OPTIMISING PROGRAMMING TO REDUCE SIDE EFFECTS OF SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

Dr Viswas Vishnu Dayal

This thesis is submitted for the degree of

Doctor of Philosophy

Department of Clinical and Movement Neurosciences

UCL Institute of Neurology

University College London, 2020

Declaration of originality

I, Viswas Dayal, declare that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in the thesis.

25th August 2020

Abstract

Subthalamic nucleus deep brain stimulation (STN DBS) is a widely used treatment for Parkinson's disease patients with motor complications refractory to medical management. However, a significant proportion of treated patients suffer from stimulation induced side effects. Conventional options to address these by modulation of stimulation parameters and programming configurations have been limited. In recent years, technological advances have resulted in the emergence of novel programming features, including the use of short pulse width (PW) and directional steering, that represent further avenues to explore in this regard.

In this thesis, I will present data on the utility of these programming techniques in alleviating stimulation induced side effects, and explore mechanisms that may mediate any observed effects. The data presented here is derived from four studies. Study 1 quantified the therapeutic window using short PW stimulation at 30μs relative to conventional 60μs settings. Study 2 represents a randomised controlled trial on short PW in chronic STN DBS patients with dysarthria. Study 3 evaluated the utility of directional steering, short PW, and the combination of these features in reversing stimulation induced dysarthria, dyskinesia, and pyramidal side effects.

The findings of these studies suggest that short PW significantly increases the therapeutic window in terms of amplitude and charge, and that while it may not benefit chronic dysarthric patients collectively, directional steering and short PW can each significantly improve reversible stimulation induced side effects early in the course of STN DBS therapy. These novel techniques represent effective additional tools to conventional methods for optimising stimulation. In study 4, imaging and visualisation software are used to model and explore shifts in volume of tissue activated based on

clinical data from study 3, and quantitatively compare charge per pulse, in order to explore potential mechanisms underlying the changes seen with these techniques.

Impact statement

This thesis presents data on the utility of two major developments in STN DBS therapy in recent years. STN DBS has been around for over 25 years and significantly reduces motor fluctuations and improves quality of life in appropriately selected patients, but the occurrence of stimulation related side effects can be a setback for many, resulting in increased hospital visits, time and effort expended by clinicians, and a significant impact on the quality of life of patients.

While novel programming techniques of short pulse and directional stimulation have been commercially available for over five years, data on their utility has been limited, particularly with respect to addressing side effects. There has been a pressing need for studies on the use of these features in order to guide clinicians on the best practice when programming STN DBS using newer devices.

The data presented clarify the utility of novel programming techniques in STN DBS patients with stimulation related side effects. In study 1, short pulse width was demonstrated to have a wider therapeutic window relative to conventional stimulation in the largest dataset reported. The randomised double blinded trial on short pulse width is the first and only such trial to date in chronic STN DBS patients. While this did not demonstrate an overall benefit in a heterogenous group, it showed equivalent measures on motor, non-motor and quality of life scales to conventional stimulation, and the pilot data provided leads on subgroups who may benefit from it. The subsequent study confirmed a significant benefit of short pulse stimulation in patients with stimulation induced dysarthria and dyskinesia who were within 3 years of surgery.

Study 3 represents the first systematically collected data on the utility of directional stimulation in addressing side effects, and the largest study on the use of novel

techniques, evaluating the effect of systematic optimisation using each feature separately, as well as both combined, on a range of side effects. The significantly positive results from this study provide the first evidence that each of these techniques is effective at reversing stimulation induced side effects, informing clinicians faced with these challenges and providing researchers with a basis for future clinical trials. This work represents foundational data, which along with other emerging data in this field, can be incorporated into much needed updated clinical guidelines and programming algorithms. This may lead to improved patient outcomes and satisfaction for a significant proportion of patients treated with STN DBS worldwide, and improve efficiency of healthcare resource use. Furthermore, demonstration of the clinical utility of novel features will encourage DBS device manufacturers to further develop and refine these technologies, along with advancing tools to streamline programming, such as integration of patient specific anatomic, connectivity and electrophysiologic information into programming platforms in order to aid the clinician in optimally utilising these features in an efficient manner.

The thesis concludes with a proposed simplified and practical algorithm to deal with stimulation induced side effects using novel features based on findings of the studies here and currently available data.

TABLE OF CONTENTS

CHAPTER 4: THE UTILITY OF DIRECTIONAL STEERING AND SHORT PULSE WIDTH IN ALLEVIATING SUBTHALAMIC NUCLEUS STIMULATION INDUCED SIDE EFFECTS

CHAPTER 5: EXPLORING MECHANISMS THAT MAY MEDIATE CHANGES IN ADVERSE EFFECTS OF STN DBS WITH THE USE OF NOVEL PROGRAMMING TECHNIQUES: VTA MODELLING AND THE ROLE OF ELECTRICAL CHARGE

List of figures

List of tables

List of abbreviations

AC - PC	Anterior commissure - posterior commissure
ADE	Adverse device event
AE	Adverse event
AEO	Apraxia of eyelid opening
AIDS	Assessment of intelligibility of dysarthric speech
ANOVA	Analysis of variance
BRAIN	The Bradykinesia Akinesia Incoordination test
CC	Constant current
Cm	Centromedian
COMT	Catechol-o-methyltransferase
CRF	Case report form
CV	Constant voltage
dMSN	Direct medium spiny neurons
DBS	Deep brain stimulation
DIR	Directional
DTI	Diffusion tensor imaging
ET	Efficacy threshold
FF	Fields of Forel
FDG-PET	Fluorodeoxyglucose positron emission tomography
F-MRI	Functional magnetic resonance imaging
FOG	Freezing of gait
FRS	Facial recognition software
GFQ	Gait and falls questionnaire
GPe	Globus pallidus externa
GPi	Globus pallidus interna

Hz	Hertz
IC	Internal capsule
iMSN	Indirect medium spiny neurons
IPG	Implantable pulse generator
LCIG	Levodopa-carbidopa intestinal gel
LFP	Local field potential
mA	milli-amperes
MDS	Movement Disorder Society
MHRA	Medicines and Healthcare products Regulatory Agency
MICC	Multiple independent current source control
MCP	Midcommissural point
MON	Monologue
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR	Magnetic resonance
MRI	Magnetic resonance imaging
nC	nanocoulombs
NMSS	Non-motor symptom scale
PD	Parkinson's Disease
PDQ-39	39-item Parkinson's Disease Questionnaire
Pf	Parafascicular
PIS	Patient information sheet
PPN	Pedunculopontine nucleus
PW	Pulse width
QoL	Quality of life
Qp	Charge per pulse
RCT	Randomised controlled trial
RDG	Reading task

REC	Research ethics committee
RM	Ring mode
SADE	Serious adverse device event
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of mean
SF	Subthalamic fascicle
SIT	Sentence intelligibility test
SMA	Supplementary motor area
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SSW	Sit – Stand – Walk
ST	Side effect threshold
STN	Subthalamic nucleus
T	Tesla
TEED	Total electrical energy delivered
TMG	Trial management group
TSC	Trial steering committee
TW	Therapeutic window
UDysRS	Unified dyskinesia rating scale
UPDRS	Unified Parkinson's disease rating scale
UI	User interface
V	Volts
VF	Verbal fluency
VIM	Ventral intermediate
VTA	Volume of tissue activated
ZI	Zona incerta

Acknowledgments

The work presented here would not have been possible without the contribution, participation, and support of numerous individuals in various different forms.

First and foremost, I would like to thank my primary supervisor, Professor Tom Foltynie, who helped make everything possible from a starting point across the planet, and whose excellent guidance, encouragement, expert ability to help navigate any obstacles that came our way - big or small - with admirable patience and stamina, and lightning-fast efficiency provided the ideal platform that has culminated in this work. I could not have asked for more in a supervisor and mentor, and will remain eternally grateful and indebted to him for the opportunities he entrusted me with.

I would also like to sincerely thank my secondary supervisor, Professor Patricia Limousin, for her guidance, teaching, help and involvement in the trial, pragmatic advice and comforting words whenever needed over the years.

I am grateful to all other members of the Unit of Functional Neurosurgery; firstly our DBS nurses, Maricel, Catherine, and Joseph, who have assisted in numerous ways, ranging from their participation in clinical research, referring patients for studies, providing moral support, and creating a pleasant and relaxed work environment despite being amidst the pressures of a busy unit; to our surgeons: Mr Harith Akram, Mr Jonathan Hyam, Professor Ludvic Zrinzo; ex- head of department Professor Marwan Hariz for his staunch support and colourfully packaged endorsements; Professor Marjan Jahanshahi; our speech therapists, in particular to Tim Grover for his expert input in all to do with speech, enthusiasm for collaboration, and ever-ready willingness to fit requests into his busy schedule; and to Alexis De Roquemaurel and Francisca Ferreira for their help with VTA modelling. I am also grateful for the friendship, companionship and

support of other research fellows, past and present, over the years: Simon Little, Philipp Mahlknecht, Dilan Athauda, James Gratwicke, Davide Cappon, Emma Scelzo, Yildiz Degirmenci, Nondas Lyros, Suzette Shahmoon, Nirosen Vijaratnam, Christine Girges, Thomas Wirth, and Ali Rajabian; and our secretaries: Linda, Haris, Debbie, Siva, Inga and Susan for always so efficiently taking care of administrative tasks and ensuring everything ran smoothly.

I am grateful for the unconditional support as always of my family, in particular my parents and brother Vachan, and all my friends for providing the necessary balance with downtime, companionship and entertainment, for being part of the memories that I shall cherish, and especially to Sara and Arti (proof-reader extraordinaire) for always being there to listen, to advise, and for their unwavering moral support from the outset.

Finally, I thank an important group who are at the centre of this work: those who participated in these studies, shared in the enthusiasm for advancing treatment, remained ever grateful and appreciative, whose tears of joy and relief in moments of success served as one of my deepest inspirations, and from whom I learnt beyond what could be acquired from any literature or authority – the patients.

Publications resulting from work related to this thesis

- PUBLICATIONS ARISING DIRECTLY FROM THIS THESIS

Dayal, V., Limousin, P. & Foltynie, T. Subthalamic nucleus deep brain stimulation in Parkinson's disease: The effect of varying stimulation parameters. *Journal of Parkinson's Disease*. 2017; 7:235–245.

Dayal, V., Grover, T., Limousin, P., Akram, H., Cappon, D., Candelario, J., et al. The effect of short pulse width settings on the therapeutic window in subthalamic nucleus deep brain stimulation for Parkinson's disease. *Journal of Parkinson's Disease*. 2018; 8:273–279.

Dayal, V., Grover, T., Tripoliti, E., Milabo, C., Salazar, M., Candelario-McKeown, J., et al. Short Versus Conventional Pulse-Width Deep Brain Stimulation in Parkinson's Disease: A Randomized Crossover Comparison. *Movement Disorders*. 2019; 1–8.

Dayal, V., De Roquemaurel, A., Grover, T., Ferreira, F., Salazar, M., Milabo, C. et al. Novel Programming Features Help Alleviate Subthalamic Nucleus Stimulation Induced Side Effects. *Movement Disorders – IN PRESS.*

International Parkinson and Movement Disorder Society (MDS) Podcast: January 2020; **Finetuning DBS in Parkinson's Disease. How much can we improve?** https://www.movementdisorders.org/MDS-Files1/Podcasts/FinetuningDBSinParkinsonsdisease.Howmuchcanweimprove.mp3

- OTHER RELATED PUBLICATIONS

Dayal, V; Akram, H; Zrinzo, L; Limousin, P; Foltynie, T. Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: Valuable Programming Insights from Anecdotal Observations. *Stereotact Funct Neurosurg.* 2020;98(1):62-64.

Dayal, V., Rajabian, A., Jahanshahi, M., Aviles-Olmos, I., Cowie, D., Peters, A. et al. Pedunculopontine Nucleus Deep Brain Stimulation for Parkinsonian disorders: A Case Series. *Stereotact Funct Neurosurg – IN PRESS.*

CHAPTER 1

Introduction

1 – Summary of chapter

This chapter provides a background on the role of STN DBS in the management of Parkinson's disease, long term side effects associated with it, postulated mechanisms of its therapeutic effects and side effects, and current programming paradigms. Published data on the effects of modulating each primary stimulation parameter including amplitude, frequency, and pulse width, as well as novel programming features of directional and adaptive stimulation are reviewed. Specific avenues for research are identified based on current knowledge, and form the basis of research aims in the framework of optimising programming to reduce side effects of STN DBS.

1.1 Parkinson's disease and the role of subthalamic nucleus deep brain stimulation

1.1.1 Parkinson's disease

Parkinson's disease (PD), the second most prevalent neurodegenerative disorder, affects an estimated 7.5 million people worldwide (Ross & Abbott, 2014). Modern medicine traces its first description as a distinct clinical syndrome to 1817 in *An Essay on the Shaking Palsy* by James Parkinson. Less consolidated accounts of Parkinsonism, however, have been present for several centuries, including its treatment using seed powder of the levodopa-containing plant *Mucuna Pruriens* in ancient Ayurvedic medicine (Manyam, 1990; Katzenshlager *et al.*, 2004; Ovallath & Deepa, 2013). PD has been subsequently attributed to nigrostriatal dopamine deficiency from loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), amongst other subsets of neuronal loss seen in the disorder. Apart from its cardinal motor manifestations of predominantly rest tremor, rigidity, bradykinesia, and in later stages postural instability, a variety of associated non-motor manifestations are well recognised in patients with PD, including autonomic and sleep disturbances, cognitive decline, mood and neuropsychiatric symptoms, olfactory dysfunction, fatigue, and pain. Some of these, such as REM sleep behaviour disorder and hyposmia may significantly precede motor symptoms (Hawkes, 2004; Trotti, 2010; Schapira, Chaudhuri & Jenner, 2017).

Pathologically, PD is characterised by depigmentation and neuronal loss in the substantia nigra pars compacta (SNc) and pontine locus ceruleus, neuronal degeneration in the dorsal nucleus of the vagus in the medulla and other brainstem nuclei, and eosinophilic cytoplasmic inclusions known as Lewy bodies which are rich in alpha-synuclein and but also contain associated proteins such as ubiquitin, parkin and

neurofilaments (Cornford, Chang & Miller, 1995). Lewy bodies in PD are widespread and are found in the substantia nigra, the basal nucleus of Meynert, locus ceruleus, cerebral cortex, sympathetic ganglia, the dorsal vagal nucleus, the myenteric plexus of the intestines, and the cardiac sympathetic plexus (Wakabayashi *et al.*, 2007).

At the network level, the striatal dopaminergic deficit results in imbalances in basal ganglia circuitry and can be used to explain the motor manifestations of PD, albeit using simplified models [Figure 1.1]. Dopamine has differential effects on the striatal D1 receptors of the direct pathway and D2 receptors of the indirect pathway, being excitatory in the former and inhibitory in the latter. The net effect of dopamine deficiency via both the direct and indirect pathways is to increase the inhibitory basal ganglia output signal to the thalamus and reduce the thalamocortical signal. In the direct pathway this is through reduced inhibition of the globus pallidus interna and substantia nigra pars reticulate (GPi, SNr), and in the indirect pathway this is facilitated via the globus pallidus externa (GPe), which has a reduced inhibitory effect on the STN, causing a functional disinhibition of the STN and a follow on increase in the inhibitory output signal from the GPi/SNr to the thalamus.

Apart from direct effects of neuronal degeneration and dopaminergic deficit, aberrant activity in surviving populations of neurons in the basal ganglia-thalamocortical circuit is thought to play a role in some key manifestations of PD. In particular, there has been accumulating evidence in recent years of the correlation between Parkinsonian motor signs and synchronised beta oscillations in the range of 13-30Hz, termed the beta-band. The pathological nature of elevated levels of these synchronised oscillations is fortified by observations that they diminish with dopaminergic treatment as well as therapeutic electrical deep brain stimulation (DBS), during which Parkinsonian motor signs are alleviated, and re-emerge upon withdrawal of these treatments, correlating with the reoccurrence of symptoms (Little & Brown, 2012, 2014; Tinkhauser *et al.*, 2017b).

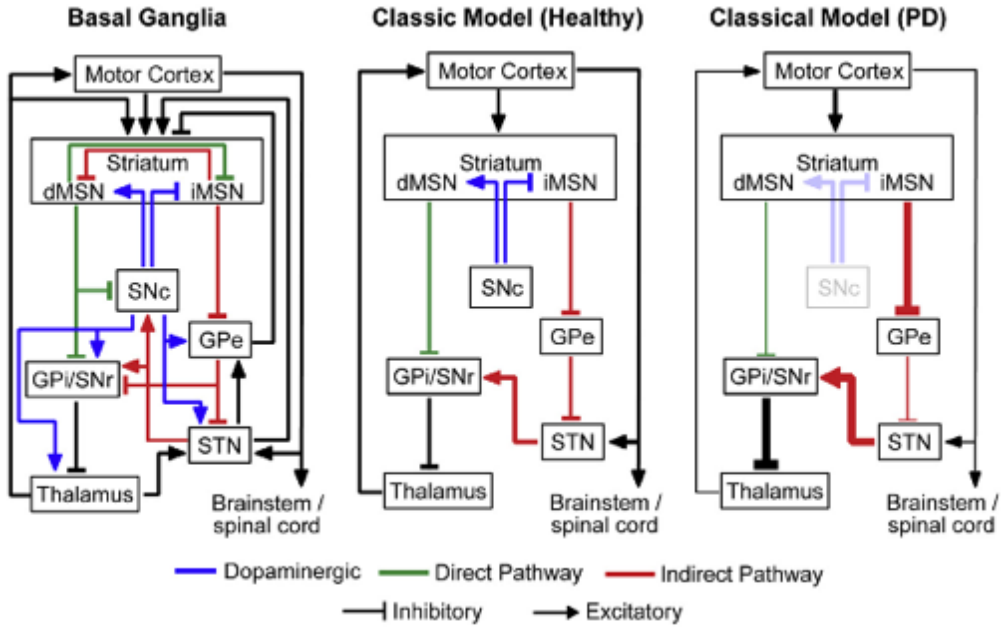


Figure 1.1. **Classical model of basal ganglia and circuit dysfunction in Parkinson's disease.**
(Adapted from McGregor et al., 2019)

Legend**:** dMSN- direct medium spiny neurons; iMSN- indirect medium spiny neurons; GPi: Globus pallidus interna; GPe- Globus pallidus externa; STN- Subthalamic nucleus; SNc- Substantia nigra pars compacta; SNr- Substantia nigra pars reticulata.

While the search for effective disease-modifying or neuroprotective treatments for PD continues (Athauda & Foltynie, 2015), an array of pharmacological agents to symptomatically manage both motor and non-motor manifestations of PD are available. Since demonstration of its dramatic effect in PD patients with intravenous administration in 1961 (Birkmayer and Hornykiewicz, 1961) and subsequent clinical trial of oral therapy (Cotzias, 1967), Levodopa remains the most potent oral drug and is the gold standard for symptomatic treatment of parkinsonian motor symptoms (Hornykiewicz, 2010).

However, since the early era of its regular use in PD, it became clear that while this drug was very effective in alleviating motor deficits, levodopa-induced dyskinesias and motor fluctuations were troublesome late complications, correlating with cumulative dose, duration of therapy, and young age of disease onset. Loss of striatal dopaminergic

terminals with disease progression is thought to contribute to the shorter duration of effect of levodopa doses due to reduced capacity to store and buffer striatal concentration of levodopa (Fabbrini *et al.*, 1987; Manson, Stirpe & Schrag, 2012). While controlled-release formulations of levodopa are available and can be practically useful for night-time use, erratic absorption and lower bioavailability limit its utility as a substitute for regular levodopa formulations, and they have not been shown to confer any advantage in the latter setting (Stocchi *et al.*, 2010). Agents to prolong the effect of levodopa such as catechol-o-methyl-transferase (COMT) inhibitors may be added on to increase o*n* time and address wearing-off symptoms, and the NMDA receptor antagonist, Amantadine, is often utilised for its benefit in reducing dyskinesias alongside its mild anti-parkinsonian effect (Wolf *et al.*, 2010). The dopamine agonists have also established their role in both initial monotherapy and adjunctive therapy, and long-acting formulations can overcome motor fluctuations with a lower number of daily doses required compared to levodopa (Sprenger & Poewe, 2013; Connolly & Lang, 2014).

Despite the wide selection of oral pharmacological agents and combinations of therapy available, advanced PD presents the issue of problematic motor fluctuations and unavoidable treatment-related dyskinesias in many patients (Manson, Stirpe & Schrag, 2012). This has led to a number of so called 'advanced therapies' in an attempt to provide a more consistent and stable therapeutic benefit while reducing the severe dyskinesias seen with conventional oral agents, albeit using more invasive techniques. These include deep brain stimulation (DBS), subcutaneous apomorphine which can be administered continuously via a pump, and levodopa-carbidopa intestinal gel (LCIG) via a percutaneous gastrojejunostomy tube connected to an external pump. While all of these therapies have been shown to reduce *off* time and improve mean *on* time without troublesome dyskinesias, they each have individual advantages and adverse effect profiles which may suit different groups of patients. However, the greatest level of

evidence in the form of prospective randomised controlled trials exists for DBS (Volkmann *et al.*, 2013; Olanow *et al.*, 2014; Wenzel *et al.*, 2014; Wirdefeldt, Odin & Nyholm, 2016).

1.1.2 Subthalamic nucleus deep brain stimulation as a treatment for Parkinson's disease

The origins of the notion of electrical stimulation of deep brain structures to treat movement disorders lie in the previously prevalent practice of stereotactic lesion surgery. Surgical lesioning and ablation of the globus pallidum using a variety of methods was studied for the relief of Parkinsonian motor symptoms, but later eclipsed by the advent of Levodopa (Svennilson *et al.*, 1960). In the mid twentieth century, thalamotomy was explored as a surgical treatment for various psychiatric and neurological disorders (Spiegel, Wycis & Freed, 1948; Wycis & Spiegel, 1950; Uematsu, Konigsmark & Walker, 1974; Lim, Tasker & Scott, 1969). It subsequently became established as an effective procedure for the treatment of tremor, in Parkinson's disease as well as for other tremor conditions (Cooper & Poloukhine, 1959; Broager & Fog, 1962; Nagaseki *et al.*, 1986).

In 1987, *Benabid et al* reported their observation that during electrical stimulation to control placement of electrodes during the established practice at the time of ventral intermedius (VIM) thalamotomy, high frequency stimulation of the VIM nucleus resulted in suppression of contralateral tremor (Benabid *et al.*, 1987). Subsequently, selective subthalamic lesioning in non-human primates with MPTP-induced Parkinsonism was shown to ameliorate Parkinsonian motor symptoms, albeit with hemiballism as an adverse consequence (Aziz *et al.*, 1991). Based on the observed similarities of the effect on tremor of electrical stimulation to surgical lesioning seen with the VIM nucleus, *Benazzouz et al* showed that electrical stimulation of the STN indeed had a parallel

alleviating effect on MPTP-induced Parkinsonian motor signs in monkeys, and did not produce hemiballism (Benazzouz *et al.*, 1993). Following the first case reports from Grenoble of the marked effect on contralateral Parkinsonian motor signs of unilateral electrode implantation and electrical stimulation of the STN (Pollak *et al.*, 1993; Benabid, 1994), *Limousin et al* demonstrated for the first time that bilateral STN stimulation had a significant and sustained effect on Parkinsonian motor signs in humans (Limousin *et al.*, 1995).

Over the ensuing decade, subthalamic nucleus deep brain stimulation (STN DBS) became well established as an effective therapeutic avenue for selected patients with Parkinson's disease. Compared to lesion surgery for PD, it offered the advantages of having lower complication rates, particularly with bilateral procedures, being programmable in its effects, and having greater reversibility (Hartmann, *et al.,* 2019). Apart from the subthalamic nucleus (STN) target, the internal globus pallidus (GPi) also became an established alternative target for DBS in PD (Obeso *et al.*, 2001; Dostrovsky, Hutchison & Lozano, 2002). A third target, the ventral intermediate (VIM) nucleus of the thalamus is sometimes used for patients with tremor predominant PD, although this does not address rigidity and bradykinesia (Benabid *et al.*, 1999). The former two targets have shown comparable long term efficacy in improvement of motor function and reduction of dyskinesia in the *on* medication state. However, this seems to be mediated by different mechanisms: STN stimulation allows a greater reduction in the required dose of dopaminergic medication, due to its effect on alleviating motor symptoms, and a reduction in dyskinesias as a result. GPi stimulation on the other hand, has a direct anti-dyskinetic effect, enabling the use of higher doses of dopaminergic medication to compliment therapeutic stimulation effects and achieve a similar overall improvement in motor symptom control and fluctuations (Odekerken *et al.*, 2013; Peng *et al.*, 2018; Anderson *et al.*, 2005).

STN DBS has been extensively examined and compared to best medical therapy in order to establish its role in the treatment of PD. A double-blinded crossover assessment of off-medication motor scores in the stimulation on and off conditions 3 months post-operatively showed a mean UPDRS-III reduction of 49% with stimulation effect, and an increase in *on* time without dyskinesias of 47% (Obeso *et al.*, 2001). A five year follow up in 2003 provided early data on the longer term efficacy of STN DBS in 49 patients, with a 54% improvement in motor scores at 5 years compared to baseline in the off medication state, and a 49% improvement in scores of activities of daily living (Krack *et al.*, 2003). Another 5 year follow up study showed similar results regarding motor efficacy (Schüpbach *et al.*, 2005). *Kleiner-Fisman* and colleagues reported a meta-analysis of outcome data from 37 cohorts: the mean UPDRS-III reduction off-medication on-stimulation was 52%, reduction from baseline in dyskinesia following surgery was 69%, reduction in daily off periods was 68%, reduction in levodopa equivalent daily dose was 56%, and improvement in quality of life was 35% (Kleiner-Fisman *et al.*, 2006).

Following these encouraging data on the use of STN DBS as a therapeutic avenue in PD with motor complications, there was a need to reproduce and demonstrate these effects against best medical therapy in randomised controlled trials. A randomised trial of neurostimulation plus medication versus medical therapy alone showed a significant improvement in quality of life (QoL) of 23%, as measured by the PDQ-39 at 6 months, and an off-medication UPDRS-III score reduction of 40.8% (Deuschl et al.,2006). The larger open-label PD-SURG trial of 366 patients randomised to best medical therapy or DBS plus medical therapy corroborated the finding of improved QoL measures in DBS treated patients at 12 months post-operatively (Williams *et al.*, 2010). *S*ubsequently, further RCTs demonstrated that DBS was more effective than best medical therapy alone in improving *on* time without troublesome dyskinesias (56 - 67% increases), as well as QoL (Weaver, 2010; Okun *et al.*, 2012).

STN DBS is considered a well-tolerated and safe procedure, and is performed routinely in many centres internationally. As with any surgical intervention, however, there are potential peri-procedural risks, and apart from those associated with anaesthesia, if this is used, the most serious include the possibility of intracranial haemorrhage, infection related to the hardware, and seizures. The reported incidence of these vary significantly according to centre, but are generally in the vicinity of 1% for symptomatic intracranial haemorrhage and 2% for infections at experienced centres (Boviatsis *et al.*, 2010; Engel *et al.*, 2018; Krack *et al.*, 2019; Aviles-Olmos *et al.*, 2014). Others include less common hardware related complications including lead fracture and lead migration.

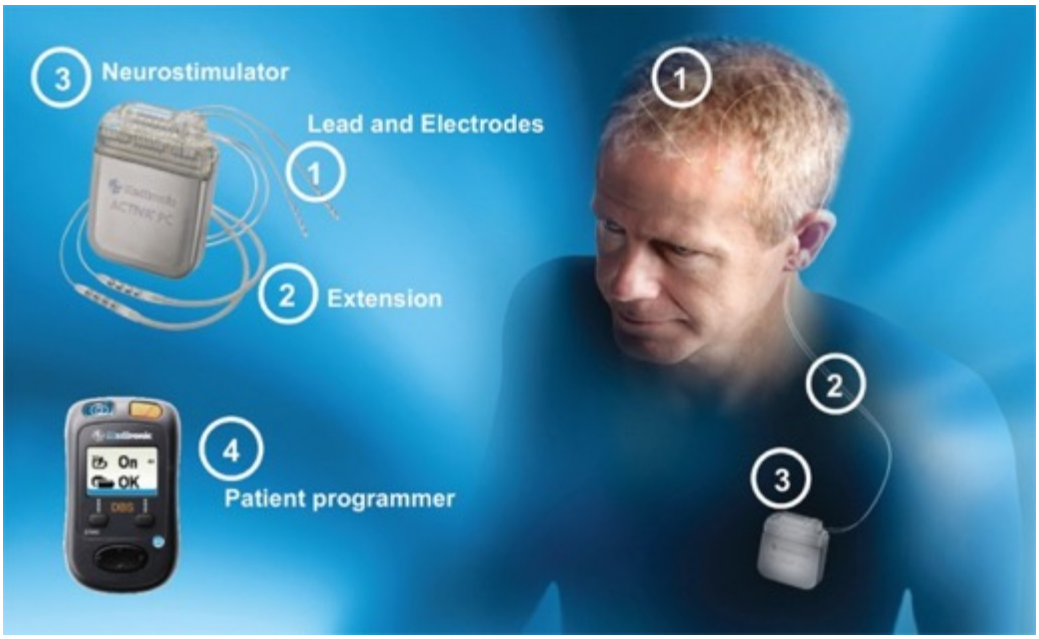


Figure 1.2. **Deep brain stimulation system (Medtronic Activa PC™ device).**
(Adapted from https://www.frontiersin.org/articles/10.3389/fnint.2011.00046)

1.1.3 Long term adverse effects of STN stimulation

The adverse effects related to varying individual stimulation parameters are discussed in detail in section 1.2. Many patients with chronic STN DBS, however, have been observed to develop certain stimulation associated side effects, and this is reflected in longer term follow up studies. In a four-year multicentre follow up of STN DBS treated patients,

speech, gait and postural stability were shown to significantly decline (Rodriguez-Oroz *et al.*, 2005). Similarly, *Guehl et al* found speech disturbance, weight gain, and postural instability to be the most common side effects of STN stimulation in 44 patients, and reported that at one year, dysarthria either worsened (in 46%) or was induced (in 15%).

In a meta-analysis of outcomes at least 6 months post-operatively in which adverse events of 778 patients from 29 studies were collated, the most common stimulation related adverse effect was dysarthria at 9.3% (Kleiner-Fisman *et al.*, 2006). Others included weight gain (8.4%), depression (6.8%), stimulation-induced dyskinesia (2.6%), and other psychiatric symptoms (5.4%). Less common effects classified as miscellaneous included muscle contractions, diplopia, postural instability and gait problems (total 4.0%).

A follow up of STN-DBS patients with a mean disease duration of 30 years (i.e. those who had early onset PD) showed that speech declined more sharply 5 years after surgery, and continued to worsen thereafter (Merola *et al.*, 2011).

Many long term side effects such as speech and gait impairment are also symptoms of disease progression in PD, and it can be difficult to elicit the relative contributions of stimulation versus disease progression in patients with worsening of these symptoms over time. While most of the studies discussed report longitudinal observational data in STN DBS patients, more convincing evidence of STN stimulation directly having a deleterious effect on speech comes from comparative data with medically managed patients, where speech intelligibility was shown to decline 17% after 1 year in STN DBS patients and 4.5% in the medical control group (Tripoliti *et al.*, 2011). Various factors relating to the patient as well as treatment have been linked to the deterioration of speech following STN DBS: long duration of disease, time since implantation, pre-existing speech impairment, medially placed electrodes in or around the STN, as well as high voltages (Tripoliti *et al.*, 2014). The findings of these studies regarding the

association of medially placed electrodes with deterioration in speech, as well as a lateralised effect of stimulation on speech, whereby the left hemispheric electrode more significantly affects speech than the right, have been corroborated by others (Santens *et al.*, 2003; Sun *et al.*, 2008).

While most studies on long term outcomes of STN DBS use patient-reported measures or UPDRS-III item 18 to rate speech, these are likely to be either less objective or less sensitive in detecting changes than specific validated scales designed to assess speech, such as the sentence intelligibility test (SIT) or perceptual assessment of speech using the Darley, Aronson and Brown scale (Darley, Aronson & Brown, 1969; Yorkston & Beukelman, 1978; Dorsey, M., Yorkston, K., Beukelman, D., & Hakel, 2007). *Tripoliti* and colleagues found, using these assessment measures, that speech intelligibility deteriorated in 78% of patients at one year post-operatively in a cohort of 32 patients, despite the expected 51% improvement in overall motor function. In contrast, using item 18 of the UPDRS-III only identified speech deterioration in 38% of these patients (Tripoliti *et al.*, 2011).

Despite acute improvements in dopa-responsive gait impairment and freezing with STN stimulation, its deleterious effect on gait and postural stability in some chronic patients has been well-recognised. A meta-regression examining long term effects of DBS on balance and gait reported that these were stable with GPi DBS five years after implantation, whereas there was a decline with STN DBS (St. George *et al.*, 2010). Furthermore, while gait and balance also deteriorate with PD progression, the direct detrimental effects on FOG when using high frequency stimulation, particularly at higher amplitudes, were demonstrated by Xie and colleagues, and is further discussed in section 1.2.4 (Xie, Kang & Warnke, 2012). This is supported by anecdotal accounts in clinical practice of improvement in FOG in some chronic STN DBS patients when the stimulation amplitude is reduced.

1.1.4 Anatomic considerations of subthalamic nucleus stimulation

Stimulation of the subthalamic nucleus may exert its effects by affecting neural elements within the STN, their projections, and surrounding structures and fibre tracts. The STN is the most prominent structure in the subthalamus, which is a part of the diencephalon ventral to the thalamus, medial to the internal capsule and lateral to the hypothalamus. It is biconvex in shape, approximately 240 cubic millimetres in size in humans, and is located superolateral to the substantia nigra in an oblique orientation. Its ventrolateral surface faces the peduncular part of the internal capsule and these fibres separate it from the globus pallidus which is located further laterally. Rostromedial to the STN are the Fields of Forel and the posterior lateral hypothalamic area. The Red nucleus lies posteromedially, and the substantia nigra and cerebral peduncle ventrally. The zona incerta and part of the fasciculus lenticularis are adjacent to the dorsal border of the STN, and these structures separate it from the ventral thalamus [Figure 1.3].

Apart from the aforementioned surrounding structures, various fibre tracts run in proximity of the STN. The prominent of these include the subthalamic fasciculus, the lenticular fasciculus, the ansa lenticularis, and the H Fields of Forel. The subthalamic fasciculus connects the STN and globus pallidus. The ansa lenticularis and lenticular fasciculus consist of GPi projection fibres to the thalamus, the latter as the H2 bundle in the Fields of Forel. The H1 Field of Forel or thalamic fasciculus is formed by the joining of the ansa lenticularis and lenticular fasciculus as well as fibres from the cerebellum and brainstem (Parent & Parent, 2004; Hamani *et al.*, 2004).

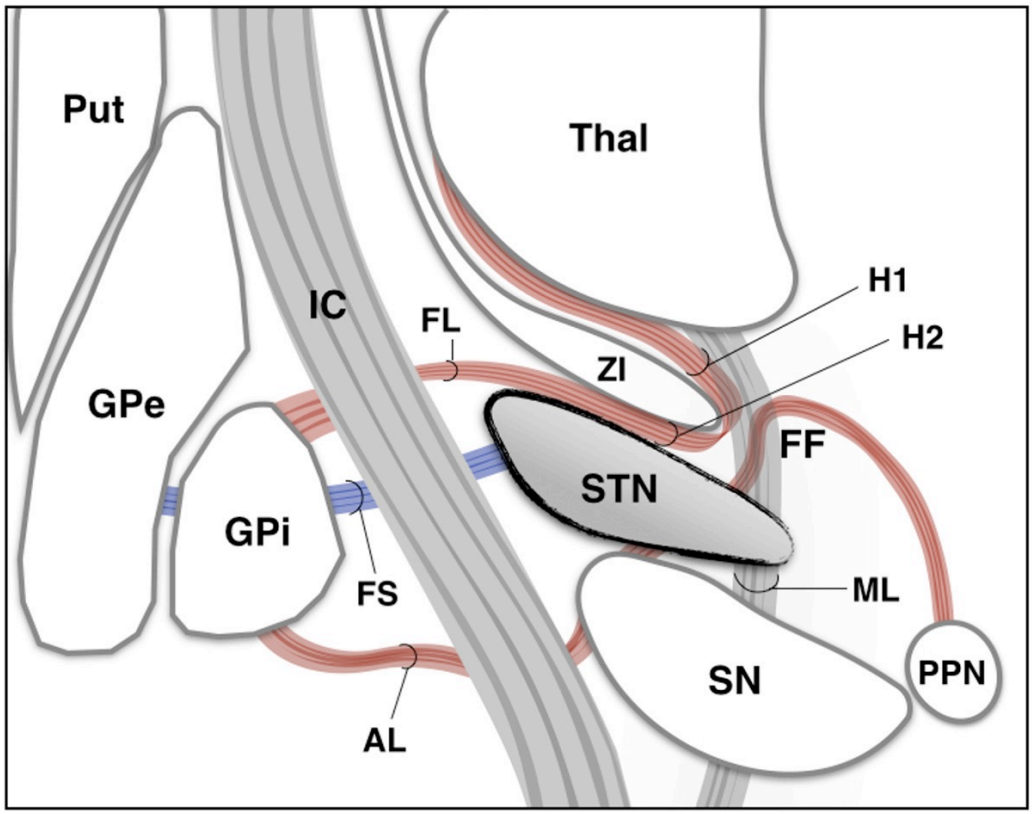


Figure 1.3. **Structures and fibres surrounding the subthalamic nucleus: coronal view**.
(*Adapted from Hamani et al., 2017).*

Legend: AL- Ansa lenticularis; FF- fields of Forel; FL- Lenticular fasciculus; FS- subthalamic fascicle; H1- H1 field of Forel (thalamic fasciculus); H2- H2 field of Forel; IC- internal capsule; ML- medial lemniscus; GPe- Globus Pallidus externa; GPi- Globus pallidus interna; PPN- pedunculopontine nucleus; Put- putamen; SN- substantia nigra; STN- Subthalamic nucleus; Thal- thalamus; ZI- zona incerta.

The STN is principally composed of glutamatergic projection neurons, with a small proportion of GABAergic interneurons which are more prevalent in the limbic and associative regions of the STN (Lévesque & André, 2005; Kawasaki *et al.*, 2018). In primates, it has been functionally subdivided into a tripartite arrangement based on physiologic characteristics and distribution of circuits with corresponding regions of the striatum, pallidum and substantia nigra reticulata (SNr). With the STN divided into thirds along the rostral-caudal axis for clarity [Figure 1.4], these are the motor division in the dorsolateral part of the rostral two-thirds and caudal third, associative division in the ventrolateral part of the rostral two-thirds, and limbic divisions in the medio-rostral part of the nucleus. However, there is now thought to be some overlap in this classic

tripartite division, so that the boundaries between these functional regions are not as strictly anatomically delineated as has been previously proposed (Alkemade, Schnitzler & Forstmann, 2015).

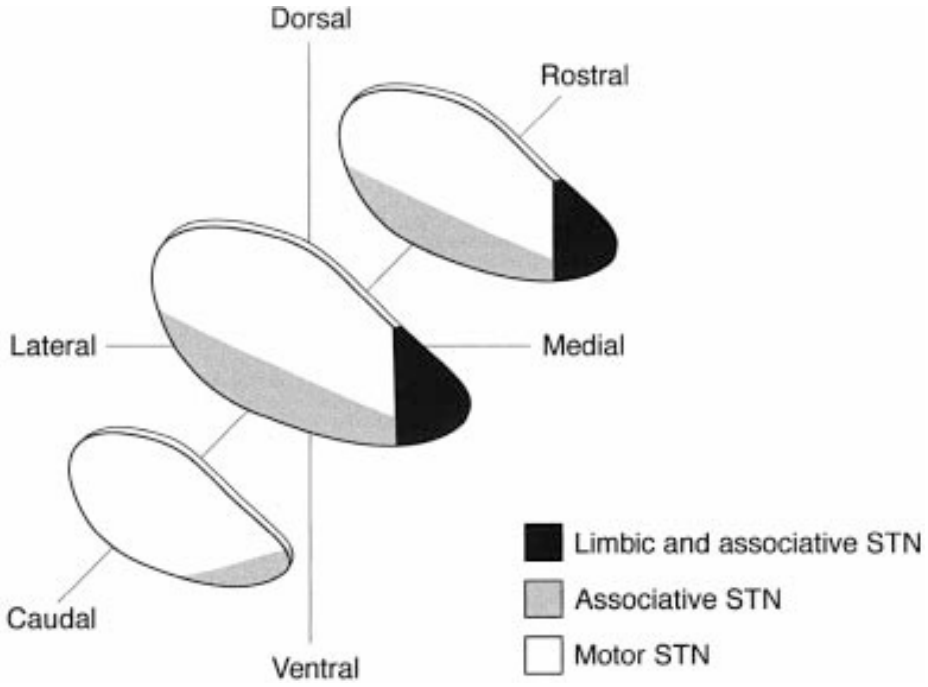


Figure 1.4. **The subthalamic nucleus represented according to functional tripartite subdivision of the basal ganglia.**
(*Adapted from Hamani et al., 2004)*.

Afferent pathways to the STN are of cortical, thalamic, pallidal, and brainstem origin. Most cortical afferents are from the primary motor cortex, supplementary motor area (SMA), pre-SMA, and dorsal and ventral pre-motor cortices, and are glutamatergic (Nambu *et al.*, 2000). The frontal and supplementary eye field areas also feed into the ventromedial STN (Matsumura *et al.*, 1992; Hamani *et al.*, 2017).

External pallidal projections to the STN via the subthalamic fasciculus are one of its major afferents. Motor and limbic portions of the GPe innervate corresponding areas of the STN, and associative pallidal afferents innervate associative and as well as motor

regions of the STN. This is the main inhibitory projection to the STN and is mediated by GABA.

Thalamic projections to the STN are mainly from the parafascicular (Pf) and centromedian (CM) nuclei. The Pf, being the predominant source of thalamic input in primates, projects to the medial third of the rostral STN which correspond to the limbic and associative territories. The CM projects to the sensorimotor region. Brainstem afferents in primates include those from the substantia nigra compacta (SNc) which are predominantly dopamine-mediated and modulate cortical and pallidal afferents (Parent & Hazrati, 1995; Parent & Parent, 2004; Hamani *et al.*, 2004).

Major efferent projections from the STN are glutamatergic and directed to the globus pallidus interna (GPi) and externa (GPe). There is also innervation of the SNr and SNc by the STN, as well as the striatum, with the caudate receiving projections from ventromedial associative and limbic regions and the putamen from dorsolateral motor regions of the STN. Apart from these, the STN has projections to the PPN and the ventral tegmental area to modulate their activity (Sharman *et al.*, 2000; Hamani *et al.*, 2017).

1.1.5 Postulated mechanisms of action of STN DBS in PD

While the precise therapeutic mechanisms underlying STN DBS in PD are not completely understood despite over two decades of experience with it, many have been proposed since its inception, and ongoing work in both animal and human studies have added to the complexity of various mechanistic notions that may mediate the effects of STN DBS.

Early ideas of STN DBS mechanisms arose from observed similarities between ablative (lesion) surgery and high frequency stimulation effects. A commonly proposed theory is of axonal depolarisation and functional inhibition of cell bodies. This so called 'depolarisation block' results in termination of spontaneous action potentials and

functional inhibition of the target, similar to that seen with lesion surgery. This notion is supported by the finding of reduced firing of STN cells near electrodes. This finding, however, can also be explained by excitation of pallidal GABAergic inputs to the STN (Filali *et al.*, 2004). Functional inhibition of the STN to treat PD motor symptoms fits with current simplified models of basal ganglia dysfunction in PD [Figure 1.1], as it is thought to normalise pathological STN hyperactivity that increases inhibitory signals of the basal ganglia output structures (GPi/SNr) in the disease state, and therefore restores excitatory thalamocortical output (Payoux *et al.*, 2004; Hamani *et al.*, 2017).

However, there are known differences between lesioning and DBS effects, with the former removing altered patterns of neuronal activity and decreasing pallidal firing rates, while stimulation has the converse effect on pallidal firing rates, and rather organises pallidal firing patterns (Hahn *et al.*, 2008). Furthermore, functional imaging including FDG-PET studies have demonstrated that STN DBS induces metabolic activation of the subthalamic region and globus pallidus, reflecting excitation of neurons in these regions. This differs from the effect of lesion surgery and cannot be explained by a depolarisation blockade (Hilker *et al.*, 2008). Functional MRI data, although limited, have corroborated the finding of increased subcortical activity with STN DBS (Jech *et al.*, 2001; Phillips *et al.*, 2006).

Furthermore, data from neural recording studies have been contradictory, with some showing suppression of activity in the nucleus (Beurrier *et al.*, 2001; Magarios-Ascone *et al.*, 2002; Filali *et al.*, 2004) while others pointed to excitation in a stimulus-synchronized regular firing pattern (Hashimoto *et al.*, 2003a). A change in firing pattern with blockade of spontaneous activity but increase in burst-like activity was then noted (Welter *et al.*, 2004). Evidence accumulated of 'decoupling' of somatic and axonal firing: while cell bodies near stimulating electrodes are inhibited, axonal projections are activated. STN stimulation therefore seems to activate its efferent fibres that influence the firing

pattern of neurons in the GPi/GPe and SNr (Maurice *et al.*, 2003; Hashimoto *et al.*, 2003a; Garcia *et al.*, 2003; McIntyre *et al.*, 2004).

A further mechanism of action may be through excitation of afferent and efferent as well as passing fibre pathways around the STN which may have effects at more distant sites, and different neurotransmitters may mediate these effects. In support of this, there is evidence that stimulation of the fields of Forel and zona incerta dorsal to the STN is clinically effective in alleviating PD symptoms (Plaha *et al.*, 2006). Rodent studies have shown an increase in GABA levels of pallidal origin in the SNr with high frequency STN stimulation, suggesting that some of the therapeutic effects of STN DBS may result from stimulation of pallidonigral fibres and pallidal GABA mediated inhibition of basal ganglia output structures (Windels, 2005). There are also data suggesting that tremor control is mediated by activation of a large fibre system in STN DBS (Ashby *et al.*, 1999).

To further complicate the theory of cell body inhibition and fibre excitation, an additional underlying mechanism has been proposed based on knowledge of the effects of a sustained depolarisation stimulus, such as high frequency electrical stimulation, on cellular membrane dynamics. This follows the notion that initial depolarisation events are not sustainable, as when neurons are held in this state there is overloading of the usual mechanisms of removing extracellular ions and neurotransmitters. While over time there is some restoration of repolarising mechanisms, there is a resultant new dynamic state with an altered equilibrium of ionic currents and concentrations of ions and neurotransmitters, and this may lead to functional blockade or tonic firing that disrupts pathological rhythmic patterns in the nucleus and its efferent targets (Florence *et al.*, 2016; Hamani *et al.*, 2017).

Network effects of STN DBS include disruption of pathological synchronous oscillatory activity in the basal ganglia thalamocortical loop that is present in PD. This pathological activity is reflected in increased prominence of beta band activity, as well as

entrainment of high frequency oscillations (phase-amplitude coupling; i.e. coupling of beta phase with gamma amplitude) and single neuron action potentials (spike-field coupling) to the beta rhythm in the cortex, STN and GPi (Kuhn *et al.*, 2008; Ray *et al.*, 2008; Bronte-Stewart *et al.*, 2009; De Hemptinne *et al.*, 2013; Herrington, Cheng & Eskandar, 2016). Dopamine-depleted basal ganglia demonstrate amplification of incoming excitation by the STN polysynaptic pathway which entrains pallidal neurons in pathogenic bursts. Additionally, STN neurons have been shown to exhibit distinct patterns of synchronous activity driven by primary motor cortex LFPs in PD, with M1 gamma activity preceding STN spikes in a phase-locked pattern to the beta rhythm, resulting in beta entrainment of the STN (Shimamoto *et al.*, 2013). High frequency STN stimulation has been shown to prevent transmission of such pathological activity to the globus pallidus, and replace these with regular small amplitude excitatory post-synaptic potentials (Wichmann, Bergman & DeLong, 1994; Hashimoto *et al.*, 2003b; Dorval *et al.*, 2008; Ammari *et al.*, 2011). This reduction in firing pattern entropy was noted in the pallidum and thalamus with therapeutic high frequency STN stimulation, and conversely increased with subtherapeutic low frequency stimulation, which is known to clinically correlate with worsening of parkinsonian motor symptoms (Dorval *et al.*, 2008; Moro *et al.*, 2002; Timmermann *et al.*, 2004; Eusebio *et al.*, 2008). The other basal ganglia nucleus that is the target of STN output, the SNr, has also been shown to exhibit stimulus-synchronized activation during STN stimulation (Galati *et al.*, 2006), and this modulation of the periodicity and pattern of neuronal activity may be induced not only in these output structures, but in the larger basal ganglia-thalamic network (Xu *et al.*, 2008). Reduced phase-amplitude coupling observed in invasive cortical recordings correspond to clinical improvement, and alleviation of this 'beta phase locking' of motor cortex neurons by STN stimulation has been implicated in improvement of cortical function (Shimamoto *et al.*, 2013; De Hemptinne *et al.*, 2015).

In line with this, PET scan studies in STN DBS have shown reductions in resting overactivity of regional metabolism, characteristic of PD, in the sensorimotor cortex and premotor cortical areas (Ceballos-Baumann *et al.*, 1999; Payoux *et al.*, 2004; Trošt *et al.*, 2006).

Additionally, in recent years the role of 'hyperdirect' pathways (afferent excitatory cortical projections to the STN) in mediating STN DBS effects has come to attention (Ashby *et al.*, 2001; McIntyre & Hahn, 2010; Akram *et al.*, 2017a). It has been proposed that antidromic cortical activation via this pathway from STN stimulation plays a part in reducing pathological synchronous oscillatory activity in the network (Li *et al.*, 2007; Walker *et al.*, 2012).

While efforts to find a unifying mechanism have been ongoing since the advent of STN DBS therapy, it may indeed be that multiple mechanisms exist non-exclusively to produce the various observed local and network-wide effects that lead to its therapeutic benefits.

1.1.6 Targeting and the optimal stimulation site in STN DBS

The dorsolateral or superolateral portion (predominantly sensorimotor functional region) of the STN has been a commonly proposed target for electrode implantation in DBS therapy for PD. However, many studies have reported that spread of current dorsal to the STN, involving white matter in the subthalamic area, where it may mediate therapeutic effects by acting on fibre tracts such as the thalamic fascicle, pallidothalamic, pallidosubthalamic tracts, or the zona incerta, is also an important effect of clinically efficacious electrodes (Voges *et al.*, 2002; Saint-Cyr *et al.*, 2002; Yelnik *et al.*, 2003). Furthermore, some have suggested targeting the caudal zona incerta is superior to the STN itself (Plaha *et al.*, 2006). This has led to a multitude of studies

aiming to define the optimal stimulation site using a variety of methods, and a selection of these are reviewed here.

Some groups have combined data from micro-electrode recordings to define STN borders with radiographically determined position of the active contact. Using this approach, *Lanotte et al* confirmed that the most effective contacts for motor outcomes were located in the upper part of the STN or just above (Lanotte *et al.*, 2002). However, *Herzog* and colleagues reported that contacts located at the electrophysiologically defined dorsolateral border or within the STN resulted in greater improvements in PD motor scores (65, 63% respectively) compared to those above the dorsolateral border (49%). Furthermore, the ratio of improvement with stimulation to pre-operative levodopa response was significantly higher with contacts at the STN border or within compared to those above (1.17, 1.11 versus 0.64), indicating that the outcome for individual patients could be optimised with stimulation sites in the former two regions regardless of variability of response to STN stimulation confounded by other factors (Herzog *et al.*, 2004).

Other groups like *Wodarg* and colleagues retrospectively analysed post-operative outcomes of patients in relation to the active contact location defined by STN borders on MRI imaging. They found laterally placed electrodes led to greater clinical improvement (reduction in UPDRS-III), lower stimulation parameters, and greater reduction in levodopa equivalent daily dose, than medially located electrodes. Anterolateral electrodes were superior to posterolaterally located ones, and these differences were present at 6- and 36-month assessments post-operatively. While this analysis was performed using a single axial plane of the STN on MRI which limited it to two dimensions, without taking the location along the z axis into account, comparing the distance of the active contact to the axial slice revealed that 86% of patients were within 1.5mm, suggesting stimulation effects within the STN. (Wodarg *et al.*, 2012).

Another imaging based study of 262 patients correlating STN DBS outcomes with contact location reported optimal improvement in motor function from contacts located in the sensorimotor or associative regions, with a 64% improvement in UPDRS-III, as compared to those in the zona incerta, where there was a 49% improvement (Welter *et al.*, 2014). However this contrasts with the findings of *Plaha et al*: they compared clinical efficacy among different cohorts of patients from their centre who had electrodes implanted either in the STN, dorsomedial/medial region to STN, or caudal zona incerta, and the corresponding improvement in motor scores were 55%, 61% and 76% respectively (Plaha *et al.*, 2006).

Bot and colleagues aimed to define the optimal stimulation point within the STN by categorising patients based on improvement in UPDRS-III 12 months postoperatively into optimal responders (>70% improvement), responders (30 - 70% improvement) and non-responders (<30% improvement). The electrode coordinates of optimal responders were used to define a theoretical 'hotspot' relative to the midcommissural point (MCP), as well as the medial STN border. They reported a significant negative correlation between motor improvement and distance of the active electrode from the defined hotspot and the medial STN border, but not the MCP. This hotspot was 2.8 mm lateral, 1.7 mm anterior and 2.5 mm superior relative to the medial STN border (Bot *et al.*, 2018).

Volume of tissue activated (VTA) modelling has also been used in recent years to create 'sweet spot' maps of the STN. Using resolution of rigidity as a marker of clinical efficacy, *Nguyen* and colleagues showed that the top 10% of most efficacious voxels were mapped to the dorsolateral STN using data from segmented contacts (Nguyen *et al.*, 2019). However, not all VTA modelling data show such uniformity. *Maks* and colleagues studied 10 patients with a range of clinical motor outcomes following STN DBS, and reported that for the five patients with best outcomes (>40% in UPDRS-III), four had

more than half their VTAs outside the STN. Conversely, of the five with worst outcomes, four had more than half the VTAs within the STN. The patterns of VTA data modelled suggested that stimulation of axonal tissue dorsal, lateral and posterior to the STN centroid resulted in optimal clinical benefit. Also of note was the finding that despite similar VTA sizes and locations in some patients, the therapeutic outcomes were significantly different, and this alludes to limitations of anatomic or image-based methods of defining sweet spots, which do not take variations in individual responses and somatotopy into account (Maks *et al.*, 2009).

Akram et al used voxel-based analysis of VTA models to map out areas corresponding to optimal effect for each cardinal motor sign of tremor, bradykinesia and rigidity separately. They found that the cluster corresponding to maximum improvement of tremor was located in the central portion of the superior STN, whereas clusters corresponding to improvement in rigidity and bradykinesia were near the superior border, more medially and posteriorly. The rigidity cluster was noted to extend beyond the superior border to the region of the zona incerta and H2 fields of Forel. Using probabilistic tractography to map DBS cortical connectivity along hyperdirect pathways, the primary motor cortex was linked to tremor control, the supplementary motor area (SMA) to improvement in bradykinesia, and both the SMA and prefrontal cortex (PFC) to improvement in rigidity (Akram *et al.*, 2017).

Taken together, these data suggest the superolateral aspect of the STN as well as neural elements in the white matter dorsal to it may play an instrumental part in mediating therapeutic effects of STN DBS. Indeed, apart from methodological variation, some of the differences between many of these studies which grouped segmental motor signs together may be due to these individual motor deficits having slightly different corresponding optimal therapeutic stimulation areas within the STN and its vicinity, as demonstrated by *Akram* and colleagues. Furthermore, as pointed out by *Maks et al.,*

near-identical electrode locations and VTAs can result in significantly different effects due to individual response and somatotopic variation.

1.1.7 Structures associated with common side effects of STN DBS therapy

Side effects of STN stimulation may be related to elements within the STN itself or anatomically distinct structures surrounding it. Stimulation induced dyskinesia is thought to fall into the first category, and while the mechanisms for this are not completely understood, it is explicable by the mechanisms proposed for the therapeutic effect of STN DBS in PD (Limousin *et al.*, 1996a; Krack *et al.*, 1999). This is supported by observations of ballistic dyskinesia with lesions in the STN (Aziz *et al.*, 1991). Mobile dystonia may also be seen as an adverse effect of stimulation of the STN itself (Tommasi *et al.*, 2008).

Other intrinsic side effects may occur from spread of current to the limbic and associative regions ventromedially in the STN, and include mood and behavioural disturbances such as hypomania or mania, depression, impulsivity, aggression, or mood lability with laughter or crying (Krack *et al.*, 2001; Kulisevsky *et al.*, 2002; Romito *et al.*, 2002; Blomstedt *et al.*, 2008; Bejjani *et al.*, 1999). However, as discussed in section 1.1.4, the classical tripartite division may not be as anatomically distinct as initially described, and these effects may also be seen when the stimulating electrode is located in the sensorimotor region (Mallet *et al.*, 2007). Furthermore, while hypomania has been linked to ventrally located electrodes, there have been suggestions that other medial or ventral structures such as the medial forebrain bundle, lateral hypothalamus, or substantia nigra may be responsible for this effect (Coenen *et al.*, 2009; Ulla *et al.*, 2011; Welter *et al.*, 2014). Stimulation of limbic elements of the STN has also been suggested as a potential contributor to the relatively commonly reported post-operative side effect

of weight gain, along with other causes such as reduced energy expenditure from resolution of dyskinesias and rigidity (Krack *et al.*, 2002).

Diffusion of current into neighbouring structures of the STN is responsible for many recognised side effects: spread to the corticobulbar and corticospinal tracts laterally or anterolaterally causes commonly seen pyramidal symptoms of facial or limb muscle contractions. Contraction of orofacial muscles may also cause dysarthria from restriction of movements during speech production. Apraxia of eyelid opening (AEO) has been noted to be both a side effect of stimulation, where corticobulbar fibres have been implicated, or to improve with stimulation in cases where this was pre-existing from the underlying neurodegenerative process in PD (Weiss *et al.*, 2010; Tommasi *et al.*, 2012).

Spread anteromedially to the lateral hypothalamic area may cause autonomic side effects such as sensation of heat, sweating and nausea. Mydriasis and ipsilateral sweating may also be caused by activation of sympathetic fibres in the zona incerta medial and posteriorly (Castrioto, Volkmann & Krack, 2013; Merola *et al.*, 2020).

Medioventrally, activation of the oculomotor nerve fibres may produce dysconjugate gaze and diplopia, although this tends to occur at high amplitudes with electrodes placed in the dorsolateral STN (Tommasi *et al.*, 2008; Akram *et al.*, 2017a).

As well as the effect of pyramidal tract activation, involvement of the cerebellothalamic fibres medial to the STN have been implicated in dysarthria (Tripoliti *et al.*, 2011; Åström *et al.*, 2010; Mahlknecht *et al.*, 2017).

Posteriorly, stimulation of the medial lemniscus commonly results in contralateral paraesthesiae, which patients tend to habituate to, as often is the case for autonomic symptoms.

Diffusion of current dorsally and medially, affecting the pallidothalamic tract can result in a blockade of levodopa effect, with improvement in dyskinesia and rigidity but

worsening of bradykinesia and gait (Tommasi *et al.*, 2007; Castrioto, Volkmann & Krack, 2013).

1.1.8 Current STN-DBS programming paradigms

The initial monopolar review following implantation is generally done once the patient is stable, able to tolerate the session, and cooperate with the programming clinician to participate in clinical testing and provide feedback on side effects. This is usually at least a few days post-operatively, although practice between centres vary, with some opting for a more delayed initiation of stimulation at a point when the 'stun' effect of the implanted lead has subsided. It is best done in the off-medication state, usually after overnight withdrawal of dopaminergic therapy, so that Parkinsonian signs can be elicited, and the isolated effect of stimulation documented. Assessment of upper limb rigidity is an objective measure of efficacy that is commonly used in research studies to document efficacy thresholds and define therapeutic windows, as it is not affected by patient effort or fatigue which confound repeated assessment of bradykinesia, and it responds fairly rapidly to stimulation changes (Castrioto, Volkmann & Krack, 2013). Tremor is often only intermittently present, if at all, but if continuous then it may be a useful sign to titrate stimulation against, along with rigidity. In the clinical setting, however, it is important to note the effects on all of these signs as well as gait and speech.

The impedances of each electrode are tested and recorded before initiating stimulation. The polarity of electrodes is then set. In most cases, stimulation is initiated using a simple monopolar configuration: the electrode is usually set as the cathode (-), and the case (IPG) as the anode (+), although the reverse configuration is possible with what is termed *anodic stimulation*. Monopolar stimulation is generally used initially, as it is more energy efficient and straightforward to program compared to bipolar stimulation,

where two electrodes are given different polarities. The latter may be useful to reduce side effects in some cases, as it allows a narrower diffusion of current around the electrodes, as compared to a spherical field of stimulation with the monopolar configuration. Additionally, a *double monopolar* setting is used occasionally, where two adjacent contacts are activated with the same polarity, when a broader field of stimulation is necessary (Volkmann *et al.*, 2002).

Based on data on stimulation parameters in terms of therapeutic effects, guidelines and algorithms have been developed and reflect the optimal initial parameters (Volkmann, Moro & Pahwa, 2006; Picillo *et al.*, 2016b). These have generally recommended 60µs for PW and 130Hz for frequency, while amplitude is titrated to clinical effect. An example of the basic initial process is shown in the Toronto Western Hospital programming algorithm in figure 1.5.

Each contact is tested individually, and therapeutic and adverse effects alongside the corresponding amplitude threshold are noted so that the therapeutic window at each contact can be evaluated. Given the large range of amplitudes, intervals of 0.5V or mA can be used initially, then further fine-tuned. The optimal contact is one that is the most efficacious (i.e. requires a relatively low amplitude for attenuation of PD motor signs) and has a wide therapeutic window (difference between threshold for optimal efficacy and first side effect). *On* medication with on-stimulation evaluation is then done and necessary adjustments, for example in the case of excessive dyskinesia, are made to dopaminergic medication doses and stimulation parameters. In STN DBS, the process of titrating stimulation up and concurrently reducing dopaminergic medications is gradually performed in the ensuing weeks. In most cases a stable setting can be reached in 3 – 6 months, although some patients may need longer, particularly if there is either suboptimal efficacy or problematic side effects. Ongoing periodic reviews, such as every six months, are then routinely arranged in order to monitor the battery and

impedances, review any issues, and make adjustments to DBS or medical therapy as appropriate.

Various options to deal with side effects such as speech and gait problems have been suggested and often utilise the potential benefit of low frequency stimulation, as reviewed in more detail in section 1.2.4, as well as measures to limit current spread into adjacent structures by using interleaving or bipolar configurations. Dyskinesia that is difficult to control with other measures can often be helped by using dorsal contacts in the region of the subthalamic white matter, where it is proposed that stimulation of pallidofugal tract fibres directly suppresses dyskinesia (Herzog *et al.*, 2007; Aquino *et al.*, 2019).

However, programming algorithms thus far have not been updated to include the role of newer features such as directional steering or short pulse width. This is largely due to lack of data on the role of these programming techniques in the clinical setting. These, along with the known effects of varying primary programming parameters, are reviewed in further detail in the following section [1.2].

Figure 1.5. **Example of a basic algorithm for STN DBS programming** (*Adapted from Picillo et al., 2016).*

1.2 The effects of varying stimulation parameters in STN DBS for Parkinson's disease

1.2.1 Introduction

Systematic exploration of electrical parameters and their various effects was carried out in the early era of DBS being made widely available, and included examining the effects of altering stimulation amplitude, frequency, and pulse width (PW) (Rizzone *et al.*, 2001; Moro *et al.*, 2002). There has since been further work on alternative parameter settings, largely focusing on the effects of modulating frequency values. The relatively recent expansion of the parameter range with regards to PW in certain devices has also led to an emergence of studies examining the effect of using shorter than conventional PW in the last two years (Bouthour *et al.*, 2018a; Steigerwald *et al.*, 2018). These are also reviewed here; However, it should be noted that that these data were not published at the time study 1 (Chapter 2) was conceptualised and carried out.

In recent years, in addition to primary stimulation parameters, novel programming techniques along with advances in technology have enabled more selective spatial control of stimulation current with directional steering, and the use of feedback signals to continuously and automatically adjust delivery of current as required with closed-loop adaptive stimulation methods. The latter feature, while studied as proof of concept using specialised equipment, is not currently available commercially or for routine clinical use.

Published data on the effects of varying electrical stimulation parameters including amplitude, frequency, and pulse width as it applies to subthalamic DBS in Parkinson's disease, as well as novel programming techniques of directional and adaptive stimulation, are reviewed here.

1.2.2 Literature review method

A structured *Pubmed* search was performed with search terms “Subthalamic Deep Brain Stimulation in Parkinson’s Disease”, “voltage”, “current”, “frequency”, “pulse width” and “side effects”. Reviewed articles included case series, observational studies, and controlled trials that examined the clinical effect of quantitatively varying one or more stimulation parameters on symptoms of Parkinson’s disease, and on the occurrence of adverse effects. For novel programming techniques, the first search term was combined with “adaptive” and “directional” respectively, and included interventional or descriptive case reports, case series and controlled trials that compared these techniques to conventional DBS.

1.2.3 The effect of varying stimulation amplitude

The amplitude has the greatest effect on ameliorating Parkinsonian motor signs relative to energy-equivalent changes in other parameters, and is the most commonly titrated parameter in the initial stages of subthalamic DBS programming. This can be done by controlling the voltage or the current, which are interrelated by the impedance factor. Implantable pulse generators (IPGs) programmed to use constant voltage (CV) titration control the maximum voltage associated with each pulse, while the current will vary depending on the impedance. Conversely, programming using constant current (CC) provides a specified electrical current while adjusting the voltage to compensate for the impedance.

In-vitro studies of constant current stimulation have demonstrated the current waveform to be more uniform in terms of intensity, exhibiting less decay than in constant-voltage stimulation. However, comparisons of CC and CV stimulation to achieve equivalent motor efficacy have not shown any significant differences in non-

motor outcomes, including cognition, mood, and quality of life in a double-blind crossover trial (Ramirez De Noriega *et al.*, 2015). A retrospective analysis of 19 patients with PD and dystonic syndromes switched from CV to CC stimulation reported no change in measured clinical outcomes and therapy satisfaction at 6 months (Preda *et al.*, 2016).

Rizzone et al carried out early systematic exploration of the impact of various parameter settings in STN DBS in a double-blinded evaluation of 10 patients. They examined the relationship of stimulus intensity in terms of current and the occurrence of therapeutic as well as adverse effects at various frequency and pulse-width settings. The intensity required to produce the clinical effect of loss of wrist rigidity ranged from 0.7 to 1.7mA, and the intensity required to produce adverse effects ranged from 1.3 to 3.4mA (Rizzone *et al.*, 2001a). The relationships between the stimulus intensity required to produce these effects and frequency as well as pulse-width are discussed in the corresponding sections below.

Subsequently, in a double blinded assessment of 12 patients, *Moro* and colleagues found that the mean highest tolerated voltage was 3.5V, while keeping frequency constant between 130 - 185Hz and PW constant between 60 - 90μs (Moro *et al.*, 2002). Bradykinesia and rigidity significantly improved at 2V and 3V with testing carried out at 1V intervals, while response to tremor was seen starting at 1V, with 2V and 3V being progressively more effective. The greatest beneficial effect on these segmental motor signs was noted to be at 3V, with no significant additive benefit at voltage settings above this.

Voltage-dependent side effects commonly consist of motor or sensory symptoms, occurring in the majority with progressive increase in voltage. Anatomically, these effects are thought to represent current spread to the pyramidal tract, causing muscle contractions, and the medial lemniscus, resulting in paraesthesias. Autonomic effects

may include excessive sweating, flushing, mydriasis, tachycardia, and a sensation of heat or cold. An intraoperative investigation of clinical effects produced by STN stimulation in 17 PD patients reported that using 130Hz and 100μs settings, the threshold for complete disappearance of wrist rigidity was 0.94V. The mean adverse effect thresholds were: 2V for paraesthesias, 3V for oculomotor effects, 3.1V for autonomic effects, and 3.4V for dystonic effects (Sauleau *et al.*, 2005).

Tommasi et al investigated pyramidal side effects of subthalamic stimulation by progressively increasing voltages through chronically used contacts while keeping PW and frequency constant at 60μs and 130Hz respectively. Motor side effects were the most frequent, seen in 27 out of 28 electrodes, followed by sensory symptoms in 23. The most frequent adverse effects included contractions involving the facial muscles, often affecting bilateral upper facial and contralateral lower facial muscles. Dysarthria was observed in about 25% of subjects. Oculomotor side effects were seen in 6 out of 28 electrodes tested, and most commonly consisted of reduced gaze ipsilateral to stimulation, progressing to contralateral gaze deviation with increasing voltage. The median voltage required to produce oculomotor effects was 5.5V, as compared to 4.5V for sensory symptoms. Nausea and excessive sweating also occurred in 6 electrodes. Non-specific effects were common and nearly half of subjects experienced symptoms such as dizziness, a sense of heavy-headedness or lightheadedness, feeling of an electric current through the body, or malaise. They noted that habituation to sensory, oculomotor, and autonomic effects such as nausea and excessive sweating occurred rapidly as opposed to pyramidal tract side effects which tended to be persistent. No affective or behavioural effects related to stimulation were noted (Tommasi *et al.*, 2008).

Eyelid opening apraxia has also been observed, and has been shown to have a mean threshold of occurrence of 5.2v, although this symptom may be present as part of PD

itself, and is occasionally relieved by stimulation (Tommasi *et al.*, 2008, 2012; Baizabal-Carvallo & Alonso-Juarez, 2016). As well as these, stimulation-induced dyskinesias were observed in 5 of 12 patients, and foot dystonia in one of these (Moro *et al.*, 2002).

In addition to voltage dependent adverse effects discussed, progressively increasing voltage (median 5.5v) at the standard frequency of 130Hz has been shown to worsen gait and increase freezing episodes, similar to the condition off-stimulation (Moreau *et al.*, 2008). Speech intelligibility and articulation are also impaired with increasing amplitude, particularly above 3.5V (Törnqvist, Schalén & Rehncrona, 2005), and a stronger correlation with high voltages in the left STN and speech impairment has been observed (Tommasi *et al.*, 2008; Tripoliti *et al.*, 2011, 2014). Stimulation related psychiatric effects such as mania are also widely recognised, and attributed to involvement of limbic structures from stimulation of anteromedial neurons in the STN. These often respond to either a reduction in stimulation intensity or shifting to using more dorsolateral electrode contacts (Greenhouse *et al.*, 2011; Chopra *et al.*, 2012).

While quantitative data on time to habituation of adverse effects is limited, anecdotal experience suggests sensory and autonomic effects tend to subside within seconds if the stimulation intensity is maintained at the threshold level at which these occur. Time to habituation of capsular effects has not been explored as they are not well-tolerated.

1.2.4 The effect of varying frequency

The use of frequencies of less than 50Hz in subthalamic stimulation has been shown not to have a clinically significant effect on measurable motor signs in Parkinson's disease, even when combined with higher compensatory values of stimulus intensity and pulse-width (Rizzone *et al.*, 2001a).

In fact, very low frequencies of 5-10Hz have been found to worsen motor symptoms, particularly bradykinesia, compared with no stimulation (Moro *et al.*, 2002; Timmermann *et al.*, 2004; Eusebio *et al.*, 2008). *Moro et al* noted that all frequencies over 50Hz significantly improved bradykinesia and tremor, while the threshold for response in terms of rigidity was 33Hz. The ceiling of beneficial effect was in the range of 130-185Hz, with progressive improvement in cardinal motor signs with increasing frequency which was significant between 50Hz and 130Hz but not between 130Hz and 185Hz or 250Hz. Observations have been made of requiring a lower stimulus intensity to achieve the same clinical effect with increasing frequencies between 90 and 170Hz, but this was not significant in a study of 10 patients (Rizzone *et al.*, 2001).

Adverse effects of stimulation seem to vary depending on frequency settings: effects produced at lower frequencies (<50Hz) include worsening of tremor and myoclonic jerks as opposed to paraesthesias, muscle contractions and dyskinesias at higher frequencies (90-170Hz). At a given stimulus intensity, a trend to a lower side effect threshold was observed with progressively higher frequency settings, from 90Hz to 170Hz (Rizzone *et al.*, 2001; Moro *et al.*, 2002). Higher rates of 185Hz and 250Hz produced lower limb dyskinesias in one of 12 patients, and a subjective sensation of a heavy head in two of these (Moro *et al.*, 2002).

In contrast to the good response seen in alleviation of segmental motor signs of PD with STN stimulation, gait dysfunction and other axial symptoms can evolve to become relatively refractory to conventional programming settings. High frequency stimulation at conventional settings of 130Hz combined with high voltage has even been associated with increased incidence of gait freezing (Moreau *et al.*, 2008; Xie, Kang & Warnke, 2012). This has led to multiple studies investigating the effect of alternative frequency settings on gait. In a randomised blinded assessment, *Moreau et al* examined 13 patients with severe gait disorders on frequency settings of 60Hz and 130Hz, with

voltages adjusted so that the total energy delivered was constant. While there was no significant difference in UPDRS gait and axial subscores, 60Hz stimulation resulted in a significantly lower number of freezing episodes and reduction in number of steps on a Stand-Walk-Sit (SWS) test. The clinical benefit on gait persisted at 8 months follow up in 85% of patients, although they were noted to be on higher doses of levodopa at this time.

A randomised trial of 14 patients with double-blind crossover design comparing 60Hz and 130Hz energy-equivalent stimulation found similar improvements in axial symptoms and akinesia with the lower frequency setting when assessed at one hour, with no significant differences in segmental signs between the two settings. Significant reductions in total UPDRS-III as well as axial and akinesia subscores, and a timed 10-metre walk test were noted with the lower frequency setting. Also of note in this study is that for 5 patients the optimal contact positions for low frequency stimulation were more ventrally located in the subthalamic nucleus than optimal contacts for 130Hz stimulation (Khoo *et al.*, 2014).

In a case series, *Xie et al* described two patients with acute worsening of freezing of gait (FOG) at standard frequency subthalamic stimulation (130Hz) following new activation of their DBS systems. These demonstrated the immediate negative effect of high frequency stimulation as distinct from chronic adverse effects and those of disease progression, which compliment findings in patients who have had stimulation for longer periods. They reported amelioration of FOG with 60Hz stimulation and initially unchanged amplitude and pulse width settings. The effect persisted at a 10 month follow up, and was present in both ON and OFF medication states. In addition to FOG, there was noted to be improvement in bradykinesia and other axial symptoms with low frequency stimulation (Xie, Kang & Warnke, 2012). Subsequently, this effect on axial symptoms was reproduced with 60Hz stimulation in a small randomised double-blind

trial, including improvement in dysphagia and aspiration frequency specifically, quantified as a 57% reduction on a modified barium swallow assessment (Xie *et al.*, 2015).

Another case series reported that in patients with dopa-responsive axial and gait dysfunction that initially worsened with high frequency stimulation (130-185Hz), there was subsequent improvement with 60Hz stimulation in four out of five patients. Immediate worsening of gait and freezing was also demonstrated on experimental switching of settings back to high frequency. Ventral contacts were used in all patients, and double monopolar configuration involving concomitant dorsal and ventral contacts was utilised in three patients due to observed beneficial effects on gait and reduction in dyskinesias (Ramdhani *et al.*, 2015).

However, the evidence for low frequency stimulation being beneficial for axial symptoms of PD is not unequivocal. The largest reported cohort studied involved 45 patients with refractory axial symptoms on high frequency (130Hz) stimulation who were switched to 80Hz settings in an open label trial, and showed no significant change in total motor UPDRS and axial and gait subscores at a median assessment period of 112 days (Sidiropoulos *et al.*, 2013). In addition, in a randomised trial of 20 patients with gait difficulties following STN stimulation, *Phibbs et al* did not find any improvement in stride length or number of freezing episodes with switching from 130Hz to 60Hz. However, notably, other parameters in this study including the stimulation intensity were kept constant at both frequency settings, resulting in a lower total electrical energy delivered (TEED) value at low frequency (Phibbs, Arbogast & Davis, 2014).

Furthermore, despite the majority of studies on the utility of low frequency stimulation showing initial improvement in gait and freezing with low frequency stimulation in the range of 60 - 80Hz (Moreau *et al.*, 2008; Xie, Kang & Warnke, 2012; Khoo *et al.*, 2014; Ramdhani *et al.*, 2015; Xie *et al.*, 2015), it is possible that these effects may not be

sustained over time. An open label trial involving 11 patients found that despite initial improvements in gait as measured by performance on the SWS test after switching from 130Hz to 80Hz at equivalent energy delivered, the benefit was not maintained at 1, 5 and 15 months. Reduction in freezing episodes was also short-lived, being sustained at one month but not subsequently (Ricchi *et al.*, 2012).

In an open label prospective analysis mixed results were reported with low frequency stimulation among 12 patients with gait dysfunction and postural instability; three could not tolerate low frequency due to worsening of segmental symptoms, two had worsening of postural stability and gait, while seven benefited (Brozova *et al.*, 2009).

In addition, although most studies have reported no significant change in control of segmental symptoms as measured by UPDRS with low frequency stimulation, it has been observed that tremor control is often worse than at standard high frequencies (Xie, Kang & Warnke, 2012; Xie *et al.*, 2015; Ricchi *et al.*, 2012). Low frequency stimulation also may not produce beneficial effects over conventional higher frequency settings in patients who do not suffer from problems with gait and postural control (Vallabhajosula *et al.*, 2015).

The majority of the studies on frequency modulation discussed have focussed on effects on postural instability and gait impairment, and until recent years, there was limited data specifically examining the effect of low frequency on stimulation induced dysarthria. *Grover* and colleagues examined the effect of frequencies between 60 and 200Hz on speech intelligibility and perceptual speech characteristics in a double-blind study of 15 patients, and found that intelligibility as well as perceptual ratings of articulation, prosody, respiration and phonation improved at lower frequencies (Grover *et al.*, 2018). Improvement in speech intelligibility using low frequency stimulation amongst those with severe impairment on standard frequency was subsequently corroborated in another cohort of 10 patients (Fabbri *et al.*, 2019).

1.2.5 The effect of varying pulse width

Pulse-width values available for use in subthalamic stimulation in PD have conventionally ranged from 60μs to 450μs. Increasing pulse-width values up to a certain level has been shown to require correspondingly lower stimulus intensities to achieve a required clinical effect. This relationship was observed by *Rizzone et al* between a low pulse width of 60μs and higher values of 210μs or 450μs, but not between these higher pulse width parameters, where the effect seems to plateau. A parallel relationship exists with the occurrence of adverse effects at increasing pulse widths: i.e. a lower stimulus intensity is required to produce adverse effects at higher pulse width values. This results in a narrower therapeutic window (magnitude of difference in the intensity value required to produce a clinical effect and that required to produce adverse effects) with increasing pulse widths (Rizzone *et al.*, 2001a).

Similarly, *Moro et al* found that of the 12 patients studied, 5 were unable to tolerate PWs of greater than 210μs when combined with a voltage of 75% of the usual chronic stimulation setting. The mean highest tolerated level was 190μs in this group. Adverse effects that limited use of higher PW values were similar to those produced by increasing stimulation intensity: muscle contractions, paraesthesias, dysarthria and postural tremor were commonly observed. Importantly, improvement in tremor control and rigidity was observed at all PWs studied between 60μs and 210μs, while reduction in bradykinesia was only significant at 60μs relative to baseline (Moro *et al.*, 2002).

For over the next decade, there had been limited further exploration of the effects of pulse width in STN DBS beyond the pioneering data available from the work of *Rizzone* and *Moro* discussed. However, more recently, interest in the effects of PWs shorter than the conventional lower limit of 60μs has emerged, as this has now become possible with advances in DBS equipment.

Reich et al recently reported their findings on the use of PWs of less than 60μs at a fixed frequency of 130Hz in a monopolar review session of four patients. An inverse relationship between PW and therapeutic window was noted in all subjects, with therapeutic window (TW) being defined as the difference in the minimum stimulation current required to produce adverse effects and that required to produce the clinical effect of loss of rigidity (efficacy threshold). Compared to standard 60μs stimulation, the TW increased by a mean of 182% with a PW of 30μs, and decreased by 46% with a PW of 120μs. TWs could not be obtained at lower PWs of 20μs due to a lack of capsular response using a predefined maximum of 10mA stimulation intensity. The corresponding stimulation current required for rigidity control increased with reducing PWs, from a mean of 1.6mA at 60μs to 2.9mA at 30μs. Furthermore, the authors noted that while this efficacy threshold in mA increased at lower PWs, the total charge per pulse required for the clinical effect of rigidity control decreased (Reich *et al.*, 2015).

Following this, the CUSTOM-DBS study provided further data on the use of shorter than conventional PW in a double-blinded trial of 15 patients involving an acute challenge of 30μs versus 60μs stimulation. The TW was found to be significantly larger at 30μs (3.8mA) compared to 60μs (2.3mA). Additionally, efficacy of treatment on motor symptoms was also assessed UPDRS-III scores and was shown to be non-inferior using 30μs settings (Steigerwald *et al.*, 2018).

Another randomised study of 10 patients examined the effect of different PWs between 10μs and 60μs on the TW (with respect to pyramidal muscle contraction), in an acute setting at least 3 months following surgery. The mean TW at 60μs of 1.6mA increased to 4.3mA at 20μs. At 10μs, the authors found that the efficacy and side effect thresholds were beyond the range of their predefined maximum testing amplitude of 10mA, and TWs could therefore not be calculated (Bouthour *et al.*, 2018a).

Table 1.1 **Key Clinical Findings from Studies Evaluating the Effects of Quantitatively Varying Stimulation Parameters**

STUDY (n)	STIMULATION PARAMETER(S) & VARIABLES EXAMINED	TIME AT ASSESSMENT/ DURATION OF FOLLOW UP	STIMULATION PARAMETERS USED AND RESPECTIVE FINDINGS		
			STIMULATION INTENSITY: VOLTAGE (V) OR CURRENT (A)	FREQUENCY (Hz)	PULSE WIDTH (µS)
Rizzone (4) n=10	Current Frequency Pulse width (Efficacy and side effects)	Immediate assessment	Threshold (CE): 0.7-1.7 mA Threshold (SE): 1.3-3.4 mA *Paraesthesias, muscle contraction, dyskinesias	10/ 50/ 90/ 130/ 170Hz -No significant difference in SE thresholds between 90 and 170Hz No therapeutic effect at ≤50Hz; *Worsening tremor and myoclonic jerks noted	60-450µS -↓therapeutic window noted with ↑PW
Moro (5) n=12	Voltage Frequency Pulse width (Efficacy and side effects)	Assessment at 2 minutes	Best clinical efficacy at 3V or higher Highest mean tolerated voltage: 3.5V *Paraesthesias, muscle contraction, dyskinesias, non-specific discomfort	Threshold (CE): 50Hz Ceiling of beneficial effect 130-185Hz *<5Hz worsened bradykinesia significantly, postural tremor at ≤50Hz *Limb dyskinesia at ≥185Hz	60-210µS Highest mean tolerated PW -190µS *Muscle contractions, paraesthesias, dysarthria, postural tremor
Sauleau (25) n=17	Voltage (Efficacy and side effect thresholds)	Immediate (intraoperative) assessment	Threshold (CE): 0.94V Threshold for: *Sensory SE: 2.04 *Oculomotor SE- 3.0V *Autonomic SE- 3.1V *Pyramidal tract SE- 3.4V	130Hz	100µS
Tommasi (26) n=14	Voltage (Side effect thresholds)	Immediate assessment (Duration of SE's ≥30s)	Threshold for: *Sensory SE - 4.5V *Pyramidal tract SE - 4.8V *Vegetative SE - 5.3V *Oculomotor SE - 5.5V	130Hz *Myoclonic jerks at 2-3Hz noted	60µS
Moreau (6) n=13	Frequency (FOG)	Follow up 8 months	Standard voltage: median 3.0v at 130Hz/4.4v at 60Hz High voltage: median 3.7v at 130Hz/ 5.5V at 60Hz	130 vs 60Hz -60Hz high voltage setting optimal to reduce freezing -Increasing voltage at high frequency associated with gait dysfunction	60µS
Sidiropoulos (7) n=45	Frequency (Speech, gait, balance)	Median follow up 112 days	Not stated TEED: 165µJ at 130Hz and 94.7µJ at 80Hz	130Hz vs 80Hz -No significant difference in UPDRS axial and gait subscores *Tremor worse with 80Hz setting in 31% of subjects	Not stated

Phibbs (8) *n=20*	Frequency (Gait)	Assessment at 1 hour	Mean 2.6V at both frequencies	130Hz vs 60Hz -No significant change in no. of steps or freezing with low frequency, with voltage and PW kept constant.	60-90μS
Khoo (9) *n=14*	Frequency (Efficacy in improving motor function)	Assessment at 1 hour	Median 3.6V at 60Hz 2.4V at 130Hz	130Hz vs 60Hz -Lower axial and akinesia UPDRS subscores and 10m walk time with 60Hz setting	60-90μS
Xie (10) *n=7*	Frequency (FOG and dysphagia)	Average follow up 6 weeks	Mean 3.15V at both frequencies	130Hz vs 60Hz -60Hz setting ↓aspiration, dysphagia, FOG and UPDRS III scores	Mean 86μS
Ramdhani (11) *n=5*	Frequency (Gait)	Follow up 2-6 months	Difference in voltages between high and low frequency settings: 0-2.5V	130-185Hz vs 60Hz -Improvement in gait and freezing with 60Hz setting	60-90μS
Ricchi (12) *n=11*	Frequency (Gait)	Follow up 15 months	Mean 3.4V at 130Hz 4.5V at 80Hz (equivalent TEED)	130Hz vs 80Hz -Improvement in gait with 80Hz stimulation immediately but not sustained at 1, 5, 15 months.	60μS
Brozova (13) *n=9*	Frequency (Gait and postural stability)	Follow up period 8-12 weeks	Average 1.3V increase with low frequency	High frequency vs 60Hz -Overall improvement in speech and gait at 60Hz; postural instability worsened in 2 subjects	Not stated
Vallabhajosula (14) *n=19*	Frequency (Gait and postural control)	Assessment at 10 minutes	Mean 2.8V at ≥130Hz and 60Hz. Maximum tolerated voltages (not stated) also compared at 30Hz and 60Hz with 130Hz	≥130Hz vs 60Hz and 30Hz -No significant improvement in gait and postural control at low frequency, in subjects without significant gait impairment	60-90μS
Reich (37) *n=4*	Pulse width (Efficacy and SE thresholds)	Immediate assessment	Mean threshold (CE) at 30/60/120μS: 2.94/ 1.59/ 0.63 mA Mean threshold (SE) at 30/60/120μS 7.94/ 3.74/ 2.60 mA	130Hz	20-120μS -TW at 30μS ↑ by 182%, and at 120μS ↓ by 46% relative to stimulation at 60μS *Muscle contractions

SE - Side effects, denoted * under respective parameters; CE - Clinical effects; FOG - Freezing of Gait; TEED - Total electrical energy delivered

1.2.6 Directional steering

Directional stimulation involves using segmented contacts which replace the conventional cylindrical or 'ring' design, so that selective activation of one or more contacts can be used to produce a field of stimulation in the desired orientation to more selectively target adjacent neural tissue.

Leads with segmented contacts have been commercially available since 2015. These most commonly used consist of 4 levels of contacts, with conventional ring contacts at the upper and lowermost levels, and segmented contacts in a tripartite design at the second and third levels [Figure 1.6]. When all the 3 segments of a segmented level are activated together, with the total current divided equally between them, the stimulation field is of a similar form to that of a conventional ring contact (Dembek *et al.*, 2017).

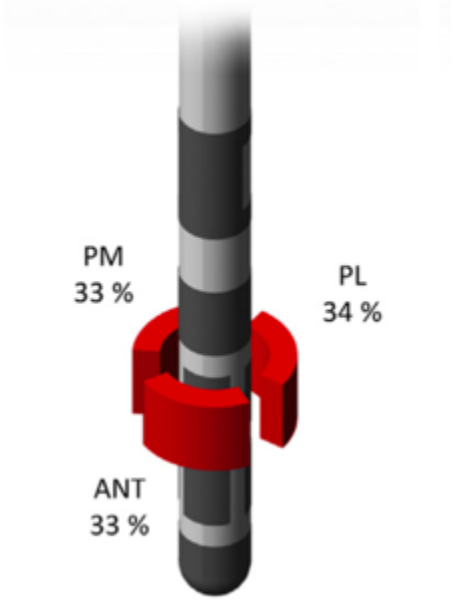


Figure 1.6 **Boston Scientific Cartesia directional lead™ showing segmented lead design**
(Adapted from Recker et al., 2016)

The orientation of the lead can be determined by post-operative scans including CT and fluoroscopy, which indicate the direction of the metallic marker, which is in line with segments 2 and 5 on the left electrode, and 10 and 13 on the right electrode [Figure 1.7]. The marker is designed to be orientated anteriorly when the lead is implanted. There is, however, invariably some degree of deviation from the intended anterior orientation in the eventual position. *Dembek et al* reported in their clinical study of 20 STNs that the mean deviation from the axis between the anterior and posterior commissures (AC - PC line) was 22.7°, and none of the electrodes needed renaming, which would be the case with deviations of greater than 60°, when more than half the current would be directed to the default position of an adjacent segment (Dembek *et al.*, 2017). However, a larger study of 100 patients (198 leads) dedicated to quantifying the deviation of directional leads from the intended orientation at implantation using post-operative CT scans found that deviations of greater than 30° were present in 42% of leads, greater than 60° in 11%, and up to 90° in a few (Dembek *et al.*, 2019).

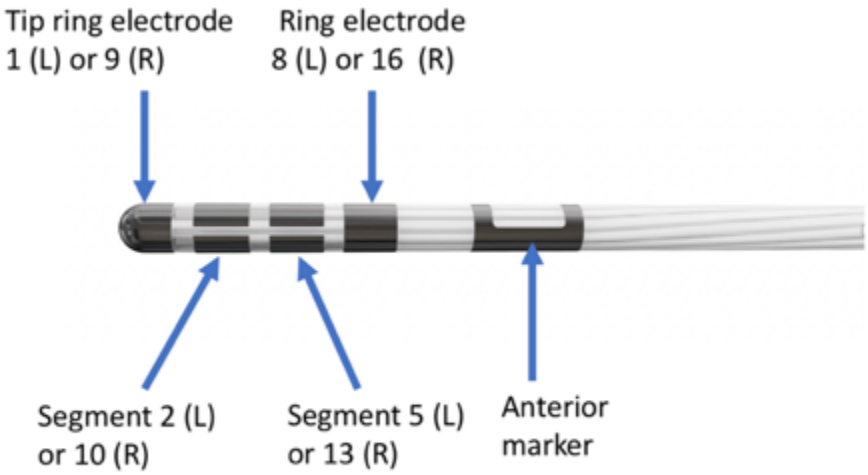


Figure 1.7. **Boston Scientific Cartesia™ directional lead showing anterior marker**
(Adapted and modified from https://www.bostonscientific.com/en-EU/products/deep-brain-stimulation-systems/Leads-and-Accessories/Physician-Resources.html)

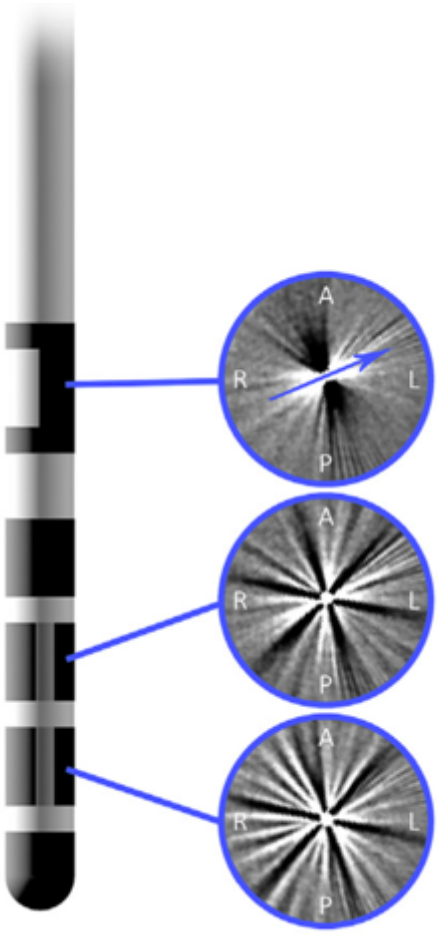


Figure 1.8. **Directional lead showing artefacts generated by stereotactic marker and segmented contacts on a CT scan.** The blue arrow indicates the orientation of the lead
(Adapted from Dembek et al., 2019).

Intra-operative proof of concept studies to explore hypotheses that directional steering of current would result in more efficient stimulation and a reduction in adverse effects have been carried out in the last few years (Pollo *et al.*, 2014; Contarino *et al.*, 2014; Bour *et al.*, 2015). The first of these showed that using a lead with six directional contacts (3 each on 2 horizontal levels, as in Figure 1.7), the widest therapeutic window obtained with directional stimulation was on average 41% larger than with omnidirectional stimulation which simulated a conventional ring-shaped electrode. The therapeutic window could be increased in 10 of 11 patients compared to using omnidirectional stimulation. In addition to this, average current threshold for

therapeutic effect was noted to be 43% lower with best directional stimulation (Pollo *et al.*, 2014).

A similar intraoperative study used 32-contact electrodes to compare directional stimulation in four steering modes to conventional spherical stimulation in a double-blinded assessment of 8 patients with Parkinson's disease. For 13 of the 15 side effects induced by conventional stimulation, steering in at least one direction led to an increase in the threshold for producing these by at least 1mA. The TW was evaluated with respect to improvement in rigidity as the therapeutic effect in 3 patients; all of whom demonstrated an increase of between 0.5 and 2.5mA with directional stimulation (Contarino *et al.*, 2014).

Following the results of intraoperative studies, *Steigerwald et al* reported their clinical experience with implantation of the CE marked *Vercise PC* (Boston scientific™) directional system with multiple independent current source control (MICC) in 7 patients with PD, using an unblinded retrospective approach. A post-operative monopolar review session was used to determine thresholds for therapeutic and adverse effects, and expansion in the TW with directional modulation seen in previous experimental studies was confirmed at 17 of 22 stimulation sites. The orientation of the segmented contacts used were determined by fusing post-operative CT scans with pre-operative MRIs and identifying the direction of the marker; the contacts with the highest TW were most often in the direction of posteromedial or anterior (5 of 11 STNs), although others included posterior (2), anteromedial (2), lateral (1) and medial (1). The most common worst direction was posterolateral (7 of 11 STNs). Of note, at the best ring level, the TW was expanded by an increase in the SE threshold rather than reduction in efficacy threshold. This study was designed to demonstrate feasibility rather than efficacy, and UPDRS-III scores were not compared between ring and directional stimulation (Steigerwald *et al.*, 2016).

Subsequently, a short term crossover double-blind clinical study on directional stimulation involving 10 patients (20 STNs) again confirmed a larger TW with best directional stimulation compared to ring mode, and the data indicated that this expansion was driven by an increase in the SE threshold rather than a reduction in the efficacy threshold (Dembek *et al.*, 2017). The four stimulation conditions examined (RM and three directional segments) were also ranked based on stimulation parameters as well as global clinical impression by blinded raters. Of the directional segments, the posteromedial one was ranked best most frequently, followed by anterior. The posterolateral segment was ranked worst more frequently than anterior and posteromedial. Additionally, efficacy of directional stimulation was compared, and UPDRS-III ratings on RM and directional stimulation showed there was no significant difference between the conditions.

These studies have demonstrated feasibility, equivalent efficacy, and a larger therapeutic window with directional stimulation. While long term data is lacking, *Dembek et al.* showed that the majority of their patients (14 of the 20 STNs) remained on directional stimulation at a follow up of three to six months, and all patients in the cohort of *Steigerwald et al.* remained on directional settings at a median follow up of 4 months. However, the utility of directional steering to alleviate side effects of STN DBS has not been systematically studied or reported to date. *Reker et al* reported a single case of avoiding dysarthria with directional stimulation by elimination of the posterolateral segment. The TW was further enhanced by using a bipolar configuration of stimulation. However, this was a theoretical case of avoiding side effects, as the thresholds for inducing dysarthria with each of the segments were noted to be different during a monopolar review, but the patient was not suffering from the side effect in a standard configuration to begin with (Reker *et al.*, 2016).

Asahi and colleagues explored side effects evoked by segmented contacts in six patients, with the segmented portion of the leads positioned at the dorsal border of the STN. Using an amplitude of up to 11mA with a PW of 30μs and frequency of 130Hz, they reported motor symptoms were the most frequent (56 contacts) and occurred most commonly in the anterolateral direction, while sensory symptoms were present in only 4 segmented contacts and occurred in the medial or posterolateral directions (Asahi *et al.*, 2019).

Regarding another aspect of directional stimulation, there have been concerns that due to the higher impedances of segmented contacts relative to ring ones, the energy consumption of directional stimulation may be higher than conventional stimulation (Eleopra *et al.*, 2019). While impedances affect energy consumption, this would also depend on the relative difference in the amplitude required compared with conventional stimulation, as the latter has an exponential rather than proportional relationship to the total electrical energy delivered (Koss *et al.*, 2005). Total energy consumption on clinically used settings have not been explicitly compared in studies so far, and this issue is becoming less relevant with the increasingly common use of rechargeable IPG batteries.

Given the vastly increased number of configuration possibilities and combinations available with segmented leads, the programming burden is significantly increased in terms of complexity and time involved, affecting both the clinician and the patient. Any routine use of directional stimulation will thus depend on demonstrating a long term clinical benefit over conventional stimulation in order to justify the increased costs and programming burden involved, and subgroups of patients who are likely to benefit from this feature will need to be identified. While the ground truth is always the clinical effect observed in individual patients, methods of modelling to predict the optimal segmented contacts in a more time-efficient manner than manual clinical exploration are being

developed. These include visualisation of stimulation field models to estimate anatomical structures affected (or volume of tissue activated; VTA), as well as using local field potentials to guide selection of the optimal segment (Tinkhauser & Pogosyan, 2018).

Nguyen and colleagues demonstrated the potential of using VTA modelling to predict whether a patient would benefit from directional stimulation. They used 272 directional contacts in 28 patients to simulate VTAs and matched these with clinical data at 4 – 6 months postoperatively. The top 10% of voxels correlating with the highest clinical efficacy were used to create a 'sweet spot' map. They found that patients who had a higher TW with directional stimulation compared to ring mode had a larger distance between the electrode and the sweet spot centroid, implying that directional stimulation may be useful in improving efficacy in cases where electrodes are not optimally placed (Nguyen *et al.*, 2019).

1.2.7 Local field potentials and adaptive stimulation

Enhanced local field potentials (LFPs) in the beta frequency (13 - 30Hz) recorded from electrodes in the STN have been shown to correlate with the degree of motor impairment in PD, and are suppressed by dopaminergic treatment or electrical stimulation in proportion to the degree of motor improvement (Kühn *et al.*, 2006; Weinberger *et al.*, 2006; Ray *et al.*, 2008; Kühn *et al.*, 2009; Little & Brown, 2012; Beudel & Brown, 2016). Most of the initial data on the β-band was collected intraoperatively or in the early post-operative period, via externalised electrodes. However, the correlation of β-band power with the clinical motor state in the longer term setting in PD was subsequently confirmed with a study that collected LFP data over 8 months with implantable sensing devices (Neumann *et al.*, 2017).

These observations have led to concepts of using abnormal oscillatory synchronisation such as β-band power as a biomarker for both identifying the optimal stimulation site within the STN, and modulating stimulation parameters. Other signals such as high frequency oscillations of >200Hz have also been studied for clinical correlates in PD, and recorded from the STN, these have been shown to correlate negatively with akinesia and rigidity (Wang *et al.*, 2014). Others have reported that gamma activity in the range of 60 - 90 Hz recorded from the motor cortex corresponds to dyskinesia (Swann *et al.*, 2016). A weaker signal was also present in the STN in this study, with coherence between the strong phases at the two recording sites.

With conventional devices using ring electrodes, studies of LFPs recorded from various electrodes have shown β-band power correlated with subsequently chosen contacts used for chronic stimulation based on clinical efficacy (Yoshida *et al.*, 2010; Ince *et al.*, 2010). *Bour et al* combined the use of LFP signals with directional stimulation by using feedback obtained with measurement of β-band power from various channels at different depths and directions using temporarily implanted 32-contact DBS leads. Despite a small sample, they demonstrated that the clinical outcome of reducing rigidity was best achieved by stimulating in the direction of the highest β-band activity, in the range of 18.5 - 30Hz (Bour *et al.*, 2015).

Subsequently, a clinical study of 12 patients measured intraoperative β activity from directional contacts in commercially available leads and compared these with clinical efficacy after a monopolar review at 4 – 7 months. Similarly, there was a positive correlation between the contacts with the highest β activity and those clinically found to be the most effective in control of rigidity, as well as those that had the highest TW (Tinkhauser & Pogosyan, 2018).

The limitations of these studies include using rigidity only in their clinical outcome measures. While bradykinesia has also been shown to closely correlate with

exaggerated β activity, tremor does not show such an association, and in fact, is associated with a reduction in β activity (Kühn *et al.*, 2009; Qasim *et al.*, 2016). Tremor severity has been shown to correlate with low gamma (31 – 45 Hz) power, and its suppression with STN DBS correlates with a reduction in LFPs in the low gamma range (Beudel *et al.*, 2015). Furthermore, apart from β-band power itself, other potential markers such as longer β burst duration and phase-amplitude coupling have been suggested as signals that may be more indicative of network pathology during PD motor dysfunction (Tinkhauser *et al.*, 2017a; Shimamoto *et al.*, 2013; Bouthour *et al.*, 2019b). In PD, exaggerated phase-amplitude interactions between beta and gamma LFPs in the motor cortex have been found, both with invasive and scalp EEG recordings (Swann *et al.*, 2015; De Hemptinne *et al.*, 2013). STN DBS has been shown to reduce this, with corresponding motor improvements. It has therefore been proposed that cortical function is improved during STN DBS by reducing excessive β phase locking of motor cortex neurons (De Hemptinne *et al.*, 2015; Tinkhauser *et al.*, 2017b).

The concept of adaptive stimulation broadly involves a means of obtaining feedback on pathological brain activity such as those discussed, and responding with varying stimulation accordingly. This has been studied with closed-loop systems which record LFPs via stimulation electrodes.

Little et al first demonstrated the utility of this approach systematically in patients with PD in 2013. Data was collected on eight patients with unilateral STN stimulation, and they reported that compared to the unstimulated state, there was a mean reduction of 50% in UPDRS motor scores on blinded assessments with the adaptive approach compared to 31% with continuous stimulation. Not only was there more effective overall control of motor symptoms, but adaptive DBS seemed to have less than half the energy requirements of continuous stimulation by virtue of its intermittent nature (Starr & Ostrem, 2013).

This was studied again by these authors with bilateral stimulation, with independent sensing and activation on each side according to the amplitude of beta activity at the electrode. Although there was no direct comparison with continuous DBS, UPDRS motor scores were 43% better relative to no stimulation, despite stimulation being on for only 45% of the time, and resulting in an energy saving similar to that found in the first study. In addition to this, adaptive DBS seemed to have a synergistic effect with Levodopa on Parkinsonian motor signs, with an appropriate reduction in stimulation in response to reduced beta activity and clinical improvement which temporally corresponded with the action of Levodopa after its administration (Little *et al.*, 2016).

However, despite the encouraging findings of adaptive DBS use in the early post-operative period, as yet data are restricted to limited testing over short time periods only. There has been one case report of the beneficial effects of adaptive DBS in a freely mobile patient being maintained at day 6 post-operatively with a testing period of 2 hours. The patient was found to have stable control of segmental motor symptoms without dyskinesias, and also demonstrated similar improvement in axial symptoms compared to conventional continuous DBS (Rosa *et al.*, 2015). Another open label non-blinded study of 13 patients assessed the feasibility of adaptive DBS over eight hours while patients performed regular daily activities and took dopaminergic medication. It demonstrated that automatic amplitude adjustments could be made by the system according to clinical *on* and *off* states, and that dyskinesias could be avoided as a result (Arlotti *et al.*, 2018). Similarly, *Rosa* and colleagues reported a reduction in dyskinesia scores and reduced total electrical energy delivered with adaptive DBS in 10 patients who received either continuous or adaptive DBS combined with levodopa (Rosa *et al.*, 2017).

Gamma activity may also play a part in adaptive stimulation systems, as shown in a report of two patients, where cortically sensed gamma oscillations, which corresponded

to the emergence of dyskinesia were used to reduce the amplitude of stimulation once a pre-set sensing threshold was exceeded. While the authors reported there were energy savings and no clinical deterioration with the closed loop phase of testing, they only demonstrated feasibility of a fully implantable system, and did not make comparisons of clinical outcomes with the conventional open loop system (Swann *et al.*, 2018).

While most approaches to adaptive DBS have focussed on responding to recorded signals with changes in amplitude, there are suggestions that using other parameters such as frequency modulation while keeping the amplitude constant may also be effective at suppressing pathological synchronous oscillatory activity (Daneshzand, Faezipour & Barkana, 2018).

The feasibility of long term closed loop adaptive systems will require portable implantable systems, reliable biomarkers and their detection, and processing of signals recorded to effectively execute appropriate outputs in terms of altering stimulation delivered. Furthermore, a clinical benefit over conventional continuous stimulation will need to be demonstrated in the longer term to establish its utility.

1.2.8 Conclusions on the effects of varying stimulation parameters and use of novel techniques

Control of stimulation intensity through titration of current or voltage has been the mainstay of DBS programming since its inception. However, this has limitations due to adverse effects with increasing stimulation, and the roles of altering other parameters for specific indications or to reduce adverse effects are becoming clearer as the effects of alternative settings are explored. This has been the case particularly for frequency modulation, with substantial evidence for improvement in FOG and other axial symptoms with the use of lower settings in the range of 60 - 80Hz (Moreau *et al.*, 2008;

Xie, Kang & Warnke, 2012; Khoo *et al.*, 2014; Xie *et al.*, 2015; Ramdhani *et al.*, 2015). The persistence of this effect however, is not certain based on current data, with some suggestion that it may not be maintained in the long term (Ricchi *et al.*, 2012). It is not clear whether this is due to wearing off and loss of efficacy of stimulation or natural disease progression counteracting the benefit over time. Moreover, amongst the studies that demonstrate an improvement in axial symptoms with lower frequency settings, this seems to be the case for a subset of patients; it has been observed that those who do not have tremor-dominant PD and have symptoms of gait dysfunction with high frequency stimulation are more likely to benefit (Ricchi *et al.*, 2012; Brozova *et al.*, 2009). It is also interesting that *Xie et al* demonstrated in a small randomised trial that the effect extends specifically to swallowing function, with a substantial reduction in aspiration (Xie *et al.*, 2015). This important finding may broaden the applicability of lower frequency stimulation to PD patients treated with DBS who suffer from the wider range of axial symptoms including dysphagia rather than just those with gait dysfunction.

It is also worth noting that the use of UPDRS axial and gait sub scores in many studies to measure outcomes may have resulted in diminished detection of effect than if more sensitive tools such as rapid 360° turns and the addition of dual-tasking were used to assess freezing of gait (Snijders *et al.*, 2012; Nonnekes *et al.*, 2014). The mechanism of low frequency stimulation and its beneficial effect on axial symptoms in selected patients is not clear. One of the proposed explanations is spread of current to neurons projecting to the pedunculopontine nucleus (PPN) which is in 5mm proximity to the STN and has reciprocal connections with it, as low frequency stimulation of this structure directly and in combination with STN stimulation has been shown to improve FOG (Mazzone *et al.*, 2005; Stefani *et al.*, 2007; Golestanirad *et al.*, 2015; Windels *et al.*, 2015). Relatively greater reduction in akinesia noted with lower frequency stimulation has also been suggested as a possible mechanism for improvement in FOG (Moreau *et*

al., 2008; Khoo *et al.*, 2014; Ricchi *et al.*, 2012). It has been postulated that the negative impact on gait with high frequency settings may be due to a change in STN function in advanced PD caused by direct high frequency stimulation, particularly when combined with high voltages, as this is likely to result in current diffusion into surrounding structures (Moreau *et al.*, 2008). The location of contacts in the STN may also influence the effectiveness of low frequency stimulation, with ventrally located contacts being favourable as demonstrated by *Khoo* and colleagues. This may also be partly responsible for the heterogeneity of data on the effectiveness of low frequency stimulation, as many of the studies that demonstrated a significant improvement tended to have largely used ventrally located contacts (Moreau *et al.*, 2008; Khoo *et al.*, 2014). It should also be noted that most studies that failed to show at least an initial improvement with low frequency stimulation in patients who had troublesome axial symptoms used lower TEED values at low frequency stimulation (Sidiropoulos *et al.*, 2013; Phibbs, Arbogast & Davis, 2014).

While a reasonable amount of work has been done on the use of alternative frequency settings, larger prospective blinded trials with detailed gait assessments and longer follow up periods are required to confirm the benefit of low frequency settings for axial symptoms in the long term, and further define phenotypic subsets of patients who may benefit most.

In contrast, there is a paucity of data on the use of alternative pulse width settings, in part due to the lack of availability of PWs shorter than 60μs until relatively recently in DBS systems. Only selected manufacturers are now producing devices with this capability for commercial use. The effect of ultra-short PWs utilised by *Reich* and colleagues using the Boston Scientific Vercise™ system is very encouraging in demonstrating the potential for significant increases in the therapeutic window with this approach. This is thought to be mediated by more selective action of stimulation on

neural fibre tracts responsible for relief of symptoms while avoiding those such as corticospinal and corticobulbar fibres that result in adverse effects. This has been demonstrated previously by *Groppa* et al in patients with essential tremor, where using strength-duration curves plotted using various PW values, the chronaxie (measure of excitability of neural elements) calculated for suppression of tremor was shown to be significantly different to that for induction of ataxia, with values of 27μs and 52μs respectively. They concluded that a stimulation PW closer to the chronaxie of tremor suppression would provide a wider therapeutic window between tremor relief and induction of side effects (Groppa *et al.*, 2014). The same concept was used by *Reich* et al to derive a strength-duration plot model for axons of different diameters, showing a divergence of action potential thresholds at lower PWs. While the exact nature of the fibres responsible for rigidity control is not known, the magnitude of effect on the TW with short PW stimulation found in these patients certainly merits further investigation. Larger randomised blinded trials to confirm the effects on pyramidal as well as other common adverse effects of stimulation such as dysarthria and axial symptoms need to be carried out, as this has the potential to have a significant clinical impact on existing and new DBS patients.

In interpreting the clinical effects of varying stimulation parameters based on the available data, one should bear in mind that most of the reviewed studies do not systematically include the effect of the exact location of electrodes or contacts used in their analyses. Data from further randomised blinded trials controlling for this variable will improve comparability between subjects and studies.

Newer techniques have added a further dimension to programming using basic parameters by modulation of stimulation in space and time using directional and adaptive stimulation respectively. Systems capable of directional stimulation and short pulse width have been made commercially available in the last few years. However,

technology is lagging behind in providing portable devices capable of adaptive programming.

Short pulse width, adaptive stimulation and directional steering all share the same goal of improving specificity of stimulation to neural elements to achieve desired clinical effects while avoiding side effects. These offer the potential of reducing troublesome side effects while maintaining therapeutic efficacy. However, studies on these novel features to date have largely focussed on feasibility, therapeutic window measurements, clinical efficacy, and energy consumption. There is a lack of data on the use of these techniques in alleviating problematic side effects which affect a significant proportion of STN DBS treated patients.

Indeed, it would also be of interest to examine whether a synergistic or cumulative effect resulting from combining these programming techniques exists. Along with defining the utility of available novel features such as directional stimulation, there is a need for more robust data on the use of simple parameters such as shorter pulse widths.

1.3 Research aims

In this thesis, I will evaluate the utility of novel programming techniques of short pulse width and directional stimulation in reducing common side effects of STN DBS therapy in Parkinson's disease.

More specifically, I aim to:

1. Determine the acute effect of short PW subthalamic nucleus stimulation using 30μs on the therapeutic window in terms of amplitude and electrical charge per pulse, and compare the total electrical energy consumption relative to standard PW stimulation at 60μs [Study 1; Chapter 2].

2. Compare the use of short PW with conventional PW stimulation in chronic STN DBS patients with dysarthric speech and evaluate if its use is associated with an improvement in speech. Other motor, non-motor, and quality of life measures will also be compared. [Study 2; Chapter 3].

3. Evaluate the utility of directional steering, and the combination of directional stimulation with short PW in reducing stimulation induced side effects of dysarthria, dyskinesia, and symptomatic pyramidal muscle contraction, compared to conventional ring mode stimulation [Study 3; Chapter 4]

4. Use imaging and stimulation field visualisation software to model volume of tissue activated (VTA) for patients in study 3, and qualitatively explore

patterns associated with the appearance/ resolution of side effects. [Study 4; Chapter 5].

While randomised double-blind clinical trials are needed in many areas of DBS therapy as they represent the highest level of evidence and minimise confounding and biases, pilot data from open label studies play an important role in providing initial indications, generating further hypotheses, and enabling sample size calculations prior to embarking on potentially costly and lengthy clinical trials. Studies 1 and 3, where there was minimal or no data on the specific areas of interest are open label studies, and study 2 is a randomised double-blind crossover trial.

CHAPTER 2

Acute Effects of Short Pulse Width Settings on the Therapeutic Window

2 - Summary of chapter

This chapter examines the effect of short pulse width (PW) on the therapeutic window (TW). The effect on speech in the acute setting is also compared. In a consecutive series of 20 post-operative STN DBS patients, monopolar review data was collected using the standard 60μs PW as well as 30μs using each of the four ring contacts per lead in ring mode. The TW was calculated in terms of both amplitude and charge per pulse, and was found to be significantly higher at 30μs relative to that at standard PW. Speech intelligibility in the acute setting was not significantly different in this asymptomatic cohort of patients, but perceptual characteristics of speech improved with short PW. Total electrical energy delivered (TEED) was also compared and was not found to be significantly different between the two PWs.

2.1 Introduction

Advances in DBS technology in the last few years have enabled the use of pulse widths (PW) as low as 10µs in some commercially available devices (Reich *et al.*, 2015). However, the default use of PW of 60µs for programming STN DBS is still the most prevalent in clinical practice, and is driven by algorithms and guidelines based on early data on the varying effects of different PWs where the lower limit in devices was 60µs (Rizzone *et al.*, 2001; Moro *et al.*, 2002; Volkmann, Moro & Pahwa, 2006; Picillo *et al.*, 2016), as well as the fact that most long term data on STN DBS treated patients is based on this parameter value. 60µs initially became the standard as it demonstrated the greatest therapeutic window (TW) within this range while providing at least an equivalent therapeutic benefit to that at higher PWs, with some data suggesting that 60µs was superior in alleviating bradykinesia than PWs higher than this (Moro *et al.*, 2002).

As the amplitude is the parameter usually titrated to produce an adequate clinical effect, while PW and frequency are kept constant (at least in the initial stages of programming a patient with STN DBS), the therapeutic window (TW) in DBS programming came to be defined in terms of the amplitude. Analogous to TWs defined for pharmacological agents, in DBS therapy this translated to the difference between the amplitude required for best therapeutic effect and the amplitude that elicited the first side effect.

Given the trend from early data on varying PW and strength-duration curves (Rizzone *et al.*, 2001), it would be expected that reducing PW below 60µs would further increase the TW. However, data confirming this effect, and the degree to which this occurs, is scant, and at the time this study was carried out, only *Reich at al* had reported indications of this trend, albeit in only 4 patients. The pattern of increasing amplitudes

required for both a therapeutic effect and side effects with decreasing PWs would mean that the magnitude of any change in TW would depend on the relative increases in these thresholds. Furthermore, electrophysiological properties of excitation of neural elements indicate there is a minimum stimulation threshold at which a particular axon or fibre type can be excited. At very short PWs, the amplitude threshold gets exponentially larger. At infinitely large PWs, this amplitude threshold approaches a minimum, known as the rheobase current (I_{rh}). At twice the rheobase current, the corresponding PW on the strength-duration curve required for excitation is termed the chronaxie, and this is an indication of neural excitability from a point of stimulation. Its relationship to the threshold current and PW is given by the equation: $I_{th}(PW) = I_{rh}\left(1 + \frac{T_{ch}}{PW}\right)$, where I_{th} is the threshold current, I_{rh} is the rheobase current, and T_{ch} is the chronaxie; the latter two being constants (Brocker & Grill, 2013). In the case of a positive TW, the chronaxie for elements mediating the therapeutic effect is therefore inherently lower than those for structures responsible for side effects. It would be of clinical and theoretical interest to confirm an expansion of this effect and the degree to which this is present at PWs below 60µs.

One approach used in studies examining the effect of alternative parameter values such as low frequency on clinical outcomes is to keep the total electrical energy delivered (TEED) constant and calculate the equivalent amplitude required with the alternative parameter. While this has been an accepted method for frequency studies, it is unclear if this approach is valid with respect to PW. This is because there is no substantial data available on clinically effective short PW parameters and the corresponding TEED relative to those at standard PW; using this method would make the assumption that the energy efficiency of short PW settings is equivalent, which may not necessarily be the case. It would, however, be useful to compare the TEED on short PW at settings that produce equivalent clinical benefit to standard PW, to either validate or reject an equivalent TEED based approach to programming with alternative PWs. There may also

be implications for device battery life in non-rechargeable systems that my become apparent from these data.

Another measure that is of interest is the electrical charge per pulse (Q_p) at short PW settings. Theoretical calculations using Weiss's original strength-duration equation, expressed in terms of charge required, $[Q_{th}(PW) = I_{rh}.PW + T_{ch}.I_{rh}]$ indicate that the threshold charge would be lower at shorter PW values, although clinical data is needed to confirm this effect and its magnitude at PWs shorter than 60µs (Brocker & Grill, 2013). The Q_p can be calculated with alternative PWs as the product of the pulse duration and amplitude, for both efficacy and side effect thresholds. Given that changing the PW also changes the 'amplitude scale', there is an argument that direct comparisons of amplitude values are not strictly valid across different PWs, and a comparison of thresholds in terms charge may provide additional data to confirm any effects found with alternative PW settings.

A wider TW enabled by using a PW shorter than 60µs may theoretically provide more scope to increase stimulation both initially and over time to the level required for optimal control of PD motor symptoms without the occurrence of adverse effects. PWs below 60µs are available on commercial devices between 20µs and 50µs at intervals of 10µs. In early experimental data, *Reich et al* reported that efficacy thresholds could not be determined in many patients at PWs below 30µs due to the need for a very high stimulation current. Therefore 30µs was used in this study, with the aim of collecting data on a larger series of STN DBS patients during a post-operative monopolar review, in order to; (i) quantitatively define the TW in terms of amplitude relative to standard 60µs settings, (ii) compare charge per pulse at efficacy and side effect thresholds, as well as the TW in terms of charge relative to standard PW, (iii) compare TEED, and (iv) explore any differences in clinical assessment of speech between standard and short PW in an acute setting.

2.2 Methods

2.2.1 Patients

Twenty consecutive PD patients who underwent DBS surgery with bilateral implantation of electrodes in the STN using Boston Scientific *Vercise*, *Vercise PC* or *Gevia*™ systems at the National Hospital for Neurology and Neurosurgery in 2017 were included. Nine were female, the mean age was 54 ± 8 years, and the mean disease duration was 13 ± 4 years. The mean preoperative UPDRS-III scores were 43 ± 9 OFF and 15 ± 6 ON medication. Five patients had the *Vercise* system*,* nine had *Vercise PC,* and six had *Vercise Gevia*.

Patients underwent surgery under general anaesthesia without microrecordings using the Leksell frame and an MRI-guided and MRI-verified technique. Using this technique, a mean perpendicular error between planned target coordinates and electrode trajectory of 0.9 ± 0.5mm has been previously reported (Holl *et al.*, 2010; Foltynie *et al.*, 2011; Akram *et al.*, 2017; Aviles-Olmos *et al.*, 2014). All patients in the series had verification of electrode placement following implantation and these were confirmed to be within 1.5mm of the intended dorsolateral STN target. Figure 2.1 is a representative illustration of electrode placement in these patients.

2.2.2 Monopolar review procedure

An extended monopolar review was performed 2 - 10 days post-operatively (mean 5 ± 3) as part of standard clinical assessment to screen for therapeutic and adverse effects of stimulation at each contact prior to initiating DBS therapy. All patients were assessed in the off-medication state, having withheld all dopaminergic medication for at least 12 hours prior to screening.

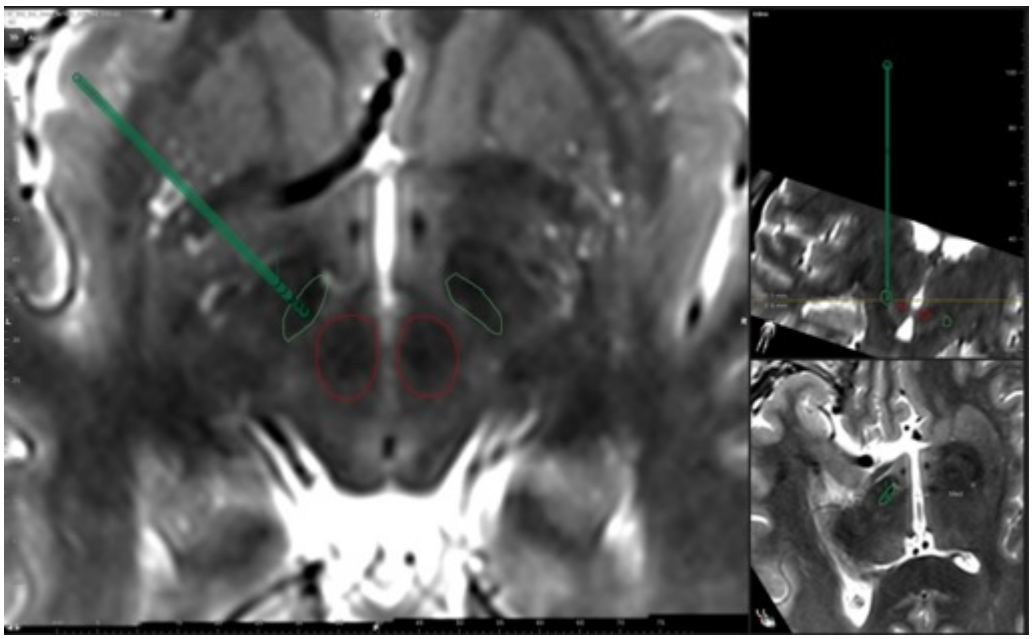


Figure 2.1 **Representative illustration of electrode placement in the subthalamic nucleus target.**

Assessments were done at standard pulse width (60μs) and repeated at short pulse width (30μs), or vice versa with a one-hour washout interval between sessions. The order of the PW condition tested was alternated with each subsequent patient for the screening, so that 10 patients were tested on PW60 then PW30 and 10 in the reverse order. Patients did not have knowledge of PW settings at the time of assessments. Stimulation was programmed in ring mode only for each of the four contact groups per STN lead. The frequency setting was kept constant at 130Hz for all patients, and the implantable pulse generator (IPG) was always programmed as anode.

Each of the four contacts on each lead was screened in ring mode to determine the efficacy threshold (ET) and the side effect threshold (ST) to the nearest 0.1mA. The ET was defined as the lowest current required to produce complete or near complete loss of contralateral upper limb rigidity.

Rigidity was assessed at the wrist, initially with 0.5mA increments of stimulation current at 60-second intervals until maximal loss of rigidity was achieved. The exact threshold was then determined with assessments at 0.1mA increments. The same procedure was

followed to determine the side effect threshold, which was defined as the first clinically evident side effect reported by the patient or observed by the assessing clinician that either persisted for longer than two minutes or was not tolerated by the patient for this length of time.

2.2.3 Therapeutic window, charge, and TEED measurements

The TW was calculated as the difference between the side effect and efficacy thresholds for each contact at 60µs and 30µs. This was done in terms of stimulation amplitude, in mA, and in terms of charge (Q), in nanocoulombs (nC).

The charge per pulse (Q_p) in nanocoulombs was calculated for the ET and ST separately as the product of the relevant amplitude threshold (mA) and PW (µs).

TEED was calculated using the formula [$Current^2$ x Frequency x Pulse width x Impedance] (Koss *et al.*, 2005).

2.2.4 Speech assessments

Speech assessment consisted of; (i) intelligibility rating using the Sentence Intelligibility Test (SIT), and (ii) rating of perceptual characteristics of speech using a 60-second monologue (MON) and a reading task (RDG); (Darley, Aronson & Brown, 1969). These were assessed *off*- medication at the ET for each PW condition. The SIT requires patients to read a randomly generated list of sentences from a standardised pool, totalling 100 words. A speech therapist transcribed the sentences for each condition without knowledge of PW settings. The SIT% score provided is the number of words transcribed correctly (Dorsey, M., Yorkston, K., Beukelman, D., & Hakel, 2007). Both the 60-second monologue and sentences read were rated using the perceptual rating scale developed

by Darley, Aronson & Brown (1969), comprising assessment in six speech domains. These were articulation, respiration, resonance, phonation, prosody and rate; each scored out of seven to give a composite score out of 42.

The order of PW conditions in the assessment speech was alternated for each subsequent patient and balanced across the cohort, as for the monopolar review.

2.2.5 Statistics

R software version 3.4.1 was used for statistical analysis (http://www.R-project.org). Normality of data and homogeneity of variances between the two conditions were verified using the Shapiro-Wilk and Bartlett tests respectively. The significance level was set to 0.05. Where data was not normally distributed, the non-parametric Wilcoxon signed rank test was used. All parametric data are presented as mean ± SD unless otherwise specified.

Two sets of analyses were performed for the therapeutic window in terms of amplitude: First, the most efficacious contact (i.e. the one with the lowest efficacy threshold at 60μs) in each STN electrode was used to compare the TW on the two PW conditions using a paired sample two- tailed t-test. A further comparison was then made with paired samples for the entire set of contacts (four per STN lead) on the two PW conditions, to determine if any change in TW was consistent across alternative contacts to those used in the clinical setting.

2.3 Results

The median post-operative UPDRS rigidity score OFF stimulation (UPDRS item 3.3) was 2 [range 0 - 3], with two patients not having any clinically detectable rigidity at the contralateral wrist (presumably resulting from the persisting stun effect of electrode implantation). Complete rigidity control with stimulation (score 0) could be achieved in all patients using the most efficacious contact. Persistent side effects at these contacts for PW60 and PW30 respectively included slurred speech (18; 15), facial (16; 16) or limb (6; 5) muscle contraction, sensory symptoms (5; 11), gaze deviation or diplopia (3; 2), autonomic symptoms (1; 3) and other (2; 2) which included head discomfort at PW60 and vertigo at PW30.

Table 2.1 shows the most efficacious contact for each patient and model of the DBS system used.

All comparative data were normally distributed except for ratings of speech intelligibility (SIT%), where the Wilcoxon signed rank test was used.

Table 2.1. **DBS system and optimal contact for each patient**

Patient	DBS system	Optimal Contacts	
		Right STN	Left STN
1	Vercise PC	2-3-4	10-11-12
2	Vercise	2	10
3	Vercise	2	10
4	Vercise PC	2-3-4	9
5	Vercise PC	2-3-4	10-11-12
6	Vercise PC	2-3-4	10-11-12
7	Vercise PC	5-6-7	9
8	Vercise PC	5-6-7	13-14-15
9	Vercise	3	9
10	Vercise PC	1	10-11-12
11	Vercise	3	9
12	Vercise PC	1	13-14-15
13	Gevia	2-3-4	10-11-12
14	Gevia	1	10-11-12
15	Vercise	2	10
16	Gevia	2-3-4	10-11-12
17	Gevia	2-3-4	10-11-12
18	Gevia	2-3-4	10-11-12
19	Vercise PC	2-3-4	10-11-12
20	Gevia	2-3-4	10-11-12

The efficacy threshold was significantly greater at PW30 (3.2 ± 1.1 mA) than at PW60 (2.0 ± 0.6 mA) as was the side effect threshold at PW30 (6.5 ± 2.0 mA) compared to PW60 (3.4 ± 1.2 mA); $P < .001$ for both. These are illustrated in figure 2.2.

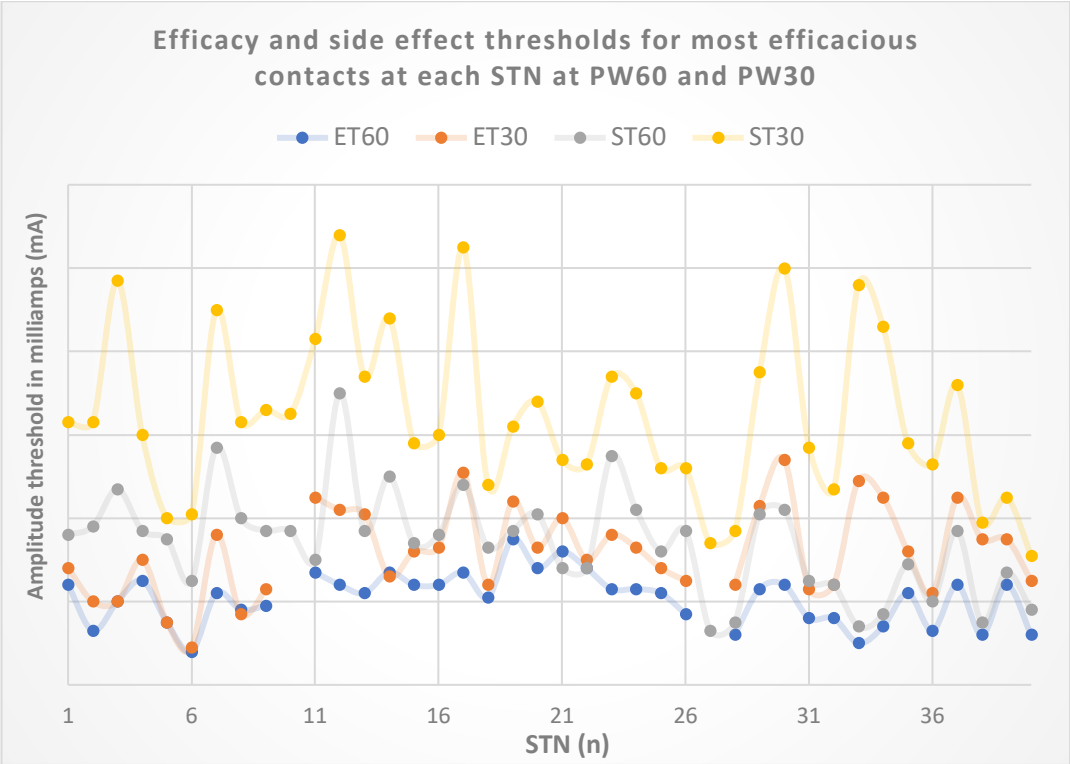


Figure 2.2. **Efficacy and side effect thresholds at PW60 and PW30 for the most efficacious contact per STN lead.**

Legend:
ET60- efficacy threshold at 60µs; ET30 - efficacy threshold at 30µs; ST60 – side effect threshold at 60µs; ST30 – side effect threshold at 30µs.

Mean ± SD for ET60 = 2.0 ± 0.6mA, ET30 = 3.2 ± 1.1mA; $P < .001$
Mean ± SD for ST60 = 3.4 ± 1.2 mA, ST30 = 6.5 ± 2.0 mA; $P < .001$.

Therapeutic windows could be calculated in 38 out of 40 STNs, (due to lack of detectable contralateral wrist rigidity in two). The TW for PW60 was 1.7 ± 1.1 mA [median 1.5; range 5.0 mA] and for PW30 was 3.7 ± 1.7 mA [median 3.3; range 6.9 mA. The mean increase in TW at PW30 was 178% compared to PW60; [t (37) = 10.9, $P \leq .001$, r = 0.92].

In the secondary analysis comparing data from all contacts of each electrode, 151 TWs could be calculated, and these remained significantly higher at PW30 (3.3 ± 1.8mA) than at PW60 (1.4 ± 1.0 mA); [t (150) = 17.9, $P \leq .001$, r = 0.92].

The charge per pulse (Q_p) at the efficacy threshold for PW60 (124.7 ± 6.1nC) was significantly greater than for PW30 (96 ± 5.2nC); t (37) = 4.9, *P* < .001. The Q_p at the side effect thresholds were not significantly different (204.6 ± 11.7 vs 194.0 ± 9.5nC respectively); *P* = .26. The TW in terms of charge at PW30 (100.3 ± 7.7) was significantly greater than at PW60 (82.7 ± 10.2); t (37) = 2.5, *P* = .018. These are illustrated in figures 2.3 and 2.4.

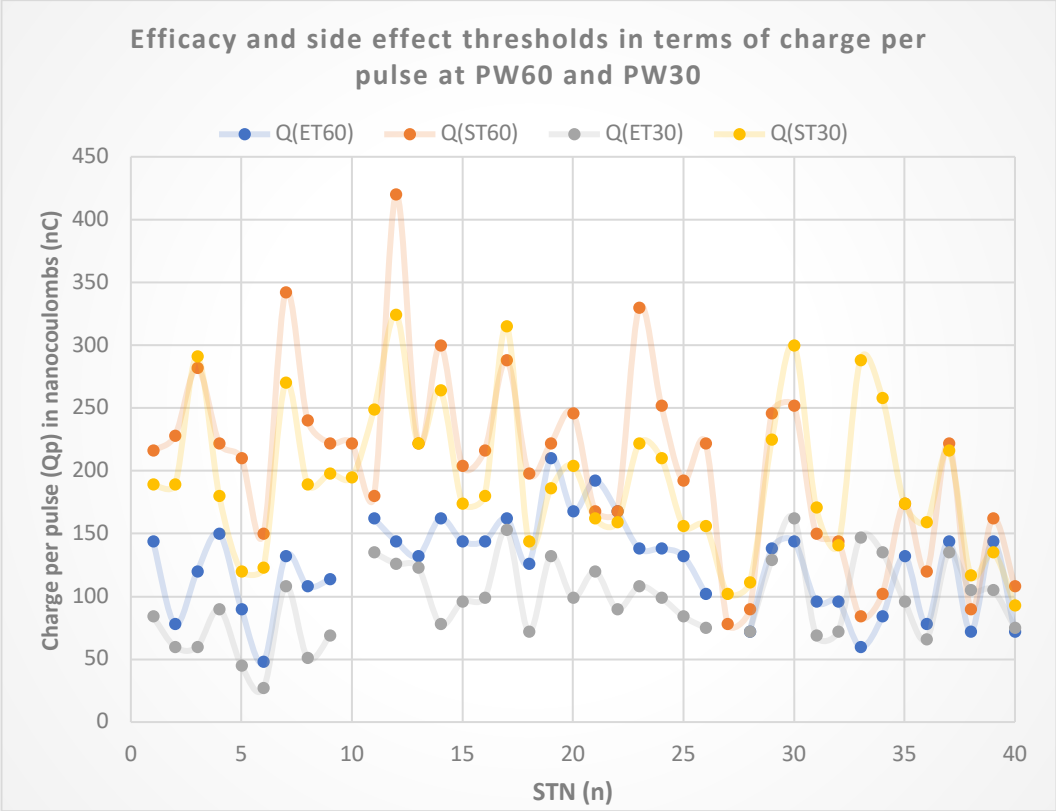


Figure 2.3. **Charge at efficacy and side effect thresholds for each PW condition at each STN**

Legend:
Q(ET60)- charge per pulse at efficacy threshold at 60µs; Q(ET30) - charge per pulse at efficacy threshold at 30µs; Q(ST60) – charge per pulse at side effect threshold at 60µs; Q(ST30) – charge per pulse at side effect threshold at 30µs.

Mean ± SD for Q(ET60) = 124.7 ± 6.1nC, Q(ET30) = 96 ± 5.2nC; *P* < .001
Mean ± SD for Q(ST60) = 204.6 ± 11.7, Q(ST30) = 194.0 ± 9.5nC; *P* = .26.

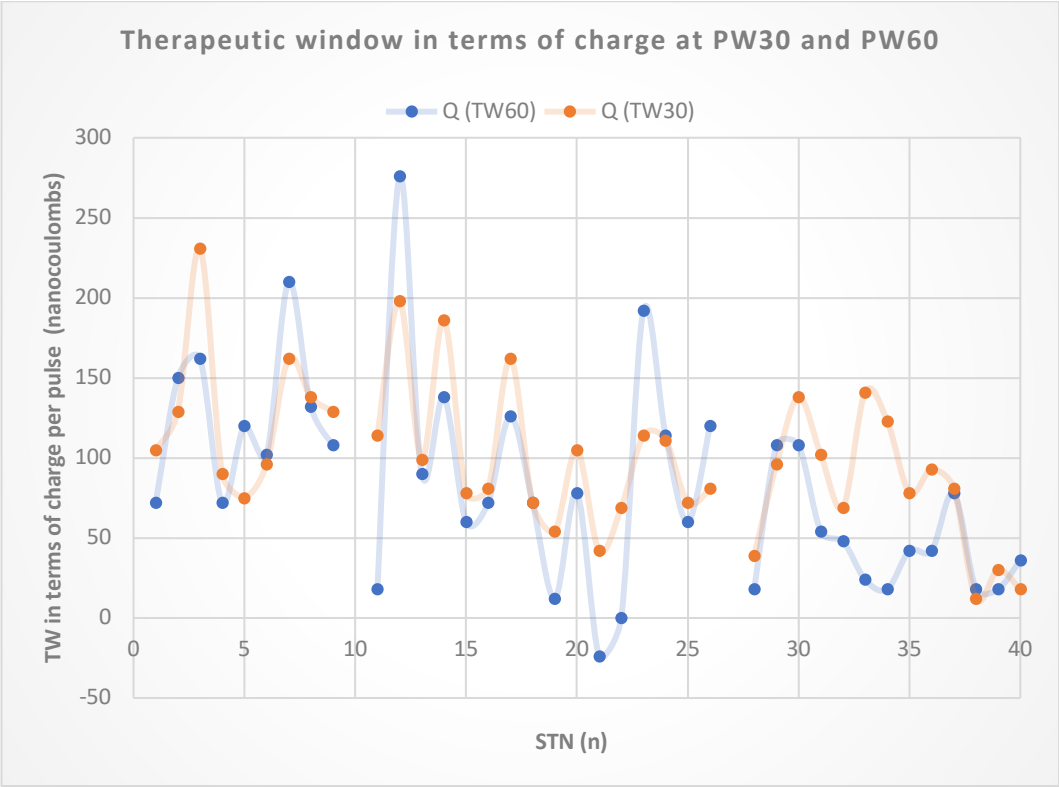


Figure 2.4. **Therapeutic window in terms of charge on each PW condition**

Legend:
Q(TW60)- therapeutic window in terms of charge at 60µs; Q(TW30) - therapeutic window in terms of charge at 30µs.

Mean ± SD for Q(TW60) = 82.7 ± 10.2nC, Q(TW30) = 100.3 ± 7.7nC; *P* = .018

The total electrical energy delivered (TEED) was not significantly different between PW60 (52 ± 38 µJ/s) and PW30 (50 ± 37 µJ/s) at the threshold for efficacy [t (37) =0.47, *P* = .64].

The SIT scores were not significantly different for PW30 (92 ± 17 %) and PW60 (90 ± 21 %); *P* = .31. The perceptual speech score for the reading task (RDG/42) was improved at PW30 (35 ± 5) compared to PW60 (33 ± 6); [t (19) = 3.56, *P* < .01]. The monologue perceptual rating (MON/42) was also higher for PW30 (34 ± 5) compared to PW60 (32 ± 5); [t (19) = 2.46, *P* = .03].

2.4 Discussion

These results show that the therapeutic window (TW) of stimulation using a short pulse width setting of 30µs is significantly greater than that at standard PW settings. The magnitude of this increase in terms of amplitude is greater than two-fold, and is consistent across all contacts of a given lead. The change in TW is characterised by a relatively greater increase in the side effect threshold than the efficacy threshold at short PW settings compared to those at standard PW. Importantly, the TW increased significantly in terms of charge as well as amplitude, suggesting that it cannot be attributed solely to the compensatory increase in amplitude required to keep the overall stimulation intensity the same when PW is reduced. The data on charge per pulse on the two PW conditions shows that the charge required to produce side effects is not significantly different, but the charge required to produce an equivalent therapeutic effect is significantly lower with a PW of 30µs. This implies that therapeutic elements of STN DBS can be selectively activated at lower levels of overall stimulation intensity at 30µs than at 60µs.

Furthermore, the energy consumption using short PW settings at the threshold for rigidity control was not significantly different to that at standard settings. This finding would not be expected with the assumption of requiring a proportional increase in stimulation amplitude, as a change in the amplitude has a relatively greater impact on energy used per unit time than PW. However, the data demonstrates that while PW is halved with 30µs settings, the stimulation amplitude that defined the efficacy threshold was only 60% higher than at standard PW (rather than double), resulting in no significant net difference in energy consumption.

The discrepancy between an equal TEED but lower charge per pulse using short PW compared to standard PW stimulation is explained by the exponential relationship of amplitude with TEED, versus a linear relationship with charge. This is known from

electrophysiological models whereby reducing PW results in an increase in charge efficiency but not energy efficiency (Brocker & Grill, 2013).

Results of perceptual speech ratings showed both the spoken (MON/42) and reading tasks (SIT/42) were significantly improved at PW30. In particular, articulation and rate subscores were noted to be sensitive to change in PW settings. However, there was no significant difference in speech intelligibility as measured by the SIT% score. This may be due the patients exhibiting only mild speech deficits at baseline and also due to assessments being performed early in the post-operative period, as speech disturbances following chronic STN DBS may appear several months following surgery (Guehl *et al.*, 2006; Kleiner-Fisman *et al.*, 2006). The mean SIT score at standard PW settings was relatively high at 90%, and patients in this study did not necessarily have symptomatic speech impairment. However, despite this, the change in perceptual ratings at short PW settings in an acute setting shows promise in using this feature to potentially benefit symptomatic patients. While the cohort of patients examined was not selected on the basis of speech impairment, and this was an exploratory outcome, this finding merits further scrutiny in patients with more profound stimulation related dysarthria.

Therapeutic and adverse effects produced by stimulation delivered through a contact are inextricably linked to the precise location of the contact in the target area. However, global patterns emerging from systematic study of changes in parameter settings are useful despite the confounding factors of natural anatomical variation, variations in surgical technique and precision of targeting. Short PW settings may therefore have beneficial clinical applications in PD patients who have STN DBS. While it may not be relevant to those on standard settings who have an adequate TW, many patients require an increasing level of stimulation over time to control progressive PD symptoms, which may exceed the side effect threshold. Indeed, some patients are found to have a very narrow or even negative TW early in the course of DBS therapy. In these cases, short PW

settings may provide an alternative that results in adequate control of motor symptoms while avoiding the emergence of side effects.

It has been proposed that reducing pulse duration may more selectively affect particular fibre pathways than others in close vicinity due to differences in chronaxies (Groppa *et al.*, 2014). An additional mechanism was suggested by *Reich et al.* (2015), who used strength-duration curves for STN stimulation in PD patients derived from a finite element electric field model coupled to populations of myelinated axon models. They demonstrated a widening difference at shorter PWs in the action potential initiation thresholds between axons close to the electrode and large diameter axons farther away (Reich *et al.*, 2015). While they focussed on pyramidal tract activation as the adverse effect and postulated that corticosubthalamic fibres (the hyperdirect pathway) may be instrumental in rigidity control, it may be that this principle applies to other structures implicated in producing both therapeutic and side effects. However, regardless of both these potential mechanisms, data from this study suggests that the charge per pulse required for an equivalent therapeutic effect is lower with 30µs stimulation. Irrespective of whether there is a sharper drop off of stimulation current with increasing distance from the site of stimulation, or whether selective neural elements within a stimulation field are activated, the TW expands as a result of the efficacy threshold in terms of electrical charge being lower with short PW. The fact that this effect is not achievable with the same lower charge at standard PW (i.e. by dropping the amplitude instead of PW) argues in favour of PW having a role in selective activation of whatever the therapeutic mechanism of STN DBS may be. A further consideration with respect to potential mechanisms is the disruption of aberrant oscillatory activity such as synchronised beta oscillations with STN DBS, and whether stimulation with a shorter pulse and a higher amplitude is more efficient in interrupting these synchronous oscillations in the basal ganglia-thalamocortical network.

Limitations of this study include non-blinded clinical assessment of rigidity and side effects, assessment early in the post-operative course, and the lack of comprehensive motor assessment and long term follow up on the two conditions. The efficacy thresholds in particular, are likely to be lower than chronic stimulation levels due to the stun effect. While assessments on the two PW conditions were performed in alternating order for each subsequent patient, and patients were not aware of PW settings during the monopolar review and speech assessments, this was not a randomised trial. It is also unclear at this stage if the increase in TW using PW30 in the acute setting will translate into a longer term clinical benefit. The reported improvement in some aspects of speech needs to be further qualified with randomised blinded trials.

Assessment of rigidity was used to define the efficacy threshold rather than bradykinesia or tremor as it is found to be the most reliable and objective of these signs during DBS screening assessments, and is not subject to fatigue or fluctuations, while providing relatively quick feedback on DBS effects.

In conclusion, this study of 20 patients, 40 STN leads, and 160 sets of therapeutic window data confirms the finding of an expansion of the TW with short PW, and provides further insights into the nature of this finding by examining the thresholds in terms of electrical charge. While a significant increase in the TW of DBS therapy is a welcome finding, randomised double blinded trials with longer term follow up in patients who suffer from stimulation induced side effects are needed to confirm the sustained efficacy, tolerability, and thereby clinical application and incorporation into DBS programming paradigms, of short pulse width neurostimulation in PD patients.

CHAPTER 3

A Double-Blind Randomised Crossover Trial of Short Pulse Width versus Conventional Pulse Width DBS in Parkinson's disease Patients with Previously Implanted DBS systems

3 - Summary of chapter

This chapter describes the first randomised double-blind trial of short PW stimulation in chronic STN DBS patients, with the objective of comparing its effect relative to standard PW on stimulation-related dysarthria. In a double-blind crossover design, 16 patients experiencing moderate dysarthria after having treatment with STN DBS for at least 12 months were randomised to DBS screening at 60μs then 30μs or vice versa, followed by treatment on one condition then the other for 4 weeks each using a four-block randomisation sequence. The primary outcome was difference in dysarthric speech measured using the Sentence Intelligibility Test (SIT) at baseline and the two PW conditions. Secondary outcomes included motor, non-motor, and quality of life assessments using the MDS-UPDRS parts I – IV, Unified Dyskinesia Rating Scale, timed 10-metre sit-stand-walk, timed hand taps, Non-motor Symptom Scale, PDQ-39, Freezing of Gait Questionnaire, Verbal Fluency, and total electrical energy delivered (TEED).

My role included recruiting, consenting, and enrolling all participants, and performing clinical assessments of all outcome measures except speech, which was done by a specialist speech and language therapist. I remained blinded to treatment conditions of all patients throughout the trial, as did the speech therapist. I saw patients during all scheduled visits and unscheduled visits, recorded any adverse events, participated in trial monitoring, and was responsible for entering blinded data and maintaining complete and accurate clinical records. An unblinded team led by a specialist DBS neurologist performed all programming tasks.

There was no significant difference found in the SIT scores between baseline and the two PW conditions after 4 weeks of treatment. There were also no differences in the motor, non-motor, and quality of life scores. The 30μs settings were well tolerated, and

adverse event rates were similar to those at conventional PW settings. The therapeutic window was significantly larger with short PW.

The mean duration of DBS in the trial patients was 6.9 years, and it was noted that 10 of the 16 patients were on low frequency settings at baseline. Post-hoc analyses indicated that dysarthric patients with a shorter duration of DBS, as well as those who had not been previously optimised using low frequency settings may benefit from short PW stimulation. No difference in clinical outcomes can be concluded from this trial, but the subgroup observations serve as hypotheses for further studies on the use of short PW in these patients.

3.1 Introduction

The trend of exponential expansion of the therapeutic window with reducing PWs has been observed since the early era of STN DBS (Rizzone *et al.*, 2001; Moro *et al.*, 2002). Data presented in the previous chapter confirmed the extrapolation of this effect to PWs lower than 60μs in the acute setting. This was also corroborated in other studies since published in proximity of each other (Steigerwald *et al.*, 2018; Bouthour *et al.*, 2018). These studies examining therapeutic window using short PW were all carried out in the acute setting, or studied the use of short PW in an acute challenge. However, clinical data on the development of adverse effects such as speech and gait disturbance indicate these problems often develop in the longer term with chronic stimulation (Krack *et al.*, 2003; St. George *et al.*, 2010; Merola *et al.*, 2011). Therefore, the relationship between pulse width and severity of these more common disabling side effects evolving after chronic stimulation remains unexplored. Moreover, none of the studies exploring the effect of pulse width have looked at specific cohorts of STN DBS patients with these side effects and whether they could be ameliorated by the use of shorter than conventional PW.

The data presented in Chapter 2 suggests there may be potential beneficial effects on speech, which is commonly adversely affected with STN DBS, particularly with chronic stimulation (Rodriguez-Oroz *et al.*, 2005; Guehl *et al.*, 2006). Patients with PD who undergo STN DBS have been reported to have a mean deterioration in speech intelligibility of 16.9% at 12 months following surgery, compared to 4.5% in a medical control group (Tripoliti et al. 2011).

Earlier studies showed that higher amplitude and frequency were both factors contributing to impairment of intelligibility (Törnqvist, Schalén & Rehncrona, 2005). In addition to higher amplitudes of stimulation, electrodes placed medially to the STN have

since been shown to correlate with the development of dysarthria following STN DBS (Sun et al., 2008; Tripoliti et al., 2014). The characteristics of stimulation related dysarthria include imprecise articulation from slowing of lip, jaw and tongue movements, and breathy hypernasal voice quality (Åström et al. 2010; Tripoliti et al. 2008). Patient –specific electric field modelling based on contact location and stimulation parameters have suggested involvement of the fasciculus cerebellothalamicus as a cause of stimulation induced dysarthria (Åström *et al.*, 2010; Fenoy, Mchenry & Schiess, 2017).

Apart from the *medial - type* speech disturbance seen with chronic STN DBS described above, characterised by strained-tight and continuous phonation, inaccurate articulation and breathing insufficiency, pyramidal tract activation (indicated by electromyographic resting motor thresholds in facial and upper limb muscles), has been shown to contribute to a *lateral type* of speech disturbance. This is characterised by monotone-flat intonation, fast rate, and reduced movement of the lips and tongue (Mahlknecht *et al.*, 2017).

It would be of interest to evaluate whether the acute effect of enlarging the therapeutic window using short PW can be clinically applied and translated to a benefit in the chronic setting, in patients who have already developed side effects. Furthermore, while side effects that defined the upper limit of the TW in studies in the acute setting discussed were commonly related to pyramidal tract activation with muscle contraction, for which a proposed mechanism of benefit using short PW has been that there is a sharper drop off of stimulation current before reaching more distant pyramidal tract fibres (Reich *et al.*, 2015), a further mechanism of such a beneficial effect in STN DBS may be postulated from the work of *Groppa et al* in patients with essential tremor treated with thalamic stimulation. In these patients, stimulation induced ataxia is a recognised side effect and could be readily induced with supratherapeutic stimulation.

Using strength-duration curves, the chronaxies (a measure of excitability of neural elements) for suppression of tremor and induction of ataxia were calculated to be 38μs and 52μs respectively. Using probabilistic tractography, it was deduced that the therapeutic effect most likely resulted from stimulation acting on the dentate-thalamo-cortical fibres, and adverse effects from stimulation effects on afferent or efferent cerebellar fibres of the red nucleus adjacent to the stimulation site. While the authors were not able to stimulate at PWs less than 60μs with devices used at the time, they could conclude that stimulating using a PW closer to the chronaxie for tremor suppression would provide a wider TW between tremor relief and induction of side effects (Groppa *et al.*, 2014).

It may be theorised therefore that a parallel application of this principle to STN DBS for PD may result in similar fibre selectivity in favour of therapeutic neural elements within the STN while avoiding adjacent fibres such as medial cerebellothalamic projections implicated in the development of dysarthria.

The aim of this study is to explore the effect of using a short PW of 30μs on the adverse effect of dysarthric speech experienced by chronically implanted STN DBS patients.

3.2 Trial Design

This investigation is designed so that each patient will be assessed using conventional (60μs) and short PW (30μs) in a randomized order for a period of four weeks, and then crossed over to the alternative condition for the same duration. The crossover design allows each patient to essentially act as their own control subject, and will maximise the ability to judge using paired statistical tests whether there is a consistent advantage in speech intelligibility and other secondary outcome measures using the shorter pulse width (30μs). It is anticipated that clinical effects from the previous setting will have completely disappeared by the end of the four-week period. Detailed assessments will be performed at baseline and at the end of each treatment condition.

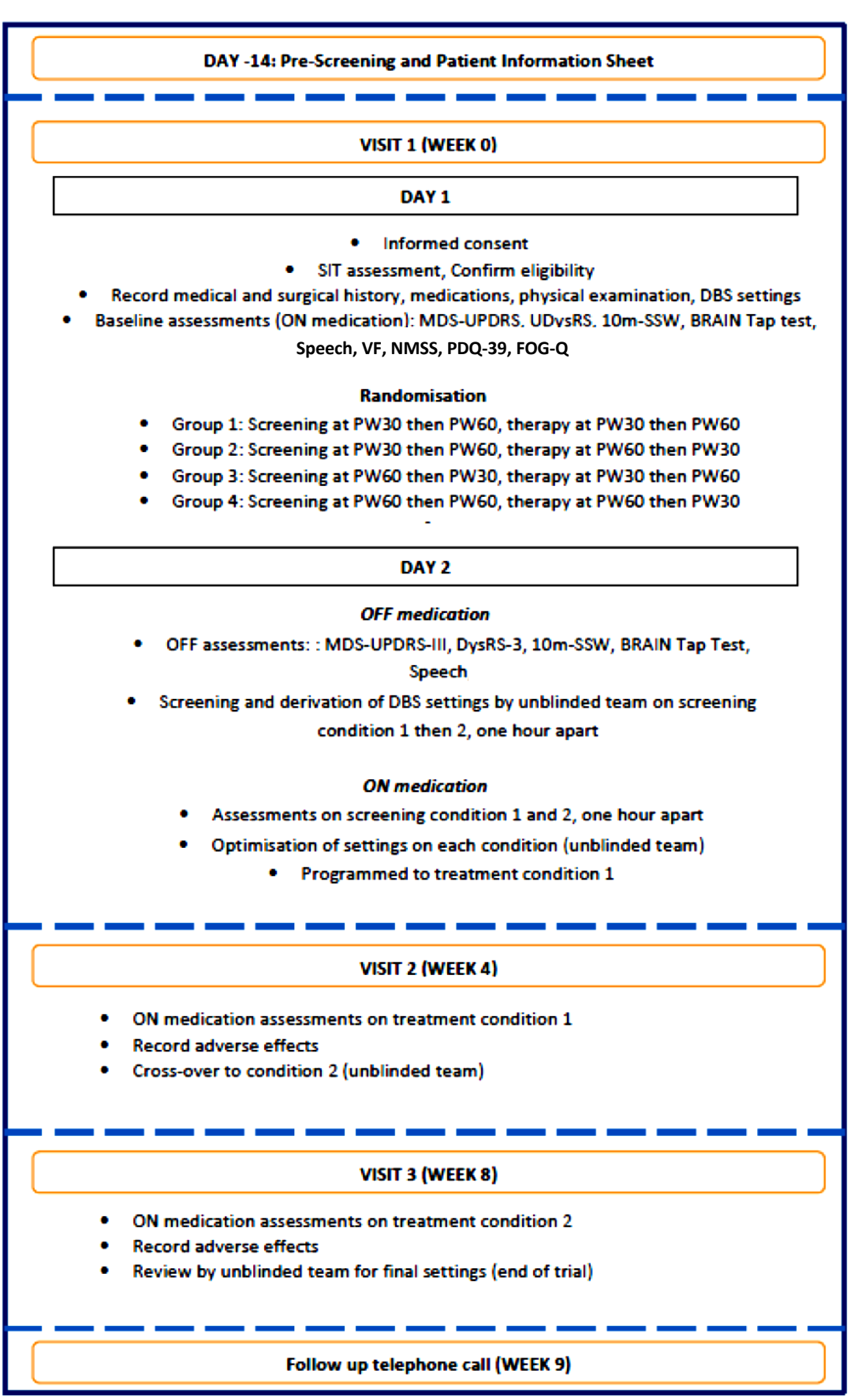


Figure 3.1 **Overview of trial design**

Legend to figure 5.1:

MDS-UPDRS: Movement disorder Society Unified Parkinson's Disease rating Scale

SIT: Sentence Intelligibility Test

UDysRS: Unified Dyskinesia Rating Scale

DysRS-3: Part III of unified dyskinesia rating scale (objective section)

10m-SSW: Timed 10-metre Sit-Stand-Walk

BRAIN-Tap test: Bradykinesia Akinesia Incoordination test (computerized, quantified assessment of bradykinesia with alternative key tapping)

VF: Verbal Fluency

NMSS: Non-motor Symptoms Scale

PDQ-39: 39-item Parkinson's Disease Questionnaire (Quality of life assessment)

FOG-Q: Freezing of Gait questionnaire

***Speech** assessment* consisted of SIT and perceptual rating of speech

***Follow up** telephone call at week 9 was carried out to ensure adequate symptom control and document any adverse events

3.3 Description of the Investigational Device

The ability to use short pulse width (30µs) DBS in chronically implanted STN DBS patients was made possible as a result of the provision of a novel software flashcard (8870 XBP application card) developed by Medtronic, compatible with the routine Medtronic N'Vision 8840 Clinician Programmer.

The 8870-XBP software is based on the DBS application found on the commercially available 8870-BBU application card and therefore the UI look and feel is identical to the existing commercial application. After activation of the application a splash-screen is shown on the 8840 to show that this software is *Exclusively for Clinical Investigation*. No specific changes to the firmware in the implant was created by the use of this application software. The changes are only in the programmed values allowed for the parameters.

Adjustment of stimulation under short pulse width (PW30) and conventional pulse width (PW60) condition were carried out by unblinded investigators. Patients had their own programmer to allow the DBS to be switched ON or OFF in emergency circumstances, but they were not be able to view or adjust the stimulation amplitude or pulse width. Confirmation of patient compliance was evaluated using the 8840 N'Vision programmer which revealed the percentage time DBS had been switched on, and any interruptions at each follow up assessment.

Figure 3.2. **Prototype of Medtronic 8870 XBP application card**

Figure 3.3. **Medtronic 8840 clinician programmer and Activa PC implantable pulse generator**

(Adapted from http://www.medtronic.com/us-en/healthcare-professionals/products/neurological/deep-brain-stimulation-systems/activa-pc.html)

3.4 Methods

3.4.1 Patient Selection

Participants were recruited from a pool of patients with Medtronic DBS systems already under routine follow up for their DBS therapy at the National Hospital for Neurology and Neurosurgery. In order to select patients with chronic side effects, those implanted for 12 months or more were deemed suitable. As speech impairment is one of the most common chronic side effects of stimulation, and speech intelligibility is readily quantifiable, those with moderate to severe dysarthria as outlined in the eligibility criteria were recruited. These patients were most likely to have developed a significant degree of stimulation induced dysarthria that may be amenable to changes with alternative programming parameters. Patients who fulfilled demographic and core clinical eligibility criteria from clinical records and were identified as potential participants had their most recent speech recordings (previously taken during clinical assessments) reviewed by a speech therapist so that appropriate candidates could be invited to take part and have an eligibility assessment on the day of planned enrolment. Patients who did not have the investigational device treatment due to not meeting the inclusion criteria were replaced. Patients who had the investigational device treatment and withdrew from the study were not replaced.

Drop out was expected to be low in view of the short duration of the study and the existing long-term relationship between the patients and the study team. The importance of complete follow up and clinical investigation completion was explained to all potential participants at the screening visit. Patients likely to have difficulty adhering to the CIP requirements were not recruited. The clinical team made every effort to establish good relationships with all participants from the first contact to maximise retention.

3.4.2 Sample Size

There are no previous data of potential effect size of short pulse width (30μs) stimulation on speech intelligibility to enable formal sample size calculations to be performed. This clinical investigation is not designed to judge efficacy of short pulse width DBS, but will be used to make estimates of the magnitude of each of the potential effects and the variance associated with use of short pulse width DBS. The pilot data generated will guide future studies, depending on any effect size if found. A sample size of 16 was chosen as it was deemed a reasonable size for a DBS trial for the purposes described above, was feasible in the timeframe available for the project with the accessible patient population, and allowed an even number for the crossover with randomisation at the DBS screening and treatment stages (in blocks of four).

3.4.3 Inclusion criteria

Eligible patients were men and women between ages 25 to 75 years with a clinical diagnosis of Parkinson's disease, treated with bilateral subthalamic nucleus deep brain stimulation with a Medtronic *Activa PC* device for at least 12 months, and had stimulation induced slurring of speech, defined as a sentence intelligibility score of 50-80% on the assessment of intelligibility of dysarthric speech (Sentence intelligibility Test) scale. They needed to be able to provide documented informed consent to participate.

3.4.4 Exclusion criteria

Those already actively participating in an investigation of a drug, device, or surgical treatment for Parkinson's disease were excluded, as were those who lacked the capacity to give informed consent, or had any medical, psychiatric or other condition which was deemed to compromise the potential participant's ability to participate in the trial fully.

3.4.5 Randomisation

Patients were randomised into one of four groups to ensure equal numbers of patients in each permutation of screening and treatment order. The four blocks had the following sequences of DBS screening and treatment condition:

- Group 1- screened at 30µs then 60µs, following which received DBS therapy at 30µs then 60µs.
- Group 2- screened at 30µs then 60µs following which received DBS therapy at 60µs then 30µs.
- Group 3- screened at 60µs then30µs following which received DBS therapy at 30µs then 60µs.
- Group 4- screened at 60µs then30µs following which received DBS therapy at 60µs then 30µs.

A randomisation service provider, *Sealedenvelope.com* was used to randomly allocate each participant to one of the four blocks using their study number. At enrolment during the baseline visit, the unblinded clinical investigator matched the patient using their study number to the randomly allocated sequence.

3.4.6 Patient Timeline, Procedures and Assessments

Pre-screening Call (2 weeks before baseline visit)

Patients who were identified as potentially eligible subjects were telephoned to provide information on the study, ascertain interest to participate, and screen for inclusion and exclusion criteria. Interested eligible subjects were provided the Patient Information Sheet (PIS) at least two weeks prior to the baseline visit.

Visit 1 (Baseline/ Week 0)

This was a two consecutive-day visit. Patients attended Day 1 in their usual *on*-medication state. Informed consent was taken, and eligibility criteria confirmed. Background medical and surgical history, medications, DBS settings and demographic information was recorded. Physical examination and vitals were recorded. The SIT assessment was done and used as the baseline rating if the patient was eligible to proceed. Other baseline assessments were performed including the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I-IV, Unified Dyskinesia Rating Scale (UDysRS), 10-metre timed Sit-Stand-Walk (10m SSW), BRAIN tap test, Verbal Fluency (VF), and the Non-Motor Symptoms Scale (NMSS). Patients self-completed the Parkinson's disease 39-item Quality of Life questionnaire (PDQ-39) and Freezing of Gait Questionnaire (FOG-Q). The Total Electrical Energy Delivered (TEED) was calculated based on baseline settings and recorded.

Dopaminergic medications were withheld overnight. Patients attended Day 2 of the baseline visit to have *off*- medication assessments and a monopolar review (screening) of DBS settings using their chronically active contact configuration. In the case of patients having double monopolar, bipolar, or interleaving configurations at baseline, these were kept the same in deriving the two treatment settings. The following assessments were performed in the *off*- medication state: MDS-UPDRS part III, UDysRS part 3, timed 10m SSW, BRAIN tap test, SIT, VF. DBS screening was then performed by a designated unblinded clinician according to the randomisation sequence allocated to the patient. DBS screening was done on each condition, either 30µs or 60µs, followed by the alternative after a one-hour washout period. The one-hour gap was to allow any residual effects from the previous PW setting to be eliminated. The effects on tremor, rigidity and bradykinesia (to determine the efficacy threshold), as well as stimulation-induced side effects and the thresholds for these were noted on each PW condition. Following this the patient took their usual dopaminergic medication so that further

optimisation of settings could be made if necessary, in the *on*- medication state. The assessments listed above except verbal fluency were repeated on each condition and fed back to the programming clinician for any further adjustments.

No change was made to the frequency parameter or the contacts used. The optimal setting derived for each PW condition was recorded and the patient was put on the first treatment condition for the first four weeks according to the randomisation sequence.

Visit 2 (Week 4)

Patients attended in the *on*- medication state and the assessments and patient questionnaires done at baseline were performed by a blinded clinician. Adverse events and any medication changes were recorded. The patient was then seen by a member of the unblinded team and switched to the second PW condition for the next four weeks. A second member of the unblinded team checked the settings.

Visit 3 (Week 8)

The same procedure as for visit 2 was carried out.

At the end of the trial, patients were able to keep whichever setting they found beneficial or revert to their baseline settings if there was no clear advantage from any of the trial settings.

Any necessary adjustments of amplitude within the same PW condition were performed by the unblinded clinician during each 4-week treatment period to deal with sub-optimal symptom control or delayed intolerable side effects.

Telephone call follow up (Week 9)

Patients were contacted via telephone one week after the last treatment day to ensure adequate symptom control and document any adverse events.

3.4.7 Blinding

The patients and rating clinicians were blinded to the randomisation order throughout the study period and until the last participant completed the trial and all data were collected, securely stored and locked in the trial database. An unblinded clinician was responsible for DBS screening and programming the stimulation, as well as recording stimulation parameters and sequence of DBS screening and treatment for each participant in securely stored master logs. Strict measures were taken so that any necessary communication between team members did not result in disclosure of information leading to inadvertent unblinding of blinded clinicians. The patient DBS controller was disabled to avoid unblinding of participants to the active trial setting. No unblinding to individual patients of the treatment condition during each period took place until all patients completed the trial.

3.4.8 Safety

Serious adverse events (SAE) and serious adverse device events (SADE) were defined as those that led to death or serious deterioration in the health of a subject resulting in a life-threatening illness or injury, permanent impairment of bodily function, or prolonged hospitalisation. These were reported to the sponsor (University College London) and the Medicines and Healthcare products Regulatory Agency (MHRA) within 48 hours of the trial team being aware of them.

3.4.9 Device accountability

An unblinded clinical investigator was responsible for the storage of two assigned Medtronic 8870-XBP flashcards clearly labelled “Exclusively for clinical investigation”. Access to the physical location of the labelled flashcards was limited to unblinded members of the clinical investigating team.

3.4.10 Data collection and handling

All data were handled in accordance with the UK Data Protection Act 1998. Data was recorded on a paper case report form (CRF). CRFs were designed by the investigator and trial team and finalised by the sponsor. Subjects were assigned an investigation identification number by the study site sequentially starting with SPW01 upon enrolment into the study. Each participant had CRFs and assessment forms labelled with their assigned study number, initials, and date of birth and these were individually filed. All information was entered in black ink with a ball-point pen. Any errors were crossed out with a single line and annotated with initials of the investigator and date. The following standard data were entered into the medical records (source) and the CRF:

- Informed consent
- Unique identification code number
- Demographic data relating to PD
- Past medical history (including documentation of all previous and ongoing medical problems)
- Medication history
- Date of DBS implantation
- Baseline DBS settings and impedances
- Family history- including age at onset of all affected relatives

- Levodopa Equivalent Dose
- Vital signs: pulse, blood pressure, weight
- Clinical examination
- Adverse events

Logs of participant identification, screening, enrolment, and completion of trial were filed in the investigator site file. Master screening, treatment and randomisation logs were completed by the unblinded clinician and stored with the investigational device in a secured cabinet accessed only by the unblinded team.

3.4.11 Data storage, management and analysis

Each participant was provided with a transparency notice detailing procedures regarding data management and storage in accordance with the EU General Data Protection regulation legislation.

A trial database was custom designed with username and password secured access to delegated members of the investigation team. Data from paper CRFs were entered into the database and each entry was electronically date and time stamped. At the conclusion of the investigation, the database was locked, and data transferred for analysis. A final copy of the database was retained. All essential documents will be archived for at least 25 years from completion of investigation.

3.4.12 Data monitoring

Regular monitoring visits at least every month during the trial were commissioned by the sponsor to an external monitor. This included monitoring of trial study files and CRFs, clinical patient notes, the electronic database, the investigator site file, and the

master file with blinded documentation, for completeness, accuracy and compliance with the clinical investigation plan. The following activities were performed by the monitor at each visit:

- 100% source verification
- Essential document review
- Consent form review
- Eligibility and medical history
- Deviation review
- Adverse event review

Review of blinded study documentation included:

- Randomisation confirmation
- DBS Screening CRFs
- DBS Treatment CRFs

The Clinical Investigators met at trial management group meetings to discuss any issues with data quality and any concerns were discussed with the Sponsor.

3.4.14 Trial Oversight

The trial was sponsored by UCL and coordinated by the Joint Research Office (JRO). Approval for use of the investigational device was obtained from the Medicines and Healthcare products Regulatory Agency (MHRA). Ethics approval was obtained from the local Research Ethics Committee (REC reference 17/NI/0203). Funding for salary support for this study was received from the Neurological Foundation of New Zealand, a

registered charity organisation. The industry did not play any role in the study apart from provide equipment.

Trial Management Group (TMG)

The TMG included the Principal Investigator and experts from relevant specialties. The TMG was responsible for overseeing the trial and was responsible for reviewing substantial amendments to the protocol prior to submission to the REC and MHRA.

3.4.15 Outcomes

The primary outcome was the difference in dysarthric speech as measured by the SIT (%) between the baseline and PW30 and PW60 conditions at the end of each 4-week period in the *on*-medication state. The results will provide a mean effect size and variance which can be used for sample size calculations in future efficacy trials.

The SIT assessment comprised of the patient reading a standardised passage with randomly generated sentences from the Sentence Intelligibility Test software (Dorsey, M., Yorkston, K., Beukelman, D., & Hakel, 2007). These were recorded and rated by a speech therapist who had not witnessed the recording prior to their assessment, and independently transcribed the number of words intelligible. This was then compared against the original transcript of the passage read by the patient, giving a percentage score of number of intelligible words (Yorkston, Beukelman 1984).

Predefined secondary outcomes were differences between the two treatment conditions and from baseline in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I-IV, Unified Dyskinesia Rating Scale (UDysRS), 10-metre timed Sit-Stand-Walk (10m SSW), BRAIN tap test, Non-Motor Symptoms Scale (NMSS), Parkinson's disease 39-item Quality of Life questionnaire (PDQ-39), Freezing of

Gait Questionnaire (FOG-Q), Verbal Fluency (VF), and Total Electrical Energy Delivered (TEED).

- The MDS-UPDRS is a comprehensive standardised 65-item assessment of both motor and non-motor symptoms associated with Parkinson's disease. 20 questions are completed by the patient or caregiver. Part I concerns *Non-motor experiences of daily living.* Part II concerns *Motor experiences of daily living.* Part III consists of a motor examination of Parkinsonian signs with a score range of 0 (normal) to a maximum of 132 (most severe disability), which may be done in the *on*- and *off*- medication states. Part IV comprises rating of motor complications (Goetz *et al.*, 2008).

- The UDysRS is a clinimetrically sound rating scale for dyskinesia in PD, demonstrating acceptable levels of internal consistency and inter- and intra-rater reliability (Goetz, Nutt & Stebbins, 2008). It consists of four parts; Part I: Historical Disability (patient perceptions) of On-Dyskinesia impact (maximum 44 points); II: Historical Disability (patient perceptions) of Off-Dystonia impact (maximum 16 points); III: Objective Impairment consisting of rating severity of dyskinesia in defined distributions over seven body regions, based on four observed activities comprising: communication, drinking, dressing, and ambulation (maximum 28 points). The total score is the sum of the highest impairment scores in each body region; IV: Objective Disability in carrying out activities in Part III (maximum 16 points). The type of dyskinesia (choreic or dystonic) is also noted.

- The Timed 10m SSW assessment is a measure of the time it takes for the patient to stand up from a seated position, walk 10 metres in a straight line, turn around and return to the seated position.

- The Bradykinesia Akinesia Incoordination (BRAIN) test is a validated computer keyboard-tapping task developed for assessing the effect of symptomatic treatment on motor function in Parkinson's disease. The test uses a computer keyboard to measure the speed and accuracy of alternately tapping two keys as rapidly and accurately a possible over a 30 second time period (Noyce *et al* , 2014). The online version of the test used in the study can be found at: https://predictpd.com/en/braintest.

- The NMSS is a validated tool to collect data on non-motor symptoms that may be experienced by patients with PD and uses 30 questions divided into 9 domains including cardiovascular symptoms, sleep and fatigue, mood and cognition, perceptual problems, attention/memory, gastrointestinal symptoms, urinary symptoms, and sexual function. Each symptom is scored in terms of severity (0-3) and frequency (1-4), and the product of these for each question is summed to give domain and overall scores.

- Verbal Fluency was assessed with recordings of phonemic and semantic fluency in a 60-second duration. The phonemic score consisted of the mean of three ratings using the letters /f/, /a/ and /s/. The semantic score consisted of the categories of *Animals* and *Boys' names*.

- The PDQ-39 is a 39-item questionnaire and is a patient reported measure of health status and quality of life. It is a validated disease-specific health status measure. Each item on the questionnaire is categorised by the patient into the

categories *Never, Occasionally, Sometimes, Often,* or *Always*. These are assigned a corresponding score of 0-4 and are summed to give an overall score.

- The FOG-Q is a self-reported questionnaire comprising of 6 questions on aspects of walking and freezing, each rated from 0 (normal) to 4 (most severe), giving a maximum possible aggregate score of 24.

- TEED was calculated using the formula [Voltage² x Pulse Width x Frequency/ Impedance], as it applies to voltage-constant devices, using individual active contact impedances. The sum of both sides is reported to give a value in microjoules/second (Koss *et al.*, 2005).

Exploratory outcomes included ratings of perceptual characteristics of speech using scales developed by Darley, Aronson, and Brown (1969). This included scoring each of the following characteristics of speech out of 7 by a speech therapist to give a composite score out of 42: articulation, respiration, resonance, phonation, prosody and rate. Perceptual characteristics were scored using a 60-second monologue (MON/42) of the patient's speech on a subject of their choice.

3.4.16 Statistical Analysis

All analyses were performed by a blinded researcher in consultation with the delegated statistician, according to a predefined statistical analysis plan with an intention-to-treat approach. These individuals remained blinded to the randomisation allocation until all data entry and exportation from the database were complete. The mean and standard deviation for each outcome measure under the 30µs and 60µs conditions are presented. A repeated-measures analysis of covariance (ANCOVA) model was used to examine any differences in SIT (%) between ratings at baseline and the two PW conditions at the end

of each four-week period of treatment, adjusting for DBS screening order as a covariate. Subsequent pairwise comparisons of assessments at each PW setting with the other and with baseline were performed using paired t-tests if indicated.

Analyses of the secondary and exploratory outcome measures were performed using the same approach outlined above.

No interim analyses were planned, and no subgroup analyses were performed.

Statistical significance was set to $P < .05$. Data were checked for normality, and Mauchly's test was used to verify sphericity in repeated-measures analysis of covariance for all outcome data. The Bonferroni method was used to correct for multiple comparisons. All data analysis was done using SPSS Statistics version 21 (IBM Corp., Armonk, NY).

3.4.16 Approach to missing data

Reasons underlying any missing data are reported. No imputation was performed. Protocol deviations and their reasons were reported to the sponsor using the appropriate documentation.

3.5 Results

Between May 2 and August 21, 2018, 18 patients were screened for eligibility, and 16 were enrolled in the trial. The two excluded patients fell below the lower SIT threshold and did not meet eligibility criteria for speech intelligibility. All 16 enrolled participants completed the trial. Fourteen were male, and the mean (± SD) age at enrolment was 65.4 ± 6.4 years, with disease duration of 20.4 ± 6.6 years, duration of DBS of 6.9 ± 4.4 years and baseline UPDRS-III score at study baseline of 39.4 ± 10.9 on medications.

3.5.1 Monopolar review data

Screening data from the monopolar review carried out prior to randomisation showed that the mean efficacy threshold was 4.8 ± 1.1 V at PW30, and 3.3 ± 0.7 V at PW60. The side effect thresholds were 6.5 ± 1.1 V and 4.2 ± 0.8 V respectively (for immediately apparent symptoms). The mean therapeutic window of 1.7 ± 1.1 V at PW30 was significantly greater than 0.94 V ± 0.6 V at PW60 [t (33) =5.0, $P < .001$]. Individual thresholds and therapeutic windows for each participant are listed in Table 1.

Table 3.1*: Monopolar review data showing efficacy and side effect thresholds, and therapeutic windows on each pulse width condition for individual participants

Patient No.	ET30		ST30		ET60		ST60		TW30		TW60	
	R	L	R	L	R	L	R	L	R	L	R	L
1	4.5	4.0	5.5	6.0	3.3	3.0	3.5	3.5	1.0	2.0	0.2	0.5
2	4.3	5.5	5.5	7.0	3.0	3.5	3.5	4.3	1.2	1.5	0.5	0.8
3	4.5	5.0	7.5	8.5	4.3	4.1	5.6	4.7	3.0	3.5	1.3	0.6
4	7.0	6.0	8.5	7.5	4.0	3.5	4.9	4.5	1.5	1.5	0.9	1.0
5	3.0	4.0/ 4.0 [B]	6.0	5.0/ 6.0 [B]	2.5	2.0/ 3.0 [B]	3.5	2.5/ 4.0 [B]	3.0	1.0/ 2.0 [B]	1.0	0.5/ 1.0 [B]
6	5.0	4.0/ 5.0[B]	7.0	6.5/ 6.0[B]	4.0	3.0/ 3.0 [B]	5.0	4.5/ 2.8 [B]	2.0	2.5/ 1.0 [B]	1.0	1.5/ -0.2[B]
7	5.3	3.5	6.9	6	3.3	2.2	4.3	3.8	1.6	2.5	1.0	1.6
8	3.5	2.1	5.0	5.5	1.8	1.7	3.7	2.7	1.5	3.4	1.9	1.0
9	5.5	6.2	5.6	6.0	3.4	3.7	3.8	4.3	0.1	-0.2	0.4	0.6
10	6.5	6.5	8.0	8.0	4.3	4.0	5.5	5.0	1.5	1.5	1.2	1.0
11	3.8	3.7	9.0	5.5	2.7	2.7	6.0	3.5	5.2	1.8	3.3	0.8
12	5.0	7.0	6.5	7.5	4.0	4.5	5.0	5.0	1.5	0.5	1.0	0.5
13	5.5	5.5	6.0	6.5	3.5	3.7	4.3	4.3	0.5	1.0	0.8	0.6
14	5.5	5.0[A]	5.3	5.9[A]	3.8	4.1[A]	5.0	4.8[A]	-0.2	0.9 [A]	1.2	0.7[A]
15	5.0	4.5	7.5	7	4.0	3.0	4.5	4.5	2.5	2.5	0.5	1.5
16	4.7	3.4	6.2	5	3.4	2.3	4.1	3.3	1.5	1.6	0.7	1.0
Mean	4.80		6.51		3.30		4.24		1.70		0.94	
SD	1.14		1.09		0.75		0.83		1.11		0.59	

***Legend**:*
ET: Efficacy threshold; ST: Side effect threshold; TW: Therapeutic Window; A: Double-monopolar configuration; B: Interleaved configuration

*All values are in Volts at the Right (R) and Left (L) STN electrodes respectively.

3.5.2 Primary outcome

The mean SIT scores were 64.0 ± 10.9 at baseline, 63.9 ± 18.5 at PW30, and 65.3 ± 22.9 at PW60. There was no significant difference in ratings between conditions (*P* = .25) after adjusting for screening order. Eight patients had a higher (improved) SIT score on the PW30 treatment condition and seven on PW60, while one had equal scores on both conditions. Table 2 shows patient characteristics, randomisation block, and DBS settings on each PW condition, with changes in individual SIT scores across conditions.

3.5.3 Secondary outcomes

There were no significant differences between baseline and the two treatment conditions in MDS-UPDRS I, III and IV, Unified Dyskinesia Rating Scale, verbal fluency, perceptual speech ratings, total electrical energy delivered, Non-motor Symptoms Severity Scale, timed 10 metre Sit-Stand-Walk, timed hand taps, Parkinson's Disease Questionnaire summary index, and Freezing of Gait Questionnaire scores [Table 3]. The ANCOVA model indicated a statistically significant difference in MDS-UPDRS part II between the three sets of ratings (*P* = .02), but subsequent corrected pairwise comparisons did not reveal a significant difference between any two conditions. There were no differences noted between conditions in any of the PDQ-39 subscales or individual non-motor symptom assessment scale domains.

***Table 3.2*: Patient characteristics, DBS settings, and primary outcome at the end of each treatment period**

No.	Group*	Age	Sex	Duration of PD (years) ǂ	Levodopa equivalent dose (mg)	Duration of DBS (months) ǂ	Stimulation parameters (Amplitude at Left STN; Right STN)			Sentence Intelligibility test (SIT) %		
							PW30	PW60	Frequency	Study baseline	PW30	PW60
1	1	52	M	16	593	30	4.0; 4.5 V	3.0; 3.3 V	130Hz	78	83	73
2	3	68	M	17	125	66	5.5; 4.3 V	3.5; 3.0 V	130Hz	68	88	82
3	4	60	F	25	1280	144	5.5/5.5[A]; 4.5 V	4.3/4.3[A]; 2.9 V	80Hz	68	65	73
4	2	62	M	13	895	63	6.0; 7.0 V	4.0; 4.6 V	80Hz	78	68	75
5	2	72	M	16	895	50	4.0/4.0[B]; 3.5 V	2.4/3.0[B]; 2.3 V	100Hz	58	38	53
6	3	67	M	22	1350	88	5.0/4.5[B]; 6.0 V	3.0/3.0[B]; 4.5 V	60Hz	68	32	32
7	1	64	M	16	600	22	3.5; 5.1 V	2.2; 3.2 V	80Hz	80	82	62
8	4	72	M	13	1093	25	3.4; 2.0 V	2.3; 2.3 V	130Hz	52	68	72
9	3	72	M	24	1348	106	5.7; 5.2 V	3.8; 3.3 V	70Hz	55	63	88
10	2	67	M	28	1000	154	6.5; 6.5 V	5.3; 4.5 V	80Hz	51	30	14
11	1	62	M	20	639	74	3.8; 3.8 V	2.8; 2.8 V	130Hz	55	50	32
12	4	56	M	19	690	78	7.0; 5.0 V	4.7; 4.2 V	80Hz	72	88	82
13	3	62	M	22	750	59	5.5; 5.5 V	3.9; 3.7 V	130Hz	62	72	58
14	4	74	M	32	850	188	5.0/5.0[A]; 5.3 V	4.1/4.1[A]; 3.8 V	80Hz	50	55	96
15	2	75	F	33	800	159	4.5; 5.0 V	4.0; 4.0V	80Hz	77	68	88
16	1	62	M	11	1314	29	3.4; 4.8 V	2.3; 3.5 V	130Hz	52	72	65
Mean (SD):		**65.4 (6.4)**		**20.4 (6.6)**	**888.9 (336.2)**	**83.4 (52.5)**				**64.0 (10.9)**	**63.9 (18.5)**	**65.3 (22.9)**

Legend:
* Randomisation block ǂ Duration at enrolment A: Double-monopolar configuration B: Interleaved configuration

***Table 3.3*: Secondary and exploratory outcomes at study baseline and at the end of each treatment period, on standard (PW60) and short pulse width (PW30) settings**

Outcome ǂ	Baseline	PW30	PW60	*P* value*
MDS-UPDRS I	12.1 (7.2)	9.4 (5.1)	11.0 (6.6)	.47
MDS-UPDRS II	19.2 (5.1)	16.1 (7.3)	16.4 (7.5)	.02
MDS-UPDRS III	39.4 (10.9)	35.2 (11.5)	34.6 (14.5)	.67
MDS-UPDRS IV	4.8 (4.9)	4.9 (4.0)	3.8 (4.3)	.12
10m SSW (s)	21.7 (6.0)	21.1 (7.1)	25.3 (22.1)	.47
UDysRS	0.3 (1.3)	1.6 (5.3)	0.6 (1.7)	.34
Hand taps in 30s (R)	39.1 (8.5)	41.8 (11.2)	44.0 (10.7)	.07
Hand taps in 30s (L)	37.7 (8.8)	39.1 (9.2)	40.1 (8.6)	.92
NMSS	52.6 (34.4)	49.6 (30.8)	53.1 (38.5)	.46
PDQ-39 SI	6.3 (2.5)	5.4 (2.3)	5.1 (2.8)	.37
FOG-Q	10.6 (4.7)	9.6 (4.8)	9.3 (5.4)	.73
Speech: Perceptual	26.4 (3.7)	24.6 (6.9)	25.6 (5.8)	.99
VF -Phonetic	10.8 (3.7)	11.8 (3.6)	11.9 (4.3)	.51
VF -Categorical	15.2 (5.2)	15.4 (5.8)	14.2 (7.3)	.36
TEED (μJ/s)	174.8 (80.0)	166.0 (66.7)	171.6 (76.5)	.97

ǂ *Outcomes presented as group means (SD) for each rating scale. All scores are on medication and on stimulation.*
**Difference between treatment conditions, adjusted for screening order*

3.5.4 Adverse events

A total of 14 adverse events were recorded in 8 patients, with 6 (43%) during the PW30 and 8 (57%) during the PW60 treatment period [Table 4]. These were expected effects of changes in stimulation settings, and all resolved with minor adjustments. No serious adverse events occurred. Adjustments to DBS settings were made for seven patients within the trial period, six of which were during the PW60 treatment condition and one during PW30. At the end of the trial, 10 patients went back to their baseline settings, 4 on the new PW60 trial settings and 2 on the PW30 trial settings. No changes in medications were made for any participant during the trial.

***Table 3.4*: Number of adverse events on each treatment condition**

Adverse event	PW30	PW60
Deterioration in motor symptom control	3	5
Deterioration in gait and balance	2	1
Increase in dyskinesias	1	0
Persistent paraesthesias	0	1
Restlessness	0	1
Total	**6**	**8**

3.6 Post-Hoc Analyses

In order to examine any subgroup effects with regards to the primary outcome, data were further scrutinised beyond the predefined analyses. These were done to generate potential hypotheses on the characteristics of patients amongst the diverse group in the trial who may have benefited from short PW. The first consideration was if there were any clear differences in patients' baseline characteristics between those who may have benefited from short PW and those who did not. Patients were classified into responders and non-responders; responders were defined as those who had an improved SIT% score in the PW30 condition compared to scores at both baseline and the PW60 condition. There were 6 responders; the distinct characteristics of patients in this group, as apparent from Table 2, included (i) a relatively short duration of DBS, and (ii) being likely to have a standard frequency setting of 130Hz rather than low frequency settings in the range of 60 - 100Hz.

The mean duration of DBS amongst responders was 47.3 ± 23.3 months (3.9 ± 1.9 years) compared to the duration amongst non-responders of 102.9 ± 53.9 months (8.5 ± 4.5 years). There was a significant difference in mean duration [P = .014] between the two groups. Furthermore, all responders had a DBS duration of less than 7 years.

The disease duration was also compared to see if these differed between the two groups; the mean duration of PD was 16.8 ± 3.7 years for responders versus 22.6 ± 7.2 years for non-responders [P = .046].

Another method of ascertaining whether baseline patient or disease characteristics may have played a part in response to the intervention of stimulation with short PW is to examine any correlations between change in the primary outcome between the two conditions and these baseline characteristics, for the entire set of patients. These were

done for patient age, disease duration, duration of DBS therapy, UPDRS-III at baseline, LEDD, and baseline severity of dysarthria. The results are presented in table 3.5.

***Table 3.5*: Correlation between baseline characteristics and change in SIT score with short PW**

Baseline characteristics	Pearson's correlation of baseline variable with change in SIT score (PW30 – PW60)
Patient age	r = -.63, *P* = .008
Duration of PD	r =, -.47, *P* = .069
Duration of DBS	r = -.56, *P* = .023
Baseline UPDRS-III	r = -.33, *P* = .21
LEDD	r = -.33, *P* = .22
Severity of dysarthria (Baseline SIT score)	r = -.21, *P* = .43

A significant negative correlation was found with improvement on PW30 settings and patient age, and duration of DBS; indicating that those with lower age and shorter DBS duration may be more likely to respond with an improvement on switching to PW30 settings.

With regards to baseline frequency settings, 5 out of 6 patients on the standard 130Hz baseline frequency settings had improved SIT scores on PW30 compared to the PW60 condition. Within the subgroup of 6 patients on standard frequency, the mean SIT scores were: 72.2 ± 13.2 at PW30 and 63.7 ± 17.5 at PW60; [t(5) = 2.75, *P* = .041], as shown in figure 3.4.

Additionally, the charge per pulse (Qp) at the efficacy threshold for PW60 was 246.6 ± 121.2 nC vs. 170.2 ± 77.3 nC for PW30 [t (31) = 8.5, *P* < .001].

3.7 Discussion

In this double-blind crossover trial of short versus conventional pulse width subthalamic nucleus stimulation in PD patients with moderately dysarthric speech, there was no evidence to indicate an overall clinical advantage of 30μs DBS in the primary outcome of speech intelligibility.

There were also no differences found in motor assessments, non-motor symptoms, and quality of life measures after four weeks of treatment using short PW stimulation. The therapeutic window during the monopolar review was significantly greater at 30μs compared to 60μs, consistent with data presented in Chapter 2 and the findings of other studies (Steigerwald *et al.*, 2018; Bouthour *et al.*, 2018).

While the acute effect of short pulse width on the therapeutic window has been well documented recently, this trial was the first to examine short PW stimulation in STN DBS beyond the setting of an acute challenge. The study was not designed to assess efficacy; however, the data suggest that using a PW of 30μs has a sustained therapeutic effect similar to 60μs PW at four weeks' duration, given that no significant differences were noted in UPDRS-III scores between the two conditions. An acceptable safety profile was also demonstrated with the use of 30μs, with a similar number of adverse events to that during the 60μs treatment period. All patients tolerated short PW settings well during the course of the trial, with no premature terminations and only one readjustment required during this treatment period.

These findings may have various implications in terms of the clinical utility of this programming feature, as well as for future research. Firstly, it may be that short PW stimulation provides no benefit over conventional stimulation in chronically implanted patients with dysarthria. However, this was a pilot trial and utilised broad recruitment criteria, and therefore the data were scrutinised to generate potential hypotheses of

effects that may differ among subgroups of patients. A post-hoc evaluation showed that responders (i.e. those participants who had improved SIT scores at PW30 compared with both baseline and PW60 scores) had a significantly lower mean duration of DBS of compared to non-responders. This observation indicates that duration of DBS may be an important factor in predicting reversibility of stimulation induced dysarthria using PW30 DBS. Disease duration may also be a factor, although the difference between those who had improved scores at PW30 versus those who did not was not as marked as for DBS duration, as evident from Table 2 and the post-hoc analyses results. This may be because progression of PD is very variable across patients, whereas duration of DBS therapy may be a more consistent marker of the stage of disease, indicating the development of motor complications, regardless of the overall course of disease progression.

Furthermore, while patients were selected on the basis of worsened dysarthria following DBS implantation for at least 12 months, decline in speech intelligibility in PD patients is multifactorial and also comprises hypophonia, festinant speech, and consonant imprecision, which may be due to disease progression rather than DBS therapy. It is plausible that these components contribute relatively more in those with longer duration of disease and duration of DBS therapy than reversible stimulation induced dysarthria.

Additionally, proposed mechanistic effects of STN stimulation apart from depolarisation block and functional target inhibition amongst others, include plasticity changes (Hamani *et al.*, 2017), and it is possible that such longer lasting DBS effects render patients with long duration since implantation less responsive to parameter changes than those at earlier stages. The relative contributions of stimulation induced dysarthria from disease progression in this group cannot be distinguished. One method of verifying the degree of stimulation induced side effects is to assess patients on and off

stimulation, which was not done in this study. However, this presents certain challenges and limitations: firstly, this approach may be applicable to side effects that are acutely responsive, but not to those that gradually develop over long periods of stimulation, including chronic dysarthria (Aviles-Olmos et al., 2014; Tripoliti et al., 2014). Secondly, there are practical difficulties with assessing these side effects with patients being off stimulation. For example, should the assessments be done in the off- medication state, which is difficult to tolerate for more than short periods for most patients, and in which case symptoms such as speech and gait significantly deteriorate and ratings would be confounded; or in the on- medication state, where this would be complicated by medications needing to be adequately adjusted to account for the lack of stimulation to ensure patients are in the optimal on state in order to isolate stimulation effects and not risk confounded ratings of speech and gait, for example, from suboptimal therapy.

Another important point of consideration that came to attention with post-hoc analyses is the diversity of baseline frequency settings amongst the study participants. Only six patients had the standard starting frequency of 130Hz, while the remainder had been changed to lower frequency settings in an attempt to reduce side effects during previous clinical optimisation. It is known that low frequency stimulation in PD patients can improve axial symptoms and speech intelligibility (Grover et al., 2018; Khoo et al., 2014; Ramdhani et al., 2015; Xie, Kang, & Warnke, 2012; Xie et al., 2017, 2015); whether this affected the degree to which dysarthria responded to further alteration in stimulation parameters is not clear. However, it is worth noting that five of the six patients at 130Hz had higher speech intelligibility ratings at PW30 than at standard PW. Post-hoc subgroup analysis indicated a significant difference in speech intelligibility ratings between the two PW conditions amongst those on standard baseline frequency settings. This observation would support the notion that there is a higher scope for reduction of side effects using short PW in patients at standard frequency stimulation than those at low frequency, possibly due to a degree of pre-existing reversal of

stimulation induced side effects in the latter group, which may not be amenable to further improvements with other parameter changes.

Additionally, while it is possible that a change in the patients' 60µs settings between their chronic (baseline) settings and those used for the 4-week trial period may have resulted in optimisation of speech and potentially negated a difference with the 30µs condition, the lack of a significant difference between baseline and either PW condition would argue against this.

As proposed in Chapter 2, one of the mechanisms by which the therapeutic window is increased when using short PW stimulation, is that a lower charge is required to achieve the same therapeutic effect compared to standard PW. This finding has been confirmed in other studies (Steigerwald *et al.*, 2018; Bouthour *et al.*, 2018). Given that stimulation settings tend to be increased over time in chronic patients, it is possible that the reduction in charge at thresholds for the therapeutic effect at short PW in these patients is not sufficient to alleviate side effects due to a higher absolute efficacy threshold and therefore electrical charge delivered in chronic patients. Comparison of charge per pulse delivered on each PW condition was not included in the trial outcomes; however, post - hoc calculations are consistent with data presented in Chapter 2, and other studies: the mean charge per pulse at PW30 of 170 nanocoulombs (nC) was significantly lower compared to 247 nC at PW60. Studies of short PW in tremor patients with thalamic stimulation have similarly showed a lower charge per pulse at the efficacy threshold, and a corresponding lower modelled volume of neural tissue activation (Moldovan *et al.*, 2018). A lower charge required for therapeutic effect implies better selectivity of neural elements responsible for these effects using short PW, as these measures are equally affected by amplitude, but the same effects are not achieved by lowering amplitude at higher PWs.

The main limitation of this study and its interpretation is its small sample size, which restricts conclusions on any potential effects of the interventions within subgroups and on efficacy. In addition to this, the intervention lasted 4 weeks, and while this is longer than those of previous studies on short PW, it is possible that an extended duration may have produced different results, in particular, as side effects in many of these patients had developed over years of DBS therapy. Moreover, while acute side effects are more clearly time-locked to stimulation, this is not always the case with chronic dysarthria, particularly with the medial type of speech disturbance (Tripoliti et al., 2011; 2014), and the degree to which each participant had reversible stimulation induced speech impairment affecting intelligibility was not necessarily apparent at enrolment. Additionally, while the inclusion criteria defined a relatively common and large range of impairment of speech intelligibility, the results are not necessarily generalisable to patients with less or more severe dysarthria than those included in the trial.

Nevertheless, a rigorous protocol of optimising stimulation settings on each PW condition on- and off- medications was utilised, and allowance made for necessary adjustments subsequently to optimise clinical benefit and ensure long term tolerability of each setting. While only two patients elected to remain on 30µs setting at the end of the trial, a further three patients requested to go back on 30µs settings at subsequent routine outpatient visits and have persisted with this as their preferred setting. It seemed one of the factors many patients elected to go back to their baseline settings rather than one of the trial settings, was that the perception of any possible benefit from trial settings was offset or negated by what was experienced as a disruptive process consisting of a lengthy monopolar review while being off medication, switching between settings on multiple occasions during the trial, and having the protocol-permitted adjustments required during the trial period to achieve an optimal new setting; all in the context of an often precarious baseline state.

In conclusion, this trial showed no overall benefit of using short PW in a heterogeneous cohort of chronically stimulated STN DBS patients with dysarthric speech, but indicates a good safety profile and sustained therapeutic effect, and paves the way for longer term efficacy trials and studies. Additionally, while post-hoc analyses cannot be used to draw conclusions, the relatively broad inclusion criteria allowed identification of groups of patients who may potentially benefit from short PW, and more data focussing on these groups is required. In particular, further exploration of the utility of short PW in those early in the course of DBS therapy and those on standard frequency settings is warranted.

CHAPTER 4

The Utility of Directional Steering and Short Pulse Width in Alleviating Subthalamic Nucleus Stimulation Induced Side Effects

4 – Summary of chapter

In this chapter, the effect of optimisation using directional steering, short PW, and the combination of both these features on stimulation induced side effects of dysarthria, dyskinesia, and pyramidal symptoms is evaluated. Patients on conventional settings who experienced these side effects at least 3 months following surgery and were confirmed to have stimulation induced worsening of symptoms had optimisation of their settings using each of these features individually and in combination. They remained on the setting that produced the greatest benefit (if any, compared to baseline) while maintaining at least an equivalent therapeutic effect, and were followed up at 6 months. There was a significant improvement in all three groups of side effects from the optimisation process, both acutely and at 6 months. The most common configuration used was the combination of short PW and directional steering.

In a secondary analysis, the side effect assessments on each of the 4 configurations during the optimisation session were compared (baseline/ring mode at standard PW, ring mode at short PW, directional at standard PW, and directional at short PW). In the dysarthria and dyskinesia groups, each of the three alternative configurations had significantly improved mean scores compared to baseline conventional settings, and in the dyskinesia group, the combination (directional with short PW) additionally had significantly improved scores over short PW alone. In the pyramidal side effect group, only directional settings (both with short and standard PW) showed significant improvements over conventional settings.

Directional settings also resulted in higher total electrical energy delivered at both PWs compared to their ring mode counterparts.

4.1 Introduction

Apart from the expansion of the stimulation parameter range enabling the use of pulse widths (PW) shorter than the conventional lower limit of 60µs, another programming feature that has become available in recent years that may offer the potential to reduce adverse effects of stimulation is directional steering, made possible by the use of leads with segmented contacts, which enable steering of current in the plane perpendicular to the lead (Pollo *et al.*, 2014; Hariz, 2014; Kühn & Volkmann, 2017). As reviewed earlier, current commercially available systems have a "1- 3 -3 -1" design, where the tip and upper most contacts are of a conventional ring design, and the two levels of contacts in between consist of three equal segments on each level [Chapter 1: Figures 1.4 and 1.5]. With the Boston Scientific Vercise PC™ and Gevia™ systems, the amount of current to each segment can be independently controlled by adjustments in small intervals of current amplitude or the percentage of total current directed to the segment. A similar system is available from St Jude Medical with the Infinity™ device, although this does not feature multiple independent current control, and is not widely used at our centre.

When the three segments have equal amounts of current split between them, this emulates the conventional omnidirectional or 'ring mode' configuration with an approximately spherical field of stimulation. At the fully directional end of the spectrum, a single segment can be configured to have 100% of the current. In between these, various possible configurations of activating two or more segments with hundreds of thousands of permutations of fractionating current to each segment in different proportions and in different directions are possible. An example of the programming platform of a device with directional leads is shown in figure 4.1.

With regards to alleviating stimulation induced side effects, the obvious utility of this feature is the potential to steer away from structures activated by stimulation in ring mode that may be responsible for these. However, so far, this theoretical application

does not have available data to substantiate a benefit in patients with existing stimulation induced side effects. Such a programming strategy would also need to ensure that the therapeutic benefit of stimulation is not compromised.

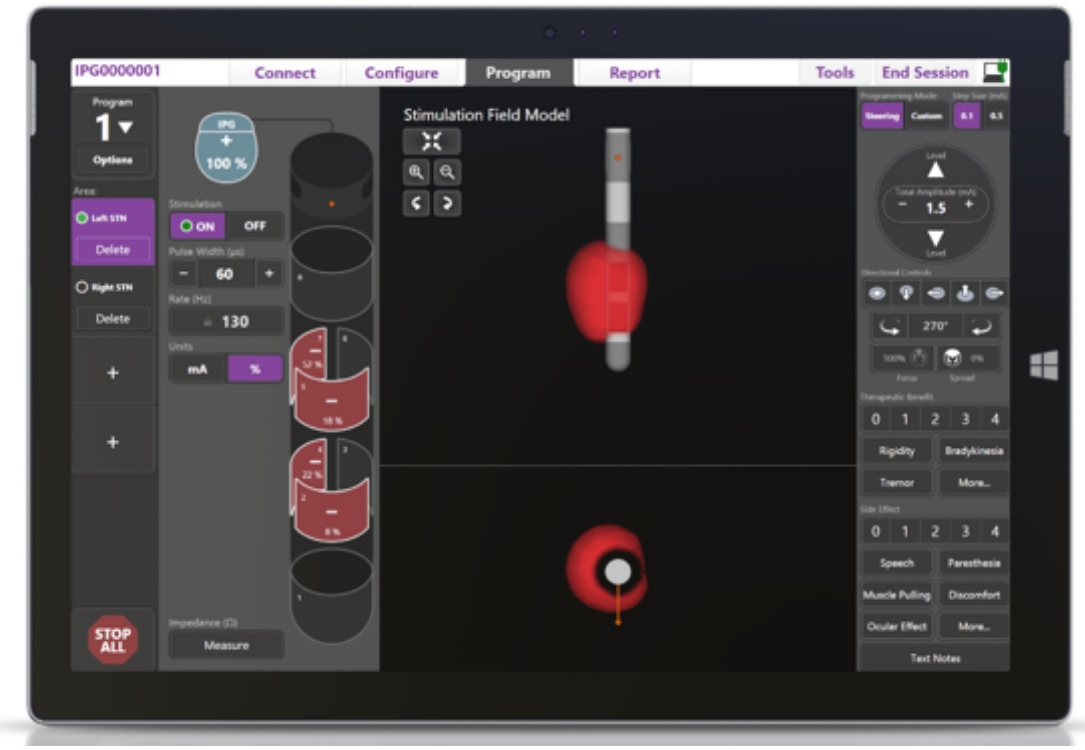


Figure 4.1. **Programming platform of the Boston Gevia™ directional system**

Adapted from *http://www.bostonscientific.com/en-EU/products/deep-brain-stimulation-systems/vercise-gevia-with-neural-navigator.html*

Early data on the use of directional systems focussed on feasibility and efficacy. Intra-operative studies with various designs of multi-electrode and segmented leads provided data on the feasibility of directional systems, which subsequently led to the development of commercially available devices. An influential factor that led to the tripartite design rather than other designs with a larger number of segmented contacts was the fact that as the surface area of electrodes got smaller, the impedances became exponentially larger, resulting in significantly increased energy consumption with decreasing size of the segments. With multi-electrode leads with very small contacts such as the 32-contact Medtronic Sapiens™ used in experimental studies, the voltage

requirement of stimulating using a single contact exceeds the output deliverable by current IPGs (Alonso *et al.*, 2016; Kühn & Volkmann, 2017). Furthermore, the charge density around segmented contacts with smaller surface areas is also significantly higher, and very small segments have the potential to exceed levels of charge density considered safe to avoid tissue damage (Buhlmann *et al.*, 2011). Other considerations include the inevitable spread of current beyond the surface boundaries of the segment due to the high metal conductance of the lead they are attached to, and whether smaller segments provided any significant differences in clinical effect, as well as the increasing complexity of programming with greater numbers of segments.

Both intraoperative data and subsequent clinical studies have confirmed that the TW is expanded by the use of the best directional segment compared to conventional ring mode stimulation (Pollo *et al.*, 2014; Contarino *et al.*, 2014; Steigerwald *et al.*, 2016; Dembek *et al.*, 2017). Efficacy of motor symptom control has been demonstrated to be equivalent at up to 6 months follow up with best directional compared to conventional stimulation (Dembek *et al.*, 2017). However, given the higher cost, complexity, and programming burden involved, the utility of directional stimulation in reversing stimulation induced side effects in the clinical setting needs to be established, as its true translatable benefit over conventional stimulation may lie herein, rather than in equivalence of efficacy or a theoretically wider TW.

In devising a method to optimise settings and collect such data, one is faced with a myriad of strategies in terms of the programming approach to use, given the vast number of possible permutations. This is, of course, in addition to deciding on the patient population and side effects to study. This can be simplified by some basic considerations: firstly, if the purpose of the programming strategy is to direct current away from side effect inducing structures, the initiation of stimulation must be demonstrably responsible for the side effect. While this approach has its limitations as

discussed in the last chapter, it importantly excludes patients with common symptoms of PD and its progression that may pose as DBS side effects, where stimulation is not the major causative factor, and therefore pursuing reversibility by changing stimulation parameters would be a futile exercise. Inclusion of these patients may confound findings of a study aiming to determine if stimulation induced side effects are able to be reversed with this programming technique.

Secondly, the programming approach needs to be balanced between attempting to achieve the best possible outcome entailing lengthy technical iterations of settings for individual patients, and the consequent increase in patient fatigue and inability to usefully cooperate, which results in the assessed outcomes being compromised. Another factor that plays a role in this regard is determining how much these small iterations influence clinical symptoms, whether they be therapeutic or adverse effects. There are fewer data to ascertain this; however, initial observations and early clinical experience with directional devices suggest that in most patients, even current shifts in steps of up to 25% across adjacent segments often produce negligible changes in clinical effect. Given that there is spread of current around the high-conductance metal lead to some degree even with activation of a single segment, and that from patterns seen on stimulation field modelling this seems to increasingly resemble the spherical shape of ring mode stimulation at higher amplitudes, it would follow that in pursuing a more selective region of stimulation to avoid activation of unwanted neural elements, the narrowest field that is able to maintain the same therapeutic effect should be utilised. With these considerations in mind, in the study that follows, a single segment on a single vertical level was used for directional stimulation unless there was a compromise in therapeutic efficacy that necessitated directing additional current to an adjacent segment.

There are several patients who experience side effects within months of initiating DBS therapy, and a larger number within the first 1 – 3 years. Conventional approaches to managing these have included reducing the amplitude of stimulation to an acceptable level (and supplementing therapy with a compensatory increase in medications if necessary), using alternative contacts, using interleaving or bipolar configurations, or attempting to stimulate in certain regions to address specific problems; such as the deepest contacts near the substantia nigra for refractory gait freezing, and the dorsal-most contacts for refractory dyskinesia (Herzog *et al.*, 2007; Weiss *et al.*, 2013; Valldeoriola *et al.*, 2019; Picillo *et al.*, 2016a; Aquino *et al.*, 2019). However, these approaches often entail some compromise in control of other symptoms or overall efficacy. The use of low frequency settings has been successful in improving some axial problems, but its use is usually limited to this group of side effects, and it may not be an option for patients who have a prominent tremor, as tremor control can be compromised with low frequency (Moreau *et al.*, 2008; Khoo *et al.*, 2014; Xie *et al.*, 2015; Zibetti *et al.*, 2016).

In the previous randomised crossover trial on short PW in chronic dysarthric patients, while there were no differences overall in the group of patients studied, there were indications from post-hoc evaluations that patients with a shorter duration of DBS therapy and those who did not have prior optimisation of settings with a change to low frequency may be more likely to benefit from short PW. An intervention with novel techniques in these patients, in the first few months to years of DBS therapy, may open up a useful new avenue if successful in reducing or reversing adverse effects. Apart from dysarthria, commonly encountered stimulation induced side effects that are problematic and those that can be objectively verified to be induced by stimulation include dyskinesia, and pyramidal tract symptoms. The latter is due to activation of the corticobulbar or corticospinal tracts which run through the posterior limb of the internal capsule and cerebral peduncle, and surround the anterolateral and lateral aspects of the

STN (Tommasi *et al.*, 2008; Mahlknecht *et al.*, 2017), usually manifesting as contralateral facial and upper limb tonic muscle contractions.

Despite being commercially available for over 5 years, it is not clear what the roles of short PW and directional stimulation in STN DBS programming and troubleshooting algorithms are (Picillo *et al.*, 2016a; Volkmann, Moro & Pahwa, 2006). Furthermore, while each of these features is known to expand the TW, by different postulated mechanisms (Groppa *et al.*, 2014; Dembek *et al.*, 2017), the effect of combining them is not known: is there an incremental benefit due to a cumulative or synergistic effect?

The objective of this study is to evaluate whether using directional steering and short PW, individually or in combination, can improve stimulation induced side effects of dysarthria, dyskinesia, and symptomatic pyramidal muscle contraction compared to conventional stimulation in PD patients treated with STN DBS.

4.2 Methods

Patients with PD treated with bilateral STN DBS with Boston Vercise PC™ or Gevia™ systems using directional leads at the National Hospital for Neurology and Neurosurgery in the 24-month period from July 2017 who experienced stimulation induced dysarthria, dyskinesia, or symptomatic pyramidal muscle contraction were included. These patients, who had persistent side effects at least 3 months after surgery despite optimisation of conventional settings, went through a 3-day DBS optimisation session using directional stimulation, short PW at 30μs, and the combination of both these features. A total of 32 patients underwent optimisation: 13 patients had dysarthria, 15 had dyskinesia, and 5 had pyramidal side effects (including one with concurrent dysarthria). The mean duration of STN DBS therapy was 7.9 ± 7.7 months [Range 3 - 32 months]. Baseline characteristics are shown in table 4.1.

***Table 4.1*. Baseline characteristics of patients at optimisation**

Age	60.1 ± 8.6 years
Sex	22M; 10F
Preoperative UPDRS-III (OFF/ON medication)	47.4 ± 13.5/ 16.5 ± 7.1
Duration since DBS surgery	7.9 ± 7.8 months
Levodopa equivalent daily dose	696.3 ± 333.33 mg
Stimulation related side effect	Dysarthria: n= 13 Dyskinesia: n= 15 Pyramidal SE: n= 5

4.2.1 Surgery

Patients underwent surgery under general anaesthesia without micro-electrode recordings, using the Leksell frame and an MRI-guided and MRI-verified technique. Using this technique, the previously reported mean perpendicular error between planned target coordinates and electrode trajectory was 0.9 ± 0.5mm (Holl *et al.*, 2010; Foltynie *et al.*, 2011). All patients in the series had MRI verification of electrode placement following implantation and these were confirmed to be within 1.5mm of the intended superolateral STN target.

4.2.2 Initial post-operative programming

A monopolar review in ring mode was conducted and stimulation was initiated in the early post-operative period (within one week of surgery). The optimal vertical level of contacts was identified based on efficacy and side effect profile, and this was activated using a conventional ring mode configuration at a PW of 60µs and frequency of 130Hz. The amplitude was titrated in an iterative manner over subsequent weeks alongside reduction in dopaminergic medications, to obtain optimal clinical effect. Patients who had side effects that could not be rectified with a reduction in stimulation using the conventional programming configuration without compromising control of motor symptoms went on to have an extended programming session after verifying that the side effect was stimulation induced and reversible. This was done by confirming an improvement in dysarthria, dyskinesia or muscle contraction when stimulation was switched off or reduced, as well as a consistent history of emergence or worsening of the symptom after having DBS. Objective ratings of side effects *off*-stimulation were used to verify this.

4.2.3 Optimisation procedure

An extended monopolar review was carried out after overnight withdrawal of dopaminergic medication. The chronically used level of contacts were screened, firstly to determine the efficacy threshold (ET) and side effect threshold (ST) in ring mode at 60µs. The responsible (i.e. contralateral) STN was screened in cases of clearly unilateral symptoms, and both STNs were screened for dysarthria and in cases of bilateral dyskinesia or pyramidal symptoms. The ET was determined by repetitive testing of rigidity in the upper limb initially at 0.5mA intervals then narrowed down to the nearest 0.1mA until maximal improvement was obtained. Bradykinesia, tremor and gait were also assessed and further adjustments to the ET were made if necessary, taking these into account, to achieve maximal overall therapeutic effect. The benchmark for motor symptom control was set to the optimal level achieved during this process in the RM60 configuration. Side effect thresholds were recorded for the responsible side effect at their earliest emergence (i.e. dysarthria, dyskinesia or muscle contraction) to the nearest 0.1mA. Each of the three segments of the ring level was then screened separately to record these thresholds using the same procedure described. The segment with the lowest side effect threshold was eliminated, and of the two remaining segments, the one with the best therapeutic window (TW) was used to derive directional settings. The same process was then repeated at 30µs. This resulted in three alternative settings to the baseline setting of ring mode at 60µs (RM60) for each patient: ring mode at 30µs (RM30), best directional stimulation at 60µs (DIR60), and best directional stimulation at 30µs (DIR30).

Patients were then assessed *on* medications and any further adjustments to each of the alternative settings were made to optimise clinical efficacy if necessary. It was ensured during this process that there was no deterioration in motor symptom control using the 3 alternative settings compared to the baseline (RM60) setting. In case a single segment

could not achieve the same clinical efficacy as RM settings, an adjacent segment with the second highest side effect threshold was used in combination with the original segment. The frequency was kept constant at 130Hz at all settings, and no medication changes were made during the optimisation period.

Treatment efficacy was evaluated using a focussed motor assessment of selected items of the UPDRS-III scale: 20, 22, 23 and 29 (rest tremor, rigidity, finger taps, and gait). A composite motor score consisting of the sum of scores of the first three items for each hemibody, as well as the gait score were recorded in the *off*- stimulation state, on the baseline settings, and on post-optimisation settings, in the *off*- medication state in order to isolate stimulation effects.

4.2.4 Assessments

All side effect assessments during the optimisation period were done in the *on*-medication state after at least 3 hours on each stimulation condition. The order of the conditions assessed was balanced across the cohort by varying the order of the four stimulation conditions for each patient.

In patients with stimulation induced dysarthria, the Sentence Intelligibility Test (SIT) (Dorsey *et al.*, 1996) was used to rate speech intelligibility. Perceptual characteristics of speech were also scored using a recorded 60- second monologue of the patient's speech using scales developed by Darley and colleagues (Darley, Aronson & Brown, 1969). This included scoring each of the following characteristics of speech of 7 (articulation, respiration, resonance, phonation, prosody, and rate) by a speech therapist to give a composite score out of 42. Intelligibility scoring on each condition was done at the end of the optimisation period, and both perceptual and intelligibility ratings were done by

raters unaware of the stimulation settings for each recording, which were labelled conditions 1 – 4 and decoded after analysis.

Dyskinesia was rated using the objective sections of the Unified Dyskinesia Rating Scale (sum of parts III and IV of UDysRS) on each stimulation condition. Part III of the UDysRS consists of rating the severity of dyskinesia in 7 defined body segments during activities performed by the patient including; communication, drinking, dressing, and ambulation, on a scale of 0 – 4 for each body segment. The highest ratings during each activity were added and combined with the score for part IV (functional impairment during the 4 activities rated on a scale of 0- 4 for each) to give the final rating score for dyskinesia. Video recordings were made of each assessment using the Rush filming protocol for verification of initial ratings.

For pyramidal tract symptoms, the thresholds for eliciting these, as reported by the patient or observed by the clinician, were recorded on each stimulation condition. In order to make comparisons across the different stimulation conditions, the thresholds and TW in terms of charge per pulse (TW_Q) rather than amplitude were used.

At the end of the optimisation period, patients were put on the stimulation condition with the greatest improvement in their presenting side effect. In the case of equivalent improvement in side effects on more than one stimulation condition, patients had a trial of each before selecting the preferred condition. A full UPDRS-III score on and off medications on the final optimised stimulation condition was recorded.

4.2.5 Follow up

After the optimisation session, any further adjustments to the amplitude were made as necessary according to standard clinical practice, and the next best alternative stimulation condition was used if the originally selected condition was not satisfactory

despite amplitude adjustments. Patients were followed up at 6 months after the initial optimisation. Stimulation settings were recorded, and side effects of dysarthria and dyskinesia were objectively rated as described for the initial post-optimisation rating. For patients with pyramidal tract symptoms, any recurrence of these symptoms and the TW_Q were recorded.

4.2.6 Total Electrical Energy Delivered (TEED)

The total electrical energy delivered was compared between the derived settings of the 4 conditions during optimisation using the formula: TEED = I^2 x PW x F x Z in microjoules/second; where I = current (amplitude), F = Frequency, Z = Impedance. For ring mode configurations, the current was divided into 3 to calculate the TEED for each segment and the sum of these was used.

4.2.7 Statistical analysis

The primary analysis compared side effect measures (speech intelligibility, dyskinesia rating scores, and TW_Q) at baseline to the post-optimisation assessment and the 6-month follow up assessment using pairwise comparisons.

To examine differences between the different stimulation conditions in the acute setting, a secondary analysis with repeated measures analysis of variance (ANOVA) was used, with subsequent pairwise comparisons between the 4 conditions. The TEED was compared using the same method between the 4 conditions.

IBM SPSS™ software (version 26.0) was used for all statistical analyses. Sphericity was verified using Mauchly's test prior to carrying out ANOVA analyses. All data were checked for normality, and non-parametric tests (Wilcoxon matched-pair signed-rank

test and related measures Friedman's two-way ANOVA by ranks) were used for data that was not normally distributed. Statistical significance was set to 0.05, and the Bonferroni correction method was applied to adjust for multiple comparisons.

4.3 Results

In the extended monopolar review, 18 responsible STNs were identified for stimulation induced dysarthria, 17 for dyskinesia, and 7 for pyramidal symptoms, on conventional settings (RM60). One patient presented with both dysarthria and facial muscle contraction and was included in assessment of both side effects. Of the 32 patients, an improvement in side effects during the optimisation session using at least one of the alternative stimulation conditions could be achieved in all patients. However, one patient did not tolerate any of the alternative settings due to delayed onset of off symptoms, and reverted to RM60 settings. The mean efficacy and side effect thresholds and TW on each condition from the extended monopolar review are presented in Table 4.2.

4.3.1 Side effect outcomes

In the dysarthria group, the Sentence Intelligibility Test (SIT%) at baseline settings was 75.5 ± 21.0% [median 82%, range: 11 - 90], and was significantly improved post-optimisation [mean 95.7 ± 4.7%, median 98%, range: 83 - 100; $P = .002$] and at the 6 month follow up [mean 90.9 ± 6.6%, median 91.0%, range: 78-100; $P = .016$] compared to baseline (Table 4.3). The mean SIT% with stimulation turned off improved to 89.8 ± 9.6%; median 93% [67 - 99] from baseline stimulation-on settings ($P = .03$).

In the dyskinesia group, the UDysRS (III + IV) at baseline was 16.9 ± 6.8, and was significantly improved post-optimisation [mean 1.9 ± 3.2; $t(14) = 7.77$, $P < .001$] and at the 6 month follow up [mean 1.0 ± 1.7; $t(13) = 7.9$, $P < .001$) compared to baseline. The mean dyskinesia score off stimulation improved to 0.2 ± 0.6 from baseline stimulation-on settings ($P < .01$).

***Table 4.2*: Efficacy and side effect thresholds and therapeutic windows overall and in each subgroup**

	RM60	RM30	DIR60	DIR30
Dysarthria (18 STNs)				
Efficacy threshold (mA)	2.8 ± 1.2	4.1 ± 1.9	2.0 ± 0.8	**3.2 ± 1.4**
Side Effect threshold (mA)	2.1 ± 0.7	4.2 ± 1.5	3.0 ± 1.2	**4.3 ± 1.4**
Therapeutic Window (mA)	-0.7 ± 0.7	0.1 ± 1.2	1.0 ± 0.9	**1.1 ± 1.4**
Dyskinesia (17 STNs)				
Efficacy threshold (mA)	2.6 ± 0.7	4.0 ± 1.2	2.4 ± 0.8	**3.6 ± 1.4**
Side Effect threshold (mA)	2.2 ± 1.2	5.2 ± 2.6	3.8 ± 1.3	**6.0 ± 3.3**
Therapeutic Window (mA)	-0.4 ± 1.0	1.2 ± 2.1	1.4 ± 1.5	**2.4 ± 3.1**
Pyramidal Side Effect (7 STNs)				
Efficacy threshold (mA)	2.7 ± 0.7	4.2 ± 1.3	2.1 ± 0.8	**3.9 ± 1.4**
Side Effect threshold (mA)	2.3 ± 1.2	5.4 ± 2.7	2.9 ± 1.3	**5.7 ± 3.4**
Therapeutic Window (mA)	-0.4 ± 1.0	1.2 ± 2.1	0.7 ± 1.5	**1.8 ± 3.2**
Overall (42 STNs)				
Efficacy threshold (mA)	2.7 ± 0.7	4.1 ± 1.4	2.2 ± 0.6	**3.5 ± 1.7**
Side Effect threshold (mA)	2.2 ± 0.7	4.8 ± 2.9	3.3 ± 0.8	**5.2 ± 2.4**
Therapeutic Window (mA)	-0.5 ± 0.1	0.7 ± 2.1	1.1 ± 0.5	**1.8 ± 1.4**

Values are reported as mean ± SD.
*Mode of optimised setting condition marked in **bold**.*

In the pyramidal side effect group, the TW_Q at baseline was -22.3 ± 9.0 nC and was significantly improved post-optimisation [mean 67.3 ± 54.1; t(6) = -4.28; *P* = .01] and at 6 months [mean 32.6 ± 41.1; t(6) = -3.39, *P* = .03]. One patient complained of a mild recurrence of pyramidal symptoms at the follow up visit, and this corresponded to a negative TW_Q at one STN.

The final optimised condition in the dysarthria group was DIR30 in 11 patients (one of these subsequently reverted to RM60 and 1 had concurrent pyramidal side effect), and DIR60 in 2 patients. In the dyskinesia group, 12 were on DIR30, 2 on DIR60, and 1 on RM30. In the pyramidal side effect group, 3 were on DIR30 (including one who also had dysarthria), and 2 on DIR60. Six patients were programmed using two directional segments, and the remaining used only one segment for directional settings.

Twenty-nine patients were included in the analysis of follow up data, excluding the following from the original cohort of 32: 2 patients from the dysarthria group (1 could not tolerate any alternative setting and 1 was lost to follow up), and 1 in the dyskinesia group who needed to be reprogrammed using a different configuration to the 3 alternative conditions studied, where the dorsal-most contact was additionally used due to inadequate control of dyskinesia. At the 6-month follow up, the numbers of patients on each condition was as follows: 20 on DIR30, 7 on DIR60, 2 on RM30, and 1 on RM60. The breakdown of numbers on each condition from each side effect group is shown in figures 4.2 (post-optimisation) and 4.3 (6-month follow up).

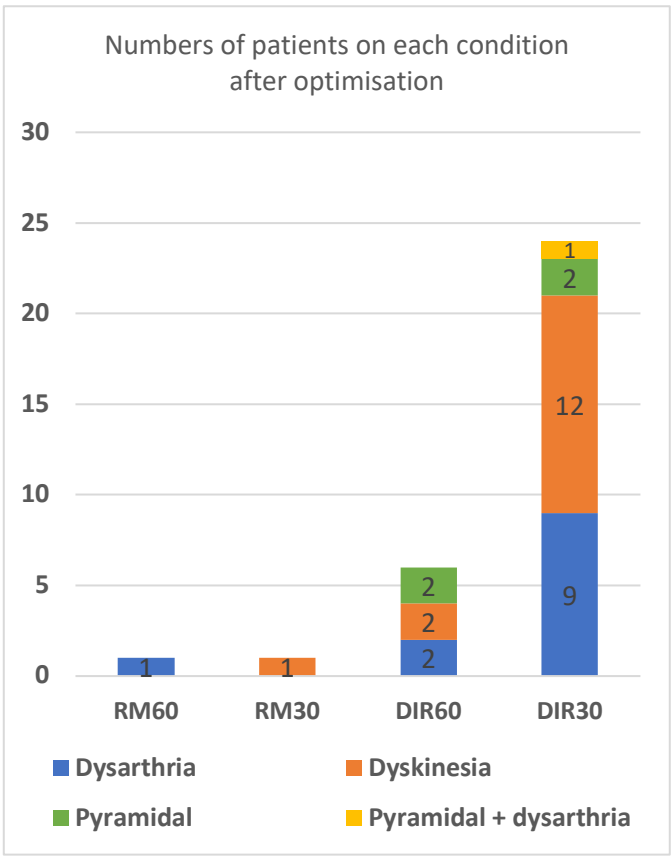


Figure 4.2. **Numbers of patients on each condition after optimisation**

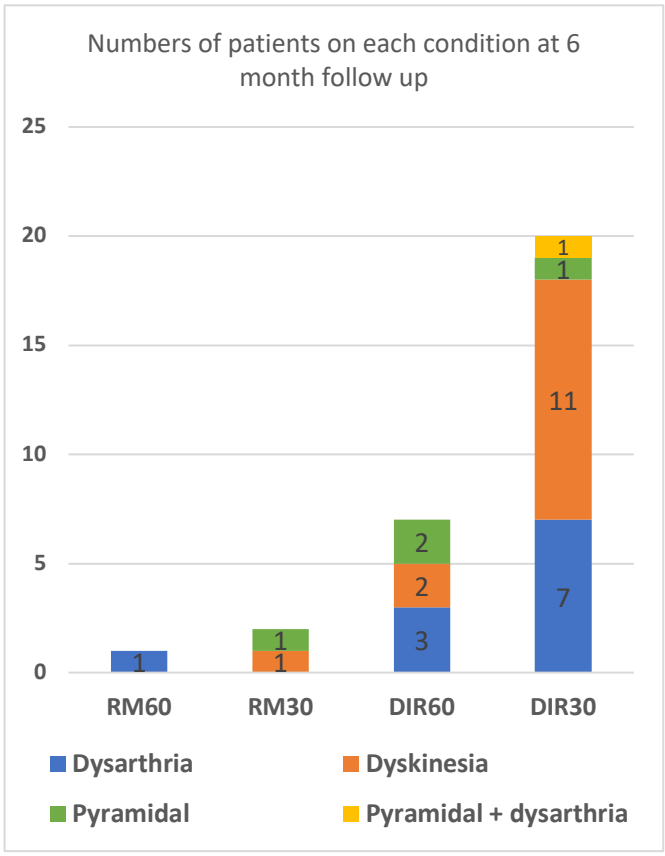


Figure 4.3. **Numbers of patients on each condition at 6-month follow up**

Table 4.3: **Comparison of side effect assessments at baseline, post-optimisation and at 6 months**

Side Effect Assessment	n	Baseline	Post-optimisation	At 6-month follow up	Baseline vs:	
					Post-optimisation	Follow up at 6m
Sentence Intelligibility Test (SIT) %	13	82 [11-90]	98 [83-100]	91.0 [78-100]	*P = .002*	*P = .016*
Dyskinesia rating score (UDysRS III + IV)	15	16.9 ± 6.8	1.9 ± 3.2	1.0 ± 1.7	*P < .001*	*P < .001*
TW for pyramidal symptoms (TW_Q in nC)	5	-22.3 ± 9.0	67.3 ± 54.1	32.6 ± 41.1	*P = .01*	*P = .03*

Values are reported as Median [Range] for non-parametric data and Mean ± SD for parametric data.

In the secondary analysis of comparisons between the 4 stimulation conditions during the optimisation session, there were significant differences in SIT scores between RM60 and each of the three alternative conditions with pairwise comparisons [vs RM30: *P = .019, vs DIR60: P = .015, and vs DIR30: P < .001*]. There were no significant differences between any of the 3 alternative conditions. Significance of differences in perceptual speech scores between conditions followed the same pattern as for speech intelligibility (Table 4.4, Figures 4.4 – 4.6). For dyskinesia ratings, all 3 alternative conditions had significantly lower scores than RM60 [*P = .013, P < .001, P < .001* respectively], and the DIR30 condition also had significantly lower scores than RM30 [*P = .01*]. For pyramidal symptoms, significant differences in TW_Q were only found between RM60 vs DIR60 [*P = .009*], and RM60 vs DIR30 [*P = .023*].

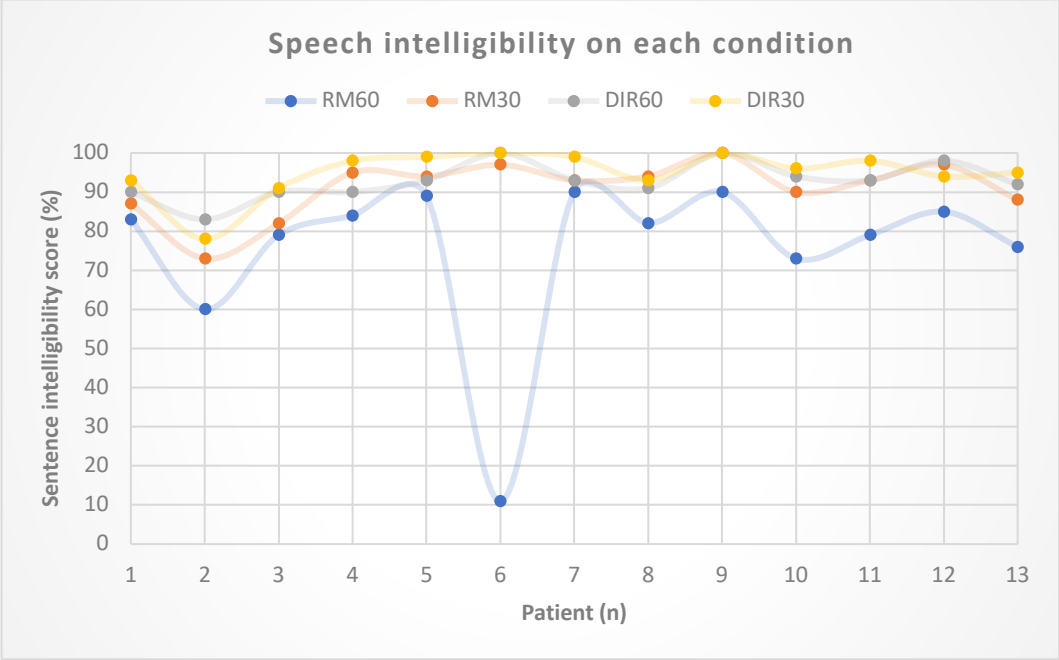


Figure 4.4. **Speech intelligibility score on each condition**

RM60 (75.5 ± 21.0%) vs RM30 (91.0 ± 7.2): *P = .019, vs DIR60 (*92.8 ± 4.6)*: P = .015, and vs DIR30 (*94.9 ± 5.9)*: P* < .001. *P* > .05 for comparisons between RM30, DIR60 and DIR30.

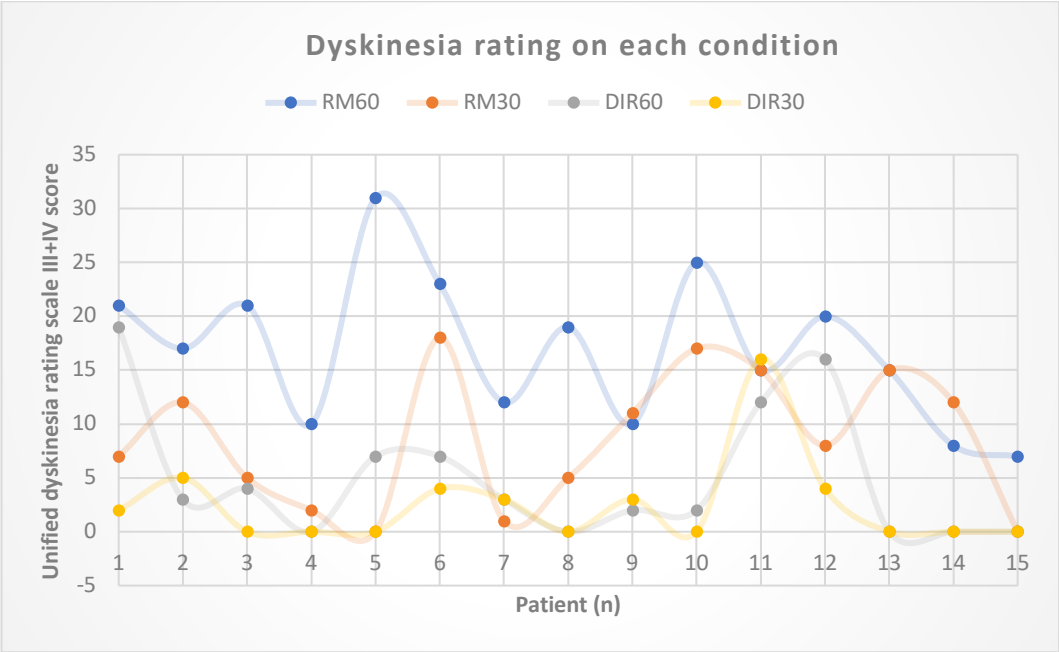


Figure 4.5. **Dyskinesia rating score on each condition**

RM60 (16.9 ± 6.8) vs RM30 (8.5 ± 6.3): *P* = *.013,* vs DIR60 *(*5.0 ± 6.1)*: P* < .001, and vs DIR30 (2.5 ± 4.2)*: P* < .001. DIR30 vs RM30: *P* = .01. Other pairwise comparisons: *P* > .05.

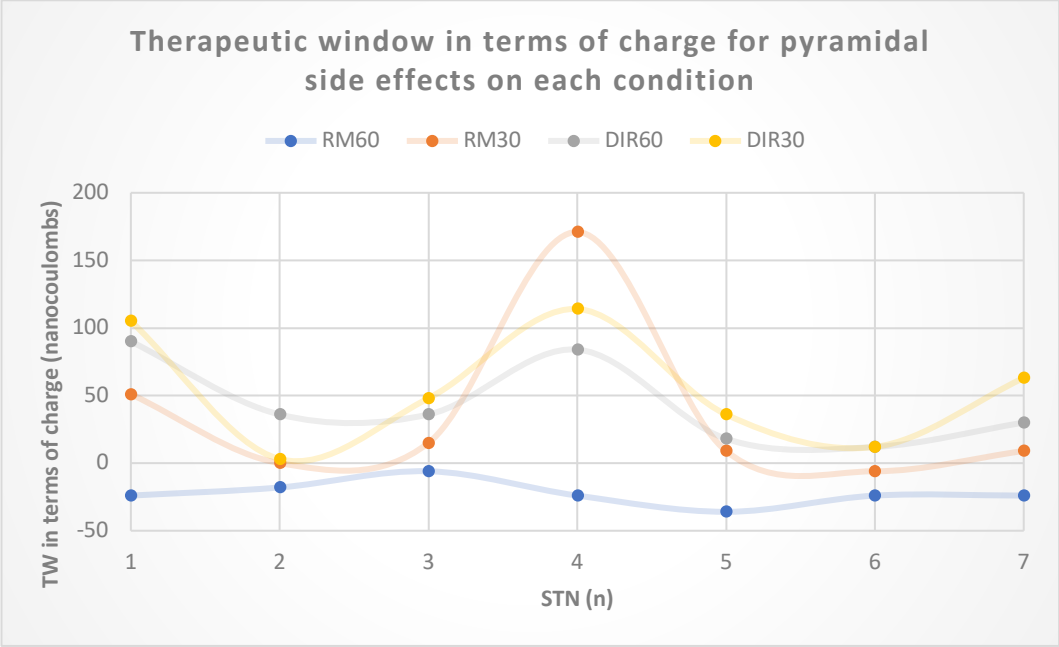


Figure 4.6. **Therapeutic window in terms of charge for pyramidal side effect on each condition.**

RM60 (-22.3 ± 9.0nC) vs RM30 (35.6 ± 62.5): *P* = .32; vs DIR60 (43.7 ± 30.9nC): *P* = *.009;* vs DIR30 (54.4 ± 42.8): *P* = .023. Other pairwise comparisons: *P* > .05.

***Table 4.4*: Comparison of side effect assessments on the 4 stimulation conditions**

ASSESSMENT	RM60 [a]	RM30 [b]	DIR60 [c]	DIR30 [d]
Sentence Intelligibility Test (SIT) %	75.5 ± 21.0 [b,c,d] Med 82 [11-90]	91.0 ± 7.2 [a] Med 93 [73-100]	92.8 ± 4.6 [a] Med 93 [83-100]	94.9 ± 5.9 [a] Med 99 [78-100]
Perceptual Speech Score (out of 42)	29.2 ± 3.6 [b,c,d]	32.9 ± 4.1 [a]	33.8 ± 4.5 [a]	34.1 ± 4.8 [a]
Dyskinesia Rating (UDysRS III + IV)	16.9 ± 6.8 [b,c,d]	8.5 ± 6.3 [a,d]	5.0 ± 6.1 [a]	2.5 ± 4.2 [a,b]
TW_Q for Pyramidal symptoms (in nC)	-22.3 ± 9.0 [c,d]	35.6 ± 62.5	43.7 ± 30.9 [a]	54.4 ± 42.8 [a]

Values are reported as mean ± SD; non-parametric data also reported as median [range].

Significant pairwise differences versus RM60 [a], RM30 [b], DIR60 [c], DIR30 [d] are indicated in superscript where $P < .05$.

4.3.2 Motor scores

The mean post-optimisation UPDRS-III score was 24.6 ± 11.2 off medication and 14.1 ± 6.8 on medication.

Focussed motor scores for each STN optimised (composite of UPDRS-III items 20, 22, 23) were as follows: Off-medication off-stimulation: median 5 [range 4 - 9]; Pre-optimisation off-medication on-stimulation: median 2 [range 1 - 4]; Post-optimisation off-medication on-stimulation: median 2 [range 1 - 4].

The gait score (item 29) off-medication off-stimulation was median 2 [range 1 - 4]; off-medication on-stimulation pre-optimisation: median 1 [range 1 - 2]; off-medication on-stimulation post-optimisation: median 1 [range 0 - 1]. A reduction in gait scores of 1 - 2 points was seen in 10 patients in the dyskinesia group post-optimisation compared to their pre-optimisation assessments.

4.3.3 Total Electrical Energy Delivered (TEED)

The mean ± SD and median [range] of TEED calculated for each condition was as follows:

RM60: 43.7 ± 33.3; Med 39.1 [11.8 – 201.2] μ J/s;

RM30: 51.6 ± 41.5; Med 36.7 [11.5 – 253.5] μ J/s;

DIR60: 81.2 ± 54.9; Med 66.0 [13.7 – 244.2] μ J/s;

DIR30: 107.9 ± 89.8; Med 79.2 [14.1 – 342.6] μ J/s.

As data did not fit a normal distribution, the non-parametric Friedman's two-way ANOVA by ranks was used: there was a significant difference across the 4 conditions [χ^2 (3) = 53.9, $P < .001$].

Pairwise comparisons with the Wilcoxon signed-rank test showed significant differences between all pairs ($P < .001$) except for RM60 vs. RM30, and DIR60 vs. DIR30.

4.4 Discussion

The results of this study show that novel programming techniques using directional stimulation with segmented contacts and short pulse width can significantly improve stimulation induced side effects of dysarthria, dyskinesia, and symptoms of pyramidal tract activation in patients with STN DBS on conventional ring mode settings. Using either one or a combination of these techniques resulted in significant improvements in speech intelligibility, dyskinesia rating scores, and therapeutic window with regards to pyramidal tract symptoms. These improvements were present acutely following optimisation and persisted at the 6-month follow up compared to baseline assessments. The optimal condition out of the three alternatives for the greatest improvement in side effects varied for individuals; however, the combination of directional stimulation with short pulse width (DIR30) was the most common in all side effect groups. This is reflected in the greatest number of patients going on DIR30 settings both at the end of the optimisation session and at the 6-month follow up. The data also demonstrate the feasibility of combining directional stimulation with short PW; a technique that has not been reported previously.

During the optimisation session, compared to baseline (RM60), all of the alternative stimulation conditions resulted in improvements in the side effects studied, except in the pyramidal group where RM30 did not result in significant improvements in the TW_Q. While there was a trend to having the greatest improvement on the DIR30 condition, comparisons between the alternative conditions did not show statistically significant differences, except in the dyskinesia group, where DIR30 was superior to RM30.

The early induction of dyskinesia after electrode implantation and initiation of stimulation is usually seen as reassuring confirmation of accurate placement in the target for alleviation of PD motor symptoms. It may therefore seem counterintuitive to direct stimulation away from the segment producing this. However, it is possible that in

patients who have intractable stimulation induced dyskinesia even at low amplitudes on ring mode settings, that the current is too focussed in this region. In the group of patients with dyskinesia in this series, the thresholds for producing dyskinesia were lower than efficacy thresholds at conventional settings [table 4.2] as dyskinesia tended to occur as a delayed effect after programming the amplitude for optimal efficacy to control motor symptoms and gait. A simple reduction in amplitude using conventional stimulation to the level where stimulation induced dyskinesias cease may not result in optimal motor control, as was the case with the patients in this series, who had undergone extensive adjustments on conventional settings for at least 3 months post-operatively and either had persistent dyskinesias or suboptimal motor control. Consistent with this, another study reported an approach to programming using segmented contacts where directing only a small proportion of the total current to the dyskinesia inducing contact and the remainder to other segments or different vertical levels resulted in excellent overall control of motor symptom (Bouthour *et al.*, 2019). Further examination of the degree of shift in the stimulation field with directional stimulation using VTA modelling may provide more information in this regard.

Comparison of TEED on the four conditions showed that directional settings using either PW consumed more energy (approximately double) relative to the corresponding ring mode counterparts. This is due to the fact that of all parameters, the amplitude influences energy consumption the most. With ring mode settings, the current is divided between 3 segments, and the amplitude at each segment is as a result much lower than a single higher amplitude at one segment with directional stimulation. As found in both the previous studies, there was no significant difference in the TEED between 60µs and 30µs PW settings, and the data here show that this also applies to the directional configuration (i.e. DIR60 vs DIR30).

Additionally, following on from the data in the trial on short PW in Chapter 3, these results confirm that in dysarthric patients who have not previously been optimised using low frequency settings and are earlier in the course of DBS therapy do benefit from short PW. In the current study, all patients were on 130Hz frequency settings and were within 3 years' duration of STN DBS therapy (with a mean duration of 7.9 months). While these data show that using each of the alternative conditions resulted in a significant improvement in dysarthria from standard (RM60) settings, firm conclusions cannot be drawn about differences between the alternative conditions in the dysarthria group, other than to note a trend to higher scores with DIR30 compared with DIR60 and RM30. The mean TW in the dysarthria group [table 4.2] at RM30 is noted to be quite narrow and just positive, and while this is still a significant increase from the negative TW in RM60, it is not as large as those achieved with directional settings. This may be due to the ability of directional steering to more easily avoid structures responsible for dysarthria than using ring mode with short PW.

In the dyskinesia group, however, there seems to be an additional improvement with the use of directional stimulation, as both directional conditions (60μs and 30μs) showed significantly lower dyskinesia scores compared to their ring mode counterparts. In the pyramidal side effect group, only directional stimulation appears to be of benefit rather than the use of short PW when compared to standard settings. However, this group had a very small sample, and the trends seen with improved scores with 30μs in both ring mode and directional settings need to be explored in larger studies to ascertain any possible significance.

Limitations of this study include its open-label design, and small sample sizes, particularly in the pyramidal symptom group. This restricts interpretation of differences between the alternative stimulation conditions in particular. Speech assessments were recorded and done without the assessor having knowledge of the stimulation condition.

However, this was not possible in the dyskinesia or pyramidal symptom group in this study. Observer bias for dyskinesia ratings was minimised by video recording the standardised assessments for each patient and verifying the scores objectively on each condition. Systematic biases were minimised by balancing the order of conditions assessed across the cohort. Patients were also not aware of the details of each setting or the order of conditions tested during the optimisation session.

It should also be noted that the cohort of patients in this study had clearly reproducible and reversible stimulation induced side effects on conventional settings, and the results are only applicable to such patients. This was verified by improvement of symptoms with stimulation turned off, and is evident from improved speech intelligibility and dyskinesia scores in the stimulation off condition compared to baseline (RM60). It is well known that despite the therapeutic effects of STN stimulation being largely immediately apparent, several stimulation induced side effects are not acute, nor do they resolve within a short period of programming changes. These include gait impairment, and some types of speech disturbance. Whether novel programming techniques have a role in alleviating these chronic side effects is not clear at this stage. The methodology used in this study involved identifying the segment with the lowest side effect threshold and eliminating this to derive directional settings. Side effect symptoms that are not time-locked to stimulation changes are more challenging to study systematically, particularly with directional stimulation.

Another criticism may be the lack of comprehensive motor assessments with a full UPDRS-III score on each condition. The repetitive nature of testing during the extended monopolar review and optimisation session made this impractical to perform 8 times (*on* and *off* for the 4 conditions), not only due to time constraints, but the progressive fatigue experienced by patients during such a process would also make repetitive ratings unreliable. Secondly, whilst these scores may have served to provide information on

potential small differences in efficacy or certain subscores of the UPDRS-III between the conditions, they were not deemed necessary given the methodology of the monopolar review process and derivation of settings, where the emphasis was to ensure that there was no deterioration from baseline in the selected items comprising the focussed motor assessments, which the settings on each condition were titrated against. These composite focussed motor scores showed no differences from baseline following optimisation, apart from in the dyskinesia group, where an improvement in gait subscores was noted in the majority of patients following optimisation due to significant improvements in dyskinesia severity and consequently improved gait. In fact, on the other hand, it can be argued that a meticulous individualised focus to ensure no deterioration in selected segmental motor signs and gait, combined with an overall clinical impression of PD symptom control, provides a more reliable assessment in this regard than the UPDRS-III score, which often does not reflect clinically detectable differences within a patient due to the wide range of symptom severity possible within each subscore interval. Furthermore, the mean UPDRS-III score in the off-medication state post-optimisation in these patients showed a 48% improvement over the pre-operative off medication score, which is well within the range of expected therapeutic effect of STN-DBS reported in the literature, ranging from a collective mean of 35% improvement in randomised trials to 52% in uncontrolled studies (Krack *et al.*, 2019).

A limited number of configurations with directional settings was used from the numerous permutations possible, and the directional monopolar review was done in steps of entire segments, or 120° (unless necessary to preserve the optimal therapeutic benefit). In spite of this minimalistic approach, the optimisation process took 3 days. It is possible that further fine-tuning of directional settings may have resulted in even more desirable individual outcomes. However, further adjustments if necessary were carried out following the initial optimisation, as would be in the usual clinical care of DBS

patients, and the high retention rate of one of the alternative optimised programs at 6 months is testament to the effectiveness of this type of approach.

Electrode placement was confirmed to be in the STN target in all patients in this study; this indicates that despite optimal placement of electrodes in the intended region, a proportion of patients develop troublesome side effects. These are not always predictable, and the responsible neural elements for each side effect may have differing and often opposing spatial orientation relative to the stimulating electrode. Factors that may determine whether an individual develops a given side effect apart from the specific electrode location include their predisposition based on pre-existing symptoms, the specific stimulation parameters required for optimal therapeutic effect, and individual somatotopy of the STN and surrounding structures. Therefore, even with the best processes for selection of patients and meticulous pre-operative planning and surgical technique, clinicians are often faced with patients with 'optimally' sited electrodes and good therapeutic benefit, but accompanying side effects. Novel programming features using directional steering and an expanded parameter range with respect to PW give the programming clinician further tools to refine STN stimulation in these cases.

This cohort represents not only the largest set of data on the use of these novel programming techniques but also the first study on the clinical utility of directional stimulation in reducing stimulation induced side effects, with significant and sustained results. This will help inform further clinical trials and studies looking at longer term outcomes, as well as clinicians frequently faced with the challenges of dealing with treatment related side effects of STN DBS. Given the significant findings of this study, it would now be of interest to dissect the possible mechanisms responsible for these effects.

CHAPTER 5

Exploring Mechanisms That May Mediate Changes in Adverse Effects of STN DBS with the Use of Novel Programming Techniques: VTA Modelling and the Role of Electrical Charge

5 - Summary of chapter

This chapter will explore potential mechanisms behind the clinical results found in study 3. This is done by modelling the volume of tissue activated (VTA) for each patient before and after optimisation, and qualitatively describing shifts in the stimulation field to find any collective patterns of change with optimisation for each type of side effect. VTAs of the directional segment with the lowest threshold for producing side effects are also modelled. The VTA modelling process required post-operative CT scans for each patient in order to obtain information on the orientation of the lead, image co-registration of MRI and CT scans into the VTA visualisation software, segmentation of individual basal ganglia nuclei, lead detection and localisation, and input of stimulation parameters to model the stimulation fields.

In addition to this, the electrical charge injection of each of the four stimulation conditions are compared quantitatively.

There were different broad patterns of shift in VTAs in each category of side effects, which correspond to the regions of known structures that may be responsible for them. The electrical charge was significantly lower with the 3 alternative conditions compared to standard settings, and the charge at short PW settings of both ring mode and directional configurations were lower than those at the corresponding standard PW.

5.1 Introduction

In exploring the mechanisms that may mediate the changes in adverse effects seen with the use of novel programming techniques, one must consider how activation of neural elements responsible for these side effects are spared. The study in Chapter 4 demonstrated significant differences in terms of clinical effect, but was carried out devoid of any assumptions of the effects of stimulating anatomical structures in and around the STN; it was purely based on observed clinical effects and objective assessments related to systematic alterations in stimulation, without knowledge of the exact contact location or orientation of electrodes used. The next step would be to ascertain if there were any patterns of modifying stimulation for the different groups of side effects. Identifying such patterns would significantly reduce the amount of time taken to optimise programming for patients presenting with side effects who have imaging information available, as well as help contribute to data required for the formulation of updated programming algorithms and guidelines.

It would be necessary to define the location and orientation of the lead and direction of stimulation as a first step in this process. This would need to be done in a patient-specific manner, registering the lead placement and orientation in individual brain scans. The stimulation field can then be modelled using specialised software, approximating the volume of tissue activated (VTA), in order to visualise the effects of defined stimulation parameters. Software such as Brainlab's Elements™ package offers such a platform.

Using this software, the basal ganglia anatomy is segmented using MRI data sets that define tissue densities using an algorithm. In order to specifically recognise basal ganglia structures, the universal atlas was trained using patients who were scanned with 1.5

Tesla, 3 Tesla and 7 Tesla MRI. Manual segmentation on 7 Tesla images by neuroanatomists served as a ground truth for validation.

This approach allows for the simultaneous non-linear registration of up to six different MR sequences to yield consistent and patient-specific segmentation. The algorithm has been evaluated qualitatively and quantitatively, the latter by comparing it to manual delineation by experts. The method of MRI based automatic segmentation of the STN has also been compared to intra-operative microelectrode recordings and shown good concordance (Reinacher *et al.*, 2019). The algorithm first offers a proposal of structures, then gives the opportunity to edit these manually.

The orientation of metal anisotropic marker on the lead can be determined by imaging with either a CT scan or fluoroscopy. Comparisons of the accuracy of these methods using epoxy phantoms with implanted Cartesia™ leads of known orientation have shown that the mean deviation from ground truth with fluoroscopy ranged from -12 to 14°, and with CT this was -4.6 to 6.6° within a polar angle of 40° (Sitz *et al.*, 2017).

The patterns of artefact on CT are distinct at the level of the segmented electrodes and at the level of the marker, as shown in figure 5.1. The *Elements Lead localisation*™ component has an inbuilt algorithm to calculate the orientation of the lead using these artefacts. Using a similar algorithm, the accuracy of the determined orientation relative to ground truth has been reported to be -0.6 ± 1.5° [range: -5.4 to 4.2°] in a validation study using 60 different configurations (Hellerbach *et al.*, 2018).

VTA models are commonly based on estimating the extent of axonal tissue activation in the stimulation field. In the type used in *Elements Guide XT*™ software, the model is created from a 3D brain atlas warped to the patient's brain MRI, and a finite element model of the electric field coupled to a neuronal activation model (Butson *et al.*, 2007). The neuronal model is a validated set of non-linear differential equations that describe the activity of axons. To determine whether tissue is activated, the electric field is

impressed upon the neuron model to determine if an action potential would be generated. This model was calculated assuming homogenous and isotropic tissue conductivity of 0.3S/mm, and neural activation threshold was based on myelinated axon models 5.7µm in diameter, and oriented perpendicular to the lead orientation vector**.** The model also incorporates bulk tissue capacitance, an electrode electrolyte interface, and a tissue encapsulation area (Butson 2005). Models similar to the one implemented here showed good reliability in predicting corticospinal tract activation when measured on electromyogram recordings (Butson et al 2007).

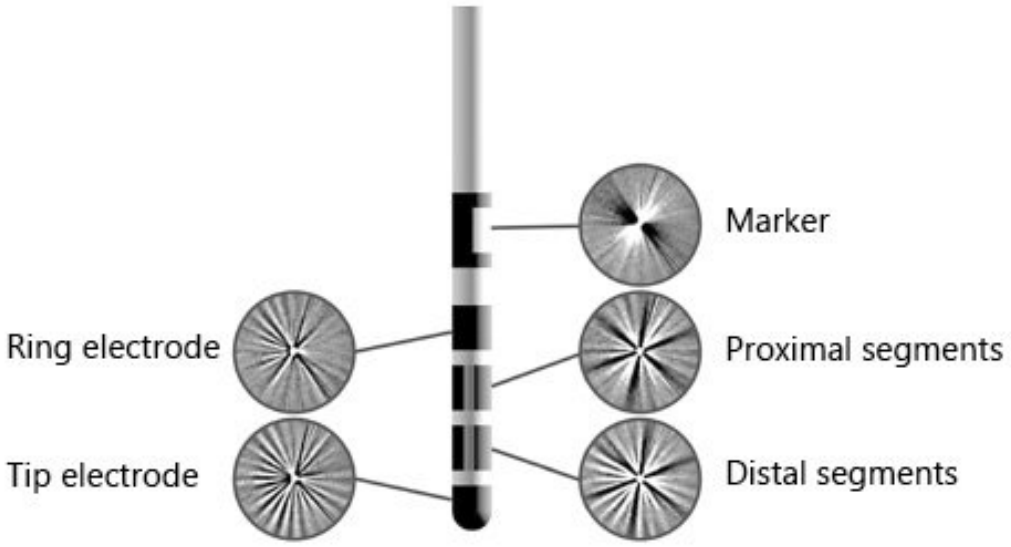


Figure 5.1. **Directional lead and pattern of artefacts on CT at different levels**
(Adapted from Hellerbach et al, 2018).

Another consideration in exploring mechanisms of alleviating side effects using novel programming features, as previously discussed with regard to short PW and the therapeutic window, is the electrical charge used. A comparison between the settings used in the group of patients in the previous chapter, who had inducible stimulation related side effects may provide additional information on underlying reasons for the

observed differences between the stimulation conditions, apart from spatial shifts in the stimulation field depicted by VTA modelling.

This study will explore mechanisms that may mediate changes in stimulation induced side effects of STN DBS with the use of novel programming techniques of short PW and directional stimulation. This will be done using data and imaging on patients from study 3 (Chapter 4) in order to compare; (i) shifts in volume of tissue activated from baseline to optimised settings, noting the direction of the side effect relative to these, and (ii) the charge injection per pulse at the efficacy threshold for the 4 stimulation conditions.

5.2 Methods

5.2.1 Patient imaging

Patients underwent stereotactic MRI pre- and post- lead implantation (on a 1.5T Siemens Magnetom Espree interventional MRI scanner), in line with the stereotactic MRI-guided and MRI-verified surgical approach used for DBS surgery at our centre.

Pre-implantation scan consisted of a T2-weighted axial scan with voxel size of 1.0 × 1.0mm^2 (slice thickness = 2mm, 26 slices) and a T1-weighted 3D -MPRAGE scan with a 1.5mm^3 voxel size (160 slices).

Post implantation imaging involved a T1-weighted 3D-MPRAGE scan with a 1.5mm^3 voxel size (160 slices) as well as a T2 low specific absorption rate (SAR) scan to confirm electrode placement.

Following the optimisation session in study 3 (Chapter 4), patients had a non-stereotactic CT scan to confirm electrode orientation using the following settings: Pixel matrix 512 X 512, Field of view 310mm, slice thickness 0.8mm, Helical mode, pitch 0.39, Filter type UB (soft tissue). This was done at least 3 months post-operatively.

Images were processed using Brainlab *Elements*® software.

5.2.2 Image registration and segmentation of basal ganglia nuclei

Automatic segmentation of the basal ganglia was performed based on the pre-implantation T1- and T2- weighted MRI scans using *Elements Anatomical Mapping*®. For each patient, the pre-implantation T1-weighted MRI was rigidly co-registered to the post-implantation CT. T2-weighted MRI scans were then also co-registered using the

pre-implantation T1 MRI as reference. The lead position as detected on the post-implantation CT could then be visualised on the segmented pre-implantation MRI. The automatic segmentation of the STN was then systematically reviewed and manually refined in case of any inaccuracies. Other basal ganglia nuclei segmented included the red nucleus, thalamus and globus pallidus. The globus pallidi were not included in the final VTA images in order to avoid obstructing the view of the subthalamic nucleus and VTA models.

5.2.3 Lead detection and orientation

In *Elements Lead Localization*®, the lead position (tip and axis) was automatically detected on post-implantation CT imaging**.** After assigning the Boston Scientific Vercise Cartesia™ directional lead model in the software, the lead orientation was determined by the software algorithm based on the same characteristic CT artefact patterns described by *Hellerbach* and colleagues and using the intended implantation orientation as input (i.e. the marker in the anterior orientation relative to the AC - PC axis); (Hellerbach *et al.*, 2018). The CT artefact is symmetrically reflected at 180° and the software is not able to distinguish which of these indicates the actual marker if there are very large deviations from the intended orientation at implantation. The surgical practice at our centre was therefore to consistently place the marker anteriorly at implantation in order to minimise the deviation.

5.2.4 Measurements to define electrode location

The AC – PC line was manually drawn using the pre-implantation MRI scans. At the level of the active contact in the axial plane, the longest STN axis was drawn, as well as the medio-lateral axis, perpendicular to the longest axis. The position of the active contact on these axes within the axial section of the STN was described as anterior, posterior, medial, or lateral. Where the electrode lay in the centre of the dividing line, the location was described as 'mid' with respect to the anterior-posterior or medial-lateral axis. Where the electrode came into contact with a dividing line but was predominantly located to either side of it, 'mid' was prefixed to the description of the predominant location. Additionally, the position of the active contact along the longest supero-inferior axis of the STN was determined, and active contacts were categorised as superior (dorsal) or inferior (ventral), with the 'mid' prefix using the same criteria described above if necessary.

For directional stimulation with segmented contacts, the orientation of the active contact was described in relation to the AC – PC axis in degrees.

Similarly, the longest antero-posterior axis of each STN, which is oblique to the AC – PC line, was manually drawn using an axial slice at the level of maximal STN axial surface, and the angle between the STN long axis and the AC – PC line was measured, in order to report the orientation of the STN relative to the AC – PC axis and therefore provide information on the direction of stimulation relative to the STN itself.

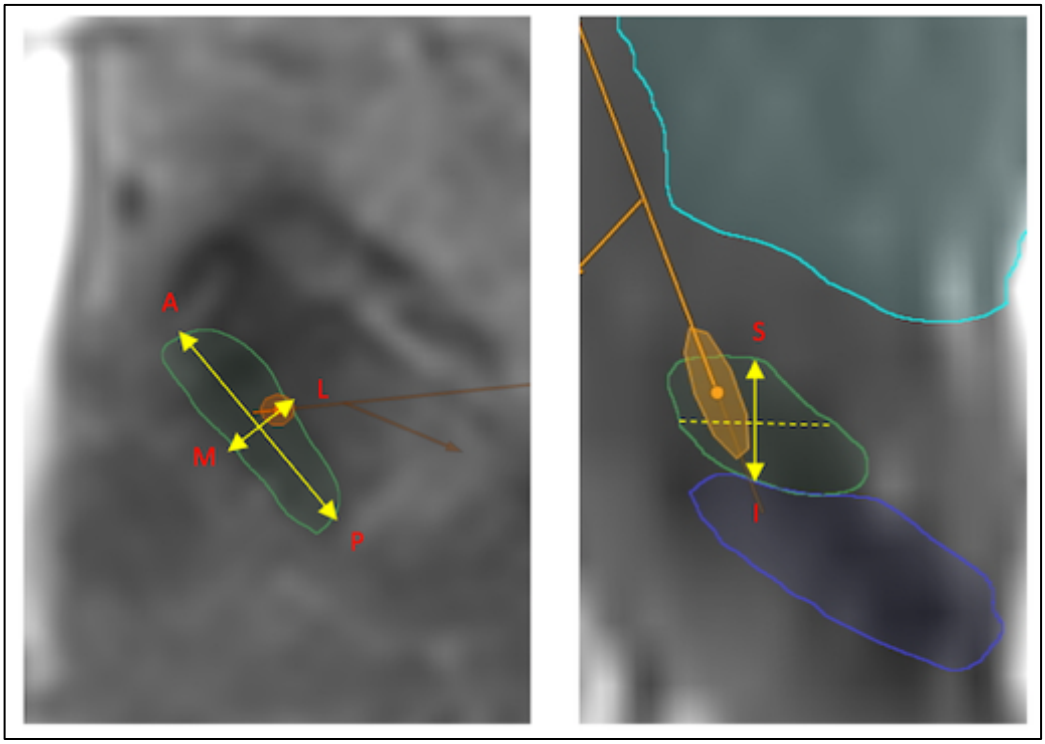


Figure 5.2. **Axial view (left) of segmented STN (green), illustrating quadrants used to describe the electrode location relative to the STN in the axial plane. The coronal view (right) was used to describe the location as superior or inferior in the STN.**

Legend:
A- anterior, P- posterior, M- medial, L- lateral, S- Superior, I- Inferior.
STN- green, Substantia nigra- Indigo, Thalamus- Turquoise.

5.2.5 VTA modelling

Stimulation field models were constructed using *Elements Guide XT*™ software. For each STN optimised (i.e. where there was an identifiable side effect induced by stimulation), VTAs of the baseline (RM60) and optimised settings were modelled. The segment with the lowest side effect threshold was also modelled using the amplitude which produced the side effect at standard PW settings. Where two directional segments produced side effects within a 0.3mA threshold of each other, both are shown. Baseline, optimised and side effect VTAs are denoted in different colours on the segmented STN. The patterns of shift from baseline to optimised VTAs were described for each patient in terms of the

shift away from areas outside the STN and the final position relative to the STN. For each side effect group separately (dysarthria, dyskinesia, pyramidal), it was then determined if there were any predominant overall patterns of shift in VTAs following optimisation. Volumetric measurements of pre- and post-optimisation VTAs were also compared using pairwise tests. For a quantitative representation, the angles of segments with the lowest side effect thresholds for each STN were calculated and the mean (SD) angle from the AC – PC axis and the long axis of the STN in the axial plane presented in each side effect category. As per mathematical convention, angles were measured in the anticlockwise direction (with AC – PC starting point as 0°). In order to perform combined quantitative analyses for both hemispheres, angles for the right hemisphere were standardised to mirror angles of the left, so that the same anatomical region was reflected by the angle. In addition, the mean deviation of the optimal directional segment used post optimisation from the AC – PC axis was calculated and presented for each side effect category.

5.2.6 Charge per pulse

The charge per pulse (Qp) at was calculated using the efficacy threshold for RM60, RM30, DIR60 and DIR30 conditions using data from study 3, using: Qp (ET) = A (ET) x PW. This was done for individual patients on each stimulation condition. ANOVA was performed to look for any significant differences across the 4 groups, followed by pairwise tests for between-group comparisons. This was done for the entire set of patients, and for each subgroup of side effects separately. The Bonferroni correction method was applied for multiple comparisons.

5.3 Results

There were 13 patients (18 STNs optimised) in the dysarthria group, 15 in the dyskinesia group (17 STNs optimised), and 5 in the pyramidal side effect group (7 STNs optimised). Of the 32 patients optimised in total, post-operative CT scans were done for 31. In the results and figures that follow, these are labelled S1 – S13, D1 – D15, P1 – P5 respectively, with *a* and *b* indicating left and right hemispheres respectively where both were optimised in a single patient. One patient from the dysarthria group in the clinical study did not have a post-operative CT scan done (S9) and VTAs could not be modelled. One patient was in both the dysarthria and pyramidal side effect group due to concurrent presenting side effects (S10/ P5).

Co-registration of images, lead detection and orientation, and automatised segmentation of basal ganglia nuclei was successfully performed and reviewed for all patients who had post-operative CT scans. Minor manual adjustments to the borders of the automatised STN segmentation were performed for 18 STNs.

5.3.1 Lead location, orientation, and VTA modelling

VTAs were modelled for 40 STNs. The mean deviation of the anterior marker of the lead in the axial plane was 36.2 ± 25.4° either medially or laterally from the AC - PC axis. In 33 leads, the rotation was not significant enough to relabel the segmented contacts, or for the majority of current to switch to the default direction of an adjacent segment (i.e. the deviation was less than 60°). The mean angle of the long axis of the STN in the axial plane relative to the AC – PC line was 35.4 ± 4.7°. A description of the active contact location within each STN, the orientation of the optimal directional segment used, and angle of side effects as detailed in the method are presented in table 5.1.

The volume of the baseline stimulation field was 0.06 ± 0.03 cm^3 [median 0.06, range 0.01 – 0.13], and post-optimisation this was 0.07 ± 0.04 cm^3 [median 0.07, range 0.01 – 0.19], with no significant differences between the two on paired comparisons (Z = 1.86, *P* = .06).

Individual VTAs for each optimised STN are shown in figures 5.4 – 5.44. 3D models are shown on the left (anterior view), accompanied by segmented nuclei and VTAs marked on the patients' T2 weighted MRI scans on the right, consisting of an *inline* view (along axis of the lead) at the top right, and a perpendicular view to this at the bottom right. An example with labels to illustrate these are shown in figure 5.3 below.

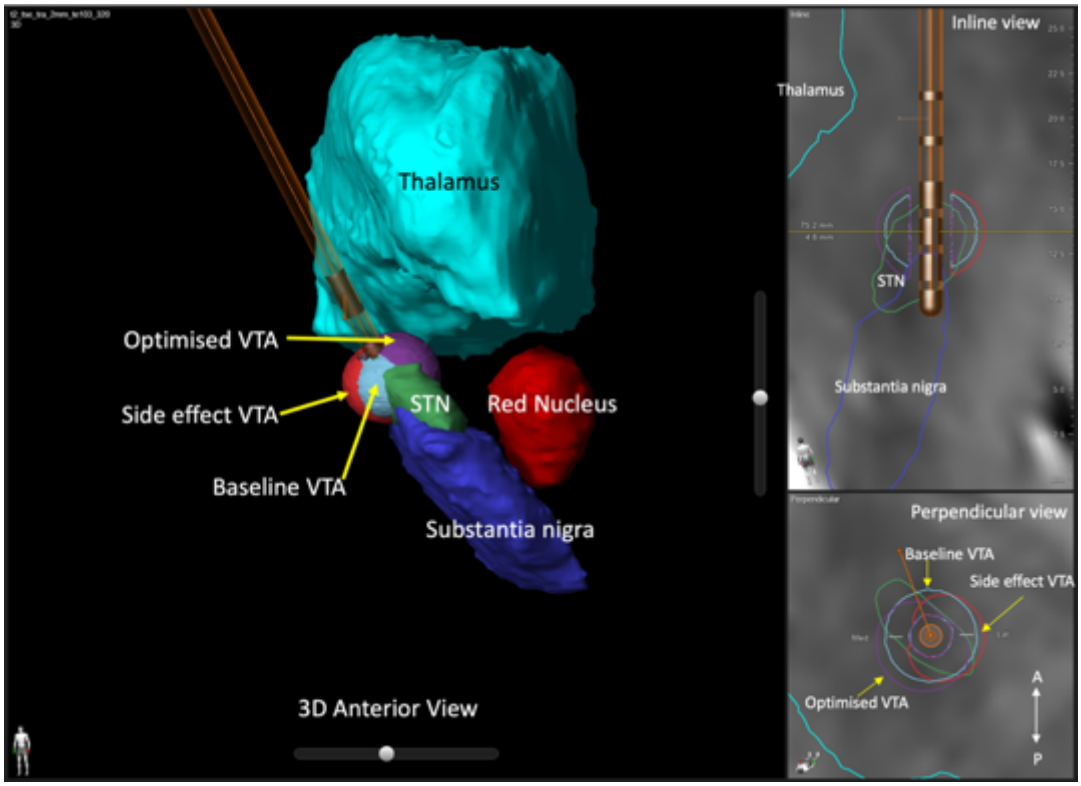


Figure 5.3. **VTA models on individualised template of basal ganglia nuclei and lead placement**

Legend for VTAs: Baseline – Light blue, Optimised – Purple, Direction with lowest side effect threshold – Red

Table 5.1. **Active contact location, orientation, and shift in VTA with optimisation for each STN optimised**

Patient (STN)	Active contact location in STN			Orientation of directional contact used relative to AC – PC axis (Direction, [a] angle [b])		Side effect angle [b] relative to:		Volume of stimulation field (cubic centimetres)		VTA shift: Baseline to post-optimisation	
	Superior /Inferior	Anterior /Posterior	Medial /Lateral			AC-PC axis	STN long axis	Baseline	Optim -ised		
S1	S	P	L	AL	24.9	294.9	327	0.07	0.05	PM*	PL
S2	S	A	L	A	3.3	123.3	154.8	0.06	0.10	M, L	A
S3	Mid-S	Mid-A	L	AM	-32.6	207.4	242.6	0.05	0.04	M	AL
S4	I	Mid-A	L	AM	-26.4	206.4	247.8	0.03	0.02	M	L
S5a	Mid	Mid-A	Mid	A	-15.6	224.4	255.6	0.07	0.07	M	AL
S5b	S	P	Mid	A	-16	196	237.4	0.03	0.05	PM	PL
S6a	S	P	L	AL	30.5	210.5	242.9	0.04	0.10	PM	PL
S6b	Mid	Mid-P	L	AM	46.5	135.5	170.5	0.03	0.07	PM, PL	A
S7a	Mid	Mid-P	L	L	81.5	261.5	291.6	0.05	0.07	M*	L
S7b	Mid-S	P	L	A	-8	128	163.1	0.08	0.11	PM	L
S8	Mid	A	M	M	-76.5	43.5	80.1	0.09	0.09	AL*	AM
S9	S	P	L	(Post-operative CT not done – VTA not modelled).							
S10	Mid-S	A	L	PM	-127.4	112.6	145.1	0.03	0.02	L	C,M
S11	S	A	L	AM	-49.7	70.3	102.7	0.12	0.08	AL	AM
S12a	Mid	P	Mid-L	A	3.7	243.7	275.3	0.09	0.07	PM	PL
S12b	Mid-S	P	Mid	AM	23.1	96.9	129.3	0.06	0.1	P	P*

S13a	Mid	Mid-A	L	AL	53	293	320	0.02	0.04	M	L
S13b	Mid-S	A	L	A	15.3	224.7	263.9	0.03	0.04	M*	AL
Mean					**-8.2**	**180.6**	**214.7**	*(At bottom of table for entire set of data)*			
SD					**49.8**	**76.4**	**75.7**				
D1	Mid	Mid	L	A	20.1	260.1	305.8	0.11	0.08	M	L
D2	Mid-S	Mid-P	Mid-L	A	7.7	187.7	224.1	0.06	0.05	PM	C
D3	S	P	L	AM	-35.4	84.6	118	0.13	0.06	PL	A,C
D4	Mid-S	P	M	AM	55.4	64.6	95.9	0.12	0.19	PL	M,C
D5	S	Mid-P	Mid-L	PM	137.8	102.2	141	0.05	0.05	L	C
D6a	Mid-I	Mid-P	L	PM	-118.1	121.9	157.2	0.04	0.04	L	C
D6b	Mid-I	A	L	AM	53.9	66.1	107.7	0.05	0.08	L	AM
D7	Mid-S	P	Mid	AM	31	89	122	0.10	0.08	PL	M,C
D8	Mid-I	P	L	P	-164	76	110.7	0.07	0.04	L	P*
D9	Mid-I	P	L	M	84.3	144.3	181.2	0.03	0.04	L, PL	C
D10	Mid	A	L	AM	29.7	90.3	130.9	0.06	0.05	L	AL
D11	Mid-S	P	L	A	2.3	122.3	151.7	0.03	0.09	PL	C,L
D12a	Mid-I	Mid	L	AM	-30	90	125.3	0.01	0.01	PL	C,L
D12b	I	Mid-A	L	P	157.1	37.1	75.4	0.02	0.04	L	C,P
D13	Mid-I	Mid-P	L	A	-18.1	109.1	139.1	0.05	0.06	PL	C
D14	S	A	L	AM	-24.5	155.5	191	0.11	0.15	PL	A
D15	Mid	Mid	L	AL	29.9	149.9	190.3	0.03	0.03	PL	C,L
Mean					**-32.8**	**114.7**	**151**	*(At bottom of table for entire set of data)*			
SD					**73.0**	**53.4**	**55.3**				

P1	Mid-I	A	L	L	-68.8	171.2	206.4	0.12	0.12	L	AM
P2a	Mid-S	Mid-A	L	AM	-25.5	94.5	128.4	0.7	0.05	L	C,M
P2b	Mid-S	P	L	M	72.2	47.8	85.6	0.05	0.08	L	AM
P3	I	A	L	AL	39.2	80.8	127.7	0.11	0.11	L	AM
P4a	Mid-S	Mid-P	Mid-L	AM	-27.2	92.8	125.8	0.09	0.12	L	AM
P4b	I	Mid-P	Mid-M	AM	49.2	130.8	163.8	0.09	0.12	M,L	C
P5	Mid-S	A	L	PM	-127.4	112.6	145.1	0.09	0.14	L	C
Mean					**-58.5**	**104.4**	**140.4**	**0.063**	**0.071**		
SD					**35.5**	**39.2**	**37.5**	**0.033**	**0.038**		

Legend: A- Anterior, P- Posterior, M- Medial, L- Lateral, S- Superior, I- Inferior, AM- Anteromedial, AL- Anterolateral, PM- Posteromedial, PL- Posterolateral, C – Central; * Within STN

Patients with: Speech impairment: S1 - S13; Dyskinesia: D1 - D15; Pyramidal side effect: P1 - P5

a- Orientation of active contact is to the nearest octant relative to the AC – PC axis in the axial plane (as denoted in legend above). The midpoint of the segmented electrode is used to determine the angle relative to the AC – PC line. Where two directional contacts were used, the mean orientation is reported.

b- Angles standardised to those of left hemisphere for combined quantitative directional analysis

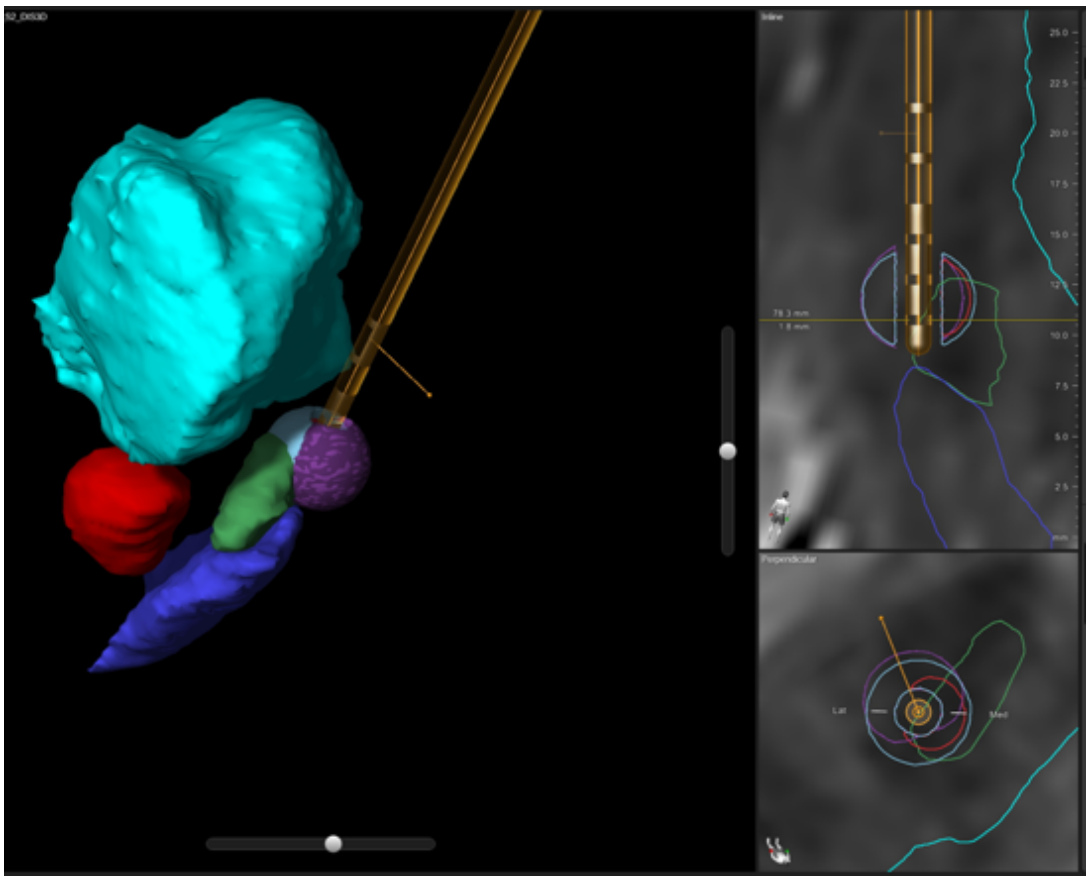


Figure 5.4. S1 – (L) STN

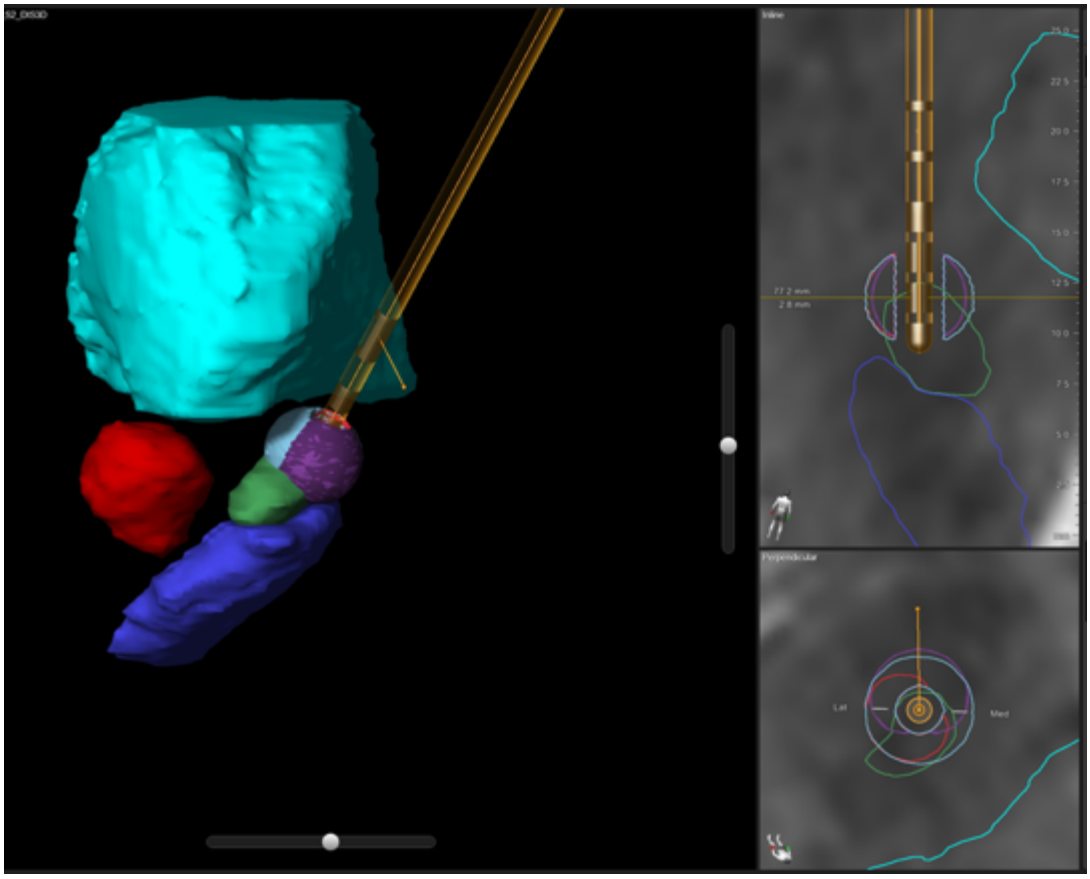


Figure 5.5. S2 – (L) STN

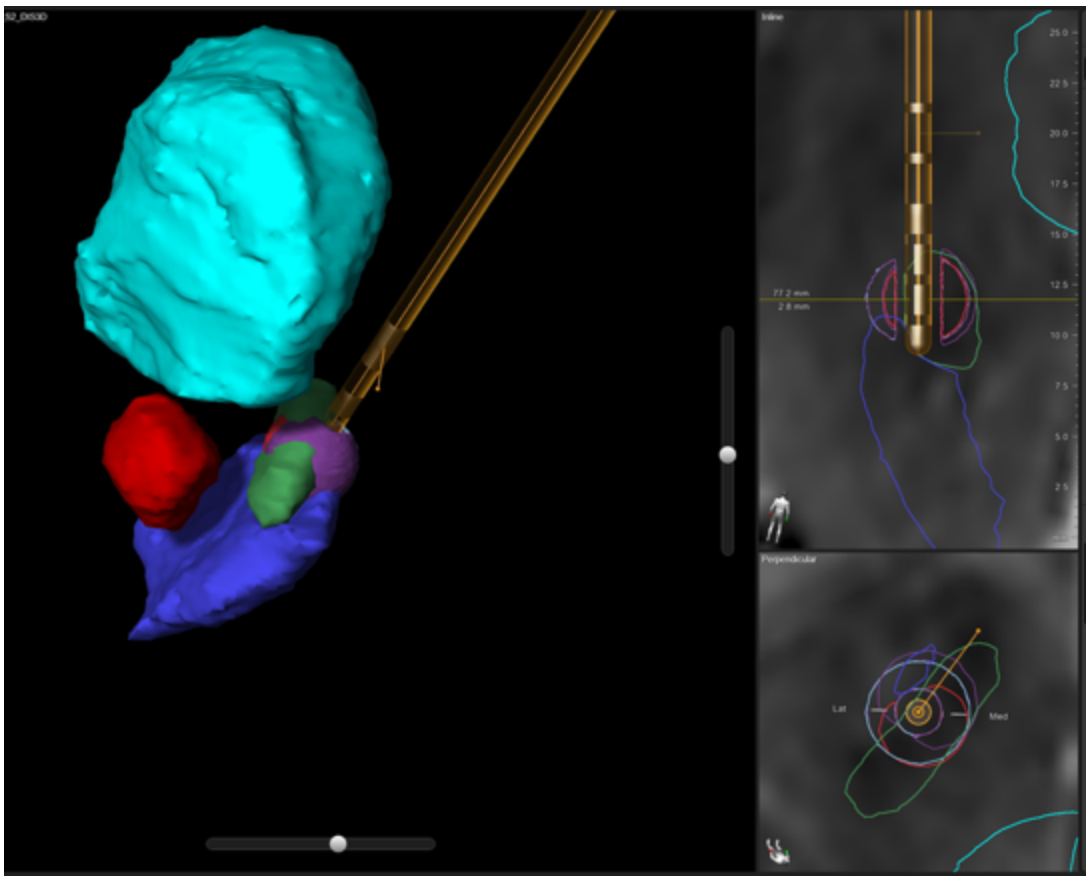


Figure 5.6. S3 – (L) STN

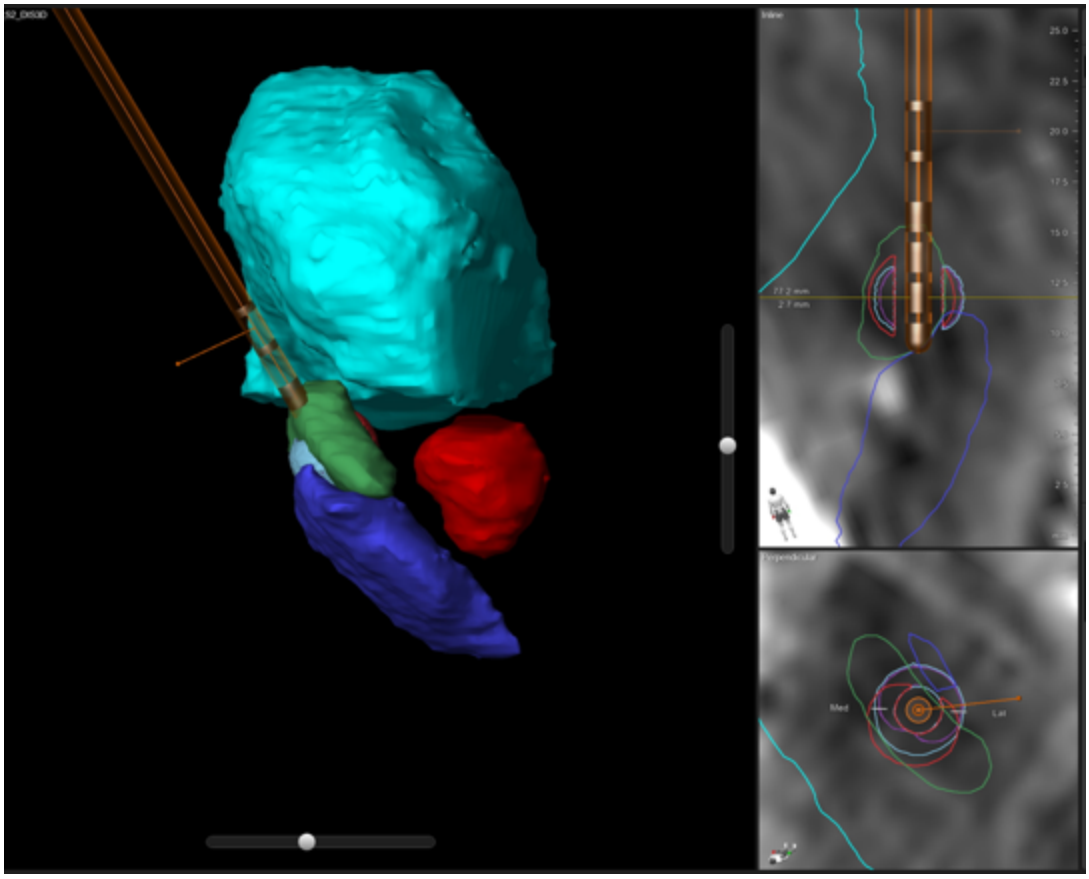


Figure 5.7. S4 – (R) STN

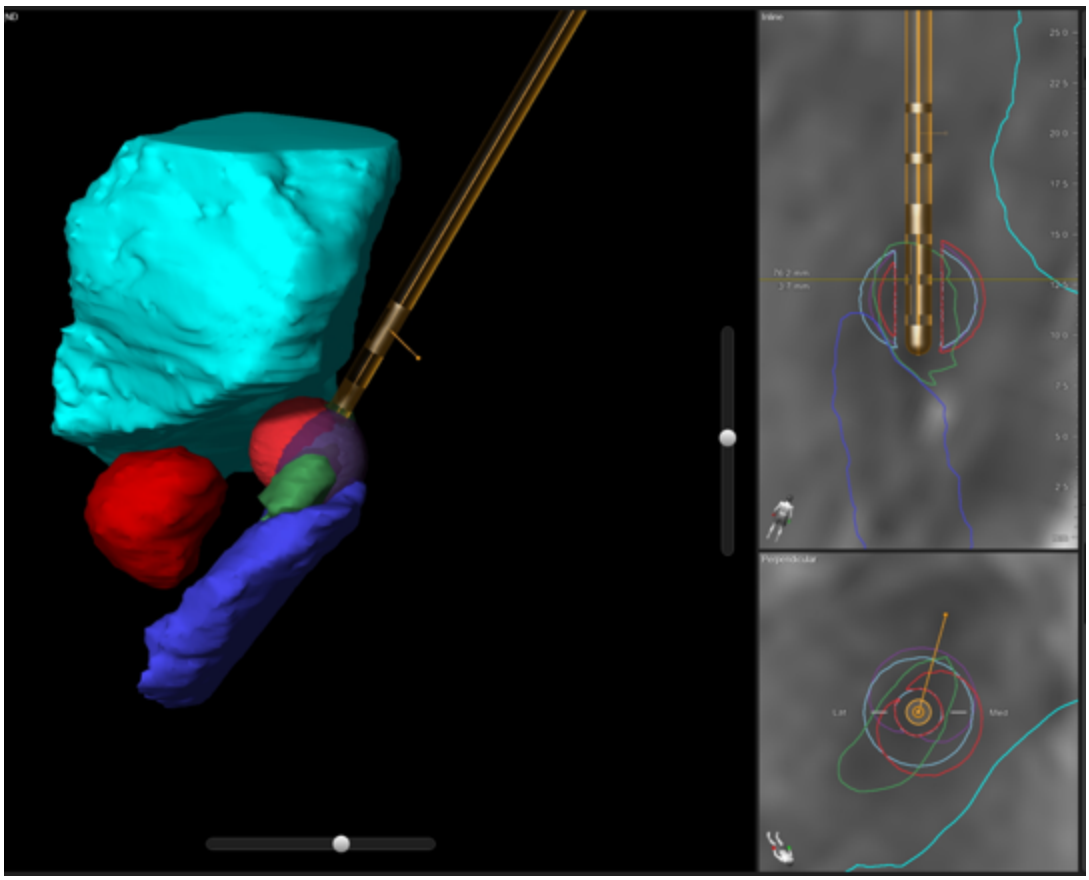


Figure 5.8. S5a – (L) STN

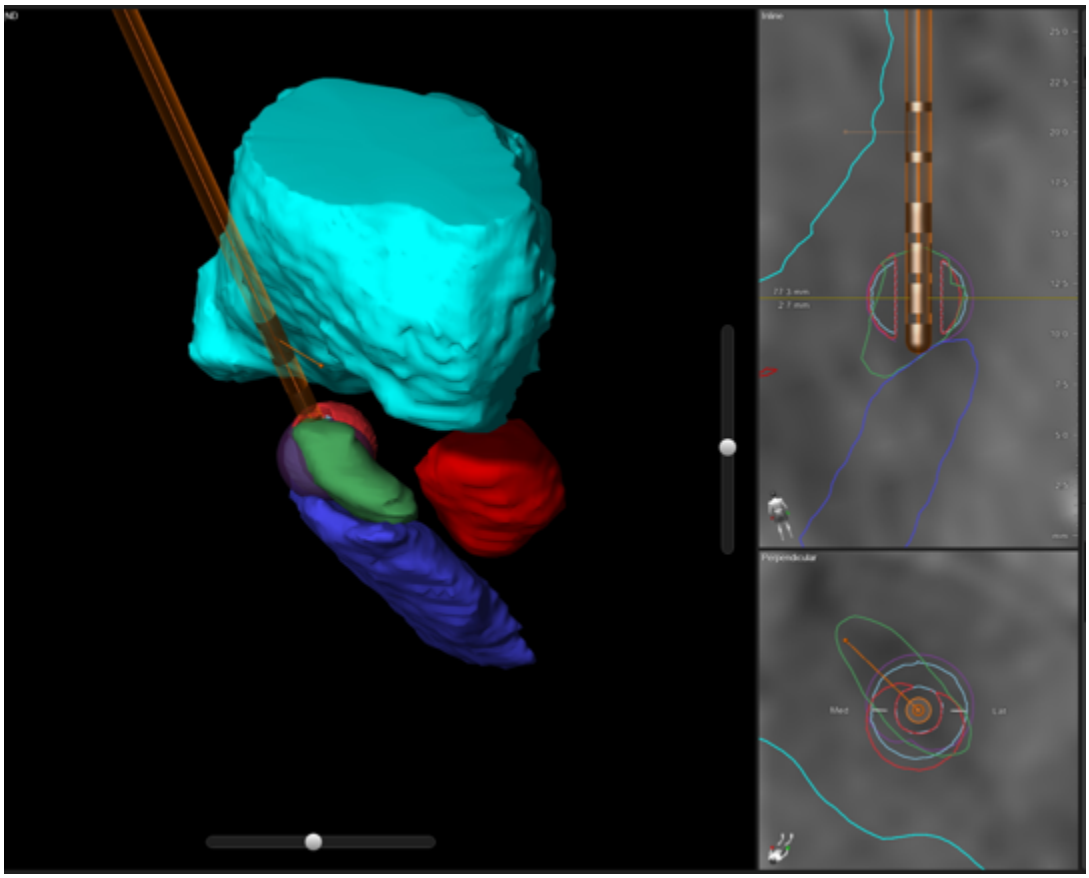


Figure 5.9. S5b– (R) STN

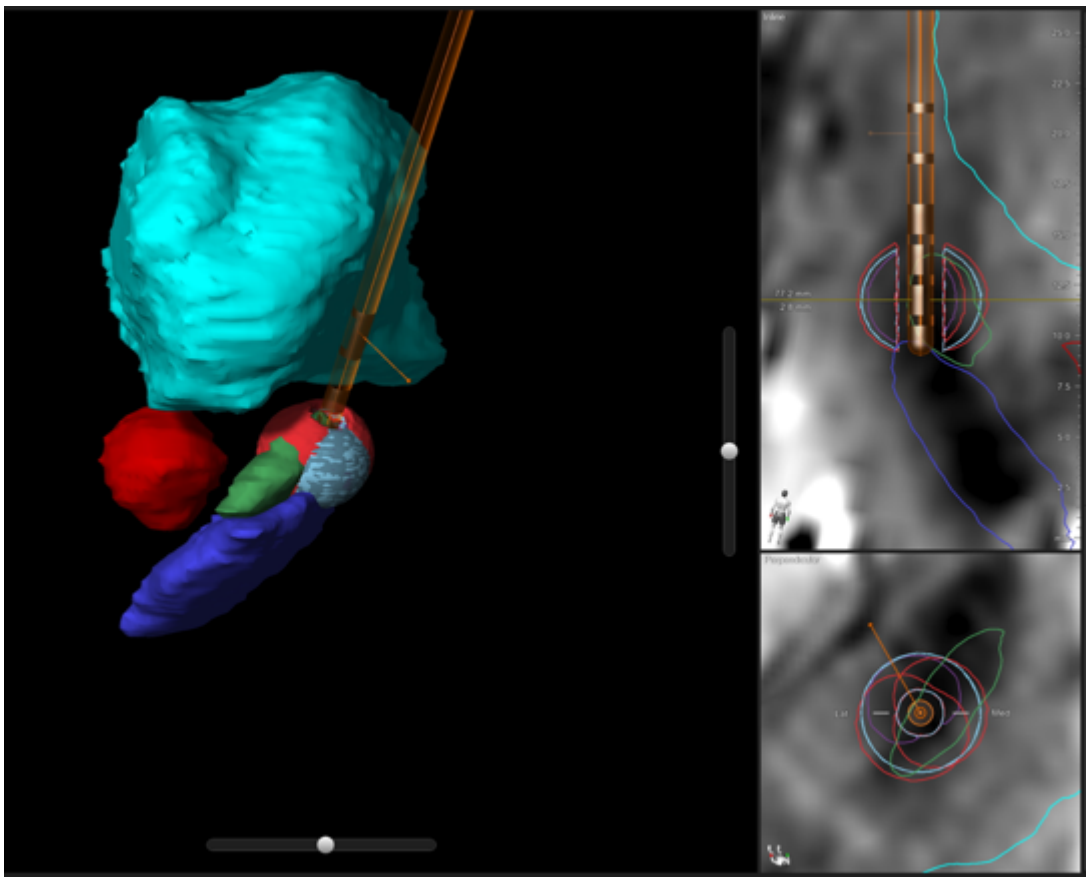


Figure 5.10. S6a – (L) STN

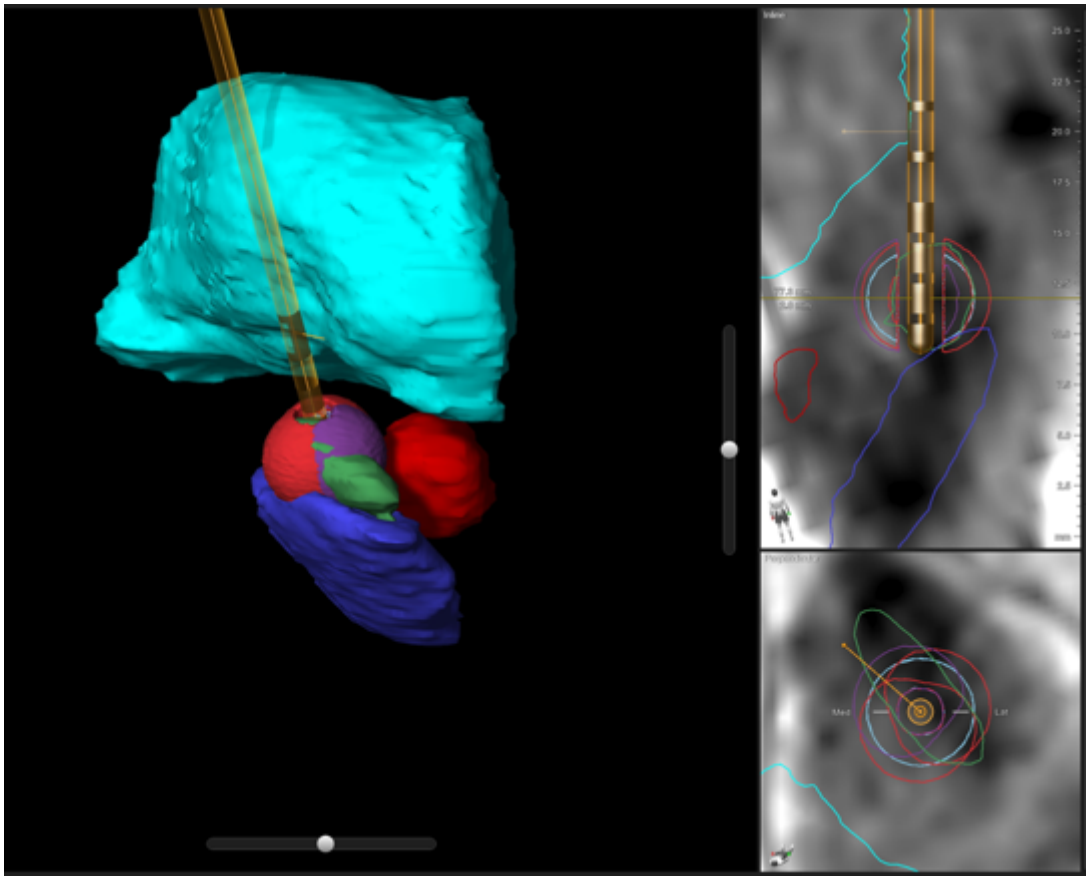


Figure 5.11. S6b – (R) STN

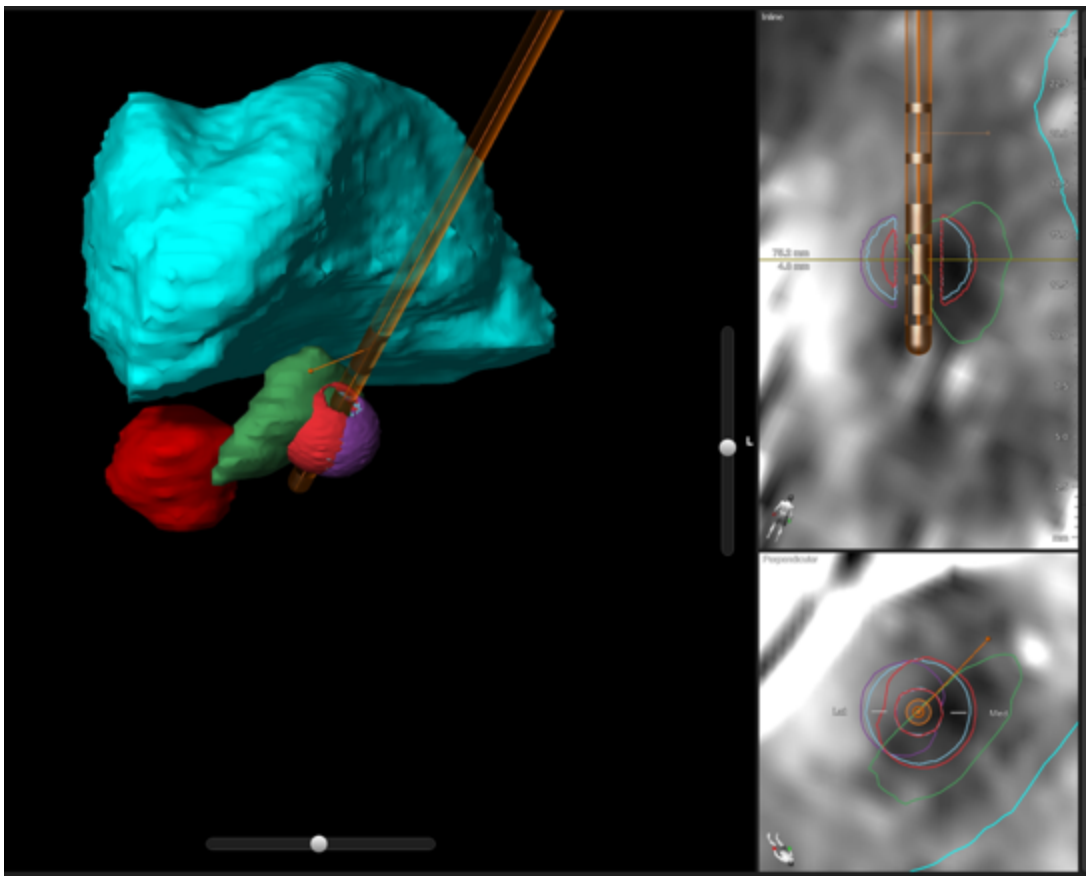


Figure 5.12. S7a – (L) STN

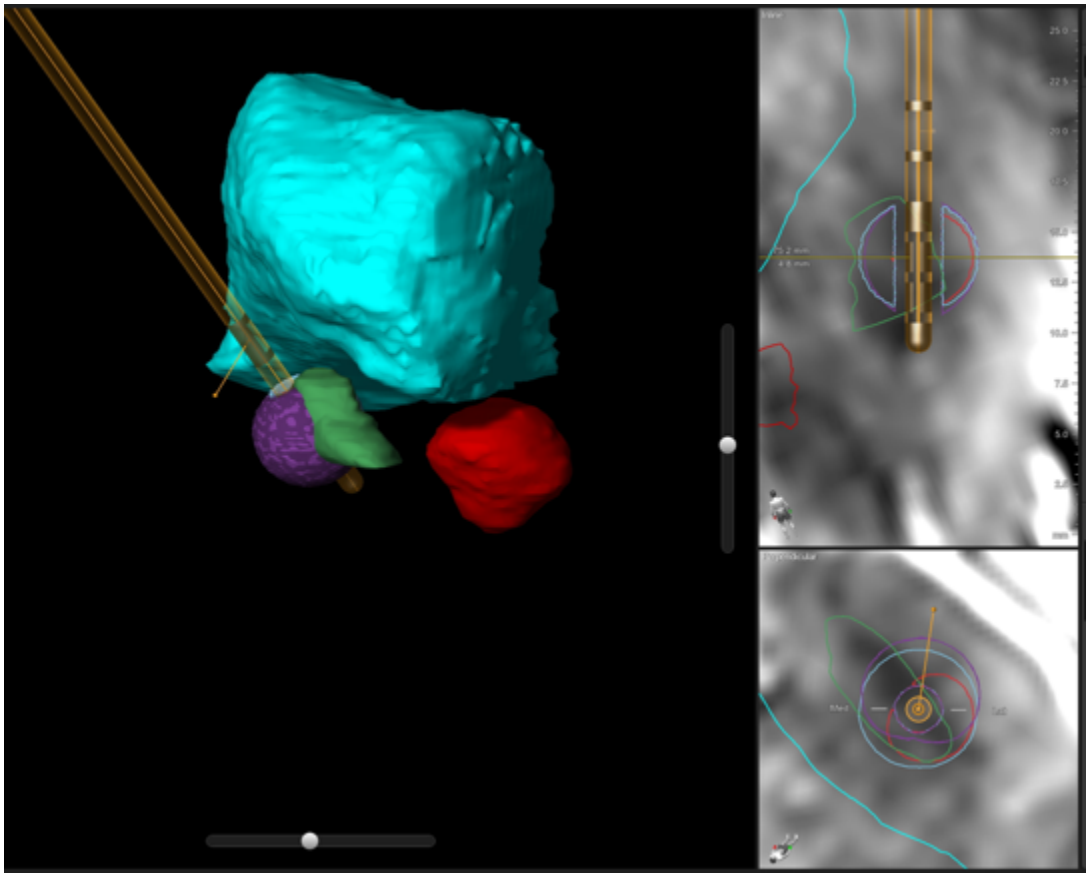


Figure 5.13. S7b – (R) STN

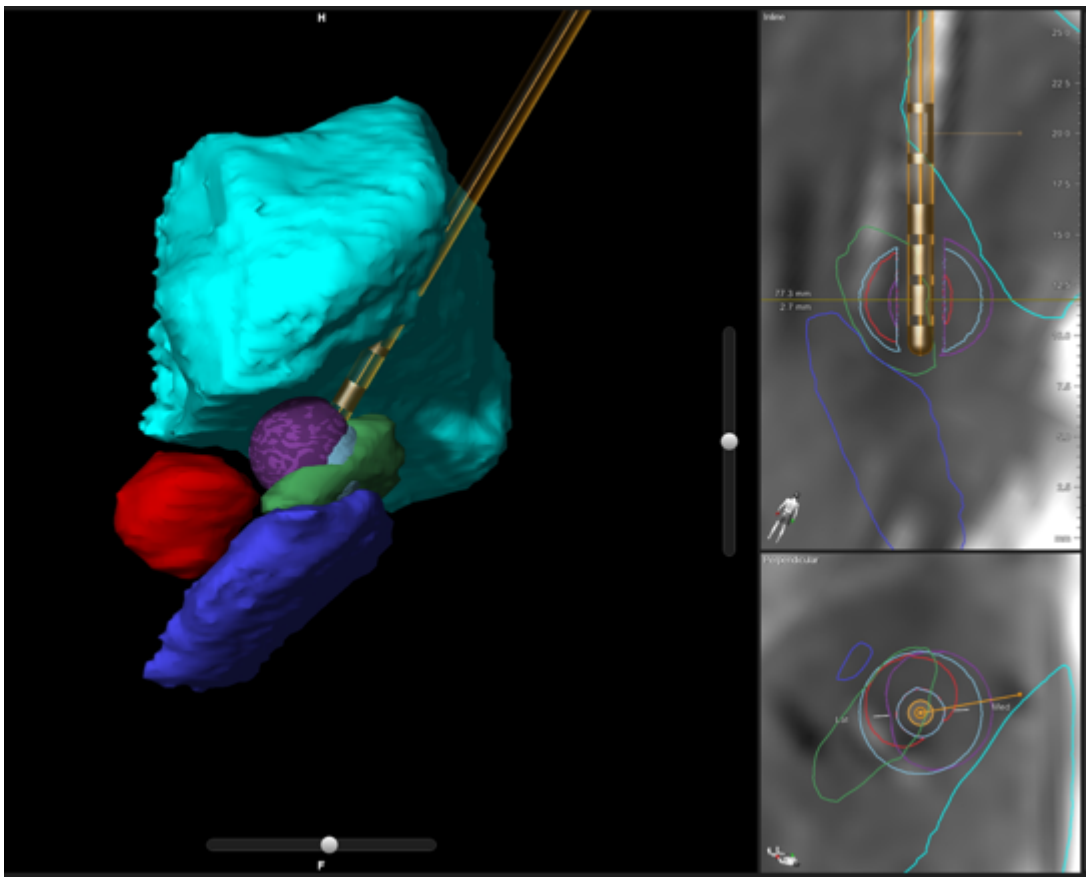


Figure 5.14. S8 – (L) STN

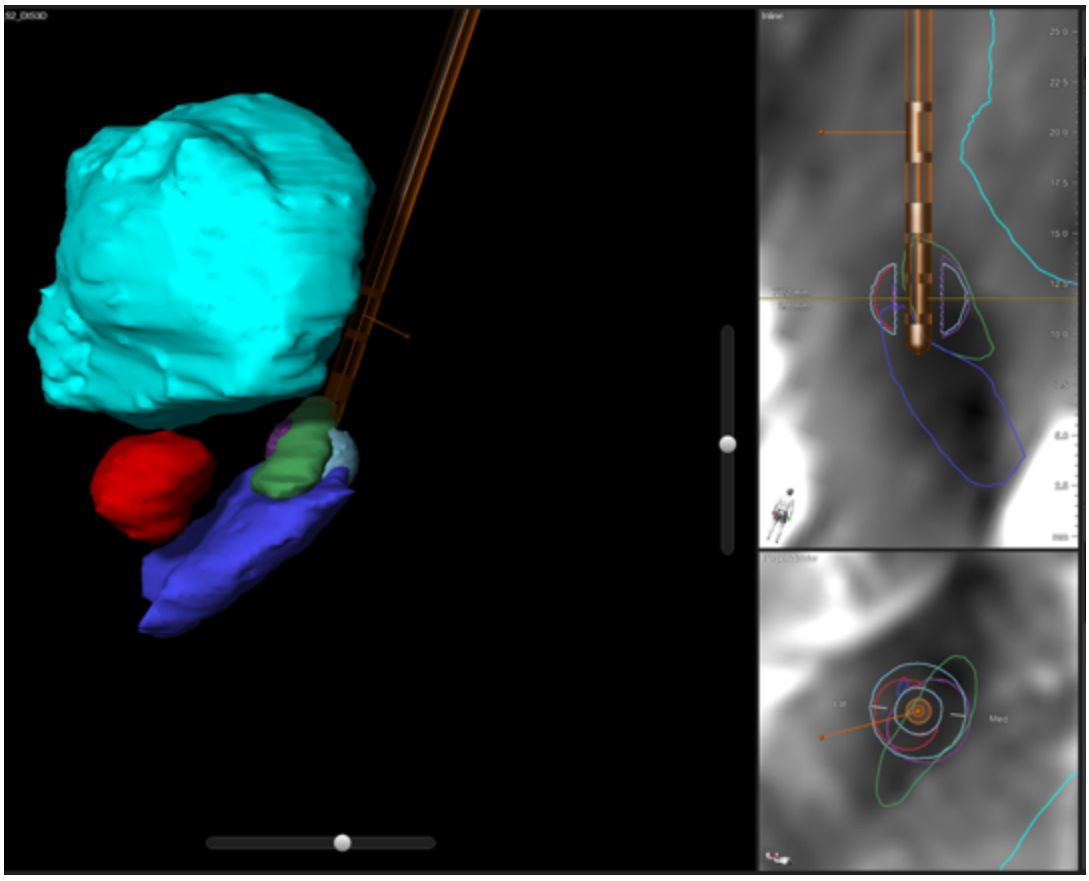


Figure 5.15. S10 – (L) STN

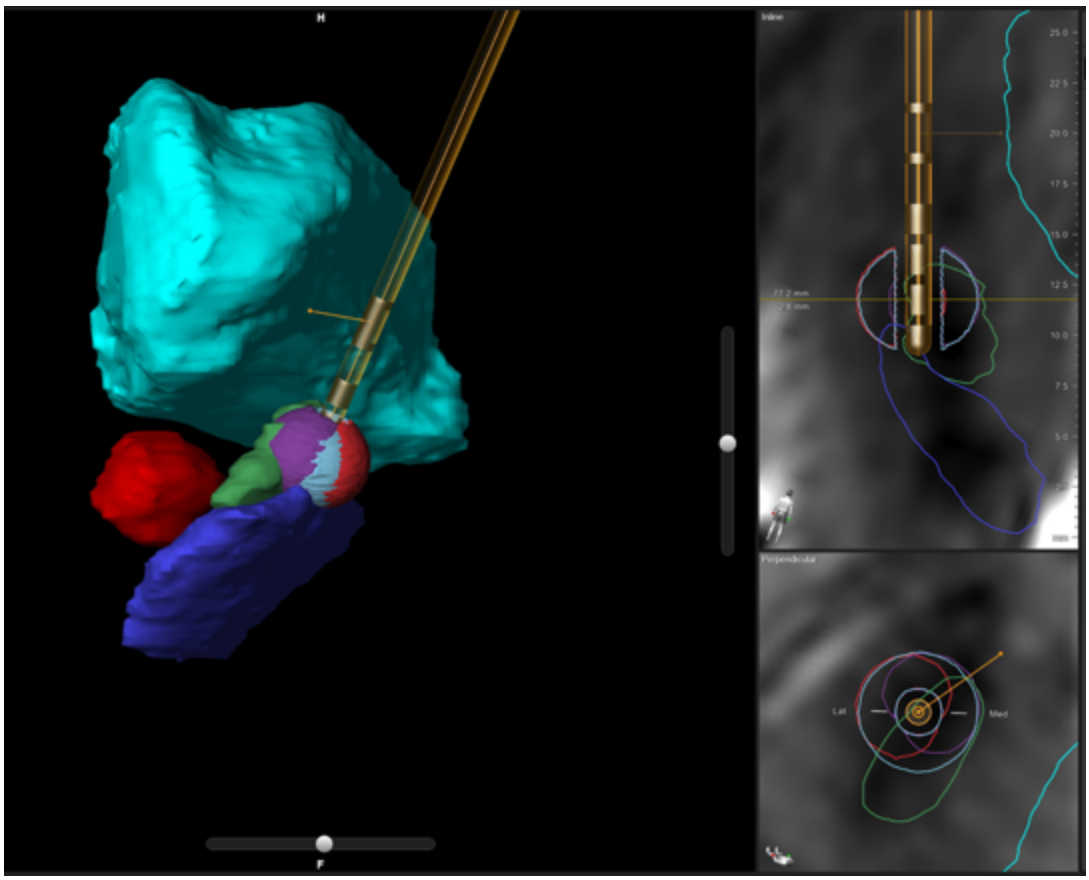


Figure 5.16. S11 – (L) STN

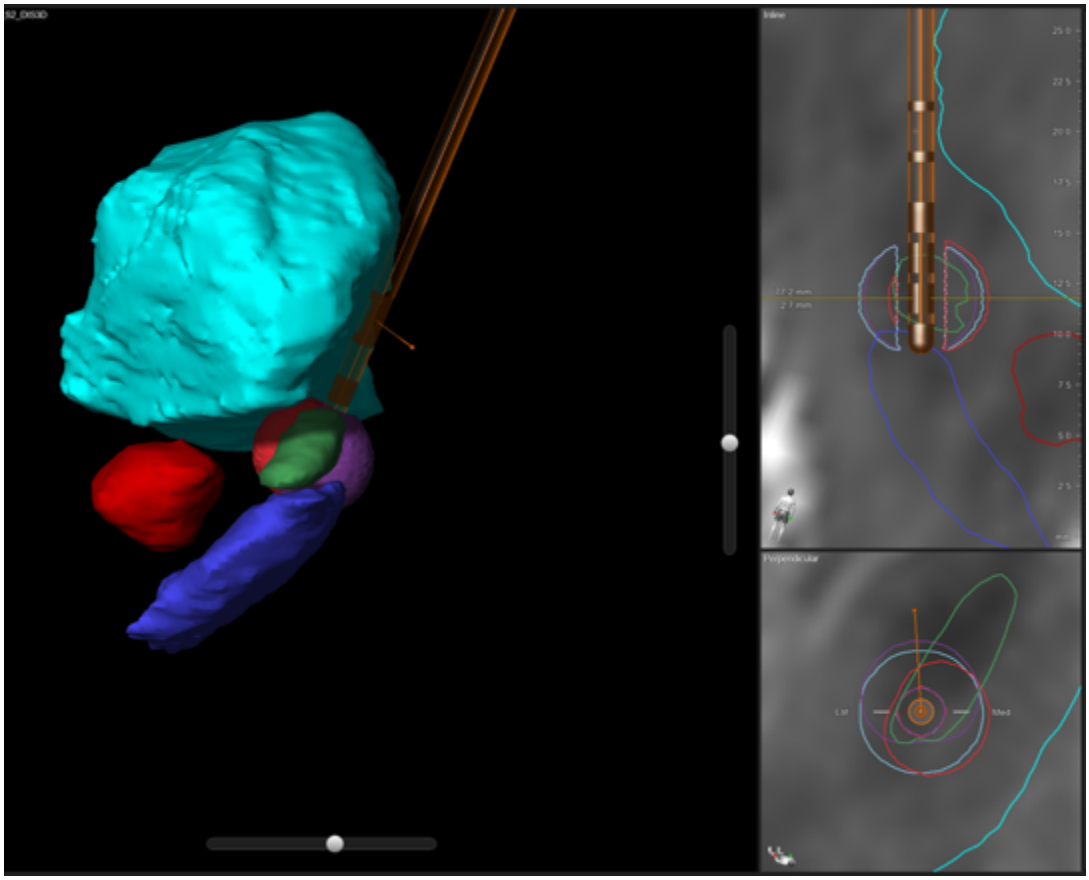


Figure 5.17. S12a – (L) STN

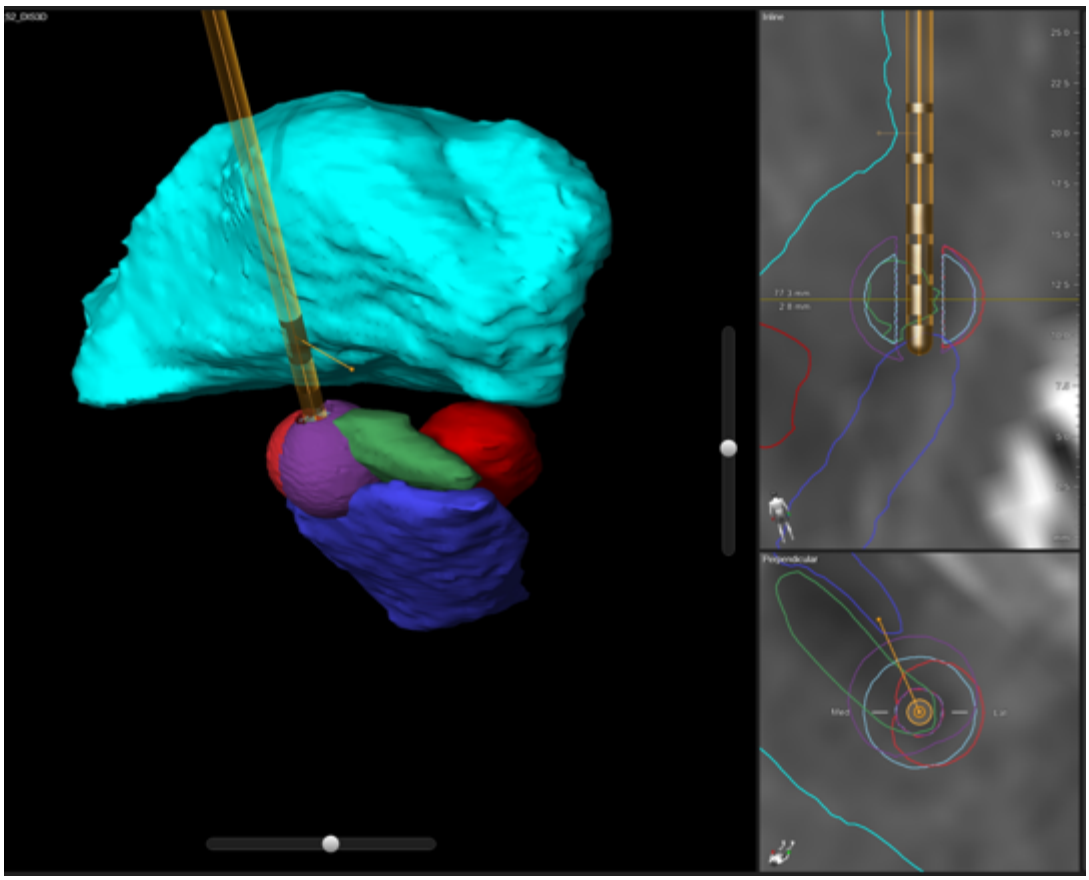


Figure 5.18. S12b – (R) STN

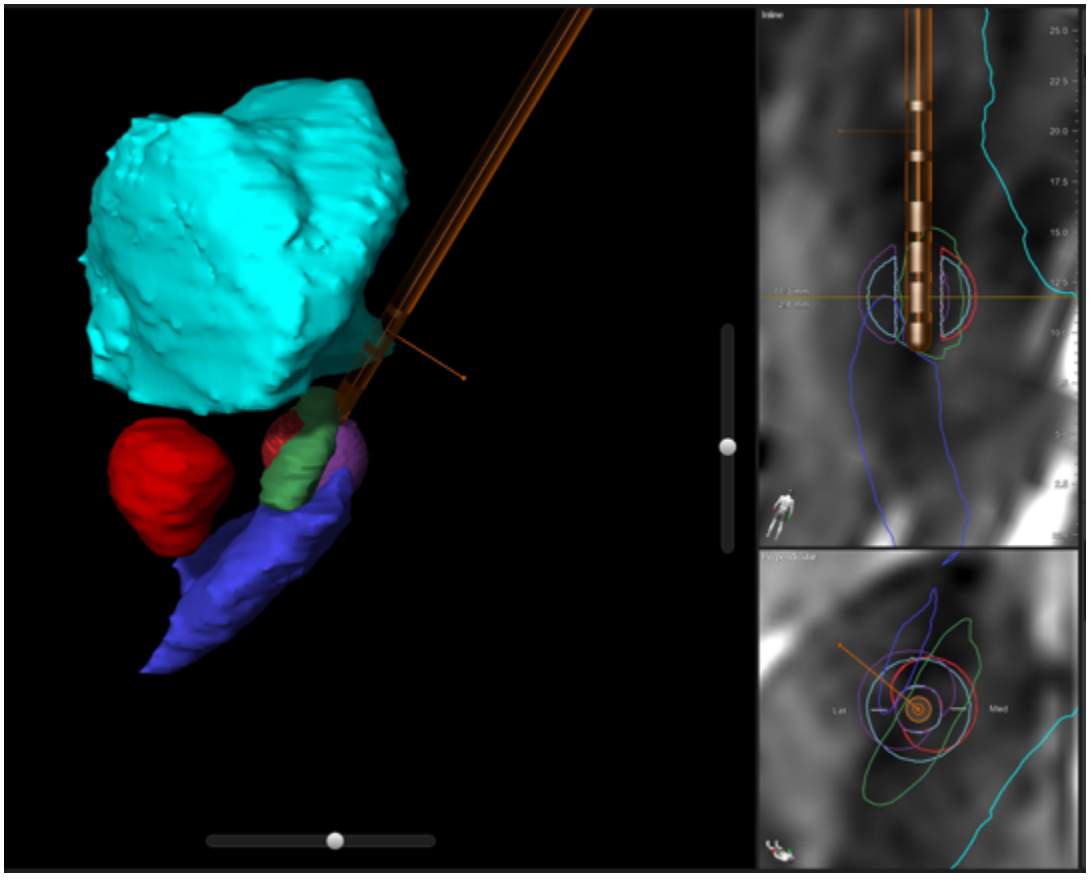


Figure 5.19. S13a – (L) STN

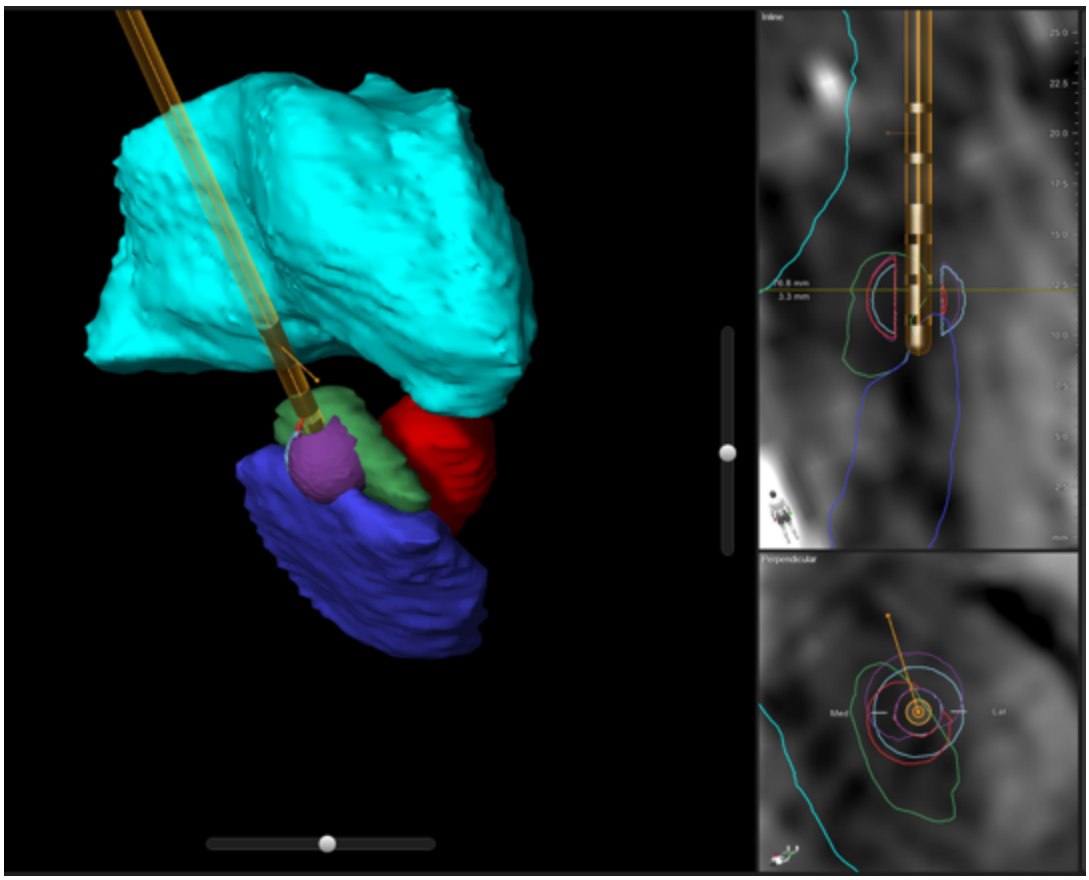


Figure 5.20. S13b – (R) STN

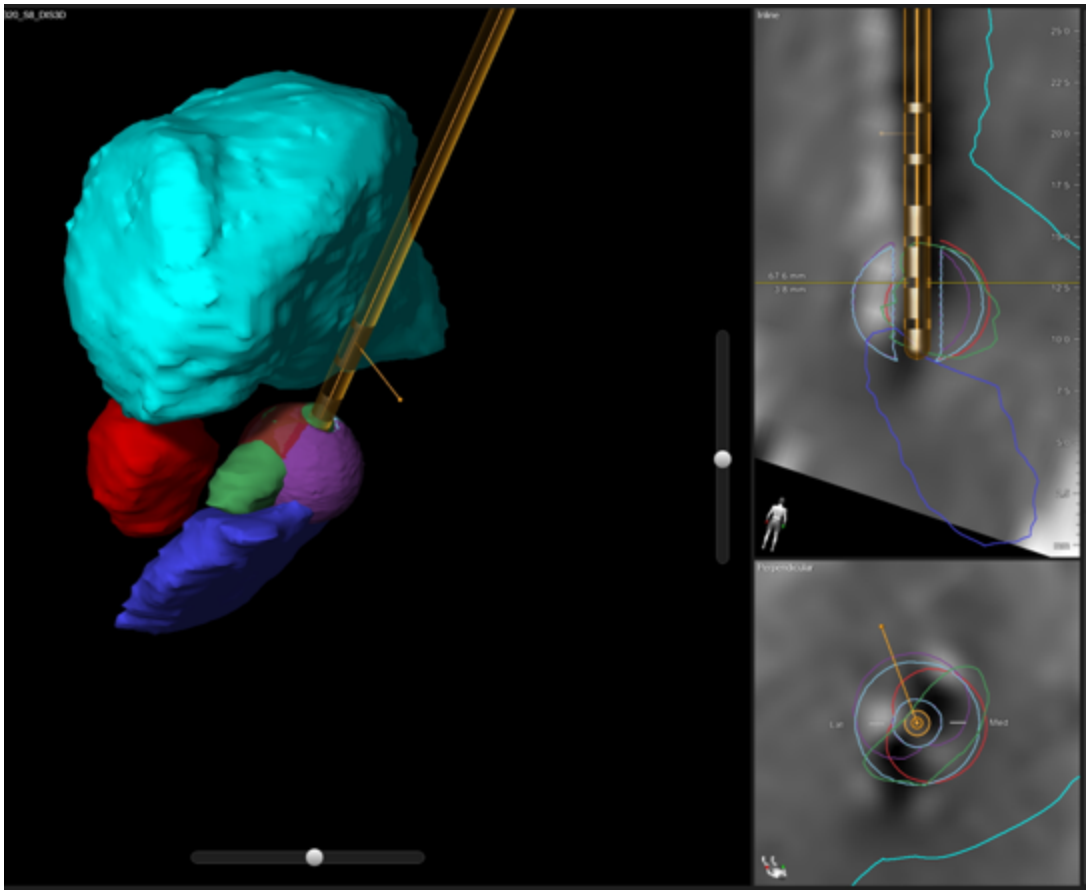


Figure 5.21. D1 – (L) STN

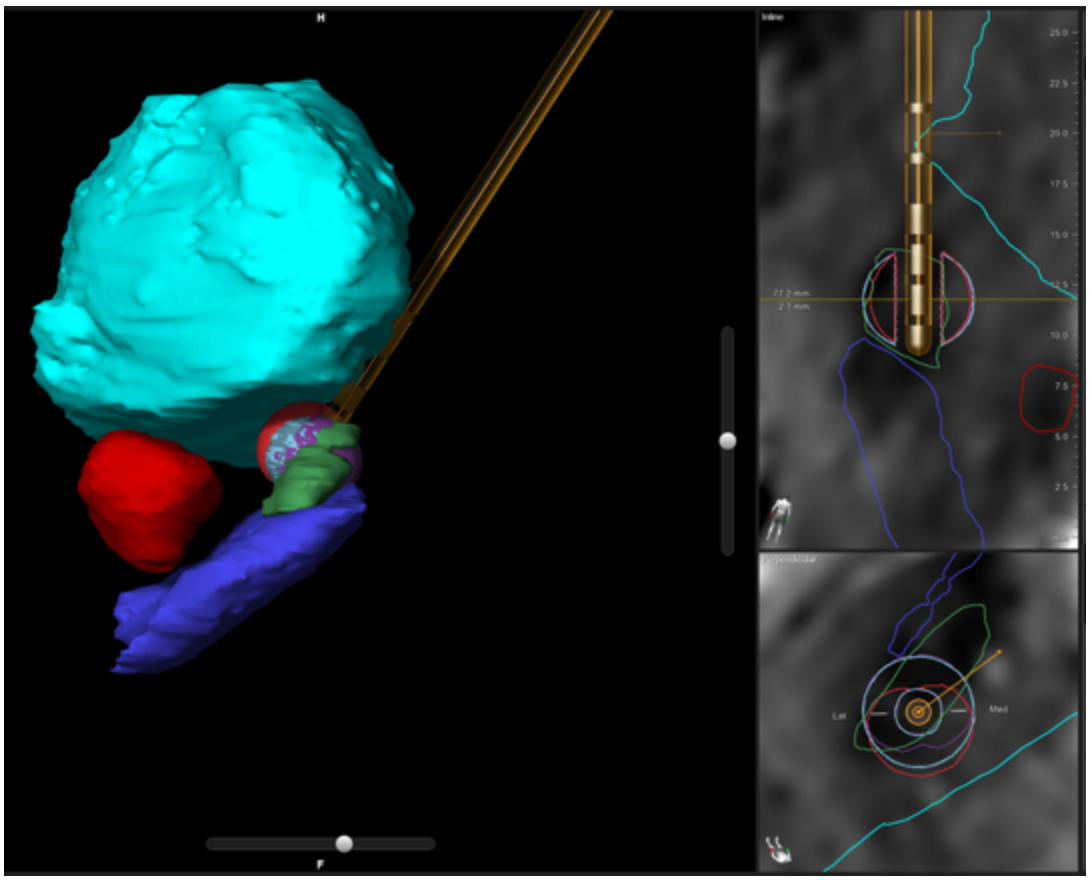


Figure 5.22. D2 – (L) STN

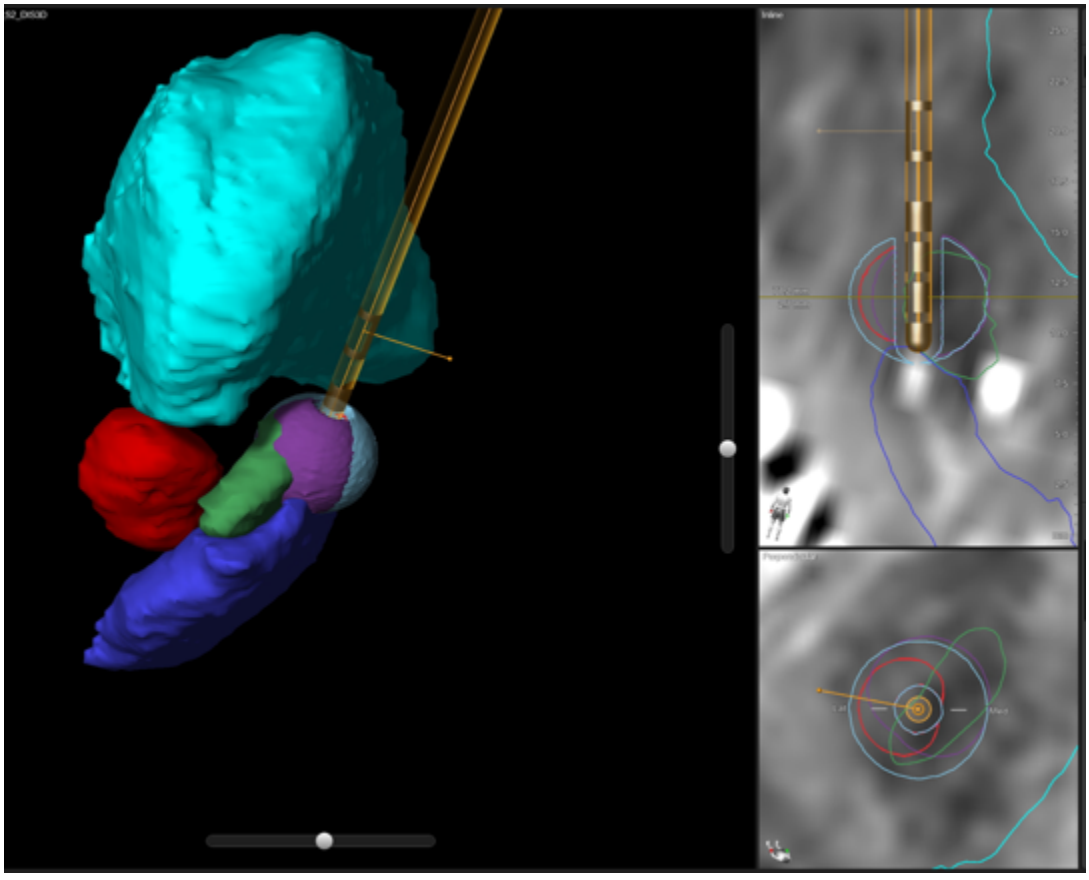


Figure 5.23. D3 – (L) STN

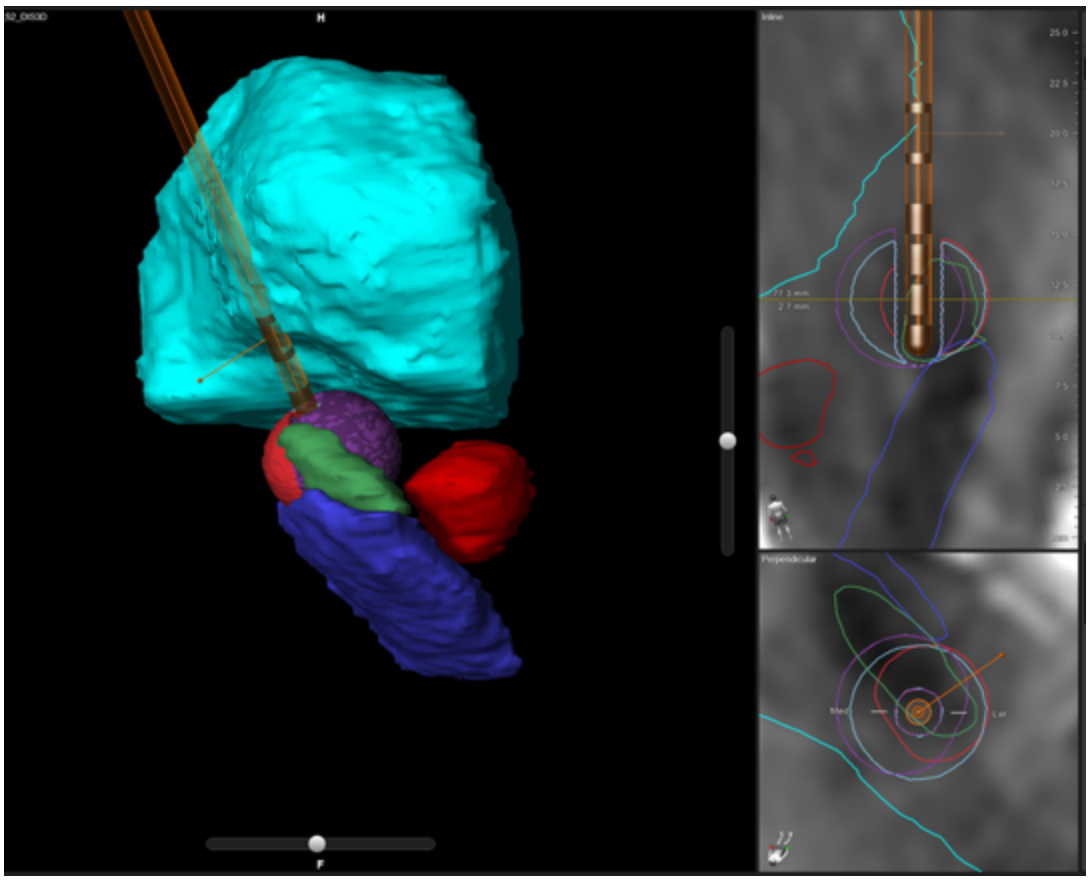


Figure 5.24. D4 – (R) STN

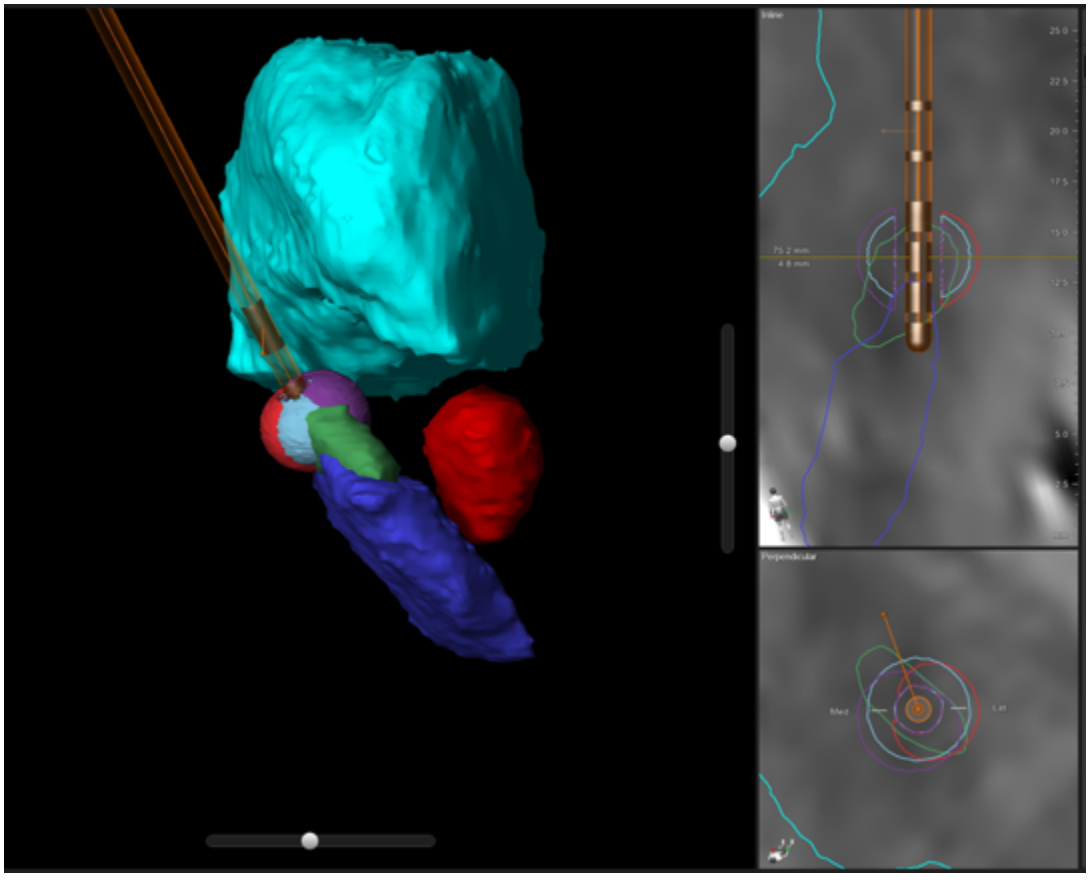


Figure 5.25. D5 – (R) STN

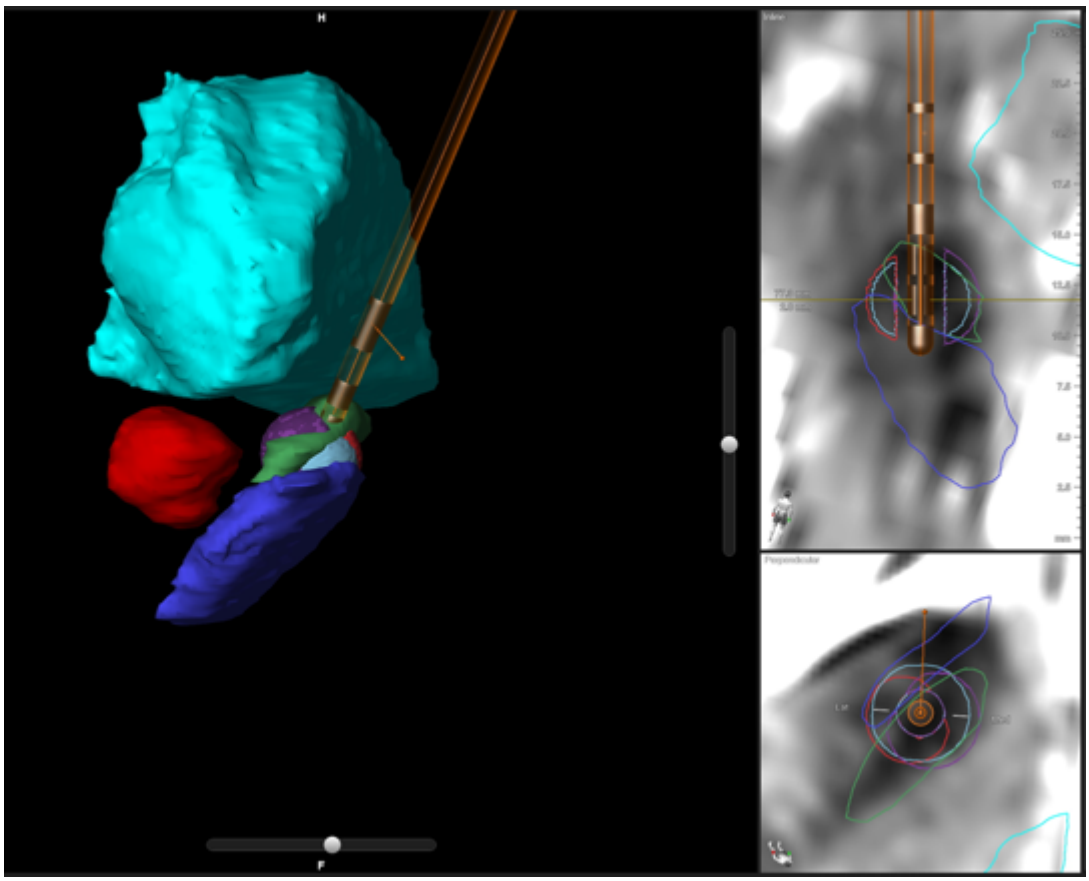


Figure 5.26. D6a – (L) STN

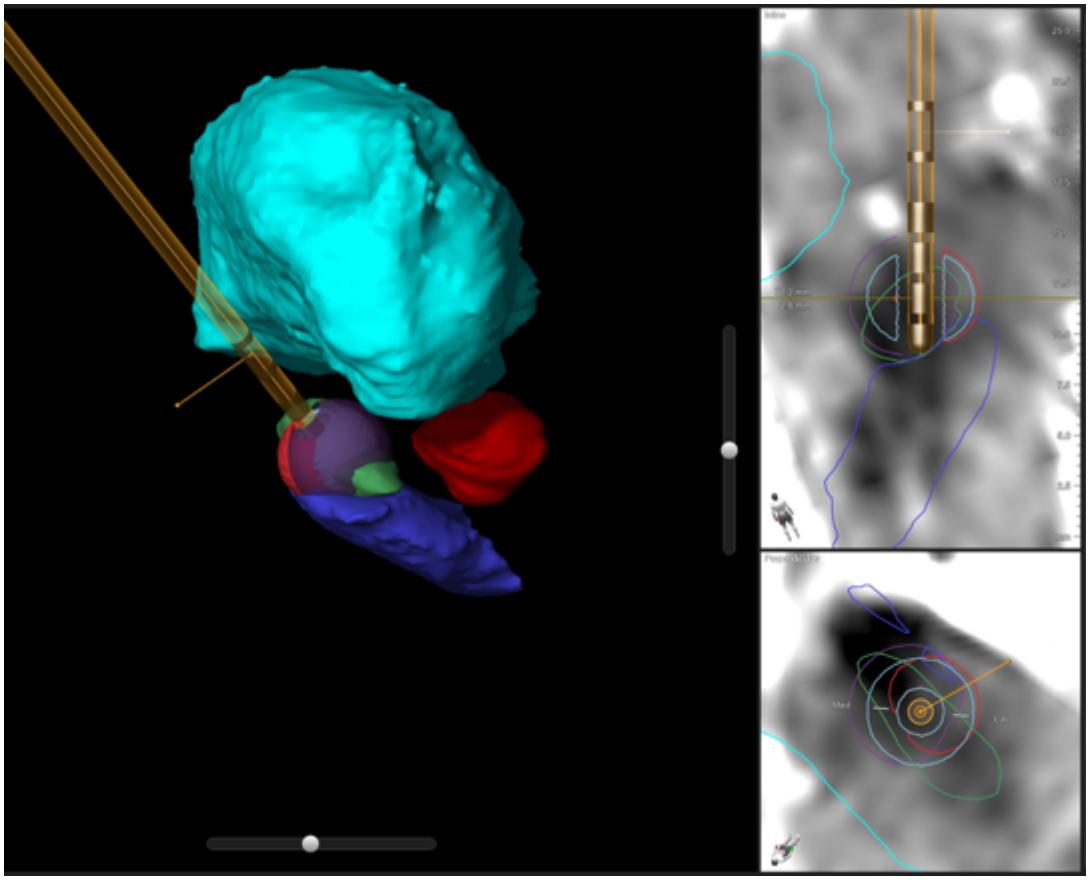


Figure 5.27. D6b – (R) STN

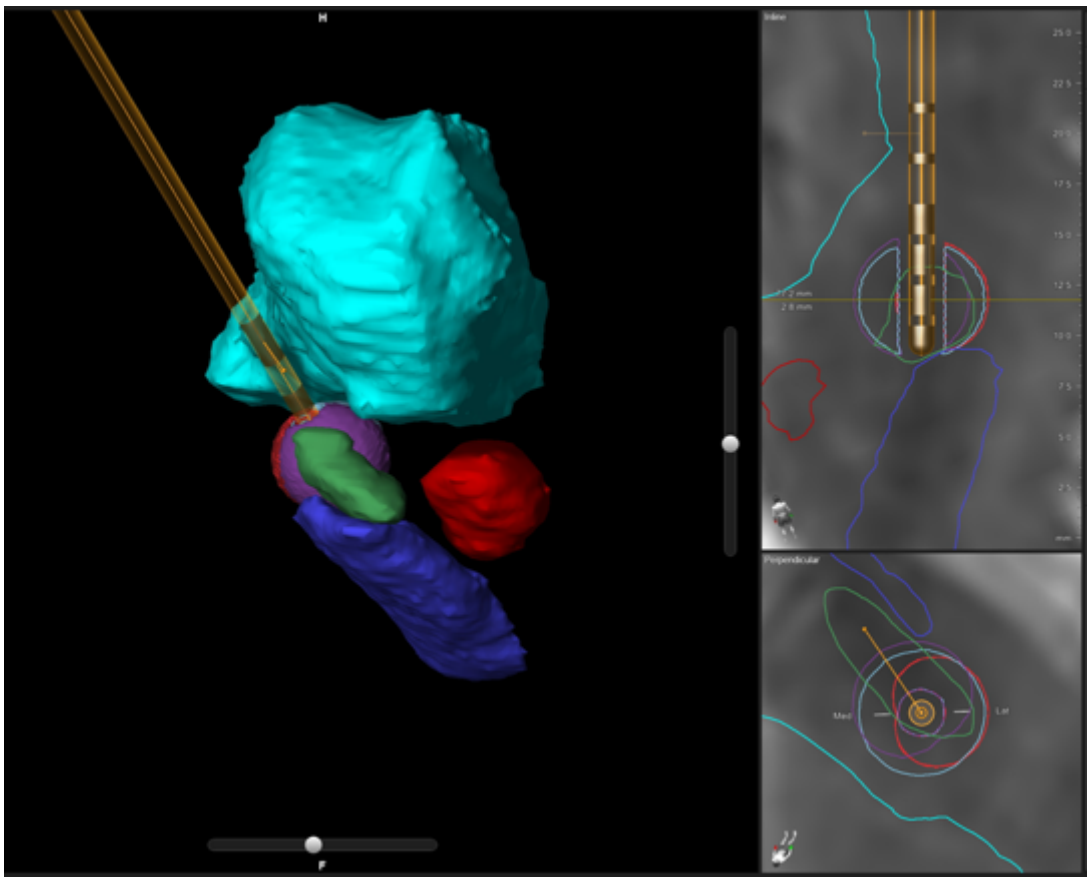


Figure 5.28. D7 – (R) STN

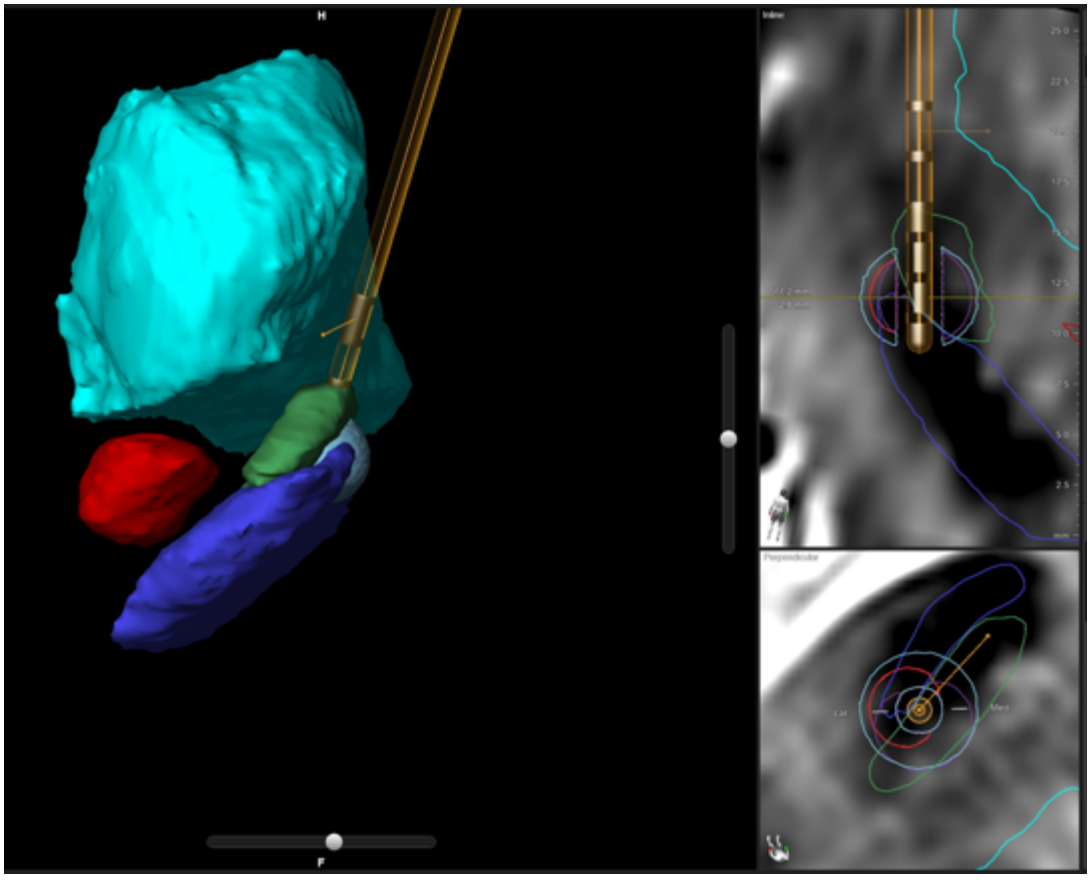


Figure 5.29. D8 – (L) STN

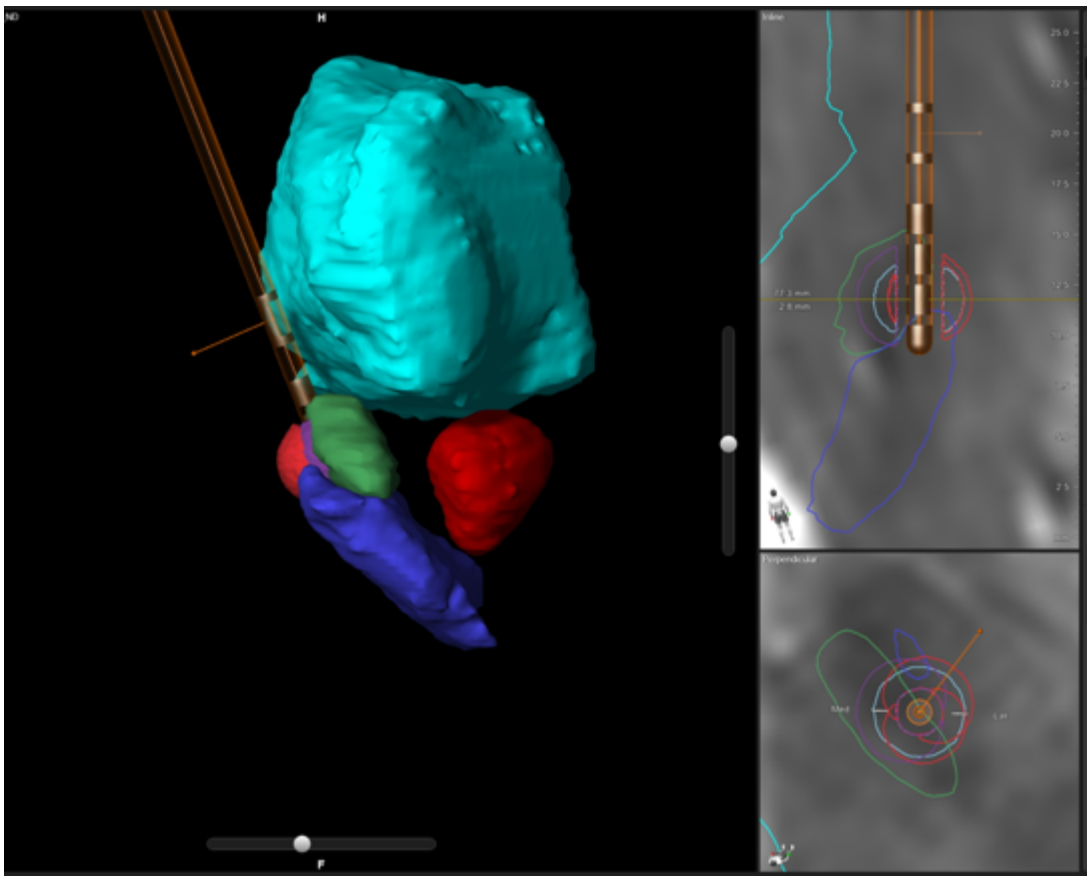


Figure 5.30. D9 – (R) STN

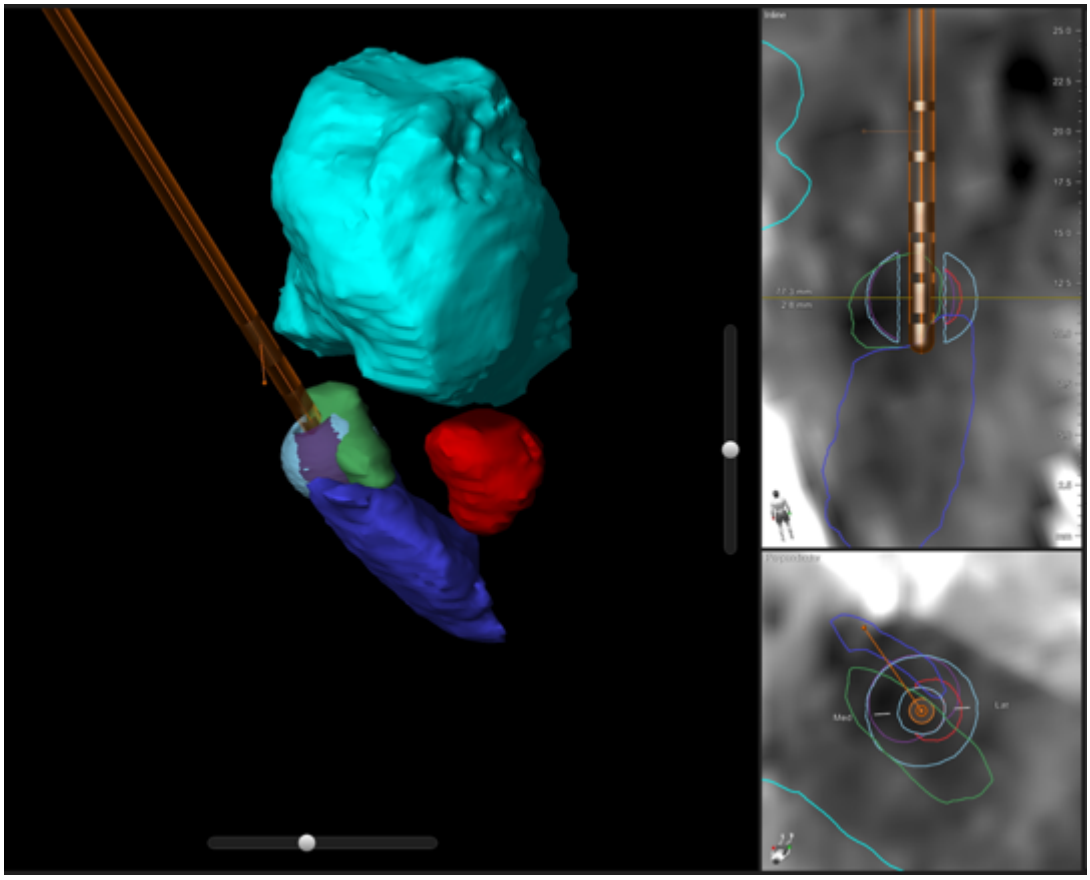


Figure 5.31. D10 – (R) STN

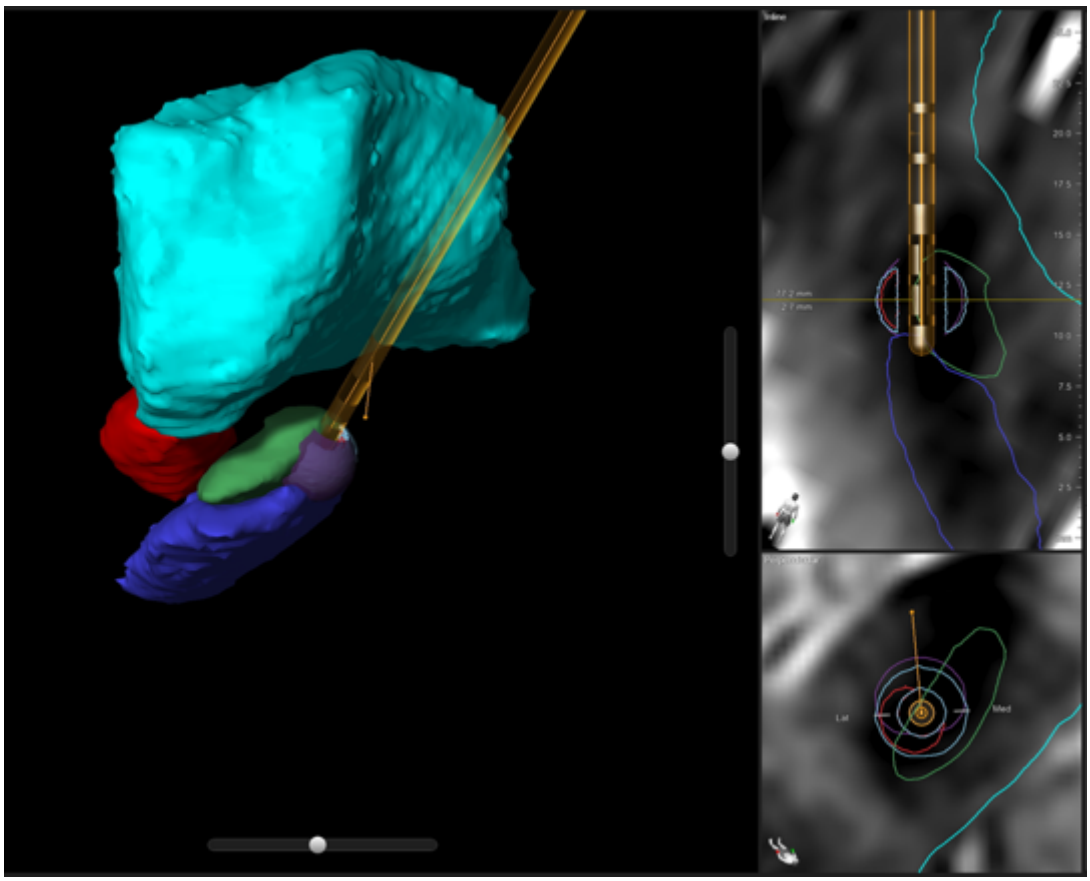


Figure 5.32. D11 – (L) STN

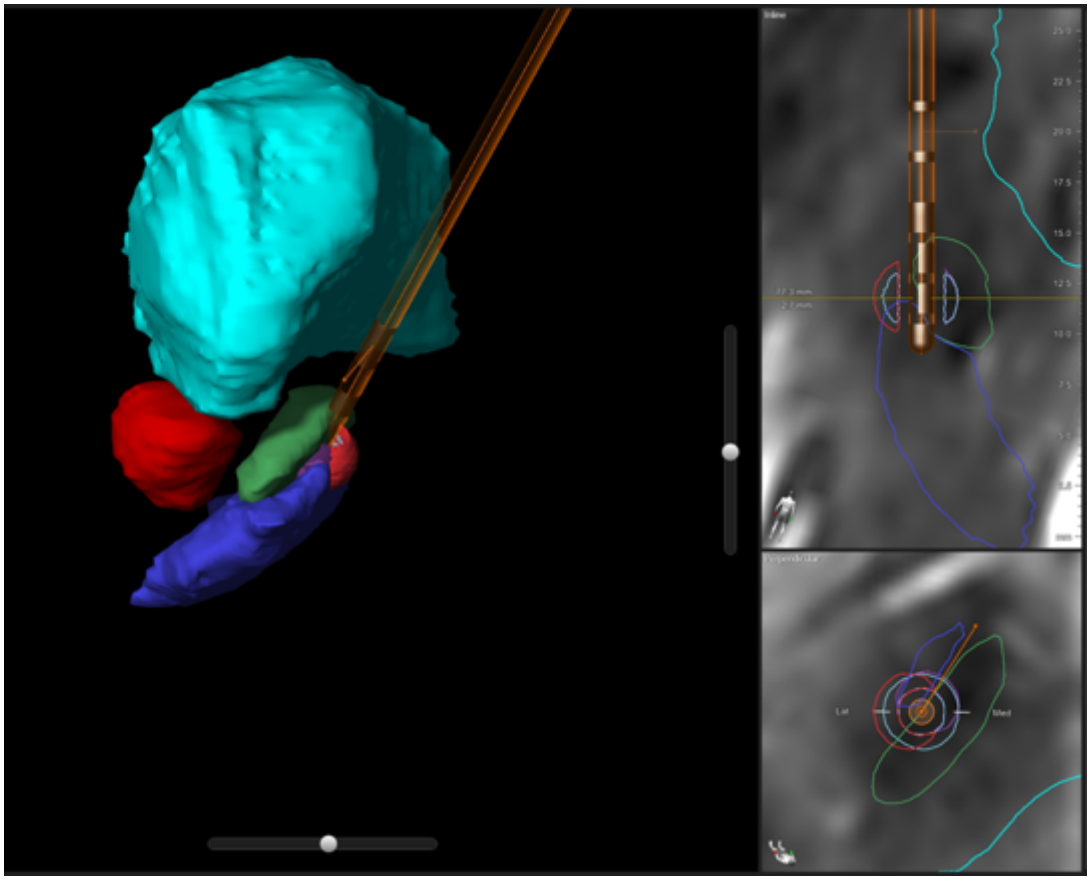


Figure 5.33. D12a – (L) STN

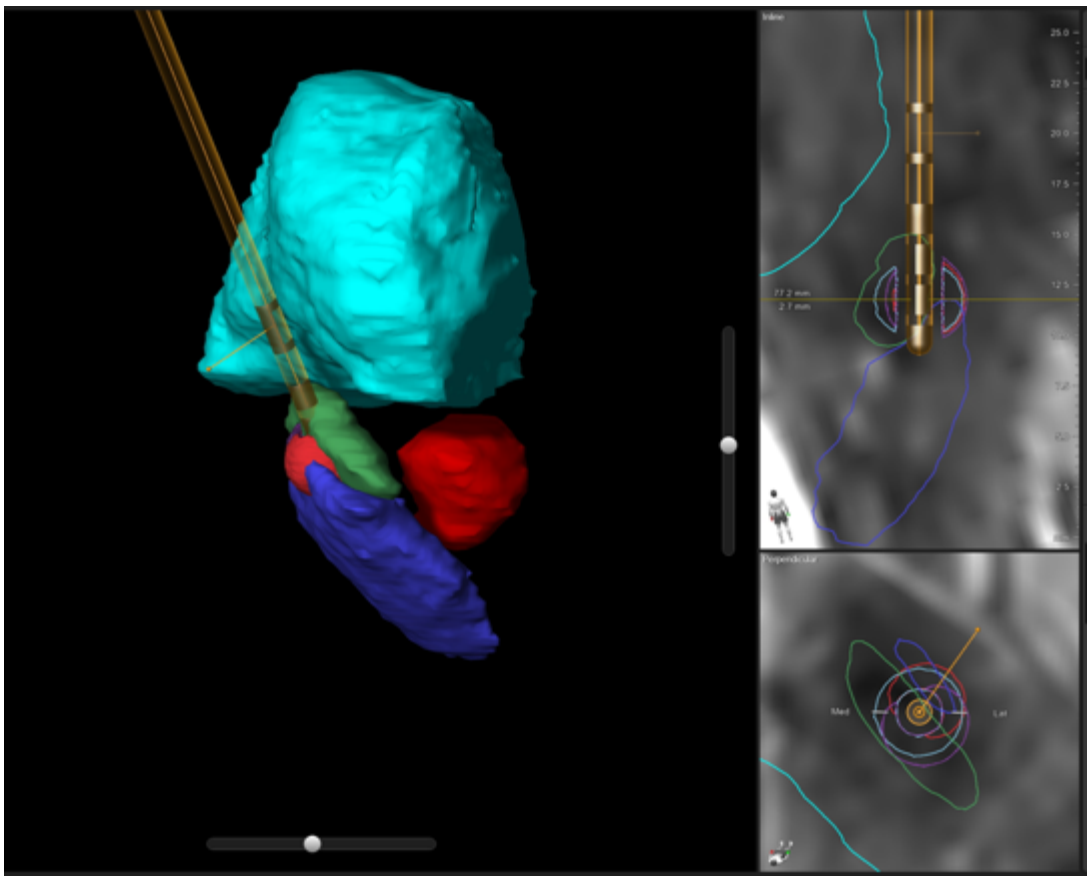


Figure 5.34. D12b – (R) STN

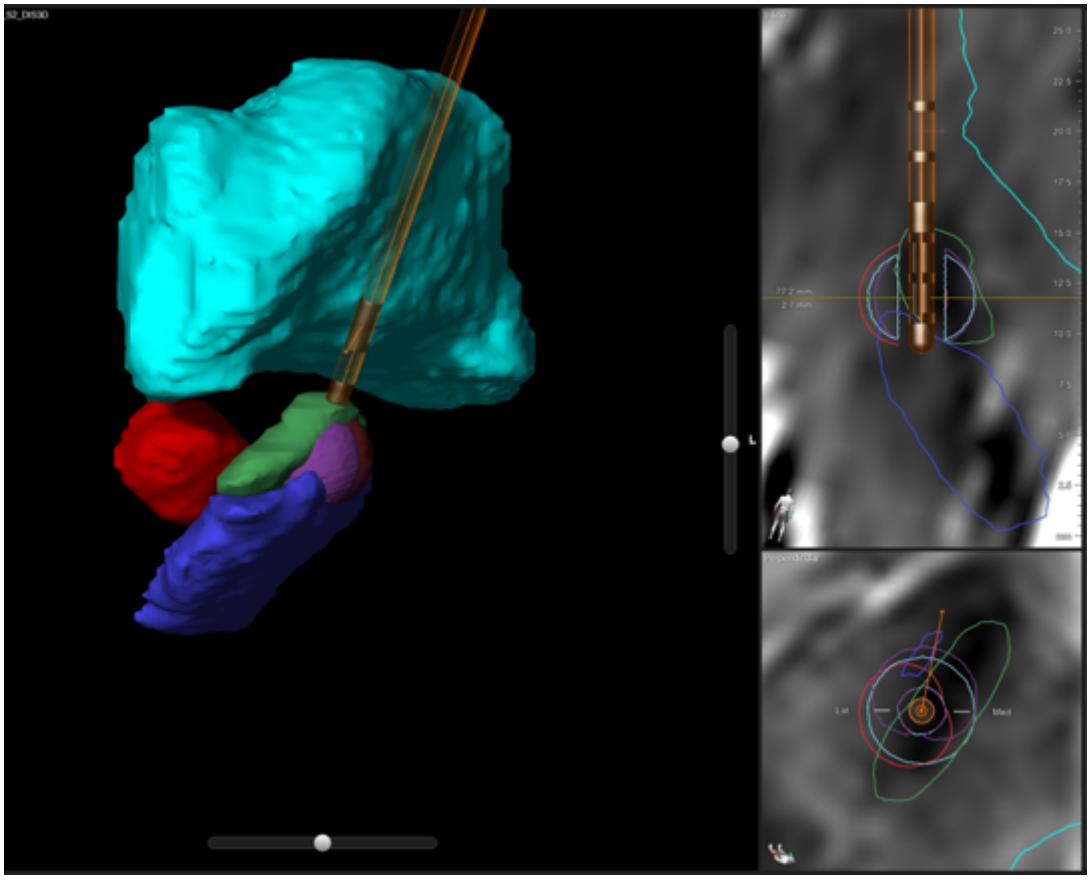


Figure 5.35. D13 – (L) STN

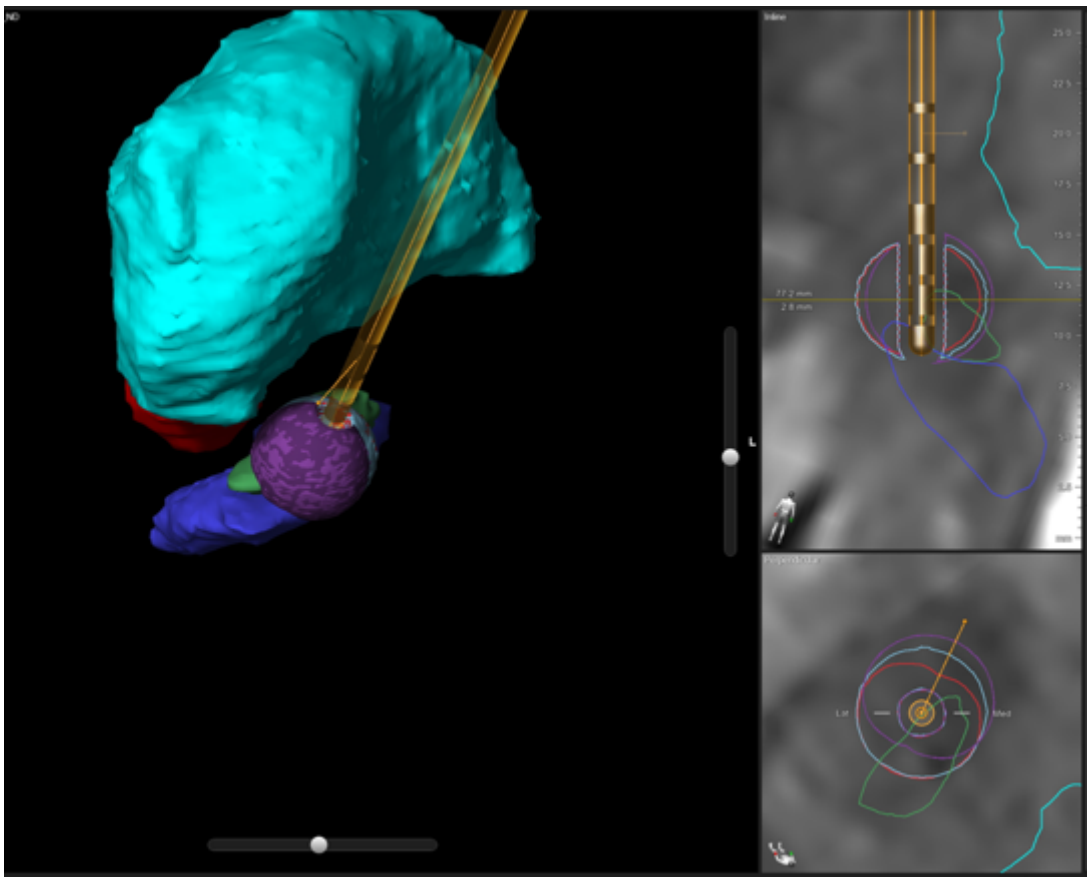


Figure 5.36. D14 – (L) STN

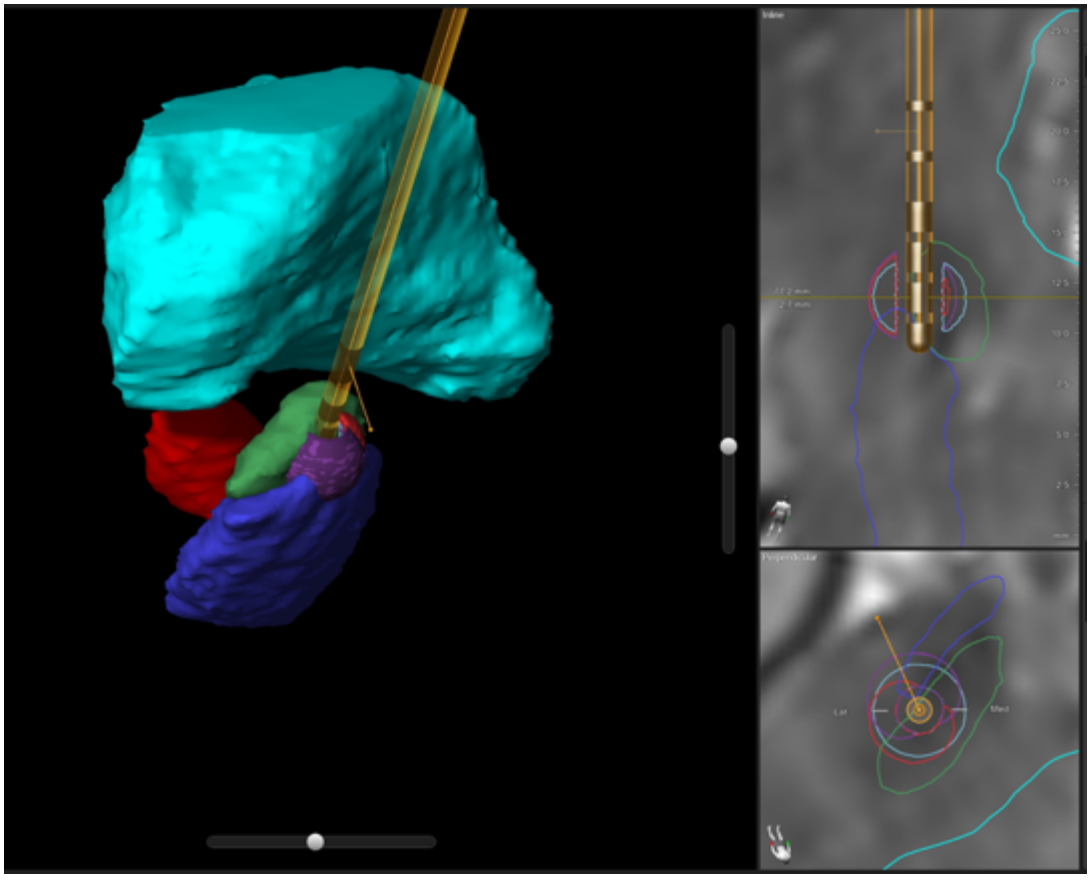


Figure 5.37. D15 – (L) STN

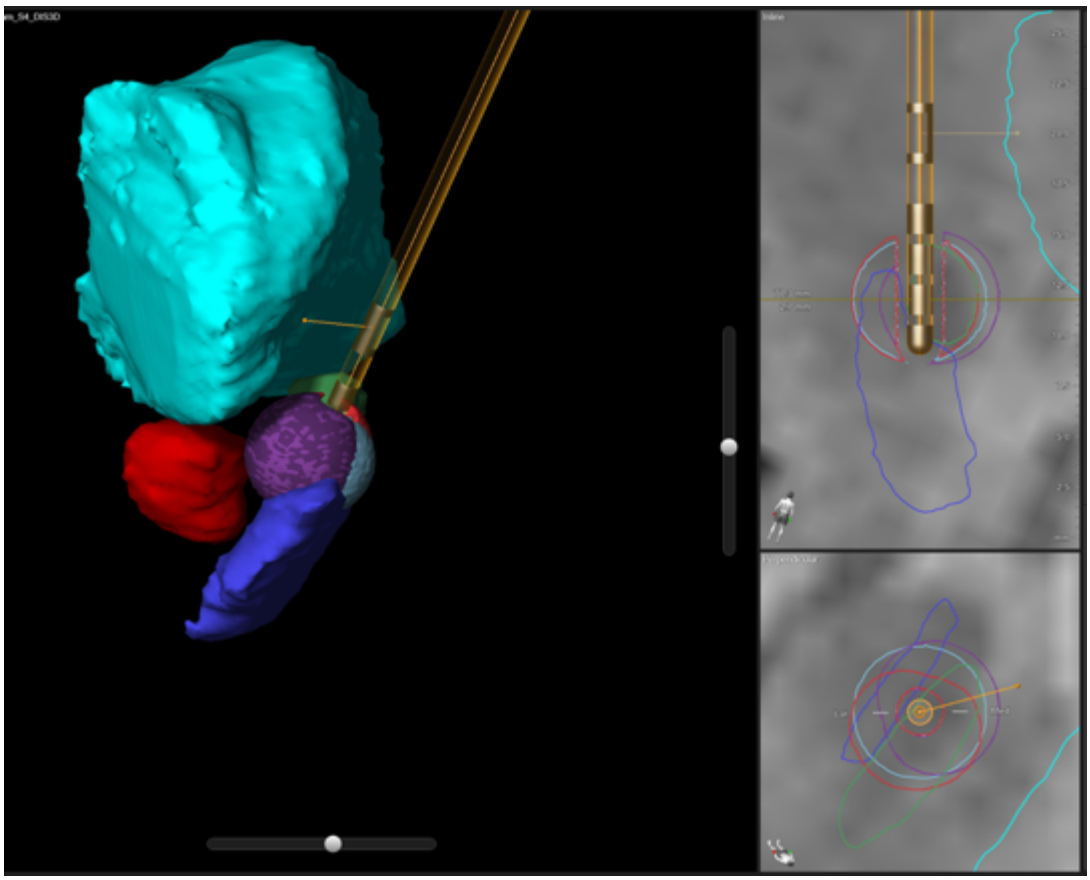


Figure 5.38. P1 – (L) STN

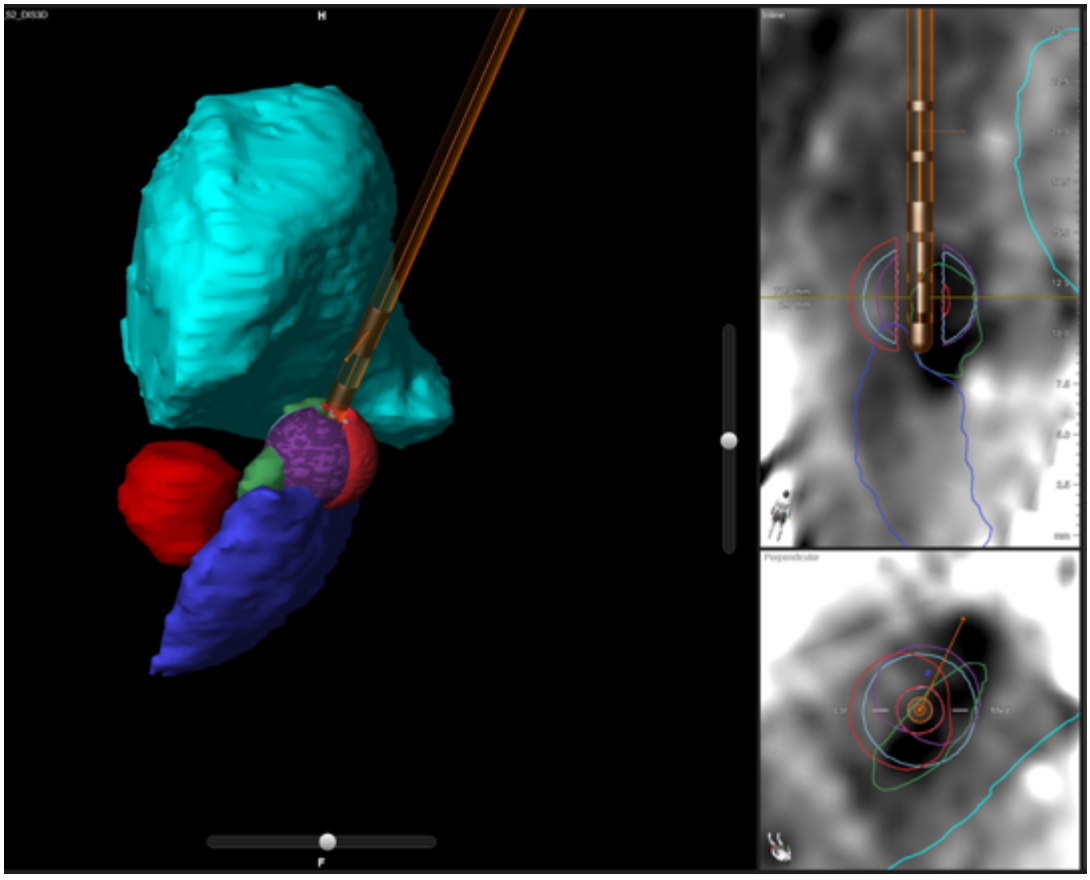


Figure 5.39. P2a – (L) STN

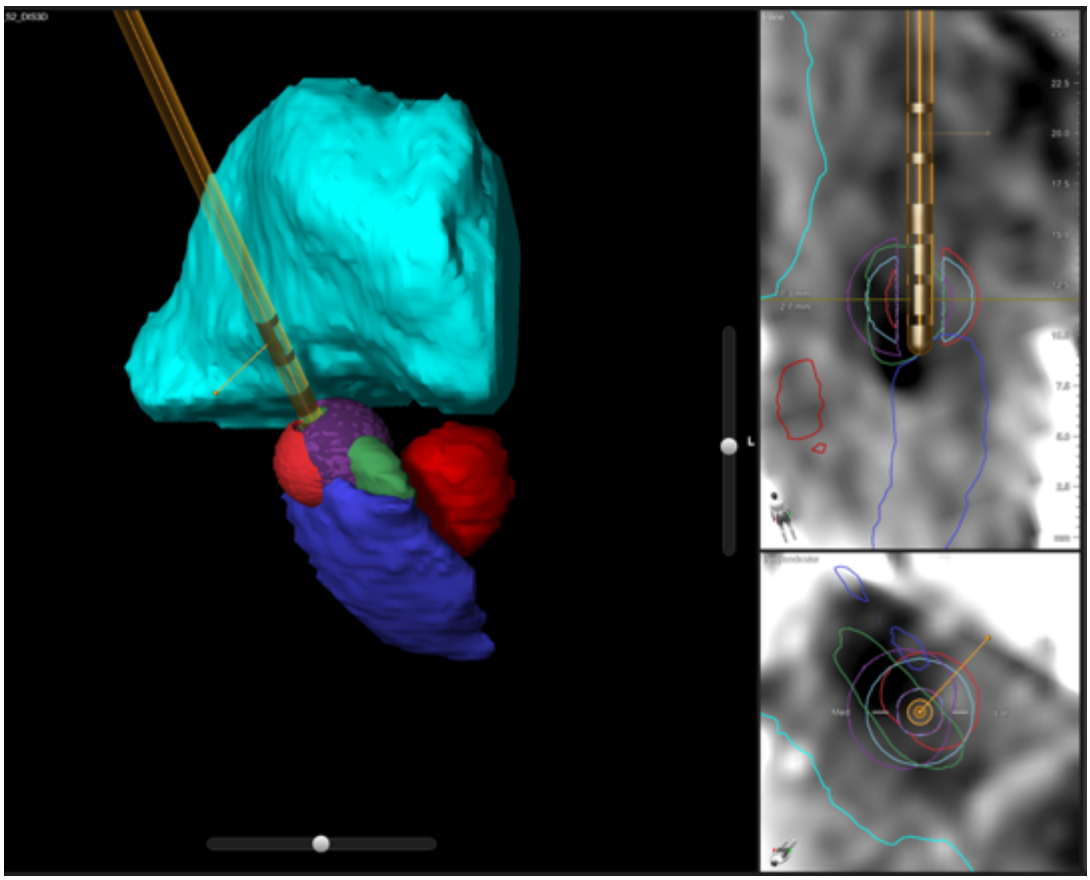


Figure 5.40. P2b – (R) STN

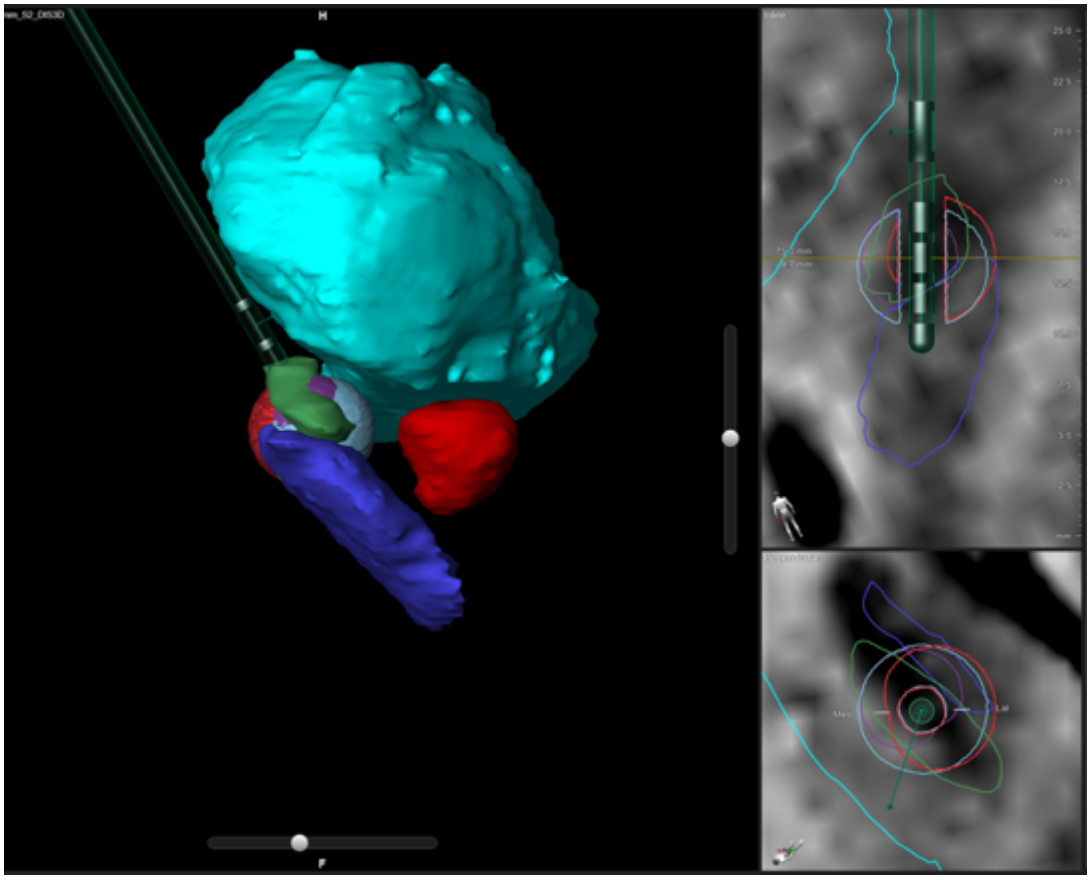


Figure 5.41. P3 – (R) STN

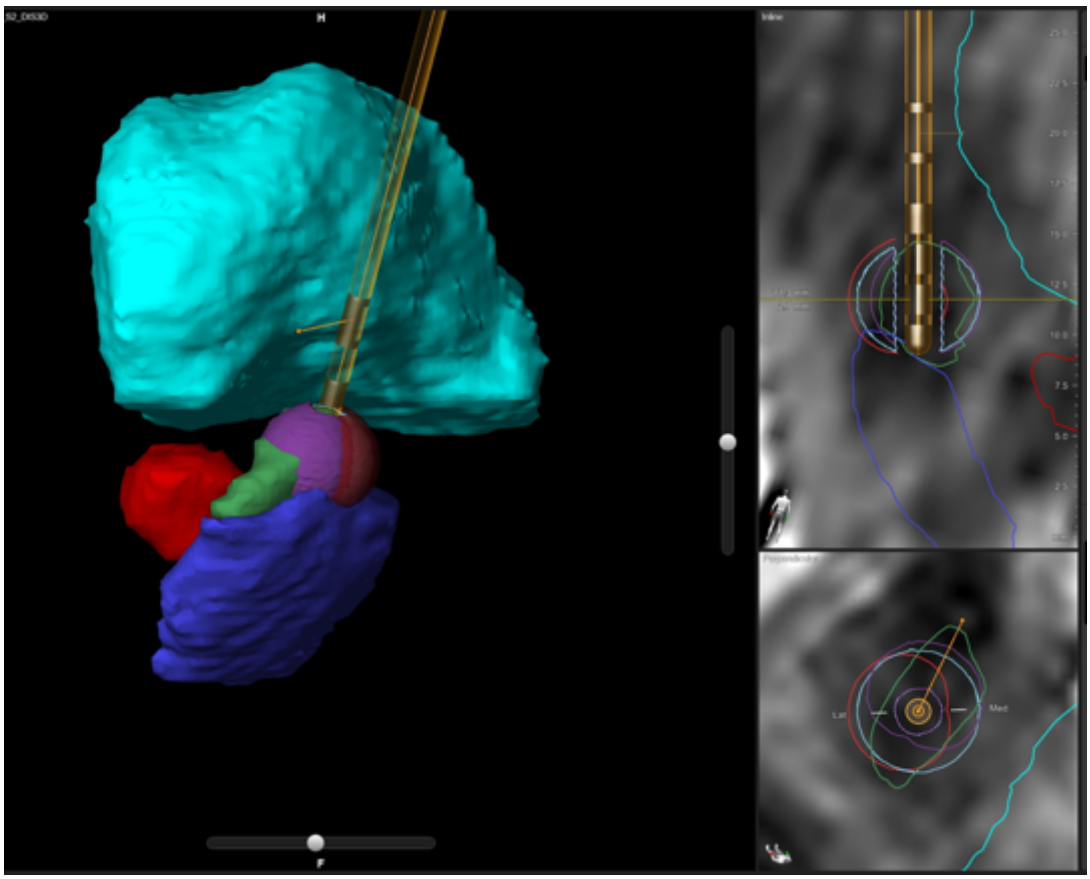


Figure 5.42. P4a – (L) STN

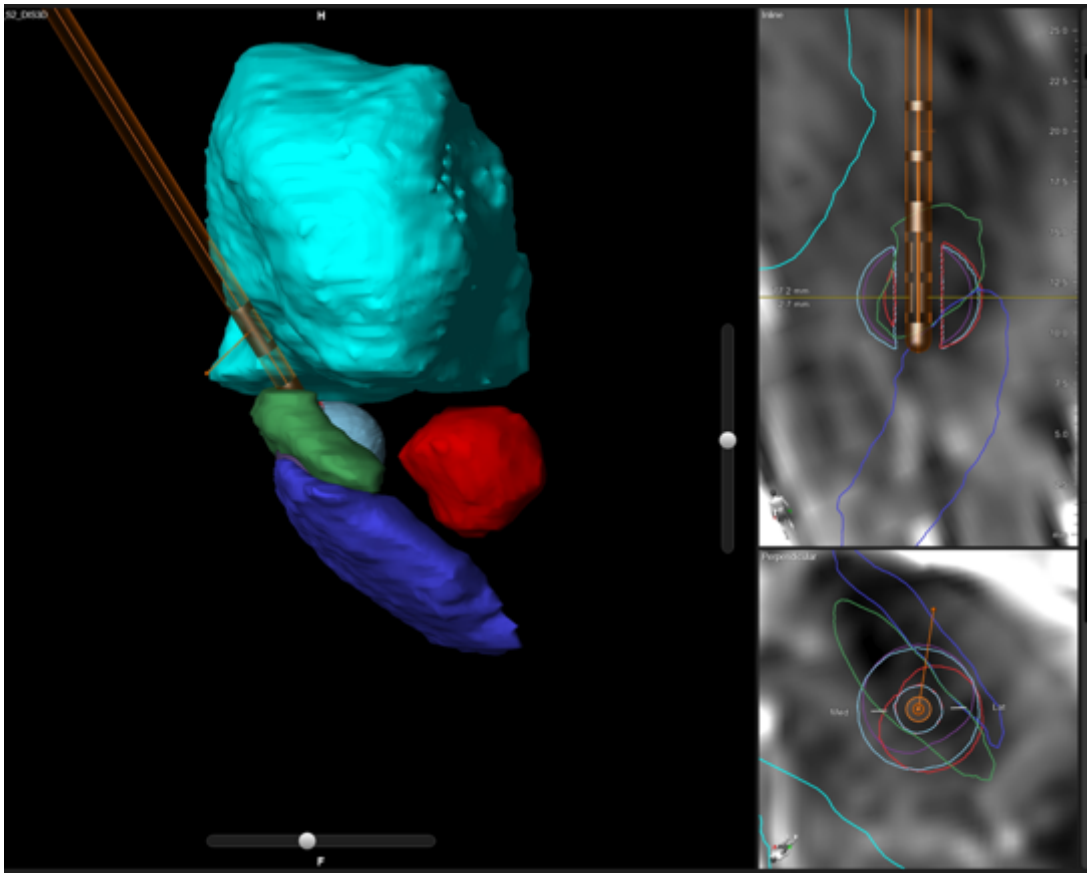


Figure 5.43. P4b – (R) STN

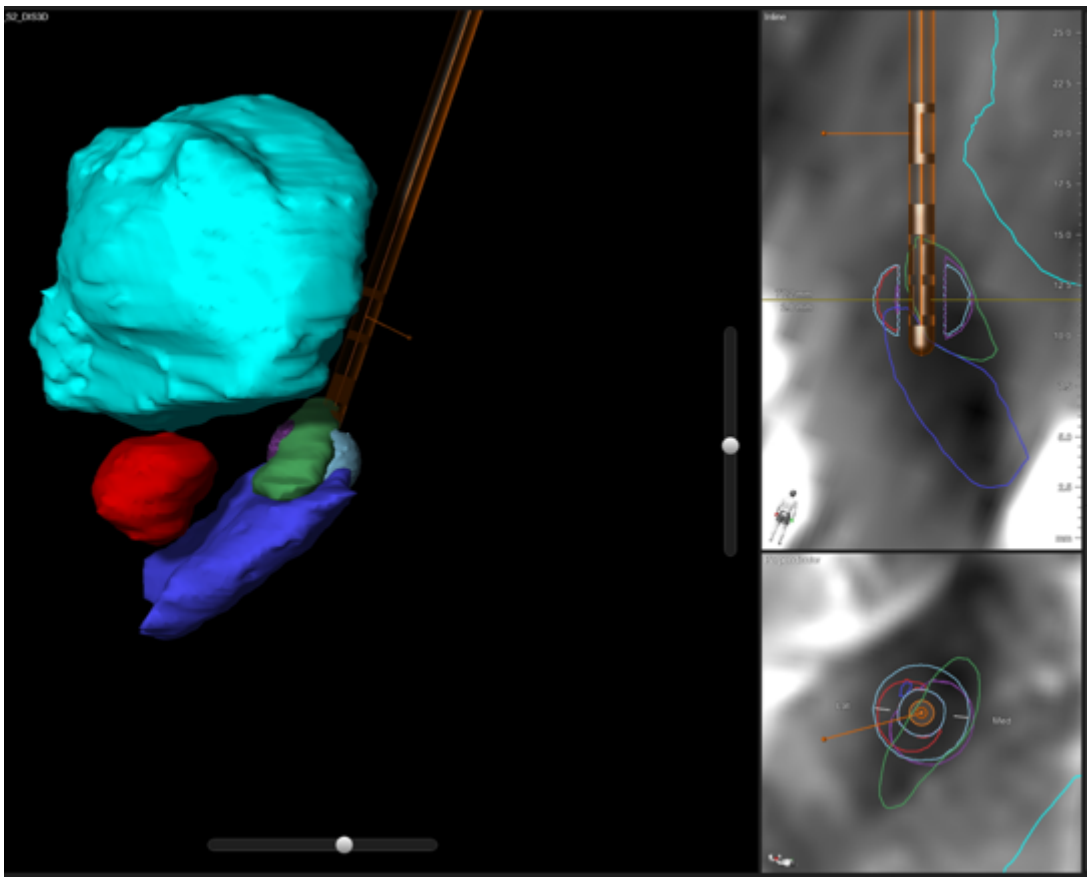


Figure 5.44. P5 – (L) STN

***Legend*:**
Nuclei; Subthalamic nucleus – green, substantia nigra – indigo, red nucleus – red, thalamus – turquoise

VTAs; Baseline settings – light blue, optimised settings – purple, lowest side effect direction – red

In the dysarthria group, 11 of 17 VTAs showed a lateral (including posterolateral/ anterolateral) shift after optimisation from medial or posteromedial areas outside the STN at baseline. The remaining ones included anterolateral to anteromedial (2), lateral to medial (1), lateral and medial to anterior (2), posterior to within STN (1). The mean angle of segments inducing dysarthria at the lowest threshold was 180.6 ± 76.4° from the AC – PC line (214.7 ± 75.7° from the STN long axis in the axial plane), which corresponds to the posteromedial region outside the STN. The mean angle of the optimal directional segment in this side effect group was -8.2 ± 49.8° (i.e. anterior).

In the dyskinesia group, 15 of 17 STNs showed a shift away from lateral or posterolateral areas outside the STN to more centrally within the STN, anteriorly or medially. The remaining 2 shifted from medial to lateral and posteromedial to central STN. Both these patients, as well as one from the former group of 15 had experienced stimulation induced dystonic symptoms as their main side effect. The mean angle of segments inducing dyskinesia at the lowest threshold was 114.7 ± 53.4° from the AC – PC line (151.0 ± 55.3° from the STN long axis in the axial plane), which corresponds to the posterolateral region outside the STN. The mean angle of the optimal directional segment in this side effect group was -32.8 ± 73.0° (i.e. anteromedial).

In the pyramidal symptom group, all 7 STNs had a shift away from lateral areas outside the STN (including 1 from medial and lateral) to the central or anteromedial STN post-optimisation. The mean angle of segments inducing pyramidal side effects at the lowest threshold was 104.4 ± 39.2° from the AC – PC line (140.4 ± 37.5° from the STN long axis in the axial plane), which corresponds to the lateral region outside the STN. The mean angle of the optimal directional segment in this side effect group was -58.5 ± 35.5° (i.e. anteromedial).

5.3.2 Charge Per Pulse (Qp)

The mean charge per pulse (Qp) at the efficacy threshold for RM60 was 160.6 ± 55.8 nC, for RM30: 122.2 ± 45.2 nC, for DIR60: 131.3 ± 45.8, and for DIR30: 104.7 ± 43.1. As data did not fit a normal distribution, the non-parametric Friedman's two-way ANOVA by ranks was used, followed by the Wilcoxon signed-rank test. There was a significant difference among the 4 conditions [χ^2 (3) = 68.4, P < .001]. Pairwise comparisons showed significant differences between all pairs except RM30 vs DIR60 (P = .38) and RM30 vs DIR30 (P = .067), as shown in figure 5.45.

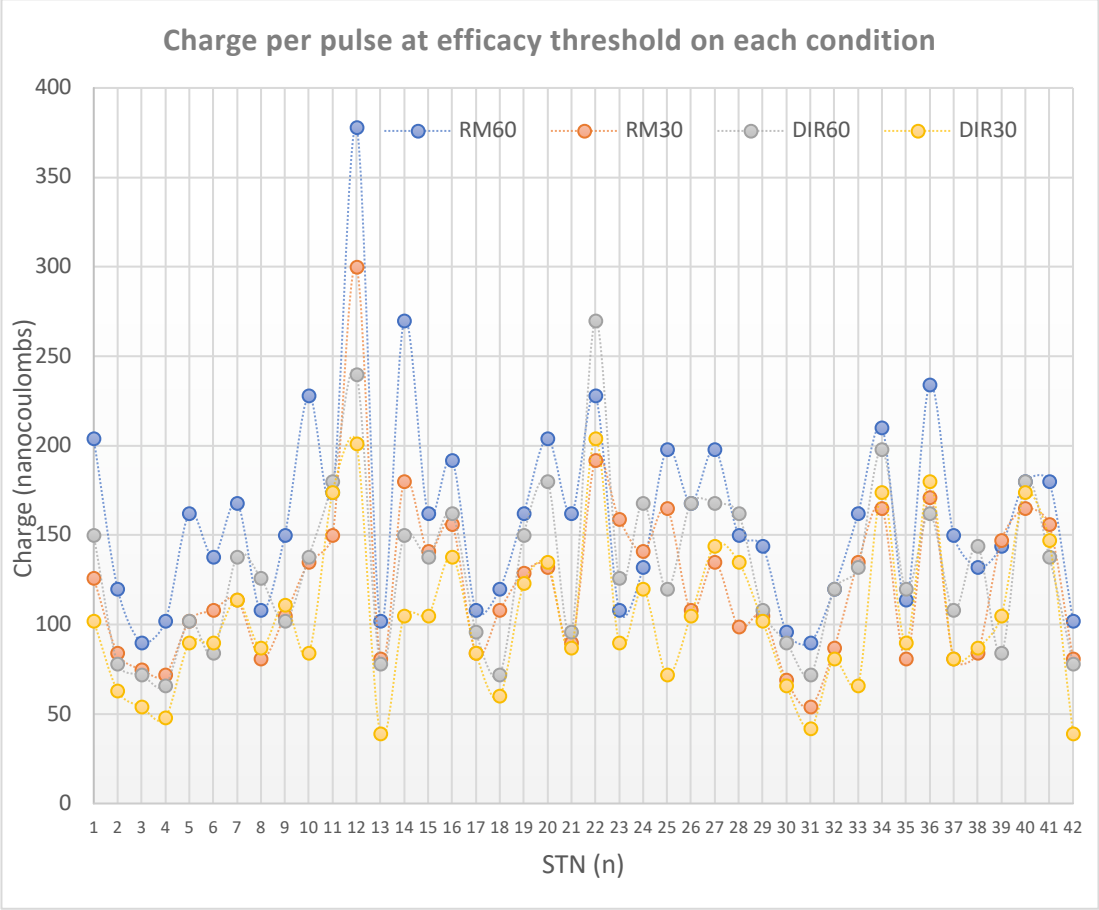


Figure 5.45 **Charge per pulse at the efficacy threshold for each stimulation condition**
(P values presented in table 5.2 below).

***Table 5.2. P* values of pairwise comparisons of charge per pulse at the efficacy threshold between the 4 stimulation conditions, overall and in side effect subgroups.**

CONDITION	RM60	RM30	DIR60	DIR30
Overall: n = 42; χ^2 (3) = 68.4, *P <.001*				
RM60	-----	< .001	.002	< .001
RM30	< .001	-----	.38	.067
DIR60	.002	.38	-----	< .001
DIR30	< .001	.067	< .001	-----
Dysarthria: n = 18; χ^2 (3) = 35.1, *P < .001*				
RM60	-----	.003	.005	< .001
RM30	.003	-----	1.00	.12
DIR60	.005	1.00	-----	.085
DIR30	< .001	.12	.085	-----
Dyskinesia: n = 17; χ^2 (3) = 32.5, *P < .001*				
RM60	-----	.002	1.0	< .001
RM30	.002	-----	.032	1.0
DIR60	1.0	.032	-----	< .001
DIR30	< .001	1.0	< .001	-----
Pyramidal SE: n = 7; χ^2 (3) = 7.77, *P = .051*				

In the pyramidal side effect group, no significant difference was found in Qp across the 4 stimulation conditions; pairwise comparisons were therefore not carried out. In the dysarthria group, significant differences were found between RM60 and the other 3 conditions, but not between the 3 alternative conditions. In the dyskinesia group, significant differences were present between all groups except RM60 vs DIR60 and RM30 vs DIR30.

5.4 Discussion

Study of the individualised VTA models in patients with stimulation induced side effects before and after optimisation revealed some general patterns of shift in each side effect group. In the dysarthria group, this was most commonly away from the medial and posteromedial areas, either within or outside the STN. In a smaller number of patients, the VTAs shifted away from the lateral regions outside the STN. It is recognised that stimulation induced dysarthria can be caused by both pyramidal tract activation affecting oromandibular muscle function, and by spread of current medially, where involvement of the cerebellothalamic and pallidothalamic tracts have been implicated (Tommasi *et al.*, 2008; Tripoliti *et al.*, 2014; Mahlknecht *et al.*, 2017; Fenoy, Mchenry & Schiess, 2017).

In the pyramidal group, there was a consistent pattern of shift away from the lateral regions outside the STN, as would be expected in modulating the stimulation field to avoid activation of pyramidal tract fibres. In the dyskinesia group, the shift was generally away from the posterolateral regions of and around the STN.

Data on the exact structures responsible for stimulation induced dyskinesia is less explicit in the literature. It has been commonly seen to be an effect of 'excessive stimulation' of the therapeutic elements of the STN and its surroundings, and the induction of dyskinesia following DBS surgery is conventionally thought to be a sign of accurate targeting that would result in good anti-bradykinetic effect in the longer term. However, a temporal dissociation between therapeutic stimulation effects and stimulation induced dyskinesias has been observed and is commonly seen in practice, with the latter usually having an extended and variable latency of onset (Limousin *et al.*, 1996). Furthermore, while bradykinesia and dyskinesia are seen as a continuum that may be modulated by stimulation localised to a single region, there are suggestions that

the effect on rigidity and tremor may be dissociated from this (Krack *et al.*, 2002; Castrioto, Volkmann & Krack, 2013); these symptoms have been shown to have different VTA clusters within the STN using probabilistic voxel-based morphometry studies (Butson *et al.*, 2011; Akram *et al.*, 2017). This is consistent with the clinical problem in some patients with stimulation induced dyskinesia such as those included in this study, where a simple reduction in stimulation amplitude is not a satisfactory solution as it may achieve a balance on the bradykinesia-dyskinesia continuum but results in suboptimal control of other symptoms such as tremor. Additionally, further data supporting the notion that the pathophysiology of dyskinesia may not be exactly the same as the mechanism for therapeutic effects come from LFP recordings in the basal ganglia, which have showed that the occurrence of dyskinesia correlates not only with the expected attenuation of beta power (13 – 30Hz) in the motor *on* state (Silberstein *et al.*, 2005), but that a more distinct electrophysiologic correlate of dyskinesia was increased activity in the 4 – 10 Hz range (Alonso-Frech *et al.*, 2006).

It is evident from the VTA modelling data that often only a subtle shift in the stimulation field with directional stimulation was sufficient to resolve stimulation induced dyskinesia, corresponding to significant reductions in dyskinesia scores, as reported in the last chapter. The pattern of shift in patients with dyskinesia was consistently away from the posterolateral region around the STN and most commonly towards the medial and central STN post-optimisation. In the 2 patients who had VTA shifts away from medial or posteromedial regions, the clinical picture was of stimulation induced dystonia rather than choreiform or ballistic dyskinesia that was present in the others.

Dyskinesia inducing segmented contacts have recently been localised on imaging to the ventral region of the dorsolateral STN (Bouthour *et al.*, 2019). This finding is consistent with the VTA data in the current study, where in 15 of the 17 STNs optimised for dyskinesia (those with the choreiform type), there is a striking uniformity in the

direction and location of the side effect VTAs (representing induction of dyskinesia), which appear posterolateral in the axial/perpendicular view and lateral in the in-line/coronal view, covering the lateral and ventral aspects of the dorsolateral STN.

There are several limitations to be aware of in interpreting the VTA modelling data. As with any computational model, there are numerous assumptions used in simulating the VTAs, and these include assumptions of homogeneity and isotropy of tissue for the electric field model, and the following for the axonal model: that there is no spontaneous activity, axons are perpendicular to the electrode, are straight, and have the same diameter. EMG recordings to verify pyramidal tract activation have been used in the validation of the model and improve its accuracy in predicting the stimulation field. However, neural elements with different excitation properties are not taken into account, and which neural tissue within the field is activated is not discernible. This presents restrictions in studying the effect of different PWs using such models. Furthermore, even the most accurate anatomic models do not take individual somatotopic and physiologic differences into account. Any distant effects of fibres within the stimulation field are also not accounted for. The accuracy of VTA models can be further improved by incorporating data from diffusion tensor imaging (DTI), where the tensor field provides a 3D representation of anisotropic and inhomogeneous tissue conductivity rather than using the assumptions above (Butson *et al.*, 2006).

Nevertheless, the objective of using the VTA models in this study was to determine gross patterns of shift based on the orientation of the lead and segmented contacts used, and the accuracy of the CT based method of determining lead orientation has been shown to be within approximately 5°. The differences pre- and post- optimisation seen with the VTAs are largely due to directional steering, which all but one patient had post-optimisation. Minor inaccuracies resulting from the modelling algorithm and its assumptions, therefore, are less relevant to this application than if the VTAs were used

to precisely study structures affected, or derive settings based on modelling (i.e. the reverse process of what was done here).

The detection of the lead orientation also relied on a consistent intended implantation angle, and the relatively small mean deviation of 35° from the anterior position detected by the software makes it unlikely that the detected orientation was erroneous and that the true orientation was the alternate position at 180°. In this study, additional methodological factors that may have affected the accuracy of the side effect VTAs in particular, is that the direction of testing was limited to each of the three segments, rather than finer angles.

Nevertheless, there is a high consistency of the patterns of shift in patients with pyramidal side effects and dyskinesia. In the dysarthria group, the two patterns found also implicate the likely involvement of anatomical structures thought to be responsible for stimulation induced speech impairment. The types of speech disturbance caused by pyramidal tract activation ('lateral-type') and that associated with medially placed electrodes and presumed involvement of the cerebellothalamic tract ('medial type') have been previously clinically characterised as discussed in Chapter 3 (section 3.1). However, in practice, categorisation of dysarthria into these types is not always straightforward, and in the group of dysarthric patients in this study, a reliable relationship overall could not be found between type of dysarthria and VTA shifts. This may be due to various factors: speech can be affected in each hemisphere in different ways within a patient (i.e. lateral on one side and medial on the other), or indeed affecting both lateral and medial areas outside the STN of the same hemisphere in some cases due to large VTAs, resulting in an indeterminate or a mixed classification; it can be affected by Parkinsonism as well (both acute motor symptoms or chronic disease state) which can cloud the picture; and the small sample in this cohort may not have been sufficient to find such correlations, which may become apparent with larger numbers.

The improvement in severity of adverse effects by using directional steering and spatial shaping of the stimulation field is explicable by knowledge of anatomical pathways. However, the clinical data from the study in Chapter 4 suggest that there is a trend to an additive beneficial effect when short PW is combined with best directional stimulation. While this was not statistically significant in this cohort when compared to directional only stimulation at standard PW, the greatest improvement in each side effect group was achieved with the use of 30μs combined with directional stimulation, and this configuration was consequently the most commonly used both initially post-optimisation and in the longer term. Furthermore, in the dysarthria and dyskinesia groups, the use of short PW in ring mode showed significantly improved side effect scores compared with those at standard PW. The comparison of charge per pulse at the efficacy thresholds on each condition shows that at short PW the charge is significantly lower than at standard PW in both ring mode and directional configurations. In the dyskinesia group, the Qp relative to RM60 is not lower with DIR60 settings, but is with short PW settings (RM30 and DIR30), indicating that the clinical improvement seen with the alternative conditions can be attributed to shifts in VTA for DIR60 and lower charge for the short PW settings, with DIR30 combining both aspects. Given that many side effects are stimulation intensity- dependent and get worse with increasing amplitudes and PWs, the use of settings with a lower charge that is able to provide an equivalent therapeutic effect may explain the differences observed beyond those that can be attributed to spatial shifts in stimulation.

CHAPTER 6

General Discussion

6.1 Summary of main findings in perspective

Stimulation induced side effects have been recognised since the advent of STN DBS therapy. Despite the remarkable improvements in motor fluctuations and quality of life offered by this intervention, the occurrence of side effects can be a disappointing setback for many patients, having a negative impact on their daily activities and function, including aspects of communication, mobility, and consequently mood. The incidence of speech and gait disturbances as early as 6 months post-operatively have been reported to be 22% and 28% respectively with STN DBS, while almost 80% experienced a reversible stimulation related neurological or psychiatric adverse effect (Buhmann et al., 2017).

For the programming clinician, achieving a good therapeutic effect from well-placed electrodes is generally a straightforward task, but much time and effort is expended in troubleshooting side effects of stimulation over the course of this lifelong treatment.

Various programming techniques within the confines of conventional devices have been studied and used over the years, often with either limited benefit, or entailing compromises in therapeutic effect. Much work has focussed on the use of low frequency, and the data overall seems to indicate at least an initial benefit for many axial symptoms. Despite its utility in some patients, shaping of the electrical field along the axis of the lead with interleaving and bipolar configurations using ring electrodes, however, has presented limitations in the extent to which this can be done compared to newer technologies using segmented electrodes. The expansion of the pulse width parameter range and the possibility of horizontal directional steering represented major new avenues for enhancing programming techniques to address stimulation related problems.

It has been over five years since these features became commercially available, and expectedly, much data in the early stages focussed on the feasibility of their use, efficacy, and differences compared to conventional parameters and configurations in the acute setting. With regards to short pulse width, the therapeutic window was one such area of interest, given the expected trend of further expanding this from known patterns of earlier strength-duration data. The study in Chapter 2 represents the largest set of therapeutic window data reported with the use of short PW, comprising systematic measurements at 160 electrodes. This confirmed a greater than two-fold increase in the therapeutic window with respect to amplitude, and importantly, the effect was present in terms of electrical charge as well. These findings have since been corroborated by other studies (Bouthour *et al.*, 2018; Steigerwald *et al.*, 2018). The latter of these also established the non-inferiority of short pulse settings in efficacy of motor symptom control compared to conventional PW using a double blinded design.

An expanded therapeutic window is potentially useful in the longer term as the relative ceiling for hitting the side effect threshold is higher, and many patients need increasing levels of stimulation over time. It may also be useful in patients who have a very narrow or even negative therapeutic window early in the course of initiating DBS therapy, where the side effect experienced with conventional PW may be able to be avoided.

However, there was a lack of data on the potential utility of short PW in chronically implanted patients with side effects. The double-blind randomised crossover trial on short versus conventional PW aimed to address this with regards to dysarthria. The primary outcome of speech intelligibility did not show any differences overall between the two PW conditions in a heterogenous sample of patients. However, this trial was instrumental in providing much needed data on short PW stimulation in various aspects. From a clinical perspective, while the most favourable outcome would have been a benefit reflected in improved side effect outcomes while maintaining the therapeutic

benefit with short PW, even the feasibility of this parameter in chronic patients and equivalent longer-term efficacy was not established prior to these data being available. The trial was not designed to assess efficacy; however, it provided the first set of data on the use of short PW in STN DBS beyond an acute setting and is the only such study in chronic patients, showing equivalent motor, non-motor, and quality of life outcomes to conventional PW in this group.

Furthermore, despite the overall non-significant result, the trial provided pilot data that could be used to generate further hypotheses on characteristics and subgroups of patients from the heterogenous sample who may have benefited. Prior to the availability of novel programming techniques, the use of low frequency was one of the few options to deal with these side effects, and was relatively widely used in clinical practice. The inclusion criteria for the trial was based on having a moderate degree of speech impairment, and a significant proportion of patients who fit these criteria and were recruited (10 of 16) had had previous optimisation of their settings using low frequency for a range of axial problems. It is possible that short PW did not have any additive benefit to the probable improvements in speech intelligibility achieved by low frequency. Moreover, patients on low frequency who had potential prior reversal of the stimulation induced component of dysarthria with frequency modulation but still had moderately severe dysarthria were perhaps more likely to have advanced PD contributing relatively more to this symptom. This is reflected in age, duration of DBS, and to a lesser extent disease duration, having inverse correlations with improvements in speech intelligibility with the use of short PW in post-hoc evaluations. Differences in response related to duration of DBS therapy may be due to factors such as disease progression, with less reversible symptoms in advanced stages, or possibly long-term maladaptive effects of stimulation that render patients with longer duration of DBS less likely to improve with programming changes.

Indeed, in the subgroup of 6 patients with standard frequency settings of 130Hz at baseline, the primary outcome was significantly improved. However, this post-hoc result on the small number of patients needs to be interpreted with caution, and no firm conclusions can be drawn in this respect from this trial alone.

The need to further scrutinize the potential benefit of short PW in patients not previously programmed to low frequency settings, and those more likely to have reversible stimulation induced dysarthria led to study 3. In addition to dysarthria, commonly encountered side effects of dyskinesia and pyramidal tract symptoms were also studied, and the programming interventions apart from short PW included directional steering. A key difference in the sample of patients included in this study apart from the aforementioned factors was that only those with a demonstrable reversible side effect with reduction of stimulation (within a span of hours at most) were included.

This study confirmed an 11% improvement in median speech intelligibility with short PW alone compared to conventional baseline settings. The same degree of median improvement was seen with directional steering, and a trend to a higher improvement (a further 6%) with the combination of these two features was seen, although this additional benefit was not significant in this sample of 13 patients. Not unexpectedly, the perceptual speech ratings followed the same trends as intelligibility ratings.

In patients with dyskinesia the combination of directional steering and short PW provided an additional benefit to short PW alone, and for pyramidal effects only directional steering provided a significant benefit compared to conventional settings. In all three side effect groups, there was a trend to having the highest improvement with the combination of both features. The vast majority of patients who were optimised with the best individual configuration using either one or both of these features (29 out

of the 31 followed up) stayed on the optimised setting, and the benefit was maintained after 6 months in each group.

VTA modelling based on data from study 3 provided further information on gross patterns and areas steered away from with optimised directional stimulation. Avoidance of pyramidal tract symptoms expectedly led to shifts from lateral regions outside the STN medially towards the central and anterior sensorimotor STN. This is consistent with data from previous studies on probabilistic tractography derived corticobulbar and corticospinal tract modelling and their overlap with therapeutic VTAs, confirmed with EMG recordings (Mahlknecht *et al.*, 2017).

Stimulation induced speech impairment has widely been assumed to result from pyramidal tract activation as well (Krack *et al.*, 2002; Akram *et al.*, 2017). This may be due to the commonly seen acute effect during programming of pyramidal tract symptoms consisting of facial muscle contraction and simultaneous difficult articulation of speech, which is often noticed by the patient and clinician. However, various previous studies have reported medial placement of electrodes correlate with reduced speech intelligibility following STN DBS (Åström *et al.*, 2010; Tripoliti *et al.*, 2014; Fenoy, Mchenry & Schiess, 2017). The commonest pattern seen in optimised dysarthric patients in study 3 was a shift away from medial or posteromedial regions outside the STN, with a smaller proportion having the converse shift away from lateral regions, presumably due to pyramidal tract involvement. This pattern in the dysarthria group is consistent with stimulation field modelling done with conventional leads in previous studies which have implicated involvement of the cerebellothalamic tract posteromedial to the STN, between the STN and red nucleus, in stimulation induced speech impairment (Åström *et al.*, 2010; Fenoy, Mchenry & Schiess, 2017). It is possible that in the longer term, speech intelligibility is found to be compromised more commonly due to current spread

medially than laterally as pyramidal tract symptoms are more explicitly expressed and are not well tolerated and are thus often avoided during programming.

Among those with choreiform and ballistic dyskinesia, the posterolateral regions of the STN axially, and the ventrolateral aspects of the superior portion of the STN in the coronal plane, were consistently involved in the dyskinesia producing directional electrode segment; this was also recently found in another study on dyskinesia with directional systems, although the study was not focussed on patients who experienced this as a side effect (Bouthour *et al.*, 2019).

The commonest orientation of directional segments used following optimisation were anteromedial and anterior, followed by anterolateral; while medial, lateral, posterior and posterolateral were the least common. The locations of the active contacts and shape and orientation of the STN would result in the latter group producing larger stimulation fields outside the STN, where structures producing side effects are more likely to be involved. Other studies that have systematically examined acute effects of directional segments have also found the posterolateral direction the worst for side effects out of the 3 segments, and variably but most commonly the posteromedial, anterior or anteromedial segments optimal in terms of efficacy and side effect balance (Steigerwald *et al.*, 2016; Dembek *et al.*, 2017). While there is general concordance in these patterns of directional stimulation, it must be remembered that the optimal direction is heavily dependent on the exact placement of the electrode within the STN and varies with each patient, as well as with targeting practices at different centres.

A consistent and important finding relating to underlying mechanisms of short pulse stimulation is the ability to achieve an equivalent therapeutic effect to conventional PW with a lower electrical charge per pulse. This was demonstrated across all three studies here as well as others that have reported on the use of short PW (Bouthour *et al.*, 2018; Steigerwald *et al.*, 2018). Collectively, the data on short PW and directional stimulation

suggest the therapeutic window is widened by each technique by predominantly different mechanisms: with short PW, the efficacy threshold is lowered (while the side effect threshold is largely unchanged) with respect to charge, and with directional steering, the side effect threshold is increased more significantly than changes in the efficacy threshold. Side effects can therefore be alleviated by each in different ways: by spatial modulation of the stimulation field away from elements associated with them and thereby increasing the threshold required to produce these effects, or by lowering the overall electrical charge delivered for an equivalent therapeutic benefit which makes it less likely to reach side effect thresholds. These mechanisms may also explain the synergistic effect of combining them indicated in the data from study 3.

Taken together, the set of studies presented here suggest that short PW and directional steering can both alleviate stimulation induced side effects of dysarthria, dyskinesia, and pyramidal effects. The benefit is sustained beyond the immediate intervention period and the use of these features is generally well tolerated, although individualised manual programming sessions exploring the large range of permutations can be time consuming. A simplified algorithm summarising the utility of short PW and directional steering in patients with side effects is presented in figure 6.4.

6.2 Limitations of data presented and directions for future research

Several limitations of the data presented and its interpretation need to be considered. With regards to short pulse width, only 30µs was used in all three studies. The conclusions are therefore limited to this PW rather than other values lower than 60µs that could be potentially used (10 - 50µs). Previously reported pilot data on very short PWs of 10 - 20µs have suggested either lack of an effect or very large amplitudes required to produce clinical effects (Reich *et al.*, 2015; Bouthour *et al.*, 2018). This lack of sufficient effect with reducing PWs below 30µs fits with chronaxie data of candidate structures for STN DBS effects: 30 - 200µs for large myelinated axons and 200 - 700µs for grey matter (Ranck, 1975; Brocker & Grill, 2013).

While 30µs was a pragmatic value of half the current standard used and it is unlikely that significantly different outcomes would have been achieved with different PWs around this, slightly variable results cannot be ruled out. A particular consideration is that strength-duration relationships of therapeutic effects in STN DBS predict exponentially increasing amplitudes at very low PWs. Therefore, while the charge per pulse drops at the moderately low PWs tested, it would be expected to increase at very low PWs, and there may be a 'sweet spot' on this curve where stimulating at a certain PW results in the lowest charge per pulse and produces equivalent therapeutic efficacy (and is therefore most likely to avoid side effects). This needs to be defined with large sets of data examining thresholds at different PW intervals.

In the randomised short PW crossover trial, the relative contributions of stimulation induced versus PD related symptoms were not able to be discerned. This was practically complicated by the lack of immediate reversibility with stimulation changes of longer-term side effects such as chronic dysarthria, and the inability of patients with more

advanced disease to tolerate long periods *off* stimulation, and may have resulted in inclusion of some patients with little or no scope for reversibility of the symptom even with prolonged programming interventions.

While study 3 provided more conclusive data on the potential benefit of short PW in the selected population of patients with STN DBS following on from indications in the post-hoc analyses of the randomised trial, the sample sizes for each side effect group were still small. These were sufficient to demonstrate a significant benefit of one of the optimised configurations compared to conventional programming, but any differences between the 3 alternative configurations will need to be examined further in larger samples. This study was not a randomised blinded trial; however, it provided the first open label data indicating significant benefits of using novel techniques to alleviate stimulation induced side effects, and provides directions for further clinical trials. Data on the utility of novel programming features in dealing with a wider set of adverse stimulation related effects including those such as gait dysfunction is also required. The findings from this study apply to stimulation induced side effects that were reversible with reduction of stimulation within minutes to hours; whether this applies to other adverse effects that are less acutely responsive needs to be established in further studies. Short PW can be readily applied to patients with any adverse stimulation effect. However, programming with directional steering can be more challenging when an immediate response is not evident, as feedback on the occurrence and resolution of side effects is the basis of optimising stimulation with segmented electrodes. This may be substituted with anatomical information using visualisation software and stimulation field modelling for side effects with known structures responsible for causing them; however, the origins of some side effects are currently not completely understood or well-localised. Another method would involve prolonged trials of stimulation using different segments to ascertain which one is most likely associated with the side effect.

Selection of segmented contacts based on therapeutic effect and refining the direction can also be time-consuming, and as local field potential (LFP) sensing technology becomes incorporated into directional stimulation systems, this process may become more streamlined. The utility of LFP-based contact selection has been demonstrated in intraoperative studies in humans (Bour *et al.*, 2015; Telkes *et al.*, 2020), intraoperative LFP data correlated with longer term post-operative clinical outcomes (Tinkhauser *et al.*, 2018), and longer term data collected in non-human primates (Zhang *et al.*, 2018). Furthermore, adaptive or closed loop stimulation that relies on consistent and sensitive biomarker feedback in the form of LFPs may benefit from a greater number and spatially more distinct sampling sources with the use of multiple directional segments as this feature becomes available in commercial devices in the future.

The beneficial effect of low frequency stimulation on dysarthria has been noted in previous studies on frequency modulation (Moreau *et al.*, 2008; Xie, Kang & Warnke, 2012; Grover *et al.*, 2019; Fabbri *et al.*, 2019). How the magnitude of the improvement in speech intelligibility with low frequency compares with that achieved with the use of short PW in the data presented here is not known, as methodological differences and the lack of uniform quantification in the frequency studies preclude such direct comparisons. However, it is worth considering that some patients do not tolerate low frequency settings due to the emergence of tremor, and the use of short PW may offer an advantage in this respect.

Apart from the inherent assumptions of the VTA modelling algorithms previously discussed, the design of study 3 meant the 'optimised' VTAs modelled were not necessarily the most efficacious, nor always one that represented the area with the lowest likelihood of producing side effects (if this compromised efficacy), but rather often in the intermediate spectrum between these where side effects could be diminished as much as possible without compromising baseline efficacy. Side effect

VTAs were included in the modelling along with baseline and optimised VTAs to provide more information, and the accuracy of these could be improved in future studies by using smaller steering steps than whole segments, as well as including vertical steering in the screening. The objective in this study to collect data on four different conditions for each patient resulted in an extended programming duration, and this could be further streamlined to focus on separate components such as directional steering only, and collecting data using a more exhaustive iterative programming process on a single type of configuration instead of optimising multiple programs for each patient. Nevertheless, the advantage of the approach used, particularly in the pilot stages of data collection in this field when the relative effectiveness of the different techniques was not known, was that the various conditions could be compared in each patient. Moreover, it also became evident that while there were overall patterns found in the population studied, the optimal condition for individual patients varied; some patients achieved the best outcome with directional stimulation only, some with short PW only, and others with both combined. Therefore, while such data can generate general guidelines, there is an argument for an individualised approach in clinical practice.

The insights on differing mechanisms of avoidance of side effects with the two techniques studied and the potential to combine them to produce a synergistic effect is reflected in the clinical data. However, one question regarding the mechanisms discussed for short PW stimulation remains: why is the use of short PW able to produce an equivalent benefit using a lower charge? This takes us back to mechanisms of STN DBS, where many unanswered questions remain after nearly three decades of work. Fibre selectivity is a commonly proposed notion used to initially theorise and then to explain differences in stimulation effects with various PWs (Groppa *et al.*, 2014). Factors including fibre size and their distance from the stimulation site determine their excitability, and models have been proposed to explain the observed strength-duration curves with differences in action potential initiation in axons of varying diameters at

varying distances from the stimulation site, using the corticosubthalamic fibres (hyperdirect pathway) as a candidate for therapeutic effects (Reich *et al.*, 2015). The findings on charge per pulse and short PW reported in the current studies are not at odds with these concepts, and in fact imply superior selectivity of therapeutic elements with short PW. Why this may be the case is an area for further investigation. In particular, given the pathologic oscillatory patterns of activity seen in the basal ganglia-thalamocortical network in PD and their attenuation with therapeutic interventions including dopaminergic therapy and STN stimulation, could it be that stimulating using shorter pulses but higher amplitudes is more effective at disrupting aberrant β activity and phase-amplitude coupling associated with motor dysfunction?

While amplitude and PW both affect the charge per pulse, and changes in each are reflected in the size of the VTA, it is not known exactly how electrical charge relates to the VTA in the model used with respect to *relative* changes of amplitude and PW. However, the fact that a lower charge injection is required for therapeutic effect with short PW but the same charge per pulse as conventional PW produces side effects implies differential selectivity of each responsible element, which would render unified VTA models such as those currently used simplistic, as the output generated is a single field of activation without distinguishing these effects. This arises from a major limitation of VTA models that define tissue activation spatially using stimulation fields assuming homogeneity of tissue within in regardless of differences in therapeutic and side effect elements and the potential varying mechanisms and thresholds for producing them. Moreover, conventional concepts of DBS mechanisms and VTA models are based on the generation and propagation of axonal action potentials, whereas the notion of using electrical current to disrupt pathological network activity at the site of stimulation as a therapeutic mechanism may not necessarily require this. The effect of frequency is also not reflected in the VTA model, and it is well known that independent of the other parameters, frequency is a major determinant of clinical effect. High frequency STN

stimulation attenuates β hypersynchrony and alleviates Parkinsonism while values less than 50Hz (i.e. closer to the β range) exacerbate symptoms such as bradykinesia and tremor, further highlighting the crucial mechanistic role of network activity modulation.

Some limitations of conventional VTA models can be overcome by correlating individual voxels within VTA models with observed clinical effects to generate a probabilistic stimulation atlas by assigning each voxel a corresponding clinical score and averaging these over large numbers of patients and stimulation sites on a per symptom basis to provide the likelihood of individual voxels producing an effect. Such probabilistic voxel derived maps have been demonstrated using small numbers of patients largely focussing on therapeutic effects; incorporating side effect profiles using larger samples would improve their accuracy and clinical utility (Butson *et al.*, 2011; Akram *et al.*, 2017). As data on the origins of various side effects from voxel-based morphometry accumulate, and technology to incorporate this information in programming platforms evolves, it may be possible in future to use voxel by voxel analysis during programming to avoid regions significantly associated with adverse effects.

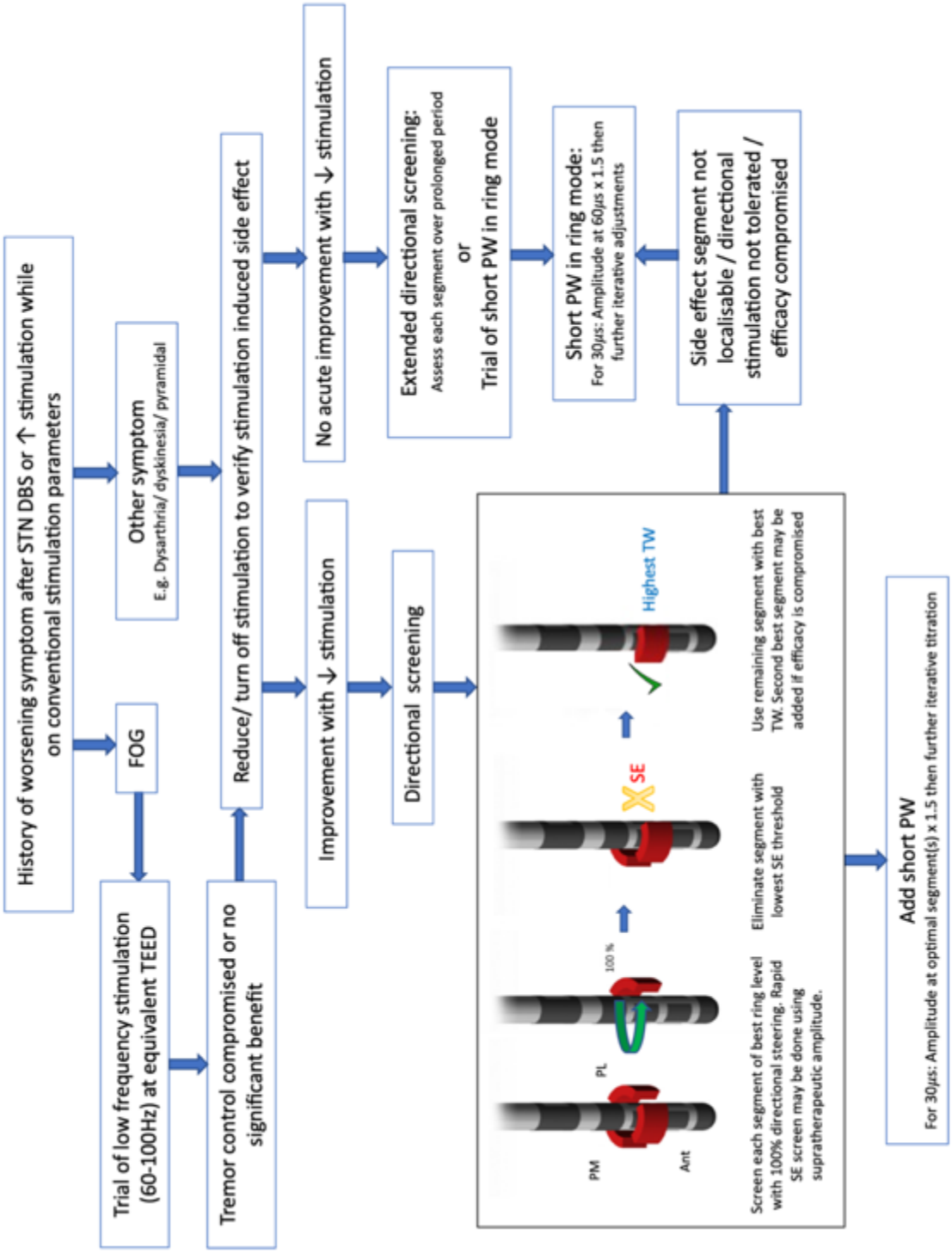
The optimisation process in study 3 focussed on control of motor symptoms as the benchmark; given the significant improvements in side effect symptoms in many patients, it would be of interest to see how this is reflected in quality of life assessments. In addition, any effect on non-motor symptoms, particularly from directional steering, should also form part of the assessment in future studies.

Finally, the hierarchy of these novel techniques in relation to each other and to conventional methods in the optimisation sequence, and the utility of their combination with previously available techniques such as bipolar stimulation, anodic stimulation, and low frequency, will become clearer with accumulation of further data from studies looking at these aspects and their impact on therapeutic benefit and stimulation related adverse effects.

6.3 Concluding remarks

The explosive increase in the number of possible programming configurations with the availability of novel features in recent years has exceeded the capacity of clinicians to explore these routinely in the systematic manner of a conventional monopolar review. Some degree of automation or assisted programming in narrowing down these options using both anatomic and functional information is inevitable if the full potential of these features is to be utilised. Technologies to facilitate these are emerging, albeit in early stages. The future of STN DBS programming could include platforms with automatised feedback from integrated visualisation software incorporating individualised anatomical and connectivity information, combined with sensing and processing of local field potentials to guide selection of electrodes for optimal therapeutic benefit, and perhaps closed loop systems with dynamic and responsive adjustment of stimulation parameters based on neuronal and peripheral biosignals. However, while these technologies are being developed to the levels of complexity and sophistication required for routine clinical use, simplified and practical evidence-based guidelines are needed on the use of currently available techniques so that these can be utilised to help alleviate side effects and further optimise the highly effective therapy that STN DBS has become firmly established as. The data presented here represent some foundational steps towards this process.

6.4 A proposed simplified optimisation algorithm for stimulation induced side effects of STN DBS using novel techniques



Legend:
FOG: Freezing of gait; TW: Therapeutic window; SE: Side effect; PW: Pulse width; TEED: Total electrical energy delivered: Ant: Anterior: PM: Posteromedial: PL: Posterolateral.

Bibliography

Akram, H., Georgiev, D., Mahlknecht, P., Hyam, J., Foltynie, T., Limousin, P., et al. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. *NeuroImage*. 2017; 158:332–345.

Alkemade, A., Schnitzler, A. & Forstmann, B.U. Topographic organization of the human and non-human primate subthalamic nucleus. *Brain Structure and Function*. 2015; 220(6):3075-86.

Alonso-Frech, F., Zamarbide, I., Alegre, M., Rodríguez-Oroz, M.C., Guridi, J., Manrique, M., et al. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. *Brain*. 2006; 129(Pt 7):1748-57.

Alonso, F., Latorre, M.A., Göransson, N., Zsigmond, P. & Wårdell, K. Investigation into deep brain stimulation lead designs: A patient-specific simulation study. *Brain Sciences*. 2016; 6(3):39.

Ammari, R., Bioulac, B., Garcia, L. & Hammond, C. The Subthalamic Nucleus becomes a Generator of Bursts in the Dopamine-Depleted State. Its High Frequency Stimulation Dramatically Weakens Transmission to the Globus Pallidus. *Frontiers in Systems Neuroscience*. 2011; 5:43.

Anderson, V.C., Burchiel, K.J., Hogarth, P., Favre, J. & Hammerstad, J.P. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Archives of Neurology*. 2005; 62:554–560.

Aquino, C.C., Duffley, G., Hedges, D.M., Vorwerk, J., House, P.A., Ferraz, H.B., et al. Interleaved deep brain stimulation for dyskinesia management in Parkinson's disease. *Movement Disorders*. 2019; 34:1722–1727.

Arlotti, M., Marceglia, S., Foffani, G., Volkmann, J., Lozano, A.M., Moro, E., et al. Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. *Neurology*. 2018; 90:e971–e976.

Asahi, T., Ikeda, K., Yamamoto, J., Tsubono, H. & Sato, S. Pilot Study for Considering Subthalamic Nucleus Anatomy during Stimulation Using Directional Leads. *Journal of Movement Disorders*. 2019; 12:97–102.

Ashby, P., Kim, Y.J., Kumar, R., Lang, A.E. & Lozano, A.M. Neurophysiological effects of stimulation through electrodes in the human subthalamic nucleus. *Brain*. 1999; 122 (Pt 10):1919-31.

Ashby, P., Paradiso, G., Saint-Cyr, J.A., Chen, R., Lang, A.E. & Lozano, A.M. Potentials recorded at the scalp by stimulation near the human subthalamic nucleus. *Clinical Neurophysiology*. 2001; 112(3):431-7.

Åström, M., Tripoliti, E., Hariz, M.I., Zrinzo, L.U., Martinez-Torres, I., Limousin, P., et al. Patient-specific model-based investigation of speech intelligibility and movement during deep brain stimulation. *Stereotactic and Functional Neurosurgery*. 2010; 88:224–233.

Athauda, D. & Foltynie, T. The ongoing pursuit of neuroprotective therapies in Parkinson disease. *Nature Reviews Neurology*. 2015; 11:25–40.

Aviles-Olmos, I., Kefalopoulou, Z., Tripoliti, E., Candelario, J., Akram, H., Martinez-Torres, I., et al. Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. *Journal of Neurology, Neurosurgery and Psychiatry*. 2014; 85:1419–1425.

Aziz, T.Z., Peggs, D., Sambrook, M.A. & Crossman, A.R. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism in the primate. *Movement Disorders*. 1991; 6:288–292.

Baizabal-Carvallo, J.F. & Alonso-Juarez, M. Low-frequency deep brain stimulation for movement disorders. *Parkinsonism and Related Disorders*. 2016; 31:14–22.

Bejjani, B.P., Damier, P., Arnulf, I., Thivard, L., Bonnet, A.M., Dormont, D., et al. Transient acute depression induced by high-frequency deep-brain stimulation. *New England Journal of Medicine*. 1999; 340(19):1476-80.

Benabid, A., Pollak, P., Louveau, A., Henry, S., de Rougemont, J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl. Neurophysiol.* 1987; 50:344–346.

Benabid, A.L., Pollak, P. et al Acute and Long-Term Effects of Subthalamic Nucleus Stimulation in Parkinson's Disease. *Stereotact Funct Neurosurg*. 1994; 62:76–84.

Benabid, A.L., Benazzouz, A., Gao, D., Hoffmann, D., Limousin, P., Koudsie, A., et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus and of other nuclei as a treatment for Parkinson's disease. *Techniques in Neurosurgery*. 1999; 5:5–30.

Benazzouz, A., Gross, C., Féger, J., Boraud, T. & Bioulac, B. Reversal of Rigidity and Improvement in Motor Performance by Subthalamic High-frequency Stimulation in MPTP-treated Monkeys. *European Journal of Neuroscience*. 1993; 5:382–389.

Beudel, M. Adaptive Brain Stimulation for Parkinson's Disease. *Closed Loop Neuroscience*. 2016; 22:213–222.

Beudel, M., Little, S., Pogosyan, A., Ashkan, K., Foltynie, T., Limousin, P., et al. Tremor reduction by deep brain stimulation is associated with gamma power suppression in Parkinson's disease. *Neuromodulation*. 2015; 18(5):349-54.

Beurrier, C., Bioulac, B., Audin, J. & Hammond, C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *Journal of Neurophysiology*. 2001; 85(4):1351-6.

Birkmayer, W. & Hornykiewicz, O. The L-dihydroxyphenylalanine (L-DOPA) Effect in Parkinson's Syndrome in Man: On the Pathogenesis and Treatment of Parkinson Akinesis. *Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr. 1*962; 203:560–574.

Blomstedt, P., Hariz, M.I., Lees, A., Silberstein, P., Limousin, P., Yelnik, J., et al. Acute severe depression induced by intraoperative stimulation of the substantia nigra: A case report. *Parkinsonism and Related Disorders*. 2008; 14(3):253-6.

Bot, M., Schuurman, P.R., Odekerken, V.J.J., Verhagen, R., Contarino, F.M., De Bie, R.M.A., et al. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. *Journal of neurology, neurosurgery, and psychiatry*. 2018; 89(5):493-498.

Bour, L.J., Lourens, M.A.J., Verhagen, R., De Bie, R.M.A., Van Den Munckhof, P., Schuurman, P.R., et al. Directional recording of subthalamic spectral power densities in Parkinson's disease and the effect of steering deep brain stimulation. *Brain Stimulation*. 2015; 8:730–741.

Bouthour, W., Béreau, M., Kibleur, A., Zacharia, A., Tomkova Chaoui, E., Fleury, V., et al. Dyskinesia-inducing lead contacts optimize outcome of subthalamic stimulation in Parkinson's disease. *Movement Disorders*. 2019a; 34:1728–1734.

Bouthour, W., Mégevand, P., Donoghue, J., Lüscher, C., Birbaumer, N. & Krack, P. Biomarkers for closed-loop deep brain stimulation in Parkinson disease and beyond. *Nature Reviews Neurology*. 2019; 15(6):343-352.

Bouthour, W., Wegrzyk, J., Momjian, S., Péron, J., Fleury, V., Tomkova Chaoui, E., et al. Short pulse width in subthalamic stimulation in Parkinson's disease: a randomized, double-blind study. *Movement Disorders*. 2018; 33:169–173.

Boviatsis, E.J., Stavrinou, L.C., Themistocleous, M., Kouyialis, A.T. & Sakas, D.E. Surgical and hardware complications of deep brain stimulation. A seven-year experience and review of the literature. *Acta Neurochirurgica*. 2010; 152(12):2053-62.

Broager, B. & Fog, T. Thalamotomy for the Relief of Intention Tremor in Multiple Sclerosis. *Acta Neurologica Scandinavica*. 1962;38(3):153-6.

Brocker, D.T. & Grill, W.M. Principles of electrical stimulation of neural tissue. In: *Handbook of Clinical Neurology*. 2013; 116:3-18

Bronte-Stewart, H., Barberini, C., Koop, M.M., Hill, B.C., Henderson, J.M. & Wingeier, B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. *Experimental Neurology*. 2009; 215(1):20-8.

Brozova, H., Republic, C., Barnaure, I., Alterman, R.L. & Tagliati, M. STN-DBS Frequency Effects on Freezing of Gait in Advanced Parkinson Disease. *Neurology*. 2009; 72:770–771.

Buhlmann, J., Hofmann, L., Tass, P.A. & Hauptmanna, C. Modeling of a segmented electrode for desynchronizing deep brain stimulation. *Frontiers in Neuroengineering*. 2011; 4:15.

Buhmann, C., Huckhagel, T., Engel, K., Gulberti, A., Hidding, U., Poetter-Nerger, M., et al. Adverse events in deep brain stimulation: A retrospective long-term analysis of neurological, psychiatric and other occurrences. *PLoS ONE*. 2017; 12:1–21.

Butson, C.R., Cooper, S.E., Henderson, J.M. & McIntyre, C.C. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. *NeuroImage*. 2007; 34(2):661-70.

Butson, C.R., Cooper, S.E., Henderson, J.M. & McIntyre, C.C. Predicting the effects of deep brain stimulation with diffusion tensor based electric field models. In: *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*. 2006; 9(Pt 2):429-37.

Butson, C.R., Cooper, S.E., Henderson, J.M., Wolgamuth, B. & McIntyre, C.C. Probabilistic analysis of activation volumes generated during deep brain stimulation. *NeuroImage*. 2011; 54:2096–2104.

Castrioto, A., Volkmann, J. & Krack, P. Postoperative management of deep brain stimulation in Parkinson's disease. In: *Handbook of Clinical Neurology*. 2013;116:129-46.

Ceballos-Baumann, A.O., Boecker, H., Bartenstein, P., Von Falkenhayn, I., Riescher, H., Conrad, B., et al. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: Enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. *Archives of Neurology*. 1999; 56(8):997-1003.

Chopra, A., Tye, S.J., Lee, K.H., Sampson, S., Matsumoto, J., Adams, A., et al. Underlying Neurobiology and Clinical Correlates of Mania Status After Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A Review of the Literature. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 2012; 24:102–110.

Coenen, V.A., Honey, C.R., Hurwitz, T., Rahman, A.A., McMaster, J., Bürgel, U., et al. Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. *Neurosurgery*. 2009; 64(6):1106-14.

Connolly, B.S. & Lang, A.E. Pharmacological treatment of Parkinson disease: A review. *JAMA - Journal of the American Medical Association*. 2014; 311(16):1670-83.

Contarino, M.F., Bour, L.J., Verhagen, R., Lourens, M.A.J., De Bie, R.M.A., Van Den Munckhof, P., et al. Directional steering: A novel approach to deep brain stimulation. *Neurology*. 2014; 83:1163–1169.

Cooper, I.S. & Poloukhine, N. NEUROSURGICAL RELIEF OF INTENTION (CEREBELLAR) TREMOR.; A Preliminary Report. *Journal of the American Geriatrics Society*. 1959;

Cornford, M.E., Chang, L. & Miller, B.L. The neuropathology of parkinsonism - an overview. *Brain and Cognition*. 1995; 28:321–341.

Cotzias GC, Van Woert MH, S.L. Aromatic amino acids and modification of parkinsonism. *N Engl J Med. 1967*. 1967; Feb 16;276:374–379.

Daneshzand, M., Faezipour, M. & Barkana, B.D. Robust desynchronization of Parkinson's disease pathological oscillations by frequency modulation of delayed feedback deep brain stimulation. *PLoS ONE*. 2018; 13(11): e0207761.

Darley, F.L., Aronson, A.E. & Brown, J.R. Differential diagnostic patterns of dysarthria. *Journal of speech and hearing research*. 1969; 12:246–269.

Dembek, T.A., Hoevels, M., Hellerbach, A., Horn, A., Petry-Schmelzer, J.N., Borggrefe, J., et al. Directional DBS Leads Show Large Deviations from their Intended Implantation Orientation. *bioRxiv*. 2019; 631325.

Dembek, T.A., Reker, P., Visser-Vandewalle, V., Wirths, J., Treuer, H., Klehr, M., et al. Directional DBS increases side-effect thresholds—A prospective, double-blind trial. *Movement Disorders*. 2017a; 32:1380–1388.

Dembek, T.A., Reker, P., Visser-Vandewalle, V., Wirths, J., Treuer, H., Klehr, M., et al. Directional DBS increases side-effect thresholds—A prospective, double-blind trial. *Movement Disorders*. 2017b; 32:1380–1388.

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., et al. A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. *New England Journal of Medicine*. 2006; 355:896–908.

Dorsey, M., Yorkston, K., Beukelman, D., & Hakel, M. Speech intelligibility test for windows. *Lincoln, NE: Institute for Rehabilitation Science and Engineering at Madonna RehabilitationHospital*. 2007;

Dorsey, M., Beukelman, D., Ph, D., Hakel, M. & Ph, D. *Speech Intelligibility Test for Windows*. 1996;

Dorval, A.D., Russo, G.S., Hashimoto, T., Xu, W., Grill, W.M. & Vitek, J.L. Deep brain stimulation reduces neuronal entropy in the MPTP-primate model of Parkinson's disease. *Journal of Neurophysiology*. 2008; 100(5):2807-18.

Dostrovsky, J.O., Hutchison, W.D. & Lozano, A.M. The globus pallidus, deep brain stimulation, and Parkinson's disease. *Neuroscientist*. 2002; 8:284–90 67.

Eleopra, R., Rinaldo, S., Devigili, G., Lettieri, C., Mondani, M., Auria, S.D., et al. Clinical Neurophysiology Brain impedance variation of directional leads implanted in subthalamic nuclei of Parkinsonian patients. *Clinical Neurophysiology*. 2019; 130:1562–1569.

Engel, K., Huckhagel, T., Gulberti, A., Pötter-Nerger, M., Vettorazzi, E., Hidding, U., et al. Towards unambiguous reporting of complications related to deep brain stimulation surgery: A retrospective single-center analysis and systematic review of the literature. *PLoS ONE*. 2018; 13(8):e0198529.

Eusebio, A., Chen, C.C., Lu, C.S., Lee, S.T., Tsai, C.H., Limousin, P., et al. Effects of low-frequency stimulation of the subthalamic nucleus on movement in Parkinson's disease. *Experimental Neurology*. 2008; 209:125–130.

Fabbri, M., Zibetti, M., Ferrero, G., Accornero, A., Guimaraes, I., Rizzone, M.G., et al. Is lowering stimulation frequency a feasible option for subthalamic deep brain stimulation in Parkinson's disease patients with dysarthria? *Parkinsonism and Related Disorders*. 2019; 64:242–248.

Fabbrini, G., Juncos, J., Mouradian, M.M., Serrati, C. & Chase, T.N. Levodopa pharmacokinetic mechanisms and motor fluctuations in Parkinson's disease. *Annals of Neurology*. 1987; 21(4):370-6.

Fenoy, A.J., Mchenry, M.A. & Schiess, M.C. Speech changes induced by deep brain stimulation of the subthalamic nucleus in Parkinson disease: Involvement of the dentatorubrothalamic tract. *Journal of Neurosurgery*. 2017; 126(6):2017-2027.

Filali, M., Hutchison, W.D., Palter, V.N., Lozano, A.M. & Dostrovsky, J.O. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. *Experimental Brain Research*. 2004; 156:274–281.

Florence, G., Sameshima, K., Fonoff, E.T. & Hamani, C. Deep Brain Stimulation: More Complex than the Inhibition of Cells and Excitation of Fibers. *Neuroscientist*. 2016; 22(4):332-45.

Foltynie, T., Zrinzo, L., Martinez-Torres, I., Tripoliti, E., Petersen, E., Holl, E., et al. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: Efficacy and safety. *Journal of Neurology, Neurosurgery and Psychiatry*. 2011; 82:358–363.

Galati, S., Mazzone, P., Fedele, E., Pisani, A., Peppe, A., Pierantozzi, M., et al. Biochemical and electrophysiological changes of substantia nigra pars reticulata driven by subthalamic stimulation in patients with Parkinson's disease. *European Journal of Neuroscience*. 2006; 23(11):2923-8.

Garcia, L., Audin, J., D'Alessandro, G., Bioulac, B. & Hammond, C. Dual effect of high-frequency stimulation on subthalamic neuron activity. *Journal of Neuroscience*. 2003; 23 (25) 8743-8751.

St. George, R.J., Nutt, J.G., Burchiel, K.J. & Horak, F.B. A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD. *Neurology*. 2010; 75:1292–1299.

Goetz, C.G., Nutt, J.G. & Stebbins, G.T. The unified dyskinesia rating scale: Presentation and clinimetric profile. *Movement Disorders*. 2008; 23:2398–2403.

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*. 2008; 23:2129–2170.

Golestanirad, L., Elahi, B., Graham, S.J., Das, S. & Wald, L.L. Efficacy and Safety of Pedunculopontine Nuclei (PPN) Deep Brain Stimulation in the Treatment of Gait Disorders: A Meta-Analysis of Clinical Studies. *Canadian Journal of Neurological Sciences*. 2015; 43:120–126.

Greenhouse, I., Gould, S., Houser, M., Hicks, G., Gross, J. & Aron, A.R. Stimulation at dorsal and ventral electrode contacts targeted at the subthalamic nucleus has different effects on motor and emotion functions in Parkinson's disease. *Neuropsychologia*. 2011; 49:528–534.

Groppa, S., Herzog, J., Falk, D., Riedel, C., Deuschl, G. & Volkmann, J. Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. *Brain*. 2014; 137:109–121.

Grover, T., Georgiev, D., Kalliola, R. & Mahlknecht, P. *Effect of Low versus High Frequency Subthalamic Deep Brain Stimulation on Speech Intelligibility and Verbal Fluency in Parkinson ' s Disease : A Double-Blind Study*. 2019; 9:141–151.

Grover, T., Georgiev, D., Kalliola, R., Mahlknecht, P., Zacharia, A., Limousin, P., et al. Effect of Low versus High Frequency Subthalamic Deep Brain Stimulation on Speech Intelligibility and Verbal Fluency in Parkinson's Disease: A Double-Blind Study. *Journal of Parkinson's Disease*. 2018; 9:141–151.

Guehl, D., Cuny, E., Benazzouz, A., Rougier, A., Tison, F., MacHado, S., et al. Side-effects of subthalamic stimulation in Parkinson's disease: Clinical evolution and predictive factors. *European Journal of Neurology*. 2006; 13:963–971.

Hahn, P.J., Russo, G.S., Hashimoto, T., Miocinovic, S., Xu, W., McIntyre, C.C., et al. Pallidal burst activity during therapeutic deep brain stimulation. *Experimental Neurology*. 2008; 211(1): 243–251.

Hamani, C., Florence, G., Heinsen, H., Plantinga, B.R., Temel, Y., Uludag, K., et al. Subthalamic Nucleus Deep Brain Stimulation: Basic Concepts and Novel Perspectives. *Eneuro*. 2017; 4:ENEURO.0140-17.2017.

Hamani, C., Saint-Cyr, J.A., Fraser, J., Kaplitt, M. & Lozano, A.M. The subthalamic nucleus in the context of movement disorders. *Brain*. 2004; 127:4–20.

Hariz, M. Deep brain stimulation: new techniques. *Parkinsonism and realted Disorders*. 2014; 20:S192–S196.

Hartmann, Christian; Fliegen, Sabine; Groiss, Stefan; Wojtecki, Lars; Schnitzler, A. An update on best practice of deep brain stimulation in Parkinson's disease. *Therapeutic Advances in Neurological Disorders*. 2019; 12:1–20.

Hashimoto, T., Elder, C.C.M., Okun, M.S., Patrick, S.K. & Vitek, J.L. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *The Journal of …*. 2003a; 23:1916–1923.

Hashimoto, T., Elder, C.M., Okun, M.S., Patrick, S.K. & Vitek, J.L. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *Journal of Neuroscience*. 2003b; 23(5):1916-23.

Hawkes, C. Olfactory testing in parkinsonism. *Lancet Neurology*. 2004; 3:393–394.

Hellerbach, A., Dembek, T.A., Hoevels, M., Holz, J.A., Gierich, A., Luyken, K., et al. DiODe: Directional orientation detection of segmented deep brain stimulation leads: A sequential algorithm based on CT imaging. *Stereotactic and Functional Neurosurgery*. 2018; 96(5):335-341.

De Hemptinne, C., Ryapolova-Webb, E.S., Air, E.L., Garcia, P.A., Miller, K.J., Ojemann, J.G., et al. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2013; 110(12):4780-5.

De Hemptinne, C., Swann, N.C., Ostrem, J.L., Ryapolova-Webb, E.S., San Luciano, M., Galifianakis, N.B., et al. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nature Neuroscience*. 2015; 18(5): 779–786.

Herrington, T.M., Cheng, J.J. & Eskandar, E.N. Mechanisms of deep brain stimulation. *Journal of Neurophysiology*. 1;115(1):19-38.

Herzog, J., Fietzek, U., Hamel, W., Morsnowski, A., Steigerwald, F., Schrader, B., et al. Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. *Movement Disorders*. 2004; 19(9):1050-4.

Herzog, J., Pinsker, M., Wasner, M., Steigerwald, F., Wailke, S., Deuschl, G., et al. Stimulation of subthalamic fibre tracts reduces dyskinesias in STN-DBS. *Movement Disorders*. 2007; 22:679–684.

Hilker, R., Voges, J., Weber, T., Kracht, L.W., Roggendorf, J., Baudrexel, S., et al. STN-DBS activates the target area in Parkinson disease: An FDG-PET study. *Neurology*. 2008; 71(10):708-13.

Holl, E.M., Petersen, E.A., Foltynie, T., Martinez-Torres, I., Limousin, P., Hariz, M.I., et al. Improving targeting in image-guided frame-based deep brain stimulation. *Neurosurgery*. 2010; 67:437–447.

Hornykiewicz, O. A brief history of levodopa. *Journal of Neurology*. 2010; 257:249–252.

Ince, N.F., Gupte, A., Wichmann, T., Ashe, J., Henry, T., Bebler, M., et al. Selection of optimal programming contacts based on local field potential recordings from subthalamic nucleus in patients with Parkinson's disease. *Neurosurgery*. 2010; 67(2):390-7.

Jech, R., Urgošík, D., Tintěr, J., Nebuželský, A., Krásenský, J., Liščák, R., et al. Functional magnetic renonance imaging during deep brain stimulation: A pilot study in four patients with parkinson's disease. *Movement Disorders*. 2001; 16(6):1126-32.

Katzenshlager, R., Evans, A., Manson, A., Palsalos, P.N., Ratnaraj, N., Watt, H., et al. Mucuna pruriens in Parkinson's disease: A double blind clinical and pharmacological study. *Journal of Neurology, Neurosurgery and Psychiatry*. 2004; 75(12):1672-7.

Kawasaki, T., Shin, M., Kimura, Y., Umitsu, Y., Matsumura, G., Yokochi, F., et al. Topographic anatomy of the subthalamic nucleus localized by high-resolution human brain atlas superimposing digital images of cross-sectioned surfaces and histological images of microscopic sections from frozen cadaveric brains. *Journal of Clinical Neuroscience*. 2018; 53:193–202.

Khoo, H.M., Kishima, H., Hosomi, K., Maruo, T., Tani, N., Oshino, S., et al. Low-frequency subthalamic nucleus stimulation in Parkinson's disease: A randomized clinical trial. *Movement Disorders*. 2014; 29:270–274.

Kleiner-Fisman, G., Herzog, J., Fisman, D.N., Tamma, F., Lyons, K.E., Pahwa, R., et al. Subthalamic nucleus deep brain stimulation: Summary and meta-analysis of outcomes. *Movement Disorders*. 2006; 21:S290–S304.

Koss, A.M., Alterman, R.L., Tagliati, M., Shils, J.L., Moro, E., Lang, A.E., et al. Calculating total electrical energy delivered by deep brain stimulation systems [1] (multiple letters). *Annals of Neurology*. 2005; 58:168–169.

Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin, C., et al. Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease. *New England Journal of Medicine*. 2003; 349:1925–1934.

Krack, P., Fraix, V., Mendes, A., Benabid, A.L. & Pollak, P. Postoperative management of subthalamic nucleus stimulation for parkinson's disease. *Movement Disorders*. 2002; 17(S3):S188 - S197.

Krack, P., Kumar, R., Ardouin, C., Dowsey, P.L., Mc Vicker, J.M., Benabid, A.L., et al. Mirthful laughter induced by subthalamic nucleus stimulation. *Movement Disorders*. 2001; 16(5):867-875.

Krack, P., Pollak, P., Limousin, P., Benazzouz, A., Deuschl, G. & Benabid, A.L. From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity. *Brain*. 1999; 122(Pt 6):1133-46.

Krack, P., Volkmann, J., Tinkhauser, G. & Deuschl, G. Deep Brain Stimulation in Movement Disorders: From Experimental Surgery to Evidence-Based Therapy. *Movement Disorders*. 2019; 34:1795–1810.

Krishnan, D., Ismail, S.M. & Siwar, C. Upstream households' willingness to pay (WTP) for forested watershed protection in Langat Basin, Selangor, Malaysia. *Malaysian Forester*. 2015; 78:125–132.

Kuhn, A.A., Kempf, F., Brucke, C., Gaynor Doyle, L., Martinez-Torres, I., Pogosyan, A., et al. High-Frequency Stimulation of the Subthalamic Nucleus Suppresses Oscillatory Activity in Patients with Parkinson's Disease in Parallel with Improvement in Motor Performance. *Journal of Neuroscience*. 2008; 28:6165–6173.

Kühn, A.A., Kupsch, A., Schneider, G.H. & Brown, P. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *European Journal of Neuroscience*. 2006; 23:1956–1960.

Kühn, A.A., Tsui, A., Aziz, T., Ray, N., Brücke, C., Kupsch, A., et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. *Experimental Neurology*. 2009; 219(1):58-61.

Kühn, A.A. & Volkmann, J. Innovations in deep brain stimulation methodology. *Movement Disorders*. 2017; 32:11–19.

Kulisevsky, J., Berthier, M.L., Gironell, A., Pascual-Sedano, B., Molet, J. & Parés, P. Mania following deep brain stimulation for Parkinson's disease. *Neurology*. 2002; 59(9):1421-4.

Lanotte, M.M., Rizzone, M., Bergamasco, B., Faccani, G., Melcarne, A. & Lopiano, L. Deep brain stimulation of the subthalamic nucleus: Anatomical, neurophysiological, and outcome correlations with the effects of stimulation. *Journal of Neurology Neurosurgery and Psychiatry*. 2002; 72(1):53-8.

Lévesque, J.C. & André, P. GABAergic interneurons in human subthalamic nucleus. *Movement Disorders*. 2005; 20(5):574-84.

Li, S., Arbuthnott, G.W., Jutras, M.J., Goldberg, J.A. & Jaeger, D. Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. *Journal of Neurophysiology*. 2007; 98(6):3525-37.

Lim, J.K., Tasker, R.R. & Scott, J.W. Quantitative assessment of thalamotomy for Parkinsonism. *Confinia neurologica*. 1969; 31(1):11-21.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J.F., Perret, J.E., et al. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *The Lancet*. 1995; 345:91–95.

Limousin, P., Pollak, P., Hoffmann, D., Benazzouz, A., Perret, J.E. & Benabid, A.L. Abnormal involuntary movements induced by subthalamic nucleus stimulation in parkinsonian patients. *Movement Disorders*. 1996a; 11:231–235.

Limousin, P., Pollak, P., Hoffmann, D., Benazzouz, A., Perret, J.E. & Benabid, A.L. Abnormal involuntary movements induced by subthalamic nucleus stimulation in parkinsonian patients. *Movement Disorders*. 1996b; 11(3):231-5.

Little, S., Beudel, M., Zrinzo, L., Foltynie, T., Limousin, P., Hariz, M., et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*. 2016; 87:717–721.

Little, S. & Brown, P. The functional role of beta oscillations in Parkinson's disease. *Parkinsonism and Related Disorders*. 2014; 20:S44–S48.

Little, S. & Brown, P. What brain signals are suitable for feedback controzl of deep brain stimulation in Parkinson's disease? *Annals of the New York Academy of Sciences*. 2012; 1265:9–24.

M Rizzone, M Lanotte, B Bergamasco, A Tavella, E Torre, G Faccani, A Melcarne, L.L. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Effects of variation in stimulation parameters. *J Neurol Neurosurg Psychiatry*. 2002; 71:215–219.

Magarios-Ascone, C., Pazo, J.H., Macadar, O. & Buo, W. High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: A possible cellular mechanism in Parkinson's disease. *Neuroscience*. 2002; 115(4):1109-17.

Mahlknecht, P., Akram, H., Georgiev, D., Tripoliti, E., Candelario, J., Zacharia, A., et al. Pyramidal tract activation due to subthalamic deep brain stimulation in Parkinson's disease. *Movement Disorders*. 2017; 32:1174–1182.

Maks, C.B., Butson, C.R., Walter, B.L., Vitek, J.L. & McIntyre, C.C. Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. *Journal of Neurology, Neurosurgery and Psychiatry*. 2009; 80(6): 659–666.

Mallet, L., Schüpbach, M., N'Diaye, K., Remy, P., Bardinet, E., Czernecki, V., et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. *Proceedings of the*

National Academy of Sciences of the United States of America. 2007; 104(25):10661-6.

Manson, A., Stirpe, P. & Schrag, A. Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life. *Journal of Parkinson's Disease*. 2012; 2:189–198.

Manyam, B. V. Paralysis agitans and levodopa in "Ayurveda": Ancient Indian medical treatise. *Movement Disorders*. 1990; 5(1):47-48.

Matsumura, M., Kojima, J., Gardiner, T.W. & Hikosaka, O. Visual and oculomotor functions of monkey subthalamic nucleus. *Journal of Neurophysiology*. 1992; 67:1615–1632.

Maurice, N., Thierry, A.M., Glowinski, J. & Deniau, J.M. Spontaneous and Evoked Activity of Substantia Nigra Pars Reticulata Neurons during High-Frequency Stimulation of the Subthalamic Nucleus. *Journal of Neuroscience*. 2003; 23(30):9929-36.

Mazzone, P., Lozano, A., Stanzione, P., Galati, S., Scarnati, E., Peppe, A., et al. Implantation of human pedunculopontine nucleus: A safe and clinically relevant target in Parkinson's disease. *NeuroReport*. 2005; 16:1877–1881.

McCrea, S. Transforming teachers, transforming schools: Turning 'sages' into 'guides on the side'. *Turkish Online Journal of Distance Education*. 2012; 13:11–16.

McIntyre, C.C. & Hahn, P.J. Network perspectives on the mechanisms of deep brain stimulation. *Neurobiology of Disease*. 2010. 38(3):329-37.

McIntyre, C.C., Savasta, M., Kerkerian-Le Goff, L. & Vitek, J.L. Uncovering the mechanism(s) of action of deep brain stimulation: Activation, inhibition, or both. *Clinical Neurophysiology*. 2004;115(6):1239-1248.

Merola, A., Romagnolo, A., Krishna, V., Pallavaram, S., Carcieri, S., Goetz, S., et al. Current Directions in Deep Brain Stimulation for Parkinson's Disease—Directing Current to Maximize Clinical Benefit. *Neurology and Therapy*. 2020; 9: 25–41.

Merola, A., Zibetti, M., Angrisano, S., Rizzi, L., Ricchi, V., Artusi, C.A., et al. Parkinson's disease progression at 30 years: A study of subthalamic deep brain-stimulated patients. *Brain*. 2011; 134:2074–2084.

Moldovan, A.S., Hartmann, C.J., Trenado, C., Meumertzheim, N., Slotty, P.J., Vesper, J., et al. Less is more – Pulse width dependent therapeutic window in deep brain stimulation for essential tremor. *Brain Stimulation*. 2018; 11:1132–1139.

Moreau, C., Defebvre, L., Destée, A., Bleuse, S., Clement, F., Blatt, J.L., et al. STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. *Neurology*. 2008; 71:80–84.

Moro, E., Esselink, R.J.A., Xie, J., Hommel, M., Benabid, A.L. & Pollak, P. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology*. 2002a; 59:706–713.

Moro, E., Xie, J., Hommel, M., Benabid, A.L. & Pollak, P. *The impact on Parkinson's disease of electrical parameter settings in STN stimulation*. 2002b; 59:706–713.

Nagaseki, Y., Shibazaki, T., Hirai, T., Kawashima, Y., Hirato, M., Wada, H., et al. Long-term follow-up results of selective VIM-thalamotomy. *Journal of Neurosurgery*. 1986; 65(3):296-302.

Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., et al. Excitatory Cortical Inputs to Pallidal Neurons Via the Subthalamic Nucleus in the Monkey. *Journal of Neurophysiology*. 2000; 84:289–300.

Neumann, W.J., Staub-Bartelt, F., Horn, A., Schanda, J., Schneider, G.H., Brown, P., et al. Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. *Clinical Neurophysiology*. 2017; 128(11):2286-2291.

Nguyen, T.A.K., Nowacki, A., Debove, I., Petermann, K., Tinkhauser, G., Wiest, R., et al. Directional stimulation of subthalamic nucleus sweet spot predicts clinical efficacy: Proof of concept. *Brain Stimulation*. 2019; 12:1127–1134.

Nonnekes, J., Janssen, A.M., Mensink, S.H.G., Oude Nijhuis, L.B., Bloem, B.R. & Snijders, A.H. Short rapid steps to provoke freezing of gait in Parkinson???s disease. *Journal of Neurology*. 2014; 261:1763–1767.

Noyce, A. Nagy, S. Acharya, S. Hadavi, J. Bestwick, J. Fearnley, A. Lees, G.G. Bradykinesia-Akinesia Incoordination Test: Validating an Online Keyboard Test of Upper Limb Function. *PLoS ONE*. 2014; 9:e96260.

Obeso, J.A., Olanow, C.W., Rodriguez-Oroz, M.C., Krack, P., Kumar, R. & Lang, A.E. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus

pallidus in Parkinson's disease. *New England Journal of Medicine*. 2001; 345(13):956-63.

Odekerken, V.J.J., van Laar, T., Staal, M.J., Mosch, A., Hoffmann, C.F.E., Nijssen, P.C.G., et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): A randomised controlled trial. *The Lancet Neurology*. 2013; 12:37–44.

Okun, M.S., Gallo, B. V, Mandybur, G., Jagid, J., Foote, K.D., Revilla, F.J., et al. Articles OA Subthalamic deep brain stimulation with a constant-current device in Parkinson ' s disease : an open-label randomised controlled trial. *Lancet Neurology*. 2012; 4422:1–10.

Olanow, C.W., Kieburtz, K., Odin, P., Espay, A.J., Standaert, D.G., Fernandez, H.H., et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study. *The Lancet Neurology*. 2014; 13:141–149.

Ovallath, S. & Deepa, P. The history of parkinsonism: Descriptions in ancient Indian medical literature. *Movement Disorders*. 2013; 28(5):566-8.

Parent, A. & Hazrati, L. *REVIEWS Functional anatomy of the basal ganglia . II . The place of subthalamic nucleus and external pallidum in basal ganglia circuitry*. 1995; 20:128–154.

Parent, M. & Parent, A. The pallidofugal motor fiber system in primates. *Parkinsonism and Related Disorders*. 2004; 10:203–211.

Payoux, P., Remy, P., Damier, P., Miloudi, M., Loubinoux, I., Pidoux, B., et al. Subthalamic nucleus stimulation reduces abnormal motor cortical overactivity in Parkinson disease. *Archives of Neurology*. 2004; 61(8):1307-13.

Peng, L., Fu, J., Ming, Y., Zeng, S., He, H. & Chen, L. The long-term efficacy of STN vs GPi deep brain stimulation for Parkinson disease: A meta-analysis. *Medicine*. 2018; 97:e12153.

Phillips, M.D., Baker, K.B., Lowe, M.J., Tkach, J.A., Cooper, S.E., Kopell, B.H., et al. Parkinson disease: Pattern of functional MR imaging activation during deep brain stimulation of subthalamic nucleus - Initial experience. *Radiology*. 2006; 239(1):209-16.

Picillo, M., Lozano, A.M., Kou, N., Munhoz, R.P. & Fasano, A. *Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms*. 2016a; 9(3):425-437.

Picillo, M., Lozano, A.M., Kou, N., Puppi Munhoz, R. & Fasano, A. Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms. *Brain Stimulation*. 2016b; 9:425–437.

Plaha, P., Ben-Shlomo, Y., Patel, N.K. & Gill, S.S. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. *Brain*. 2006; 129(Pt 7):1732-47.

Pollak, P., Benabid, A.L., Gross, C., Gao, D.M., Laurent, A., Benazzouz, A., et al. Effects of the stimulation of the subthalamic nucleus in Parkinson disease. *Revue neurologique*. 1993; 149:175–176.

Pollo, C., Kaelin-Lang, A., Oertel, M.F., Stieglitz, L., Taub, E., Fuhr, P., et al. Directional deep brain stimulation: An intraoperative double-blind pilot study. *Brain*. 2014; 137:2015–2026.

Preda, F., Cavandoli, C., Lettieri, C., Pilleri, M., Antonini, A., Eleopra, R., et al. Switching from constant voltage to constant current in deep brain stimulation: A multicenter experience of mixed implants for movement disorders. *European Journal of Neurology*. 2016; 23:190–195.

Qasim, S.E., de Hemptinne, C., Swann, N.C., Miocinovic, S., Ostrem, J.L. & Starr, P.A. Electrocorticography reveals beta desynchronization in the basal ganglia-cortical loop during rest tremor in Parkinson's disease. *Neurobiology of Disease*. 2016; 86:177-86.

R Foundation for Statistical Computing R. Development Core Team: R: A language and environment for statistical computing. *ISBN 3-900051-07-0, http://www.R-project.org.* [Online].

Ramdhani, R.A., Patel, A., Swope, D. & Kopell, B.H. Early Use of 60 Hz Frequency Subthalamic Stimulation in Parkinson's Disease: A Case Series and Review. *Neuromodulation*. 2015; 18:664–669.

Ramirez De Noriega, F., Eitan, R., Marmor, O., Lavi, A., Linetzky, E., Bergman, H., et al. Constant current versus constant voltage subthalamic nucleus deep brain

stimulation in parkinson's disease. *Stereotactic and Functional Neurosurgery*. 2015; 93:114–121.

Ranck, J.B. Which elements are excited in electrical stimulation of mammalian central nervous system: A review. *Brain Research*. 98(3):417-40.

Ray, N.J., Jenkinson, N., Wang, S., Holland, P., Brittain, J.S., Joint, C., et al. Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. *Experimental Neurology*. 2008; 213:108–113.

Reich, M.M., Steigerwald, F., Sawalhe, A.D., Reese, R., Gunalan, K., Johannes, S., et al. Short pulse width widens the therapeutic window of subthalamic neurostimulation. *Annals of Clinical and Translational Neurology*. 2015; 2:427–432.

Reinacher, P.C., Várkuti, B., Krüger, M.T., Piroth, T., Egger, K., Roelz, R., et al. Automatic Segmentation of the Subthalamic Nucleus: A Viable Option to Support Planning and Visualization of Patient-Specific Targeting in Deep Brain Stimulation. *Operative Neurosurgery*. 2019; 17(5):497-502.

Reker, P., Dembek, T.A., Becker, J., Visser-vandewalle, V. & Timmermann, L. Parkinsonism and Related Disorders Directional deep brain stimulation : A case of avoiding dysarthria with bipolar directional current steering. *Parkinsonism and Related Disorders*. 2016; 31:156–158.

Ricchi, V., Zibetti, M., Angrisano, S., Merola, A., Arduino, N., Artusi, C.A., et al. Transient effects of 80 Hz stimulation on gait in STN DBS treated PD patients: A 15 months follow-up study. *Brain Stimulation*. 2012; 5:388–392.

Rizzone, M., Lanotte, M., Bergamasco, B., Tavella, a, Torre, E., Faccani, G., et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. *Journal of neurology, neurosurgery, and psychiatry*. 2001a; 71:215–219.

Rizzone, M., Lanotte, M., Bergamasco, B., Tavella, A., Torre, E., Faccani, G., et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Effects of variation in stimulation parameters. *Journal of Neurology Neurosurgery and Psychiatry*. 2001b; 71:215–219.

Rodriguez-Oroz, M.C., Obeso, J.A., Lang, A.E., Houeto, J.L., Pollak, P., Rehncrona, S., et al. Bilateral deep brain stimulation in Parkinson's disease: A multicentre study with 4 years follow-up. *Brain*. 2005; 128:2240–2249.

Romito, L.M., Raja, M., Daniele, A., Contarino, M.F., Bentivoglio, A.R., Barbier, A., et al. Transient mania with hypersexuality after surgery for high-frequency stimulation of the subthalamic nucleus in Parkinson's disease. *Movement Disorders*. 2002; 17(6):1371-4.

Rosa, M., Arlotti, M., Ardolino, G., Cogiamanian, F., Marceglia, S., Di Fonzo, A., et al. Adaptive deep brain stimulation in a freely moving parkinsonian patient. *Movement Disorders*. 2015; 30:1003–1005.

Rosa, M., Arlotti, M., Marceglia, S., Cogiamanian, F., Ardolino, G., Fonzo, A. Di, et al. Adaptive deep brain stimulation controls levodopa-induced side effects in Parkinsonian patients. *Movement Disorders*. 32(4): 628–629.

Ross, G.W. & Abbott, R.D. Living and dying with Parkinson's disease. *Movement Disorders*. 2014; 29:1571–1573.

Saint-Cyr, J.A., Hoque, T., Pereira, L.C.M., Dostrovsky, J.O., Hutchison, W.D., Mikulis, D.J., et al. Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. *Journal of Neurosurgery*. 2002; 97(5):1152-66.

Santens, P., De Letter, M., Van Borsel, J., De Reuck, J. & Caemaert, J. Lateralized effects of subthalamic nucleus stimulation on different aspects of speech in Parkinson's disease. *Brain and Language*. 2003; 87(2):253-8.

Sauleau, P., Raoul, S., Lallement, F., Rivier, I., Drapier, S., Lajat, Y., et al. Motor and non motor effects during intraoperative subthalamic stimulation for Parkinson's disease. *Journal of Neurology*. 2005; 252:457–464.

Schapira, A.H.V., Chaudhuri, K.R. & Jenner, P. Non-motor features of Parkinson disease. *Nature Reviews Neuroscience*. 2017; 18:435–450.

Schüpbach, W.M.M., Chastan, N., Welter, M.L., Houeto, J.L., Mesnage, V., Bonnet, A.M., et al. Stimulation of the subthalamic nucleus in Parkinson's disease: A 5 year follow up. *Journal of Neurology, Neurosurgery and Psychiatry*. 2005; 76(12): 1640–1644.

Sharman, A., Hirji, R., Birmingham, J.T. & Govind, C.K. Dopaminergic innervation of the subthalamic nucleus in the normal state, in MPTP-treated monkeys, and in Parkinson's disease patients. *Journal of Comparative Neurology*. 2000; 425:121–129.

Shimamoto, S.A., Ryapolova-Webb, E.S., Ostrem, J.L., Galifianakis, N.B., Miller, K.J. & Starr, P.A. Subthalamic nucleus neurons are synchronized to primary motor cortex local field potentials in Parkinson's disease. *Journal of Neuroscience*. 2013; 33(17):7220-33.

Sidiropoulos, C., Walsh, R., Meaney, C., Poon, Y.Y., Fallis, M. & Moro, E. Low-frequency subthalamic nucleus deep brain stimulation for axial symptoms in advanced Parkinson's disease. *Journal of Neurology*. 2013; 260:2306–2311.

Silberstein, P., Oliviero, A., Di Lazzaro, V., Insola, A., Mazzone, P. & Brown, P. Oscillatory pallidal local field potential activity inversely correlates with limb dyskinesias in Parkinson's disease. *Experimental Neurology*. 2005; 194(2):523-9.

Sitz, A., Hoevels, M., Hellerbach, A., Gierich, A., Luyken, K., Dembek, T.A., et al. Determining the orientation angle of directional leads for deep brain stimulation using computed tomography and digital x-ray imaging: A phantom study: A. *Medical Physics*. 2017; 44:4463–4473.

Snijders, A.H., Haaxma, C.A., Hagen, Y.J., Munneke, M. & Bloem, B.R. Freezer or non-freezer: Clinical assessment of freezing of gait. *Parkinsonism and Related Disorders*. 2012; 18:149–154.

SPIEGEL, E.A., WYCIS, H.T. & FREED, H. Thalamotomy in mental disorders. *AMA Arch Neurol Psychiatry*. 1950 Oct;64(4):595-8.

Sprenger, F. & Poewe, W. Management of motor and non-motor symptoms in parkinson's disease. *CNS Drugs*. 2013; 27:259–272.

Starr, P.A. & Ostrem, J.L. Commentary on "Adaptive deep brain stimulation in advanced Parkinson disease". *Annals of Neurology*. 2013; 74:447–448.

Steigerwald, F., Müller, L., Johannes, S., Matthies, C. & Volkmann, J. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device. *Movement Disorders*. 2016; 31:1240–1243.

Steigerwald, F., Timmermann, L., Kühn, A., Schnitzler, A., Reich, M.M., Kirsch, A.D., et al. Pulse duration settings in subthalamic stimulation for Parkinson's disease. *Movement Disorders*. 2018; 33:165–169.

Stocchi, F., Rascol, O., Kieburtz, K., Poewe, W., Jankovic, J., Tolosa, E., et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: The STRIDE-PD study. *Annals of Neurology*. 2010; 68:18–27.

Sun, H.P., Jung, H.H., Lee, J.Y., Kim, C., Beom, S.J. & Dong, G.K. Electrode position determined by fused images of preoperative and postoperative magnetic resonance imaging and surgical outcome after subthalamic nucleus deep brain stimulation. *Neurosurgery*. 2008; 63(5):925-36.

Svennilson, E., Torvik, A., Lowe, R. & Leksell, L. TREATMENT OF PARKINSONISM BY STEREOTACTIC THERMOLESIONS IN THE PALLIDAL REGION. A clinical evaluation of 81 cases. *Acta Psychiatrica Scandinavica*. 1960; 35(3):358-77.

Swann, N.C., De Hemptinne, C., Aron, A.R., Ostrem, J.L., Knight, R.T. & Starr, P.A. Elevated synchrony in Parkinson disease detected with electroencephalography. *Annals of Neurology*. 2015; 78(5):742-50.

Swann, N.C., De Hemptinne, C., Miocinovic, S., Qasim, S., Wang, S.S., Ziman, N., et al. Gamma oscillations in the hyperkinetic state detected with chronic human brain recordings in parkinson's disease. *Journal of Neuroscience*. 2016; 36(24):6445-58.

Swann, N.C., De Hemptinne, C., Thompson, M.C., Miocinovic, S., Miller, A.M., Gilron, R., et al. Adaptive deep brain stimulation for Parkinson's disease using motor cortex sensing. *Journal of Neural Engineering*. 2018; 15(4):046006.

Telkes, I., Sabourin, S., Durphy, J., Adam, O., Sukul, V., Raviv, N., et al. Functional Use of Directional Local Field Potentials in the Subthalamic Nucleus Deep Brain Stimulation. *Frontiers in Human Neuroscience*. 2020; 8;14:145.

Timmermann, L., Wojtecki, L., Gross, J., Lehrke, R., Voges, J., Maarouf, M., et al. Ten-hertz stimulation of subthalamic nucleus deteriorates motor symptoms in Parkinson's disease. *Movement Disorders*. 2004; 19:1328–1333.

Tinkhauser, G. & Pogosyan, A. *Directional Local Field Potentials : A Tool to Optimize Deep Brain Stimulation Results Relationship Between Beta Activity and*. 2018; 33:159–164.

Tinkhauser, G., Pogosyan, A., Debove, I., Nowacki, A., Shah, S.A., Seidel, K., et al. Directional local field potentials: A tool to optimize deep brain stimulation. *Movement Disorders*. 2018; 33:159–164.

Tinkhauser, G., Pogosyan, A., Little, S., Beudel, M., Herz, D.M., Tan, H., et al. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. *Brain*. 2017a; 140(11):2968-2981.

Tinkhauser, G., Pogosyan, A., Tan, H., Herz, D.M., Kühn, A.A. & Brown, P. Beta burst dynamics in Parkinson's disease off and on dopaminergic medication. *Brain*. 2017b; 140(11):2968-2981.

Tommasi, G., Krack, P., Fraix, V., Le Bas, J.F., Chabardes, S., Benabid, A.L., et al. Pyramidal tract side effects induced by deep brain stimulation of the subthalamic nucleus. *Journal of Neurology, Neurosurgery and Psychiatry*. 2008; 79:813–819.

Tommasi, G., Krack, P., Fraix, V. & Pollak, P. Effects of varying subthalamic nucleus stimulation on apraxia of lid opening in Parkinson's disease. *Journal of Neurology*. 2012; 259:1944–1950.

Tommasi, G., Lopiano, L., Zibetti, M., Cinquepalmi, A., Fronda, C., Bergamasco, B., et al. Freezing and hypokinesia of gait induced by stimulation of the subthalamic region. *Journal of the Neurological Sciences*. 2007; 258(1-2):99-103.

Törnqvist, A.L., Schalén, L. & Rehncrona, S. Effects of different electrical parameter settings on the intelligibility of speech in patients with Parkinson's disease treated with subthalamic deep brain stimulation. *Movement Disorders*. 2005; 20:416–423.

Tripoliti, E., Limousin, P., Foltynie, T., Candelario, J., Aviles-Olmos, I., Hariz, M.I., et al. Predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease. *Movement Disorders*. 2014; 29:532–538.

Tripoliti, E., Zrinzo, L., Martinez-Torres, I., Frost, E., Pinto, S., Foltynie, T., et al. Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. *Neurology*. 2011; 76:80–86.

Tripoliti, E., Zrinzo, L., Martinez-Torres, I., Tisch, S., Frost, E., Borrell, E., et al. Effects of contact location and voltage amplitude on speech and movement in bilateral subthalamic nucleus deep brain stimulation. *Movement Disorders*. 2008; 23:2377–2383.

Trošt, M., Su, S., Su, P., Yen, R.F., Tseng, H.M., Barnes, A., et al. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. *NeuroImage*. 2006; 31(1): 301–307.

Trotti, L.M. REM Sleep behaviour disorder in older individuals: Epidemiology, pathophysiology and management. *Drugs and Aging*. 2010; 27:457–470.

Uematsu, S., Konigsmark, B. & Walker, A.E. Thalamotomy for alleviation of intractable pain. *CONFIN.NEUROL.* 1974; 36(2):88-96.

Ulla, M., Thobois, S., Llorca, P.M., Derost, P., Lemaire, J.J., Chereau-Boudet, I., et al. Contact dependent reproducible hypomania induced by deep brain stimulation in Parkinson's disease: Clinical, anatomical and functional imaging study. *Journal of Neurology, Neurosurgery and Psychiatry*. 2011; 82(6):607-14.

Vallabhajosula, S., Haq, I.U., Hwynn, N., Oyama, G., Okun, M., Tillman, M.D., et al. Low-frequency versus high-frequency subthalamic nucleus deep brain stimulation on postural control and gait in parkinson's disease: A quantitative study. *Brain Stimulation*. 2015; 8:64–75.

Valldeoriola, F., Muñoz, E., Rumià, J., Roldán, P., Cámara, A., Compta, Y., et al. Simultaneous low-frequency deep brain stimulation of the substantia nigra pars reticulata and high-frequency stimulation of the subthalamic nucleus to treat levodopa unresponsive freezing of gait in Parkinson's disease: A pilot study. *Parkinsonism and Related Disorders*. 2019; 60:153-157.

Voges, J., Volkmann, J., Allert, N., Lehrke, R., Koulousakis, A., Freund, H.J., et al. Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: Correlation of therapeutic effect with anatomical electrode position. *Journal of Neurosurgery*. 2002; 96(2):269-79.

Volkmann, J., Albanese, A., Antonini, A., Chaudhuri, K.R., Clarke, C.E., De Bie, R.M.A., et al. Selecting deep brain stimulation or infusion therapies in advanced Parkinson's disease: An evidence-based review. *Journal of Neurology*. 2013; 260:2701–2714.

Volkmann, J., Herzog, J., Kopper, F. & Geuschl, G. Introduction to the programming of deep brain stimulators. *Movement Disorders*. 2002;17 Suppl 3:S181-7.

Volkmann, J., Moro, E. & Pahwa, R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. *Movement Disorders*. 2006; 21:284–289.

Wakabayashi, K., Tanji, K., Mori, F. & Takahashi, H. The Lewy body in Parkinson's disease: Molecules implicated in the formation and degradation of α-synuclein aggregates. *Neuropathology*. 2007; 27:494–506.

Walker, H.C., Huang, H., Gonzalez, C.L., Bryant, J.E., Killen, J., Cutter, G.R., et al. Short latency activation of cortex during clinically effective subthalamic deep brain stimulation for Parkinson's disease. *Movement Disorders*. 2012; 27(7):864-73.

Wang, J., Hirschmann, J., Elben, S., Hartmann, C.J., Vesper, J., Wojtecki, L., et al. High-frequency oscillations in Parkinson's disease: Spatial distribution and clinical relevance. *Movement Disorders*. 2014; 29(10):1265-72.

Weaver Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease: A Randomized Controlled Trial. *The Journal of the American Medical Association*. 2010; 301:63.

Weinberger, M., Mahant, N., Hutchison, W.D., Lozano, A.M., Moro, E., Hodaie, M., et al. Beta Oscillatory Activity in the Subthalamic Nucleus and Its Relation to Dopaminergic Response in Parkinson's Disease. *Journal of Neurophysiology*. 2006; 96:3248–3256.

Weiss, D., Wächter, T., Breit, S., Jacob, S.N., Pomper, J.K., Asmus, F., et al. Involuntary eyelid closure after STN-DBS: Evidence for different pathophysiological entities. *Journal of Neurology, Neurosurgery and Psychiatry*. 2010; 81(9):1002-7.

Weiss, D., Walach, M., Meisner, C., Fritz, M., Scholten, M., Breit, S., et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. *Brain*. 2013; 136(Pt 7):2098-108.

Welter, M.L., Houeto, J.L., Bonnet, A.M., Bejjani, P.B., Mesnage, V., Dormont, D., et al. Effects of High-Frequency Stimulation on Subthalamic Neuronal Activity in Parkinsonian Patients. *Archives of Neurology*. 2004; 61(1):89-96.

Welter, M.L., Schüpbach, M., Czernecki, V., Karachi, C., Fernandez-Vidal, S., Golmard, J.L., et al. Optimal target localization for subthalamic stimulation in patients with Parkinson disease. *Neurology*. 2014; 82(15):1352-61.

Wenzel, K., Homann, C.N., Fabbrini, G. & Colosimo, C. The role of subcutaneous infusion of apomorphine in Parkinson's disease. *Expert Review of Neurotherapeutics*. 2014; 14:833–843.

Wichmann, T., Bergman, H. & DeLong, M.R. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. *Journal of Neurophysiology*. 1994; 72(2):521-30.

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *The Lancet Neurology*. 2010; 9:581–591.

Windels, F. Pallidal Origin of GABA Release within the Substantia Nigra Pars Reticulata during High-Frequency Stimulation of the Subthalamic Nucleus. *Journal of Neuroscience*. 2005; 25:5079–5086.

Windels, F., Thevathasan, W., Silburn, P. & Sah, P. Where and what is the PPN and what is its role in locomotion? *Brain*. 2015; 138:1133–1134.

Wirdefeldt, K., Odin, P. & Nyholm, D. Levodopa–Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review. *CNS Drugs*. 2016; 30:381–404.

Wodarg, F., Herzog, J., Reese, R., Falk, D., Pinsker, M.O., Steigerwald, F., et al. Stimulation site within the MRI-defined STN predicts postoperative motor outcome. *Movement Disorders*. 2012; 27:874–879.

Wolf, E., Seppi, K., Katzenschlager, R., Hochschorner, G., Ransmayr, G., Schwingenschuh, P., et al. Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. *Movement Disorders*. 2010; 25:1357–1363.

WYCIS, H.T. & SPIEGEL, E.A. The effect of thalamotomy and pallidotomy upon involuntary movements in chorea and athetosis. *Surgical forum*. 1950; 329-32.

Xie, T., Kang, U.J. & Warnke, P. Effect of stimulation frequency on immediate freezing of gait in newly activated STN DBS in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*. 2012; 83:1015–1017.

Xie, T., Padmanaban, M., Bloom, L., MacCracken, E., Bertacchi, B., Dachman, A., et al. Effect of low versus high frequency stimulation on freezing of gait and other axial symptoms in Parkinson patients with bilateral STN DBS: A mini-review. *Translational Neurodegeneration*. 2017; 6:13.

Xie, T., Vigil, J., MacCracken, E., Gasparaitis, A., Young, J., Kang, W., et al. Low-frequency stimulation of STN-DBS reduces aspiration and freezing of gait in patients with PD. *Neurology*. 2015; 84:415–420.

Xu, W., Russo, G.S., Hashimoto, T., Zhang, J. & Vitek, J.L. Subthalamic nucleus stimulation modulates thalamic neuronal activity. *Journal of Neuroscience*. 2008; 28 (46) 11916-11924.

Yelnik, J., Damier, P., Demeret, S., Gervais, D., Bardinet, E., Bejjani, B.P., et al. Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. *Journal of Neurosurgery*. 2003; 99(1):89-99.

Yorkston, K.M. & Beukelman, D.R. A comparison of techniques for measuring intelligibility of dysarthric speech. *Journal of Communication Disorders*. 1978; 11(6):499-512.

Yoshida, F., Martinez-Torres, I., Pogosyan, A., Holl, E., Petersen, E., Chen, C.C., et al. Value of subthalamic nucleus local field potentials recordings in predicting stimulation parameters for deep brain stimulation in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*. 2010; 81(8):885-9.

Zhang, S., Connolly, A.T., Madden, L.R., Vitek, J.L. & Johnson, M.D. High-resolution local field potentials measured with deep brain stimulation arrays. *Journal of Neural Engineering*. 2018; 15(4):046019.

Zhunussova, A., Sen, B., Friedman, L., Tuleukhanov, S., Brooks, A.D., Sensenig, R., et al. Tumor microenvironment promotes dicarboxylic acid carrier-mediated transport of succinate to fuel prostate cancer mitochondria. *American Journal of Cancer Research*. 2015; 5:1665–1679.

Zibetti, M., Moro, E., Krishna, V., Sammartino, F., Picillo, M., Munhoz, R.P., et al. Low-frequency Subthalamic Stimulation in Parkinson's Disease: Long-term Outcome and Predictors. *Brain Stimulation*. 2016; 9(5):774-779.