of chronic pain remained elusive. This small pocket of patients provided neurosurgeons with an opportunity to continue exploring the effects of neurostimulation and to try neurostimulation as a therapy in its own right. The Wisconsin-based Norman Shealy was the first neurosurgeon to adapt cardiac pacemaker technology into a therapy for chronic pain. Electrodes were implanted within the spinal cords of a group of patients and connected to implanted Medtronic pacemakers modified to produce the higher frequency of stimulation required to modulate the perception of pain (Shealy et al., 1967: 490). At that time, standard, battery-powered pacemakers were unable to produce the necessary frequency of electrical pulses required to interfere with the conduction of pain. Shealy used a modified Medtronic 'Radio Frequency' (RF) system where energy (in the form of radio waves) is transferred through the skin to an implanted receiver. Shealy reported his 'promising' results to colleagues at a conference in 1969, many of whom were sufficiently convinced that they began to offer the therapy at their own centres (Shatin et al., 1986). Similarly, a team from California used pacemakers to stimulate areas deep within the brain. Hosobuchi and his team had been using stereotactic-guided ablative surgery to provide relief to patients with chronic pain. DBS trials were conducted on a few

patients who failed to respond satisfactorily to ablative therapy: electrodes were stereotactically implanted within the thalamus and connected to a pacemaker (Hosobuchi et al., 1973). Hosobuchi reported that pain was sufficiently masked in three of his four original patients.

Soon there was sufficient interest among neurosurgeons treating chronic pain to encourage the medical device industry to develop a specific neurostimulator device. Medtronic was the first to do so in 1968, followed by Avery Laboratories in 1972 and then Cordis, the second largest producer of pacemakers behind Medtronic (Rossi, 2003: 10). As Shealy had illustrated, pacemaker components such the power source, the circuit board and the device casing could be adapted for the neurostimulation therapies, and pacemaker producers were able to use their existing manufacturing skill set to produce many of the neurostimulator components (Stuart, 2012). Companies subsidised the development and production of these components with returns from the highly lucrative pacemaker market (Upton, 1986). Medtronic officially established a neurological division in 1975, and it was while marketing its device for the treatment of pain that Medtronic trademarked the term 'DBS' (Coffey, 2009).

During the 1970s, these neurostimulators were disseminated throughout specialist centres within the United States and Europe and were incorporated into therapies for a range of conditions. These were conditions that had previously been shown by neurosurgeons undertaking ablative surgery to respond to electro-stimulation: various motor disorders, cerebral palsy, epilepsy, schizophrenia and severe depression. Different areas of the nervous system were stimulated: the spinal cord, the cerebral cortex, and, within those centres that had retained the ability to carry out stereotactic surgery, areas deep within the brain such as the thalamus. The well-known US neurosurgeon Irving Cooper, for instance, used the newly developed neurostimulators to stimulate the cerebellum and deep brain as treatments for cerebral palsy, epilepsy or dystonia in around 200 patients (Cooper et al., 1980; Cooper and Upton, 1978). Up to 200 patients were treated; the results were good and 'worthy of immediate notice' (Rosenow et al., 2002). In Germany, Fritz Mundinger (1977) used Medtronic neurostimulators to stimulate areas within the thalamus to treat dystonia, arguing that the reversible nature of the treatment made it preferable to ablation. His views were echoed by Orlando Andy (1983) of Mississippi, who was using stimulation of areas within the thalamus to treat nine patients with PD who had failed to respond to levodopa therapy. At Tulane University, Robert Heath adopted Medtronic neurostimulators into his treatments for psychiatric disorders, particularly schizophrenia, reporting that some of these patients subsequently became symptom free (Heath, 1977; Heath et al., 1980). In Southampton, United Kingdom, during the late 1970s, Brice and McLellan were using DBS to treat a small number of patients with multiple sclerosis–associated intention tremor. They reported that some of their patients improved significantly: one patient who was initially totally disabled was subsequently able to 'feed herself, light her own cigarettes, fasten her own buttons, and control bed light and radio' (Brice and McLellan, 1980).

In a recent retrospective, Philip Gildenberg, a stereotactic neurosurgeon at the time, gives us some idea as to why neurosurgeons were receptive to neurostimulation technology. The introduction of levodopa for the treatment of PD in 1967 had left a void for functional neurosurgeons with training in stereotactic techniques. Neurostimulation

provided an opportunity, for some neurosurgeons at least, to utilise their skills and equipment and provide potentially effective surgical treatments for other conditions or for those few patients with PD who could not tolerate levodopa (Gildenberg, 2009: 14). The skills, knowledge and tools that had been developed during stereotactic surgery's earlier period of rapid growth could easily be transferred into DBS therapies: the stereotactic apparatus, in conjunction with imaging technologies, was used to identify target areas and plan the surgical procedure necessary to implant permanent electrodes; intra-operative stimulation was often used to ensure that the correct target area had been located; and these target areas were often the same as those that, in the past, would have been ablated. Neurosurgeons, then, had the necessary skill set, and the technology provided them with a vehicle for intervening in complex neurological conditions in an era when drug-based therapies tended to dominate.

Diffusion was enabled by the flexibility of the technology. As Faulkner (2009: 18) argues, the material qualities of a device interact in more or less flexible ways with social actors, impinging upon their possibilities for adoption and usage. The material qualities of neurostimulation technology, such as its small size, its biocompatibility and its ability to deliver precise electrical stimulation to a region decided upon by the clinician, permitted its adoption into a range of therapies. This is not to say that the diffusion of the device was unproblematic. Problems with components were not unusual and these were subject to incremental modifications: the electrodes used in DBS could fray and turn on their axis (Siegfried and Shulman, 1987); complications arose from lead implantation and the power source could fail (Shatin et al., 1986). In the 1980s, some of these difficulties were overcome. Lithium batteries enabled the production of a neurostimulator that could be implanted for several years and provide the necessary level of ongoing stimulation. New neurostimulator leads were produced based on endocardial (pacemaker) leads, and a device was created that could be programmed via a wireless console programmer. Again, these incremental developments were the result of technology transfer from the ongoing financially lucrative improvements associated with the pacemaker (Shatin et al., 1986).

Additionally, it is likely that the diffusion of the neurostimulator was linked to the success of a cardiac pacemaker in a broader sense. As Blume (2010) argues, the cardiac pacemaker gave 'the notion of an implantable device legitimacy and appeal' (p. 34). It enabled clinicians to significantly improve the lives of a large body of patients and was heralded as a major advancement in modern medicine. This encouraged wider acceptance of implantable devices among the public and no doubt encouraged those working in neurostimulation to emulate the success of this pacemaker.

Medical device regulation

During this period, clinicians reported that many of their patients were responding well to the neurostimulation therapies. In 1978, Cooper stated that there had been a clinical improvement in the majority of the 700 patients who had undergone cerebral stimulation for the treatment of either cerebral palsy or epilepsy (Cooper and Upton, 1978). Andy reported that the results of stimulating the thalamus at high frequencies in nine patients with motor disorders were 'fair to excellent' (Blomstedt and Hariz, 2010: 431),

and Heath et al. (1980), reporting on a study of 38 patients, argued that those with depression, 'behavioral pathology consequent to epilepsy, and those with psychotic behavior consequent to structural brain damage' responded well to neurostimulation of the cerebellum (p. 243).

Yet prior to medical device regulation, it was not exactly clear what constituted a 'clinical improvement' or a 'fair to excellent' outcome in this area. In effect, the opinion of a clinician was sufficient to determine whether a medical therapy was effective and thus whether or not the use of a medical device could be justified. This reflected the sentiment of the early 20th century, when 'efficacy' was considered 'a matter of opinion, not a fact' (Bodewitz et al., 1989). With the advent of medical device regulation, however, 'efficacy' was delineated as something that should be objectively verifiable, thus necessitating clinical assessment tools and outcome measures that would enable the quantification of a patient's response to an intervention. Here, we will see that there were few such tools for the conditions being treated with neurostimulation, and subsequently, neurostimulation therapies such as DBS for chronic pain were not approved in the new regulatory climate.

In 1976, after 7 years of political debate, the US Congress passed the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, granting the FDA authority over all medical devices. This was in response to a spate of device failures: between 1960 and 1970, medical devices were implicated in 10,000 injuries and over 700 deaths, and between 1972 and 1975, over 22,000 potentially defective pacemakers were recalled by manufacturers (Foote, 1978). The intention of the amendments was to provide a 'reasonable assurance of safety and effectiveness for all devices' (Foote, 1978). With pharmaceutical regulation, the gold standard for determining efficacy became the double-blind trial. With medical devices, which are often not amenable to double-blind trials, the FDA stated that efficacy would be determined 'on the basis of well-controlled investigations, including clinical investigations where appropriate, by experts qualified by training and experience' (Foote, 1978). Consequently, efficacy was rendered something objectively verifiable: it would have to be demonstrable to an FDA-appointed panel of experts who were not directly involved in the treatment in question.

With regard to neurostimulation technology used in DBS and cerebral stimulation therapies, the FDA decided that clinical trials would be necessary before it could be marketed (Coffey and Lozano, 2006). Medtronic, Avery and NeuroMed, the three manufacturers of neurostimulation technology, were offered time to perform the necessary trials and produce the required documentation. All, however, eventually declined. The probable reason for this is provided by Adrian Upton, a UK-based neurologist: a major problem in the application of neurostimulation, he stated, was the lack of standardised, quantifiable measures for determining the effectiveness of the treatment (Upton, 1986). Pain, for instance, was especially difficult to measure. In a recent summary of neurostimulation treatments for pain, Coffey and Lozano (2006) refer to the

> paradox of pain – its simultaneous reality and subjectivity makes the assessment of pain relief therapies susceptible to observer- or patient-related influences … Unintentional cues, learned responses, or knowledge that a treating physician … is conducting the assessment can affect how patients rate analgesic treatments.

Cooper's neurostimulation therapies, including his DBS therapies, were also problematic in this regard. Despite Cooper's belief that they 'yielded promising clinical results', the lack of uniform objective evaluations to quantify and measure clinical improvement meant that the 'true benefit' could not 'be elucidated' (Rosenow et al., 2002).

Thus, DBS and other neurostimulation treatments were not amenable to clinical trials because the conditions being treated were not quantifiable: there were no generally accepted clinical assessment tools that could be used to demonstrate clinical improvement. The clinical trials that were now needed to demonstrate efficacy and safety were also expensive, and Upton stated that the costs of further development would need to be offset by a large market (Upton and Lazorthes, 1987). Upton specifically referred to PD as a potential market for neurostimulators. The problem with PD, he claimed, was an over-reliance on medications, and thus, the promising findings of earlier neurostimulation treatments for movement disorders were therefore being overlooked (Upton, 1986).

The Unified Parkinson's Disease Rating Scale: generating immutable mobiles

By the mid-1980s, neurostimulation was in a precarious position. On the one hand, the medical device industry had the manufacturing skills necessary to produce neurostimulator technology, and there were neurosurgeons with the expertise required to incorporate the technology into working therapies. On the other hand, the new regulatory climate had effectively put a halt to the dissemination of many neurostimulation therapies, restricting the market for the technology. In effect, medical device regulation endowed the FDA with the responsibility of assessing efficacy and safety of therapeutic interventions, and as a result, it became a gatekeeper, either preventing or permitting dissemination of new device-based therapies. Manufacturers such as Medtronic would be required to calculate the safety and efficacy of their devices and submit these calculations to the FDA in order to obtain approval and to access lucrative markets.

A distance was created between the point of therapeutic intervention (the clinic or the research site) and the point at which efficacy and safety of those interventions are audited (an FDA-appointed panel of experts). Such distance was deemed necessary to reduce the influence of bias on the assessment of an intervention and thus provide a level of protection to patients and consumers. Yet, in order for the FDA to function as an auditor and a gatekeeper, this distance must be traversed; the two points must, somehow, be brought together. This can be achieved via the production of immutable mobiles: renderings of entities of interest that are capable of circulating between the two locations without losing their meaning in the process (Latour, 1987).

Clinical assessment tools are a means of generating immutable mobiles and creating an equivalency of meaning between the sites of intervention and the FDA, thus enabling the latter to act as an auditor of the safety and efficacy of devices. In the mid-1980s, such a tool was developed for one particular condition that was known to respond to neurostimulation: PD. This tool, along with several other developments, encouraged Medtronic to pursue regulatory approval for a neurostimulation therapy for PD.

In the mid-1980s at University Hospital in Grenoble, France, a team led by Alim-Louis Benabid was using ablative therapies to treat cases of PD, dystonia and a few psychiatric conditions that had failed to respond to drug-based therapies. The team was one of the specialist centres that had retained the stereotactic tools and skill set developed during the subspecialty's period of growth. For each patient, a stereotactic apparatus was used in conjunction with imaging technologies to identify the areas for ablation and to plan the surgical procedure. Additionally, intra-operative electro-stimulation was used to ensure that the correct area had been located, and like others before him, Benabid noted that higher frequency stimulation could reduce some of the motor symptoms of PD. Benabid set about conducting trials of chronic neurostimulation as a therapy in its own right. Importantly, Benabid and his team had been using neurostimulation to treat chronic pain and were familiar with the equipment and methods that would be required to provide chronic stimulation: 'We had the method. We had the electrodes. We had the stimulating leads' (Benabid, in Talan, 2009: 41). From 1987 onwards, Benabid used Medtronic equipment to conduct trials of DBS of the areas within the thalamus to treat tremor in patients with either PD or essential tremor, some of whom showed complete relief (Benabid et al., 1987). While Benabid and his team were repeating what others had done a decade earlier, a particular conjunction of circumstances meant that his work was to have a far greater influence.

First, Benabid's team coupled DBS to PD at a time when clinicians were looking for a surgical alternative to levodopa-based therapies. Clinicians were becoming aware that while medications such as levodopa are initially effective in managing the symptoms of PD, they lose their effectiveness in the long run. By the mid-1980s, a reservoir of severely affected PD patients with symptoms no longer adequately managed had emerged. Alternative therapies were needed, and neurosurgeons were beginning to revisit pre-levodopa-era stereotactic surgical procedures (Bergman et al., 1990; Laitinen et al., 1992).

Second, the accidental discovery of a neurotoxin led to the production of primate models of PD. The resulting studies enabled Benabid to consolidate particular areas deep within the brain as effective targets for DBS. In two separate incidents (1976 and 1983), recreational drug users inadvertently manufactured and ingested a compound that left them with severe PD-like symptoms. The substance was identified as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and an autopsy later revealed that it had destroyed the dopamine producing cells of the substantia nigra, the same area that degenerates in PD (Porras et al., 2012). Subsequently, MPTP was used to create the first non-human primate models of PD (Chiueh et al., 1984; Langston et al., 1984), enabling new avenues of research into the underlying pathology, research that would have been unethical on afflicted human subjects. One such avenue of research produced a model of a pathological chain of neural activity, in which the STN and the globus pallidus (GPi) are overactive (DeLong, 1990). By surgically ablating these areas, researchers at Johns Hopkins University noted that they could reduce the induced-PD symptoms in primates (Bergman et al., 1990). The STN first had been identified as an effective target in late 1960s (Nashold and Slaughter, 1969), but the resulting model now provided a scientific rationale, prompting Benabid to direct his attention to the area as a target for DBS.

And third, Benabid and his team coupled DBS treatments to PD at a time when the disease could be quantified. In 1987, a consortium of movement specialists established the Movement Disorder Society and produced the Unified Parkinson's Disease Rating Scale (UPDRS). Their intention was to create a comprehensive and flexible system that would replace the numerous and idiosyncratic scales being used at various PD research sites (Fahn and Elton, 1987). The variability of the scales in use at the time made comparative assessments difficult: the unified system would standardise clinical assessment across centres (Goetz et al., 2003). The UPDRS has five parts, each using a scale system to determine the severity of particular PD symptoms, including mentation, behaviour and mood, speech and swallowing, facial expression, tremor at rest, rigidity and finger tapping. For each symptom, a number from 0 to 4 is used to assess severity (0 being normal or unaffected and 4 being the most severe), and an overall score for each of the five parts of the UPDRS can be assigned to the patient. The severity of a patient's PD, therefore, can be represented with a series of numbers. In order to ensure that these numbers are equivalent across contexts, the Movement Disorder Society produced a teaching videotape, specifically designed to aid new researchers and those conducting multi-centre trials (Goetz et al., 1995). The resulting equivalence would enable patients to be compared before and during treatment, across research centres, and would thus permit the calculations required to determine efficacy.

Given the considerable demand for surgical treatments and a tool to quantify PD, it is not surprising that Medtronic enthusiastically aligned themselves with the Grenoble-based French team. In the early 1990s, Benabid presented his results to Medtronic. Engineers at Medtronic had conducted studies to assess the use of their stimulation technology to manage pain, but these were abandoned due to the lack of any definitive results (the findings were eventually published in Coffey, 2001). Benabid's work illustrated that the same technology could be used to treat PD, and that the results could be demonstrated to regulators: 'Changes in movement are pretty obvious … pain is something that is not so obvious' (Medtronic engineer, quoted in Talan, 2009). Subsequently, Benabid was employed by Medtronic to design international (Europe and United States), multi-centre clinical trials assessing DBS for the treatment of PD. The STN or the GPi were to be tested as target areas, both of which were supported by the newly developed model of deep brain function. Medtronic funded the trials, and the UPDRS was used in all sites. Over the next few years, 113 people with PD and 83 with essential tremor were involved in the trials (Talan, 2009).

Clinical trials

In a laboratory trial, complexity is elided by having a few metabolic parameters 'stand in' for health, parameters that can be measured, counted and used in the construction of factual statements (Latour and Woolgar, 1986; Mol, 2008). The UPDRS (like outcome measures in general) enabled the purification and inscription required to 'construct' factual statements regarding the efficacy of DBS. Because the UPDRS was adopted in all the Medtronic's DBS clinical trials, all patients were subjected to the same standardised regimes of examination, quantification and comparison. Each patient, regardless of his or her unique personal history or social context, was rendered as a set of comparable numbers representing the severity of their symptoms.

This quantification and the elision of messy and cumbersome personal detail, therefore, had three important functions. First, it enabled calculation: it permitted each participant to become a nexus linking the DBS technology to a clearly delineated region of the brain in a manner that could be clearly measured: the effect of DBS on particular regions of the brain, the STN or the GPi, could be determined by noting and comparing the numerical changes associated with each body. Second, these numerical renderings of the impaired body are mobile: they can be collected, pooled together, charted, graphed, compared and computed, and these resulting inscriptions can then be circulated as 'proof' or 'evidence', with much more fluidity than fleshy bodies. These mobile numerical inscriptions are also immutable: they hold same meaning across particular centres, enabling the establishment of a common language. Third, as Porter (1994) has made quite clear, by eliding personal detail, such renderings are imbued with an authority resulting from their supposed objectivity. The UPDRS, therefore, was an essential part of an apparatus for producing facts, in an era when 'efficacy' was institutionally deemed something objectively verifiable. In effect, through a process of purification and inscription, the UPDRS created the immutable mobiles that bridged the distance between the point of treatment (the clinic) and the point of assessment (the FDA) that had been created with the advent of medical device regulation.

FDA approval

In March 1997, UPDRS-derived data were presented to the FDA's Neurological Devices Panel Advisory Committee by consultants managing the trials on behalf of Medtronic. The intention was to gain approval for the 'Medtronic 3382 DBS lead and the Medtronic ITREL stimulation system for the suppression of tremor due to essential tremor or Parkinson's disease; unilateral or bilateral' (FDA, 1997). Slides of the results were shown to the panel and explained by a consultant who drew attention to both individual improvements in UPDRS and statistical analyses of overall UPDRS data. He stated that there was a statistically significant reduction in tremor and global disability and that the efficacy of the treatment appeared to be greater than that of available medications. There was more to the panel hearing than the presentation of numerical data, however. A portion of the hearing was reserved for members of the public to voice their opinion. Four individuals spoke to the panel, all in support of the therapy. The testimony of these four speakers highlighted the day-to-day difficulties of living with a movement disorder and the hope and expectations that had been invested in the DBS. Two were representing patient advocacy groups and two were being successfully treated with DBS therapy as part of the clinical trial (three of the four had also been brought to the hearing by Medtronic).

At the end of the hearing, members of the panel expressed their initial impressions. All members believed that the efficacy of DBS had been demonstrated. Some, however, said that they were not convinced of its safety: although no major safety issues had been identified, potential adverse effects could not be ruled out (FDA, 1997). As one member put it, 'unless that side effect slaps you in the face or is quite profound, you may not find subtle effects like the neurological changes' (FDA, 1997). As a result of the panel's findings, the FDA formally approved the use of unilateral DBS for the treatment of essential tremor and PD. For the latter, however, it could only be used in patients with severe

tremor, due to uncertainty regarding possible adverse reactions. Medtronic continued to sponsor trials exploring the longer term effects of stimulation, and in 2002, confident that sufficient evidence of safety had been demonstrated, the FDA approved DBS for more general cases of PD. In 1998, the same clinical trials were used by Medtronic to gain the CE mark for their technology, thus permitting the use of DBS to treat PD within the European Union.

Discussion

Within 10 years of being approved for the market within the United States, over 40,000 individuals had been treated with DBS for PD or essential tremor (Talan, 2009), and DBS had gone from being a marginal therapy to an 'effective', 'standard and accepted treatment for Parkinson's Disease' (Montgomery and Gale, 2008). Currently, PD patients can undergo DBS therapy at specialist centres in North America, Australia, the United Kingdom and much of Europe. In their 2010 annual report, Medtronic highlighted a 9 per cent increase in net revenues from the previous year in their neuromodulation division (from US$1.4 billion to US$1.5 billion), driven largely by a substantial increase in demand for their DBS technology in both Europe and the United States (Medtronic, 2010).

DBS for PD, then, has proven highly lucrative for Medtronic. The company is attempting to replicate some of this success by developing DBS as a treatment for other conditions. While PD is by far the most common DBS indication, a small number of patients have now undergone DBS for the treatment of dystonia, epilepsy, OCD and depression. Again, the flexibility of the technology has enabled it to be easily adapted to other treatments: as one financial analyst recently puts it, 'deep brain stimulation provides [a] stimulating market … because with a single platform, companies can address several diseases with large populations' (Stuart, 2012). In 2003, Medtronic DBS technology was fully approved for the treatment of dystonia within the European Union and partially approved for it within the United States. Like PD, many of the symptoms of severe dystonia are clearly visible: pathogenic neural activity causes limbs to become rigid and bodies to become painfully contorted. The rate of severe dystonia is significantly lower than that of severe PD, and therefore, the resulting trials using Medtronic equipment were smaller in scale. As with PD, standardised clinical assessment tools have been co-opted in order to generate the immutable mobiles necessary to demonstrate efficacy to regulatory agencies. The Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS), like the UPDRS, uses a series of numbers to indicate the severity of symptoms (Burke et al., 1985). Medtronic-sponsored trials assessing DBS for epilepsy and OCD have also adopted clinical assessment tools that produce computable, mobile, impersonal renderings of the patient.

Consequently, neurosurgeons with training in stereotactic techniques are once again gaining access to a pool of patients with conditions inadequately managed with medications. In 1990, stereotactic surgery 'was the realm of a relatively small group of subspecialists' (Gildenberg, 2000: 309). By the end of the 1990s, 'more stereotactic surgery was being practiced by more neurosurgeons than ever before, and stereotactic techniques made inroads to become needed skills for every practicing neurosurgeon' (Gildenberg,

2000: 309). Importantly, diffusion has been driven by an increasing realisation of the limitations of drug-based therapies. As Ackerman points out, neurologists are now far more inclined to recommend surgical therapies to patients. Indeed, in the majority of centres offering DBS, patients are managed by teams that include both a neurosurgeon and a neurologist (Ackerman, 2006: 111).

The development and stabilisation of DBS therapies were contingent upon the co-development and diffusion of standardised methods of rendering the affected body. By eliding complexity and foregrounding specific phenomena as 'significant', a clinical assessment tool and the immutable mobiles they produce can have a commercial utility. This particular case study suggests that this utility has facilitated their diffusion. The UPDRS, for example, has been adopted throughout Europe and North America and is now considered the standard reference scale for PD. Between 1994 and 2003, out of all articles using a PD rating scale, well over two-thirds were using the UPDRS, and the scale was used in most clinical trials of both drug and surgical treatments for PD. Consequently, United States and European regulatory agencies have come to rely on the UPDRS (Goetz et al., 2003: 740). The diffusion of such tools is part of what several authors have referred to as 'rationalisation healthcare', linked to the EBM movement (Hunter, 2003; Porter, 1995; Wehrens and Bal, 2012). Rationalisation has involved a move towards predefined processes aimed at improving efficiency, an emphasis on quantitative over qualitative characteristics, and creating uniformity over multiple sites (Ritzer, 1996). Proponents of EBM are wary of a clinician's experience alone, and argue that clinical practice should be guided by trials that have objectively determined the effects of an intervention. The current rationalisation in healthcare began in the 1980s, driven by attempts to reduce unnecessary interventions and limit healthcare costs and facilitated by the emergence of information technologies (Timmermans and Berg, 2003). This case study suggests that commercial and professional interests have also assisted this process. The emergence of clinical assessment tools and outcome measures, facilitated by companies in alliance with particular health professionals, is an important part of this rationalisation process: they enable 'efficacy' to be verified by a third party; no longer is it a clinician's 'matter of opinion' (Bodewitz et al., 1989).

This case study has also shown that the necessity of clinical assessment tools in the era of regulation can shunt the development and application of a medical device towards a particular therapeutic intervention. In effect, medical device regulation not only restricts which devices can be marketed, it also limits which illnesses can be treated with devices. This was the case with the use of neurostimulation to treat chronic pain. Standardised clinical assessment tools did not exist, and an evidence base for the therapy could not be produced. Consequently, Medtronic directed its resources towards treatments for other conditions. There is therefore a financial incentive for both the medical device industry and pharmaceutical industry to open up new avenues for innovation by promoting the development of standardised clinical assessment tools. In 2002, a consortium of pain specialists held the first meeting as part of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). The aim of the initiative was to develop 'consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain'

(Dworkin et al., 2005). Importantly, the initiative has sought to develop a standardised clinical assessment tool, as the current 'variability in outcome measures across clinical trials hinders evaluations of the efficacy and effectiveness of treatments' (Dworkin et al., 2005). Johnson & Johnson, Pfizer, Bristol-Myers Squibb and Boehringer Ingelheim sponsored the initiative.

Given the importance of clinical assessment tools in creating an evidence base in an era dominated by EBM, and given the commercial and professional interests entwined in such tools, it is necessary to scrutinise their application in research contexts. This is particularly so in relation to expensive, invasive and potentially ethically problematic interventions such as DBS. In the past, proponents of psychosurgery were criticised for damaging brain structures without a firm evidence base demonstrating the efficacy of the intervention (Breggin, 1972). Current clinical trials of DBS as a treatment for depression are using the Hamilton Rating Scale for Depression (HRSD) to generate the necessary evidence (Mayberg et al., 2005; Schlaepfer et al., 2008). Via a process of purification and extraction, a patient's depression is rendered as a number, an immutable mobile. Yet, from within psychiatry, the HRSD has been labelled as sufficiently 'psychometrically and conceptually flawed' that it warrants replacement (Bagby et al., 2004). Thus, while such a tool may generate the necessary 'objective evidence' to legitimate the intervention and enable device manufacturers to market their device, it may not be capturing clinical changes that are meaningful to patients and their families. It may be that DBS offers much-needed relief, but to avoid the errors of past psychosurgery and guard against false promises, it is necessary to ensure that scales reflect the patient's interests and not just those of professionals and manufacturers.

Declaration of conflicting interests

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Author biography

John Gardner is a PhD student at the Centre for Biomedicine and Society at Brunel University, London. His research interests are the dynamics of innovation and social change and the relationship between technology, the body and sociality. In 2010, he was awarded a Wellcome Trust PhD studentship and he is currently undertaking an ethnographic study of a clinical team using deep brain stimulation to treat children with severe motor disorders. John also has an interest in biomedical ethics and is a member of the London and Brighton Translational Ethics Centre (LABTEC).