Title: MRI-Verified "Asleep" Deep Brain Stimulation in Malta Through Cross Border Collaboration: Clinical Outcome of the First Five Years

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ABSTRACT

Introduction: Deep Brain Stimulation (DBS) requires a specialist multidisciplinary approach and lifelong follow-up. Patient access can be a challenge for small nation states. Malta is an island nation with a population of just under 450 000. The number of patients likely to benefit from DBS is around 5 to 10 per year. This study explores the outcome of a cross border collaboration between specialist services at Queen Square, London and a tertiary centre in Malta.

Material and methods*:* Between 2011 and 2015, 35 patients underwent MRI-Guided and MRI-Verified DBS with 29 receiving bilateral subthalamic nucleus (STN) DBS for Parkinson's Disease under general anaesthesia. Pre-operative motor function was compared with one year post-operative motor function assessments in 26 patients (16 male; age 60 ± 9, range 32-70; disease duration 8.8 ± 2.7). Pre-operative and post-operative quality of life scores were also completed in 24 patients.

Results: There was significant improvement in off-medication Unified Parkinson's Disease Rating Scale (UPDRS) III motor function (41.7%), reduction in Levodopa Equivalent Dose (LED) (30.6%) and improvement in quality of life as measured by the Parkinson's Disease Questionnaire (PDQ-39) (52.3%) ($p<0.001$). All PDQ-39 dimensions showed significant improvement except communication, with greatest benefit in activities of daily living (ADLs) (72.4%) and stigma (66.3%). Surgical complications did not lead to any permanent deficit. Patients receiving DBS to other targets and for different indications also benefitted from surgery.

Conclusion: An MRI-guided and MRI-verified approach to DBS was successfully implemented through cross border collaboration with achievement of expected clinical results. This healthcare collaboration developed out of necessity and opportunity, taking advantage of a UK-based neurosurgeon from Malta. The UK healthcare system benefits from numerous immigrants at Consultant level. Such a mutually beneficial arrangement could enable such individuals to offer their expertise to citizens in the UK as well as their country of origin.

Key words: Deep Brain Stimulation, cross border collaboration, UPDRS III, quality of life, PDQ-39, Malta

INTRODUCTION

Deep Brain Stimulation (DBS) is an established procedure for the symptomatic treatment of Parkinson's Disease. Surgical treatments for Parkinson's Disease were developed before the introduction of levodopa [1] and later re-emerged to overcome difficulties of motor fluctuations with medical treatment. Stereotactic ablation of various Central Nervous System (CNS) targets for movement disorders are effective [2] but carry a relatively high risk of axial side effects when performed bilaterally. Deep brain stimulation offers an adjustable and reversible alternative that carries less risk of permanent side effects, especially when performed bilaterally. Globus Pallidus internus (GPi) DBS was successfully introduced for the management of bradykinesia and rigidity. [3] After the discovery of the key part played by the Subthalamic Nucleus (STN) hyperactivity in the pathophysiology of Parkinson's Disease, the first experiences of STN DBS highlighted that the STN could become the target of choice for DBS in Parkinson's Disease. [4] The pioneers of STN DBS used microelectrode recording and microstimulation to verify final lead location and many centres still follow this traditional approach to DBS. [5] However, other centres have developed image-guided and image-verified techniques to confirm accurate lead placement during surgery. [6,7,8]

Whichever surgical technique is employed, optimal results require collaboration between high specialised individuals that form a multidisciplinary team including functional neurosurgeon, specialist movement disorder neurologist, neurophysiologist, MR physicist, neuroradiologist, neuropsychologist, specialist nurses and other healthcare professionals. Patient access to such specialised teams can be a challenge for remote communities or small nation states since the required expertise cannot be acquired from the relatively small numbers of patients.

Malta is a small island nation in the middle of the Mediterranean Sea with a population of just under 450 000. Neurosurgical services are currently provided by two consultant (attending) general neurosurgeons supported by visiting super-specialists or referrals abroad when required. There are four consultant neurologists, two with extensive experience in the management of movement disorders. The number of patients likely to benefit from DBS was envisaged to be around 5 to 10 per year. Such small numbers make it impossible for a neurosurgeon to develop or maintain the required skill set. Possible solutions were to refer such patients abroad for treatment or to train local supporting staff and arrange for a Visiting Consultant Neurosurgeon. DBS was introduced as a new service in Mater Dei Hospital in Malta in 2011 through a cross border collaboration between specialist services at Queen Square, London and Mater Dei Hospital, a tertiary centre in Malta. [9] This review of the first five years of this programme allowed an assessment of the clinical outcomes of this service.

METHODS

New service

The introduction of DBS to Malta as a new service was possible after the request and approval of the national healthcare authorities. Equipment that allowed an MRI-guided and MRI-verified approach was purchased and financial approval obtained for the procurement of implantable hardware for around 5-10 patients per year. Training was also provided for the local neurology and operating theatre staff at the London centre.

Study Design

A non-blinded technique was used for clinical assessments with all data being collected prospectively and analysed retrospectively.

Patients

Patients in the Maltese health care system referred for consideration of DBS were assessed preoperatively by the local neurologists. Patients diagnosed with Parkinson's Disease and disabling motor fluctuations on medical therapy underwent formal Levodopa Challenge tests with Unified Parkinson's Disease Rating Scale (UPDRS) scores off medication and then on medication with the equivalent of one and a half times their usual dose of levodopa. Magnetic Resonance Imaging (MRI) of the brain was performed in all patients. Neuropsychological assessment was carried to exclude patients with significant cognitive impairment or psychiatric issues. Quality of life (QOL) was assessed using the Parkinson's Disease Questionnaire (PDQ-39).

Patient selection was finalised through a joint multi-disciplinary clinic involving the local neurologist (JA) and psychologist and the visiting neurosurgeon from the Unit of Functional Neurosurgery at the National Hospital for Neurology and Neurosurgery in London (LZ). Surgeries were subsequently performed by the visiting neurosurgeon using an MRI-guided and MRI-verified technique under general anaesthesia without the use of microelectrode recording. [8] Subsequent adjustment of medication and optimisation of stimulation was carried out post-operatively by the local neurology team.

Patients with a diagnosis of Parkinson's Disease selected for Deep Brain Stimulation who have been operated in Mater Dei Hospital between 2011 and 2015 with Bilateral STN DBS underwent the following clinical assessments:

1. Unified Parkinson's Disease Rating Scale (UPDRS)
    a. Pre-operative
        i. off medication
    b. after levodopa challengeOne year post-operative UPDRS:
        i. off medication/off stimulation
        ii. off medication/on stimulation
        iii. on medication/off stimulation
        iv. on medication/on stimulation
2. Parkinson's Disease Questionnaire (PDQ-39)
    a. Pre-operative
    b. One year post-operative
3. Complications and adverse events

Twenty-nine patients with Parkinson's Disease underwent bilateral STN DBS between July 2011 and August 2015 at Mater Dei Hospital. Out of these, 26 patients were assessed at one year with UPDRS III scores and 24 with the Parkinson's Disease Questionnaire-39 (PDQ-39). The other 3 patients failed to attend the one year follow up formal assessment scores and were not included in the study.

In addition, three patients with Parkinson's Disease received bilateral GPi DBS, 1 patient with PD received bilateral thalamic ventralis intermediate nucleus (Vim) DBS as a staged

procedure, 1 patient with Primary Generalised Dystonia received bilateral GPi DBS and 1 patient with Holmes Tremor received unilateral Vim DBS, bringing the total of patients having surgery in this period to 35. These patients were not included in the study despite positive results because of the small numbers in each group. All data from the assessment scores was recorded in a database. Table 1 gives a summary of the indications for surgery and the sites targeted for DBS.

Surgical procedure and stimulation programming

Implantation of bilateral quadripolar DBS electrodes (3389 Medtronic Minneapolis, MN) was performed under general anaesthesia using the Leksell G frame (Elekta Instruments, Sweden) and an MRI-guided and MRI-verified technique. Stereotactic T2-weighted MRI sequences (GE Healthcare Signa, 1.5T) were used to visualise the STN and targeting was performed on planning software (Medtronic). Immediate post-op MRI was obtained in all patients to assess correct lead placement. (Figure 1) One patient underwent immediate re-positioning of one lead with satisfactory placement following repositioning. Final lead location was within 1.5mm of the intended target in all patients. All pulse generators (Activa PC or SC) were implanted in the subclavicular area except one which was implanted intra-abdominally at the patient's request for cosmetic reasons. Stimulation commenced in the first few days post-operatively and adjusted after a formal ranking process was carried out in the subsequent weeks. Stimulation settings were adjusted longitudinally according to clinical response. The visiting stereotactic functional neurosurgeon provided guidance in the initial patients. However, with increasing experience, the local neurologist now oversees this role. Table 2 shows the stimulation parameters at one year after surgery.

Statistical Analysis

Data were analysed using SPSS statistical package (SPSS, V20.0, Chicago, Illinois, USA). Data was first checked for normality using Kolmogrov-Smirnov and Shapiro-Wilk analysis. Normally distributed data comparing pre- and post-op scores were analysed using a paired student t-test. All outcomes are presented as mean ± standard deviation. Significance was set at p values less than 0.05.

RESULTS

A full data set for pre-operative and one year post-operative UPDRS III was available for 26 of the 29 patients with Parkinson's Disease who underwent bilateral STN DBS. Table 3 shows a summary of the baseline demographic characteristics for these 26 patients. In the three patients who defaulted to follow up of planned UPDRS III, routine follow up visits documented meaningful clinical improvement. Of these 26 patients, 24 also completed their pre-operative and one year post-operative PDQ-39.

Motor Outcomes

UPDRS-III scores in the off-medication-on-stimulation assessment showed significant improvement at one year after STN DBS as compared to off-medication baseline scores (mean difference 22.2 ± 16.2 $p<0.001$). This represents an improvement in motor scores of 41.7%. When comparing on-medication scores pre-operatively to on-medication-on-stimulation scores at one year, there was no significant difference (mean difference 2.0 ± 10.7 $p=0.39$).

Levodopa Equivalent Dose (LED)

LED decreased by 30.6% at one year post-STN DBS implantation (from 863 ± 211 to 599 ± 273 $p<0.001$).

Parkinson's Disease Questionnaire (PDQ-39)

Quality of life score PDQ-39 showed significant improvement at one year after implantation (from 37.5 ± 14.7 to 17.9 ± 9.5 $p<0.001$) showing a 52.3% improvement over baseline scores. Table 4 shows a summary of the results of STN DBS on the UPDRS III on and off medication, on the Levodopa equivalent dose reduction and on the PDQ-39

Sub analysis of Dimensions of the PDQ-39

Results from the PDQ-39 were further analysed to measure the improvement in quality of life in the eight different dimensions of mobility, activities of daily living (ADLs), emotional well-being, stigma, social support, cognition, communication and bodily discomfort. **S**ignificant improvement ($p<0.05$) was observed in all dimensions except communication. Greatest benefit was observed in ADLs and stigma as well as in social support, emotional well-being and mobility in that order.

Adverse Events

Surgery related complications were limited to two patients. The patient who underwent bilateral GPi DBS for Primary Generalised Dystonia suffered seizures secondary to infection

with Methicillin-Resistant-Staph-Aureus (MRSA). Removal of hardware, antibiotic treatment and re-implantation of a new DBS system a year later was followed by significant improvement in dystonia and quality of life. The second patient underwent bilateral STN DBS for Parkinson's disease presented with hypoxia secondary to a pulmonary embolism a week after surgery. Anticoagulation with heparin was followed by left facial paresis and pyramidal drift secondary to delayed haemorrhage along the right intracranial lead manifested. The haemorrhage resolved completely with no residual neurological deficit and good outcome in PD motor scores at 1-year post surgery.

After bilateral STN DBS some patients experienced other issues. In the short term, one patient suffered transient hypomania which improved after altering stimulation parameters. Another patient developed hyper-sexuality and compulsive gambling immediately after surgery. A third patient complained of intractable Restless Leg Syndrome which was present prior to surgery but seemed to worsen after surgery.

The single death was in a patient who had received bilateral GPi DBS a year earlier after a 20-year history of motor symptoms of PD. Dyskinesias improved significantly following surgery however, she suffered significant cognitive decline with visual hallucinations and psychosis in her last months. Table 6 shows a summary of these complications and adverse events.

DISCUSSION

This small study assesses the implementation of a cross border collaboration with delivery of a specialist DBS service using an asleep MRI-guided and MRI-verified approach. The data demonstrate statistically significant improvement in off-medication UPDRS III motor scores

at one year post-surgery in patients receiving bilateral STN DBS for Parkinson's Disease. Similarly, there was a statistically significant reduction in the Levodopa equivalent dose of medication post-surgery as well as improved quality of life using the PDQ-39. The non-significance in p value (0.39) for the on-medication UPDRS III motor scores pre- and post-surgery reflects the reality that STN DBS tends to improve the quality and reduce the duration of the off-medication state.

Clinical outcome

Overall, clinical outcomes were in keeping with the expected results after STN DBS in the literature. Data from the collaborating London centre document a mean improvement scores of 52% in the off-medication UPDRS III motor scores and an 18% improvement in PDQ-39 at one year. The Levodopa equivalent dose at follow up was reduced by a mean of 39%. [10]

One meta-analysis of open label studies of 21 patient populations showed a mean improvement of 52% in UPDRS III and 34.5% in PDQ-39 after STN DBS, with a 55.9% reduction in LED. [11] In other meta-analysis there was an improvement of 54% in UPDRS III motor scores at a median of 6-months post-surgery and 56% 1-year after surgery, with reduction of LED reported to be 52% after surgery. [12,13] Two large randomised control trials evaluated outcomes at 6-months post-surgery. One reports 41% mean improvement in off-medication UPDRS III motor scores of and 25% in the PDQ-39. [14] The second trial reports 29% improvement in motor scores. [15]

Sub analysis of the PDQ-39 dimensions in other meta-analysis [11] also showed significant improvement particularly in stigma (54.4% ± 18.1%), activities of daily living (51.6% ±18.2%), mobility (38.5% ± 18.2%) and bodily discomfort (35.8% ± 15.4%).

To our knowledge, this is the first study to provide PDQ-39 data 1-year after MRI-guided MRI-verified STN DBS under general anaesthesia. Although numerous studies provide PDQ-39 data following STN DBS, relatively few provide both UPDRS III and PDQ-39 data at baseline and at 12-months follow-up. The results from the literature are summarised in Table 7 and Figure 2. Together, these studies suggest that there is no simple correlation between percentage improvement in motor scores and quality of life scores. Indeed, many other factors are at play including gender (females tend to enjoy greater improvement in PDQ-39) [16] and non-motor factors such as apathy. [17] Differences in patient population may account for such discrepancies. For example, comparing the Malta with the London patient cohorts reveals a shorter disease duration (8.8 ± 2.7 vs. 13.4 ± 7.0 years) with less severe baseline disease (UPDRS III scores of 45.9 ± 14.3 vs. 51.5 ± 14.9). [18] Other medical comorbidities, such as arthritis, may limit improvement in quality of life in individual patients, despite significant improvement in the motor symptoms of Parkinson's disease.

Adverse events

Significant morbidity in the immediate post-operative period was limited to two patients in this study. Scrupulous pre-operative screening and microbial eradication where necessary has been implemented following this to minimise the risk of further infections. The patient who suffered a pulmonary embolism and delayed haemorrhage around the left DBS lead following treatment with heparin had severe off periods preoperatively. In retrospect, she had clearly been

immobile during long off periods prior to surgery. She recovered fully with good benefit on motor scores and quality of life with DBS. Subsequently we have emphasized the importance of maximising mobility as far as possible in the immediate pre-operative period despite dopamine agonist dose reduction as well as the use of elastic and pneumatic compression stockings in the perioperative period.

The patient who developed hyper-sexuality and compulsive gambling after the surgery only presented several months after the surgery. Such impulse control disorders (ICDs) are a known complication of Parkinson's Disease therapies, possibly due to overstimulation of the mesolimbic system by dopaminergic medication. Although there are reports of specific ICDs developing after DBS, by allowing a decrease in dopaminergic medication ICDs are now be viewed as an indication for STN DBS. [30]

Withdrawal of dopamine medication because of visual hallucinations in the patient with intractable Restless Leg Syndrome (RLS) may have led to the exacerbation of symptoms, a phenomenon that has been documented in other reports. [31, 32] However, other studies have concluded that STN DBS can reduce the severity of concomitant RLS. [33]

Target selection

Although the STN was the most commonly chosen target for deep brain stimulation for Parkinson's Disease in Malta during the first five years, a different target was chosen in a select few. Three patients underwent Globus Pallidus internus (GPi) DBS. One was an elderly patient aged 73 years with a long history of Parkinson's Disease and disabled by severe dyskinesias. A second patient, aged 60 years was troubled by dyskinesias, even on low doses of medication.

The third patient, aged 68 years suffered from medication resistant tremors and marked dystonia of the face and right hand. A fourth patient with Parkinson's Disease received staged thalamic ventralis intermedius nucleus (Vim) stimulation for tremor predominant PD effecting the head and jaw.

The outcome was generally satisfactory with an improvement in motor function in all these patients. The two patients with dyskinesias had immediate resolution of these symptoms. The elderly patient did however eventually develop severe visual hallucinations which did not resolve despite withdrawal of dopamine agonists followed by rapid cognitive decline until she passed away a year later. The patient with severe tremors responded well to bilateral GPi stimulation although there was little improvement in facial dystonia with blepharospasm as well as severe dystonia of his left forearm muscles. Botox injection helped the blepharospasm. The patient with Vim stimulation responded well with marked improvement of head and jaw tremor. A staged approach to this target was adopted to limit deterioration in speech, gait and balance. Two years from surgery she has been prescribed low doses of levodopa and dopamine agonist for onset of rigidity and bradykinesia.

Other indications included in the first years of our functional neurosurgery programme were one patient with Primary Generalised Dystonia who received bilateral GPi DBS and one patient with left Holmes Tremor from a right subthalamic infarct sustained in early childhood. Both patients experienced improvement with a marked improvement of quality of life. The patient with Primary Generalised Dystonia that was crippling mobility to such an extent that she required institutionalisation now has an upright posture, normal mobility and lives independently with her new partner. The patient with Holmes Tremor is in gainful employment and is satisfied with the improvement in symptoms.

Logistical issues

With the surgical approach adopted, a stereotactic MRI is required prior to surgery and after lead implantation. However, surgery is performed in a traditional operating room, the patient being transported between the MRI suit and the operating room by the anaesthetic team. Time invested in optimising MRI sequences means that imaging can be obtained in 20 min with minimal detraction from other MRI activities. Even hospitals with stretched resources and busy MRI schedules can accommodate this approach. Indeed, DBS was introduced to Malta at a time when there was only one MRI machine within the Maltese Department of Health. It would not have been possible to accommodate DBS if the whole procedure had to be performed in the MRI suite as required by other MRI-verified approaches. [34]

Implementing an MRI-guided and MRI-verified approach requires the availability of a stereotactic frame and the engagement of a functional neurosurgeon who is well-versed in the technique, a neurologist with an interest in movement disorders and the desire to learn new skills pertaining to patient selection and management of patients after DBS, as well as the collaboration of a local MRI physicist to optimise imaging and supervise MRI safety. However, it does not require the additional expertise of a neurophysiologist or the extensive equipment required to perform microelectrode recording that can elevate the cost of the procedure from 187 to 359%. [35]

Cross border collaboration

In 2006, class I evidence became available that confirmed the efficacy of DBS in patients with dystonia and with severe motor complications of PD. [36,37] Maltese patients and physicians approached the Maltese Department of Health to enquire how they could gain access to this treatment. One solution was to refer patients for treatment at a specialised centre abroad. However, another possible solution became apparent and the Department of Health approached a Maltese National who had specialised in Functional Neurosurgery in London (LZ). He was employed as a Visiting Consultant on a sessional basis during his personal time to support a DBS service delivered in Malta. This was clearly preferable for Maltese patients and their families, was less costly for the Malta Department of Health and placed less burden on the already stretched UK NHS service.

The introduction of a functional service led to a number of "knock-on" effects. For example, the purchase of Malta's first stereotactic frame enabled the local neurosurgeons to perform stereotactic biopsies. Electronic links between Malta and London were developed to allow image transfer and timely discussion of challenging patients. Other highly specialised neurosurgical services were introduced with pituitary and skull base surgeons visiting Malta from London once or twice a year.

Clearly, this model is not suited to all areas of medicine and may not work in all countries. The Maltese healthcare system is modelled on the UK NHS. Functional neurosurgery is an elective speciality and patients can "wait" for yearly clinics and surgical procedures. However, many foreign nationals pursue postgraduate training and are eventually appointed to consultant posts in the UK. Such individuals can serve as a bridge between different countries with minimal cultural and language barriers and their expertise could benefit the citizens of their country of origin as well as those of their adopted home.

Limitations

Our study was limited by the small number of patients, although dropout rate was low. The UPDRS III scoring was performed by 3 examiners, all experienced in performing UPDRS scoring. The PDQ-39 questionnaires were conducted in English since there is no validated Maltese version. In some cases, where English was not the first language, help was required from the physician for the questionnaire to be completed.

CONCLUSION

The MRI-guided and MRI-Verified approach to DBS surgery under general anaesthesia is a cost effective and patient-friendly method that appears to deliver equivalent clinical results to more traditional methods and is associated with a lower risk of haemorrhage leading to death or disability. [18] This approach to DBS was successfully introduced to Malta through an on-going cross border collaboration between an experienced London centre and the Maltese tertiary health service. Bilateral STN DBS in carefully selected patients with Parkinson's Disease provided benefit in both motor function and quality of life. Patients receiving DBS treatment with CNS targets other than the STN and for movement disorders other than Parkinson's Disease, also showed substantial improvement.

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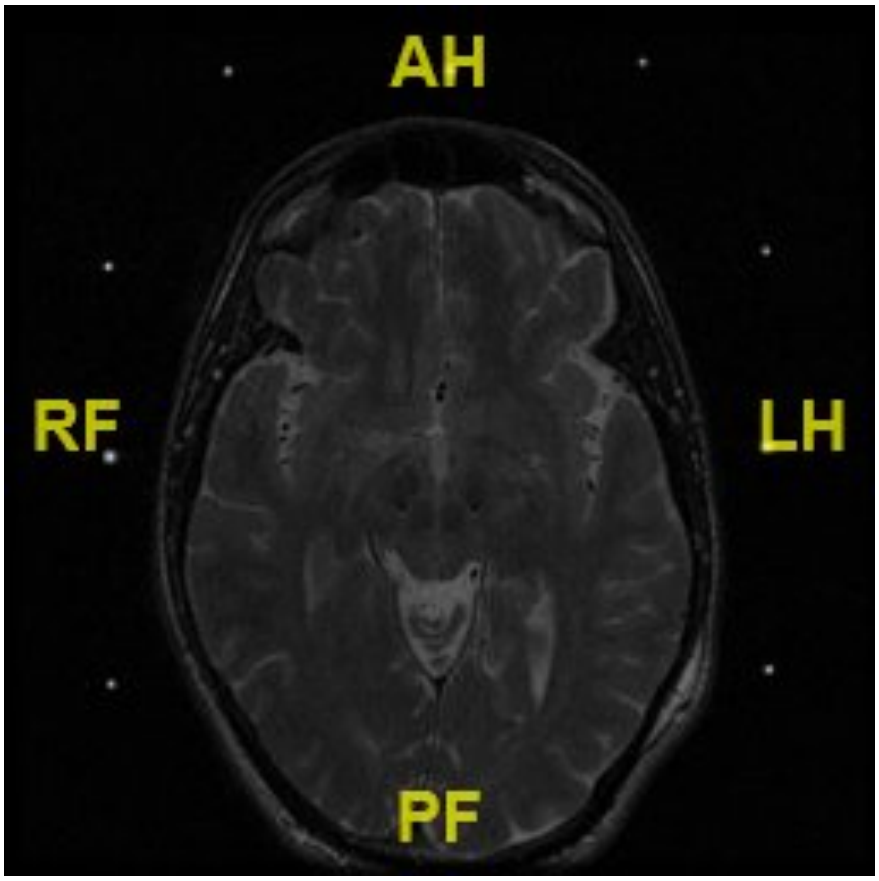
Figure 1: MRI verification of lead placement in STN bilaterally in one of our patients



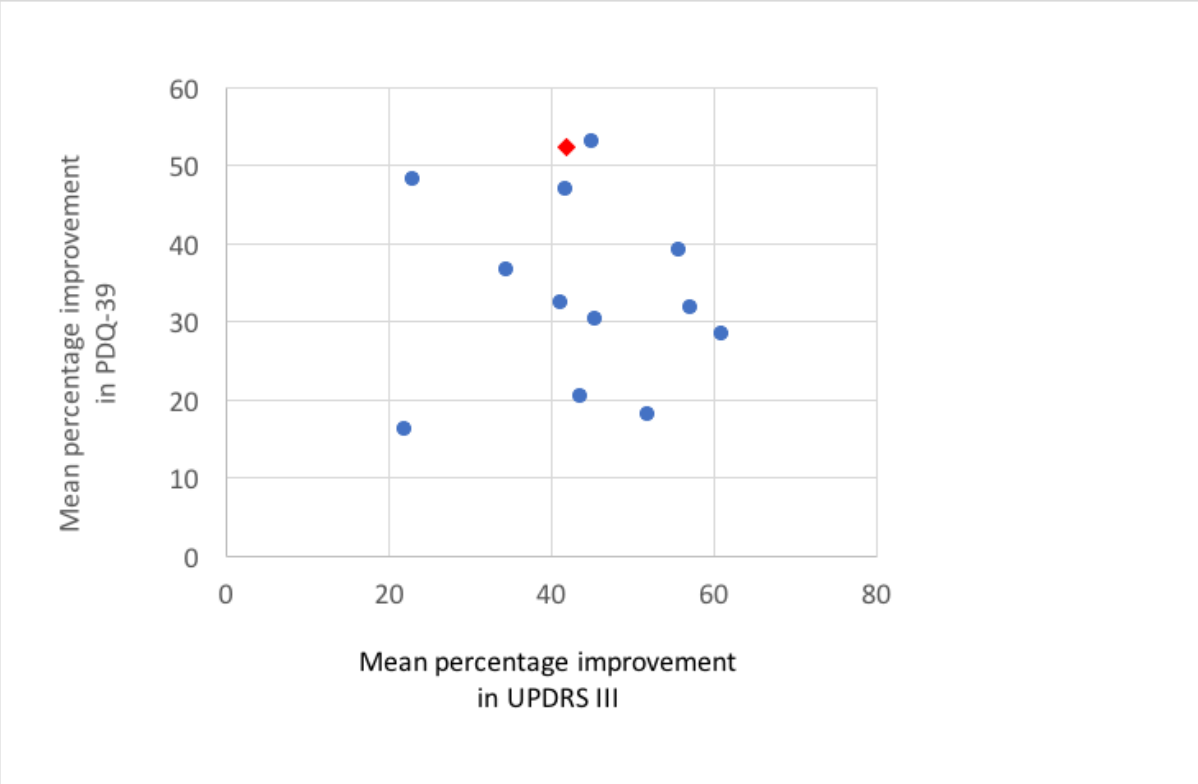


Figure 2: Studies presented in Table 6 with percentage improvement in PDQ-39 plotted against percentage improvement in UPDRS III. Current study marked by red diamond shaped data point.

Table 1: Indications for surgery and sites targeted for DBS			
Indication	**STN DBS**	**GPi DBS**	**Vim DBS**
Parkinson's Disease	**29**	**3**	**1**
Primary Generalised Dystonia	**0**	**1**	**0**
Holmes Tremor	**0**	**0**	**1**

Table1: Summary of the indications for surgery and sites targeted for DBS.

Table 2	**Left STN Voltage**	**Right STN Voltage**	**Left STN Pulse Width**	**Right STN Pulse Width**	**Frequency**
Mean ±SD	2.81±0.70	2.81±0.52	66.9±12.9	64.6±11.0	105.8±28.6

Table 2: shows the mean ± SD of the stimulation parameters at one year after surgery

Table 3: Baseline Characteristics (n=26)	
Gender	16 males, 10 females
Age at motor symptom onset (mean±SD), range	51.0 ± 10.3 (23.0-62.0)
Age at surgery (mean±SD), range	60.2 ± 9.3 (32-70)
Disease duration (mean±SD), range	8.8 ± 2.7 (4.0-15.0)
Levodopa Equivalent Dose (mean ±SD)	863 ± 211

Table 3: Summary of the baseline demographic characteristics for the 26 patients included in the study.

Table 4: Effects of STN DBS on UPRS III on and off medication, LED, PDQ-39					
Mean ± SD	**Baseline pre-op**	**1 year post-op**	**Mean difference**	**p-value**	**Percentage Improvement**
OFF med (n=26)	45.9 ±14.3	26.7±11.5	22.2 ±16.2	<0.001	41.7%
ON med (n=26)	19.5±12.2	17.5±8.8	2.0±10.7	0.39	
LED (n=26)	863 ±211	599 ±273	264 ±277	<0.001	30.6%
PDQ-39 (n=24)	37.5±14.7	17.9±9.5	19.6±15.6	<0.001	52.3%

Table 4: Summary of the results of the effects of STN DBS on UPDRS III on and off medication, LED dose reduction, PDQ-39

Table 5: PDQ-39 Sub analysis of Dimensions					
Mean ±SD (n=24)	**Baseline pre-op**	**1 year post-op**	**Mean difference**	**p-value**	**Percentage Improvement**
Mobility	60.5±22.9	28.9±20.2	31.7±33.2	<0.001	52.3%
ADLs	50.8±26.2	14.0±13.2	36.8±27.4	<0.001	72.4%
Emotional Well-Being	38±19.7	17.7±17.3	20.3±19.4	<0.001	53.4%
Stigma	38.8±27.6	13.1±17.5	25.7±21.4	<0.001	66.3%
Social Support	16.3±22.3	7.2±12.4	9.0±18.0	0.022	55.9%
Cognition	27.9±21.8	16.1±15.6	11.7±21.5	0.014	42.3%
Communication	29.8±25.5	21.8±19.3	8.0±26.9	0.160	26.9%
Bodily Discomfort	32.6±25.2	19.2±16.8	13.4±23.9	0.012	41.1%

Table 5: Summary of the results from sub analysis of the eight dimensions of PDQ-39

Table 6: Complications and adverse events			
	STN DBS	**GPi DBS**	**Vim DBS**
Haemorrhage resulting in permanent neurological deficit	0	0	0
Haemorrhage resulting in transient neurological deficit	1*	0	0
Asymptomatic haemorrhage	0	0	0
Infection	0	1**	0
Seizures	0	1**	0
Pulmonary embolus	1*	0	0
Pneumonia	1*	0	0
Hard ware malfunction	0	0	0
Transient hypomania	1	0	0
Impulse control disorder	1	0	0
Restless legs syndrome	1	0	0
Cognitive decline and death	0	1	0

Table 6: Summary of adverse events that occurred in 6 of the 35 patients receiving DBS surgery during the five-year period.

* Complications occurred in a single patient

** Complications occurred in the same patient

Table 7: Studies showing mean percentage improvement in UPDRS III and PDQ-39				
Year	**No. of patients**	**Mean percentage improvement in UPDRS III**	**Mean percentage improvement in PDQ-39**	**Surgical approa**
2017	24	41.7	52.3	MRI, asleep
2016	18	57.1	31.8	MER, awake
2016	64	34.6	36.5	MER, awake
2015	25	43.6	20.4	Not reported
2015	25	23	48.2	Not reported
2014	16	45.5	30.2	MER awake
2012	74	55.8	39.2	Not reported
2011	49	52	18	MRI, asleep / awake
2011	24	41.8	46.9	MER awake
2005	59	41.2	32.3	MER awake
2005	27	21.9	16.2	Ventriculography, Mac awake
2004	14	45	53	MER awake
2003	16	61	28.3	MRI awake

Table 7: Summary of studies providing both UPDRS III and PDQ-39 data at baseline and at 12-months follow-up. [10, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29]