Imperial College London

MRC Medical Research Council

PhD Thesis

Effects of pedunculopontine nucleus deep brain stimulation in reducing falls, improving gait and postural control in Parkinson's disease

M Jawad Naushahi
MRC Clinical Research Fellow in Functional Neurosurgery

CID: 00607559
E-mail: m.naushahi@imperial.ac.uk
Web: http://www1.imperial.ac.uk/medicine/people/m.naushahi/



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Acknowledgements

In the borrowed terms of many of my predecessors…

This thesis is dedicated to:

"My teachers and seniors, past, present and future, in particular Dip Nandi, Peter Bain & Adolfo Bronstein, who have inspired and guided me;

my colleagues, students and juniors, who keep me intrigued;

and, above all, my loving wife, Nelofer, and children, Ayesha, Bilal, Haroon & Ariana, who continue to put-up with me!"

Declarations

This thesis is my own original work and all material contained herein has been duly acknowledged.

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Abbreviations

ADL – Activity of Daily Living

CT – Computed Tomography

DBS – Deep Brain Stimulation

DTI – Diffusion-Tensor Imaging

DWI – Diffusion-Weighted Imaging

GABA – Gamma Amino Butyric Acid

GPe – Globus Pallidus Externus

GPi – Globus Pallidus Internus

MPTP – 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MRI – Magnetic Resonance Imaging

PET – Positron Emission Tomography

PD – Parkinson's Disease

PDT – Probabilistic Diffusion Tractography

PPN – Pedunculopontine Nucleus

SNc – Substantia Nigra Pars Compacta

SNr – Substantia Nigra Pars Reticulata

STN – Subthalamic Nucleus

UPDRS – Unified Parkinson Disease Rating Scale

Vim – Ventral Intermediate Nucleus

Abstract

Keywords: deep brain stimulation (DBS), subthalamic nucleus (STN), pedunculopontine nucleus (PPN), Parkinson's disease (PD)

Objective: To determine the advantage of bilateral PPN-DBS in reducing falls, improving gait and postural control in patients with advanced PD.

Background: In recent years, PPN-DBS has been explored to address the axial motor symptoms of gait freezing and loss of postural control (adding to tremor, rigidity and bradykinesia as drivers of disease burden in advanced PD). However, the role of PPN-DBS remains unclear.

Methods: A prospective, four-phase, within-subject cross-over, double-blinded study where bilateral STN (Med. 3389) and PPN-DBS (Med. 3387) electrodes were implanted in six patients with advanced PD and axial motor symptoms while on optimal medical therapy. The primary endpoint was the reduction in falls and improvement in gait. Performance was recorded on optimal medical therapy only (open-label phase), bilateral STN or PPN-DBS and simultaneous bilateral STN & PPN-DBS (ALL neurostimulation in conjunction with optimal medical therapy; 6-months each). The study received local ethics approval and informed written consent was obtained from all patients.

Results: There was 100% decrease (Wilcoxon signed-ranks test; $p < 0.05$) in ICNG Index (falls / 1000 steps) with simultaneous bilateral STN (at 2.6 ± 0.2 V, 140 Hz, 60 μs) & PPN-DBS (at 1.5 ± 0.2 V, 20 Hz, 60 μs) in conjunction with optimal medical therapy compared to optimal medical therapy only. PPN-DBS was generally well tolerated and only induced momentary ipsilateral oscillopsia at commencement on ≥ 2.0 V with rapid habituation, consistent with previous findings. No other complications were reported with PPN-DBS.

Conclusion: In appropriately selected patients, simultaneous bilateral STN & PPN-DBS, in conjunction with optimal medical therapy, targeting the mid-lower PPN with the aid of DWI / DTI scans with PDT analysis and resultant saccadic modulation coupled with performance changes in the relevant axial motor segments, offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD. DWI / DTI scans with PDT analysis of the PPN region may be used as a pre-operative tool to localise the electrode placement site, and they may also be useful as a post-operative tool to reassess electrode position.

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Chapter 1

Pedunculopontine Nucleus-Deep Brain Stimulation Trial

Keywords: deep brain stimulation (DBS), subthalamic nucleus (STN), pedunculopontine nucleus (PPN), Parkinson's disease (PD)

ABSTRACT

Objective: To determine the advantage of bilateral PPN-DBS in reducing falls, improving gait and postural control in patients with advanced PD.

Background: STN-DBS has been in routine use in the treatment of patients with advanced PD, refractory to medical therapy. In recent years, PPN-DBS has been explored to address the axial motor symptoms of gait freezing and loss of postural control (adding to tremor, rigidity and bradykinesia as drivers of disease burden in advanced PD). However, the role of PPN-DBS remains unclear.

Methods: A prospective, four-phase, within-subject cross-over, double-blinded study where bilateral STN (Med. 3389) and PPN-DBS (Med. 3387) electrodes were implanted in 6 patients with advanced PD and axial motor symptoms while on optimal medical therapy. The primary endpoint was the reduction in falls and improvement in gait. Performance was recorded on optimal medical therapy alone (open-label phase), bilateral STN or PPN-DBS and simultaneous bilateral STN & PPN-DBS (ALL neurostimulation in conjunction with optimal medical therapy; 6-months each). The study received local ethics approval and informed written consent was obtained from all patients. Patients and carers maintained a Falls & near-Falls Diary and contemporaneous pedometer records of mobility. The posture and gait

components of the Unified Parkinson's Disease Rating Scale (UPDRS) Part II ADL (13 – 15) and Part III Motor (27 – 30) were recorded. The Timed Get-Up & Go Test, The Berg Balance Scale and Quality of Life (EQ-5D & SF-36) assessments were also applied. Additionally, neuropsychological evaluation and neurophysiological tests for postural control and freezing of gait (FOG) analysis were conducted.

Results: There was an 89%, 92% and 100% decrease (Wilcoxon signed-ranks test; $p < 0.05$) in ICNG Index (falls / 1000 steps) with bilateral STN-DBS (at 2.6 ± 0.2 V, 140 Hz, 60 μs), bilateral PPN-DBS (at 1.5 ± 0.2 V, 20 Hz, 60 μs) and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy, respectively, compared to optimal medical therapy only. Additionally, significant improvements were noted in almost all variables under consideration, most notably, UPDRS (Motor) and balance & gait assessments (Wilcoxon signed-ranks test; $p < 0.025$) with simultaneous bilateral STN & PPN-DBS. Neurophysiological findings are reported separately in subsequent chapters. PPN-DBS was generally well tolerated and only induced momentary ipsilateral oscillopsia at commencement on ≥ 2.0 V with rapid habituation, consistent with previous findings. No other complications were reported with PPN-DBS.

Conclusion: Simultaneous bilateral STN & PPN-DBS offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD.

INTRODUCTION

Parkinson's disease

James Parkinson's "*An essay on the shaking palsy*" (Parkinson 1817) was the first to describe the progressive, debilitating neurodegenerative disorder that is today commonly referred to as idiopathic Parkinson's disease (PD). PD is still diagnosed predominantly based on clinical assessment. The most common characteristics of PD are the limb motor symptoms of rest tremor, bradykinesia, muscular rigidity and in the advanced stages additional axial motor symptoms of gait freezing and loss of postural control (Hughes, Daniel et al. 1992). Therapeutic response to levodopa (L-dihydroxyphenylalanine; L-dopa) both supports the diagnosis of PD (Olanow, Watts et al. 2001) and has remained the gold standard of treatment from the late 1960s. However, diagnostic accuracy varies from 73 to 92 percent depending on the clinical criteria used (Rajput, Rozdilsky et al. 1991; Hughes, Daniel et al. 1992; Daniel and Lees 1993; Litvan, MacIntyre et al. 1998; Jankovic, Rajput et al. 2000). Global estimates of age-adjusted annual incidence of PD range from 9.4 to 22.1 per 100, 000 and the estimated prevalence from 59 to over 200 per 100, 000 population (Marttila 1983; Rajput 1992; Zhang and Roman 1993; Errea, Ara et al. 1999). Incidence increases further to 30 per 100, 000 person-years in subjects aged 55 to 65 years, to 440 per 100, 000 person-years for those aged 85 years or more (de Lau, Giesbergen et al. 2004) with intensive case-finding methods such as in-person screening.

Age is considered to be the most important predictive factor in PD; most people develop PD between 50 and 79 years of age (Marttila and Rinne 1987). The incidence of PD seems to increase with age from 30 per 100, 000 at 55 – 65 years of

age to 440 per 100, 000 at 85 years of age and older (de Lau, Giesbergen et al. 2004). Socioeconomic status (Caslake, Taylor et al. 2013) and gender have not been considered as a risk factor for PD, however, there are recent data suggesting that men seem to have a higher risk for PD (de Lau, Giesbergen et al. 2004). Other adverse prognostic factors include greater baseline impairment, early cognitive disturbance, and lack of tremor at onset (Marras, Rochon et al. 2002). In the absence of dementia, only a modest increased mortality risk, dependent on disease duration, is associated with PD (de Lau, Schipper et al. 2005).

Pharmacological treatment of Parkinson's disease

Lewy bodies (characteristic intracellular cytoplasmic inclusions of aggregated alpha-synuclein) are the primary histopathological finding in PD leading to progressive neuronal loss in the pigmented nuclei of the midbrain, in many subcortical nuclei and cortex (Jellinger 1999). The resulting depletion of melanin containing cells and tyrosine hydroxylase positive cells leads to striatal dopamine deficiency (Forno 1996). The said dopamine deficiency correlates with motor disability and dopamine replacement with L-dopa, although does not halt the progression of disease, remains the mainstay of optimal medical therapy (Cotzias, Van Woert et al. 1967; Uitti, Ahlskog et al. 1993) despite the advent of dopamine agonists and preclinically neuroprotective monoamine oxidase B (MAO-B) inhibitors. However, over the last three decades it has become apparent that chronic treatment with L-dopa is associated with complications including onset and / or exacerbation of orthostatic hypotension possibly resulting in falls, "On"-"Off" fluctuations, "On"-dyskinesias that may also result in falls, reduced "On"-time and progressive axial symptoms further resulting in falls (Marsden and Parkes 1976; Rinne 1987; Miyawaki, Lyons et al. 1997).

Surgical treatment of Parkinson's disease

Neurosurgery of the basal ganglia with notable improvement in the limb motor symptoms of PD was performed as early as 1939, but with a high mortality rate of 12% (Meyers 1951). Due to the severe adverse effects of this traditional open surgery, surgical treatment for PD did not achieve popularity at the time. However, the development of stereotactic frames / stereotactic neurosurgery made it possible to restrict the size of lesions (Cooper, Bravo et al. 1958; Svennilson, Torvik et al. 1960) and ultimately enable pallidotomies and subsequently thalamotomies; in particular lesions of the ventral intermediate nucleus (Vim) proved to be safer and more effective as a treatment of contralateral tremor (Laitinen 1966; Selby 1967; Fox, Ahlskog et al. 1991; Lenz, Normand et al. 1995; Schuurman, Bosch et al. 2000). Later the subthalamic nucleus (STN) was also explored as a target for ablative surgery (Albin, Young et al. 1989; DeLong 1990). However, lesions are irreversible and were also associated with complications (unilateral thalamotomies: hemiparesis, ataxia and speech disturbances; bilateral thalamotomies: severe gait disturbances and aphonia (Fox, Ahlskog et al. 1991); bilateral pallidotomies: increased mortality (Samuel, Caputo et al. 1998; Shannon, Penn et al. 1998) and long-term speech disturbances, difficulties in swallowing and deterioration of cognitive abilities (Jankovic, Cardoso et al. 1995; Giller, Dewey et al. 1998); subthalamotomies: long-term decrease in spontaneity, initiative, satiability, environmental interest combined with an increased interest in food (Andy, Jurko et al. 1963), difficulties in swallowing and hemiballismus (Vidakovic, Dragasevic et al. 1994; Henderson and Dunnett 1998)). Nonetheless, following a temporary but remarkable decline in surgical treatment options for PD with the introduction of L-dopa interest in ablative surgery was

renewed when it was noticed that posteroventral pallidotomy relieved not only PD symptoms, but also peak phase L-dopa induced dyskinesias (Laitinen, Bergenheim et al. 1992).

Subsequent development and introduction of (reversible) deep brain stimulation (DBS) was initially restricted to use in combination with thalamotomy in patients with bilateral PD (Benabid, Pollak et al. 1987) to avoid the irreversible adverse effects associated with ablative surgery. Later studies showed DBS (e.g., Vim) to be as effective as ablative surgery, but with fewer risks (Schuurman, Bosch et al. 2000) and DBS also permitted bilateral treatment (e.g., STN) (Limousin, Pollak et al. 1995; Krack, Benazzouz et al. 1998; Krack, Pollak et al. 1998; Limousin, Krack et al. 1998; Olanow, Brin et al. 2000). As with thalamotomy, Vim-DBS was effective for tremor, but had limited effect on other parkinsonian symptoms (Benabid, Pollak et al. 1996; Koller, Pahwa et al. 1997) and did not affect the origin of tremor, as symptoms were shown to return immediately following cessation of years of continued high frequency stimulation (Pollak, Benabid et al. 1997). However, STN-DBS in particular has been shown to be effective in treating the limb motor symptoms of advanced PD and allowing a significant reduction in the daily L-dopa dose (Krack, Pollak et al. 1998; Kumar, Lozano et al. 1998; Limousin, Krack et al. 1998; Moro, Scerrati et al. 1999; Pinter, Alesch et al. 1999; Houeto, Damier et al. 2000; Molinuevo, Valldeoriola et al. 2000; Lopiano, Rizzone et al. 2001; Volkmann, Allert et al. 2001; Ostergaard, Sunde et al. 2002; Tavella, Bergamasco et al. 2002; Anderson, Burchiel et al. 2005; Goetz, Poewe et al. 2005; Rodriguez-Oroz, Obeso et al. 2005; Odekerken, van Laar et al. 2013).

Thus from the early 1990s, Vim-DBS, globus pallidus internus (GPi)-DBS and in particular STN-DBS has become an important aspect of the management of advanced PD. It is estimated that between ten and twenty percent of patients with advanced PD will qualify for such DBS surgery. However, more recently it has been appreciated that the most debilitating axial symptoms of advanced PD such as loss of postural control, resulting in falls, and freezing of gait (FOG), also potentially resulting in falls, are refractory to both drug treatment and contemporary DBS surgery, namely STN or GPi-DBS. Indeed, as alluded to above, further pharmacological treatment may in fact be associated with onset and / or exacerbation of orthostatic hypotension as well as "On"-dyskinesias, possibly too resulting in falls. Falls, in particular, result in considerable social and economic costs. Indeed, falls secondary to postural instability and gait dysfunction (in addition to falls due to orthostatic hypotension and "On"-dyskinesias) are the most common reason for emergency department visits and the largest contributor to health-care costs among patients with advanced PD (Bloem, Boers et al. 2001; Bloem, Grimbergen et al. 2001; Schrag, Ben-Shlomo et al. 2002). Furthermore, the fear of falling is associated with an increased recurrence of falls and leads to loss of independence and depression (Adkin, Frank et al. 2003).

Pedunculopontine nucleus

Though effective in alleviating tremor, bradykinesia, rigidity and dyskinesia of advanced PD, contemporary treatments have little effect on patients' stability, including falls, or mobility (Allert, Volkmann et al. 2001; Krack, Batir et al. 2003; Rodriguez-Oroz, Obeso et al. 2005). Consequently, recent research has focussed on novel brain targets for improving mobility and stability in appropriate patients with advanced PD. One area of interest in this respect is the pedunculopontine nucleus

(PPN) (Benarroch 2013), a small nuclear structure in the rostral brainstem tegmentum extending from the mid-collicular to the mid-pontine level (**Figures 1 & 2**).

PPN anatomy and neural connections have been studied in great detail in both animal and human models (Jackson and Crossman 1983; Parent, Sato et al. 2000). There is extensive evidence that the PPN is an important structure involved in, among other functions, locomotion and postural control, with special regard to PD (Pahapill and Lozano 2000; Nandi, Stein et al. 2002; Ballanger, Lozano et al. 2009; Karachi, Grabli et al. 2010). Chemical and electrical stimulation of the PPN in rats, decerebrate cats and monkeys causes stepping movements (Garcia-Rill, Houser et al. 1987; Garcia-Rill, Kinjo et al. 1990). Unilateral lesions of the PPN in non-human primates result in hemi-akinesia and bilateral lesions produce profound generalised akinesia, similar to that seen in advanced PD (Kojima, Yamaji et al. 1997; Munro-Davies, Winter et al. 1999).

Autopsy studies in patients with PD have revealed degeneration of the PPN cholinergic neurons, the degree of which correlates with the clinical severity of PD (Zweig, Jankel et al. 1989). Similar loss of PPN neurons has been noted in autopsies of multi-system atrophy (MSA) and progressive supra-nuclear palsy (PSP) patients (Jellinger 1988) in whom parkinsonian gait problems are prominent.

Recently, it has been demonstrated that chemical stimulation of the PPN with GABA-A antagonist bicuculline, in a MPTP induced primate model of PD, resulted in significant improvement in akinesia, including postural control and gait (Nandi, Aziz et al. 2002). Subsequently, it was established that low frequency PPN-DBS in a

similar model also improved activity (Jenkinson, Nandi et al. 2004); the improvement was greatest when L-dopa and PPN-DBS were used in conjunction (Jenkinson, Nandi et al. 2006).

Interest in translational research has led to these experimental findings being rapidly transferred to the clinical field. Recent feasibility studies have reported on the safety of implanting DBS electrodes (DBSe) in bilateral PPN with / without simultaneous STN-DBS, using standard functional neurosurgical imaging and stereotactic tools, in patients with PD (Mazzone, Lozano et al. 2005; Plaha and Gill 2005; Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Hamani, Moro et al. 2011).

These short-term clinical results in a small number of patients provide some data to suggest improvement in postural control and gait function. These were important observational pilot studies; however, they did not have dedicated clinical and neurophysiological paradigms to specifically assess postural control and gait function in detail. Consequently studies using rigorous prospective, double-blinded, controlled trial methodology involving validated, quantifiable, relevant clinical and neurophysiological end-points, such as the present study, are urgently required to establish whether PPN-DBS is an effective clinical treatment.

There is a strong neuroanatomical basis for the present study design, namely the simultaneous implantation of PPN and STN-DBS in each appropriate patient with advanced PD with marked axial symptoms. The principal outflow from the basal ganglia via the GPi is distributed almost equally – the cranial half is directed towards the motor thalamus and the caudal half projects predominantly on the PPN area

(Pahapill and Lozano 2000; Jenkinson, Nandi et al. 2009). An important therapeutic issue here is that targeting the PPN alone may lead predominantly to alleviation of the axial motor symptoms of postural dysfunction and FOG, while the limb motor symptoms such as tremor may not be well served. This was predicted on the basis of non–human primate studies and it appears from preliminary clinical reports that this has been borne out (Nandi, Aziz et al. 2002; Nandi, Liu et al. 2002; Plaha and Gill 2005; Moro, Hamani et al. 2010). The studies involving PPN-DBS alone in patients with PD found improvement in some aspects of motor performance (gait and akinesia) and not others (tremor) (Plaha and Gill 2005; Moro, Hamani et al. 2010); on the other hand with simultaneous PPN and STN-DBS there was significant improvement in all the motor scores (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Hamani, Moro et al. 2011).

AIMS & OBJECTIVES

The aim of the present study was to establish a rational approach to the selection of appropriate DBS targets for individual patients with PD by determining the effect of bilateral PPN-DBS in reducing falls, improving gait and postural control in patients with advanced PD. The effect of PPN-DBS on the physical, psychological and social well-being of patients with advanced PD, as well as health and social service related resources, could be quite considerable, particularly as we anticipated that there will be a major effect on reducing falls and improving mobility.

PRINCIPAL HYPOTHESES

Bilateral PPN-DBS with stereotactically implanted DBSe will reduce falls and improve mobility of selected patients with advanced PD. This improvement will be greater than that obtained with optimal medical therapy alone or with optimal medical therapy in conjunction with STN-DBS. The greatest improvement will be observed with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy.

METHODS, MATERIALS & PARTICIPANTS

Selection criteria

Recruited PD patients satisfied all the current internationally accepted criteria for STN-DBS (The NICE deep brain stimulation for Parkinson's disease guidance (IPG19), 2003), and in addition, had a significant impairment of postural control and gait function, defined by a minimum of six falls and / or near-falls (defined as an event that requires patients to be supported, either by holding-on to something themselves or by someone else holding them, to prevent an otherwise certain fall) in the preceding three-months (once per fortnight), a score of six in Unified Parkinson's Disease Rating Scale (UPDRS) (**Appendix A**) Part II ADL (items 13-15 (max: 12)) and a score of six on UPDRS Part III Motor (items 27-29 (max: 12)).

Standard assessments

There is an established programme of DBS for PD within Imperial College Neuromodulation Group (ICNG), wherein patients are thoroughly evaluated by clinical history and examination, rating scales – UPDRS, quality of life scores (SF-36 and EuroQol EQ-5D Questionnaire) (**Appendix B & C**), neuropsychological evaluation and magnetic resonance imaging under general anaesthetic (GA-MRI). The GA-MRI scans were a 3-Tesla T2-weighted FLAIR sequence volume acquisition study with additional T2-weighted VISTA acquisition through the area of interest (basal ganglia and upper brainstem). The patients also underwent a diffusion-weighted imaging (DWI) / diffusion-tensor imaging (DTI) scan for probabilistic diffusion tractography (PDT) analysis. The entire scan time was approximately thirty minutes. This preoperative work-up took place during a short admission in our designated programmed investigation unit (PIU).

Additional assessments of balance and gait for this study

1. Clinical postural and gait tests already validated for PD clinical trials:

    a) Patients and carers maintained a Falls & near-Falls Diary (**Appendix D**) starting from 3 months prior to recruitment.

    b) The posture and gait components of the UPDRS Part II ADL (13-15) and the UPDRS Part III Motor (27-29) were recorded as part of the regular assessment along with video-recording of the examination of posture and gait, including 'postural reflexes' (trunk pull-pushes; UPDRS Part III Motor (30)).

c) The Timed Get-Up and Go Test (Podsiadlo and Richardson 1991) (**Appendix E**) that generates a simple and quantitative gait measure correlated with clinical disability. This variable has been validated in PD (Lim, van Wegen et al. 2005), including DBS trials (Vrancken, Allum et al. 2005).

d) The Berg Balance Scale (**Appendix F**) assessment also validated as a screening tool for balance problems in patients with PD and for on-going assessment (Qutubuddin, Pegg et al. 2005).

e) A pedometer was also attached to each patient and a record of daily mobility maintained, starting at the same time as the Falls & near-Falls Diary (Keenan and Wilhelm 2005).

2. Neurophysiological test for FOG analysis:

In addition to the validated (Giladi, Shabtai et al. 2000; Giladi, Tal et al. 2009) FOG questionnaire (FOG-Q) (**Appendix G**), a neurophysiological paradigm recently developed in our laboratory (Hollands, Ziavra et al. 2004; Anastasopoulos, Ziavra et al. 2009; Anastasopoulos, Ziavra et al. 2011) in which the subject reorients gaze, trunk and feet towards visual targets appearing in the periphery of the visual field was applied. The neurophysiological findings are reported separately in subsequent chapters.

Patient recruitment

Patients thus recruited from the DBS clinic at Charing Cross Hospital (and their families / carers and / or GP) had the study including potential benefits and risks carefully explained to them (**Appendix H & I**). The principal serious risks of DBS procedures were occurrence of an intra-cerebral haemorrhage (ICH) and / or infection. The former can lead to operative mortality or severe neurological deficit. The internationally accepted incidence of this adverse event is about 1 – 3 percent in most published series (Krack, Batir et al. 2003; Seijo, Alvarez-Vega et al. 2007). The majority of these series involve implantation of two DBSe in each patient. There is however published experience with implantation of four DBSe in each patient (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Hamani, Moro et al. 2011). There is no evidence to suggest that this significantly increases the risk of the procedure (Mazzone, Lozano et al. 2005; Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010). However, we accepted that there might be a marginally increased risk of ICH when implanting four instead of two DBSe in each patient. We must point out however, that there is published evidence which shows that the method of DBS implantation that we used, i.e., without micro-electrode recording (MER), has a significantly reduced risk of ICH compared to those centres that routinely use MER, without any loss of clinical efficacy (Honey, Berk et al. 2001). Several international centres routinely perform DBS without using MER (Aziz, Nandi et al. 2001; Plaha, Ben-Shlomo et al. 2006; Voges, Waerzeggers et al. 2006). Similarly, there is a theoretically increased risk of infection (standard risk 5%) when implanting four instead of two DBSe in each patient. Again, increased incidence of infection has not been reported in the existing cases (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Hamani, Moro et al. 2011). Other risks include electrode-lead fracture, electrode-lead migration, seizures, skin erosion and hardware failure (Hariz 2002;

Krack, Batir et al. 2003; Voges, Waerzeggers et al. 2006; Seijo, Alvarez-Vega et al. 2007). Informed written consent (**Appendix J**) was obtained from each patient.

Thus, 6 patients (all male; median age (IQR) 60.0 ± 3.8 years; median disease duration 10.5 ± 2.0 years) with advanced PD and axial motor symptoms while on optimal medical therapy were recruited. A brief summary of each patient is as follows (**Table 1**):

P1: A 56-years-old right-handed gentleman who initially presented with reduced dexterity in his left hand and in the subsequent 8-years went on to develop not only bilateral limb motor symptoms of advanced idiopathic PD but also severe axial motor symptoms refractory to optimal medical therapy. Any further increase in doses of medication was prohibited by development of worsening obsessive-compulsive symptoms and paranoid ideation.

P2: A 55-years-old left-handed gentleman with marked "Off" akinesia and "On" dyskinesia who required the use of an wheel chair and suffered from two-to-three falls per day due to postural instability and freezing of gait during his 17-years history of advanced idiopathic PD despite having previously undergone a left pallidotomy with consequently severely hypophonic speech.

P3: A 67-years-old right-handed gentleman with 10-years history of advanced idiopathic PD manifesting with two-to-three falls per week, postural instability, freezing of gait and marked "Off" akinesia and "On" dyskinesia requiring use of an daily Apomorphine subcutaneous infusion.

P4: A 64-years-old right-handed gentleman who initially presented with right hand rest tremor, micrographia and tripping over his right foot. In the subsequent 6-years he rapidly went on to develop not only bilateral limb motor

symptoms of advanced idiopathic PD but also severe axial motor symptoms refractory to optimal medical therapy in the form of both gait ignition failure and freezing of gait resulting in recurrent falls and necessitating use of a walking stick and at times also a wheel chair.

P5: A 57-years-old right-handed gentleman who during his 13-years history of advanced idiopathic PD had progressed to such severe disability that not only did he require the use of an wheel chair and daily carers but also he had to be admitted as an inpatient in the pre-trial period for treatment of multiple (~20) necrotic ulcers and potential septicaemia related to the use of an daily Apomorphine subcutaneous infusion.

P6: A 63-years-old left-handed gentleman with 11-years duration of advanced idiopathic PD who initially presented with left hand tremor and left leg bradykinesia with freezing of gait particularly on turning. Subsequently, he developed severe axial motor symptoms refractory to optimal medical therapy with daily multiple falls in addition to severe bilateral limb motor symptoms.

Surgical procedure

Patients were admitted to the neurosurgical ward a day prior to surgery. Our surgical routine is described in detail elsewhere and is one that has been used for the last 10 years (Aziz, Nandi et al. 2001; Liu, Rowe et al. 2001; Bittar, Burn et al. 2005). On the morning of surgery PD medication is omitted; a Cosman-Roberts-Wells (CRW) stereotactic frame base ring is applied to the skull under local anaesthetic and a stereotactic CT brain is performed. This is then fused to the pre-operative GA-MRI using Radionics Image Fusion. The target co-ordinates for the STN and the PPN are then calculated. The STN can often be directly visualised on current MRI software;

the PPN is localised relative to adjacent structures that can be seen on MRI, e.g., decussation of the superior cerebellar peduncle (SCP), substantia nigra (SN) and the pons. The Schaltenbrand Wahren (SW) anatomic atlas was also used with the image fusion software to further help radiological localisation of the STN (but does not extend caudal enough to demonstrate the PPN) and the pre-operative DWI / DTI scans with PDT analysis were used to further help radiological localisation of the PPN by demonstrating the relative adjacent structures, as alluded to above. The patient was then returned to the operating theatre and bilateral DBSe (Medtronic 3389 & 3387) were then passed to target (STN and PPN in turn, respectively) and trial stimulation was performed. Sedation was reversed and careful neurological assessment performed to detect changes in PD symptoms and signs like tone, tremor and bradykinesia; any undesired effects such as pyramidal weakness, speech or visual dysfunction, cognitive change, etc., were also noted. Real-time feedback from LFP recordings from the DBSe in conjunction with on-table clinical examination was used to aid placement. Once satisfactory placement was achieved, the DBSe was fixed to the skull with a titanium plate and screws. A similar procedure is followed for implantation of all the DBSe. Four DBSe were implanted in each patient – bilateral STN and PPN (**Figure 3**). The DBSe were then connected to short extension leads and exteriorised sub-galeally. A repeat stereotactic CT brain was performed to confirm placement and exclude any immediate complications such as ICH. Antibiotics covered the procedure.

The following week was then used for trial stimulation in the ward and effective parameters of DBS for each patient were noted. Where possible, LFP were recorded during these stimulation sessions and the pre-operative trial-based gait and balance

tests were repeated. In addition, correlation of DBSe signals with gait turning and FOG behaviour were performed. At the end of the week, the patient was returned to the operating theatre and bilateral (Implantable Pulse Generator) IPGs were implanted in subclavicular subcutaneous pockets and connected to the DBSe through subcutaneously tunnelled extension leads. The patients were then discharged with all DBS switched OFF.

The DBS assessment protocol

This was a four-phase, within-subject cross-over, and double-blinded study design involving three trial intervention conditions. The order of conditions was allocated to subjects based on the William's square design balanced for order (to control for disease progression) (**Table 2**). Following a three-months post-operative period without stimulation, patients were initially allocated to one of three groups: 'A' (STN stimulation) *vs*. 'B' (PPN stimulation) *vs*. 'C' (STN & PPN-DBS) for six-months and assessed at nine-months post-operatively. The subjects were then reallocated according to the William's square design into one of the two remaining stimulation modes and assessed once more fifteen-months post-operatively. Finally the subjects were re-allocated to receive the remaining stimulation mode for the final six-month phase and assessed at twenty-one-months. Thus, all patients sequentially received all three types of stimulation for six-months. In addition the three-month pre-operative and three-month post-operative periods provided optimal medical therapy only control data (open-label phase).

Follow-up

Routine arrangements were made to review each patient in the DBS clinic three-months after surgery. DBS was then commenced according to the William's protocol. At the nine-month visit, a repeat GA-MRI was performed to accurately localise DBSe placement by individual contact. The Falls & near-Falls Diary, clinical rating scores, quality of life scores, neuropsychological tests, pedometer readings and balance and gait assessments were repeated. The effects of different parameters of DBS during "On"-"Off" drug conditions were assessed. All untoward effects were recorded and treated as appropriate. This assessment regimen was then repeated (apart from MRI scan) fifteen and twenty-one-months after surgery. The investigator (myself) who performed the objective clinical assessments including the gait and balance tests, was blinded to the state of the DBS, i.e., whether DBS is switched "On" or "Off" and in the former situation whether the STN and / or the PPN DBSe is active. The patient and carer were also blinded to the state of DBS activity and this was confirmed at each visit by the patient and carer consistently incorrectly reporting which phase of the trial they believed they were in at the time. Experimental data from neurophysiological experiments described above was also compared before and after DBS. Although the latter data can be used as corroborative evidence of individual patient improvement, it was primarily devoted for pathophysiological investigation of the posture and gait disorder in PD.

Analysis

Sample size and power calculations:

Data was analysed using a within-subjects repeated measures crossover design. In the case of falls, we looked for a clinically decisive result of stimulation; therefore,

assuming a large effect size of 50% reduction in falls, 6 subjects would be required to detect a significant effect of intervention in the range $0.02 \geq p \leq 0.05$ with 80% power.

Each patient served as his own control. Objective data was analysed from the test paradigms detailed above. Further clinical and quality of life improvement data was also analysed. The standard UPDRS data was analysed to ensure other parameters of PD severity are alleviated in accordance with acceptable international standards. A careful analysis of any and all untoward effects of treatment was conducted and compared with published major series. Particular note of ICH and / or infection rates was made as this treatment involves four DBSe and two IPGs; most common implantation would involve two DBSe and one IPG. However, the selection criteria in this study admitted strictly advanced PD patients with marked axial dysfunction who were likely to respond poorly to the conventional two DBSe STN surgery alone (Allert, Volkmann et al. 2001; Krack, Batir et al. 2003; Rodriguez-Oroz, Obeso et al. 2005).

Primary endpoint:

The effect of optimal medical therapy alone, bilateral STN or PPN-DBS and simultaneous bilateral STN & PPN-DBS on falls. Comparing falls on optimal medical therapy alone for six-months (three-months pre-operatively & three-months post-operatively with no stimulation) to that in months three – nine, nine – fifteen and fifteen – twenty-one post-operatively. The number of falls were correlated with the contemporaneous pedometer records of mobility to avoid any false conclusions arising from markedly reduced mobility leading to reduced falls simply due to the subject being bed bound or chair bound, for example.

Secondary endpoints:

1. To establish if there is significant change in the UPDRS Part II ADL (13-15), UPDRS Part III Motor (27-29) and UPDRS Part III Motor (30) between the conditions above.
2. To establish if there is a significant change in the Timed Get-Up and Go Test, the Berg Balance Scale assessment and pedometer records of daily mobility.
3. Quantitative differences in the physiological tests within the different conditions of the study.

Ethics

The principal ethical issue in the present study was the simultaneous implantation of bilateral STN & PPN DBSe (total four) with two IPGs in each patient. Most DBS procedures involve one pair of DBSe and one IPG. There is a theoretical increased risk of ICH directly due to the surgical procedure and also an increased risk of infection. The existing levels of risk for DBS operations (two DBSe) and the literature from four DBSe implants have been discussed earlier (Hariz 2002; Krack, Batir et al. 2003; Mazzone, Lozano et al. 2005; Voges, Waerzeggers et al. 2006; Seijo, Alvarez-Vega et al. 2007; Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Hamani, Moro et al. 2011). The estimated increase in risk was small (less than one percent). Also, as highlighted earlier, there is an inherent lower risk of ICH in our surgical protocol (Honey, Berk et al. 2001). Patients and carers were fully informed (including printed information) of the risks (including the additional risks from our study over standard DBS treatment) and the potential benefits, prior to obtaining written consent. The present study was also approved (08/H0711/137 & NAND2001)

by the Imperial College Clinical Research Governance Office (CRGO) and the Imperial College / Charing Cross Hospital Research Ethics Committee (CCHREC).

RESULTS

Four patients (P1, P3, P4 and P6) completed all 4-phases of the trial, albeit P4 and P6 opted to undergo only 72-hours of bilateral PPN-DBS as they began the stimulation part of the trial on simultaneous bilateral STN & PPN-DBS (i.e., maximum treatment) and therefore found it difficult to tolerate reduction in treatment to bilateral PPN-DBS only, although they were able to tolerate bilateral STN-DBS only. This suggests that although axial motor symptoms of advanced PD may be adding to the drivers of disease burden, alleviation of these in isolation from tremor, rigidity and bradykinesia / dyskinesia is not a practical option.

P5 only participated in the simultaneous bilateral STN & PPN-DBS (i.e., maximum treatment) phase of the stimulation part of the trial as in view of his pre-trial complications, as detailed in the methodology, clinically and ethically it was considered inappropriate to burden him with anything other than maximum treatment. P2, regrettably, fractured his patella following a fall during the pre-stimulation part of the trial and therefore only incomplete data is available for P2 for the stimulation part of the trial.

Four of the five, in whom sufficient data was available, did not experience any further falls with simultaneous bilateral STN & PPN-DBS and the fifth experienced an

extremely low frequency of falls (ICNG Index (falls / 1000 steps) 0.014). P4 was able to mobilise independently following simultaneous bilateral STN & PPN-DBS (required walking stick and at times also a wheel chair on optimal medical therapy alone). P5 began to spend time outside of his wheel chair undertaking hobbies such as gardening / DIY following simultaneous bilateral STN & PPN-DBS while P6 was able to commence taking dancing lessons.

Overall, there was an 89%, 92% and 100% decrease (Wilcoxon signed-ranks test; $p < 0.05$) in ICNG Index (falls / 1000 steps) with bilateral STN-DBS (at 2.6 ± 0.2 V, 140 Hz, 60 μs; P2 STN-DBS data excluded as outlier), bilateral PPN-DBS (at 1.5 ± 0.2 V, 20 Hz, 60 μs) and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy, respectively, compared to optimal medical therapy alone. Additionally, significant improvements were noted in almost all variables under consideration, most notably, UPDRS (Motor) and balance & gait assessments (Wilcoxon signed-ranks test; $p < 0.025$) with simultaneous bilateral STN & PPN-DBS. These findings are summarised in **Table 3** and **Figures 4 – 14**.

Furthermore, it should be noted that an equivalent or better improvement was noted even in those few variables where the results were not statistically significant / there was insufficient data for statistical analysis with either or both bilateral PPN-DBS and simultaneous bilateral STN & PPN-DBS. Parameters of PD severity were also noted to be alleviated in accordance with acceptable international standards for bilateral STN-DBS (80% improvement in ADLs compared to "Off" medication; 52% improvement in UPDRS (Motor) compared to "Off" medication; 80% improvement in quality of life scores compared to "Off" medication; as far as possible, medication

dose was intentionally kept constant for each patient to standardise the trial). Neurophysiological findings from this study are reported separately in subsequent chapters.

PPN-DBS was generally well tolerated and only induced momentary ipsilateral oscillopsia at commencement on ≥ 2.0 V with rapid habituation, consistent with previous findings (Ferraye, Gerardin et al. 2009). No other complications were reported with PPN stimulation, in particular there was a zero ICH and / or infection rate in this study. There were also no untoward effects of treatment identified in the post-operative neuropsychological assessments (data not shown).

ALL six-patients remain on simultaneous bilateral STN & PPN-DBS at 12-months post-trial follow-up with good symptomatic control and no reported side-effects.

DISCUSSION

In this study we have demonstrated that simultaneous bilateral STN & PPN-DBS offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD. There could be possible clinical applications not just for patients with advanced PD, but also for selected patients with MSA, PSP and vascular Parkinsonism that respond poorly to current therapies. This seems especially likely as it has been shown that the beneficial effects of PPN-DBS and L-dopa therapy on posture and gait in primate PD models are complementary (Jenkinson, Nandi et al. 2006). This also has implications for the treatment of patients with

advanced PD who respond poorly to L-dopa, a situation that would at present lead to most functional neurosurgery centres to decline DBS treatment (Krack, Batir et al. 2003; Machado, Rezai et al. 2006). Thus, PPN-DBS could possibly become part of the standard clinical treatment in appropriately selected advanced PD patients. Although this will increase the cost of surgical treatment, there would be significant long-term cost reduction implications for the NHS.

Our findings are broadly consistent with existing literature (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Moro, Hamani et al. 2010; Hamani, Moro et al. 2011). The greater efficacy of PPN-DBS in the present study, compared with some previously published studies (Ferraye, Debu et al. 2010; Moro, Hamani et al. 2010), may be explained by factors such as more accurate DBSe placement with the aid of PDT studies, and / or, longer follow-up ensuring adequate 'wash-out' period following bilateral PPN, bilateral STN and simultaneous bilateral STN & PPN-DBS thus eliminating the possibility of prolonged maintenance of benefit after cessation of chronic stimulation confounding results, as highlighted by the greatest reduction in ICNG Index (falls / 1000 steps) during the bilateral STN phase of the stimulation part of the trial in those two-patients (P1 & P3) who were first in either bilateral PPN or in simultaneous bilateral STN & PPN-DBS phase of the stimulation part of the trial (Thevathasan, Coyne et al. 2011).

Furthermore, Falls & near-Falls diaries together with contemporaneous pedometer record of daily mobility (i.e., ICNG Index (falls / 1000 steps)) have likely better captured this important endpoint than standard but insensitive clinical measures routinely employed such as UPDRS (Thevathasan, Coyne et al. 2011). Additionally,

our selection criteria ensured we selected patients with severe axial symptoms refractory to optimal medical therapy, however, in some previous studies, patients were selected who had severe motor fluctuations requiring STN-DBS and only variable degrees of gait disturbance (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Moro, Hamani et al. 2010; Hamani, Moro et al. 2011).

The more modest reduction in ICNG Index (falls / 1000 steps) observed with bilateral STN-DBS may be attributed to amelioration of the limb and possibly dopamine sensitive axial motor symptoms of advanced PD without concomitant improvement in gait and postural control afforded by PPN-DBS thus predisposing subjects to an higher risk of falls from increased mobility without accompanying improved balance. Equally, P4 and P6 may have opted to undergo only 72-hours of bilateral PPN-DBS not only as they began the stimulation part of the trial on simultaneous bilateral STN & PPN-DBS (i.e., maximum treatment) and therefore found it difficult to tolerate reduction in treatment to bilateral PPN-DBS only, but also as excitatory reciprocal efferents from PPN to STN may result in worsening of limb motor symptoms of advanced PD during bilateral PPN-DBS only.

Future work should consider larger prospective controlled double-blinded trials with an even longer follow-up as well as early *vs*. late addition of PPN-DBS to the surgical management of advanced PD and the efficacy of unilateral (dominant symptomatic side) STN & PPN-DBS to reduce DBSe & IPG requirement from 4 to 2 and 2 to 1 respectively. This may be possible due to PPN contralateral connections.

CONCLUSION

Simultaneous bilateral STN & PPN-DBS offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD.

Chapter 2

Effects of bilateral subthalamic and pedunculopontine nucleus-deep brain stimulation on gaze displacement and axial mobility in whole body turning in advanced Parkinson's disease

Keywords: Parkinson's disease (PD), deep brain stimulation (DBS), subthalamic nucleus (STN), pedunculopontine nucleus (PPN), saccades

ABSTRACT

Objective: To investigate the effects of chronic bilateral STN & PPN-DBS on gaze displacement and axial mobility in whole body turning in patients with advanced PD.

Background: Recently, principal component analysis established that eye-to-foot turning synergy is preserved in early-stage PD and that turning problems do not result from inability to assemble multisegmental movements, as patients' ability to control numerous degrees of freedom is preserved; the original three mechanical degrees of freedom (i.e., eye-head-trunk) are reduced to two kinematic degrees of freedom. Rather, the primary pathology appears to be reduced frequency of single-step gaze shifts, thus prolonging target acquisition time, so-called freezing of gaze. DBS of the STN is an established treatment for advanced PD. It is highly successful in alleviating the levodopa responsive symptoms of tremor, rigidity and bradykinesia more effectively than optimal medical therapy alone and concurrently, permits treatment at reduced drug dosages, decreasing the occurrence of associated motor fluctuations and dyskinesias that come with long term medical management. However, axial motor symptoms including problems with initiation of walking, sudden freezing of gait (FOG; as many as over half the advanced cases may develop this unusual, episodic loss of motor function) and difficulty turning are also more pronounced in the advanced stages. Alongside gait disturbances, patients experience

postural instability comprising inappropriate responses of axial muscles to external stimuli and failure in adjusting their posture in a procedural context causing loss of mobility and high risk of falls. By contrast, these extremely debilitating axial motor symptoms are less responsive to levodopa replacement therapy and currently there is no definitive consensus on the efficacy of chronic bilateral STN-DBS on axial motor disturbances owing to inconsistencies in clinical outcomes.

FOG as a phenomenon, in particular, is one of the least understood gait disorders associated with advanced PD and usually results in a steady deterioration in the quality of life for most patients. Treatment of FOG has proven to be quite difficult and patient responses have been inconsistent at best. FOG usually appears in the 'Off' state although 'On' state episodes may occur in a small number of patients. Cases of FOG in 'On' states are considerably more challenging to treat with medication alone. Reduction in L-Dopa therapy have been shown to reduce 'On' state FOG in certain cases, however this resulted in deterioration of other symptoms well controlled by medication alone.

While DBS of other targets has been explored, DBS of the STN remains the final method of treating balance disorders in advanced PD. Stimulation of this area has been shown to lessen the effect of 'Off' state FOG but has proven unable to treat 'On' state cases. It has recently been shown however, that simultaneous bilateral STN & PPN-DBS has been able to successfully reduce FOG in patients with 'On' period gait disturbances.

Methods: Six-patients with advanced PD and axial motor symptoms, while on optimal medical therapy, underwent bilateral STN (Med. 3389) and PPN-DBS (Med. 3387) implantation as part of a prospective, four-phase (6-months each), within-subject cross-over, double-blinded clinical trial, as described in **Chapter 1**. At the end of each 6-months phase, these participants stood upright in the dark and voluntarily reoriented eyes and body to illuminated targets of eccentricities up to ±180 degrees. The effects of target location, visibility, and predictability on movement parameters were evaluated. 5 age-matched and 5 young subjects served as controls.

Results: Chronic bilateral STN-DBS, in conjunction with optimal medical therapy, significantly decreased the number of saccades required for target acquisition ($p < 0.05$) thus ameliorating the hypometric saccades of advanced PD. PPN-DBS, in conjunction with optimal medical therapy, produced 35% reduction in foot latency and 45% increase in foot velocity (both $p < 0.000001$). Simultaneous bilateral STN & PPN-DBS, in conjunction with optimal medical therapy, produced significantly reduced latencies and increased velocities (excluding head velocity) in all axial motor segments (all $p < 0.05$).

Conclusion: Simultaneous bilateral STN & PPN-DBS, in conjunction with optimal medical therapy, offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD. The motor paradigm adopted provides objective evidence of performance changes in the relevant axial motor segments. These findings offer new insight into the way STN and PPN-DBS may improve axial motor ability in the surgical management of advanced PD.

INTRODUCTION

PD is a degenerative neurological disorder that affects approximately 0.2% of individuals in the UK and over 1% of individuals over the age of 60. The hallmark symptoms associated with PD and other Parkinsonian diseases include rest tremors, bradykinesia (slowness of movement), akinesia (impaired initiation of movement), and muscular rigidity. The loss of motor function in PD develops when up to 70% of the dopaminergic neurons within the SNc of the BG, an important generator of voluntary movement and the primary source of the neurotransmitter dopamine containing upwards of 80% of the brain's supply, have been lost (Kandel 1998).

In the majority of PD patients, the loss of SNc neurons is idiopathic and this unpredictable nature of PD-onset prevents a clear distinction between PD and other Parkinsonism disorders, such as PSP, at an early stage dominated mostly by tremors that in most cases can be successfully mediated by symptomatic treatments. For mild to moderate PD, the most commonly used treatment strategy is the dopamine precursor L-dopa (Cotzias, Van Woert et al. 1967; Uitti, Ahlskog et al. 1993) and in advanced PD optimal pharmacological therapy may be combined with surgical treatment, particularly STN-DBS (Krack, Benazzouz et al. 1998; Krack, Pollak et al. 1998; Kumar, Lozano et al. 1998; Limousin, Krack et al. 1998; Moro, Scerrati et al. 1999; Pinter, Alesch et al. 1999; Houeto, Damier et al. 2000; Molinuevo, Valldeoriola et al. 2000; Lopiano, Rizzone et al. 2001; Volkmann, Allert et al. 2001; Ostergaard, Sunde et al. 2002; Tavella, Bergamasco et al. 2002; Thobois, Corvaisier et al. 2003; Anderson, Burchiel et al. 2005; Goetz, Poewe et al. 2005; Rodriguez-Oroz, Obeso et al. 2005; Odekerken, van Laar et al. 2013).

DBS of the STN is now an established treatment for advanced PD (Weaver, Follett et al. 2009; Mandat, Tykocki et al. 2011). It is highly successful in alleviating the L-dopa responsive symptoms of tremor, rigidity and bradykinesia more effectively than optimal medical therapy alone (Krack, Batir et al. 2003; Awan, Lozano et al. 2009; Benabid, Chabardes et al. 2009) and concurrently, permits treatment at reduced drug dosages, decreasing the occurrence of associated motor fluctuations and dyskinesias that come with long term medical management (Bonnet, Loria et al. 1987; Deuschl, Schade-Brittinger et al. 2006; Awan, Lozano et al. 2009).

Axial motor symptoms including disturbance of gait and balance are more pronounced in the advanced stages causing loss of mobility and high risk of falls (Wood, Bilclough et al. 2002; Maurer, Mergner et al. 2003). By contrast, these extremely debilitating symptoms are less responsive to L-dopa replacement therapy and it has been suggested that this may result from progressive involvement of non-dopaminergic pathways (Bonnet, Loria et al. 1987; Welter, Houeto et al. 2002; Wood, Bilclough et al. 2002; Maurer, Mergner et al. 2003). Parkinsonian gait is initially slow and shuffling with a reduced stride length and velocity and limited range of movement at joints. With disease progression problems appear with initiation of walking, sudden FOG and difficulty turning (Xie, Krack et al. 2001; Ferrarin, Rizzone et al. 2004; Boonstra, van der Kooij et al. 2008). Alongside gait disturbances, patients experience postural instability comprising inappropriate responses of axial muscles to external stimuli and failure in adjusting their posture in a procedural context (Xie, Krack et al. 2001; Welter, Houeto et al. 2002; Maurer, Mergner et al. 2003; Ferrarin,

Rizzone et al. 2004; Boonstra, van der Kooij et al. 2008; Chastan, Westby et al. 2009).

Currently, there is no definitive consensus on the efficacy of chronic bilateral STN-DBS on axial motor disturbances owing to inconsistencies in clinical outcomes (Boonstra, van der Kooij et al. 2008; Ferraye, Debu et al. 2008; Johnsen, Mogensen et al. 2009). Contradictory findings may be due to differing levels of proficiency and procedural techniques across various groups (Boonstra, van der Kooij et al. 2008; St George, Nutt et al. 2010). Numerous studies have showed STN-DBS relayed significant improvement specifically in postural stability and gait (Benabid, Chabardes et al. 2009). However, these studies did not focus on strict assessment of axial motor symptoms in particular and most studies were limited in their quantification of gait characteristics having used clinical measurement strategies such as the UPDRS when in fact gait evaluation may be better achieved by automatic motion analysis techniques (Ferrarin, Lopiano et al. 2002; Ferrarin, Rizzone et al. 2004; Ferrarin, Rizzone et al. 2005). Conversely, a meta-analysis by George *et* al. concluded that marked improvement in parkinsonian limb motor disability in those with chronic bilateral STN-DBS was not accompanied by significant improvement in axial motor symptoms (St George, Nutt et al. 2010).

Multiple comparisons between chronic bilateral STN-DBS, L-dopa therapy and a combination of both treatment types have been reported. Reports have consistently shown comparable improvements between L-dopa and STN-DBS on axial symptoms (Bejjani, Gervais et al. 2000; Faist, Xie et al. 2001; Maurer, Mergner et al. 2003; Ferrarin, Rizzone et al. 2004; Shivitz, Koop et al. 2006). In addition, differential

effects of STN-DBS and L-dopa have been noted in certain features of gait and posture with some studies showing greater enhancement in axial signs (Bejjani, Gervais et al. 2000; Stolze, Klebe et al. 2001; Ferrarin, Rizzone et al. 2004; Shivitz, Koop et al. 2006; Chastan, Westby et al. 2009). Another recurring finding across studies is the amplified improvement in axial signs due to a combination of L-dopa and STN-DBS (Bejjani, Gervais et al. 2000; Faist, Xie et al. 2001; Ferrarin, Rizzone et al. 2004; Shivitz, Koop et al. 2006). Assuming that dopamine transmission contributes to axial symptomatology, a synergistic effect of combination treatment suggests variant pathways for L-dopa and STN-DBS or even a downstream output of STN-DBS on the dopaminergic route for consequential control processes of gait and postural instability (Bejjani, Gervais et al. 2000; Ferrarin, Rizzone et al. 2004; Guehl, Dehail et al. 2006). However dopaminergic transmission may not solely contribute to axial signs. Indeed, dissimilar effects of STN-DBS and L-dopa therapy suggest that STN-DBS could contribute to putative non-dopaminergic systems involved in the regulation process of axial mobility. This is compatible with the fact that L-dopa does not completely alleviate axial abnormalities.

Demonstration of treatment efficacy on axial motor abnormalities can not only be clinically useful but provide further insights into the pathophysiological mechanisms of balance and gait especially with regards to impairments in their constituent features described above. Visual cues are also a principal aspect for maintenance of balance whereby target acquisition provides visual feedback for postural stabilisation and plays a particularly dynamic role in PD (Bronstein, Hood et al. 1990; Maurer, Mergner et al. 2003). Indeed it is suggested that STN-DBS restores circuits in the initiation and inhibition of saccades (both impaired in PD) either through BG-

thalamocortical pathways or improvement in superior colliculus functionality (Yugeta, Terao et al.). The improvement seen in postural control may be due to this contribution in the normalisation of saccade accuracy.

However, as PD progresses, many patients also develop late onset axial motor symptoms of balance and gait dysfunction that have proven fairly resistant to existing pharmacological and surgical treatments. Of these advanced cases, over half may develop an unusual, episodic loss of motor function known as (FOG) (Fahn 1995). FOG as a phenomenon is one of the least understood gait disorders associated with advanced Parkinsonism and usually results in a steady deterioration in the quality of life for most patients. In addition, FOG has also been observed in other Parkinsonian diseases such as PSP, idiopathic intracranial hydrocephalus and vascular Parkinsonism indicating that the loss of dopaminergic neurons is not the absolute cause of its onset (Fahn 1995).

During a FOG episode, patients are unable to initiate conscious movements and consequently, they feel as though there is a "glass wall" in their way or that they are "stuck to the floor". This disruption of motion may cause patients to become unbalanced, often resulting in a fall. In patients prone to FOG, such falls become progressively more frequent, inevitably limiting independent movement. The psychological effect of FOG related falls and the resulting medical costs places it among the most debilitating symptoms of advanced PD.

Unusually for a motor disorder, FOG episodes have specific and well-defined triggers and releases. Freezing normally occurs during turning or at the start of a movement

(start hesitation) (Jarman, Hurwitz et al. 2002) but, may also manifest itself when a patient is asked to move through a confined space (tight space hesitation) (Jarman, Hurwitz et al. 2002) or during periods of cognitive load – for example, speaking while walking. Hesitation also occurs during activities with time constraints or during stressful situations (Okuma 2006; Okuma and Yanagisawa 2008; Rahman, Griffin et al. 2008). Conversely, FOG episodes may be interrupted by specific stimuli. Visual and auditory cues as well as moderate levels of emotional stress frequently release patients from FOG (Stern, Lander et al. 1980). The common and at times unavoidable nature of FOG triggers and further exasperates the effect that advanced PD has on patient's daily life.

Treatment of FOG has proven to be quite difficult and patient responses have been inconsistent at best. FOG usually appears in the 'Off' state although 'On' state episodes may occur in a small number of patients. To treat FOG during 'Off' states, increased doses of dopaminergic agents have confirmed to be moderately effective (Giladi, McDermott et al. 2001). Cases of FOG in 'On' states are considerably more challenging to treat with medication alone. Reduction in L-Dopa therapy have been shown to reduce 'On' state FOG in certain cases, however this resulted in deterioration of other symptoms well controlled by medication alone.

While DBS of other targets has been explored (Chastan, Westby et al. 2009; Weiss, Walach et al. 2013), chronic DBS of the STN remains the final method of treating balance disorders in advanced PD. Stimulation of this area has been shown to lessen the effect of 'Off' state FOG but has proven unable to treat 'On' state cases (Katayama, Kasai et al. 2000; Bakker, Esselink et al. 2004; Davis, Lyons et al. 2006).

It has recently been shown however, that chronic simultaneous bilateral STN & PPN-DBS has been able to successfully reduce FOG in patients with 'On' period gait disturbances (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2008; Ferraye, Debu et al. 2010; Schweder, Hansen et al. 2010; Acar, Acar et al. 2011). The inclusion of the PPN suggests that the brainstem locomotor nuclei play a major role in FOG.

However, only one study has tested the effects of DBS on turning in advanced PD (Naushahi MJ 2012) and only one other has examined the effects of DBS on oculomotor control during turning (Lohnes and Earhart 2012). In this study we report the efficacy of simultaneous bilateral STN & PPN-DBS on gaze displacement and axial mobility in whole body turning in patients with advanced PD using a neurophysiological paradigm (Hollands, Ziavra et al. 2004; Anastasopoulos, Ziavra et al. 2009; Anastasopoulos, Ziavra et al. 2011) in which the subject reorients gaze, trunk and feet towards visual targets appearing in the periphery of their visual field.

We presently consider the differential outcomes in specific parameters of axial mobility related to age, advanced PD on optimal medical therapy only (over and above age), bilateral STN or PPN-DBS in conjunction with optimal medical therapy and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy in order to shed light on the underlying locomotor mechanisms. Therefore, this study is unique in that it reports analysis of turning motion during bilateral STN and / or PPN-DBS encompassing eyes, head, trunk and foot displacements in response to a visual stimulus in order to determine the effects of STN and / or PPN-DBS on turning performance and related oculomotor performance in advanced PD. Whole body rotation emphasises axial rigidity, inter-limb coordination and

asymmetry (Boonstra, van der Kooij et al. 2008) and thus is a good indicator of voluntary axial control of movement.

METHODS, MATERIALS & PARTICIPANTS

Participants

Six-patients with advanced PD and axial motor symptoms, while on optimal medical therapy, underwent bilateral STN (Med. 3389) and PPN-DBS (Med. 3387) implantation as part of a prospective, four-phase (6-months each), within-subject cross-over, double-blinded clinical trial, as described in **Chapter 1**. At the end of each 6-months phase, these participants stood upright in the dark and voluntarily reoriented eyes and body to illuminated targets of eccentricities up to ±180 degrees. The effects of target location, visibility, and predictability on movement parameters were evaluated. 5 age-matched (median age 63 ± 6.5 years) and 5 young subjects (median age 25 ± 4.8 years) served as controls.

All subjects gave informed written consent. Subjects were excluded from the trial if there was cognitive, other neurological, musculoskeletal or visual impairment that could influence the study. Study protocol was approved by the Clinical Research Governance Office (CRGO) and the Imperial College / Charing Cross Hospital Research Ethics Committee (CCHREC).

Experimental Protocol and Data Acquisition

An experimental paradigm recently developed in the clinical laboratory of the Department of Neurology and Clinical Neurophysiology of Charing Cross Hospital, Imperial College Healthcare NHS Trust was used to study spatiotemporal parameters of various axial body segments during whole body rotation towards a visual target (Hollands, Ziavra et al. 2004; Anastasopoulos, Ziavra et al. 2009). Participants stood in the center of a circular array of 8 light-emitting diodes (LEDs), placed at 45 degrees intervals at eye level (radius of 1.2 m) in darkness. Initially participants were required to fixate and align their head, body and feet with a central LED located at 0 degree. After a delay of 10 seconds the 0 degree LED was extinguished and the visual target moved to another LED in one of the 7 eccentric locations (45 degrees, 90 degrees, 135 degrees either right or left and 180 degrees) cueing the subject to find and fixate on the lit LED and turn and align their whole body with that target. After an interval of 15 seconds the eccentric LED was extinguished prompting the subject to return to the initial, central position at 0 degree (**Figure 15**).

Prior to each experiment the apparatus was calibrated. A total of 4 sensors were used to record the movement of patients during each trial. These sensors were calibrated in all 3 Cartesian coordinates and through rotational motion about the z-axis. For calibration in the Cartesian plane, each sensor was mounted to the zero line upon a fixed rule. Each sensor was moved in increments of 1cm up to 15cm in both the positive and negative directions at 10s intervals. Linear traces of 15 distinct steps were obtained for both directions for all 4 sensors. The resolution for each sensor was also obtained in the Cartesian plane in a similar manner, with increments of 5mm up to 2cm in the positive and negative directions. Again, linear traces of 20 distinct steps were obtained for both directions. For rotational calibration, the sensors were

mounted upon a freely moving protractor. As with the Cartesian planes, the sensors were moved by 10° in both the positive (clockwise) and negative directions up to 360 degrees. Likewise, the rotational resolution of the sensors was obtained by moving the sensors by 1° up to 20° in 10s intervals. Linear traces with distinct steps in both the positive and negative directions were again observed.

Head in space, trunk and feet horizontal (yaw plane) movements were recorded using Polhemus™ Fastrak® motion analysis system (sampling frequency 30 Hz, latency 4 ms, accuracy 0.15 degrees RMS) acquiring at 100 Hz. Body position markers were placed on a lightweight adjustable helmet, the spinous process of C7 vertebra and dorsally on each foot. Surface electro-myography (EMG) signals were recorded from the left and right tibialis anterior (TA) muscle with the skin surface electrodes placed on the anterior shin. EMG signal was acquired at a sampling rate of 2 kHz, low-pass filtered by a second order Butterworth filter (cut-off 10 Hz). Horizontal eye in head rotations was recorded using bitemporal direct current electro-oculography (DC-EOG) and skin surface electrodes were placed on the external canthus of each eye and an earth electrode on the glabella. EOG signal was acquired at 250 Hz. In each trial, calibration of the EOG signal was carried out frequently by asking patients to shift their vision from a central visual target to one placed at 30 degrees left and right whilst keeping their head still.

The patients were instructed to find and align their body with the targets 'as quickly as possible' thus executing time-optimal turns. An octagonal wooden pen (diameter and height of 1.0 m) surrounded the subject to allow for safety and support, if necessary, during the experiment. However, subjects were instructed to not hold on to

the pen. Arrangement of all equipment was such that it would allow for unhindered whole body rotation and unrestricted 360 degrees visualisation. The sequence of LED signals was random and all subjects underwent two different sequences of LED cues that included 10 signals in each, with a break in-between of two minutes to allow for rest. Random sequences were used in order to prevent bias from learning effects (i.e., familiarity with the pattern of LED cues).

Data of timing of LED cues, kinematic characteristics of eye, head, trunk and feet during whole body rotation, EMG and EOG signals were acquired for offline analysis using 'Spike2 version 5.00' [Cambridge Electronic Design 1988-2003; Serial number 051327]. With the aid of this software we were able to quantitatively analyse latencies of movement onset (ms), gaze latency (ms), head-on-trunk displacement (ms), peak angular velocities of movement (degrees ms^{-1}), gain of first step (%) and number of steps (n) for each foot, latencies of muscle activity (ms), primary gaze amplitude (degrees), primary saccade amplitude (degrees) and number of saccades (n).

Latency of onset of movement was defined as the time taken to initiate movement after the appearance of the target (calculated for eyes and body segments). In turn, addition of eye and head latencies generated gaze latencies and subtracting the trunk from the head latencies yielded a head-on-trunk displacement signal. Peak velocities of head, trunk, right and left foot movement were obtained by differentiating Polhemus™ Fastrak® signals and calculated during the period of each visual cue. Gain of first step was taken to be the percentage of displacement in degrees obtained with the first step compared to the final desired displacement of the individual foot. The number of steps required to achieve final displacement was also noted. TA

latencies were measured from the onset of the visual cue to the EMG burst threshold (defined as 2-standard deviations from baseline). An average of the left and right TA EMG signal was taken due to insufficient number of traces to compare left and right signals independently. Primary gaze amplitude was obtained by adding EOG and head displacement signals and defined as the first burst in movement. Primary saccade amplitude was assessed as the initial eye movement after each visual cue and number of saccades was judged on the number of large fluctuations in the trace after each cue assessed by visual inspection. Traces were subject to background noise and movement in the baseline, thus primary saccade amplitudes were rejected if they were greater than 35 degrees (Anastasopoulos, Ziavra et al. 2009; Anastasopoulos, Ziavra et al. 2011).

The protocol of the trial was such that initial outward movement was unpredictable as subjects were not informed of the sequence of LED cues nor which way to turn and would thus have to randomly shift their gaze to locate the target and move in the corresponding direction. Conversely the return movement was predictable, as subjects knew to return back to the central LED target located at 0 degree. For analysis we subdivided data into unpredictable (outbound) and predictable (inbound) turns. Any occurrence of eye and body segment movement in the incorrect direction was excluded from analysis. Unpredictable targets were further subdivided into initially visible (45 degrees) and initially non-visible (90 degrees, 135 degrees, 180 degrees). This allowed us to investigate how prior awareness of target positioning can influence the parameters of spatiotemporal movements. Thus we were able to analyse responses to non-predictable initially visible targets (NP-V), non-predictable initially non-visible targets (NP-NV) and predictable (P) targets, most representative of

voluntary internally generated spontaneous movements of advanced PD, and in addition overall responses (O). Median (IQR) of NP-V, NP-NV, P and O conditions were calculated for each of the spatiotemporal parameters described above for all groups. Differences in medians were compared using Wilcoxon signed-ranks test ($p < 0.05$) to assess the significance of the differences between groups. In this way we were able to assess differences with age, advanced PD on optimal medical therapy only, bilateral STN or PPN-DBS in conjunction with optimal medical therapy and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy. Patients showed symmetric UPDRS limb scores (data not shown) and neither patients nor control spatiotemporal movements data were asymmetrical; thus, responses to 270 degrees and 225 degrees targets were pooled with those to 90 degrees and 135 degrees, respectively.

RESULTS

General Patterns

General inspection of the kinematic profiles of the different groups revealed strong co-ordination of eye, head, trunk and feet movement (**Figure 16**). Patterns of movement were initiated by eye saccades followed by head, trunk and feet, respectively. Traces with minimal artefact were obtained for both young and age-matched controls. Movement was least smooth in advanced PD subjects on optimal medical therapy only. These overall results are summarised in **Table 4**.

Latencies of movement

Median latencies were shortest in young controls, longer in age-matched controls, significantly increased further in advanced PD patients on optimal medical therapy only and slightly reduced with bilateral STN-DBS with further significant reductions noted with both bilateral PPN-DBS and simultaneous bilateral STN & PPN-DBS (ALL neurostimulation in conjunction with optimal medical therapy).

Advanced PD patients on optimal medical therapy only had significantly ($p < 0.02$) longer foot latencies compared to young controls that were reduced in age-matched controls and with bilateral STN-DBS in conjunction with optimal medical therapy, but not significantly. Bilateral PPN-DBS in conjunction with optimal medical therapy produced 35% reduction in foot latency ($p < 0.000001$). Simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy produced significantly reduced latencies in all axial motor segments (all $p < 0.05$). These findings are summarised in **Figure 17**.

In P conditions, trunk latencies were significantly increased in advanced PD on optimal medical therapy only compared to young controls ($p < 0.03$); again there was reduction in these latencies for age-matched controls and bilateral STN-DBS in conjunction with optimal medial therapy; however, this was not statistically significant. For NP-V condition, gaze latencies in advanced PD on optimal medical therapy were significantly longer compared to young controls ($p < 0.02$) and these were again reduced for age-matched and bilateral STN-DBS in conjunction with optimal medial therapy, but not significantly. There was insufficient eye / gaze latency data with bilateral PPN-DBS in conjunction with optimal medial therapy for analysis.

Head-on-trunk displacement

The overall head-on-trunk displacement was significantly increased in advanced PD on optimal medical therapy only compared with young ($p < 0.02$) and age-matched controls ($p < 0.05$). Noticeably, only simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy, produced significantly reduced head-on-trunk displacement ($p < 0.05$) as compared to advanced PD on optimal medical therapy only.

Peak angular velocities

The overall peak angular velocities were significantly different across groups in all body segments: peak head velocity ($p < 0.01$); peak trunk velocity ($p < 0.0001$); peak foot velocity ($p < 0.0001$) as compared to young controls. Differences between advanced PD on optimal medical therapy only as compared to age-matched controls or bilateral STN-DBS in conjunction with optimal medical therapy were not statistically significant despite relatively higher angular velocities exhibited with bilateral STN-DBS in conjunction with optimal medical therapy. Bilateral PPN-DBS in conjunction with optimal medical therapy produced 45% increase in foot velocity ($p < 0.000001$) as compared to advanced PD on medical optimal medical therapy only. Simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy produced significantly increased velocities (excluding head velocity) in all axial motor segments (all $p < 0.05$) as compared to advanced PD on medical optimal medical therapy only.

EMG latencies

EMG latencies of TA muscle were significantly longer in advanced PD with optimal medical therapy only compared to young controls ($p < 0.02$). In NP-V condition, TA latencies were significantly decreased in both young and age-matched controls compared to advanced PD with optimal medical therapy only ($p < 0.02$). There was reduction in TA latency with bilateral STN-DBS in conjunction with optimal medical therapy compared to advanced PD on optimal medical therapy only, but not significantly. There was, however, a significant reduction in TA latency with both bilateral PPN-DBS and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy group compared to advanced PD on optimal medical therapy only (both $p < 0.001$).

Primary saccade amplitudes, primary gaze amplitudes and number of saccades

There was no significant variance amongst values of initial saccade and gaze amplitudes in the different NP and P conditions between young controls, age-matched controls and advanced PD on optimal medical therapy only. However the overall number of saccades was significantly different across these three groups. A significant increase in number of saccades was noted in advanced PD on optimal medical therapy only compared to age-matched controls and young controls ($p < 0.05$) and ($p < 0.0001$), respectively, and the number of saccades was also higher in age-matched controls than young controls ($p < 0.005$).

With bilateral STN-DBS in conjunction with optimal medical therapy a reduction in number of saccades was noted compared to advanced PD patients on optimal medical therapy only ($p < 0.001$). There was no significant difference in the number of saccades between young, age-matched controls and bilateral STN-DBS in conjunction

with optimal medical therapy. Similarly, significantly reduced number of saccades were noted with bilateral STN-DBS in conjunction with optimal medical therapy and young controls when compared to advanced PD patients on optimal medical therapy only in the NP-NV condition ($p < 0.01$). These findings are summarised in **Figure 18**.

There was insufficient data to analyse changes in saccadic performance with bilateral PPN-DBS in conjunction with optimal medical therapy. Therefore, changes in saccadic performance with bilateral PPN-DBS in conjunction with optimal medical therapy along with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy are explored and discussed further in detail in **Chapter 3**, subsequently.

Maximum gain of displacement with first step and the number of steps

The overall percentage of displacement achieved with the first step (gain) was significantly higher in controls (young and age-matched) compared to advanced PD on optimal medical therapy only and bilateral STN-DBS in conjunction with optimal medical therapy. Gain was significantly higher in young controls compared to the advanced PD on optimal medical therapy only ($p < 0.001$) and STN-DBS in conjunction with optimal medical therapy ($p < 0.003$). Gain was significantly higher in age-matched controls compared to the advanced PD on optimal medical therapy only ($p < 0.03$). There was no statistically significant difference in gain between young and age-matched controls nor was there a statistically significant difference between age-matched controls and bilateral STN-DBS in conjunction with optimal medical therapy groups.

Gain was significantly higher in bilateral PPN-DBS in conjunction with optimal medical therapy and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy compared to the advanced PD on optimal medical therapy only ($p < 0.005$). There was again no statistically significant difference between age-matched and bilateral PPN-DBS in conjunction with optimal medical therapy and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy. The same results were found across NP and P conditions.

The overall number of steps was significantly increased in advanced PD on optimal medical therapy compared to young ($p < 0.01$) and age-matched ($p < 0.02$) controls. There was a reduction in number of steps with STN-DBS in conjunction with optimal medical therapy but this was not statistically significant. The overall number of steps was significantly decreased with bilateral PPN-DBS in conjunction with optimal medical therapy and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy compared to the advanced PD on optimal medical therapy ($p < 0.001$).

DISCUSSION

Chronic bilateral STN-DBS has been proposed to alleviate axial movement disturbances in advanced PD (Bejjani, Gervais et al. 2000; Faist, Xie et al. 2001; Maurer, Mergner et al. 2003; Ferrarin, Rizzone et al. 2004; Shivitz, Koop et al. 2006). We investigated numerous parameters including gaze displacement and axial motor

segment co-ordination during whole body turning in patients on optimal medical therapy with bilateral STN-DBS, bilateral PPN-DBS and simultaneous bilateral STN & PPN-DBS. 5 age-matched and 5 young subjects served as controls.

Our results indicate that STN-DBS in conjunction with optimal medical therapy reduces the number of saccades (4.4 ± 0.2 *vs*. 2.1 in advanced PD patients on optimal medical therapy only, $p < 0.001$). Greater number of saccades denotes a longer time in acquisition of the target in advanced PD patients on optimal medical therapy only compared to STN-DBS in conjunction with optimal medical therapy and thus a reduced ability to execute eye displacement. In addition, despite the eye latencies not being statistically significantly reduced in STN-DBS in conjunction with optimal medical therapy compared to advanced PD patients on optimal medical therapy only, they were nonetheless reduced in all conditions. We also confirmed the number of saccades to be greater in age-matched controls compared to younger subjects indicating a strong contribution of age on saccadic performance (Peltsch, Hemraj et al. 2011). What is more interesting is the further deterioration in accurate eye movement with advanced PD on optimal medical therapy only which is consistent with other studies in which PD patients are seen to be less able to suppress saccades (Chan, Armstrong et al. 2005) and show characteristic incidence of multiple saccades (Crawford, Henderson et al. 1989; Lueck, Tanyeri et al. 1992).

The BG is dysfunctional in PD and part of complex neuronal circuits integrating activity from multiple cortical areas with numerous outputs including those of the thalamo-cortical and brainstem pathways (Obeso, Rodriguez-Oroz et al. 2002). The STN is the only glutamatergic projection in the BG and thus its hyperactivity in PD

produces excessive excitation of the GPi and substantia nigra pars reticulata (SNr) neurons that over inhibit these thalamocortical and brainstem motor networks. The SNr neurons terminate onto the superior colliculus (SC) of the brainstem (Kato, Grantyn et al. 2006) and this BG-SC pathway serves to control saccadic eye movement. Thus the STN acts to modulate saccades by acting on the SNr. In PD, the SC is excessively inhibited due to STN hyperactivity. In contrast, stimulation of the STN could act to improve deficits in saccadic eye-movement control reversing this over-activity. Indeed a study by Yugeta *et* al. has associated particular saccadic eye movement and STN-DBS (Yugeta, Terao et al.).

In PD patients, the motion of turning challenges the subjects' ability to adequately balance their body's centre of gravity, more so than with linear movement and in addition requires adequate shift in gaze. PD patients are more inclined to be selectively dependent on visual information for motor actions (Bronstein, Hood et al. 1990; Guehl, Dehail et al. 2006) and we suggest that longer latency in eye movement can thus compromise postural stability. The observed sequence of individual body segment movement commencing with eye re-orientation, consistent with previous findings using the same paradigm (Hollands, Ziavra et al. 2004; Anastasopoulos, Ziavra et al. 2009; Anastasopoulos, Ziavra et al. 2011), also suggests that the co-ordination of eye and inter-segmental body movement (most significantly seen between eyes and feet) demonstrates a principal eye-limb coupling network (Hollands, Ziavra et al. 2004).

It is already well established that visual cues such as obvious lines on the floor can normalise patterns of gait in PD patients (*a phenomena known as kinesia paradoxa*)

indicating that the BG favours cognitive processes that lead to motor actions. Neurophysiological evidence of decision signals has been found in multiple areas of the brain including the SC (Horwitz, Batista et al. 2004; Horwitz, Batista et al. 2004). We thus postulate that eye movement accuracy may be a prerequisite in neural decision making for motor segment movement and suggest that STN-DBS through the STN-SNr circuit can contribute to the improvement in axial mobility through improved visual information. What remains to be investigated is the circuitry in which visual information arises to afford support for movement in the dysfunctional BG. Considering recent anatomical studies revealing projections from the SC to the BG, substantia nigra pars compacta (SNc), the ventral tegmental area (VTA) and the STN, it is possible that this visual information reaches the BG via these pathways (Shires, Joshi et al. 2010).

The implications of establishing improvements in saccadic eye movements in patients with STN-DBS are that, in knowing that saccade parameters are an indicator of BG output (due to the BG-SC pathway) it may be a potential measure of post-operative outcome in patients with STN-DBS. Indeed, previous studies have investigated these parameters as potential biomarkers in monitoring disease and disease progression (Michell, Xu et al. 2006) but further investigation is needed into its applicability in tracking performance of STN-DBS patients.

Our observation that bilateral STN-DBS in conjunction with optimal medical therapy has only restricted efficacy on parameters of whole body rotation is surprising given the documented synergistic improvement of STN-DBS and L-dopa in comparison to L-dopa alone on axial movement of gait and posture control (Bejjani, Gervais et al.

2000; Faist, Xie et al. 2001; Ferrarin, Rizzone et al. 2004). The disparity with previous findings may be due to the different protocol used in these studies that did not assess rotational movement and measured either different parameters of gait analysis or used the clinical UPDRS sub-scores that may not be sensitive enough (Ferrarin, Rizzone et al. 2004). Most studies assessed linear movement (linear gait) that is known to be less challenging in instigating postural control than angular movement. The restricted improvement in our study may suggest different underlying neural circuits for rotational movement. Conversely Xie *et* al. detailed only moderate enhancement in gait performance with STN-DBS and Krack *et* al. also found that gait disorders respond poorly to STN-DBS (Xie, Krack et al. 2001; Krack, Batir et al. 2003). The limited improvement in our results is reflective of these previous findings.

Having said this, there was some improvement consistently across all parameters: latencies of movement were shorter, peak angular velocities were increased, as was the gain in first step and number of steps were reduced with bilateral STN-DBS in conjunction with optimal medical therapy compared to advanced PD on optimal medical therapy only. In some cases these showed improvement to the level of age-matched controls – statistical analysis showed distinctive differences between age-matched and advanced PD on optimal medical therapy only but not age-matched and STN-DBS in conjunction with optimal medical therapy. The differential effects seen is consistent with a study by Guehl *et* al. that demonstrated STN-DBS does not have the same effect as L-dopa therapy on various posturometric parameters (Guehl, Dehail et al. 2006). Despite amelioration in most variables, these were not statistically significant. Limitations in our findings may possibly include small sample size under-powering our study.

The minimal improvement of STN-DBS on axial mobility suggests non-dopaminergic systems may be involved in postural regulation (Maurer, Mergner et al. 2003). We have already suggested a role for the BG-SC pathway in cognitive proceedings intervening between vision and motor action, such as target acquisition and saccade performance.

In addition to the SNr, the PPN, another terminal site for basal ganglia output, is also under the influence of the STN (Garcia-Rill, Kinjo et al. 1990). The PPN has been implicated as a potential region for improving gait and balance disorders and a target for DBS in advanced PD (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Moro, Hamani et al. 2010; Hamani, Moro et al. 2011; Thevathasan, Coyne et al. 2011). Clinical improvements on axial motor disturbances may be consequential to its role in axial mobility projecting efferent pathways to the brainstem and spinal cord. Thus, direct manipulation of the PPN itself may influence direct pathways that control movement via non-dopaminergic pathways (Jenkinson, Nandi et al. 2009). As projections from the STN input onto the PPN, STN-DBS may also be indirectly affecting axial motor symptoms via the PPN (Guehl, Dehail et al. 2006).

Direct stimulation of the SNr has been seen to improve axial motor symptoms but not distal mobility (Chastan, Westby et al. 2009). Chasten *et* al. found that by contrast, STN-DBS improved both distal and axial symptoms and suggested that as the SNr and STN project descending efferents to the PPN, stimulation of these regions accounts for their efficacy on axial motor disturbance.

The majority of significant improvement of STN-DBS (and L-dopa therapy) has consistently been seen in symptoms of tremor, rigidity and bradykinesia (Benabid, Chabardes et al. 2009). Having observed a lack of improvement in our own axial parameters with STN-DBS, it is possible that on top of previous dopaminergic dysfunction accounting for limb signs, the engagement of non-dopaminergic systems in advanced PD explains the origin of axial motor symptoms. Our series of six advanced PD patients on optimal medical therapy only exhibited the worst axial mobility in all parameters with the highest number of steps and least amount of displacement in their first step suggesting other non-dopaminergic system involvement affecting motor capacity.

Noticeably, head-on-trunk displacement was significantly greater in advanced PD on optimal medical therapy only and with bilateral STN-DBS in conjunction with optimal medical therapy. This could indicate that rotational movement is less en-bloc in advanced PD due to trunk rigidity and is not alleviated by bilateral STN-DBS in conjunction with optimal medical therapy. Indeed abnormal trunk flexion is a typical feature of PD (Ferrarin, Rizzone et al. 2004). Assessing each leg independently can allow us to determine contribution of each to turning mobility as PD is characteristically an asymmetrical disease (Boonstra, van der Kooij et al. 2008). Uneven findings in the foot were, however, not noted in our studies.

We also identified that velocity of angular rotation was the principal age-related deterioration in movement as all of the older groups had significantly reduced angular velocities in comparison to young controls.

Above, we established that beneficial effects of STN-DBS on saccade performance might partially help to improve the axial motor symptoms of advanced PD. The pathophysiological mechanisms of gait and balance disturbance and its modification by STN-DBS remain speculative. As such, further studies, such as this, were warranted to determine the role of STN-DBS as well as PPN-DBS on visuopostural control and how visual circuitry feeds back to the BG. This may allow for better management of the particularly difficult and debilitating problems of posture and gait dysfunction in advanced PD.

The minimal improvement of STN-DBS on axial mobility discussed above suggested non-dopaminergic systems may be involved in postural regulation (Maurer, Mergner et al. 2003). We have already suggested a role for the BG-SC pathway in cognitive proceedings intervening between vision and motor action, such as target acquisition and saccade performance, as one possible explanation.

The present study demonstrated that bilateral PPN-DBS in conjunction with optimal medical therapy produced 35% reduction in foot latency and 45% increase in foot velocity (both $p < 0.000001$). Furthermore, simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy produced significantly reduced latencies and increased velocities (excluding head velocity) in all axial motor segments (all $p < 0.05$), providing objective evidence of performance changes in the relevant axial motor segments, to account for at least some of the clinical improvements observed in **Chapter 1**, in keeping with recent literature (Thevathasan, Cole et al. 2012): simultaneous bilateral STN & PPN-DBS offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD.

CONCLUSION

Beneficial effects of bilateral STN-DBS on saccade performance may partially help to improve the axial motor symptoms of advanced PD. The pathophysiological mechanisms of gait and balance disturbance and its modification by STN-DBS still remain speculative. Performance changes in the relevant axial motor segments due to bilateral PPN-DBS associated with bilateral STN-DBS, in conjunction with optimal medical therapy, may be useful in improving gait ignition failure (freezing) for the treatment of gait disturbance in advanced PD. This may allow for better management of the particularly difficult and debilitating problems of posture and gait dysfunction in advanced PD.

Chapter 3

Effects of subthalamic and pedunculopontine nucleus-deep brain stimulation on saccades in advanced Parkinson's disease

Keywords: deep brain stimulation (DBS), subthalamic nucleus (STN), pedunculopontine nucleus (PPN), Parkinson's disease (PD), saccades, antisaccades

ABSTRACT

Objective: To explore one possible mechanism by which the improvement in axial motor symptoms of advanced PD with STN & PPN-DBS treatment may be mediated.

Background: The STN, a component of the basal ganglia (BG), is known to be involved in controlling saccades. The PPN has extensive connections with the BG. Recently, PPN-DBS has been explored as a possible target to treat the axial motor symptoms (principally gait freezing and loss of postural control) of advanced PD. Here we consider the relative effects of STN and / or PPN-DBS on both initiation and inhibition of saccades in advanced PD.

Methods: 5-patients with advanced PD, while on optimal medical therapy, performed two different oculomotor tasks whilst OFF-DBS, ON bilateral STN-DBS, ON bilateral PPN-DBS and ON simultaneous bilateral STN & PPN-DBS. Twelve healthy young volunteers, age-matched individuals and age-matched patients with early PD acted as controls. The first task involved visually guided saccades (that are reflexive) and the second, antisaccades (that are volitional). Saccadic latency, accuracy and velocity were recorded for both the visually guided and antisaccade tasks, while prosaccades (errors) were measured for the antisaccade task alone.

Simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy produced the greatest improvement in the latencies and accuracies for the visually guided saccades compared to OFF-DBS ($p < 0.001$). Interestingly, however, simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy also produced a significant additional improvement compared to STN-DBS in conjunction with optimal medical therapy alone on the number of prosaccades ($p < 0.01$) and the velocity ($p < 0.05$), indicating a significant contribution in saccadic improvement due to PPN-DBS.

Conclusion: PPN-DBS may thus influence the functional output of the superior colliculi for both saccade initiation and inhibition in advanced PD in addition to the effects of STN-DBS. This is a novel finding in the neurophysiological influence of the PPN and may help to explain some of the observed clinical effects of PPN-DBS on axial motor function, in particular, on postural control and prevention of falls in advanced PD.

INTRODUCTION

PD is a progressive neurodegenerative disease with loss of dopaminergic neurons in the BG that is characterised clinically by tremor, rigidity, bradykinesia and postural instability (Parkinson 1817; Tian, Tang et al. 2011). The BG, whose dysfunction is central to PD pathology, have two output pathways implicated in the control of voluntary movement: the thalamocortical parallel pathways (Alexander, DeLong et al. 1986) and the brainstem motor networks (Hikosaka, Takikawa et al. 2000). Part of the oculomotor fibres of the thalamocortical pathways project back to the frontal eye field and supplementary eye field, although not much is known about its neurophysiological and pathophysiological aspects. In contrast however, the role of the brainstem outflow tracts on saccadic eye movement has been shown not only anatomically but also physiologically and pharmacologically (Hikosaka, Takikawa et al. 2000; Fawcett, Dostrovsky et al. 2005). Through the BG-SC pathway and the corticotectal pathways, the superior colliculus is the common terminal for controlling saccadic eye movements. Therefore, saccades reflect the output of the basal ganglia, and can be a good indicator of basal ganglia function (Yugeta, Terao et al.).

PD impairs not only somatomotor functions, but oculomotor functions as well. Saccades are defined as "rapid eye movements that are used to quickly bring the fovea, the portion of the retina that picks up the most detailed visual information, to bear on specific portions of the visual field" (Trottier and Pratt 2005). As the ability to acquire high acuity visual information is critical to our successful interaction with the environment, and as the fovea only subtends about three degrees of the visual field (Findlay and Walker 1999), saccades are produced frequently throughout each day.

Therefore, any problem in saccade processing, as occurs in PD, has a profoundly detrimental effect on the functional independence of patients, including in complex motor functions that are aided by visual feedback like gait and postural control (for prevention of falls).

Contemporary research has explored the PPN in primate models as a possible target for intervention to improve some of the axial motor symptoms in advanced PD (Nandi, Aziz et al. 2002; Nandi, Liu et al. 2002; Jenkinson, Nandi et al. 2005; Jenkinson, Nandi et al. 2006). Simultaneous bilateral stimulation of the STN and PPN using DBS has been proposed as a treatment option for severe PD patients who are not only refractory to medical therapy but also have prominent axial symptoms *viz*. gait disturbance and postural instability (Ferraye, Debu et al. 2008). In recent studies on patients with advanced PD, PPN-DBS associated with standard STN-DBS was shown to be useful in improving gait and optimising the dopamine-mediated ON-state, particularly in those whose response to STN only DBS has deteriorated over time (Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010; Hamani, Moro et al. 2011).

However, STN and PPN-DBS studies to date have not attempted to consider the effects of this therapy on eye movements. The aim of this study was to assess the effects of this novel modality of DBS *viz*. both STN and PPN-DBS, on saccades – a measure that has been demonstrated to be a valid adjunct for quantifying the outcomes of DBS in PD patients, as well as being a source for functional improvement in everyday life, especially balance and co-ordination (Yugeta, Terao et al. ; Kato, Miyashita et al. 1995). Furthermore, the results should help provide novel insights into the pathophysiology of PD and the neural networks involved.

METHODS, MATERIALS & PARTICIPANTS

Subjects

Four groups of subjects took part in the study. The first group consisted of 5-patients with advanced PD undergoing bilateral STN and PPN-DBS (from **Chapter 1**; excluding P5 due to clinical and ethical reasons as detailed in **Chapter 1**). They were all Hoehn and Yahr Scale Stage 3 (mild to moderate bilateral disease; some postural instability; physically independent) and above in the OFF-DBS condition. All continued to take their usual anti-parkinsonian medication as usual during the study (optimal medical therapy). Twelve patients with early PD (Hoehn and Yahr Scale Stage 2 and below, i.e., bilateral disease, without impairment of balance) who did not have DBS (68 ± 8.36 years), 12 age-matched healthy subjects (62.75 ± 5.57 years) and twelve healthy young controls (25.83 ± 3.76 years) served as controls. All control groups contained equal numbers of male and female participants. The Ethics Committee of Imperial College Healthcare NHS Trust approved the study. Written informed consent was obtained from all participants in the study. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Experimental setup

For this study, the experimental setup reported by Yugeta *et* al., 2010 and Kato *et* al., 1995 was utilised (Yugeta, Terao et al. ; Kato, Miyashita et al. 1995). The subjects were seated in a customised chair and their head immobilised with the built-in

occipital clamp. Direct current (DC) electro-oculogram (EOG) was recorded with 3 Ag-AgCl gel electrodes (bilateral outer canthi for horizontal eye movement and one on the glabella to earth the circuit) with low-pass filtering at 20 Hz and digitising at a sampling rate of 500 Hz. EOG was calibrated prior to each experiment up to a maximum laser target point at 30 degrees left or right of the midline (**Figure 19**).

Experimental procedures

Two oculomotor tasks – visually guided saccades (VGS) and antisaccades (AS) were performed during bilateral STN-DBS, bilateral PPN-DBS, diagonal stimulation (unilateral STN-DBS and contralateral PPN-DBS), unilateral STN and PPN-DBS and simultaneous bilateral STN & PPN-DBS. At least one hour after turning the DBS OFF, the same tasks were performed in the five patients in the OFF-DBS state, on optimal medical therapy only. To exclude order effects, the ON-DBS and OFF-DBS experiments were randomised in the five patients. The study was thus a double-blinded controlled trial, because both the experimenter and the subjects did not know their stimulation status. All experiments were performed 90 – 120 minutes after administration of patients' usual anti-parkinsonian medication (optimal medical therapy).

VGS task: a fixation laser point was turned on at 0 degree, and the subjects were instructed to fixate on this point. This was then turned off after 3 seconds, and simultaneously a new target laser point (cue) was turned on at 5, 10, 15, 20 or 30 degrees to the left or right randomly, and the subjects were instructed to make a saccade as quickly as possible to the new position.

AS task: a fixation point and a cue point were turned on and off in the same way as in the VGS task but this time only at 30 degrees to the left or right randomly; the subjects were instructed to make a saccade towards the opposite direction of the location of the cue point. In other words, the actual target point for the saccade was a point opposite to where the cue stimuli appeared and had to be a full 30 degrees to the opposite side.

Data analysis and statistical assessment

In order to omit artefactual saccades, inclusion and exclusion criteria were set. All the data was extracted into Analysis© software, which was used for calibrating and measuring saccades (**Figure 20**). An eye movement (candidate for a saccade) was included in the analysis if its velocity and acceleration exceeded threshold values (28 degrees s^{-1} and 90 degrees s^{-2} respectively). Also, after the onset of a saccade the velocity had to exceed 88 degrees s^{-1}, and this suprathreshold velocity had to be maintained for at least 10 msec. Saccades with a latency of less than 60 ms were classified as anticipatory and were excluded from further analyses. Calibration for both tasks was carried out separately, both before and after starting the tasks in order to ensure accuracy. Due to the small number of subjects Wilcoxon signed-ranks test ($p < 0.05$) was used for statistical analysis.

Four parameters were measured: latency, accuracy and velocity for both the VGS and AS tasks, and the number of prosaccades was calculated exclusively for the AS task. The saccade accuracy was calculated as the ratio of the amplitude of the first saccade in degrees to the actual target presented in degrees. The number of prosaccades was calculated by counting the number of saccades the subjects made toward the target in

error rather than the opposite direction as required of the AS task. The velocity was calculated using digital differentiation. In the antisaccade task, prosaccadic velocities were not included in the velocity analysis. This was because prosaccades tend to be hypometric and fragmented and their number reduces with DBS – to look at the effects of DBS on velocity alone, they had to be omitted.

RESULTS

Visually Guided Saccades (VGS) Task

All the subjects performed better in the VGS task as compared to the AS task (reduction in latency and number of prosaccades and an increase in accuracy and velocity), from the young controls to advanced PD on optimal medical therapy only. The general trend of the results was that with increasing age the latencies seemed to increase, the longest recorded in advanced PD on optimal medical therapy only. An improvement, i.e., a reduction in latency and increase in accuracy for reflexive saccades and decrease in latency and number of prosaccades whilst an increase in velocity was seen for volitional saccades with bilateral STN-DBS in conjunction with optimal medical therapy. Simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy produced an even greater on-top effect of improvement in the volitional saccade task (AS) velocities (increased) and prosaccades (decreased). **Figure 21** illustrates the findings for the different groups, while **Figure 22** summarises the results for the individual subjects. The overall results of only the groups (i.e., a common pool of saccades per group) have been included for ease of

understanding because the individual patient results were in agreement with the grouped data.

The general trend of increasing latencies from the young healthy controls to the age-matched and PD patients (early and advanced, in that order) on optimal medical therapy only and a decrease with DBS was found to be statistically significant ($p < 0.001$). Bilateral STN-DBS in conjunction with optimal medical therapy produced a significant decrease of 40.70% ($p < 0.05$) in the latency as compared to advanced PD patients on optimal medical therapy only. Furthermore, a greater decrease of 49.62% ($p < 0.01$) was produced by simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy, again in comparison to advanced PD patients on optimal medical therapy only. Though producing a greater improvement in the latency, simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy was not statistically significantly different to bilateral STN-DBS in conjunction with optimal medical therapy. Also, bilateral PPN-DBS in conjunction with optimal medical therapy produced only a limited decrease in the latency.

The next parameter considered was the accuracy of the saccades. Accuracy was defined as the ratio of the first saccade to the actual desired target angle. There was a general trend of decreasing accuracy from the younger to older controls, with the advanced PD patients on optimal medical therapy only executing the least accurate saccades. Interestingly, the near perfect accuracies seen in the healthy controls can be attributed to a phenomenon called the floor-ceiling effect – slight overshooting and undershooting of saccades averages out to give values close to 1 (Kan, Niel et al. 2012). Bilateral STN-DBS in conjunction with optimal medical therapy, however,

seemed to improve their accuracy on its own, and, in combination with bilateral PPN-DBS whereas PPN-DBS in conjunction with optimal medical therapy alone appeared to have no effect. This result was statistically significant ($p < 0.001$).

Bilateral STN-DBS in conjunction with optimal medical therapy produced an increase of 109.70% ($p < 0.05$) in the accuracy compared to optimal medical therapy only. An increase of 117.07% ($p < 0.05$) in the accuracy was noted with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy as compared to optimal medical therapy only, however, the difference between the additive effect of simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy over bilateral STN-DBS in conjunction with optimal medical therapy on its own was not statistically significant (**Figure 21**).

A general trend was noted towards decreasing velocities with age, with advanced PD on optimal medical therapy only being the slowest. Simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy seemed to improve velocities as well as bilateral STN-DBS in conjunction with optimal medical therapy alone. This pattern of velocities was not statistically significant, however. Once again, bilateral PPN-DBS in conjunction with optimal medical therapy on its own did not produce any statistically significant improvement in the velocities.

Antisaccade (AS) task

The AS task followed a similar pattern to the parameters in the VGS task, with latencies tending to increase with age and with the advanced PD patients on optimal medical therapy having the longest latencies compared to young controls ($p < 0.001$).

DBS did improve the latencies as compared to optimal medical therapy only, however, with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy producing a decrease in latency of 50.44% ($p < 0.01$) and bilateral STN-DBS in conjunction with optimal medical therapy only, producing a decrease of 46.89% ($p < 0.01$).

Bilateral PPN-DBS in conjunction with optimal medical therapy in this case increased the latency by 16.72% as compared to optimal medical therapy only but this was not statistically significant. A graphical representation of the AS task data is given for the data as divided into groups (**Figure 23**) and for each individual patient (**Figure 24**). Once again, only the statistically significant data for the pooled data across all subjects in each group was included for ease of interpretation and due to the agreement of the individual data with the grouped set.

There was similarly a general trend of decreasing accuracy from the younger to older controls, with the advanced PD patients on optimal medical therapy performing least accurately. Bilateral STN-DBS in conjunction with optimal medical therapy, however, both alone and in combination with bilateral PPN-DBS seemed to improve their accuracy whereas bilateral PPN-DBS in conjunction with optimal medical therapy alone seemed to have only a negligible effect. This trend was not statistically significant.

In keeping with published literature we used the total number of prosaccades as a measure of improvement or worsening in the AS task (Yugeta, Terao et al. ; Kato, Miyashita et al. 1995). The general trend of worsening of the parameters with age

and advanced PD on optimal medical therapy only, with young controls having 70% fewer prosaccades per 20 saccadic trials compared to advanced PD patients on optimal medical therapy. Bilateral STN-DBS in conjunction with optimal medical therapy, both alone and in combination with bilateral PPN-DBS decreased the number of prosaccades whereas bilateral PPN-DBS in conjunction with optimal medical therapy alone increased the number of prosaccades.

The 63.79% improvement (i.e., reduction in number of prosaccades) produced by simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy as compared to optimal medical therapy only was statistically significant ($p < 0.01$). The 31.76% improvement produced by bilateral STN-DBS in conjunction with optimal medical therapy as compared to optimal medical therapy only was also found to be statistically significant ($p < 0.01$). The effect of simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy was significantly different from the effect of STN-DBS in conjunction with optimal medical therapy alone ($p < 0.01$). The slight decrease in the number of prosaccades produced by PPN-DBS in conjunction with optimal medical therapy alone was not statistically significant when compared to optimal medical therapy only.

Saccadic velocity in AS results also matched the previous trend of parameters decreasing with age and being slowest in the advanced PD patients on optimal medical therapy only. This overall trend was found to be statistically significant ($p < 0.001$). There was an increase of 48.85% ($p < 0.01$) produced by simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy as opposed to a smaller increase of 37.89% ($p < 0.01$) produced by bilateral STN-DBS in

conjunction with optimal medical therapy alone when compared to optimal medical therapy only. The on-top effect seen with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy when compared to bilateral STN-DBS in conjunction with optimal medical therapy alone was statistically significant ($p < 0.05$). These findings are summarised in **Table 5**.

The next best improvement was produced by ON diagonal stimulation (unilateral STN and contralateral PPN-DBS) followed by ON unilateral STN and PPN-DBS, both in conjunction with optimal medical therapy (both $p < 0.001$). The main findings of the study are depicted in **Figures 25 & 26** for the VGS task and **Figure 27** for the AS task. The results can be summarised as follows:

1). Both reflexive and volitional saccades are affected by age. Early and advanced PD patients were the most seriously affected in that order, faring worse than age-matched controls.

2). Bilateral STN-DBS in conjunction with optimal medical therapy produces improvement in latency and accuracy for reflexive saccades and latency, velocity and number of prosaccades for volitional saccades.

3). Simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy produces an even greater on-top effect of improvement in the volitional saccade task (AS) velocities and prosaccades.

4). The next best improvement was produced by diagonal stimulation (unilateral STN and contralateral PPN-DBS), followed by unilateral STN and PPN-stimulation (both $p < 0.001$).

5). Bilateral PPN-DBS alone has no statistically significant effect on volitional or reflexive saccades.

DISCUSSION

In this study, it was found that both reflexive saccades like VGS and volitional ones like AS deteriorate with age and are significantly affected by PD, but may be improved by DBS.

The former finding has been found by numerous studies looking at the effects of age and PD on saccades (Rascol, Clanet et al. 1989; Vidailhet, Rivaud et al. 1994; Briand, Hening et al. 2001). Thus, our results confirm those in the current literature demonstrating that indeed age and PD are detrimental to all parameters of both volitional and reflexive saccades. The reason behind this has been discussed previously – with age there is a significant loss of neurons and neural processing takes longer, and hence it may be reasoned that all motor responses, both reflexive and voluntary are adversely affected (White, Saint-Cyr et al. 1983; White, Saint-Cyr et al. 1983; Rascol, Clanet et al. 1989; Vidailhet, Rivaud et al. 1994; Briand, Hening et al. 2001).

The fact that bilateral STN-DBS in conjunction with optimal medical therapy produces an improvement in various saccadic parameters has been documented before, although there are some differences with our findings. Yugeta *et* al. showed that STN-DBS improves both reflexive and volitional saccades – they found that with STN-DBS there were shorter latencies and increased amplitudes for the reflexive saccade tasks ($p < 0.001$) (Yugeta, Terao et al.). This was similar to our findings in

that latencies were improved ($p < 0.01$); however the change in velocity in our study was not statistically significant. Yugeta *et* al. also found that in the volitional AS tasks the improvement in accuracy with STN-DBS was not statistically significant (Yugeta, Terao et al.), in contrast to the improvement documented in this study. The number of prosaccades (errors) in the AS task was found to be significantly decreased ($p < 0.001$) by Yugeta *et* al. (Yugeta, Terao et al.), a finding confirmed in the present study (**Figure 21**).

There are two current theories regarding BG function and DBS that may be invoked for analysing the bilateral STN-DBS in conjunction with optimal medical therapy findings of this study. The first is the rate model which proposes that when DBS is applied to the STN, it reduces its firing rate and hence the excessive inhibitory output through the GPi-SNr circuit, implying that bilateral STN-DBS should not only facilitate initiation of saccades but also increase the frequency of unwanted prosaccades to cue in the AS task (Inagaki, Hirata et al. 2011). This should result in bilateral STN-DBS producing an improvement in the VGS task but more prosaccades and worse accuracy in the AS task. This, however conflicts with the results of the present study. Bilateral STN-DBS in conjunction with optimal medical therapy decreased the frequency of prosaccades and improved AS accuracy, suggesting that DBS at least partially restored the inhibitory control of reflexive saccades. This restorative effect indicates that bilateral STN-DBS helps to modulate the inhibitory function of the BG in PD, setting the excitability of SC at an appropriate threshold, both for initiating and inhibiting saccades. This result seems consistent with the suggestion that the STN plays an important role in keeping the eye position fixed (Matsumura, Kojima et al. 1992).

The second model of the BG circuit known as the oscillation model, better explains our results as compared to the rate model mentioned above. Studies performed recently on the BG and its related structures have taken into account oscillations in the BG (Boraud, Bezard et al. 1996; Wichmann, Bergman et al. 1999; Raz, Vaadia et al. 2000; Brown and Williams 2005). In PD, beta band oscillations in BG are abnormally elevated. A disruption in the synchronisation of these beta band oscillations by gamma band oscillation is required to fulfil motor commands and override the elevated threshold for saccade generation, because the gamma band appears to be more conducive to movement. Therefore, bilateral STN-DBS would decrease the pathological beta band oscillations and facilitate movement in PD by enhancing the gamma band.

Although this process lowers the threshold for movement for the BG, it does so by actually reducing the output of the BG to its connecting structures. According to Yugeta *et* al., "reduction in the oscillatory activities by DBS would help maintain the appropriate SC excitability required for saccade initiation and inhibition by normalising the 'leaky' suppression exerted by the BG and decrease the emergence of unwanted saccades to cue" (Yugeta, Terao et al.). Therefore, bilateral STN-DBS facilitates the initiation commands for saccades while offsetting the inhibition commands. Furthermore, it has been proposed by the same authors that the pathological beta band oscillations might also disrupt the processing involved in saccade inhibition at the cortical and subcortical regions via disruption of the BG-thalamocortical pathway (Murer, Tseng et al. 2002). Bilateral STN-DBS would

occlude this disruptive input and enable effective neural processing in these cortical and subcortical circuits, thus facilitating saccades.

The AS task has been used as a gold standard for measuring the ability to inhibit unwanted saccades *viz*. it is a volitional task. In this study, the frequency of prosaccades in the AS task was higher in patients with advanced PD on optimal medical therapy only than in controls, which is consistent with previous reports (Kitagawa, Fukushima et al. 1994; Briand, Strallow et al. 1999; Chan, Armstrong et al. 2005). The occurrence of prosaccades in the AS task has been explained by the failure of the prefrontal cortex to inhibit the SC directly via the descending pathway (Fukushima, Fukushima et al. 1994; Condy, Rivaud-Pechoux et al. 2004; Pierrot-Deseilligny, Milea et al. 2004) although some involvement of the BG (i.e., the caudate nucleus) has also been suggested for AS (Lasker, Zee et al. 1987; Everling and Fischer 1998; Peltsch, Hoffman et al. 2008). Therefore, bilateral STN-DBS might specifically affect the inhibitory mechanism of saccades mediated by the BG output through the GPi-SNr outflow rather than that mediated by the frontal cortex, leaving the frequency of prosaccades unaffected.

Until now, the discussion has focussed on the effects of bilateral STN-DBS on saccades in advanced PD. However, the novel aspect in our study was the effect of bilateral PPN-DBS in conjunction with optimal medical therapy on saccades in advanced PD patients. These effects alone and in combination with bilateral STN-DBS were recorded. Interestingly, acting alone bilateral PPN-DBS in conjunction with optimal medical therapy had no statistically significant effect on any of the parameters for both the AS and VGS tasks. However, bilateral PPN-DBS in

conjunction with optimal medical therapy and in combination with bilateral STN-DBS produced an increased improvement in the velocity and prosaccade parameters for the VGS (reflexive) task and the accuracy and prosaccades in the AS (volitional) task. This is an important finding, especially as studies that have looked at bilateral PPN-DBS hitherto have not reported any effects on eye saccades.

Also, anatomically and physiologically, the role of the PPN in the functional loops controlling saccades mentioned above has not been ascertained; unlike the well-documented involvement proposed for the STN. This enhancing effect brought on by the combination of bilateral PPN-DBS with bilateral STN-DBS in conjunction with optimal medical therapy was statistically significantly larger than the effect of bilateral STN-DBS in conjunction with optimal medical therapy alone for the AS velocities and number of prosaccades. Furthermore, as DBS produces improvement of saccades towards the contralateral side, diagonal stimulation (unilateral STN-DBS and contralateral PPN-DBS in conjunction with optimal medical therapy) was superior to unilateral STN & PPN-DBS in conjunction with optimal medical therapy because it improves saccades for both right and left gaze, as opposed to unilateral STN & PPN-DBS in conjunction with optimal medical therapy that only improves saccades towards one side, highlighting the contribution of PPN-DBS (in addition to STN-DBS) to improvements in saccadic performance. This novel observation that PPN-DBS facilitates the effects of STN-DBS suggests a role for it in the GPi-SNr-SC loop; a finding that opens up interesting neurophysiological and neuroanatomical possibilities, in particular, it may help explain the manner in which PPN-DBS may influence axial motor function in PD as discussed below.

Some studies that have considered the effect of PPN-DBS have shown that modulation of the activity of PPN with DBS may be beneficial in the treatment of gait dysfunction and akinesia (Mena-Segovia, Bolam et al. 2004). This is because the PPN is involved in locomotion, control of posture, and behavioural states (i.e., wakefulness, rapid eye movement sleep). Interestingly, a study by Thevathasan *et* al. (Thevathasan, Coyne et al. 2011) set out to investigate how PPN-DBS improved gait employed two possible mechanisms: attentional augmentation and enhanced motor function. Their results suggested that the improvements seen in certain parameters of gait were due to a benefit in motor performance, rather than augmentation of attention (Thevathasan, Coyne et al. 2011). Our study may shed further light on the neurophysiological pathways that help to achieve this, i.e., the influence of bilateral PPN-DBS on the GPi-SNr inhibitory outflow.

Another study on PPN-DBS demonstrated that "stimulation of the PPN induced significant regional cerebral blood flow increment in subcortical regions such as the thalamus, cerebellum and midbrain as well as different cortical areas involving medial sensorimotor cortex extending into caudal supplementary motor area" (Ballanger, Lozano et al. 2009). In the said study the authors demonstrated that PPN-DBS in advanced PD resulted in blood flow and presumably neuronal activity changes in subcortical and cortical areas involved in balance and motor control, including the mesencephalic locomotor region (e.g., PPN) and closely interconnected structures within the cerebello-(rubro)-thalamo-cortical circuit. This suggested that stimulation of the PPN might cause functional changes in neural networks associated with motor control. The fact that these very motor cortex regions as well as the midbrain (more specifically the SC) are involved in the control of saccades may suggest a role for the

PPN in controlling eye movements. However, the fact that bilateral PPN-DBS in conjunction with optimal medical therapy alone in the present study found no statistically significant improvement in any saccadic parameter suggests these structural circuits are more complex than those of the STN.

Furthermore, the amplified improvement when STN and PPN-DBS were combined suggests that there is some overlap and interaction in the neural circuits controlling saccades from both these nuclei. The present study thus demonstrates that bilateral PPN-DBS in conjunction with optimal medical therapy has no direct effect on controlling saccades on its own, in keeping with our earlier findings in **Chapter 2**, but does have an indirect, beneficial, modulatory effect on them, evidenced by the fact that bilateral PPN-DBS in conjunction with optimal medical therapy produces improvement in both reflexive and volitional saccadic parameters when deployed in combination with bilateral STN-DBS.

Various studies have reported that of the BG nuclei, the substantia nigra pars compacta and the STN receive the bulk of the PPN efferents (Lavoie and Parent 1994; Nandi, Jenkinson et al. 2008). This suggests that a possible mechanism for the improvement in various saccadic parameters by the combination of STN and PPN-DBS could be via these anatomical connections with the STN. This added improvement produced by the PPN working with the STN could perhaps be facilitated by helping the STN improve saccadic function through the oscillation model alluded to above.

CONCLUSION

The present study demonstrates that simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy work synergistically to improve both reflexive and voluntary saccades in advanced PD. This is a novel finding and builds on previous work that looked at the effect of STN-DBS alone and provides an insight into the possible neural motor control mechanisms and pathways involved in PD.

In the current clinical management of advanced PD, PPN-DBS is being explored as an important adjunct to STN-DBS in patients with prominent axial motor and balance problems. The results from the present study add further data that supports the clinical usefulness of simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy in improving motor function in advanced PD; simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy helps to improve eye movements that are an important part of balance, gait and interaction with the environment (Anastasopoulos, Ziavra et al. 2011). This could be particularly relevant for the prevention of falls in these patients, a source of considerable morbidity.

Future work should involve investigating larger numbers of patients with bilateral PPN-DBS in conjunction with optimal medical therapy to further explore the effects on saccades and also correlating those findings with clinical and imaging findings. The latter may include fMRI and PET scans to establish a more complete picture of the neurobiological and metabolic changes involved, as well as computational

modelling studies as have been previously performed for bilateral STN-DBS (Yousif, Purswani et al. 2010; Yousif, Borisyuk et al. 2012).

Chapter 4

Surgical targeting of the human pedunculopontine nucleus using diffusion tensor imaging and probabilistic tractrography in advanced Parkinson's disease

Keywords: deep brain stimulation (DBS), subthalamic nucleus (STN), pedunculopontine nucleus (PPN), Parkinson's disease (PD), diffusion-weighted imaging (DWI) / diffusion-tensor imaging (DTI), probabilistic diffusion tractography (PDT)

ABSTRACT

Objective: To clarify the optimal target site for PPN-DBS.

Background: As PD progresses, many patients develop axial motor symptoms of postural dysfunction and gait problems (including freezing of gait) that are generally resistant to optimal medical therapy. DBS of the STN is the current surgical method of treating these advanced PD patients. Stimulation of this area has been shown to improve the limb motor symptoms (tremor, rigidity and bradykinesia / akinesia) of advanced PD but has been less effective in treating the axial motor symptoms. It has recently been shown however, that a combination of bilateral DBS of the STN and PPN may improve both the axial motor symptoms as well as the limb motor symptoms of advanced PD. Despite these encouraging results, targeting of the human PPN remains a challenge.

The anatomy of the brainstem is complex and structures such as the PPN, recently used to surgically treat the medically refractory axial motor symptoms of advanced PD using DBS, cannot be directly visualised on structural images. PPN location must therefore be deduced by reference to identifiable adjacent structures, such as the

superior cerebellar peduncle and its decussation. DWI / DTI scans with PDT analysis of the PPN region, although unable to differentiate afferent from efferent pathways and limited to picking up mainly large-fiber pathways, has been proposed as an useful pre-operative tool to localise the DBSe placement site.

Methods: Here we report on our series of six-patients implanted with bilateral PPN DBSe with the aid of DWI / DTI scans and PDT analysis, in addition to simultaneous bilateral STN DBSe implantation, for the treatment of advanced PD with prominent axial motor symptoms. Post-operative MRI scans of the six patients were interrogated to calculate mean co-ordinates for the active contacts in each of the four DBSe in all patients.

Results: Mean PPN co-ordinates for the active contacts were: Lateral (x / perpendicular to mid-AC-PC) 5.2 mm, AP (y / dorsal to PC) -0.5 mm (if the figure is negative this means the electrode lies anterior to the PC line) and Vertical (z / perpendicular to mid-AC-PC) 14.0 mm.

Conclusion: Simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy, targeting the mid-lower PPN, offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD. DWI / DTI scans with PDT analysis of the PPN region can be used as a pre-operative tool to localise the electrode placement site, and they may also be useful as a post-operative tool to reassess electrode position.

INTRODUCTION

The early stages of PD are dominated by resting tremor, muscular rigidity and bradykinesia amenable to pharmacological treatment. However, as PD progresses, many patients develop axial motor symptoms of postural dysfunction and gait problems (including freezing of gait) that are generally resistant to optimal medical therapy. DBS of the STN is the current surgical method of treating these advanced PD patients. Stimulation of this area has been shown to improve the limb motor symptoms (resting tremor, muscular rigidity and bradykinesia / akinesia) of advanced PD but has been less effective in treating the axial motor symptoms (Kleiner-Fisman, Fisman et al. 2003; Bakker, Esselink et al. 2004; Davis, Lyons et al. 2006).

The PPN is a small nuclear structure in the rostral brainstem tegmentum extending from the mid-collicular to the mid-pontine level (**Figure 1 & 2**) (Jenkinson, Nandi et al. 2009). There is extensive evidence that the PPN is an important structure involved in, among other functions, locomotion and postural control, with special regard to PD (Pahapill and Lozano 2000; Nandi, Stein et al. 2002; Ballanger, Lozano et al. 2009; Karachi, Grabli et al. 2010). Chemical and electrical stimulation of the PPN in rats, decerebrate cats and monkeys causes stepping movements (Garcia-Rill, Houser et al. 1987; Garcia-Rill, Kinjo et al. 1990). Unilateral lesions of the PPN in non-human primates result in hemi-akinesia and bilateral lesions produce profound generalised akinesia, similar to that seen in advanced PD (Aziz, Davies et al. 1998; Munro-Davies, Winter et al. 1999). Autopsy studies in patients with PD have revealed degeneration of the PPN cholinergic neurons, the degree of which correlates with the clinical severity of PD (Zweig, Jankel et al. 1989). Similar loss of PPN

neurons has been noted in autopsies of MSA and PSP patients (Jellinger 1988) in whom parkinsonian gait problems are prominent. Finally, recent positron emission tomography (PET) studies measuring regional cerebral blood flow (rCBF) with PPN stimulation have provided evidence that PPN-DBS induces rCBF changes in brain structures that are associated with control of lower limb movements (Strafella, Lozano et al. 2008; Ballanger, Lozano et al. 2009; Khan, Gill et al. 2012) and another recent prospective clinical study found stimulation of the mid-lower PPN (more caudal than previous reports) without co-stimulation of other brain targets may be beneficial for the subgroup of patients with PD who experience severe gait freezing and postural instability with frequent falls, that persist even while on optimal medical therapy (Thevathasan, Coyne et al. 2011).

It has also recently been shown that a combination of bilateral stimulation of the STN and PPN may improve both the axial motor symptoms as well as the limb motor symptoms of advanced PD (Mazzone, Lozano et al. 2005; Plaha and Gill 2005; Stefani, Lozano et al. 2007; Ferraye, Debu et al. 2010). This may be because akinesia in advanced PD is caused by excessive GABAergic inhibition of the PPN that is not affected by STN-DBS as confirmed by microinjection of the GABA receptor A antagonist, bicuculline, into the PPN, or low-frequency stimulation of the PPN in monkeys to overcome the inhibition of PPN neurons and significantly improve akinesia (Nandi, Aziz et al. 2002; Nandi, Liu et al. 2002; Jenkinson, Nandi et al. 2004).

Despite these encouraging results targeting of the human PPN remains a challenge. The anatomy of the brainstem is complex and structures such as the PPN, recently

used to surgically treat the medically refractory axial symptoms of advanced PD using DBS, cannot be directly visualised on structural images. PPN location must therefore be deduced by reference to identifiable adjacent structures, such as the superior cerebellar peduncle and its decussation. DWI / DTI and PDT analysis of the PPN region, although unable to differentiate afferent from efferent pathways and limited to picking up mainly large-fiber pathways, has been proposed as an useful pre-operative tool to localise the DBS electrodes (DBSe) placement site (Muthusamy, Aravamuthan et al. 2007). Here we report on our series of six-patients implanted with bilateral PPN-DBSe with the aid of DWI / DTI scans and PDT analysis, in addition to simultaneous bilateral STN-DBSe implantation, for the treatment of advanced PD with prominent axial symptoms.

METHODS, MATERIALS & PARTICIPANTS

Participants

Six male patients with advanced idiopathic PD and history of freezing of gait, postural instability, marked "Off" akinesia and "On" dyskinesia resulting in falls underwent simultaneous bilateral STN & PPN-DBS implantation as part of an prospective, controlled, double-blinded cross-over MRC funded clinical trial as described in **Chapter 1**.

Target localisation

Patients were admitted to the neurosurgical ward a day prior to surgery. Our surgical routine is described in detail elsewhere and is one that has been used for the last 10

years (Aziz, Nandi et al. 2001; Bittar, Burn et al. 2005). On the morning of surgery PD medication is omitted; a Cosman-Roberts-Wells stereotactic frame base ring is applied to the skull under local anaesthetic and a stereotactic computed tomography (CT) brain scan is performed. This is then fused to the pre-operative magnetic resonance imaging brain scan performed under a general anaesthetic (GA-MRI) using Radionics Image Fusion. The target co-ordinates for the STN and the PPN are then calculated.

The STN can be directly visualised on current MRI software (T2 axial volumetric acquisition). The PPN cannot be identified as a discrete structure on structural MRI brain scans in current clinical use. Thus, PPN localisation was carried out relative to adjacent structures that can be seen on DWI / DTI scans with PDT analysis studies performed additionally, e.g., decussation of the superior cerebellar peduncle, substantia nigra and the pons. The Schaltenbrand Wahren anatomic atlas was also used with the image fusion to further help radiological localisation although its use was again limited to STN localisation as the Schaltenbrand Wahren anatomic atlas does not go caudal enough to delineate the PPN.

Diffusion tractography is a non-invasive 3D reconstruction method to delineate neural tracts by using anisotropic diffusion to identify axonal organisation of the brain. According to anisotropic diffusion, the spread of molecules (i.e., diffusion) is faster along the axons rather than across them in cerebral white matter. By measuring the diffusion in many different directions, one would be able to observe that the diffusion in a particular direction being faster than the others, and hence deduce the direction of fibre bundles at every point in the brain.

Axons (in the order of 1 μm) are much smaller than voxels (measurement of the fibre directions in the scale of 1-2 mm) and this result in many thousands of axons existing within one voxel all of which may not be traveling in the same direction. In probabilistic tractography, the most likely fibre orientation is estimated first. This is performed using different colour coding according to the direction of diffusion: Green denotes anterior-posterior, Red denotes medial-lateral, Blue denotes superior-inferior.

Next, the fibre connections are traced (that are estimated according to the probability) many times, each time using different orientations. These different traces are then collectively measured using different colour assignment (Black – zero connection probability, Red – intermediate probability, White – high probability) to give the overall connection likelihood. The orientations of the fibres at every point in the brain are then joined up to form entire pathways and hence brain connections.

Thus, structures adjacent to the PPN, e.g., decussation of the superior cerebellar peduncle, medial lemniscus, substantia nigra and the pons are delineated and the PPN localised (**Figure 28**).

Surgical procedure

The patient was then returned to the operating theatre and bilateral DBSe (Medtronic 3389 & 3387) were then passed to target (STN and PPN in turn, respectively) and trial stimulation was performed. Sedation was reversed and careful neurological assessment performed to detect changes in PD symptoms and signs like tone, tremor and bradykinesia; any undesired effects such as pyramidal weakness, speech or visual

dysfunction, cognitive change, etc., were also noted. Real-time feedback from LFP recordings from the DBSe in conjunction with on-table clinical examination was used to aid placement. Once satisfactory placement was achieved, the DBSe was fixed to the skull with a titanium plate and screws. A similar procedure is followed for implantation of all the DBSe. Four DBSe were implanted in each patient – bilateral STN and PPN. A repeat stereotactic CT brain was performed to confirm placement and exclude any immediate complications such as ICH. Antibiotics covered the procedure.

Analysis

Post-operative MRI scans (**Figure 3**) of the six-patients were interrogated to calculate mean co-ordinates for the active contacts in each of the four DBSe in all patients.

RESULTS

There was an 89%, 92% and 100% decrease (Wilcoxon signed-ranks test; $p < 0.05$) in ICNG Index (falls / 1000 steps) with bilateral STN-DBS (at 2.6 ± 0.2 V, 140 Hz, 60 μs), bilateral PPN-DBS (at 1.5 ± 0.2 V, 20 Hz, 60 μs) and simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy, respectively, compared to optimal medical therapy only. Additionally, significant improvements were noted in almost all variables under consideration, most notably, UPDRS (Motor) and balance & gait assessments (Wilcoxon signed-ranks test; $p < 0.025$) with simultaneous bilateral STN & PPN-DBS. PPN-DBS was generally well tolerated and only induced

momentary ipsilateral oscillopsia at commencement on ≥ 2.0 V with rapid habituation, consistent with previous findings. No other complications were reported with PPN-DBS. Detailed clinical findings have been presented earlier in **Chapter 1**.

Mean PPN co-ordinates for the active contacts were: Lateral (x / perpendicular to mid-AC-PC) 5.2 mm, AP (y / dorsal to PC) -0.5 mm (if the figure is negative this means the electrode lies anterior to the PC line) and Vertical (z / perpendicular to mid-AC-PC) 14.0 mm. All measurements were taken from the center of the electrodes. Electrode diameter = 4mm; radius = 2mm. Therefore AP / Lateral measurements up to ± 2 mm, effectively = 0.

DISCUSSION

In our series of six male patients with advanced PD complicated by severe and medically refractory axial motor symptoms, we found simultaneous bilateral STN & PPN-DBS offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD as detailed earlier in **Chapter 1**.

The optimal target for PPN-DBS remains a matter for debate. Level of degeneration of the PPN cholinergic neurons, reported to be most numerous in the caudal PPN region (Jenkinson, Nandi et al. 2009), correlates with the axial clinical disturbance and severity of PD (Jellinger 1988; Zweig, Jankel et al. 1989; Bohnen, Muller et al. 2009; Karachi, Grabli et al. 2010). Therefore, although the bulk of the PPN appears to be at the rostral level, targeting the mid-lower PPN, more caudal than previous

reports in humans but similar to the target in the non-human primate is proposed (Jenkinson, Nandi et al. 2004; Ferraye, Debu et al. 2010; Thevathasan, Coyne et al. 2011). Findings of the present study support this assertion.

CONCLUSION

Simultaneous bilateral STN & PPN-DBS, in conjunction with optimal medical therapy, targeting the mid-lower PPN, offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD. DWI / DTI scans with PDT analysis of the PPN region can be used as a pre-operative tool to localise the electrode placement site, and they may also be useful as a post-operative tool to reassess electrode position.

Chapter 5

Discussion

STN-DBS has been in routine use in the treatment of patients with advanced PD, refractory to medical therapy. In recent years, PPN-DBS has been explored to address the axial motor symptoms of gait freezing and loss of postural control (adding to tremor, rigidity and bradykinesia as drivers of disease burden in advanced PD). However, the role of PPN-DBS has remained unclear.

In this thesis, a prospective, four-phase, within-subject cross-over, double-blinded clinical trial and associated studies where bilateral STN (Med. 3389) and PPN-DBS (Med. 3387) electrodes were stereotactically implanted in six male patients with advanced PD and axial motor symptoms (while on optimal medical therapy) and performance was recorded on optimal medical therapy alone (open-label phase), bilateral STN or PPN-DBS and simultaneous bilateral STN & PPN-DBS (ALL neurostimulation in conjunction with optimal medical therapy; 6-months each).

Our principal hypothesis was confirmed and the greatest improvement observed was 100% decrease (Wilcoxon signed-ranks test; $p < 0.05$) in ICNG Index (falls / 1000 steps) with simultaneous bilateral STN (at 2.6 ± 0.2 V, 140 Hz, 60 μs) & PPN-DBS (at 1.5 ± 0.2 V, 20 Hz, 60 μs) in conjunction with optimal medical therapy compared to optimal medical therapy only. Additionally, significant improvements were noted in almost all variables under consideration, most notably, UPDRS (Motor) and balance & gait assessments (Wilcoxon signed-ranks test; $p < 0.025$) with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy.

PPN-DBS was generally well tolerated and only induced momentary ipsilateral oscillopsia at commencement on ≥ 2.0 V with rapid habituation, consistent with

previous findings. No other complications were reported with PPN-DBS.

Therefore, we conclude, in appropriately selected patients, simultaneous bilateral STN & PPN-DBS, in conjunction with optimal medical therapy, targeting the mid-lower PPN with the aid of DWI / DTI scans and PDT analysis and resultant saccadic modulation coupled with performance changes in the relevant axial motor segments, offers the possibility of ameliorating both the axial motor symptoms as well as the limb motor symptoms of advanced PD. DWI / DTI scans with PDT analysis of the PPN region may be used as a pre-operative tool to localise the electrode placement site, and they may also be useful as a post-operative tool to reassess electrode position.

We propose larger studies with longer follow-up to explore the potential of routine use of simultaneous bilateral STN & PPN-DBS in the treatment of patients with advanced PD complicated by axial motor symptoms.

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Tables

	Age	PD Duration	Total L-dopa equivalent dose (mg / day)	STN voltage (V)	STN pulse width (µs)	STN frequency (Hz)	PPN voltage (V)	PPN pulse width (µs)	PPN frequency (Hz)
	56	8	872.00	2.4	60	140	0.8	60	20
	55	17	1450.00	2.7	60	140	1.6	60	20
	67	10	749.00	2.5	60	140	1.7	60	20
	64	6	680.50	2.9	60	140	1.5	60	20
	57	13	852.25	2.3	60	140	1.4	60	28
	63	11	895.00	3.3	60	140	1.0	60	20
Median (IQR)	**60.0 ± 3.8**	**10.5 ± 2.0**	**862.13 ± 57.22**	**2.6 ± 0.2**	**60 ± 0**	**140 ± 0**	**1.5 ± 0.2**	**60 ± 0**	**20 ± 0**

Table 1: Summary of PPN-Trial patient characteristics, optimal medical therapy and stimulation parameters.

Subject	Order of DBS groups
1	ABC
2	BCA
3	CAB
4	CBA
5	ACB
6	BAC

Table 2: William's Square Design for 6 subjects (A = bilateral STN-DBS, B = bilateral PPN-DBS and C = simultaneous bilateral STN & PPN-DBS; ALL neurostimulation in conjunction with optimal medical therapy).

OVERALL	Optimal medical therapy (OMT)	+ STN	+ PPN	+ STN & PPN	Wilcoxon Signed-Rank Test (*p*)
UPDRS (Q13 - Q15)	10	2	5	5	OMT *v* +STN and OMT *v* +PPN (0.025) OMT *v* +STN & PPN, +STN *v* +PPN and +STN *v* +STN & PPN (0.05)
UPDRS (Q27 - Q29)	3	3	4	5	ALL *v* ALL (0.05) except OMT *v* +PPN and +STN *v* +PPN (ns)
UPDRS (Q30)	2	1	1	2	OMT *v* +STN and OMT *v* +PPN (0.05)
UPDRS (Motor)	25	24	24	38	ALL *v* ALL (0.05) except +STN *v* +STN & PPN (0.025)
SF-36	91	99	99	98	ALL *v* ALL (0.05)
EQ-5D	71	83	38	73	ALL *v* ALL (0.05) except OMT *v* +PPN and +PPN *v* +STN & PPN (0.025)
TGUGT	10.9	7.8	8.7	8.9	ALL *v* ALL (0.05) except +STN *v* +PPN (0.025)
BBS	46	48	48	52	ALL *v* ALL (0.05) except OMT *v* +STN & PPN and +PPN *v* +STN & PPN (0.025)
FOG-Q	20	6	15	14	OMT *v* ALL (0.025) +STN *v* +PPN, +STN *v* +STN & PPN and +PPN *v* +STN & PPN (0.05)
ICNG Index (Falls / 1000 steps)	0.071	0.008	0.006	0.000	ALL *v* ALL (0.05) except +PPN *v* +STN & PPN (ns)

Table 3: Overall (median) results of the PPN-DBS Trial (ns = not statistically significant).

		Young Controls	Age-Matched Controls	OMT	+ STN	+ PPN	+ STN & PPN
Latencies (ms)	**Eye**	341.8	408.8	587.0	515.3	-	548.4
	Head	407.3	561.5	723.0	635.5	654.5	655.3
	Trunk	470.4	717.3	912.5	882.1	850.2	773.6
	R Foot	821.6	913.4	1576.6	1565.0	1024.8	1194.0
	L Foot	811.5	936.9	1595.2	1531.0	1036.9	1180.5
	Gaze	749.1	970.3	1310.0	1150.8	-	1203.7
Head on trunk displacement (ms)		63.1	155.8	189.5	246.6	195.7	118.3
Peak angular velocities (degrees s^{-1})	**Head**	585.6	254.2	82.6	96.8	122.4	127.8
	Trunk	526.0	241.4	70.0	86.3	109.8	156.8
	R Foot	676.7	273.7	149.6	150.2	216.9	227.3
	L Foot	653.3	266.8	142.4	171.2	206.5	232.4
Primary Saccade Amplitude (degrees)		26.2	25.5	20.1	22.8	19.7	20.2
Primary Gaze Amplitude (degrees)		53.1	48.0	38.7	43.4	40.0	39.1
Number of Saccades (n)		1.3	1.5	3.8	1.8	-	2.6
TA Latencies (ms)		583.3	656.8	929.7	856.4	733.7	686.3
Gain (%)	**R Foot**	94.8	60.4	41.6	48.6	56.8	58.5
	L Foot	83.7	59.4	35.1	49.4	54.3	52.6
Number of Steps (n)	**R Foot**	1.1	2.2	5.1	3.4	2.3	2.1
	L Foot	1.4	2.5	4.9	2.8	2.3	2.3

Table 4: Predictable conditions: (median) whole body rotation parameters obtained in all groups with different modes of therapy.

Group	[§]Number of Prosaccades (n)	[†]Angular Velocities (degrees s^{-1})	Wilcoxon Signed-Rank Test (*p*)
Young controls	3.34	375.37	-
Age-matched controls	5.05	316.26	-
Early PD on OMT	8.7	287.57	-
Advanced PD on OMT	11.24	202.33	*v* Both control groups ($p < 0.001$)[§ †]
+ STN-DBS	7.67	279	*v* Advanced PD on OMT ($p < 0.01$)[§ †]
+ PPN-DBS	10.98	213.75	*v* ALL (ns)[§ †]
+ STN & PPN-DBS	4.07	301.18	*v* Advanced PD on OMT and + STN-DBS ($p < 0.01$)[§] *v* Advanced PD on OMT ($p < 0.01$) and + STN-DBS ($p < 0.05$)[†]

Table 5: Number of prosaccades and angular velocities for the AS task obtained in all groups with different modes of therapy.

Figures

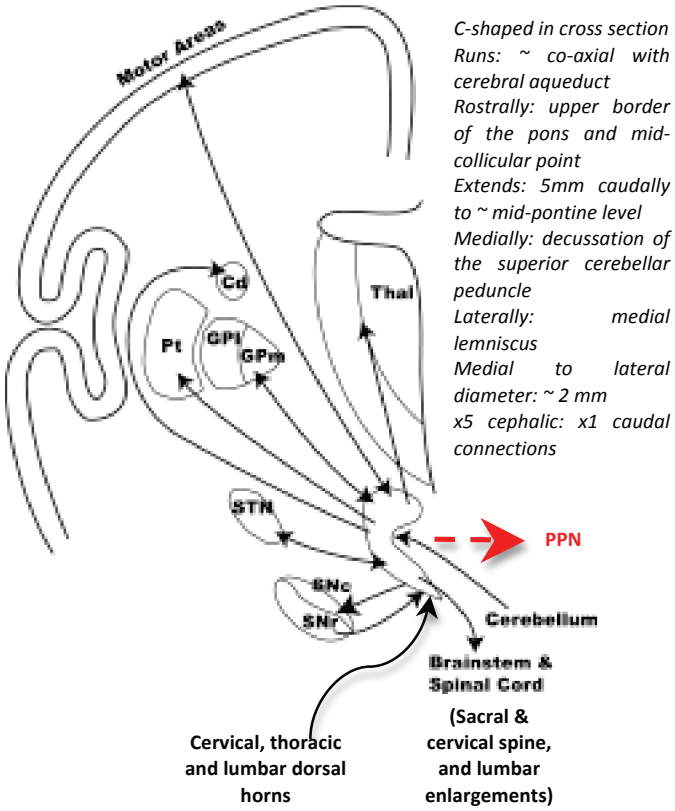


Figure 1: PPN anatomy and neural connections (adapted from Jenkinson N, *et* al. Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. *Mov Disord*. 2009 Feb 15; 24 (3): 319-28.).

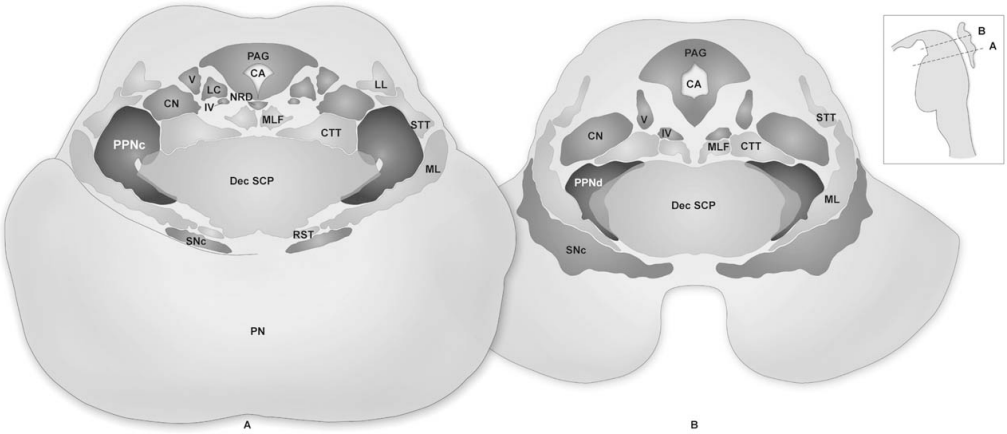


Figure 2: Pedunculopontine nucleus relationships at the level of the decussation of the superior cerebellar peduncles and the inferior colliculus (A) and of the trochlear nucleus and the intercollicular area (B). The main nuclei are labelled on the left and the long fibre tracts on the right side. STT, spinothalamic tract; CA, cerebral aqueduct; CN, cuneiform nucleus; CTT, central tegmental tract; Dec SCP, decussation of the superior cerebellar peduncles; LC, locus coeruleus; LL, lateral lemniscus; ML, medial lemniscus; MLF, medial longitudinal fasciculus; NRD, nucleus raphé dorsalis; PAG, periaqueductal gray; PN, pontine nuclei; PPNc, pedunculopontine nucleus pars compacta; PPNd, pedunculopontine nucleus pars dissipata; SNc, substantia nigra pars compacta; RST, rubrospinal tract; IV, trochlear nucleus; V, mesencephalic nucleus of the trigeminal nerve (Fournier-Gosselin M-P, *et* al. Regional anatomy of the pedunculopontine nucleus: Relevance for deep brain stimulation. *Mov Disord*. 2013 Aug 7; 28: 1330–1336).

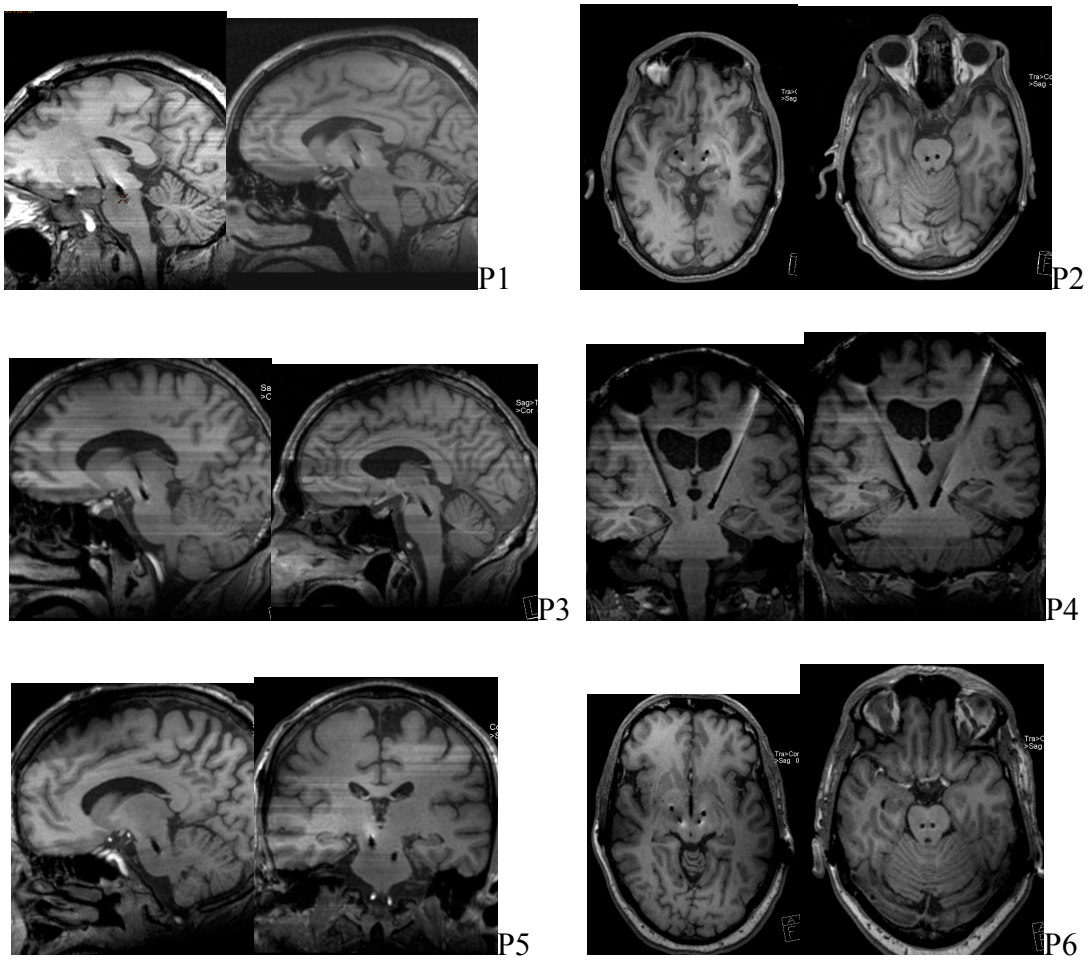


Figure 3: Post-operative MRI scans showing bilateral STN and PPN electrodes implanted with the aid of DWI / DTI scans and PDT analysis.

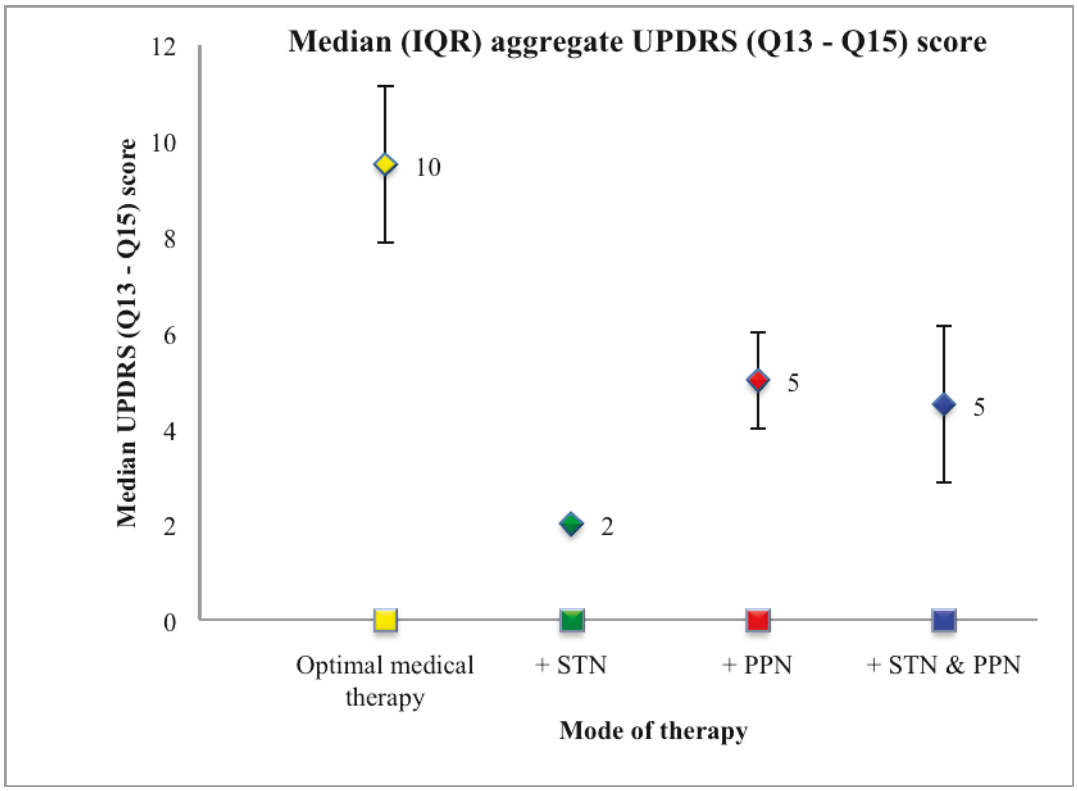


Figure 4: Median (IQR) aggregate UPDRS (Q13 – Q15) score with different modes of therapy (please refer to Appendix A).

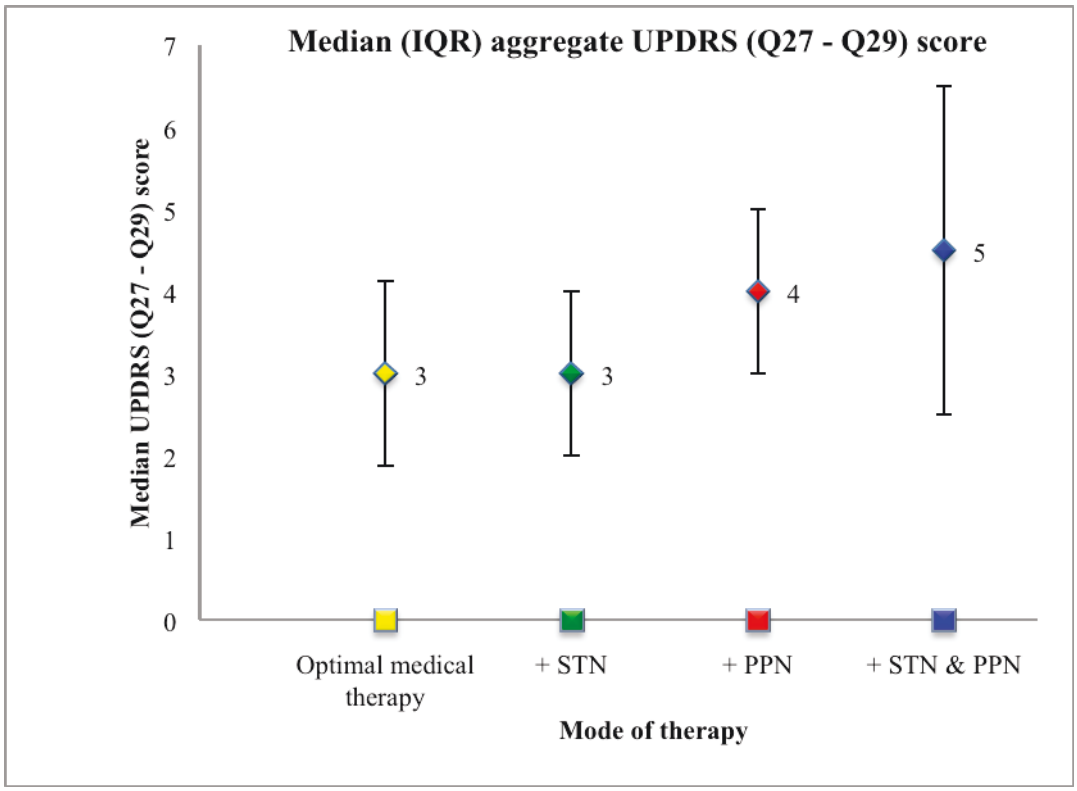


Figure 5: Median (IQR) aggregate UPDRS (Q27 – Q29) score with different modes of therapy (please refer to Appendix A).

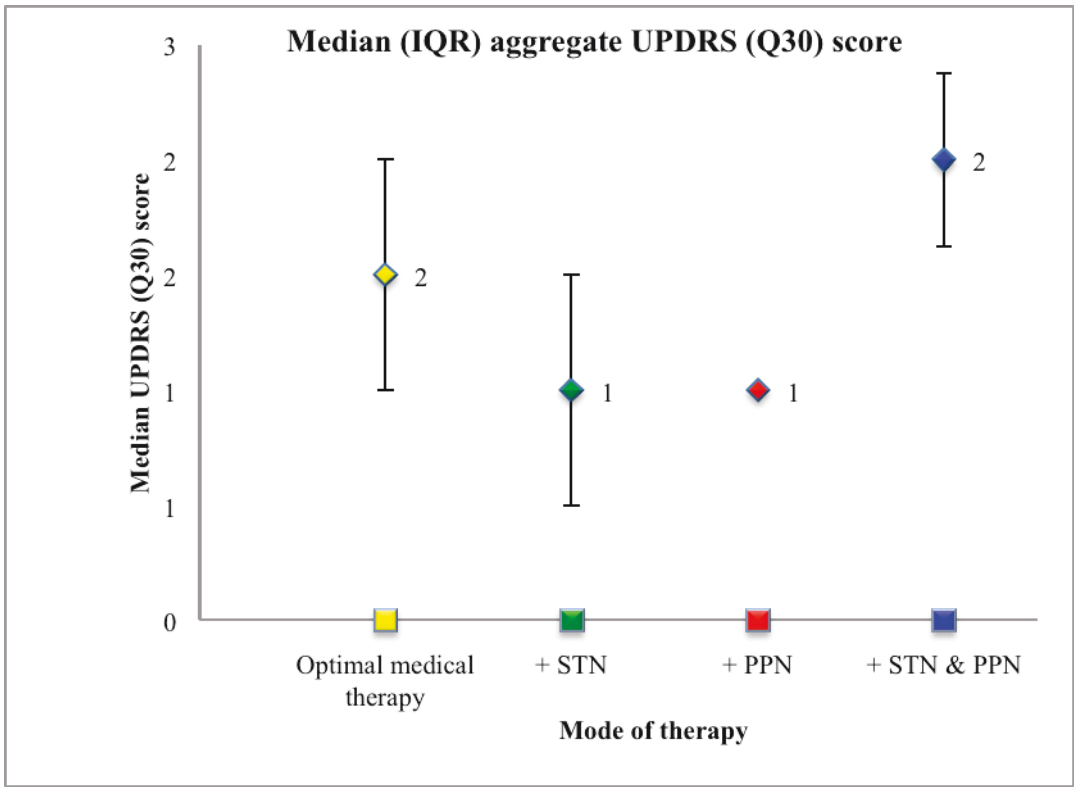


Figure 6: Median (IQR) UPDRS (Q30) score with different modes of therapy (please refer to Appendix A).

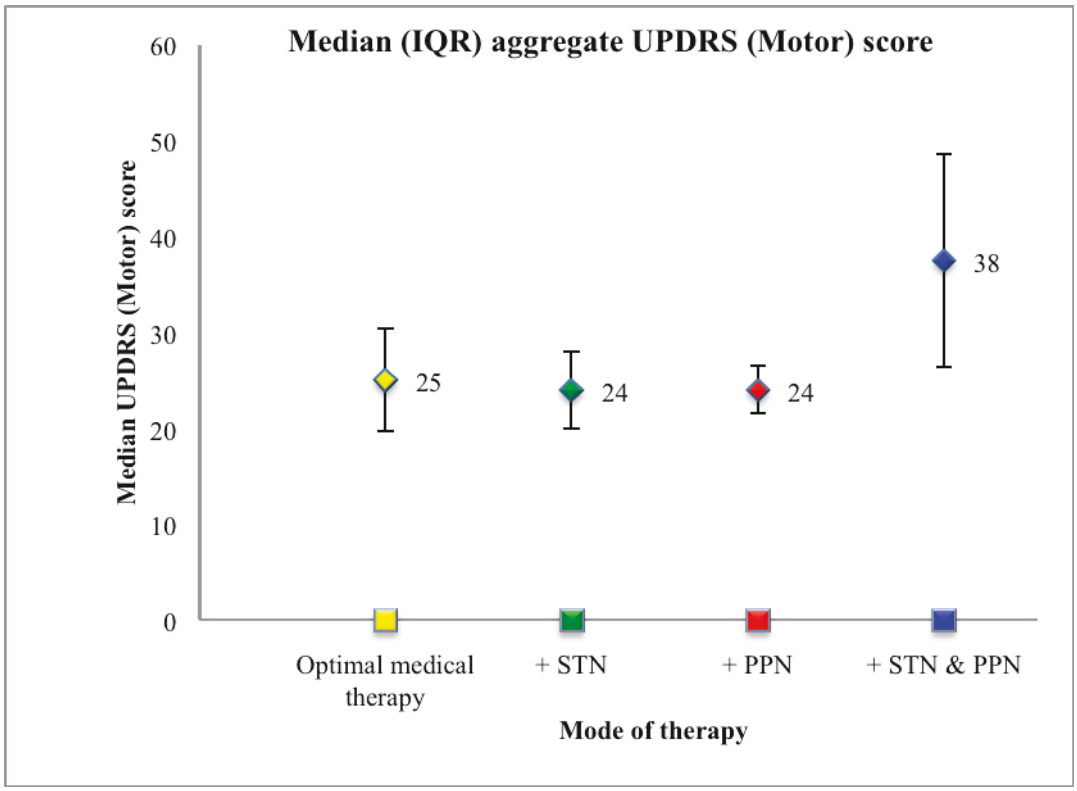


Figure 7: Median (IQR) aggregate UPDRS (Motor) score with different modes of therapy (please refer to Appendix A).

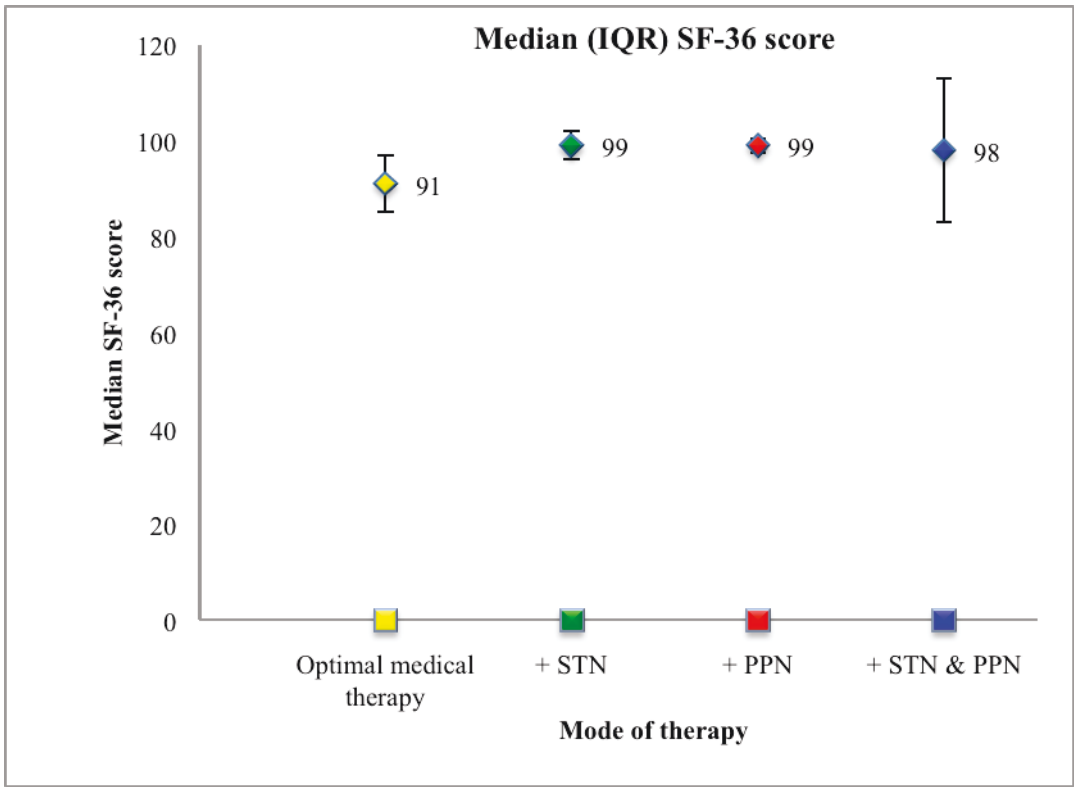


Figure 8: Median (IQR) SF-36 score with different modes of therapy (please refer to Appendix B).

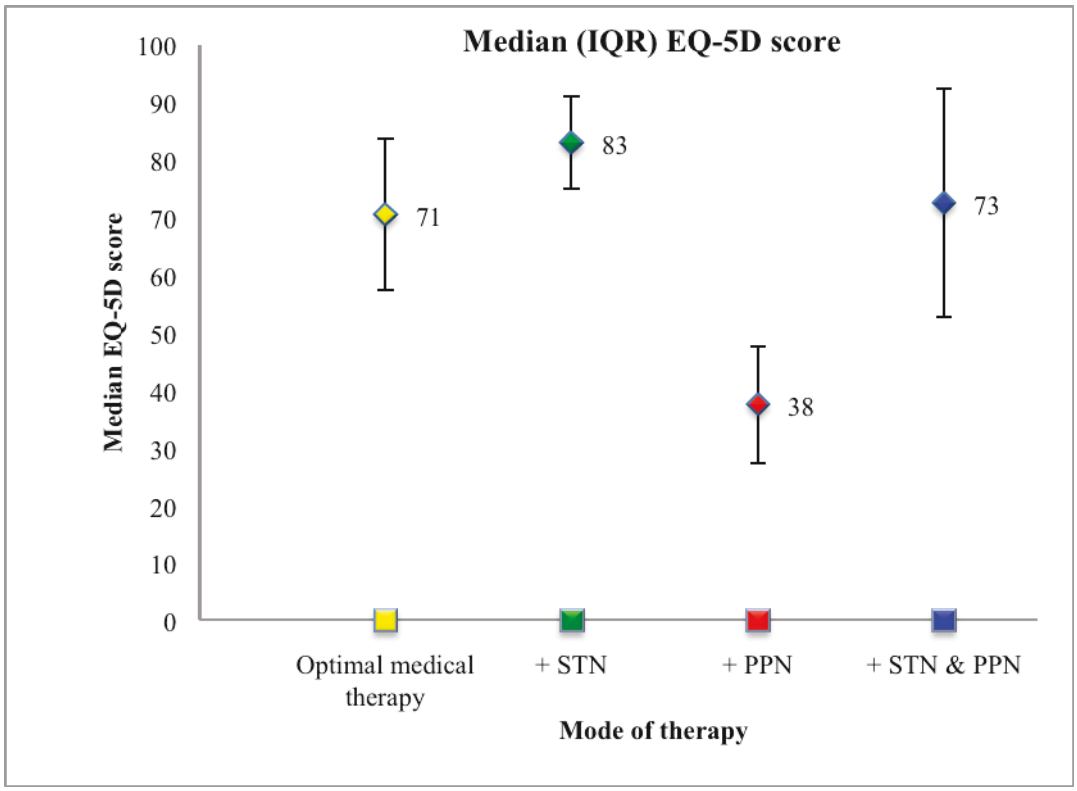


Figure 9: Median (IQR) EQ-5D score with different modes of therapy (please refer to Appendix C).

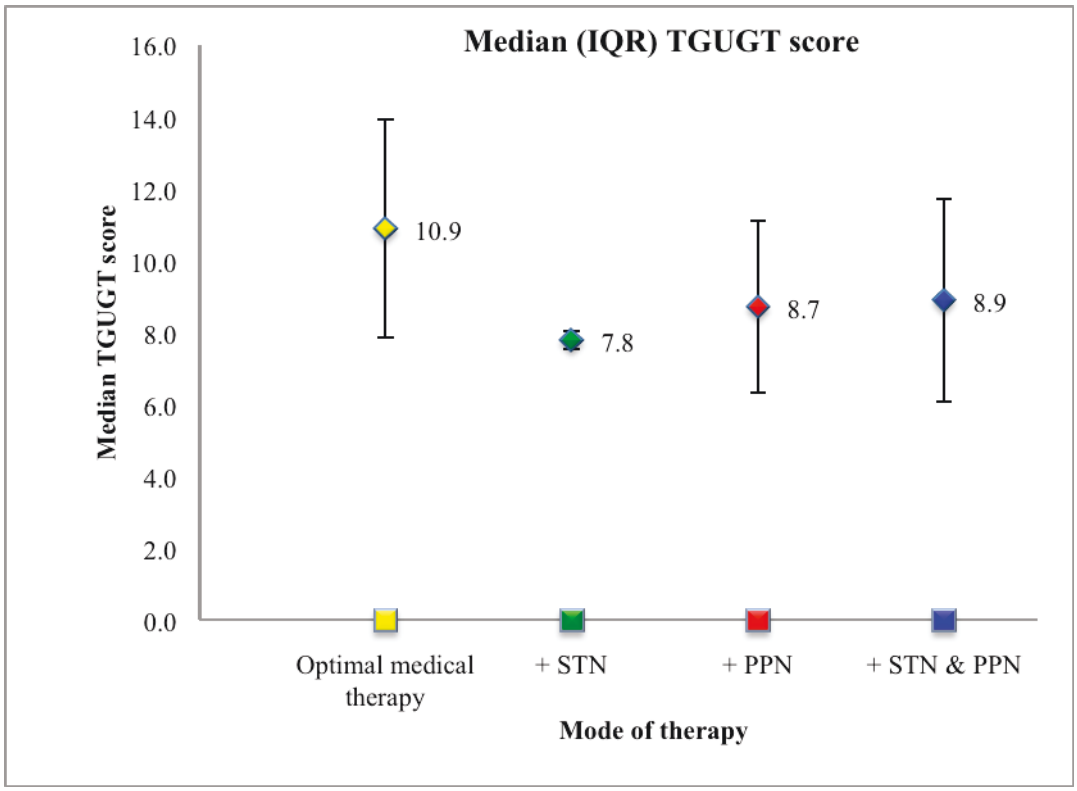


Figure 10: Median (IQR) TGUGT score with different modes of therapy (please refer to Appendix E).

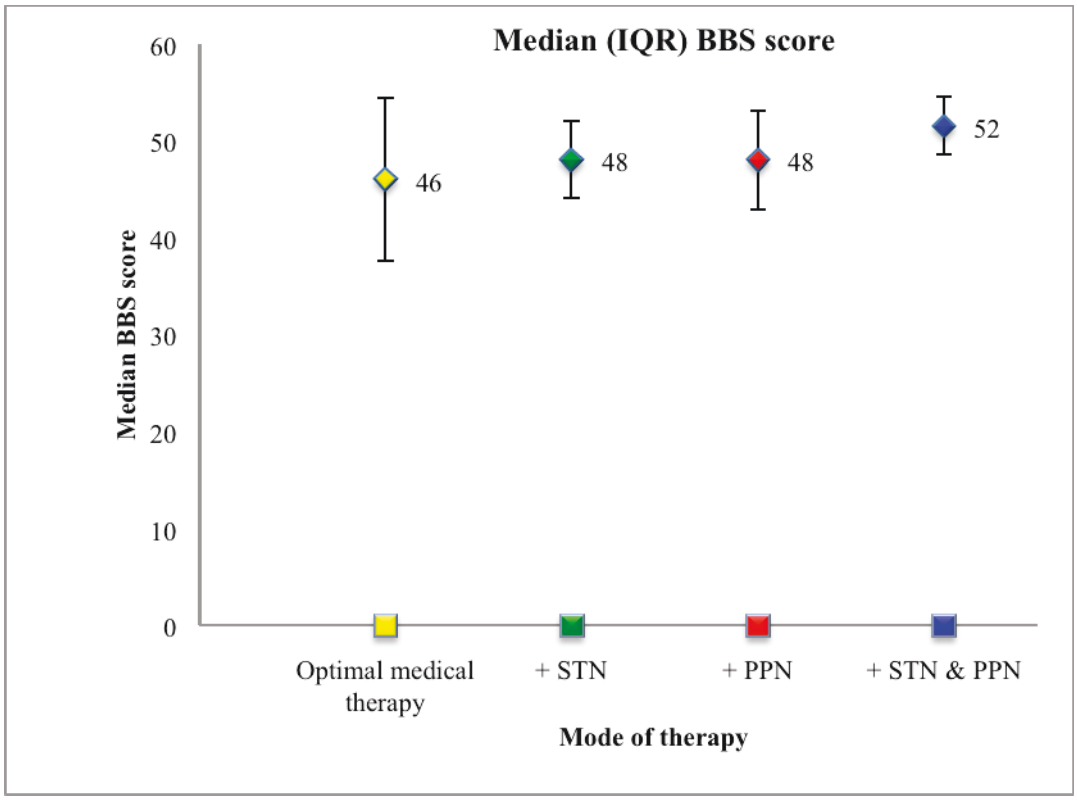


Figure 11: Median (IQR) BBS score with different modes of therapy (please refer to Appendix F).

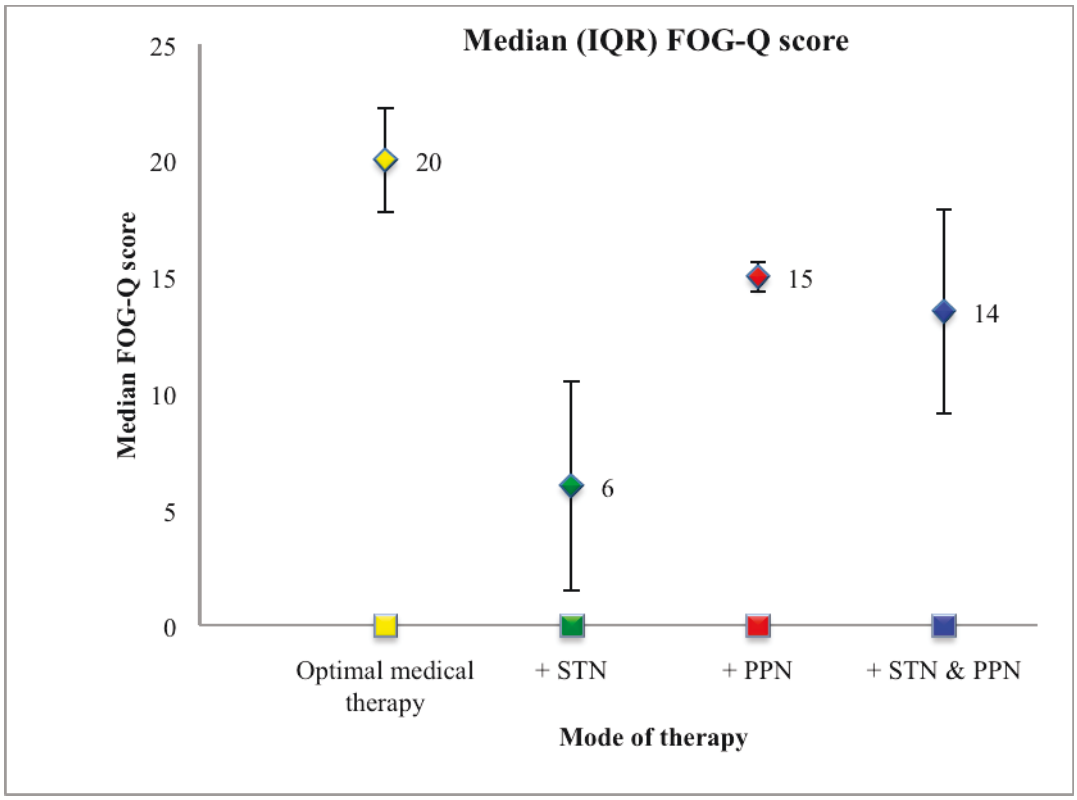


Figure 12: Median (IQR) FOG-Q score with different modes of therapy (please refer to Appendix G).

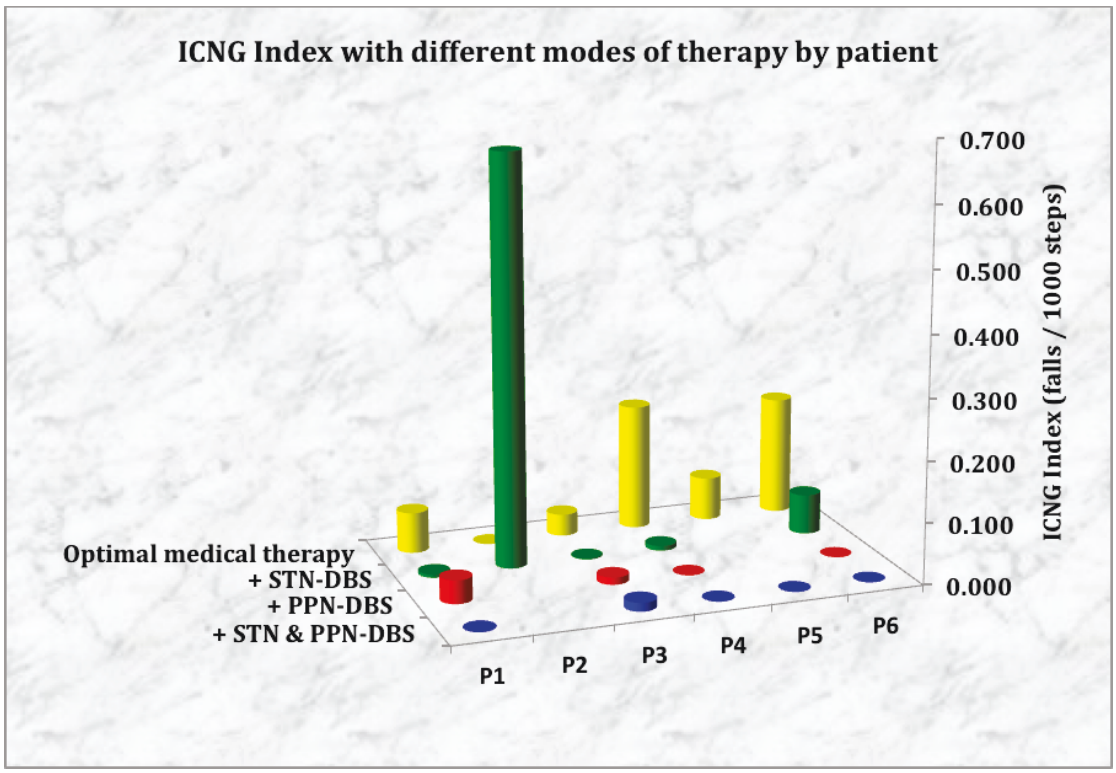


Figure 13: ICNG Index (falls / 1000 steps) with different modes of therapy by patient (please refer to Appendix D).

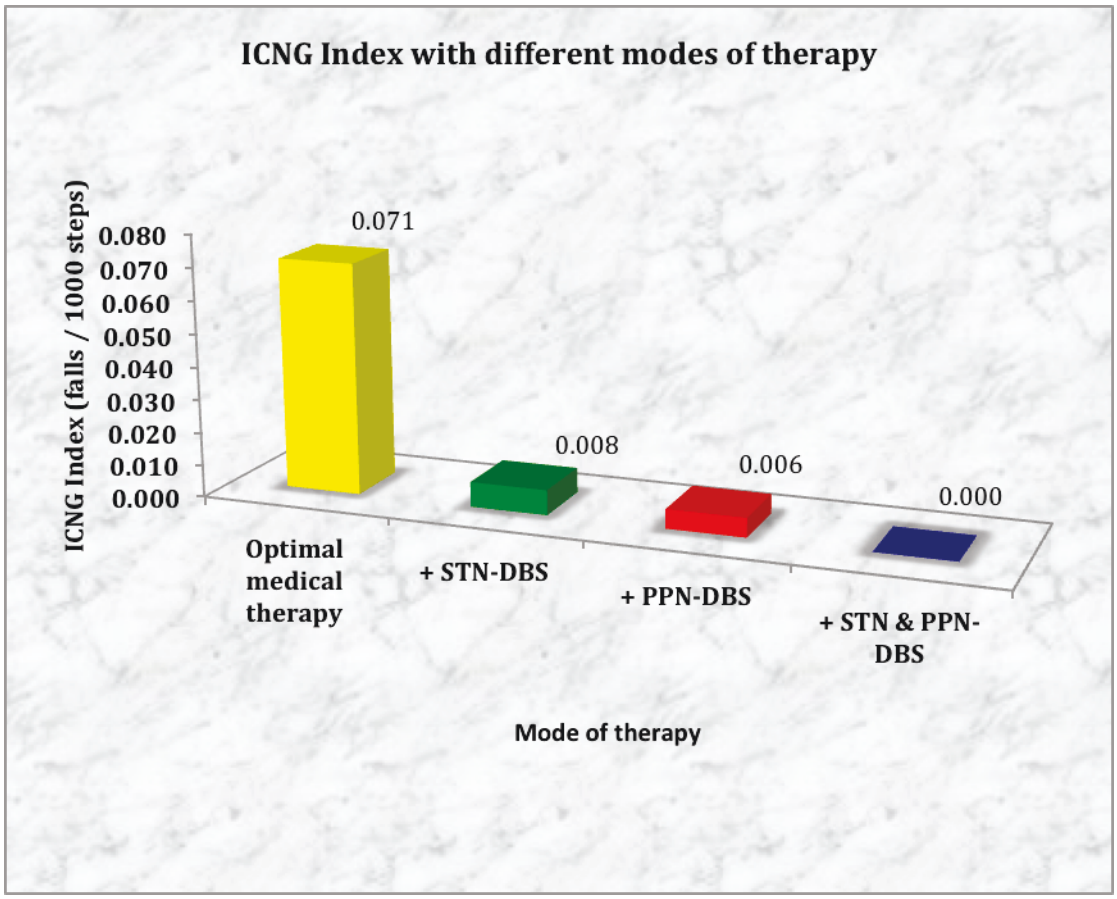


Figure 14: Overall (median) ICNG Index (falls / 1000 steps) with different modes of therapy; P2 STN-DBS data excluded as outlier (please refer to **Table 3** and Appendix D).

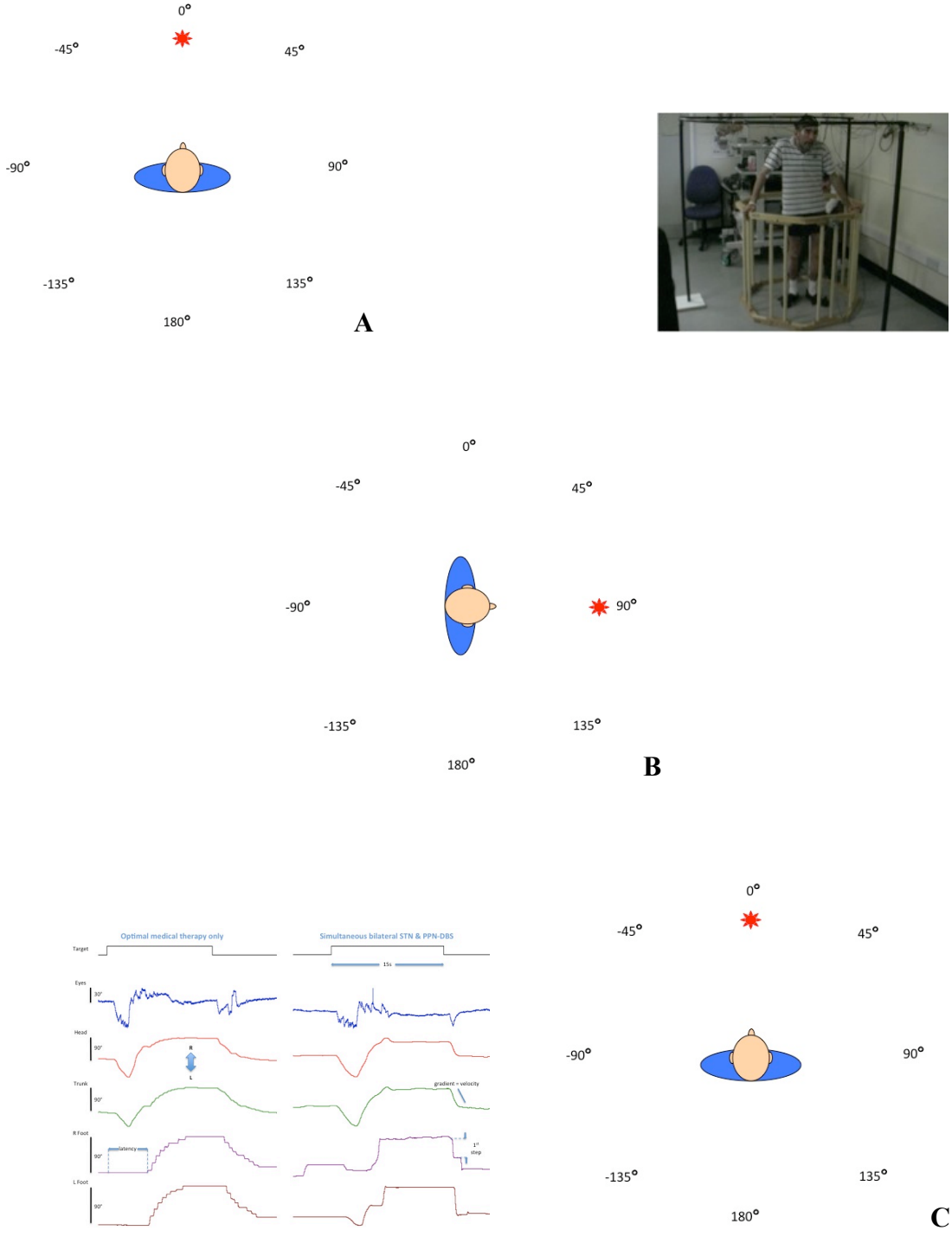


Figure 15: Horizontal eye, head, trunk and feet rotations towards appearance of a non-predictable initially non-visible target 90 degrees to the right (**A** > **B**) and then return left to the predictable target at zero (**C**).

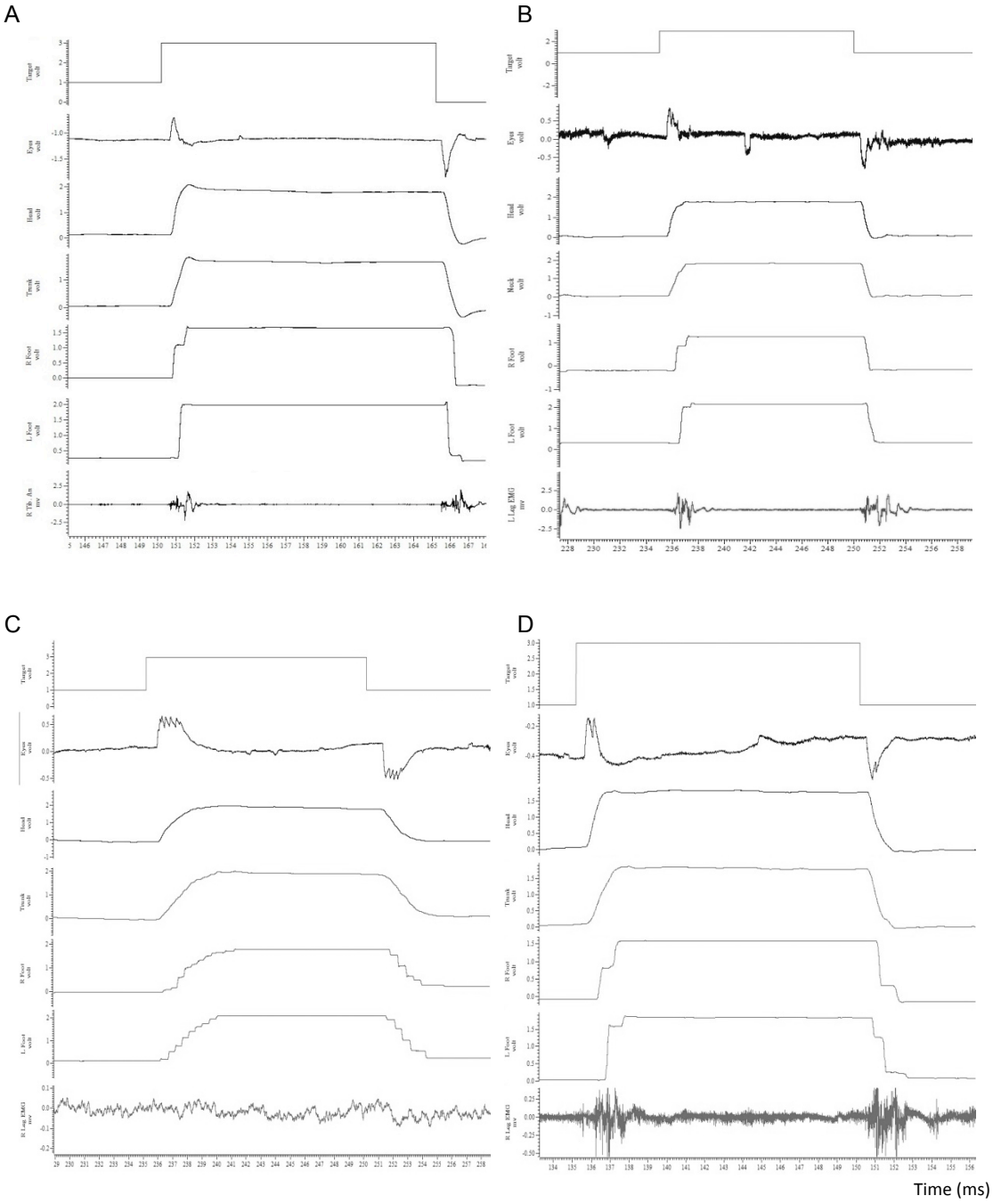
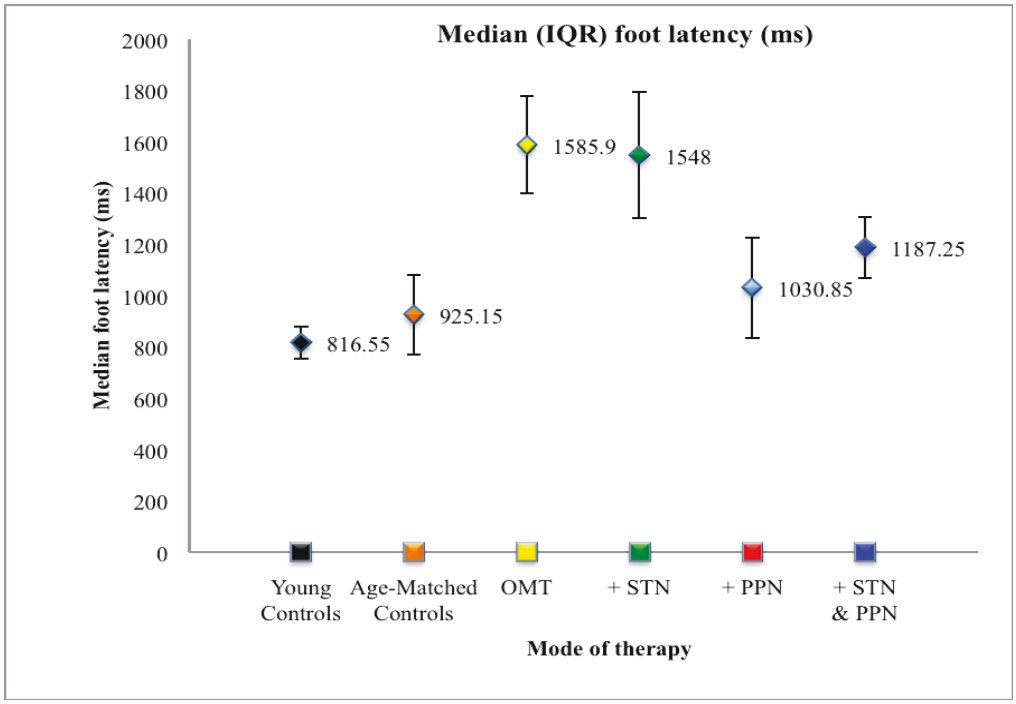
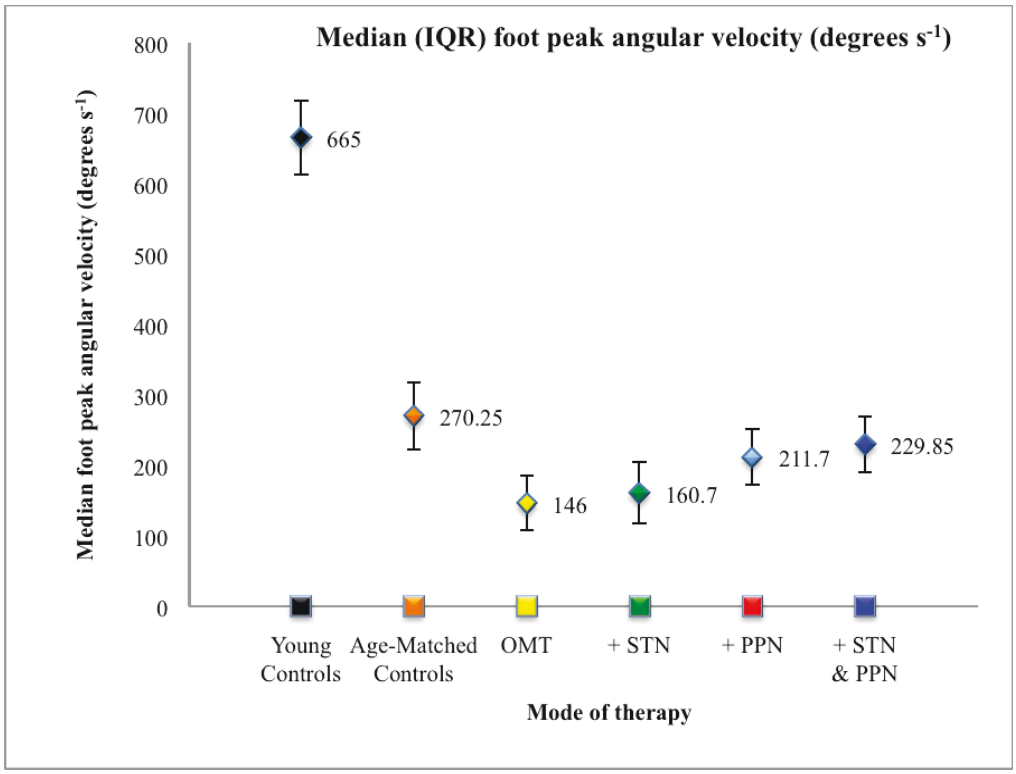


Figure 16: Kinematic profiles (raw data) of an outbound and inbound response to a 90 degrees target to the right in four individual subjects: A. Young control, B. Age-matched control, C. Advanced PD patient, D. STN-DBS patient. In all figures, positive deflection represents rotation to the right. The number of saccades was significantly reduced in STN-DBS patients compared to advanced PD subjects.



A



B

Figure 17: Median (IQR) foot latency (**A**) and peak angular velocity (**B**) with different modes of therapy.

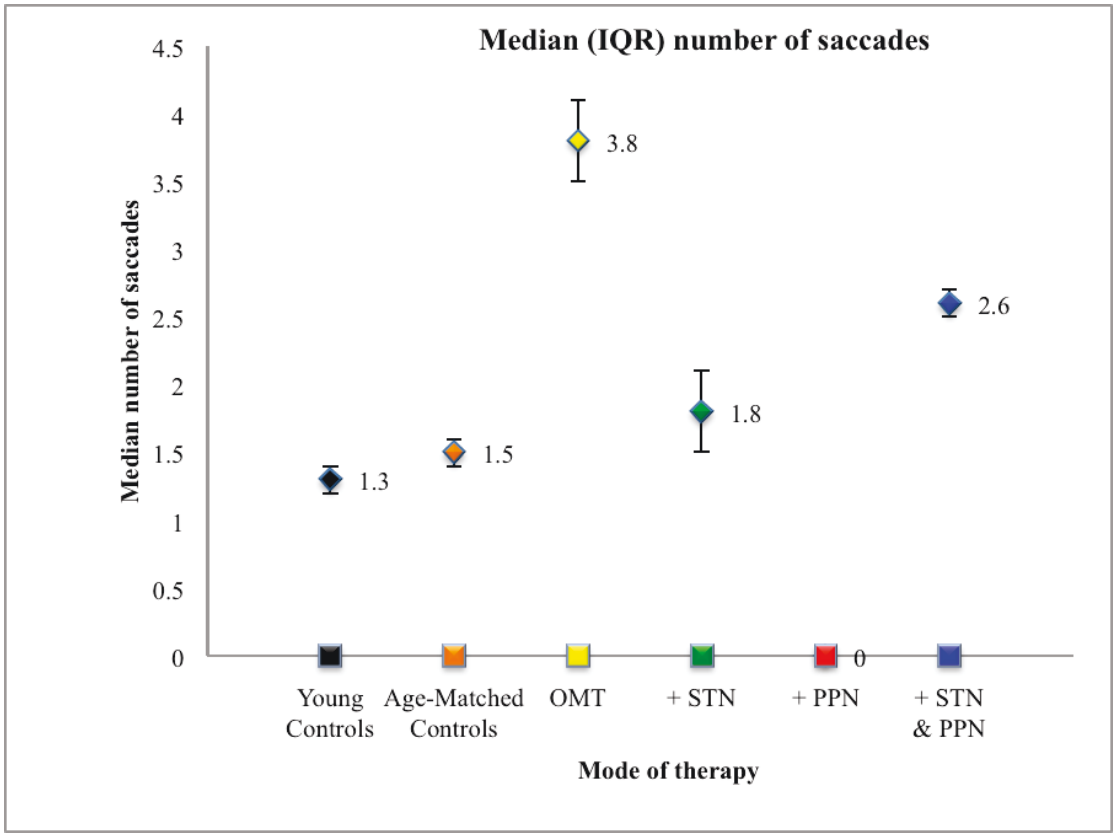


Figure 18: Median (IQR) number of saccades with different modes of therapy.

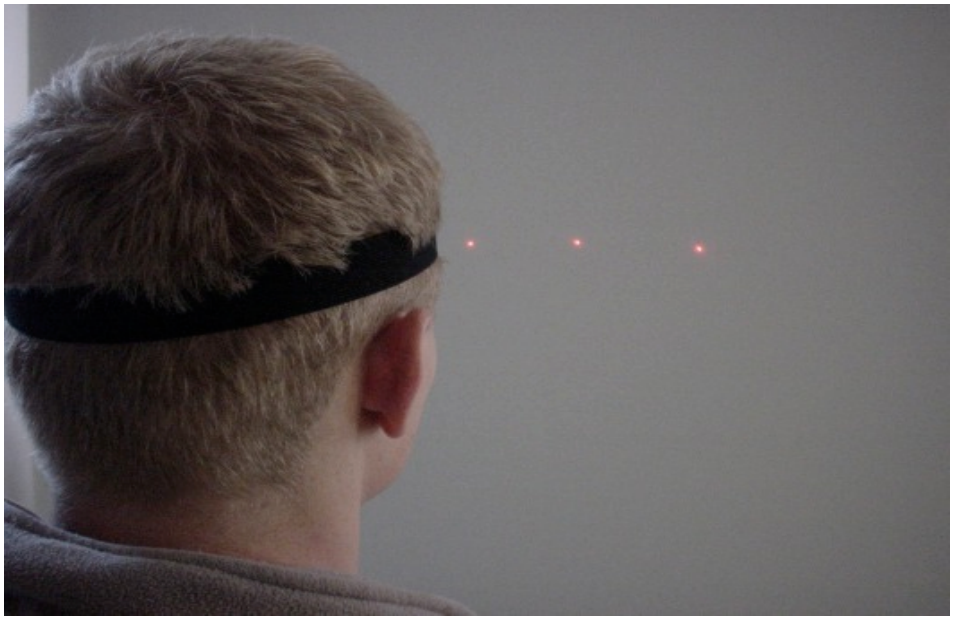


Figure 19: Laser target was shone at different angles as shown and the saccades measured using the EOG apparatus.

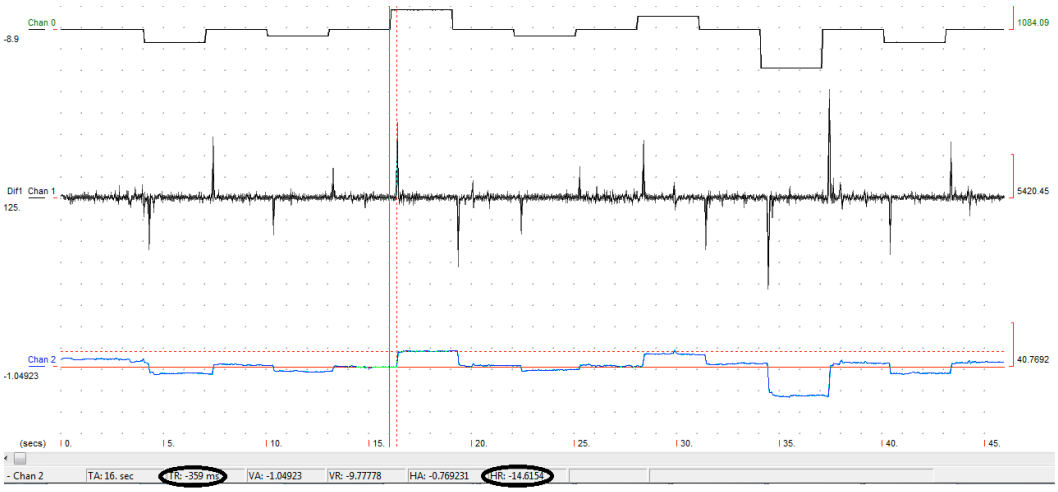


Figure 20: This figure depicts the reflexive visually guided saccadic (VGS) task being performed by a young, healthy control subject. The top trace is of the laser targets. The amplitude of the lower trace (circled as HR – 14.61 degrees) represents the amplitude of the measured saccades, while the amplitude of the middle trace represents velocity, measured in degrees s^{-1}. The horizontal distance between the two vertical cursors indicates the latency of each saccade – circled as TR: 359 ms.

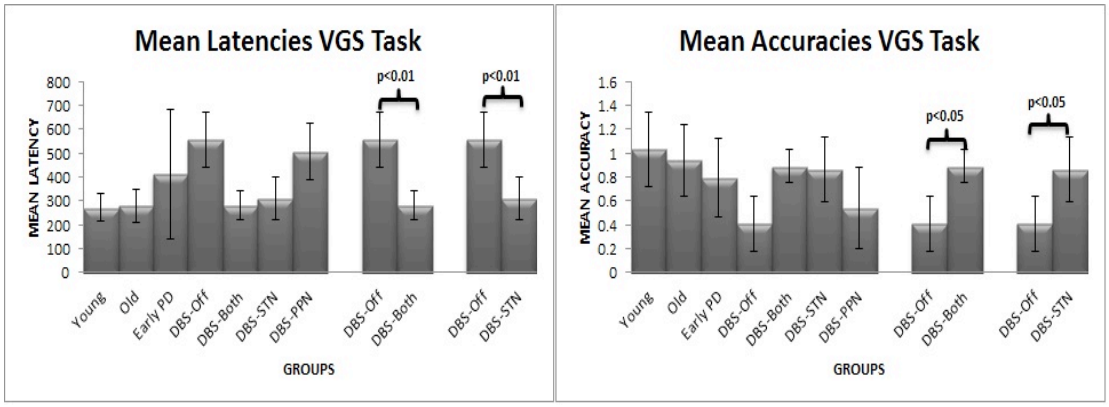


Figure 21: Parameters for the VGS Task. Latencies and accuracies are represented here and the statistically significant results have been highlighted with parentheses. The vertical lines represent the standard deviations.

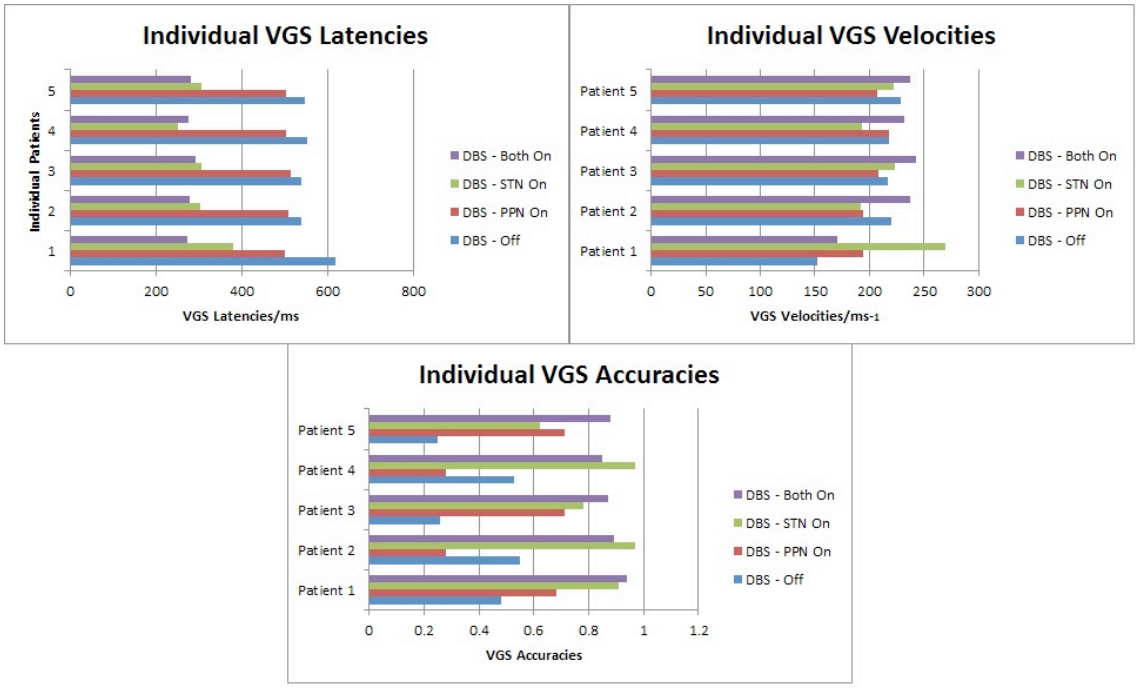


Figure 22: The individual patients showed a similar trend of improvement of parameters for the reflexive VGS saccades with DBS. The greatest improvement was seen with the combined DBS of STN and PPN ($p < 0.01$).

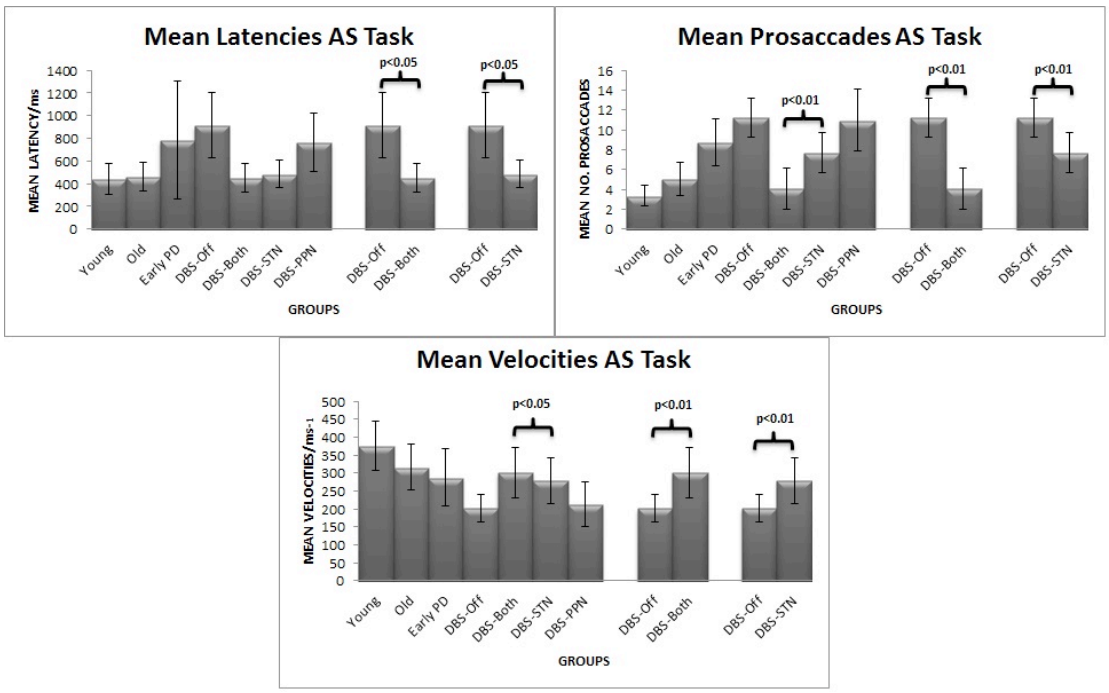


Figure 23: Graphical representation of the Antisaccade (AS) task in terms of latencies, prosaccades and velocities. The significant results have been annotated with parentheses and the vertical lines represent the standard deviations.

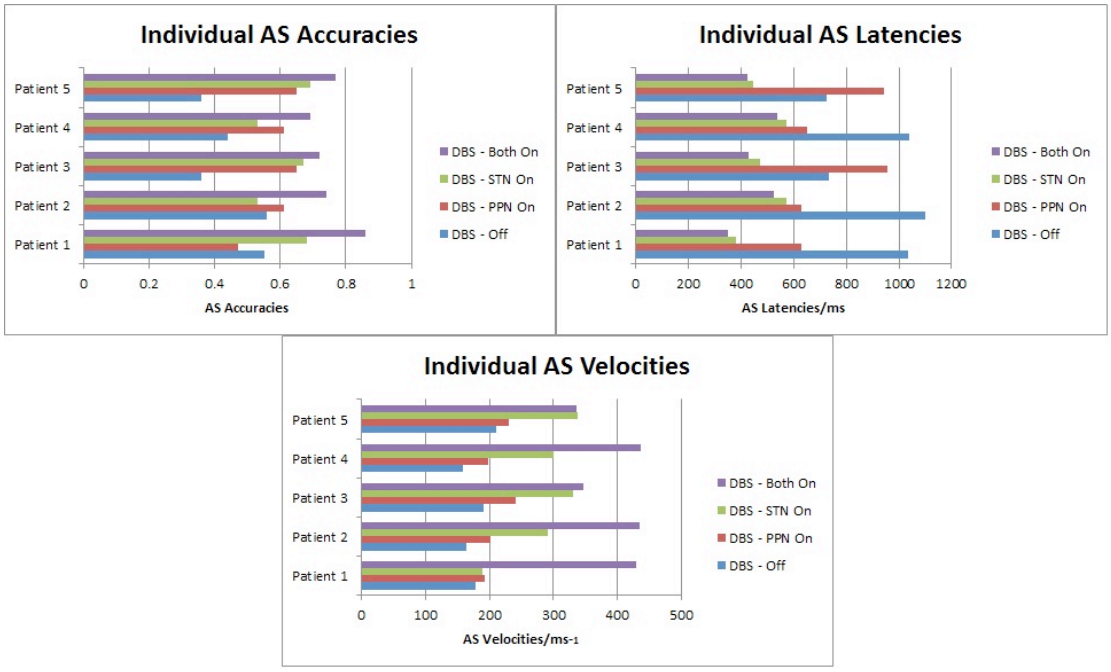


Figure 24: Individual represtation of patients with respect to the volitional antisaccade (AS) task.



Figure 25: The upper saccadic trace shows an advanced PD patient on optimal medical therapy only performing the reflexive visually guided saccadic (VGS) task. The lower trace shows the same patient with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy, performing the same task. There is marked improvement in the accuracy – 26.15 degrees compared to 20.25 degrees (circled numbers on the right), both aiming for the 30 degrees target. Similarly, the latency improves from 540 ms to 359 ms (circled numbers on the left) with the DBS treatment.

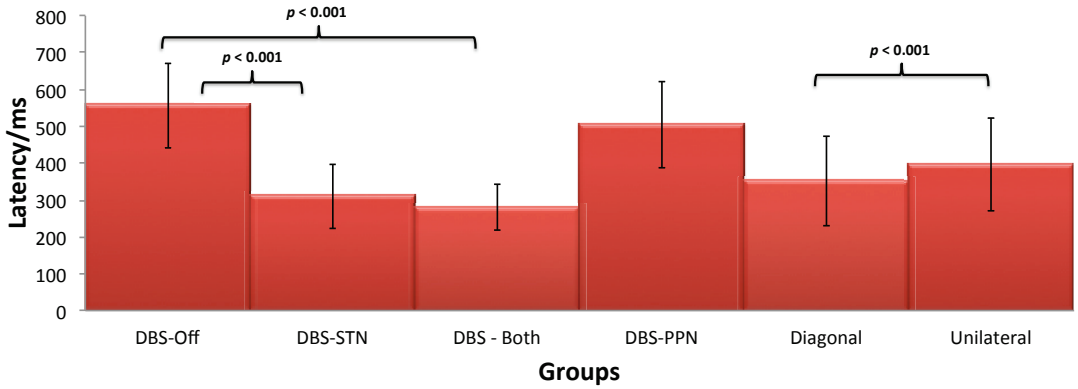


Figure 26: VGS Latency with different modes of therapy.

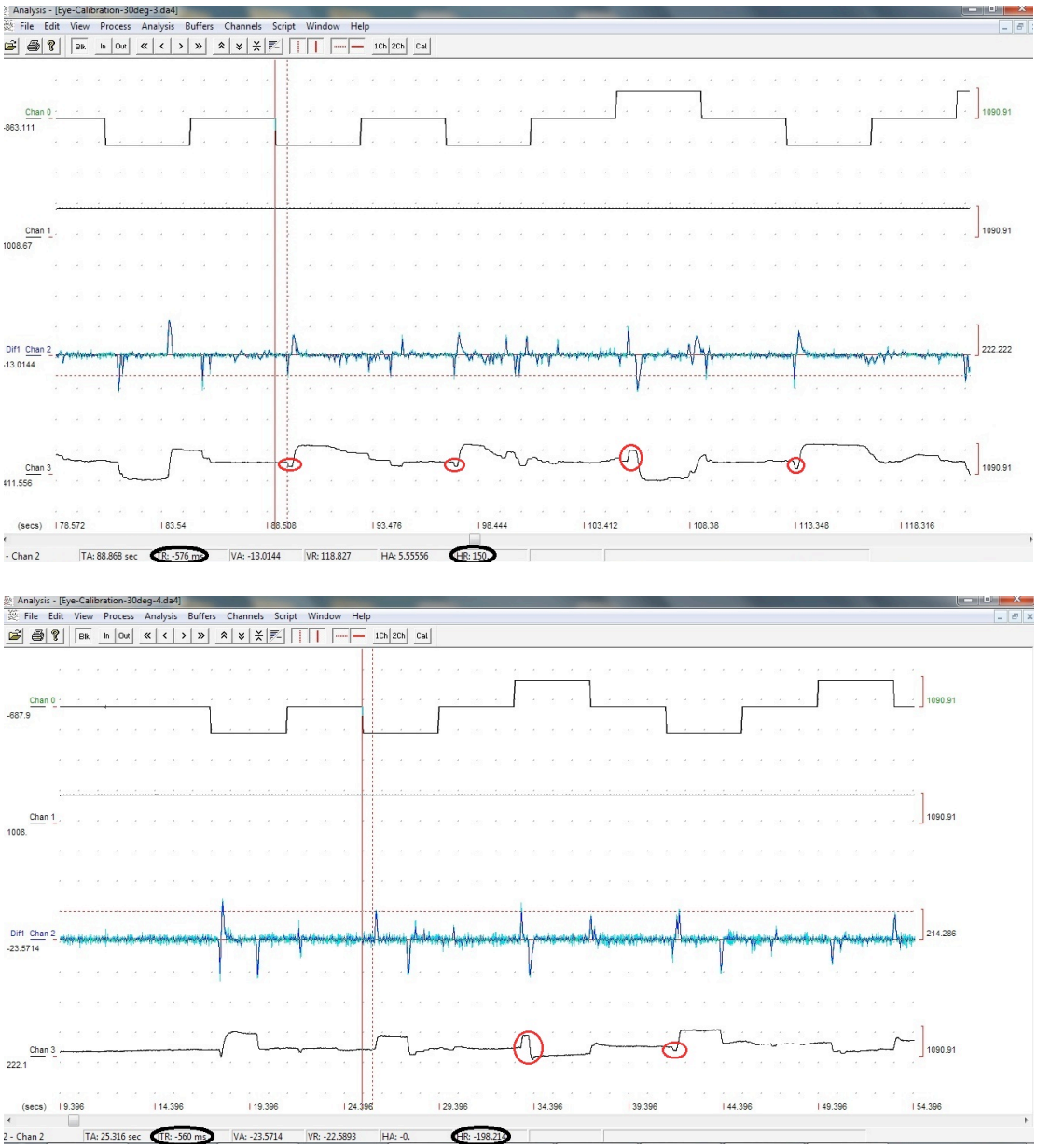


Figure 27: The upper saccadic trace shows an advanced PD on optimal medical therapy only and the lower trace is of the same patient with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy. The blue trace in the middle of the diagrams shows the velocity measured in degrees s^{-1}. The prosaccades are circled in red and the bottom right hand reading circled in black is the velocity (degrees s^{-1}) and the left hand reading circled in black is the latency (ms). As shown, the number of prosaccades decreases and the velocity increases from 150 degrees s^{-1} to 198.21 with simultaneous bilateral STN & PPN-DBS in conjunction with optimal medical therapy (lower trace).

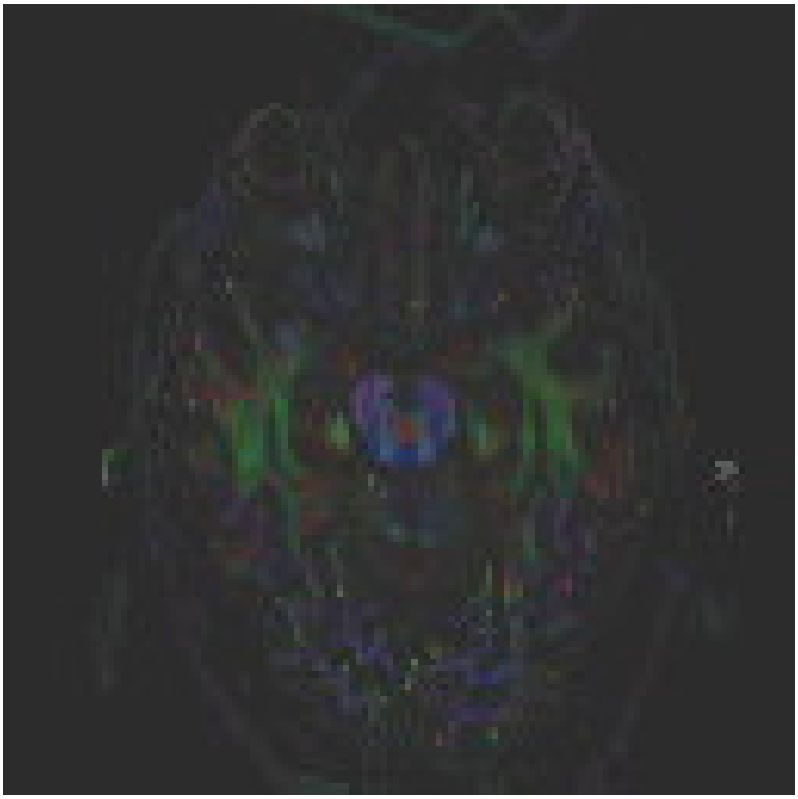


Figure 28: Example DWI / DTI scan with PDT analysis demonstrating structures adjacent to the PPN. The PPN is located just lateral and dorsal to decussation of the superior cerebellar peduncles (in red; centre of image) and medial to the medial lemniscus (in blue).

Appendix

A: Unified Parkinson's Disease Rating Scale (UPDRS)

Patient:
Date:

UPDRS I. MENTATION, BEHAVIOR AND MOOD	Score
1. Intellectual Impairment **0** = None. **1** = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties. **2** = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting. **3** = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems. **4** = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.	
2. Thought Disorder (Due to dementia or drug intoxication) **0** = None. **1** = Vivid dreaming. **2** = "Benign" hallucinations with insight retained. **3** = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities. **4** = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.	
3. Depression **0** = None. **1** = Periods of sadness or guilt greater than normal, never sustained for days or weeks. **2** = Sustained depression (1 week or more). **3** = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest). **4** = Sustained depression with vegetative symptoms and suicidal thoughts or intent.	
4. Motivation/Initiative **0** = Normal. **1** = Less assertive than usual; more passive. **2** = Loss of initiative or disinterest in elective (non-routine) activities. **3** = Loss of initiative or disinterest in day-to-day (routine) activities. **4** = Withdrawn, complete loss of motivation.	
Total score (worst score 16)	

Patient:
Date:

II. ACTIVITIES OF DAILY LIVING 1/2	**Off**	**On**
5. Speech **0** = Normal **1** = Mildly affected. No difficulty being understood **2** = Moderately affected. Sometimes asked to repeat statements **3** = Severely affected. Frequently asked to repeat statements **4** = Unintelligible most of the time		
6. Salivation **0** = Normal **1** = Slight but definite excess of saliva in mouth; may have night-time drooling **2** = Moderately excessive saliva; may have minimal drooling **3** = Marked excess of saliva with some drooling **4** = Marked drooling, requires constant tissue or handkerchief		
7. Swallowing **0** = Normal **1** = Rare choking **2** = Occasional choking **3** = Requires soft food **4** = Requires NG tube or gastrotomy feeding		
8. Handwriting **0** = Normal **1** = Slightly slow or small **2** = Moderately slow or small; all words are legible **3** = Severely affected; not all words are legible **4** = The majority of words are not legible		
9. Cutting food and handling utensils **0** = Normal **1** = Somewhat slow and clumsy, but no help needed **2** = Can cut most foods, although clumsy and slow; some help needed **3** = Food must be cut by someone, but can still feed slowly **4** = Needs to be fed		
10. Dressing **0** = Normal **1** = Somewhat slow, but no help needed **2** = Occasional assistance with buttoning, getting arms in sleeves **3** = Considerable help required, but can do some things alone **4** = Helpless		

Patient:
Date:

II. ACTIVITIES OF DAILY LIVING 2/2	**Off**	**On**
11. Hygiene **0** = Normal **1** = Somewhat slow, but no help needed **2** = Needs help to shower or bathe; or very slow in hygienic care **3** = Requires assistance for washing, brushing teeth, combing hair, going to bathroom **4** = Foley catheter or other mechanical aids		
12. Turning in bed and adjusting bed clothes **0** = Normal **1** = Somewhat slow and clumsy, but no help needed **2** = Can turn alone or adjust sheets, but with great difficulty **3** = Can initiate, but not turn or adjust sheets alone **4** = Helpless		
13. Falling (unrelated to freezing) **0** = None **1** = Rare falling **2** = Occasionally falls, less than once per day **3** = Falls an average of once daily **4** = Falls more than once daily		
14. Freezing when walking **0** = None **1** = Rare freezing when walking; may have start hesitation **2** = Occasional freezing when walking **3** = Frequent freezing. Occasionally falls from freezing **4** = Frequent falls from freezing		
15. Walking **0** = Normal **1** = Mild difficulty. May not swing arms or may tend to drag leg **2** = Moderate difficulty, but requires little or no assistance **3** = Severe disturbance of walking, requiring assistance **4** = Cannot walk at all, even with assistance		
16. Tremor (Symptomatic complaint of tremor in any part of body) **0** = Absent **1** = Slight and infrequently present **2** = Moderate; bothersome to patient **3** = Severe; interferes with many activities **4** = Marked; interferes with most activities		
17. Sensory complaints related to parkinsonism **0** = None **1** = Occasionally has numbness, tingling, or mild aching **2** = Frequently has numbness, tingling, or aching; not distressing **3** = Frequent painful sensations **4** = Excruciating pain		
Total score (worst score 52)		

Patient
Date:
Current treatment:

III. UPDRS Motor Score	Time:				
		Off	**On**	**On**	**On**
18. Speech 0 = Normal 1 = Slight loss of expression, diction and/or volume 2 = Monotone, slurred but understandable; moderately impaired 3 = Marked impair 4 = Unintelligible					
19. Facial Expression 0 = Normal 1 = Minimal hypomimia, could be normal "Poker Face" 2 = Slight but definitely abnormal diminution of facial expression 3 = Moderate hypomimia; lips parted some of the time 4 = Masked or fixed facies with severe or complete loss of facial expression					
20. Tremor at rest (head, upper and lower extremities) 0 = Absent 1 = Slight and infrequently present 2 = Mild in amplitude and persistent. Or moderate in amplitude but only intermittently present 3 = Moderate in amplitude and present most of the time 4 = Marked in amplitude and present most of the time		H RU LU RL LL	H RU LU RL LL	H RU LU RL LL	H RU LU RL LL
21. Action or Postural Tremor of hands 0 = Absent 1 = Slight; present with action 2 = Moderate in amplitude, present with action 3 = Moderate in amplitude with posture holding as well as action 4 = Marked in amplitude; interferes with feeding		RU LU	RU LU	RU LU	RU LU
22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cog-wheeling to be ignored) 0 = Absent 1 = Slight or detectable only when activated by mirror or other movements 2 = Mild to moderate 3 = Marked, but full range of motion easily achieved 4 = Severe, range of motion achieved with difficulty		N RU LU RL LL	N RU LU RL LL	N RU LU RL LL	N RU LU RL LL

III. UPDRS Motor Score	Off	On	On	On
23. Finger Taps (Patient taps thumb with index finger in rapid succession) 0 = Normal 1 = Mild slowing and/or reduction in amplitude 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement 4 = Can barely perform the task	RU LU	RU LU	RU LU	RU LU
24. Hand Movements (Patient opens and closes hands in rapid succession) 0 = Normal 1 = Mild slowing and/or reduction in amplitude 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement 4 = Can barely perform the task	RU LU	RU LU	RU LU	RU LU
25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously) 0 = Normal 1 = Mild slowing and/or reduction in amplitude 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement 4 = Can barely perform the task	RU LU	RU LU	RU LU	RU LU
26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches) 0 = Normal 1 = Mild slowing and/or reduction in amplitude 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement 4 = Can barely perform the task	RL LL	RL LL	RL LL	RL LL
27. Arising from Chair (Patient attempts to rise from a straight-backed chair, with arms folded across chest) 0 = Normal 1 = Slow; or may need more than one attempt 2 = Pushes self up from arms of seat 3 = Tends to fall back and may have to try more than one time, but can get up without help 4 = Unable to arise without help				

III. UPDRS Motor Score	Off	On	On	On
28. Posture 0 = Normal erect 1 = Not quite erect, slightly stooped posture; could be normal for older person 2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side 3 = Severely stooped posture with kyphosis; can be moderately leaning to one side 4 = Marked flexion with extreme abnormality of posture				
29. Gait 0 = Normal 1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion 2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion 3 = Severe disturbance of gait, requiring assistance 4 = Cannot walk at all, even with assistance				
30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared) 0 = Normal 1 = Retropulsion, but recovers unaided 2 = Absence of postural response; would fall if not caught by examiner 3 = Very unstable, tends to lose balance spontaneously 4 = Unable to stand without assistance				
31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm-swing, small amplitude, and poverty of movement in general) 0 = None 1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons Possibly reduced amplitude 2 = Mild degree of slowness and poverty of movement which is definitely abnormal Alternatively, some reduced amplitude 3 = Moderate slowness, poverty or small amplitude of movement 4 = Marked slowness, poverty or small amplitude of movement				
Total (worst score 140)				
Percentage improvement	===			

Patient:
Date:

IV. COMPLICATIONS OF THERAPY (In the past week)	**Score**
A. DYSKINESIAS	
32. Duration: What proportion of the waking day are dyskinesias present? (Historical information) **0** = None **1** = 1-25% of day **2** = 26-50% of day **3** = 51-75% of day **4** = 76-100% of day	
33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination) **0** = Not disabling **1** = Mildly disabling **2** = Moderately disabling **3** = Severely disabling **4** = Completely disabled	
34. Painful Dyskinesias: How painful are the dyskinesias? **0** = No painful dyskinesias **1** = Slight **2** = Moderate **3** = Severe **4** = Marked	
35. Presence of Early Morning Dystonia (Historical information) **0** = No **1** = Yes	
Total score (worst score 13)	

Patient:
Date:

IV. COMPLICATIONS OF THERAPY (In the past week)	**Score**
B. CLINICAL FLUCTUATIONS	
36. Are "off" periods predictable? **0** = No **1** = Yes	
37. Are "off" periods unpredictable? **0** = No **1** = Yes	
38. Do "off" periods come on suddenly, within a few seconds? **0** = No **1** = Yes	
39. What proportion of the waking day is the patient "off" on average? **0** = None **1** = 1-25% of day. **2** = 26-50% of day. **3** = 51-75% of day. **4** = 76-100% of day.	
Total score (worst score 7)	

IV. OTHER COMPLICATIONS	**Score**
40. Does the patient have anorexia, nausea, or vomiting? **0** = No **1** = Yes	
41. Any sleep disturbances, such as insomnia or hypersomnolence? **0** = No **1** = Yes	
42. Does the patient have symptomatic orthostasis? (Record the patient's blood pressure, height and weight on the scoring form) **0** = No **1** = Yes	

Patient:
Date:

V. MODIFIED HOEHN AND YAHR STAGING

☐ **STAGE 0** = No signs of disease

☐ **STAGE 1** = Unilateral disease

☐ **STAGE 1.5** = Unilateral plus axial involvement

☐ **STAGE 2** = Bilateral disease, without impairment of balance

☐ **STAGE 2.5** = Mild bilateral disease, with recovery on pull test

☐ **STAGE 3** = Mild to moderate bilateral disease; some postural instability; physically independent

☐ **STAGE 4** = Severe disability; still able to walk or stand unassisted

☐ **STAGE 5** = Wheelchair bound or bedridden unless aided

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

☐ **100%** = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty

☐ **90%** = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty

☐ **80%** = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness

☐ **70%** = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores

☐ **60%** = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible

☐ **50%** = More dependent. Help with half, slower, etc. Difficulty with everything

☐ **40%** = Very dependent. Can assist with all chores, but few alone

☐ **3 0%** = With effort, now and then does a few chores alone or begins alone. Much help needed

☐ **2 0%** = Nothing alone. Can be a slight help with some chores. Severe invalid

☐ **10%** = Totally dependent, helpless. Complete invalid

☐ **0%** = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden

B: The SF-36 Questionnaire (SF-36)

Date when completing form:

SF-36 Health Survey

INSTRUCTIONS: This survey asks your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

When complete, please return the questionnaire in the envelope provided.

---

1. In general, would you say your health is:

	(circle one)
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?

	(circle one)
Much better now than one year ago	1
Somewhat better than one year ago	2
About the same as one year ago	3
Somewhat worse than one year ago	4
Much worse now than one year ago	5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing several flights of stairs	1	2	3
Climbing one flight of stairs	1	2	3
Bending, kneeling or stooping	1	2	3
Walking more than a mile	1	2	3
Walking half a mile	1	2	3
Walking one hundred yards	1	2	3
Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were limited in the kind of work or other activities	1	2
Had difficulty performing the work or other activities (for example, it took extra effort	1	2

5.During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(circle one)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been with you during the past 4 weeks.
For each question please give the one answer that comes closest to the way you have been feeling.
How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	1	2	3	4	5	6
Have you been a very nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt downhearted and low?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

(circle one)

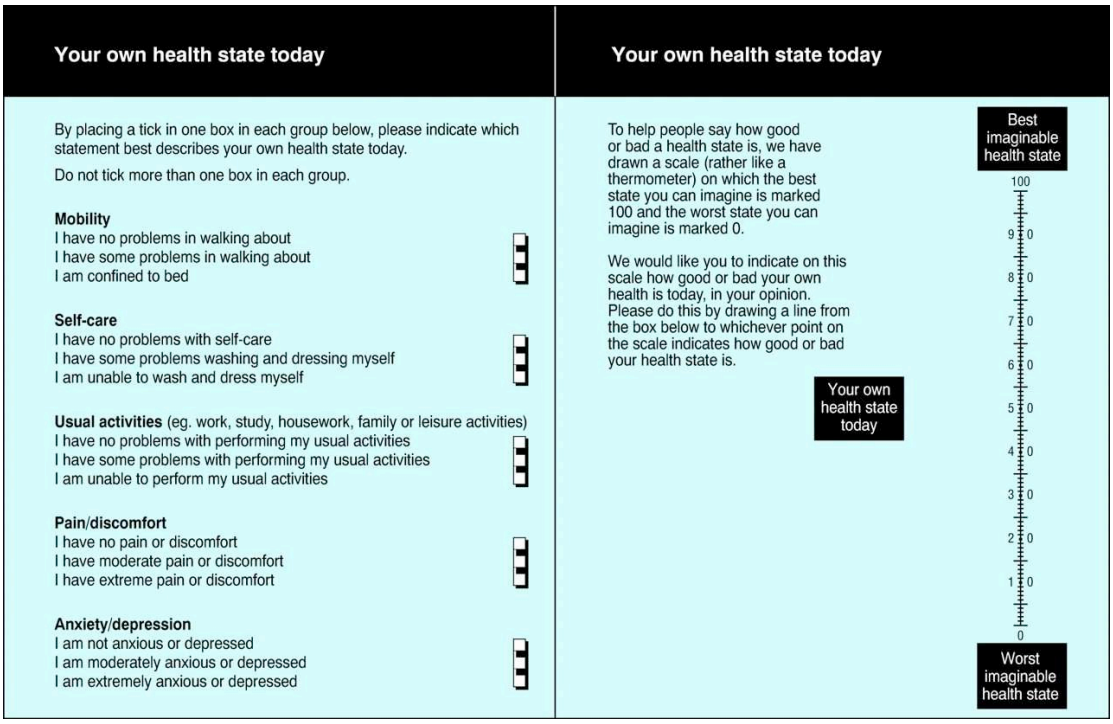
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements to you?

(circle one number on each line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
I seem to get ill more easily than other people	1	2	3	4	5
I am as healthy as anybody I know	1	2	3	4	5
I expect my health to get worse	1	2	3	4	5
My health is excellent	1	2	3	4	5

C: EuroQol EQ-5D Questionnaire (EQ-5D)



Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-care
I have no problems with self-care
I have some problems washing and dressing myself
I am unable to wash and dress myself

Usual activities (eg. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Your own health state today

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Your own health state today

Best imaginable health state

100
90
80
70
60
50
40
30
20
10
0

Worst imaginable health state

D: Falls & near-Falls Diary, AND, Daily Mobility Record

near-Fall: “an event that requires you to be supported, either by holding-on to something yourself or by someone else holding you, to prevent an otherwise certain fall”.

Instructions for use:
Circle “Y” on any day where you experienced a Fall / near-Fall.
Also, record details of EACH episode on the pages at the back.
Record total No. of steps & distance at the END of each day.

Date:
(near)-Falls: Y / N
Steps:
Distance: ……Km

Date & Time you (near)-fell?

Where were you when you (near)-fell?

What were you trying to do at the time?

What do you think caused you to (near)-fall?

How did you land?

What injuries did you sustain?

How did you get up again?

What health care did you receive?

E: The Timed Get-Up and Go Test

Measures mobility in people who are able to walk on their own (assistive device permitted)

Name_____

Date_____

Time to Complete_____**seconds**

Instructions:

The person may wear their usual footwear and can use any assistive device they normally use.

1. Have the person sit in the chair with their back to the chair and their arms resting on the arm rests.
2. Ask the person to stand up from a standard chair and walk a distance of 10 ft. (3m).
3. Have the person turn around, walk back to the chair and sit down again.

Timing begins when the person starts to rise from the chair and ends when he or she returns to the chair and sits down.

The person should be given 1 practice trial and then 3actual trial. The times from the three actual trials are averaged.

Predictive Results

Seconds	Rating
<10	Freely mobile
<20	Mostly independent
20-29	Variable mobility
>20	Impaired mobility

F: The Berg Balance Scale

BERG BALANCE SCALE

Patient Name: _____

Rater Name: _____

Date: _____

Balance Item	Score (0-4)
1. Sitting unsupported	_____
2. Change of position: sitting to standing	_____
3. Change of position" standing to sitting	_____
4. Transfers	_____
5. Standing unsupported	_____
6. Standing with eyes closed	_____
7. Standing with feet together	_____
8. Tandem standing	_____
9. Standing on one leg	_____
10. Turning trunk (feet fixed)	_____
11. Retrieving objects from floor	_____
12. Turning 360 degrees	_____
13. Stool stepping	_____
14. Reaching forward while standing	_____

TOTAL (0–56): _____

Interpretation

0–20, wheelchair bound
21–40, walking with assistance
41–56, independent

G: Freezing of Gait questionnaire (FOG-Q)

All answers, except in response to item 3, should be based on your experience over the last week. This questionnaire should be completed by the researcher after asking and demonstrating freezing phenomenon, if necessary.

1. During your worst state - do you walk:

0 Normally
1 Almost normally - somewhat slow
2 Slow but fully independent
3 Need assistance or walking aid
4 Unable to walk

2. 2. Are your gait difficulties affecting your daily activities and independence?

0 Not at all
1 Mildly
2 Moderately
3 Severely
4 Unable to walk

3. Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?

0 Never
1 Very rarely - about once a month
2 Rarely - about once a week
3 Often - about once a day
4 Always - whenever walking

4. How long is your longest freezing episode?

0 Never happened
1 1-2 s
2 3-10 s
3 11-30 s
4 Unable to walk for more than 30 s

5. How long is your typical start hesitation episode (freezing when initiating the first step)?

0 None
1 Takes longer than 1 s to start walking
2 Takes longer than 3 s to start walking
3 Takes longer than 10 s to start walking
4 Takes longer than 30 s to start walking

6. How long is your typical turning hesitation (freezing when turning)?

0 None
1 Resume turning in 1-2 s
2 Resume turning in 3-10 s
3 Resume turning in 11-30 s
4 Unable to resume turning for more than 30 s

H: Patient Information Leaflet

Imperial College Neuromodulation Group

Neurosurgeon	D Nandi
Neurologist	P Bain, N Pavese & S Molloy
Neurophysiologist	X Liu
Clinical Research Fellow	M J Naushahi
Neuropsychologist	D Murphy
Administrator	J Watson

Gyanamrhe Suswasthasya Pratikam

Imperial College Healthcare NHS Trust

Charing Cross Hospital
Fulham Palace Road
London, W6 8RF

Tel: +44 (0) 20 8846 1182
www.imperial.nhs.uk

Pedunculopontine Nucleus-Deep Brain Stimulation Trial
Patient Information Leaflet

You are being invited to participate in a clinical trial, funded by the Medical Research Council (MRC) and sponsored by Imperial College London, investigating better symptom control in advanced Parkinson's disease (PD) using a surgical device (deep brain stimulation – DBS) that is in current use (for the last twenty-years) worldwide for treating particular patients with PD. **The innovation being tested in this trial is the use of DBS in a new target in the brain – the pedunculopontine nucleus (PPN)**.

You have been referred to us by your local Neurologist for consideration of DBS. By this stage, you have been clinically thoroughly assessed by our Multi-disciplinary team (MDT) called the Imperial College Neuromodulation Group (ICNG) based in Charing Cross Hospital, who are running this trial. This would have included a detailed neurological assessment (Drs. Peter Bain and Nicola Pavese), neuropsychological assessment (Dr. David Murphy and his team), MRI brain scan under general anaesthetic (Dr. Chris Hopkins), and possibly some electro-physiological and balance tests (Prof. Adolfo Bronstein and his team). You would have also met and discussed DBS treatment with your Neurosurgeon (Mr. Dipankar Nandi).

You have been found suitable for and have been offered DBS treatment targeting a part of the brain called the sub-thalamic nucleus (STN). This is the standard treatment most specialist centres in the world would consider at this stage of your PD. It is approved by NICE in the UK (since November 2003) and by the regulatory authorities in the US (FDA) and in Europe. The procedure and the potential benefits and risks have been explained to you and / or your carer.

The reason you are being invited to receive PPN-DBS (as part of the trial), in addition to the standard STN-DBS, is that you have specific symptoms that affect your balance and walking. You may have had spontaneous stumbles and falls recently and experienced episodes of suddenly "freezing" while starting to walk or turn. These particular symptoms have been found to be resistant to current treatments (including the standard STN-DBS and medication). Scientific studies in the last decade have shown that PPN-DBS may help with these symptoms. In the last three-years a few patients with your kind of PD symptoms have had PPN-DBS (with or without simultaneous STN-DBS) in various centres in the world (Rome, Bristol, Toronto, Brisbane and Grenoble). Early results from these pilot studies show improvement in these difficult symptoms of altered balance and walking.

Our trial proposes to examine the benefit of adding PPN-DBS to medical treatment and STN-DBS under a rigorous, controlled, prospective setting. Our application for funding to the MRC proposing the trial was assessed by independent experts and found suitable. The trial has also been approved by the local ethics committee. In addition, a medical equipment company that makes the DBS equipment (Medtronic Inc.) will provide a free set of DBS kit for every patient that is enrolled in the trial.

Should you choose to be part of this trial your treatment will proceed exactly as it would have if you had opted not to do so – with some important differences:

1. Your surgical procedure will involve implantation of FOUR DBS leads in the brain (instead of the standard TWO leads) and TWO pacemakers under the skin in the chest / abdomen (instead of the standard ONE pacemaker).
2. You (and / or your carer) will be asked to maintain a record of the falls (and near falls) that you have over the subsequent two-years. You will also be given a pedometer to be worn whenever you walk and will be asked to keep a record of the readings.
3. The duration of the trial period is two-years. We will see you in clinic (or as a day admission in our Programmed Investigation Unit) every six-months (which is also part of standard care) when we will change the DBS stimulation parameters in a statistically designed pattern (neither you nor the Neurologist assessing you will know which DBS is "On" or "Off"). On average, the follow-up assessments in your case will be three-hours longer than the standard follow-up assessments as they are much more detailed. They include tests for assessing your balance, function and stability. **However, there are NO invasive procedures or episodes of general / local anaesthetic that are needed as part of the trial follow-up**. There will be one six-month period during the trial (randomly assigned) when both the standard STN-DBS and the trial PPN-DBS will be switched "Off" and you will be treated with medication alone.
4. At the end of the trial, all DBS leads that help control your symptoms will remain switched "**ON"**. **NONE** of the DBS leads will be removed. You will remain under our standard follow-up that is offered to every patient who undergoes DBS.

There are important risk factors to consider if you choose to be part of the trial. In theory, implanting FOUR DBS leads instead of TWO may increase the risk of having a bleed in the brain and causing a stroke (the standard procedure of STN-DBS carries a 1-3% risk of this happening). There is no evidence to suggest (or quantify) the increased risk; indeed all the reports where patients have had FOUR DBS leads implanted have not shown increased incidence of bleeding or stroke. Similarly, there is a theoretically increased risk of infection (standard risk 5%). Again, increased incidence of infection has not been reported in the existing cases.

We will discuss all the issues raised above, including the potential additional benefits and risks incurred by participation in the trial, with you (and / or your carer) as and when you would like us to. **We would like to stress that the decision to enter the PPN-DBS trial is completely independent of your decision to proceed with the rest of your treatment, i.e., STN-DBS and usual medication**.

We will inform your GP / doctor about your participation in this trial, unless you do not wish us to do so. We recommend the former course of action as your GP / doctor will be integral to your continued care and the said information will aid them.

You will receive a copy of this Patient Information Leaflet and a copy of the Consent Form to keep. None of the investigators involved in the trial stand to gain financially from this trial. We will publish the results of the trial in peer-reviewed scientific and professional journals. You will not be identified in any publication. However, we will seek your express permission if we wish to show clinical assessment scores, radiological images (x-ray, CT, MRI), electrophysiological studies (EMG, EEG, LFP) and audio-visual recordings (pictures, videos) taken during your clinical assessments in national / international professional conferences or for teaching / training. We will discuss the results with you during your routine clinic visits.

What if something goes wrong?
Imperial College London holds insurance policies that apply to this trial. If you experience harm or injury as a result of taking part in this trial, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this trial then you should immediately inform the Principal Investigator (Mr. Dipankar Nandi +44 (0) 20 8846 1182) or any of the other investigators (Drs. Peter Bain and Sean O'Riordan). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Office.

I: GP Letter & GP Information Leaflet

Imperial College Neuromodulation Group

Neurosurgeon	D Nandi
Neurologist	P Bain, N Pavese & S Molloy
Neuroanaesthetist	C Hopkins
Neurophysiologist	X Liu, N Yousif
Clinical Research Fellow	M J Naushahi
Neuropsychologist	D Murphy
Administrator	J Watson



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London, W6 8RF

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[GP Details]

[Date]

Dear Dr. [Name],

Re: [Patient Details]

I am pleased to advise you that the above named patient has been offered and opted to participate in the **Pedunculopontine Nucleus-Deep Brain Stimulation Trial** run by the Imperial College Neuromodulation Group (ICNG) based in Charing Cross Hospital.

Please find attached a copy of the GP Information Leaflet explaining details of the trial. A copy of the Patient Information Leaflet provided to the patient is also included for your information.

If you have any concerns or would like to find out more about the trial please do not hesitate to contact the Imperial College Neuromodulation Group (ICNG).

Yours sincerely,

Mr. M J Naushahi, BMedSci (Hons), BM, BS, LLM, MRCS, FRSM, PhD (Candidate)
MRC Clinical Research Fellow & StR in Neurosurgery to Mr. D Nandi, Consultant Neurosurgeon
Room 10L23, Imperial College Neuromodulation Group (ICNG)
Department of Clinical Neuroscience
Faculty of Medicine, Imperial College London
Reynolds Building, Charing Cross Hospital Campus
St. Dunstan's Road, Hammersmith
London, United Kingdom, W6 8RP
☏: +44 (0) 20 3313 0663
🖷: +44 (0) 20 8846 1253
✉: m.naushahi@imperial.ac.uk
🖱: http://www1.imperial.ac.uk/medicine/people/m.naushahi/

Imperial College Neuromodulation Group

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Gyanamhe Suswasthasya Pratikam

Imperial College Healthcare NHS
NHS Trust

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Pedunculopontine Nucleus-Deep Brain Stimulation Trial
GP Information Leaflet

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It is likely your patient has been referred to us by your local Neurologist for consideration of DBS. By this stage, the patient would have been clinically thoroughly assessed by our Multi-disciplinary team (MDT) called the Imperial College Neuromodulation Group (ICNG) based in Charing Cross Hospital, who are running this trial. This would have included a detailed neurological assessment (Drs. Peter Bain and Nicola Pavese), neuropsychological assessment (Dr. David Murphy and his team), MRI brain scan under general anaesthetic (Dr. Chris Hopkins), and possibly some electro-physiological and balance tests (Prof. Adolfo Bronstein and his team). They would have also met and discussed DBS treatment with their neurosurgeon (Mr. Dipankar Nandi).

They have been found suitable for and have been offered DBS treatment targeting a part of the brain called the sub-thalamic nucleus (STN). This is the standard treatment most specialist centres in the world would consider at this stage of their PD. It is approved by NICE in the UK (since November 2003) and by the regulatory authorities in the US (FDA) and in Europe. The procedure and the potential benefits and risks have been explained to your patient and / or their carer.

The reason they have been offered a chance to receive PPN-DBS (as part of the trial), in addition to the standard STN-DBS, is that they have specific symptoms that affect balance and walking. They may have had spontaneous stumbles and falls recently and disabling gait freezing. These particular symptoms have been found to be resistant to current treatments (including the standard STN-DBS and medication). Scientific studies in the last decade (some of which were performed by members of ICNG) have shown that PPN-DBS may help with these symptoms. In the last three-years a few patients with these axial PD symptoms have had PPN-DBS (with or without simultaneous STN-DBS) in various centres in the world (Rome, Bristol, Toronto, Brisbane and Grenoble). Early results from these pilot studies show improvement in these difficult symptoms of altered balance and gait dysfunction.

Our trial proposes to examine the benefit of adding PPN-DBS to medical treatment and STN-DBS under a rigorous, controlled, prospective setting. Our application to the MRC proposing the trial was assessed by independent experts and found suitable and worthy of being funded (£400,000.00 over three-years). The trial has also been approved by the local ethics committee. In addition, a medical equipment company that makes the DBS equipment (Medtronic Inc.) will provide a free set of DBS kit for every patient that is enrolled in the trial.

Should your patient choose to be part of this trial their treatment will proceed exactly as it would have if they had opted not to do so – with some important differences:

1. The surgical procedure will involve implantation of FOUR DBS leads in the brain (instead of the standard TWO leads) and TWO pacemakers under the skin in the chest / abdomen (instead of the standard ONE pacemaker).

2. The patient (and / or carer) will be asked to maintain a record of the falls (and near falls) that you have over the subsequent two-years. They will also be given a pedometer to be worn whenever they walk and will be asked to keep a record of the readings.

3. We will see them in clinic every six months (as standard) when we will change the DBS stimulation parameters in a double-blinded, statistically designed pattern – William's square design for repeated measures (neither the patient nor the particular Neurologist assessing them will know which DBS is "On" or "Off"). Detailed follow-up assessments will be undertaken, **however, there are NO invasive procedures or episodes of general / local anaesthetic that are needed as part of the trial follow-up**.

4. At the end of the trial, all DBS leads that help control their symptoms will remain switched "**ON"**. **NONE** of the DBS leads will be removed. They will remain under our standard follow-up that is offered to every patient who undergoes DBS.

There are important risk factors to consider if they choose to be part of the trial. In theory, implanting FOUR DBS leads instead of TWO may increase the risk of having a bleed in the brain and causing a stroke (the standard procedure of STN-DBS carries a 1-3% risk of this happening). There is no evidence to suggest (or quantify) the increased risk; indeed all the reports where patients have had FOUR DBS leads implanted have not shown increased incidence of bleeding or stroke. Similarly, there is a theoretically increased risk of infection (standard risk 5%). Again, increased incidence of infection has not been reported in the existing cases.

We will discuss all the issues raised above, including the potential additional benefits and risks incurred by participation in the trial, with them and their carer, as and when they would like us to.

We would like to stress that the decision to enter the PPN-DBS trial is completely independent of their decision to proceed with the rest of their treatment, i.e., STN-DBS and usual medication.

J: Deep Brain Stimulation (DBS) Consent Form

Imperial College Neuromodulation Group

Neurosurgeon	D Nandi
Neurologist	P Bain, N Pavese & S Molloy
Neuroanaesthetist	C Hopkins
Neurophysiologist	X Liu
Clinical Research Fellow	M J Naushahi
Neuropsychologist	D Murphy
Administrator	J Watson

Gyanamrhe Suswasthasya Pratikam

Imperial College Healthcare NHS
NHS Trust

Charing Cross Hospital
Fulham Palace Road
London, W6 8RF

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www.imperial.nhs.uk

Deep Brain Stimulation Consent Form

Surname:……..……

Forename(s):……

Date of Birth:...……

Address:...……

Hospital No…..……

NHS No……

I understand that clinical assessment scores, radiological images (x-ray, CT, MRI), electrophysiological studies (EMG, EEG, LFP) and audio-visual recordings (pictures, videos) may be produced as part of my treatment.

I understand the said materials will be stored as part of patient's medical records and on computer databases in accordance with guidelines of Imperial College Healthcare NHS Trust.

I understand that Imperial College Healthcare NHS Trust is a higher education institution with research commitments.

I confirm that the above has been explained to me, that I have received and read printed information regarding my treatment and acknowledge that I have had the opportunity to discuss my treatment.

I give my consent for use of the said materials for research, training and educational purposes.

I understand that my participation is voluntary and that I may withdraw at any time, without giving any reason, with the rest of my medical care being unaffected.

Signed (Patient): ……..…….. Date:……

Name (PRINT): ……..

Signed (Doctor): ……..…….. Date:……

Name (PRINT): ……..……..…….... Grade:……..…

Original publications

Naushahi MJ, Dipankar Nandi (2013). "Pedunculopontine nucleus-stimulation in patients with Advanced Parkinson's disease". Stereotact Funct Neurosurg. **91(suppl 1)**: 1-334.

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