

Review

My 25 Stimulating Years with DBS in Parkinson's Disease

Marwan Hariz^{a,b,*}

^a*Simon Sainsbury Chair of Functional Neurosurgery, Unit of Functional Neurosurgery, UCL-Institute of Neurology, Queen Square, London, UK*

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Marwan Hariz received the Baccalauréat in Beirut (Lebanon), then studied medicine in Reims (France) and in Umeå (Sweden). He trained in neurosurgery in Umeå with Lauri Laitinen as main mentor. He received a PhD in 1990 in stereotactic neurosurgery. In 2002, he was recruited as Professor to the United Kingdom's first Chair of Functional Neurosurgery at the National Hospital for Neurology and Neurosurgery, and the University College London Institute of Neurology, Queen Square (London, UK), where he contributed to the establishment of a multidisciplinary clinical and academic Unit of Functional Neurosurgery. His main interests are in brain imaging and in surgery for movement disorders and psychiatric illness, as well as in critical appraisal of published literature in these areas.

Abstract. The year 2017 marks the 30th anniversary of the birth of modern deep brain stimulation (DBS), which was introduced by Benabid, Pollak et al. in 1987, initially targeting the motor thalamus to treat tremor, and subsequently targeting the subthalamic nucleus (STN) for treatment of symptoms of advanced Parkinson's disease (PD). STN DBS is undoubtedly "the most important discovery since levodopa", as stated by David Marsden in 1994. In 2014, The Lasker–DeBaakey Clinical Medical Research Award to "honor two scientists who developed deep brain stimulation of the subthalamic nucleus", was bestowed upon Benabid and DeLong. STN DBS remains today the main surgical procedure for PD, due to its effectiveness in ameliorating PD symptoms and because it is the only surgical procedure for PD that allows a radical decrease in medication. Future improvements of DBS include the possibility to deliver a "closed-loop", "on demand" stimulation, as highly preliminary studies suggest that it may improve both axial and appendicular symptoms and reduce side effects such as dysarthria. Even though DBS of the subthalamic nucleus is the main surgical procedure used today for patients with PD, all patients are not suitable for STN DBS; as a functional neurosurgeon performing since more than 25 years various surgical procedures the aim of which is not to save life but to improve the patient's quality of life, I consider that the surgery should be tailored to the patient's individual symptoms and needs, and that its safety is paramount.

Keywords: Parkinson's disease, deep brain stimulation, subthalamic nucleus, globus pallidus, thalamus, quality of life, pallidotomy, stereotactic neurosurgery, safety

*Correspondence to: Prof. Marwan Hariz, Unit of Functional Neurosurgery, Box 146, Institute of Neurology, Queen Square, London, WC1N 3BG, UK. Tel.: +44 7985 642 852; Fax: +44 20 7419 1860; E-mail: m.hariz@ucl.ac.uk.

“I used to wonder years ago when the anxiety, tension, and pain of the decision . . . would disappear. I now know the answer to that question. When? Never – that’s when.”

Irving S. Cooper: *The Vital Probe. My life as a brain surgeon* (1981).

INTRODUCTION

My mentor Lauri Laitinen (1928–2005), – the neurosurgeon from Umeå, Sweden, who pioneered the renaissance of surgery for Parkinson’s disease (PD) in the mid 1980s by resurrecting Leksell’s posteroventral pallidotomy [1] – wrote in 2003, in his last publication pertinent to PD:

“In my opinion, DBS of the subthalamic nucleus represents a most important step of the last decade in the surgical treatment of Parkinson’s disease. We owe a great debt to Professor Alim-Louis Benabid for his intelligence and courage to have begun the implantation of chronic electrodes in the STN” [2].

It was the discovery of Bergman, Wichman and DeLong in 1990 [3] that lesions of the subthalamic nucleus (STN) alleviated experimental parkinsonism in the MPTP monkey model of PD, that paved the way to target that nucleus with high frequency Deep Brain stimulation (DBS) in humans.

The first paper about DBS of the STN (unilateral surgery in one patient) was published in French in 1993 [4] and the second paper describing three patients bilaterally operated was published in the *Lancet* in 1995 [5]. However, already in March 1994, at the 11th Parkinson’s Disease symposium in Rome, Grenoble neurologist Pierre Pollak presented the results of DBS of the STN, including a video of the first patients. The late Professor David Marsden, who was present in the audience, publicly stated then that this was “the most important discovery since levodopa” [6]. The honeymoon had begun, and in some respect, it is still lasting. Here I retrace my 25 years of clinical and academic activity in DBS for PD, highlighting its advantages and its shortfalls, as well as providing a critical appraisal of the pertinent literature on the subject of surgery for PD.

THE EARLY EUPHORIA

2017 marks the 30th birthday anniversary of modern DBS. It was in 1987 that Benabid, Pollak et al. from Grenoble published their seminal paper on thalamic DBS for tremor [7]. This procedure did not

make a dent in the field at that time because it was only directed at the ventral intermediate nucleus (VIM) of the thalamus for treatment of tremor. By contrast, the revival of posteroventral pallidotomy, that happened at roughly the same period, addressed the whole triad of cardinal PD symptoms (bradykinesia, rigidity and tremor) as well as L dopa-induced dyskinesias. Hence, Laitinen’s posteroventral pallidotomy was the main surgical procedure performed and published worldwide in the 1990s [8]. Towards the turn of the millennium STN DBS had gained momentum, and because it could be done bilaterally in one session and was efficient for bradykinesia, rigidity and tremor, and allowed a radical decrease of medications, it almost completely superseded pallidotomy. Initially, there were some reports that STN DBS could even be neuroprotective, but this has unfortunately not been confirmed [9].

Beginning in the early 1990s, I started to perform DBS and gradually shifted from performing mainly ablative surgery (pallidotomy, thalamotomy) towards performing mainly DBS, first Vim DBS for tremor and eventually pallidal and STN DBS for advanced PD. This shift was driven by the widely held view that DBS was non-destructive, adaptable, safe and reversible, and could be done bilaterally in same surgical session [10] (which was not possible in ablative surgery). By the year 2000, some 50–60 patients had had thalamic DBS at Umeå University Hospital, where I was based, and about 12 patients had received pallidal or STN DBS. In 1999, I published one of the first reports describing the development of tolerance to VIM thalamic DBS for tremor and the appearance of severe rebound upon stopping stimulation [11]. In 2000, I published an illustrative case report about one of the first patients of the STN DBS series, who had preoperatively some cognitive decline and speech problems, and in whom there was obvious discrepancy between a striking amelioration of Parkinsonian symptoms and a negative effect on the quality of life due to two side effects of STN DBS: dysarthrophonia and increasing dementia [12]. This was one of the first published reports drawing attention to the risks of bilateral STN DBS on cognition and speech in patients who present preoperatively with symptoms in these domains.

The real and universal breakthrough of DBS in STN and in DBS in the globus pallidus internus (GPi) took place following the publication of the worldwide multicenter trial in the *New England Journal of Medicine* in September 2001, which remains one of the most quoted in the field of DBS [13]. This

was the paper on the basis on which DBS in STN and GPi was approved by the United States Food and Drug Administration. Something that was eyebrow-raising in that paper, was that in Table 5, describing adverse events, the authors mentioned only one single stimulation-induced dysarthria in the 102 bilateral STN DBS patients and zero dysarthria in the 41 bilateral GPi DBS patients. This startlingly low level of side effects enticed me to write a Letter to the Editor pointing out this lapsus and I concluded my letter stating that “Deep-brain stimulation of the basal ganglia is an efficient treatment for Parkinson’s disease, but this method may lose credibility if its side effects are not properly accounted for” [14]. Today, it is undisputed that dysarthria is one of the main side effects of bilateral DBS in the STN, varying between zero and 97% depending on how evaluation is done, when after surgery and depending of course on electrode location in the target area, among other variables [15–18].

STN DBS: SELECTION CRITERIA

In the process of elucidating the best selection criteria for patients for STN DBS, several studies correlated the improvement following surgery to various patient-specific factors. The most notable were papers by Charles et al. from Grenoble [19] and Welter et al. from Salpêtrière in Paris [20] confirming that a good preoperative response to L-dopa, a shorter disease duration, a good cognitive status and a younger age of patients were highly predictive of a good response to STN DBS. Subsequently, reports started to appear about behavioural side effects of DBS such as apathy, depression, mania, marital conflicts, cognitive decline, behavioural changes, etc [21–26], all of which did put further constraints on which patients would be considered eligible for this highly efficient procedure. Despite the stringent selection criteria, several centres only perform STN DBS and do not offer any other surgery if patients do not fulfil criteria for STN DBS. The concept of a surgical procedure tailored to the status and symptoms of the patient, that I introduced in 2000 [27] fell for many years on deaf ears before eventually being recognized and proposed by some authors [15, 28–30], and before the Task Force of the International Movement Disorders Society updated its recommendations in 2013 declaring that both STN DBS, GPi DBS and pallidotomy were evidence-based and approved for surgical treatment of PD [31].

Be it as it may, STN DBS remains today the main surgical procedure for PD, mainly, but not solely, due to its effectiveness in ameliorating PD symptoms and because it is the only surgical procedure for PD that allows a radical decrease in medication even in patients with advanced PD. The well publicized neurological, behavioural, and other side-effects of STN DBS, such as obsessive compulsive disorders, have in fact contributed to better understanding of the pathophysiology and connectivities of the STN and its surrounding area, and has drawn researchers from allied areas such as psychiatry and behaviour to study the role of DBS in these conditions [32].

MICROELECTRODE RECORDING OR NOT?

In a paper from Toulouse published in 2007, the authors evaluated the outcome of microelectrode-guided STN DBS in relation to age of the patients [33]: out of 45 consecutive patients aged 40–73 years, four patients had symptomatic cerebral bleeding of whom two patients, 71 and 69 years old, “experienced cerebral bleeding and died”. Despite this (in my opinion unacceptable) 4.5% surgical mortality, the authors did not deal with what went wrong at surgery. The issue of surgical morbidity and mortality is ever present in the discussion on surgical technique. I have never endorsed the technique of microelectrode recording (MER) in DBS other than as a scientific tool to be used in a research setting on a limited number of patients, with their informed consent, in order to answer specific scientific questions [34]. This is because the available literature demonstrates that repeated penetrations of sharp microelectrodes along several tracks in the brain do indeed increase the surgical risks including haemorrhage, death, pneumocephalus, infections, as well as increasing surgical time and costs [34–38], without providing a measurable better outcome in terms of improved UPDRS scores compared to techniques that do not use MER. A meta-analysis by Zrinzo et al. of all DBS publications with more than 40 patients has shown that MER results in far more haemorrhage than image-guided DBS [38]. Indeed, some of those who were most enthusiastic about MER DBS have now abandoned this technique in favour of image-guided DBS performed in patients either awake or under general anaesthesia [39, 40]. The technique of stereotactic MRI-guided and stereotactic MRI-verified DBS that relies on individual

imaging of the brain target, and individual imaging of the electrode *in situ* postoperatively, that I developed in Sweden in the early 1990s, and introduced to Queen Square 15 years ago [41–44], has resulted in zero surgical mortality in well over 1000 operated patients.

THE “EARLYSTIM” TRIALS

The “logical” conclusion that some have drawn from the fact that younger patients with short disease duration and good response to L-dopa would constitute better candidates for STN DBS, was that STN DBS should be performed at an earlier stage of the disease. Instead of the typical 11–13 years or more of disease duration before STN DBS [45, 46], Shüpbach et al. from Salpêtrière suggested performing surgery after about 7 years of disease, just when complications start to appear. In a report from 2007 [47], they followed 10 patients operated on “early” for 18 months and compared their outcome with 10 patients on best medical treatment. Only the operated patients exhibited improvement in UPDRS motor scores, in dyskinesia scores and in quality of life (QoL), and were able to decrease their daily doses of dopaminergic drugs by 57%. This led to the famous German-French “Earlystim” multicenter in 2013, with 2-year follow up showing better QoL in STN DBS patients than in matched patients receiving best medical treatment [48]. This study generated controversy with editorials and commentaries. The Editor of *Lancet Neurology* asked me to provide an editorial comment, in which I wrote: “There is no doubt that in the short to medium term, patients with Parkinson’s disease who receive surgery will generally experience less severe symptoms than those who remain only on best medical treatment, regardless of disease stage at baseline and even regardless of what kind of surgery they receive (DBS or pallidotomy)” [49]. Given the heterogeneity of PD and also heterogeneity of long term benefit from STN DBS, I also wrote that “We do not know in the long term who will continue to do well and who will exhibit the issues well known to affect patients on long-term STN neurostimulation, such as refractory axial problems (speech, balance, and gait) and cognitive problems.” [49]. I was comforted that my careful attitude towards offering an invasive procedure such as DBS before it is really warranted was supported by neurologists who were the very pioneers of STN DBS [50]

In any case, the “Earlystim” trial, that was successful precisely because it was conducted in highly selective and highly experienced centers, was used widely in Medtronic’s adverts “Medtronic DBS EARLYSTIM” blasting the message “Timing is everything Why wait?”

Even more disturbing is the launch at Vanderbilt University of a pilot trial for STN DBS even earlier in the course of the disease [51]. The authors included 30 patients, 15 to receive DBS and best medical treatment, and 15 to continue on only best medical treatment. Patient selection included a diagnosis of idiopathic PD with a duration of disease of more than 6 months but less than 2 years, a Hoehn & Yahr Stage of II when off medication, and the patients should not exhibit fluctuations or dyskinesias. Two of the DBS operated patients suffered “serious adverse events” including one who was left with a permanent deficit following basal ganglia infarction [51]. Despite that, the authors concluded that their study “met its primary endpoint related to safety, demonstrating that chronic stimulation does not produce greater declines in motor function compared to the control group”. In a Letter to the Editor [52] I wondered whether the rationale for this study was to demonstrate that STN DBS does not make people with PD worse? As a functional neurosurgeon who dreads most of all a complication from my surgery, a surgery-related basal ganglia infarction in one out of 15 operated patients who did not even need surgery in the first place, is simply unacceptable.

STN DBS OR GPI DBS?

Even though STN DBS has been, and still is, the most published surgical procedure for PD, it has been debated whether GPi DBS is equally effective [30, 53]. Proponents of GPi DBS, mostly in the US [15, 54–56], held the belief that it might be more lenient than STN DBS in terms of behavioural side-effects, while maintaining the same efficacy. Since efficacy on motor symptoms has been the main driver for the use of DBS, a multicenter study was designed to test which of the two procedures, STN DBS or GPi DBS, is most efficient for PD motor symptoms. This randomized trial [57] showed that both procedures showed similar results at 2 years, with 25–28% improvement in the off-medication state, rated on the motor part of UPDRS. This surprisingly modest improvement is by any standard suboptimal,

especially for STN DBS, compared to earlier work. Incidentally, this reported 25–28% improvement was in fact very similar to the extent of improvement in randomized studies on unilateral pallidotomy, which was the main surgical procedure for PD in the 1990s [58–60].

GENDER DIFFERENCES IN SURGERY FOR PD

Another issue that caught the attention of our team was the gender distribution of PD patients undergoing surgery. It started by the observation that among all patients operated for PD at Umeå University Hospital since the start of the Neurosurgery department in 1969, men were twice as many as women regardless of surgical procedure (thalamotomy, pallidotomy or DBS). This led to a comprehensive review of the international literature published between January 1985 and February 1999, focusing on gender distribution of PD patients undergoing stereotactic surgery. Regardless of the geographical origin of the publication and the surgical procedure, there were at least twice as many men with PD who had surgery as women [61]. A subsequent further review of more recent literature (2000–2009) limited to STN DBS showed similar results [62].

THE LONG-TERM RESULTS OF DBS

Publications describing long term outcomes of surgery for PD are scarce. In 2001, I published the first report on very long term (10 year) results of pallidotomy [63]. The main conclusion of that paper was: “The long term effect of posteroventral pallidotomy (PVP) on dyskinesias was not only curative but also appeared to be prophylactic. Further progression of axial and akinetic symptoms, and an eventual decline in cognition together with other concomitant illnesses, contributed to increased disability in several patients.” [63]. Indeed several studies have described “striking similarities” between pallidotomy and STN DBS at very long-term follow-up [64] with progress of “axial and akinetic symptoms”, “cognitive decline” and “comorbidities” [65–67]. These were mainly attributed to progress of the disease with appearance of non-dopaminergic features, while DBS still provided good control for other symptoms (see below).

STN DBS CREATES A NEW PHENOTYPE OF PD

Hence, in some patients, long term STN DBS does result in a dissociation between a preserved good effect on symptoms of the upper limbs, especially tremor and rigidity, and a deterioration of axial and akinetic symptoms [67]. While this is not proof that STN DBS postpones later stages of the disease, it suggests that the procedure results in late stage PD patients who do not shake, and who exhibit less rigidity and bradykinesia in the hands, but who experience difficulties with walking, and exhibit freezing episodes, falls, and cognitive decline [65]. This post-STN DBS PD phenotype, that is widely recognized today, was first described by Paul Bejjani et al. in 2008 [68].

FUTURE OF DBS FOR PD

Notwithstanding the current trials using DBS in many areas of Neurology and Psychiatry, PD remains the main indication for DBS. Moreover, DBS will remain the main surgical procedure used in PD patients, for the foreseeable future [32]. Even after 30 years, the debate continues concerning several aspects of DBS in PD. For example, is the STN or GPi the most appropriate brain target? Should surgery be performed early or late in disease? Should one use microelectrode recording during surgery or not? Should DBS surgery be performed with the patient awake or asleep?

New medical device companies have entered the DBS market and new technological advances are being introduced [69]. New DBS leads enabling the current to be directed in a specific direction perpendicular to the axis of the lead, so called directional DBS, are being tested [70–72], with the hope of avoiding side effects by focusing the high frequency stimulation at the brain target aimed at and away from structures adjacent to it, and enabling the shaping the electrical current to “conform” to the anatomy of the target. Rechargeable stimulators are now available with a total battery life reported to be between 9 and 25 years, provided they are recharged regularly. It remains to be seen whether these technological advances will improve the outcome compared to conventional DBS leads, and conventional stimulation.

Perhaps the most exciting advance for the future of DBS in PD will be the ability to provide closed-loop “on demand” stimulation. A delivery of high

frequency electrical current to the brain target, guided by the physiological state of the patient, will enable stimulation to be supplied only when required to “block” the pathological neuronal firing responsible for the cardinal symptoms of the patient. Our group at Queen Square [73], demonstrated that when the typical 130-Hz stimulation is applied in a fluctuating PD patient who happens to be in a good ‘on’ state thanks to medication, the performance on finger tapping scores deteriorates slightly, whereas when that patient is in an off motor state, STN DBS results in improved tapping scores. In other words, STN DBS can negatively interfere with ‘well functioning basal ganglia circuitry’ when the fluctuating patient is in a clinical status that does not ‘need’ DBS at that particular time. The findings of that study suggested that ‘on demand’ DBS, aka “adaptive DBS” (i.e., DBS triggered by the level of pathological local field potential Beta activity) would be a more effective way of delivering stimulation. This theory has subsequently been tested in a collaboration between our group and Peter Brown’s group in Oxford, showing that in the acute phase, during the first few days after surgery when the electrodes are externalised, an adaptive stimulation triggered by the Beta activity of the STN was more efficient than conventional stimulation, and with a 50% reduction in stimulation time and a corresponding reduction in energy requirements [74]. Our further experiments with adaptive DBS showed that it can improve both axial and appendicular symptoms and can track the need for stimulation across drug states [75], as well as reduce side effects such as dysarthria, compared to conventional continuous stimulation [76]. It remains to be seen whether these highly preliminary results, obtained during a short time frame in experimental settings of adaptive stimulation a few days after surgery, will remain valid during chronic DBS and in the long term.

CONCLUSIONS

Despite all its associated problems, STN DBS remains today the main surgical procedure for PD, mainly, but not solely, due to its effectiveness in ameliorating PD symptoms, and because it is the only surgical procedure for PD that allows a radical decrease in medication.

With over 150 000 patients operated on worldwide, DBS, especially DBS in the STN, is by far the most popular surgical procedure for PD. However, it must be kept in mind that the great majority of PD patients

worldwide who would need surgery have no access to DBS. This is mainly due to financial reasons, but also due to the decline of ablative stereotactic surgery such as pallidotomy even though it has been shown that unilateral pallidotomy does not harbour more complications than DBS [77, 78].

DBS for PD is here to stay and it will continue to fascinate scientists and clinicians alike. A PubMed search performed on February 3d, 2017, using the search words “deep brain stimulation” and “Parkinson’s disease” yielded 3731 articles. If “deep brain stimulation” is associated to “subthalamic nucleus”, the PubMed search provides 2992 papers. This is a testimony of the scientific importance of DBS and of the STN, and indeed the 2014 Lasker–DeBakey Clinical Medical Research Award honouring Alim-Louis Benabid and Mahlon DeLong stated explicitly that it was delivered to them to “honor two scientists who developed deep brain stimulation of the subthalamic nucleus”.

Despite the several decades of activity in DBS for PD, many controversies are still not resolved, many developments of the technique are being trialled and many challenges remain. Notwithstanding these, the fundamental issues of PD remain: How to tackle the progress of disease, especially the L-dopa-refractory axial symptoms, affecting speech, gait and balance, and the cognitive decline? In the meantime, the improvement brought by DBS to the quality of life of many patients is beyond doubt, and DBS and other surgical procedures, can be invaluable in treating motor and other symptoms due to the nigrostriatal degeneration, allowing the PD patient to enjoy an extended period of good quality of life.

For me, DBS, especially DBS for PD, represents a happy marriage between neurology and neurosurgery. In 2003 I baptised the child of that marriage: “Interventional Neurology” [8].

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CONFLICT OF INTEREST

The author has received honoraria and travel expenses from the Deep Brain Stimulation industry (Medtronic, StJude, Boston Scientific) for presenting talks at meetings.

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