OPTIMISING THE POST-OPERATIVE MANAGEMENT OF PARKINSON'S DISEASE PATIENTS WITH DEEP BRAIN STIMULATION

This dissertation has been submitted in accordance with requirements of the

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It is finished.

STATEMENT OF SOURCES

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other degree or diploma in any other tertiary institution.

No other person's work has been used without due acknowledgment in the main text of the thesis.

All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

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Zachary Conway **26 February 2020**

STUDENT CERTIFICATION

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Optimizing the post-operative management of Parkinson's disease patients with deep brain stimulation

Submitted for the degree:

Doctor of Philosophy

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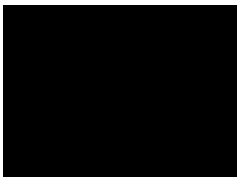

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) has become a common procedure for the management of Parkinson's disease (PD) symptoms. Based on the existing scientific evidence, it is well understood that high-frequency STN-DBS (e.g. 130 Hz) is effective at alleviating PD symptoms such as resting tremor and rigidity. However, it has been suggested that high-frequency STN-DBS stimulation may not be as effective for managing symptoms of postural instability and gait disability, symptoms strongly associated with falls in people with PD. In response to this, alternate STN-DBS parameters such as low-frequency STN-DBS has emerged as an area of clinical interest given its potential to better manage postural instability and gait disability for people with PD. This program of research addressed a series of questions concerning the post-operative management of postural instability and gait disability in people with PD following bilateral STN-DBS. Specifically, this dissertation includes four inter-related studies that sought to improve the understanding of how low-frequency STN-DBS influences both clinical and objective measures of postural and gait stability in people with PD who have STN-DBS.

The literature surrounding alternate STN-DBS parameters for the efficacy of managing PD motor symptoms were systematically reviewed in Study I. Only a small number of studies met the inclusion criteria. This meant meta-analyses were only possible for assessing the efficacy of low-frequency stimulation. The results of these analyses indicated that research in this area generally had poor methodological reporting quality, due to numerous sources of potential bias. The review suggested that research concerning the potential utility of alternate STN-DBS parameters had relied almost exclusively on outcomes derived from well-established, yet largely subjective, clinical measures. It was recommended that the

incorporation of objective measures may provide further insight into the strengths and weaknesses of alternate patterns of STN-DBS for managing people with PD.

Given the findings of the systematic review and meta-analysis (Study I), Study II sought to determine whether novel, objective measures of gait rhythmicity provide unique insights into gait stability that is not otherwise captured by the clinical measures of symptom severity, postural stability, balance confidence and mobility. This cross-sectional study recruited post-operative those with PD following STN-DBS to evaluate gait stability using body-worn tri-axial accelerometers. Specifically, the three-dimensional accelerations collected were used to calculate the harmonic ratios for the head and trunk segments. Analysis of the harmonic ratios, which provide insight into the step-to-step rhythmicity of an individual's gait, indicated that the use of body-worn sensors can provide unique gait-related information that are not captured by clinical measures.

To better understand the effect of low-frequency STN-DBS, Studies III and IV employed a double-blinded randomised cross-over design to investigate the possible benefits of low-frequency STN-DBS for managing symptoms of postural and gait stability. Sixteen post-operative people with PD completed standing and walking assessments while off medication and receiving high-and low-frequency STN-DBS therapy. In both studies, objective measures of postural stability were derived from either a force plate (Study III) or wearable sensors (Study IV) to provide insight into the efficacy of low-frequency stimulation. It was found that postural stability during the locomotion phase of gait initiation was improved with low-frequency STN-DBS, while the postural phase of gait initiation was not different (Study III). During steady-state walking, low-frequency STN-DBS improved medial-lateral and vertical trunk rhythmicity compared to high-frequency stimulation. The improvements with low-frequency STN-DBS

were independent of electrode location and total electrical energy delivered. In contrast to these noted differences in objectively measured outcomes, there were no changes observed between the two stimulation conditions for the clinical measures of mobility, motor symptom severity, or gait retropulsion. Although the long-term effects of low-frequency STN-DBS were not examined in this study, the presented findings provided evidence to suggest that low-frequency STN-DBS may improve gait initiation and gait stability for people with PD who have STN-DBS. Nevertheless, it should be noted that low-frequency STN-DBS therapy may not be suitable for all people with PD who have STN-DBS, as some experienced the re-emergence of limb tremor during low-frequency stimulation. This dissertation fills identified gaps in scientific literature and provides clinically relevant objective evidence for the potential utility of low-frequency stimulation to improve postural stability for people with PD who have STN-DBS.

NOMENCLATURE

Postural stability This term is used throughout the dissertation to describe symptoms and/or changes that affect one's balance, stability and/or equilibrium.

Standing postural stability This term is used to describe postural stability, as it relates to static activities, such as standing.

Gait stability This term is used to describe postural stability, as it pertains to the dynamic task of walking.

For consistency, inferences made from the harmonic ratio measure will be termed "gait stability". In the literature, terms that have been used synonymous with this definition include; gait stabilty; gait symmetry; head and trunk stability; dynamic stability; walking stability; step symmetry; dynamic balance; and gait smoothness.

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ABBREVIATIONS

A list of all abbreviations appears below. For convenience, all abbreviations are defined in full prior to their first use in the thesis.

ABC-6	6-item Activities-specific Balance Confidence scale
COM	Centre of mass
COP	Centre of pressure
DBS	Deep brain stimulation
PD	Parkinson's disease
PDQ-8	8-item Parkinson's disease Questionnaire
STN	Subthalamic nucleus
STN-DBS	Deep brain stimulation of the subthalamic nucleus
TEED	Total electrical energy derived
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS-III	Motor sub-section of the Unified Parkinson's Disease Rating Scale

CHAPTER 1: INTRODUCTION

Parkinson's disease (PD) is a debilitating age-related neurodegenerative condition that affects approximately 1% of Australians aged between 65 and 74 years (Parkinsons Australia, 2015). Conservative estimates suggest that the ongoing care of the more than 70,000 Australians who were living with PD in 2014 led to an estimated net expenditure of $9.5 billion (Parkinsons Australia, 2015). However, the costs and burden associated with PD are set to increase in the ensuing decades, as the ageing demographic of the Australian population is predicted to lead to an 80% increase in the prevalence of PD by 2034 (Parkinsons Australia, 2015). PD is characterized by cardinal motor symptoms that include resting tremor, rigidity, bradykinesia (slowness of movement) and postural instability (Jankovic, 2008). For the most part, motor symptoms of PD, such as tremor, respond well to standard pharmacological treatments (Deuschl, Schade-Brittinger, et al., 2006). However, 10 to 15 years after diagnosis, the presentation of the disease becomes dominated by axial symptoms, such as postural instability (de Lau & Breteler, 2006), which is linked to an increased risk of falling (Bloem, Hausdorff, Visser, & Giladi, 2004b; Bloem, van Vugt, & Beckley, 2001). Unlike tremor, axial motor symptoms, such as postural instability, are only partially responsive to pharmacological therapies (Ferraye et al., 2010). In more recent years, surgical options, such as deep brain stimulation (DBS), have become more prevalent in clinical practice and a major focus of research concerning the ongoing care of people with PD.

DBS is a surgical procedure that involves a local anaesthetic applied to the scalp to facilitate the drilling of a small hole into the skull to allow insertion of an electrode into a specific area of the brain. A battery is then is surgically buried into the sub-clavicular area within a subcutaneous pouch and connected to the electrode via a connecting lead, much like a cardiac pacemaker (Figure 1.1). The programmable emission of electricity from electrodes allows neurologists to artificially modulate the neuronal activity of targeted area. DBS of the

subthalamic nucleus (STN-DBS) has become a common procedure for improving PD symptoms (Deuschl, Schade-Brittinger, et al., 2006). Longitudinal studies have shown that high-frequency (i.e. about 130 Hz) STN-DBS is effective at alleviating symptoms of resting tremor, rigidity and bradykinesia for up to 10 years (Rodriguez-Oroz, Moro, & Krack, 2012) (Fasano et al., 2010; Krack et al., 2003). Collectively, the enhanced motor function experienced by people with PD who have STN-DBS leads to improved independence and a better overall quality of life (Weaver et al., 2009). However, despite such positive findings, current evidence suggests that high-frequency STN-DBS is ineffective for managing axial symptoms, such as postural instability (Fasano et al., 2010; Zibetti et al., 2011). In fact, high-frequency STN-DBS may further exacerbate postural instability and/or gait disability in people with PD which is considered to contribute to the increased number of falls experienced post-operatively (Weaver et al., 2009).

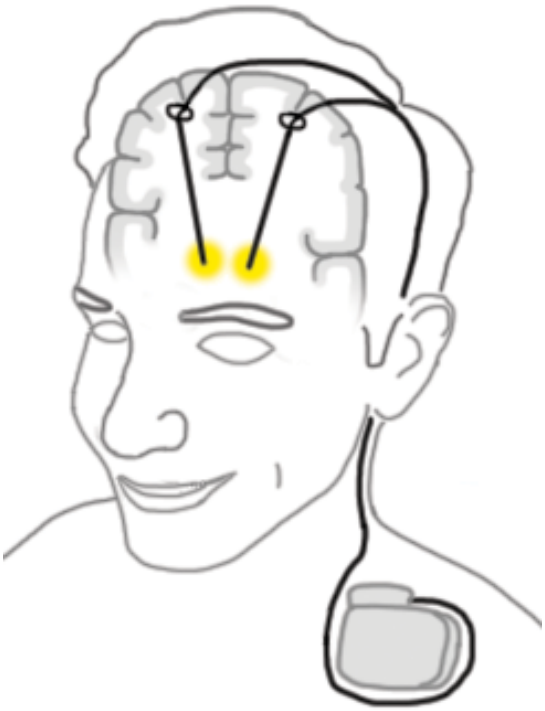

Figure 1.1: Illustration of deep brain stimulation electrodes implanted into the brain and the battery buried into the sub-clavicular area.

A noteworthy advantage of DBS is that it provides clinicians with the capacity to post-operatively alter the stimulation parameters (e.g. pulse width, voltage amplitude and stimulation frequency) to ensure symptoms remain well managed as the disease progresses. Research has sought to investigate the efficacy of alternate patterns of STN-DBS stimulation, such as low-frequency stimulation (e.g. 60-80 Hz). In a small number of experimental studies, low-frequency stimulation has improved axial motor symptoms (Khoo et al., 2014; Vallabhajosula et al., 2015; Xie et al., 2015) with no adverse effects on the management of limb tremor (Khoo et al., 2014; Xie et al., 2015). These studies provide preliminary evidence that it may be possible to improve the axial motor symptoms of PD without inadvertently diminishing the management of appendicular motor symptoms by adjusting stimulation frequency for people with PD who have STN-DBS. However, the improvements reported in most of the research have been based on well-established clinical scales. While these assessments are routinely used in clinical practice, objective measures of postural and gait stability may provide further insight into the efficacy of alternate patterns of STN-DBS.

Advancements in the use of wearable sensors, such as accelerometers in clinical sciences, has made it possible to objectively and reliably measure postural stability. Measures of postural stability derived from accelerometers are known to be capable of identifying movement deficits in people with PD who are receiving pharmacological therapy compared with controls (Lowry, Carrel, McIlrath, & Smiley-Oyen, 2010). Furthermore, these objective measures have been shown to discriminate people with PD with or without a history of falls (Latt, Menz, Fung, & Lord, 2009). Employing such objective measures to investigate the efficacy of STN-DBS for postural stability may beneficially supplement the well-established clinical scales and provide further insight into the strengths and weaknesses of alternate STN-DBS parameters.

CHAPTER 2: GENERAL LITERATURE REVIEW

2.1 Parkinson's disease

2.1.1 Pathophysiology

PD is a neurodegenerative condition that specifically targets the dopaminergic neurons of the substantia nigra pars compacta (de Lau & Breteler, 2006; Fearnley & Lees, 1991; Forno, 1996; Jankovic et al., 1990; Morris, 2000); gradually reducing their capacity to produce dopamine. In the human nervous system, the substantia nigra pars compacta makes important neural connections with other nuclear regions including but not limited to; the caudate nucleus, putamen, globus pallidus (internus and externus), substantia nigra pars reticulata and the subthalamic nucleus (STN) which together, form a neural network known as the basal ganglia (Blandini, Nappi, Tassorelli, & Martignoni, 2000). Although the basal ganglia features many parallel but functionally independent neural loops (e.g. the cortical limbic loop), the control of voluntary human movement focuses on the motor loops arising from the precentral motor (especially Brodmann areas 4 and 6) and postcentral somatosensory projections (Nambu, 2008).

Within the context of motor control, the primary role of the basal ganglia nuclei are considered to be related to the scaling, regulation and facilitation of desired movements, as well as the inhibition of undesired and potentially conflicting actions (Hikosaka, Takikawa, & Kawagoe, 2000). Although there are many models of the basal ganglia proposed for motor control, the anatomical connections that make up the functional connectivity of the basal ganglia widely supports the model that promotes unique, but complementary neural activity along a direct and indirect pathway (Albin, Young, & Penney, 1989). The direct pathway consists of striatal projections that are rich with D_1 dopamine receptor sites. Binding of dopamine to these receptor sites results in an increased inhibitory output being conveyed from the striatum to the globus pallidus internus. In turn, the increased inhibition of the globus pallidus internus reduces the capacity of this nucleus to inhibit the motor thalamus (Figure 2.1).

This increases its excitatory output to the motor areas of the cerebral cortex and promotes movement. The indirect pathway's role is to prevent unwanted movements by inhibiting the motor areas. The indirect pathway comprises striatal projections that are dense with D_2 dopamine receptors that project to the globus pallidus externus. Binding of dopamine to D_2 receptor sites inhibits the striatal output to the globus pallidus externus (Fearnley & Lees, 1991). The globus pallidus externus axons then project to the STN which, unlike the other basal ganglia nuclei, comprises glutaminergic neurons, whose actions are to promote the function of the neurons they synapse with (i.e. they are excitatory neurons). These glutaminergic projections extend from the STN to the globus pallidus internus and the substantia nigra pars reticulata, which serve to increase their inhibitory actions and prevent unwanted movements.

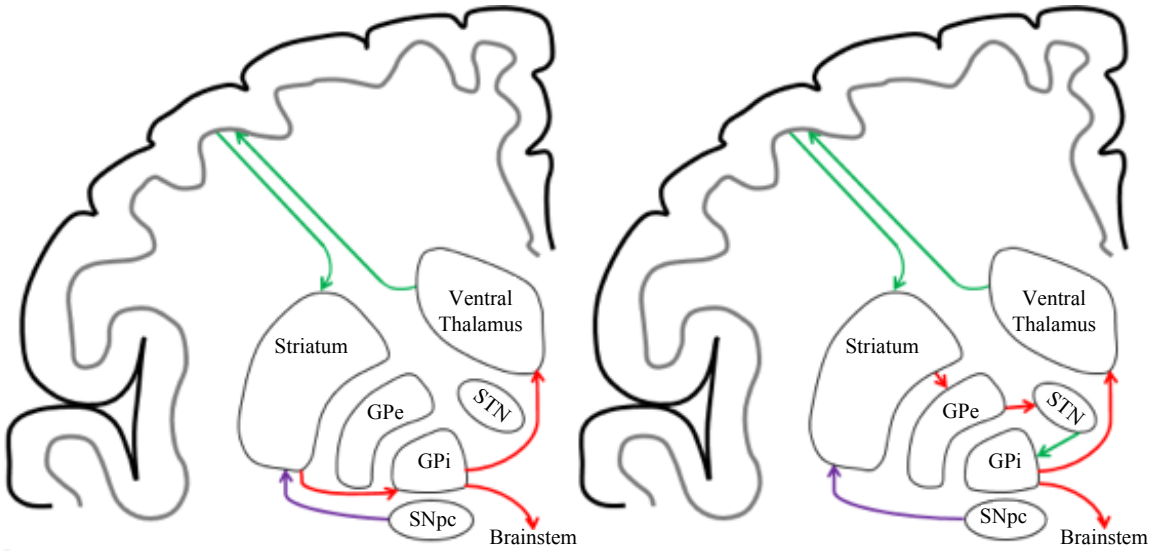

Figure 2.1: Illustration of the basal ganglia direct pathway (left) and the indirect pathway (right). Note: Red arrows: Inhibitory; green arrows: excitatory; purple: dopamine. Abbreviations; STN: Subthalamic nucleus; SNpc: substantia nigra pars compacta; GPi: globus pallidus internus; GPe: globus pallidus externus.

In PD, the loss of dopamine-producing neurons in the substantia nigra pars compacta reduces the action of the indirect and direct pathways that incorporate dopamine receptors (de Lau & Breteler, 2006; Fearnley & Lees, 1991; Jankovic et al., 1990). Firstly, a reduction in the binding of dopamine to D_1 receptors (found in the direct pathway) reduces the striatum's inhibitory influence on the globus pallidus internus (Obeso, Rodriguez-Oroz, Rodriguez, Arbizu, & Gimenez-Amaya, 2002). Additionally, the reduced concentration of dopamine results in less dopamine binding to D_2 receptors in the indirect pathway, which reduces the inhibitory influence of the globus pallidus externus on the STN nucleus (Gerfen et al., 1990). This leads to increased excitatory output from the STN (via its glutaminergic projections), which further increase the inhibitory output of globus pallidus internus. These alterations of the direct and indirect pathway models of the basal ganglia ultimately result in the difficulty and, at times, an inability to initiate and/or continue movements. It is not surprising then that PD is classified as a hypokinetic movement disorder (Jankovic, 2008), with common motor symptoms including the slowness (bradykinesia) or absence of movement (akinesia, freezing of gait) (Lewis & Barker, 2009).

Of the basal ganglia nuclei, the STN is the only one that comprises glutaminergic neurons, which makes it the sole excitatory nucleus of the basal ganglia. Not only is the STN a part of the indirect pathway, but also has cortical afferents in what is referred to as the hyperdirect pathway (Nambu, Tokuno, & Takada, 2002). Although our understanding of the hyperdirect pathway is still evolving, there has been several studies investigating its role in the clinical manifestation of motor symptoms (DeLong & Wichmann, 2010; Papa & Wichmann, 2015; Wichmann, DeLong, Guridi, & Obeso, 2011). For example, it is known that excessive beta activity in the STN is associated with increased severity of bradykinesia and rigidity symptoms (Brittain & Brown, 2014; Eusebio et al., 2011; Geng et al., 2017; Whitmer et al.,

2012), while lower gamma activity in the STN is strongly related to greater tremor severity (Beudel et al., 2015).

2.1.2 Non-motor symptoms

Despite its classification as a movement disorder (Jankovic, 2008), people with PD also experience a vast range of non-motor symptoms that contribute towards decrements in an individual's quality of life (Martinez-Martin, Rodriguez-Blazquez, Kurtis, Chaudhuri, & Group, 2011). The range of non-motor symptoms may include neuropsychiatric (e.g. depression, anxiety, dementia), autonomic (e.g. sexual dysfunction, bladder disturbances, dry eyes), gastrointestinal (e.g. constipation, reflux, nausea), sensory (e.g. pain, paresthesia, olfactory disturbance) and sleep disorders (e.g. vivid dreaming, insomnia, disordered breathing during sleep) (Chaudhuri, Healy, & Schapira, 2006; Chaudhuri, Yates, & Martinez-Martin, 2005). Although these symptoms can be as debilitating as the motor symptoms experienced by people with PD, this dissertation has primarily focused on the management of motor symptoms in people with PD.

2.1.3 Motor Symptoms

For people with PD, motor symptoms typically do not appear until approximately 60-70% of the dopamine-producing neurons have already been depleted (Rodriguez-Oroz et al., 2009). Although motor symptoms of PD may include difficulties with speech (hypokinetic dysarthria) and/or impaired swallowing, the cardinal motor symptoms include resting tremor, rigidity, bradykinesia and postural instability (Jankovic, 2008). While not considered a cardinal symptom by some, akinesia, which describes the absence of intended movements such as freezing of gait, may present in the latter stages of the disease or not at all (Bloem et al., 2004b). Assessment of PD motor symptoms is typically done by administering the part three (motor

sub-section) of the Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008).

2.1.3.1 Tremor

Tremor is defined as an involuntary and approximately rhythmic, smooth periodic oscillating movement associated with a particular amplitude and frequency (Jankovic, 2009). It is reported that up to 75% of people with PD will exhibit tremor symptoms (Hughes, Daniel, Kilford, & Lees, 1992) and these symptoms are most prominent at rest. For this reason, the tremor experienced by people with PD is often referred to as a resting tremor which occurs at the relatively low frequency of 4-6 Hz (Jankovic, 2008). While PD tremor may also be present during walking tasks, it is noted to diminish during tasks that involve voluntary movements of the affected limb(s) (e.g. reduced hand tremor during handwriting) (Jankovic, 2008). During the early stages of the disease, these symptoms typically present unilaterally and the severity is often most pronounced in the hands (Jankovic, 2008). Evidence suggests that tremor severity is strongly related to low gamma activity in the STN (Anzak et al., 2012; Beudel et al., 2015).

2.1.3.2 Rigidity

Symptoms of rigidity are characterised by an increased resting muscle tone, greater resistance to passive limb movement or increased resistance to stretching (Jankovic, 2008; Rodriguez-Oroz et al., 2009), particularly in the limbs (Andrews, Burke, & Lance, 1972). Rigidity is accompanied by hyperactive reflexes that have a longer latency and duration, which often causes them to merge with voluntary activity (Berardelli, Sabra, & Hallett, 1983). Although perhaps most notable distally in the wrists and ankles, rigidity may also present proximally in the neck, shoulder and hips (Van Emmerik, Wagenaar, Winogrodzka, & Wolters, 1999). Rigidity of proximal segments, such as the trunk, is reported to be a contributing factor

to the stooped posture associated with PD and is suggested to explain why people with PD demonstrate less coordinated and adaptive movements between the trunk and pelvis during walking (Van Emmerik et al., 1999). Symptoms of rigidity were found to be strongly associated with beta power in the STN (Kuhn, Kupsch, Schneider, & Brown, 2006), which suggests the pathological mechanisms from which symptoms of rigidity and tremor manifest are different.

2.1.3.3 Bradykinesia

Bradykinesia (also called 'hypokinesia') describes movements that have been preserved, but are slower and/or of reduced amplitude (Berardelli, Rothwell, Thompson, & Hallett, 2001). Bradykinesia has the potential to impact one's capacity to safely perform activities of daily living (Cooper, Sagar, Tidswell, & Jordan, 1994) and multiple tasks sequentially (Berardelli et al., 2001). While muscle and joint rigidity are considered to be primary contributing factors to bradykinesia, factors such as muscle weakness, tremor, movement variability and slowness of thought may also play a role (Berardelli et al., 2001). For example, rigidity could contribute to the slowness of movement that characterises PD, if longer-latency reflexes were elicited in antagonist muscles during the contraction of agonist muscles (Berardelli et al., 2001). However, much like other aspects of PD, there is a lack of consensus regarding the precise underlying mechanism of bradykinesia, but evidence suggests that it is best correlated with dopamine deficiency (Vingerhoets, Schulzer, Calne, & Snow, 1997).

2.1.3.4 Postural instability

Postural instability (also referred to as impaired balance), is characterised by disturbed postural reflexes and poor control of voluntary movement, poor trunk muscle coordination and/or increased trunk rigidity (Adkin, Bloem, & Allum, 2005; Horak, Dimitrova, & Nutt, 2005). Given its close relationship with injurious falls (Bloem, 1992; Bloem, Grimbergen,

Cramer, Willemsen, & Zwinderman, 2001; Bloem, van Vugt, et al., 2001), postural instability is one of the most disabling symptoms and a predictor of the decreased survival rate in people with PD (de Lau, Verbaan, Marinus, & van Hilten, 2014).

In comparison to otherwise healthy aged-matched older adults, the risk of falling, even when optimally-medicated, is greater in people with PD (Bloem, Grimbergen, et al., 2001; Bloem et al., 2004b; Grimbergen, Munneke, & Bloem, 2004). According to prospective studies, 65% of people with PD will fall at least once a year, while up to 50% of these go on to experience recurrent falls (Cole, Silburn, Wood, Worringham, & Kerr, 2010; Wood, Bilclough, Bowron, & Walker, 2002). Of the falls experienced by people with PD, 45% occur during ambulation (e.g. walking, turning, ascending or descending stairs) within familiar areas, such as the bedroom, of the individual's home (Ashburn, Stack, Ballinger, Fazakarley, & Fitton, 2008). During such ambulatory tasks, 60% of falls were caused by a trip or loss of balance (Ashburn et al., 2008). Given falls and their related consequences (i.e. injuries) contribute to poorer self-perceived quality of life (Schrag, Jahanshahi, & Quinn, 2000), therapeutic interventions that not only alleviate tremor, but also postural instability, are urgently needed.

2.1.4 Levodopa replacement therapy

The considered pathophysiology of PD provides reasoning for the therapeutic benefits of levodopa replacement therapy, which aims to replenishing the depleted levels of dopamine in the brain (de Lau & Breteler, 2006; Jankovic et al., 1990; Morris, 2000). Under normal conditions, the human body uses the amino acid, tyrosine, to synthesise dopamine; yet, increasing tyrosine levels has been shown to have no meaningfully impact on dopamine levels in the brain. However, when tyrosine is metabolised via tyrosine hydroxylase, a metabolite known as levo-dihydroxyphenylalanine (levodopa), is created and can cross the blood-brain

barrier (Grace, 2008; McGeer & McGeer, 1973; Molinoff & Axelrod, 1971). In the initial stages, treatment of PD will typically involve consumption of low-doses of levodopa (up to 400mg/day) and/or dopamine agonists, which are generally sufficient to improve the chemical imbalance and reduce symptom severity (Katzenschlager & Lees, 2002). However, the benefits are known to dissipate after several years (Deuschl, Schade-Brittinger, et al., 2006); typically requiring an increase in dosage. Unfortunately, for some, the increased dose may give rise to a number of side-effects such as levodopa-induced dyskinesias (Maurer et al., 2003). The management of levodopa replacement therapy becomes increasingly difficult as the disease progresses and the adjustment to medications is the primary reason for hospitalization of people with PD in Australia (Bohingamu Mudiyanselage et al., 2017).

A factor that plays a role in the efficacy of levodopa replacement therapy is the consistency with which symptoms are adequately managed, with variations referred to as ‘on/off fluctuations’. This describes the proportion of time that people with PD experience good therapeutic benefit from their anti-parkinsonian medication (‘on’ periods) compared to the proportion of time with little benefit from their therapy (‘off’ periods). Although each person’s experience will be different, ‘on’ periods typically become shorter with longer periods of medication use, ultimately contributing to the reduced efficacy of pharmacological therapies. Furthermore, the increased doses of levodopa that are often required to minimise these ‘off’ periods often lead to medication-induced side-effects, such as dyskinesias, which are reportedly experienced by 40% of people with PD receiving dopamine replacement therapy (Ahlskog & Muenter, 2001; Schrag & Quinn, 2000). A further shortcoming of pharmacological therapies is that they are known to be only partially effective for managing symptoms of postural instability and gait disability in people with PD (Ferraye et al., 2010). Given this, alternate therapies have been investigated to facilitate the long-term management of people with PD. Of the alternatives

investigated, DBS surgery has become one of the most common procedures for people with PD (Deuschl, Schade-Brittinger, et al., 2006; Weaver et al., 2009).

2.2 Deep Brain Stimulation

DBS has evolved from earlier surgical interventions that involved lesioning a target structure within the brain to destroy specific neural pathways or collection of neurons considered to be responsible for a person with PD symptomology (e.g. thalamotomy, pallidotomy). DBS is a specific form of stereotactic surgery that involves implanting an electrode into a specific location in the brain, either unilaterally (one side of the brain) or bilaterally (both sides of the brain). Briefly, the surgical procedure encompasses, a local anaesthetic applied to the scalp to facilitate the drilling of a small hole into the skull to allow the electrode to be inserted. The position of the electrode to the intended location is often guided pre-operative medical imaging and intraoperative micro-recordings (Benazzouz et al., 2002), then confirmed via a postoperative computed tomography that is fused with a preoperative magnetic resonance imagining scan (Thevathasan & Gregory, 2010). The subsequent implantation of the internal pulse generator and connecting lead allows for continuous delivery of stimulation. The generator typically lasts 3-5 years, though this varies depending on the stimulation parameters, before being replaced.

DBS has become an increasingly popular form of treatment for a range of neurological disorders including, but not limited to, essential tremor (Hubble et al., 1996), dystonia (Vidailhet et al., 2005), and Tourette's syndrome (Schrock et al., 2015), and PD (Volkmann, 2004). Despite the initial up-front cost of the procedure, DBS is considered to be more cost-effective for the ongoing care of people with PD than other therapeutic interventions (Becerra et al., 2016; Dams et al., 2013). The target of DBS for people diagnosed with PD includes the

STN, the globus pallidus internus, the ventral intermediate nucleus of the thalamus and the pedunculopontine nucleus. Therapeutic benefits differ between sites and it is widely recognised that different symptoms will respond differently to different targets (Andrade, Carrillo-Ruiz, & Jimenez, 2009; Thevathasan et al., 2012; Thevathasan et al., 2011; Thevathasan et al., 2010). Therefore, the target for stimulation is largely determined by the surgical team on an case-by-case basis depending on the presentation and severity of pre-operative symptoms (Honey et al., 2017). For example, stimulation of the ventral intermediate nucleus of the thalamus (Figure 2.2) was first used to treat those with PD who experienced limb tremor (Benabid, Pollak, Louveau, Henry, & De Rougemont, 1988). However, DBS to this site had no effect on other symptoms and therefore, ongoing treatment with anti-parkinsonian medications was required (Pahwa et al., 2006). Given the highly specific benefits, stimulation of the ventral intermediate nucleus of the thalamus is generally only considered for those people with PD whose only symptom is tremor (Benabid et al., 1996; Pahwa et al., 2006).

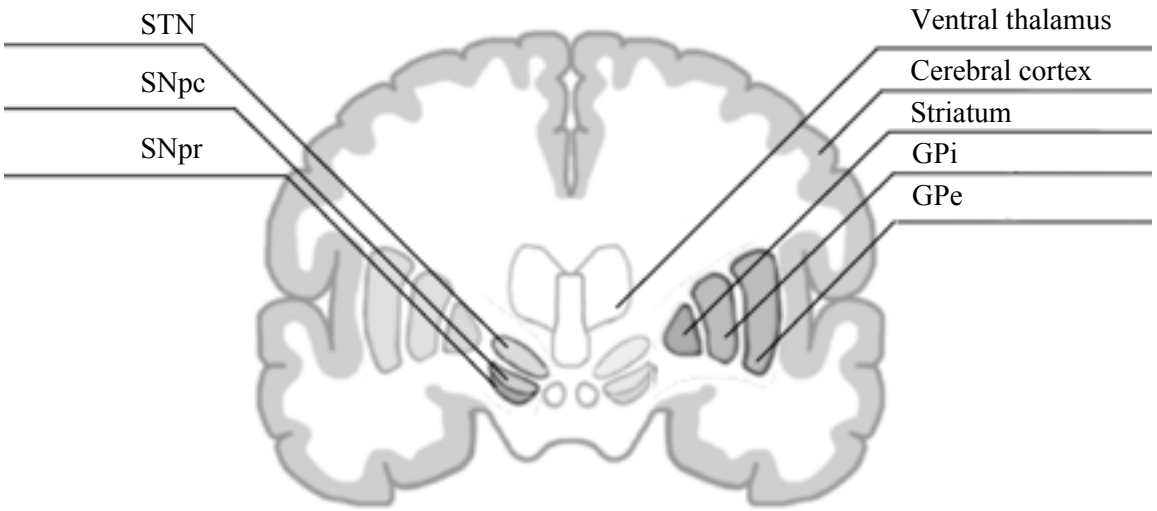

Figure 2.2: Illustration of a coronal cross section of the cerebrum to identify nuclei of the cerebrum. Abbreviations: STN: Subthalamic nucleus; SNpc: substantia nigra pars compacta; SNpr: substantia nigra pars reticulata; GPi: globus pallidus internus; GPe: globus pallidus externus.

The pedunculopontine nucleus, located deep within the brainstem (Fytagoridis, Silburn, Coyne, & Thevathasan, 2016; Hamani, Aziz, et al., 2016), is a site that is still considered by many to be experimental (Hamani, Lozano, et al., 2016) with fewer than 100 PD cases reported in the literature (Thevathasan et al., 2018). While it has been confirmed that bilateral stimulation can improve freezing of gait in people with PD (Thevathasan et al., 2012), at this time, further studies are needed to advance surgical procedures to this region (Hamani, Lozano, et al., 2016; Thevathasan et al., 2017).

For people with PD who present with more than one of the cardinal symptoms of PD and/or who experience medication-induced dyskinesias, stimulation of the STN or globus pallidus internus is often recommended (Honey et al., 2017). While dyskinesias are more effectively managed with globus pallidus internus DBS (Sankar & Lozano, 2011), DBS to

either the STN or the globus pallidus internus results in a decrease in overall motor symptom severity (based on the UPDRS motor score) (Andrade et al., 2009). Randomized control studies comparing the two targets, have found no differences for number of outcomes, including the UPDRS (Follett & Torres-Russotto, 2012; Follett et al., 2010; Moro et al., 2010; Odekerken et al., 2013; Rodriguez-Oroz et al., 2005; Weaver et al., 2012; Wong et al., 2019; Xu, Ma, Huang, Qiu, & Sun, 2016). While the globus pallidus internus remains an important site, STN-DBS has been found to reduce the need for anti-parkinsonian medication, lower economic costs, improve motor function during the off phase and improve the battery life of the implanted internal pulse generator compared to globus pallidus internus stimulation (Odekerken et al., 2013). Therefore, STN-DBS may be the preferred therapeutic approach for people with PD who are deemed to be suitable candidates for DBS surgery (Odekerken et al., 2013; Xu et al., 2017) and is the current preferred target in Australian neurosurgery (Poortvliet, Silburn, Coyne, & Chenery, 2015). As such, STN-DBS is the focus of this dissertation.

2.2.1 Targeted to the subthalamic nucleus

Targeting the STN with DBS electrodes (Figure 2.3) has extended from promising results reported in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model in higher primates which investigated the effects of lesioning the STN for motor symptoms of PD (Aziz, Peggs, Sambrook, & Crossman, 1991; Bergman, Wichmann, & DeLong, 1990). The STN is a very small target (approximately 9x7x5mm) (Hamid et al., 2005) that is located between the zona incerta dorsally and the cerebral peduncles ventrally and is encapsulated by myelinated fibre bundles (Parent & Hazrati, 1995). Given its size, location and proximity to the aforementioned structures, the successful targeting of the STN for DBS relies upon pre-operative medical imaging for the correct localization of the implanted electrode to limit spread of current to undesired areas. During the stereotactic procedure, the specific location of the nucleus is

expressed as a collection of three-dimensional coordinates within a normalized atlas space. These coordinates make reference to the anterior commissure-posterior commissure system where x = lateral, y = anterior to the posterior commissure, z = orthogonal to x and y. Based on the available data, Hamel and colleagues (2016) described the average coordinates of active electrode within the STN to be x = 12.1 mm, y = -1.4 mm and z = -1.8 mm.

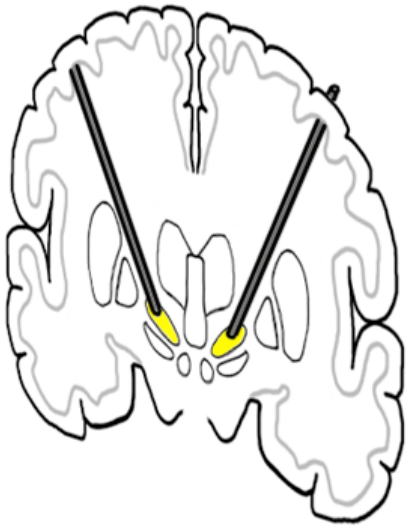

Figure 2.3: Illustration of deep brain stimulation electrodes implanted into the subthalamic nucleus (highlighted in yellow).

2.2.1.1 Physiology

The physiological changes in basal ganglia circuits have been investigated under high-frequency stimulation conditions, with many possible mechanisms proposed (Lozano, Dostrovsky, Chen, & Ashby, 2002; Lozano, Snyder, Hamani, Hutchison, & Dostrovsky, 2010). It is considered that high-frequency STN-DBS causes local inhibition of the pathological activity of the STN, which is thought to normalize the function in motor networks through downstream effect (Kopell, Rezai, Chang, & Vitek, 2006). The inhibition by STN-DBS replicates the effect of lesioning a nucleus in that both interventions act to block neuronal transmission (Kopell et al., 2006). However, compared to lesioning, DBS is more efficacious

(Esselink et al., 2006) and targets axons, not cell bodies (Lozano et al., 2002). Stimulation of the STN is also considered to be effective at suppressing the excessive beta activity associated with bradykinesia and rigidity (Brittain & Brown, 2014; Eusebio et al., 2011; Geng et al., 2017; Kuhn et al., 2006; Whitmer et al., 2012). Similarly, gamma activity in the STN is strongly related to tremor severity, and reduction in tremor severity with high-frequency STN-DBS is accompanied by reduction in gamma activity (Beudel et al., 2015).

2.2.2 Parameters

Each DBS electrode consists of contacts that are located at the end of the electrode that is inserted into the target tissue and delivers the electrical stimulation. For Medtronic devices (as used in the investigated population of this dissertation), the intercontact distance ranges from 1.5 mm to 0.5 mm between models (Figure 2.4). Each of the respective active contacts has the capacity to alter the parameters that make up the stimulation. This is a great advantage that DBS offers over other therapies, as it provides clinicians with the capacity to easily alter the active contacts of the electrodes to stimulate different areas of the targeted neural structure and offers great flexibility with respect to the adjustment of stimulation parameters. Specifically, stimulation parameters that can be post-operatively manipulated include frequency, voltage, pulse width and the electrode polarity. Each of these parameters is discussed further in the subsequent sections.

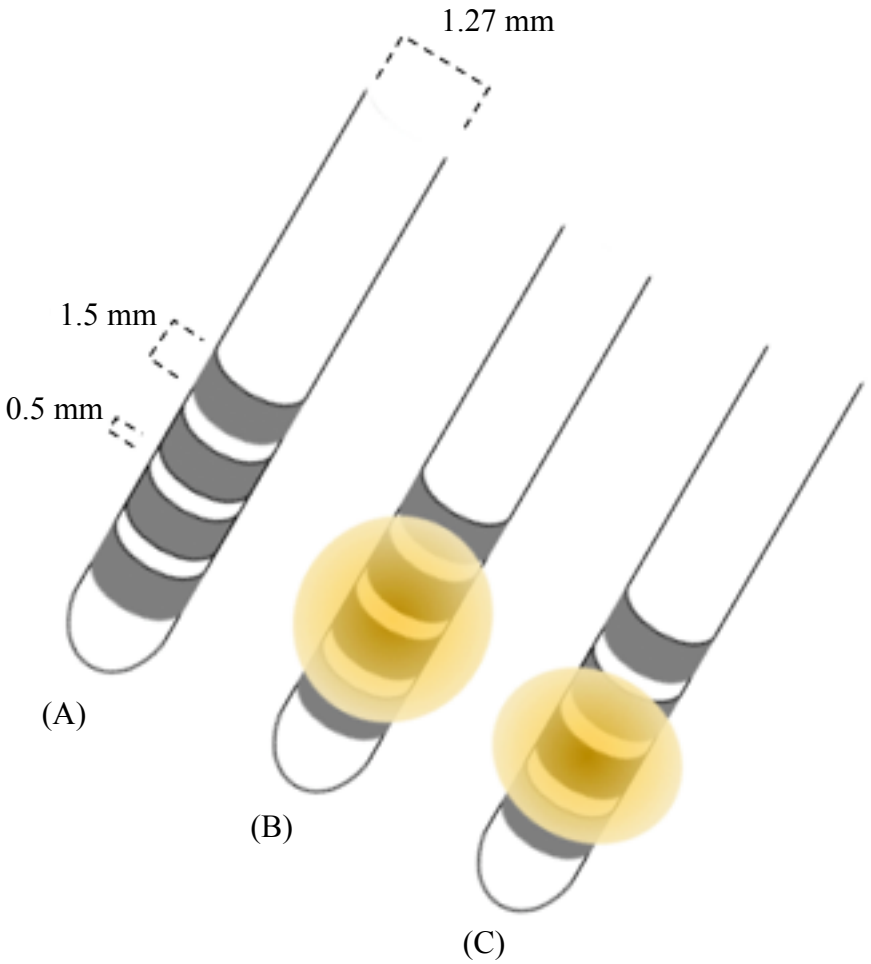

Figure 2.4: Illustration of deep brain stimulation electrodes with; (A) all contacts off; (B) two contacts active; and (C) one contact active.

2.2.2.1 Polarity

Within the structure it stimulates, contacts can be respectively programmed to function in either an anode (positive) manner for bipolar configurations or a cathode (negative) manner for monopolar configurations. Monopolar (cathode) configurations create a spherically shaped electrical stimulus around the contacts of the electrode, which provides a radial diffusion to the surrounding neural structures. In contrast, bipolar (anode) configurations require at least two contacts on the electrode to be active (one as cathode and one as anode) where the current diffusion is narrower and more focused with a greatest effect closer to the cathode (McIntyre, Mori, Sherman, Thakor, & Vitek, 2004). In practice, monopolar configurations are typically

preferred over bipolar configurations due to their demonstrated efficacy in the majority of people with PD who have STN-DBS (Krack et al., 2003). Another advantage of monopolar configurations is that they require a lower stimulation intensity than bipolar configurations, which require a greater stimulation intensity and yield a narrower area of diffusion (Deli et al., 2011; O'Suilleabhain, Frawley, Giller, & Dewey Jr, 2003).

2.2.2.2 Voltage

The voltage amplitude is an electromotive force, generated by an internal pulse generator surgically implanted below the collarbone. The pulse generator is responsible for producing the electrical charge that is passed via a connecting lead to the active contacts of each electrode. Of the parameters that can be changed post-operatively, voltage amplitude is reported to be the most influential with respect to the therapeutic benefits of STN-DBS (Moro et al., 2002). Current devices have the capacity to stimulate at amplitudes of between 0 V and 10.5 V and can be adjusted in increments of 0.1 V; providing clinicians with a substantial range of voltage amplitudes to manage symptoms. The electromotive force delivered to the target structure is either constant voltage, where the current applied depends on the biological impedance that may vary, or constant current in which the current of stimulation adapts to any changes in the biological impedance. There are no differences between constant voltage and constant current for the treatment of motor symptoms two years following surgery (Ramirez de Noriega et al., 2015).

2.2.2.3 Frequency

The frequency of stimulation refers to the rate at which stimulation is delivered to the target structure (e.g. the STN). The rate at which stimulation takes place can influence the efficacy of STN-DBS therapy for the management of PD motor symptoms (Moreau et al.,

2008), and has perhaps received the most attention in the recent literature. The frequency of stimulation is expressed in Hertz (Hz), which is defined as the number of cycles per second. Clinicians can adjust the frequency of stimulation in 5 Hz increments and, although the equipment is capable of stimulation frequencies of up to 250 Hz, frequencies of around 130 Hz (Figure 2.5) are typically chosen (Volkmann, Moro, & Pahwa, 2006).

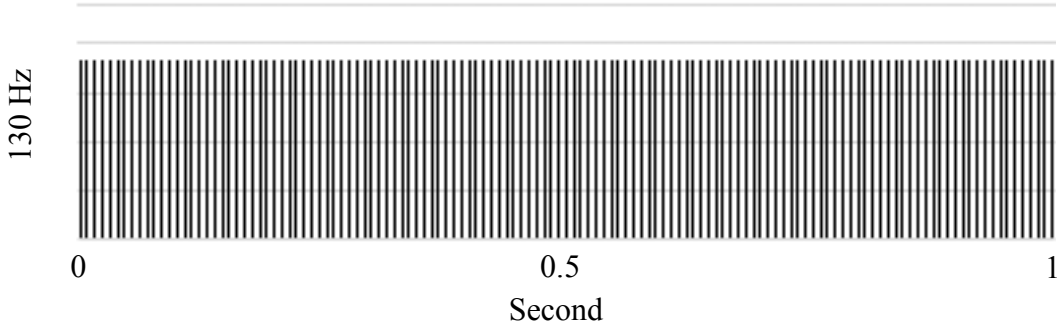

Figure 2.5: Representation of 130 Hz frequency of stimulation over one second, with each vertical line depicting the timing of each stimulation delivered to the active electrodes.

2.2.2.4 Pulse width

The pulse width of the stimulation refers to the duration of each electrical pulse emitted via the active electrodes. Longer pulse widths allow the electrical stimulation to spread over a greater area within and around the STN, while a shorter pulse width limits the effects of the stimulation to a more confined area (Figure 2.6). Longer pulse widths can be advantageous in that they can cover a larger area of the neural target (e.g. the STN), however, this may result in the stimulation of neighbouring areas that potentially leads to unwanted side effects, such a stimulation induced dysarthria (Dayal et al., 2019).

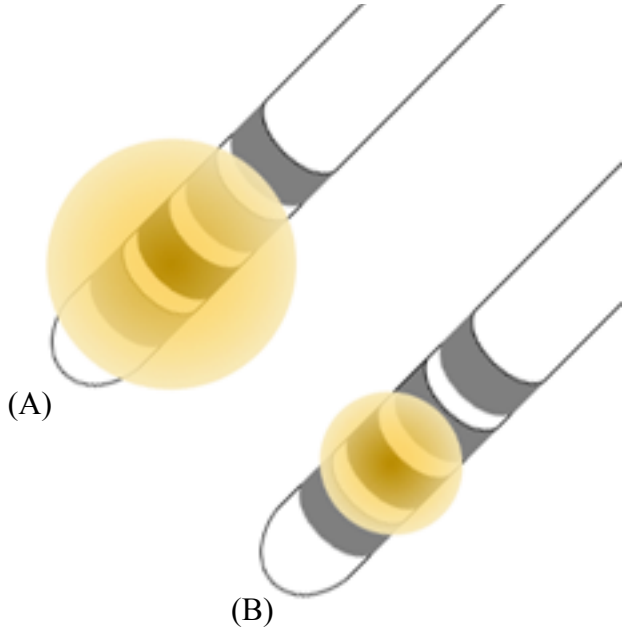

Figure 2.6: Illustration of deep brain stimulation electrodes with (A) a longer pulse width and (B) a shorter pulse width.

2.2.2.5 Chronic stimulation

Despite the heterogeneity in the presentation of people with PD symptoms and the number of options available for each of the stimulation parameters, the specific STN-DBS parameters used in clinical practice have become reasonably consistent worldwide. Typically, optimization of the stimulation parameters is guided by clinical improvements in appendicular motor symptoms (e.g. tremor, rigidity); possibly due to these symptoms being the most visually discernible. To facilitate STN-DBS programming, guides and viewpoints have been developed and published to assist clinicians to determine clinically recommended STN-DBS parameters (Picillo, Lozano, Kou, Puppi Munhoz, & Fasano, 2016; Volkmann et al., 2006).

Depending on the recovery following STN-DBS surgery and the preferences of the neurology team, the time between the surgical implantation and the initial programming session varies from several days to up to four weeks post-surgery (Cohen et al., 2007; Deuschl, Herzog,

et al., 2006; Picillo et al., 2016; Thevathasan & Gregory, 2010; Volkmann et al., 2006). During the initial STN-DBS programming session, clinicians seek to achieve three primary goals; i) maximise the clinical benefit of the therapy (i.e. reduced symptom severity); ii) avoid/minimize any adverse effects; and iii) minimize current consumption to increase the longevity of the implanted battery (Volkmann et al., 2006). Initial programming is usually performed while the person is off anti-parkinsonian medication and typically set to monopolar with a single cathode operating at a frequency of 130 Hz, and a pulse width of 60 μs (Picillo et al., 2016; Thevathasan & Gregory, 2010; Volkmann et al., 2006). Subsequently, the clinician will titrate the voltage parameter to find the lowest voltage setting (for the purpose of battery longevity) that adequately attenuates symptoms. Typically, this is done by increasing the voltage amplitude in a stepwise fashion in increments of about 0.2–0.5 V which has almost an immediate impact on tremor symptoms. To aid this process, clinicians often assess rigidity as a marker of how well the motor symptoms are being alleviated by the therapy (Volkmann et al., 2006).

Following the initial STN-DBS programming, people with PD will typically enter a stabilization period that may last up to six months. During this period, healing of the microlesions associated with the implantation of electrodes takes place, which may further contribute to the motor symptoms subsiding (Mestre, Lang, & Okun, 2016; Volkmann et al., 2006). Therefore, during the first 6-months following the surgery, the efficacy of the stimulation may be quite variable due to initially applying slightly higher voltages to compensate for the effects of the healing microlesions; and working to find the best combination of pharmacological therapy to complement the STN-DBS (Volkmann et al., 2006). Although the final voltage amplitudes will vary from person to person, higher amplitudes (e.g. 4 volts) are typically known to be more effective than lower voltages (e.g. 2 volts), with respect to improvements in the motor symptoms of PD (Tripoliti et al., 2008). When the STN-DBS

parameters have been established for chronic stimulation, the total electrical energy delivered (TEED) can be determined. The TEED (Equation 2.1) is determined by taking into consideration the voltage amplitude, stimulation frequency, pulse width and biological impedance of the system (Koss, Alterman, Tagliati, & Shils, 2005).

$$TEED_{1\ second} = \frac{Voltage^2 \times frequency \times pulse\ width}{impedance} \times 1\ second$$

(Equation 2.1)

The biological impedance is measured before initiating the programming, but the impedances for each of the four electrodes should also be recorded under standard stimulation parameters to detect any hardware problems immediately following the implantation and to use as a reference for troubleshooting future hardware problems.

2.2.3 Effect on symptoms

STN-DBS offers a number of improvements in PD symptom severity, including the alleviation of resting tremor and limb stiffness (Deuschl, Schade-Brittinger, et al., 2006). Longitudinal studies have found that people with PD who experienced symptoms of tremor (Diamond, Shahed, & Jankovic, 2007), joint stiffness and/or slowness of movement (Fasano et al., 2010; Krack et al., 2003) can experience improved symptoms from STN-DBS for at least 5 to 10 years post-surgery (Rodriguez-Oroz, Moro, & Krack, 2012). This improvement is paired with long-term reduction in doses of anti-parkinsonian medication (Aviles-Olmos et al., 2014; Deuschl, Schade-Brittinger, et al., 2006; Hamani, Richter, Schwalb, & Lozano, 2005) and improved motor function (Weaver et al., 2012), which is associated with improved overall quality of life (Just & Ostergaard, 2002; Lezcano et al., 2004; Sobstyl, Zabek, Gorecki, & Mossakowski, 2014; Weaver et al., 2009).

STN-DBS has been shown to improve measures of stride length and walking speed in people with PD (Bakker et al., 2004; Faist et al., 2001; Ferrarin et al., 2002; Ferrarin, Rizzone, Lopiano, Recalcati, & Pedotti, 2004; Roper et al., 2016; Shivitz, Koop, Fahimi, Heit, & Bronte-Stewart, 2006). Following STN-DBS, people with PD also exhibited an increased walking length during each bout that contributed to the total walking time and overall improvement in their daily activity (Rochester, Chastin, Lord, Baker, & Burn, 2012). These improvements are important as gait impairments often limit an individual's ability to complete common activities of daily life (e.g. house work, stair ambulation) (Shulman et al., 2008), which has potential implications for other health problems (e.g. cardiovascular).

2.2.3.1 Adverse effects

The adverse effects associated with STN-DBS can be broadly classified as either those relating to; i) the surgical procedure; ii) management of any complementary pharmacological therapies; and/or iii) the stimulation itself. Given the nature of the DBS surgical procedure, there are a number of surgery-related complications including transient confusion (15.6% of an investigated cohort), intracranial haemorrhage (3.9%), infection (1.7%), and seizures (1.5%) (Kleiner-Fisman et al., 2006).

Following the STN-DBS surgical procedure, anti-parkinsonian medication dosages are manipulated to account for the systematic and incremental increases in stimulation amplitude and are managed post-operatively during the routine follow-ups with the neurology team. While STN-DBS reduces the need for anti-parkinsonian medication (Odekerken et al., 2013), managing this process is critical to ensuring the best possible care as the inability to find a suitable balance between STN-DBS parameters and anti-parkinsonian medication can lead

therapy-induced dyskinesia (Deuschl, Herzog, et al., 2006). There are others that can be attributed to stimulation alone, such as the reported weight gain that some experience post-operatively, with the exact mechanisms unclear (Macia et al., 2004; Montaurier et al., 2007).

People who undergo STN-DBS are at a 3.8 times greater risk of experiencing an adverse event related to their therapy than people with PD who are treated via pharmacological intervention, however, 99% of cases are resolved within a 6-month period (Weaver et al., 2009). Compared to other forms of surgical intervention (e.g. thalamotomy, pallidotomy), STN-DBS parameters can be individualized post-operatively to suit the needs of the person and/or to minimise any adverse effects. For example, stimulation-induced dyskinesias can be alleviated by reducing the voltage of stimulation (Fasano et al., 2010; Krack et al., 2003). Given many stimulation-induced adverse effects (e.g. muscle contractions and hypomania) can be attenuated via small changes in stimulation parameters, they are generally classified as transient in nature. However, other adverse effects, such as speech impairments, may be less amenable and can persist over time (Aldridge, Theodoros, Angwin, & Vogel, 2016). Results of meta-analyses suggest (albeit with small effect sizes) that people with PD may exhibit declines in , psychomotor speed, learning and memory, attention/concentration, executive function, and verbal fluency following STN-DBS surgery (Combs et al., 2015; Xie, Meng, Xiao, Zhang, & Zhang, 2016). Furthermore, while most adverse effects that influence motor function are transient and attenuated during the titration processes, some research suggests that symptoms of gait dysfunction and akinesia may continue to worsen (Fleury et al., 2016). Considering the impact of these symptoms, the benefits of STN-DBS may come at the cost of exacerbating equally-disabling symptoms, such as postural instability, that ultimately contribute to an increased risk of falls (Fasano, Aquino, Krauss, Honey, & Bloem, 2015).

2.2.3.2 Effects on postural stability and falling

Compared to pre-STN-DBS, people with PD may experience improved postural stability (St George, Nutt, Burchiel, & Horak, 2010) and a decrease in the frequency of falls one-year following STN-DBS (Rizzone et al., 2014). However, despite these potential initial improvements, postural instability and gait disability gradually worsen over the 5-year period following STN-DBS surgery (St George et al., 2010). Therefore, there are suggestions that people with PD with high-frequency STN-DBS present as a specific phenotype characterised by alleviated resting tremor, but worsening of axial symptoms (Fasano et al., 2015; Rodriguez-Oroz et al., 2012). This is of concern, as axial symptoms such as postural instability and gait disability in people with PD are known to contribute to a greater falls risk (Bloem, Boers, Cramer, Westendorp, & Gerschlager, 2001; Bloem, Hausdorff, Visser, & Giladi, 2004a).

As mentioned earlier, PD is a neurodegenerative condition and changes that underpin the disease may continue to degrade postural stability, independent of STN-DBS (Wood et al., 2002). Therefore, it is difficult to attribute the long-term declines in postural stability directly to the STN-DBS therapy. However, compared to people with PD receiving pharmacological treatment, falls occur more frequently in people with PD who have STN-DBS (Weaver et al., 2009). Furthermore, similar to the long-term decrement in postural stability with STN-DBS (St George et al., 2010), following five and eleven years after the surgery, the frequency of falls were significantly increased compared to one year after surgery (Rizzone et al., 2014). The self-perceived mechanism for this post-operative cohort is that the proportion of fall has been attributed to poor balance (Nilsson, Rehncrona, & Jarnlo, 2011). Such perceived reasoning reflects the current evidence that suggests conventional STN-DBS stimulation strategies may not be as effective for managing symptoms of postural instability and gait difficulties; both of which are strongly associated with falls in PD (Bloem, van Vugt, et al., 2001). Given the

apparent shortcomings of high-frequency STN-DBS, there is a growing body of evidence to suggest that alternative stimulation strategies may offer greater benefits for those who experience postural instability and gait difficulties following the STN-DBS procedure.

2.2.4 Low-Frequency Stimulation effect motor symptoms

Post-operatively, clinicians can alter stimulation parameters to optimally manage symptoms while limiting unwanted side-effects. The frequency of STN-DBS for chronic stimulation is typically high-frequency stimulation (e.g. ≥130 Hz) (Volkmann et al., 2006), however, there is a growing body of literature investigating the effects of low-frequency stimulation for PD symptoms (Blumenfeld et al., 2016; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Phibbs, Arbogast, & Davis, 2014; Vallabhajosula et al., 2015; Xie et al., 2015). Compared to higher stimulation frequencies (i.e. ≥130 Hz), low-frequency of stimulation (i.e. 60-80 Hz) improves static postural stability, temporospatial gait characteristics (Vallabhajosula et al., 2015) and clinical measures of axial motor symptom severity without adversely affecting the management of limb tremor (Khoo et al., 2014; Xie et al., 2015). However, despite the apparent efficacy of low-frequency STN-DBS for managing symptoms of postural instability, a separate study by Moreau and colleagues (2008) found no such improvements in these symptoms at lower STN-DBS frequencies. Collectively, these findings highlight the need for further research to clarify the efficacy of low-frequency STN-DBS for improving postural stability in people with PD who have STN-DBS.

2.3 Assessments of postural stability

Given the relationship between postural instability and falls (Bloem et al., 2004b; Bloem, van Vugt, et al., 2001), assessing postural stability has become common practice for people with PD. There is a growing body of literature concerned with developing a robust

means of assessing postural instability that has shown multiple assessments are needed (Jacobs, Horak, Tran, & Nutt, 2006; Kerr et al., 2010; Landers et al., 2008). However, most clinical appointments (e.g. neurology clinics, physiotherapy practices) are time-sensitive, requiring such assessments to be efficient. An example of this is one item of the Movement Disorders Sponsored-UPDRS, the unexpected shoulder pull or 'pull test', which is administered by an examiner with the examinee's response scored on a five-point Likert scale ranging from '0' (normal response) to '4' (very unstable) (Visser et al., 2003). While such assessments would likely continue to be the mainstay of clinical appraisals, the subjectivity that underpins such assessment makes it difficult to use them to investigate the efficacy of interventions and to gain further insight into the underlying pathophysiology of postural instability in these patients. Therefore, research utilising quantitative assessments of postural instability in PD using measures derived from force platforms may provide complementary, unique and additional information for clinicians to utilise (Blaszczyk, Orawiec, Duda-Klodowska, & Opala, 2007).

2.3.1 Force platform derived measures

Postural stability measures derived from force platforms are based on posturography, which assesses changes in the centre of pressure (COP) from beneath the plantar surfaces of the feet during quiet stance (Blaszczyk et al., 2007; Schieppati & Nardone, 1991). During quiet stance (i.e. static conditions), postural stability is considered to be the maintenance of the body's centre of mass (COM) within its base of support (provided by the feet) (Horak, 1987). Given this definition, postural instability can be described as the difficulty or complete inability to achieve this goal (Horak & Macpherson, 1996). During bipedal quiet stance, the body is constantly exposed to a combination of external (e.g. gravity) and internal (muscular) forces that require a series of coordinated movements to maintain equilibrium. Specifically, the forces experienced by the individual introduce small postural misalignments that the individual

corrects for by rotating their body about either the hip or ankle joint (Kuo, Speers, Peterka, & Horak, 1998).

Research shows that even with clinically optimal management of motor symptoms, people with PD exhibit more postural sway than otherwise healthy aged-matched older adults (Menant, Latt, Menz, Fung, & Lord, 2011). Furthermore, worsening disease severity has also been shown to contribute to increased postural sway in people with PD (Frenklach, Louie, Koop, & Bronte-Stewart, 2009). While these posturographic measures providing insight into how equilibrium is maintained during static conditions, the majority of falls experienced by people with PD occur during dynamic tasks, such as walking (Ashburn et al., 2008). During walking, individuals are required to consistently and effectively move their COM from one foot to the other (Horak & Macpherson, 1996; Winter, 1995). This task requires considerable neuromuscular coordination and strength, which may be affected in people exhibiting symptoms of postural instability. Therefore, assessments of postural stability under dynamic conditions may be necessary to completely characterise one's stability deficits.

2.3.2 Acceleration-derived measures

For a typical adult, the trunk segment contributes approximately two thirds of the body's mass, hence an inability to adequately control the trunk during locomotion may result in a loss of balance or a fall (Winter, 1995). During gait, the trunk segment plays an important role in attenuating the movement-related forces that are transferred upward from the feet following ground contact. Given this function, the trunk has been likened to a biological shock absorber that serves to dissipate the forces before they reach the head and potentially destabilise it (Kavanagh, Barrett, & Morrison, 2006). If the trunk is unsuccessful in achieving this outcome, the resulting increase in head movement would contribute to impairing both the visual and

vestibular information that is used to regulate an upright posture (Imai, Moore, Raphan, & Cohen, 2001; Kavanagh, Morrison, & Barrett, 2005).

In people with PD, the presence of axial rigidity is a contributing factor towards postural instability as it hinders the capacity of the trunk to dissipate movement-related accelerations prior to reaching the head (Cole, Sweeney, Conway, Blackmore, & Silburn, 2016; Fasano et al., 2015; Van Emmerik et al., 1999). People with PD who went onto experience a fall in the following 12-month period exhibited greater head movement (relative to walking speed) compared with age-matched controls (Cole, Silburn, Wood, & Kerr, 2011; Cole et al., 2010). Assessment of such segmental coordination during gait is not limited to optical motion analysis systems (Cole et al., 2010), but rather can be done using wearable accelerometers to accurately and reliably provide temporospatial measures, shock attenuation and segmental accelerations during gait (Kavanagh & Menz, 2008). It is now understood that people with PD have a poorer attenuation of movement-related accelerations from the pelvis to the head, which contributes to increased motion of this segment (Buckley, Galna, Rochester, & Mazza, 2015; Cole, Sweeney, Conway, Blackmore, & Silburn, 2017). Such increases in head motion during gait would have implications for the stability of this segment; a notion that is supported by research showing impaired head and trunk control in people with PD who prospectively fall (Cole et al., 2010; Cole, Sweeney, et al., 2016). Of the wearable sensors that are currently available, tri-axial accelerometers have been one of the most widely adopted devices in gait research.

2.3.2.1 Harmonic ratio

Derived from acceleration data recorded by an accelerometer, the harmonic ratio is commonly used to assess movement rhythmicity in people with PD (Hubble, Naughton, Silburn, & Cole, 2015). The measure provides a ratio of the in-phase to out-of-phase

accelerations during walking and, hence, provides a measure of step-to-step rhythmicity (or symmetry) along each axis of movement (i.e. anterior-posterior, medial-lateral, vertical) (Bellanca, Lowry, Vanswearingen, Brach, & Redfern, 2013b). Research using the harmonic ratio has shown that people with PD demonstrate less rhythmic trunk movements in the anterior-posterior and medial-lateral directions compared with age-matched controls during unconstrained walking (Lowry, Smiley-Oyen, Carrel, & Kerr, 2009). Furthermore, people with PD who retrospectively reported falling have been shown to exhibit less rhythmic head movements in all directions, compared with those who had no history of falling (Latt et al., 2009). The use of this measure has also been able to differentiate between people with PD who present with more tremor-dominant symptoms and those who experience greater difficulties with postural instability and gait difficulties (Herman, Weiss, Brozgol, Giladi, & Hausdorff, 2014; Weiss, Herman, Giladi, & Hausdorff, 2015). Furthermore, PD fallers had lower vertical and anterior-posterior harmonic ratios recorded over a three-day period compared to non-fallers (Weiss et al., 2015). Previous research has also used this measure to investigate the effects of levodopa (Pelicioni et al., 2018), exercise-based interventions (Hubble, Naughton, Silburn, & Cole, 2018), and cueing (Lowry et al., 2010) on gait stability in people with PD. Collectively, these studies provide evidence for the use of the harmonic ratio to assess step-to-step rhythmicity in PD populations and to differentiate people based on their dominant symptom type and gait stability.

CHAPTER 3: STATEMENT OF PROBLEM

It is well understood that high-frequency stimulation of the STN is effective at alleviating some of the cardinal symptoms of PD, such as tremor. However, evidence suggests that high-frequency STN-DBS is ineffective for managing other common symptoms of the disease, including symptoms of postural instability (Fasano et al., 2010; Zibetti et al., 2011). Despite initial improvements following STN-DBS surgery, a meta-regression of studies found a gradual worsening in postural stability over the subsequent two years (St George et al., 2010). This is a problem, as deteriorating postural stability in these individuals is known to contribute to a greater falls risk (Bloem, Boers, et al., 2001; Bloem et al., 2004b). Unsurprisingly, falls occur more often in people with PD who have STN-DBS than for people with PD who are receiving pharmacological treatment only (Rizzone et al., 2014; Weaver et al., 2009). Collectively, these findings indicate that people with PD who have STN-DBS represent a specific phenotype of people with PD who experience reduced resting tremor, but a worsening of axial problems (Fasano et al., 2015; Rodriguez-Oroz et al., 2012). This is of concern as axial symptoms, such as postural instability and gait disability, are known to contribute to a greater falls risk in people with PD (Bloem, Boers, et al., 2001; Bloem et al., 2004a). Given this, further research aimed at determining whether the post-operative management of people with PD who have STN-DBS can be improved to better manage the disease is needed.

CHAPTER 4: AIMS

This program of research addresses a series of questions concerning the post-operative management of axial motor symptoms, such as postural instability and gait disability, in people with PD with bilateral STN-DBS. Specifically, this dissertation includes four inter-related studies that sought to develop an improved understanding of how STN-DBS influences postural stability under both static and dynamic conditions. The rationales, aims and hypotheses of these four studies are outlined below.

Study I: Alternate deep brain stimulation parameters for managing the motor symptoms of Parkinson's disease: A systematic review and meta-analysis

An advantage of STN-DBS is that clinicians can adjust one or more of the stimulation parameters to optimize therapy, while also limiting unwanted side-effects. Given STN-DBS appears to be more effective for managing the appendicular (and not axial) motor symptoms of PD, investigations have sought to determine whether stimulation parameters other than those traditionally used may be better suited to managing axial motor symptoms. This study aimed to systematically review the available evidence regarding changes in PD motor symptom severity in response to different stimulation frequencies, amplitudes, pulse widths and/or electrode polarities compared to chronic stimulation parameters in people with PD receiving STN-DBS. A meta-analysis was conducted to determine the evidence for using low-frequency STN-DBS to improve the severity of PD motor symptoms.

Study II: Gait stability in Parkinson's disease who have STN-DBS: Do objective measures add insight?

Of the research investigating alternate STN-DBS stimulation strategies, there appears to be a high proportion of studies that employ clinical assessments. While these assessments are well established and widely used in clinical practice, there is a lack of objective measures,

such as those derived from wearable sensors that may provide additional insight for future research investigating the efficacy of alternate STN-DBS parameters for improving postural stability. This study aimed to determine whether objective measures of gait rhythmicity (a marker of gait stability) provide unique and additional insight into the gait stability of people with PD who have STN-DBS. It was hypothesised that clinical measures of mobility, gait, postural stability and balance confidence would be predictive of the harmonic ratio, and the objective measures of postural stability.

Study III: Low-frequency STN-DBS for static postural stability in Parkinson's Disease: A double-blinded randomised cross-over trial

Research suggests that people with PD continue to experience declines in standing postural stability gait initiation with high-frequency STN-DBS (Rocchi et al., 2012). This study employed a double-blinded randomised cross-over design to evaluate the effect of lower stimulation frequencies on the magnitude, velocity, variability and regularity (sample entropy) of postural sway patterns. It was hypothesized that low-frequency stimulation would improve postural sway patterns compared to the usual high-frequency stimulation.

Study IV: Low-frequency STN-DBS for gait in Parkinson's Disease: double-blinded randomised cross-over trial

Using the same study design and participants as in Study III, this study aimed to evaluate the effect of lower stimulation frequencies on objective measures of gait stability in people with PD who have STN-DBS. It was hypothesized that low-frequency stimulation would improve gait stability in people with PD who have STN-DBS compared to their usual high-frequency stimulation.

CHAPTER 5: STUDY I - Alternate Subthalamic Nucleus Deep Brain Stimulation Parameters to Manage Motor Symptoms of Parkinson's Disease: Systematic Review and Meta-Analysis

5.1 Preface

Given the apparent long-term inefficacy of STN-DBS for managing postural stability in PD, a symptom commonly associated with falls, research has sought to investigate whether stimulation parameters other than those traditionally used to manage tremor, rigidity and/or bradykinesia may be better suited to managing axial motor symptoms. The search to identify potentially useful alternate methods for post-operatively managing people with PD following STN-DBS surgery has led to a rapidly growing body of research on this topic. However, the results of these studies have typically reported conflicting findings, which have made it difficult to draw a consensus for adopting one approach over another. Therefore, there was need for a systematic review to highlight the strengths and limitations of current research as well as to inform future directions for research in this area. This study sought to systematically review and synthesise the available evidence regarding the influence of different stimulation frequencies, voltages, pulse widths and/or electrode polarities on the efficacy of STN-DBS treatment for the management of PD motor symptoms.

This chapter of the PhD thesis has been published following peer review and the full citation is provided below.

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5.2 Introduction

STN-DBS has become one of the most prominent therapies for the management of motor symptoms associated with PD (Silberstein et al., 2009). Studies have reported patients may experience improvements in tremor, stiffness (rigidity) and slowness (akinesia) of movement for a number of years following STN-DBS, which has significant implications for their independence and overall quality of life (Fasano et al., 2010; Rodriguez-Oroz et al., 2012). However, symptoms of postural instability and gait disability (particularly gait freezing) can benefit less from STN-DBS therapy (Fasano et al., 2015). Some research has reported; i) no significant improvement in trunk rigidity (Rodriguez-Oroz et al., 2012); ii) a worsening of postural instability (Fasano et al., 2010); iii) poorer performance on clinical assessments of gait (compared to off stimulation) (Moreau et al., 2008); and iv) increased gait freezing episodes (Moreau et al., 2008; Xie et al., 2015).

A significant advantage of STN-DBS over other stereotactic neurosurgical procedures (e.g. thalamotomy) is that clinicians can adjust the stimulation parameters in response to disease progression to ensure optimal patient management. Clinicians may elect to adjust one or more stimulation parameters to find the optimal collection to manage the patient's symptoms while limiting unwanted side-effects. However, given the optimal stimulation parameters for each patient are likely to differ, programming guides have been developed (Volkmann et al., 2006). Such guides outline a number of key considerations and describe the effect of altering key parameters that include the; i) frequency (the rate at which stimulation is delivered to the target structure (e.g. the STN)); ii) amplitude (the electromotive force delivered to the target structure as either constant voltage or constant current); iii) pulse width (the duration of each stimulation pulse); and iv) electrode polarity (cathodic/anodic stimulation). When the STN-DBS parameters have been established for chronic stimulation, the TEED for the patient is calculated

by multiplying the values for amplitude, frequency, pulse width and biological impedance (Koss et al., 2005).

Given the relatively lower efficacy of STN-DBS for managing the axial versus appendicular motor symptoms of PD, investigations have targeted whether stimulation parameters other than those traditionally used may be better suited to managing axial motor symptoms. This study sought to systematically review the available evidence regarding changes in PD motor symptom severity in response to different stimulation frequencies, amplitudes, pulse widths and/or electrode polarities compared to chronic stimulation parameters in people with PD receiving STN-DBS treatment. Furthermore, a meta-analysis was conducted to determine the evidence for using low-frequency STN-DBS for improving the severity of PD motor symptoms.

5.3 Methods

5.3.1 Ethical Compliance Statement

The authors confirm that neither the approval of an institutional review board nor patient consent was required for this work.

5.3.2 Search Strategy

A search for studies indexed in three scientific databases (PubMed, EMBASE, CINAHL) was completed in February 2017 to identify studies for inclusion in this review (Appendix A). The search aimed to identify studies concerning PD, the alteration of STN-DBS parameters and the assessment of motor symptoms and was prospectively register with PROSPERO (CRD42017056565).

5.3.3 Selection Criteria

To be eligible for inclusion in the review, studies were required to: i) involve an idiopathic PD population who had undergone STN-DBS; ii) include at least one experimental condition that manipulated one or more DBS parameter (e.g. frequency, amplitude, pulse width, polarity); iii) present at least one outcome regarding tremor, rigidity, bradykinesia, postural stability or gait; and iv) include an assessment of these outcomes while the stimulators were active with the parameters recommended by their neurologist (i.e. chronic stimulation). Furthermore, all included studies were required to involve people with bilateral STN-DBS therapy, as differences have been noted for the efficacy of bilateral and unilateral STN-DBS for managing motor symptoms (Lizarraga, Jagid, & Luca, 2016). Studies that included patients receiving stimulation of any other neural region (e.g. globus pallidus internus) were deemed ineligible. Studies were also excluded if they were not; i) written in English; ii) a cohort-based study (e.g. case report, commentary or letter to the editor); or iii) a full-length original research publication (e.g. conference abstract). Following the initial search and the removal all duplicates, two authors (ZJC and MHC) independently screened the titles and abstracts to determine their eligibility. Following this process, any discrepancies between the two independent assessments were discussed until a consensus was reached for each study. The full-text of all articles considered to be potentially eligible based on their titles and/or abstracts were retrieved and further screened for possible inclusion by one assessor (ZJC). Reference lists of the retrieved studies were also screened to identify any other potentially relevant articles.

5.3.4 Methodological Reporting Quality

To assess the quality of methodological reporting for each study, a previously-developed checklist designed to accommodate both randomised and non-randomised studies was used (Downs & Black, 1998). The checklist used to evaluate the quality of methodological

reporting comprised 27 criteria (maximum total score = 32) that included; i) 25 items scored on a scale from 0 (not met) to 1 (met); ii) 1 item scored from 0 (not met) to 1 (partially met) to 2 (met); and iii) 1 item assessed on a 5-point Likert scale. The item assessed out of 5 was concerned with the reporting of statistical power, with studies that achieved <70% power for their primary outcomes assigned a score of zero, while those reporting powers of 80%, 85%, 90%, 95% and ≥99% given scores of 1 to 5, respectively. In situations where an appropriate power calculation was not reported by the authors, statistical power was estimated using data presented for the primary outcomes. If means and standard deviations were not reported, the study was given a score of zero for this criterion. Similarly, for all other items, where it was not possible or unreasonably difficult for the assessors to determine whether a particular criterion had been met in the study, a score of zero was given for that item. After each study was assessed against the 27 criteria, the scores for each individual item were summed and divided by the maximum total points to yield a final score that represented the percentage of the total points available. The percentage score was subsequently used to categorically label the overall reporting quality of each study as either very low (≤20%), low (>20%, but ≤40%), moderate (>40%, but ≤60%), high (>60%, but ≤80%) or very high (>80%).

5.3.5 Meta-analysis

For the purposes of the planned meta-analysis, the sub-score for the motor sub-section of the UPDRS (UPDRS-III) was used to provide insight into any changes in symptom severity with low-frequency STN-DBS treatment. Specifically, weighted mean differences and 95% confidence intervals were calculated for the UPDRS-III to compare different low-frequency stimulation experimental conditions with high-frequency stimulation (≥130 Hz). A Mantel–Haenszel random-effects model was used to conduct the meta-analysis, while Cochran's χ^2 and the I-squared statistic were used to identify any significant heterogeneity among the included

studies (indicated by a $p<0.10$ for Cochran's χ^2 and/or an I^2 index >50%) (Higgins, Thompson, Deeks, & Altman, 2003). Lastly, the standard GRADE evidence assessment of outcomes was used to determine the overall strength of the evidence resulting from the outcomes of the meta-analysis (Guyatt et al., 2008).

5.4 Results

The initial database search (February, 2017) identified 4157 studies and following the pre-defined inclusion criteria and study selection process (Figure 5.1), 21 articles were considered relevant for inclusion in this systematic review. Demographic data including age, disease duration, time since surgery are presented in Table 5.1.

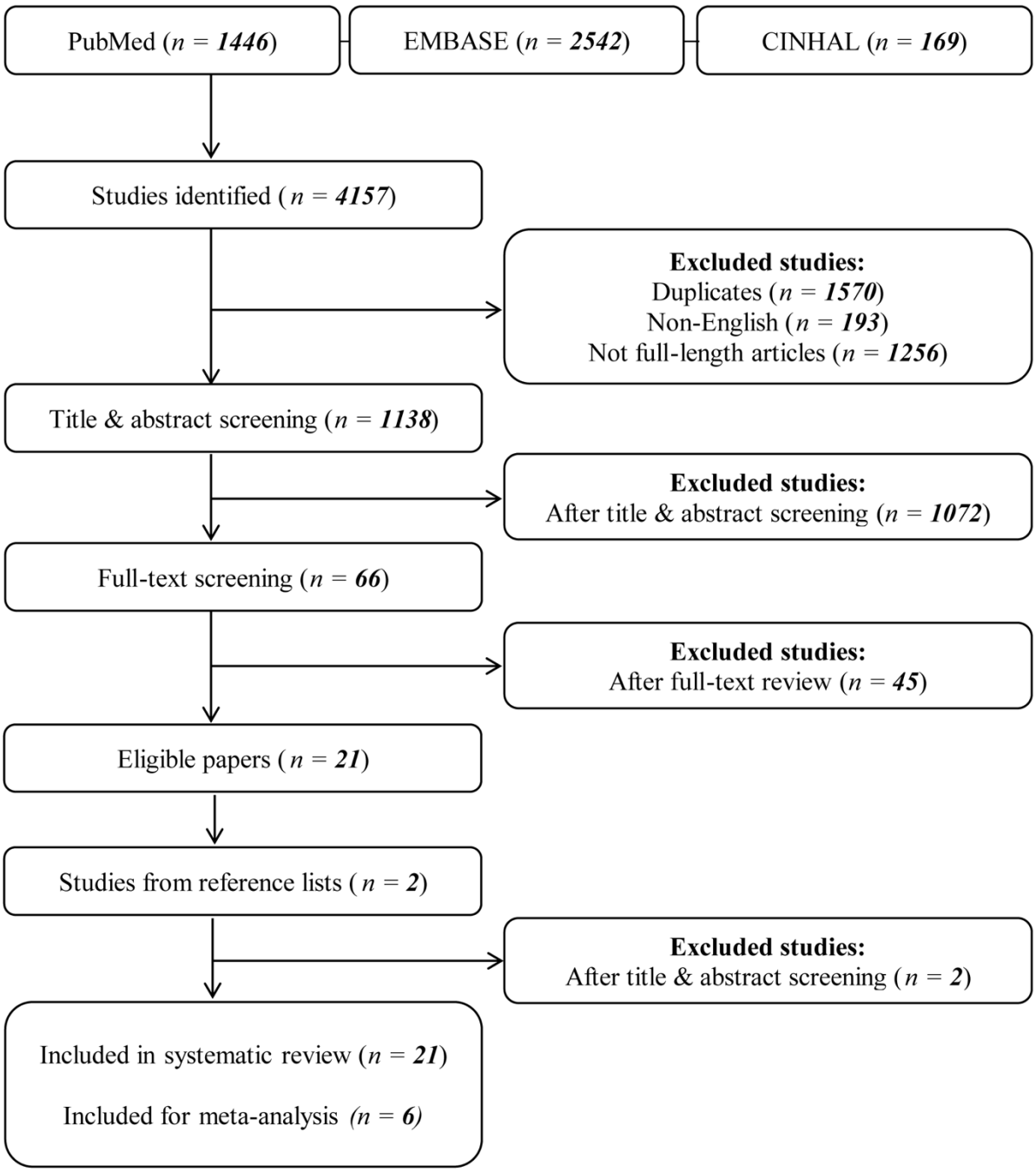

Figure 5.1: Flow diagram illustrating the systematic search strategy and review process that was used to identify the articles included in the review.

5.4.1 Methodological Reporting Quality

Based on the appraisal of methodological reporting quality, 2 (9.52%) studies were identified as having low reporting quality (range: 37.50-37.50%), 12 (57.14%) studies had moderate reporting quality (range: 40.63-59.38%) and 7 (33.33%) studies had high reporting quality (range: 62.50-71.88%) (Table 5.1). Overall, the reporting of information important for determining the statistical power, selection bias and external validity of the studies was ‘low’ or ‘very low’, while the reporting of items related to the internal validity (or bias) of the studies was generally ‘very high’.

Table 5.1: Summary of the major characteristics of the included studies' research design, participants, experimental conditions and methodological reporting quality.

Study	Methods quality	N	Age (years)	Disease duration (Years)	Time since surgery (Years)	STN-DBS Changes	Targeted Outcome(s)
Fasano 2011	High	13	63.5 ± 8.4	15.4 ± 4.5	3.5 ± 3.2	Low voltage	Symptom severity (UPDRS-III) Gait characteristics
Fogelson 2005	Moderate	10	61.4 (47.0-72.0)ŧ	15.6 (8.0-29.0)ŧ	2.8 (0.3- 9.0)ŧ	VLFS	Movement time (Finger tapping task)
Khoo 2014	High	14	60.9 ± 9.6*	16.0 ± 5.2*	2.0 ± 1.5*	LFS	Symptom severity (UPDRS-III) 10-metre timed walk test Berg Balance Scale
Krishnamurthi 2012	Moderate	4	62.3 ± 12.5*	11.3 ± 0.9*	1.6 ± 0.9*	Low voltage	Symptom severity (UPDRS-III) Standing balance measures
Little 2012	Moderate	12	61.5 ± 6.4*	13.1 ± 5.4*	2.9 ± 2.6*	VLFS	Symptom severity (UPDRS-III) Rigidity (wearable sensors)
Merola 2013	Moderate	10	59.4 ± 4.8	48.6 ± 4.5 (Onset age)	2.1 ± 1.3	LFS	Symptom severity (UPDRS-III) Complications of therapy (UPDRS-IV) Rush dyskinesia rating scale
Moreau 2008	High	13	70.0 (66.0-72.0)●	18.0 (13.0-22.0)●	5.0 (4.0-5.0)●	LFS, High voltage	Symptom severity (UPDRS-III) Stand–Walk–Sit Test
Moreau 2011	Moderate	11	69.0 (NR)₸	19.0 (17.0-23.0)₸	5.0 (3.0-8.0)ŧ	LFS	Symptom severity (UPDRS-III)

Table 5.1 continues on next page

Study	*Methods quality*	*N*	*Age (years)*	*Disease duration (Years)*	*Time since surgery (Years)*	*STN-DBS Changes*	*Targeted Outcome(s)*
Phibbs 2014	Moderate	20	62.0 (52.0-72.0)‡	12.5 (5.0-22.0)‡	3.0 (0.3-10.0)‡	LFS	Symptom severity (UPDRS-III) Gait characteristics
Reich 2015	Low	4	NR (49.0-62.0)‡	NR	0.2-0.3	Shorter pulse width, longer pulse width	Rigidity score (UPDRS item 22)
Ricchi 2012	Moderate	11	62.9 ± 4.3	46.8 ± 4.1 (Onset age)	4.5 ± 1.4	LFS	Symptom severity (UPDRS-III) Stand–Walk–Sit Test
Rissanen 2015	Low	13	57.9 ± 10.6*	NR	1.2 ± 1.0*	LFS, VHFS, Low voltage, High voltage, Longer pulse width	Symptom severity (UPDRS-III) Characteristics of biceps brachii and tibialis anterior activation Correlation between muscle activations and segmental accelerations
Sidiropoulos 2013	Moderate	45	59.5 ± 7.8	17.8 ± 5.7	NR	LFS	Symptom severity (UPDRS-III)
Stegemöller 2013	High	17	61.5 ± 9.5*	14.2 ± 4.9*	2.5 ± 1.7*	LFS	Symptom severity (UPDRS-III)
Timmermann 2004	Moderate	7	60.3 ± 6.7*	16.9 ± 3.7*	1.7 ± 0.7*	VLFS	Symptom severity (UPDRS-III)
Tsang 2012	Moderate	13	60.0 ± 6.0	15.0 ± 4.0	> 0.3	VLFS, LFS	Symptom severity (UPDRS-III)
Vallabhajosula 2015	High	19	61.8 ± 9.0	13.6 ± 4.2	NR	VLFS, LFS	Symptom severity (UPDRS-III) Gait characteristics Standing balance measures
Wojtecki 2006	Moderate	12	64.0 ± 6.3*	NR	2.3 ± 1.5*	VLFS	Symptom severity (UPDRS-III)

Table 5.1 continues on next page

Study	*Methods quality*	*N*	*Age (years)*	*Disease duration (Years)*	*Time since surgery (Years)*	*STN-DBS Changes*	*Targeted Outcome(s)*
Wojtecki 2011	High	12	64.0 ± 8.0*	18.6 ± 5.9*	3.8 ± 2.2*	VLFS	Symptom severity (UPDRS-III) Reaction time (finger tapping task)
Xie 2015	High	7	64.0 ± 8.0	12.9 ± 4.9	4.4 ± 4.9	LFS	Symptom severity (UPDRS-III) Freezing of Gait Questionnaire Stand–Walk–Sit Test
Zwartjes 2010	Moderate	6	NR (54.0-68.0)ŧ	NR	NR	Low voltage	Symptom severity (UPDRS-III) Tremor (wearable sensors) Bradykinesia (wearable sensors)

Abbreviations: **ACC**: Acceleration; **EMG**: Electromyography; **FOG**: freezing of gait; **FOG-Q**: freezing of gait questionnaire; **LFS**: low-frequency stimulation (60-80 Hertz); **NR**: not reported in the study; **UPDRS**: Unified Parkinson's Disease Rating Scale; **UPDRS-III**: Unified Parkinson's Disease Rating Scale (motor sub-score); **UPDRS-IV**: Unified Parkinson's Disease Rating Scale (motor complications sub-score); **VHFS**: very high-frequency stimulation (>130 Hertz); **VLFS**: very low-frequency stimulation (<60 Hertz).

Symbols: *: Mean and Standard Deviation (SD) calculated from reported participant values; **ŧ:** Mean and range reported; ⊽: Median and range; ●: Median and interquartile ranges.

5.4.2 STN-DBS Parameter Changes

Of the 21 included studies, 17 (80.95%) investigated the effect of changing stimulation frequency on the severity of PD motor symptoms (Table 5.2). Of these 17 studies, seven investigated very low stimulation frequencies (below 60 Hz) (Fogelson et al., 2005; Little et al., 2012; Timmermann et al., 2004; Tsang et al., 2012; Vallabhajosula et al., 2015; Wojtecki et al., 2011; Wojtecki, Timmermann, Jörgens, et al., 2006), 12 investigated low-frequencies (60–80 Hz) (Khoo et al., 2014; Merola et al., 2013; Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Phibbs et al., 2014; Ricchi et al., 2012; Rissanen et al., 2015; Sidiropoulos et al., 2013; Stegemöller et al., 2013; Tsang et al., 2012; Vallabhajosula et al., 2015; Xie et al., 2015) and one investigated very high-frequency stimulation (i.e. greater than the usual clinical recommendation of ~130 Hz) (Rissanen et al., 2015). Given these data, it is evident the majority of research has contrasted high-frequency stimulation with low-frequency stimulation. Nine of the 17 studies examining the effects of alternate stimulation frequencies did so while the other STN-DBS parameters remained unchanged from their chronic stimulation values (i.e. the TEED varied between experimental conditions) (Fogelson et al., 2005; Khoo et al., 2014; Little et al., 2012; Phibbs et al., 2014; Rissanen et al., 2015; Stegemöller et al., 2013; Timmermann et al., 2004; Wojtecki et al., 2011; Wojtecki, Timmermann, Jorgens, et al., 2006; Xie et al., 2015). In contrast, six of the remaining 8 studies increased the amplitude of stimulation in an attempt to maintain the TEED at the same level as for chronic stimulation (Merola et al., 2013; Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Ricchi et al., 2012; Sidiropoulos et al., 2013), one study increased amplitude to optimise symptom management (Khoo et al., 2014), while the other two increased the amplitude to the maximum amplitude the patients could safely tolerate (Moreau et al., 2008; Vallabhajosula et al., 2015). Despite attempts made by some researchers to maintain TEED at the chronic stimulation level, one study reported they were

unable to achieve an equivalent value at the lower frequency of stimulation (Sidiropoulos et al., 2013). Follow-up data for periods ranging up to 15 months were reported in five of the 17 studies examined the effects of altering stimulation frequency (Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Ricchi et al., 2012; Sidiropoulos et al., 2013; Xie et al., 2015).

Table 5.2: Studies that investigated changes in motor symptom severity following changes to the frequency of stimulation from chronic stimulation parameters. Note: Pulse width was unchanged during all experiments.

Study	CS Condition	Experimental condition(s)			Comparisons		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	Wash in time	Frequency Intervention	Voltage change	Outcome(s)	Vs CS	Vs Experimental condition(s) and Follow up times
Fogelson 2005	136.5 ± 16.0* Hz, 3.5 ± 0.8* V, 60.0 ± 0.0* µs / Off (0.0 ± 0.0 mg)	3-5 minutes	C1: 5 Hz	None	Kinesia time (finger tapping)	↓	NR
			C2: 10 Hz	None	Kinesia time (finger tapping)	↓	NR
			C3: 15 Hz	None	Kinesia time (finger tapping)	NR	NR
			C4: 20 Hz	None	Kinesia time (finger tapping)	NR	NR
			C5: 25 Hz	None	Kinesia time (finger tapping)	↓	NR
			C6: 30 Hz	None	Kinesia time (finger tapping)	↓	NR
Khoo 2014	130.0 ± 0.0 Hz, RHS: 2.5 (1.6-2.5)● V, LHS: 2.3 (1.5-3.0)● V, 76.1 ± 15.0 * µs / On (585.2 ± 164.3* mg)	60 minutes	C1: 60 Hz	RHS: 3.8 V (2.2-5.2)● LHS: 3.4 V (2.2-5.2)●	UPDRS-III sub-score	↑	NA
					UPDRS: Axial score	↑	NA
					UPDRS: Akinesia score	↑	NA
					UPDRS: Tremor score	=	NA
					UPDRS: Rigidity score	=	NA
					10-metre walk test: Time to complete	↑	NA
					10-metre walk test: steps to complete	↑	NA
					10-metre walk test: FOG episodes during	NA	NA
					Berg Balance Scale	=	NA

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			Comparisons		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	***Wash in time***	***Frequency Intervention***	***Voltage change***	**Outcome(s)**	**Vs CS**	**Vs Experimental condition(s) and Follow up times**
Little 2012	134.6 ± 15.9* Hz, 3.1 ± 0.3* V, 69.58 ± 15.14* μs / On (NR)	8 minutes	C1: 5 Hz	None	UPDRS: Rigidity score	=	=C2, C3, C4
					Quantitative: Rigidity	↓	=C2, C3, C4
			C2: 10 Hz	None	UPDRS: Rigidity score	=	=C1, C3, C4
					Quantitative: Rigidity	↓	=C1, C3, C4
			C3: 20 Hz	None	UPDRS: Rigidity score	=	=C1, C2, C4
					Quantitative: Rigidity	↓	=C1, C2, C4
			C4: 50 Hz	None	UPDRS: Rigidity score	=	=C1, C2, C3
					Quantitative: Rigidity	↓	=C1, C2, C3

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Merola 2013	130.0 ± 0.0 Hz, 3.2 ± 0.4* V, 60.0 ± 0.0* µs / On (522.0 ± 197.1* mg)	3 hours	C1: 80 Hz	Increased (TEED maintained)	UPDRS-III sub-score	=	NR
					UPDRS-IV sub-score	NR	NR
					UPDRS: Bradykinesia/rigidity score	=	NR
					UPDRS: Tremor score	=	NR
					UPDRS: Duration of dyskinesias score	NR	NR
					UPDRS: Disability of dyskinesias score	NR	NR
					Rush dyskinesia rating scale	↑	NR
		1 month	FU1: 80 Hz	Increased (TEED maintained)	UPDRS-III sub-score	=	NR
					UPDRS-IV sub-score	↑	NR
					UPDRS: Bradykinesia/rigidity score	=	NR
					UPDRS: Tremor score	=	NR
					UPDRS: Duration of dyskinesias score	↑	NR
					UPDRS: Disability of dyskinesias score	↑	NR
					Rush dyskinesia rating scale	↑	NR

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
		12 months	FU2: 80 Hz	Increased (TEED maintained)	UPDRS-III sub-score	=	NR
					UPDRS-IV sub-score	↑	NR
					UPDRS: Bradykinesia/rigidity score	=	NR
					UPDRS: Tremor score	=	NR

Table 5.2 continues on next page

Study	*CS Condition*		*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*		*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Moreau 2008	130.0 ± 0.0 Hz, 3.0 (2.0–3.4) V ●, 60.0 ± 0.0 µs / Off (0.0 ± 0.0 mg)	10 minutes	C1:	60 Hz	4.4 V [3.0–5.0]● (TEED maintained)	UPDRS-III sub-score	NR	NA
						UPDRS: Axial score	NR	NA
						UPDRS: Gait score	NR	NA
						UPDRS: Tremor score	NR	NA
						UPDRS: Rigidity score	NR	NA
						UPDRS: Akinesia score	NR	NA
						SWS: Time to complete	↑	↓ vs C2
						SWS: Steps to complete	↑	↓ vs C2
						SWS: FOG episodes during	↑	↓ vs C2
			C2:	60 Hz	5.5 V [5.1–6.5]● (Equivalent to a high voltage at 130 Hz)	UPDRS-III sub-score	=	NA
						UPDRS: Axial score	=	NA
						UPDRS: Gait score	=	NA
						UPDRS: Tremor score	=	NA
						UPDRS: Rigidity score	=	NA
						UPDRS: Akinesia score	=	NA
						SWS: Time to complete	↑	↑ vs C1
						SWS: Steps to complete	↑	↑ vs C1
						SWS: FOG episodes during	↑	↑ vs C1

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	***Wash in time***	***Frequency Intervention***	***Voltage change***	***Outcome(s)***	***Vs CS***	***Vs Experimental condition(s) and Follow up times***
Moreau 2011	130.0 ± 0.0 Hz, 3.0 ± 0.5* V, 60.0 ± 0.0 µs / Off (0.0 ± 0.0 mg)	60 minutes	C1: 60 Hz	4.5 ± 0.8 V (TEED maintained)	UPDRS-III sub-score	=	NA
Phibbs 2014	138.3 ± 20.2* Hz, 2.5 ± 0.7* V, 71.3 ± 14.5* µs / Off (0.0 ± 0.0 mg)	60 minutes	C1: 60 Hz	None	UPDRS-III sub-score	=	= vs C2
					UPDRS: Gait score	=	= vs C2
					UPDRS: Postural stability score	=	= vs C2
					UPDRS: Tremor score	↓	↓ vs C2
					Spatiotemporal gait characteristics	=	= vs C2
					FOG episodes	=	= vs C2
			C2: 130 Hz	None	UPDRS-III sub-score	=	= C1
					UPDRS: Gait score	=	= C1
					UPDRS: Postural stability score	=	= C1
					UPDRS: Tremor score	↑	↑ vs C1
					Spatiotemporal gait characteristics	=	= vs C1
					FOG episodes	=	= vs C1

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Ricchi 2012	130 Hz ± 0.0 Hz, RHS: 3.4 ± NR V, LHS: 3.3 ± NR V, 60.0 ± 0.0 µs / On (757.0 ± 262.0 mg)	3 hours	C1: 80 Hz	4.5 (3.9-4.5) ● V	SWS: Time to complete	↑	NR
					SWS: Steps to complete	↑	NR
					SWS: FOG episodes during	=	NR
		1 month	FU1: 80 Hz	RHS: 4.5 (3.9-4.5)● V LHS: 3.4 (3.2-3.4)● V	SWS: Time to complete	=	NR
					SWS: Steps to complete	=	NR
					SWS: FOG episodes during	=	NR
					UPDRS-III sub-score	↑	NR
					UPDRS: Tremor score	=	NR
					UPDRS: Rigidity score	=	NR
					UPDRS: Akinesia score	↑	NR
					UPDRS: Axial score	=	NR
		5 Months	FU2: 80 Hz	RHS: 4.5 (4.3-4.9)● V LHS: 4.5 (4.2-4.9)● V	SWS: Time to complete	=	NR
					SWS: Steps to complete	=	NR
					SWS: FOG episodes during	=	NR
					UPDRS-III sub-score	=	NR
					UPDRS: Tremor score	=	NR
					UPDRS: Rigidity score	=	NR
					UPDRS: Akinesia score	=	NR
					UPDRS: Axial score	=	NR

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
					SWS: Time to complete	=	NR
					SWS: Steps to complete	↓	NR
					SWS: FOG episodes during	=	NR
					UPDRS-III sub-score	=	NR
					UPDRS: Tremor score	=	NR
					UPDRS: Rigidity score	=	NR
					UPDRS: Akinesia score	=	NR
					UPDRS: Axial score	=	NR
		15 months	FU3: 80 Hz	RHS: 4.8 (4.5-5.0)● V LHS: 4.7 (4.5-5.0)● V			

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Rissanen 2015	133.1 ± 14.4* Hz, 2.97 ± 0.4* V, 60.0 ± 0.0* µs / On (NR mg)	5 min	C1:	30 Hz lower than CS	None	UPDRS: Resting tremor score	NR	NR
						UPDRS: Rigidity score	NR	NR
						Biceps brachii: EMG sample kurtosis	=	NR
						Biceps brachii: EMG recurrence rate	↓	NR
						Biceps brachii: EMG correlation dimension	↓	NR
						Biceps brachii: EMG and ACC correlation	↓	NR
						Tibialis anterior: EMG sample kurtosis	=	NR
						Tibialis anterior: EMG recurrence rate	=	NR
						Tibialis anterior: EMG correlation dimension	=	NR
						Tibialis anterior: EMG and ACC correlation	=	NR

Table 5.2 continues on next page

Study	CS Condition	Experimental condition(s)			Comparisons		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
			C2:	30 Hz higher than CS	None	UPDRS: Resting tremor score	NR	NR
						UPDRS: Rigidity score	NR	NR
						Biceps brachii: EMG sample kurtosis	=	NR
						Biceps brachii: EMG recurrence rate	↓	NR
						Biceps brachii: EMG correlation dimension	=	NR
						Biceps brachii: EMG and ACC correlation	=	NR
						Tibialis anterior: EMG sample kurtosis	=	NR
						Tibialis anterior: EMG recurrence rate	=	NR
						Tibialis anterior: EMG correlation dimension	=	NR
						Tibialis anterior: EMG and ACC correlation	=	NR

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Sidiropoulos 2013	130.0 – 185.0 Hz NR V, NR µs / On (930.5 ± NR mg)	1 to 1513 days	C1: 60 to 80 Hz	Increased (Attempt to maintain TEED, but unsuccessful)	UPDRS-III sub-score	=	NA
					UPDRS: Axial score	=	NA
					UPDRS: Gait score	=	NA
Stegemöller 2013	>129.0 Hz, CS V, CS µs / Off (0.0 ± 0.0 mg)	10 minutes	C1: 60 Hz	None	UPDRS-III sub-score	=	NA
					UPDRS: Tremor score	=	NA
					UPDRS: Bradykinesia score	=	NA
					UPDRS: Gait score	=	NA
					UPDRS: Rigidity score	=	NA
Timmermann 2004	CS (>129.0) Hz, CS V, CS µs / Off (0.0 ± 0.0 mg)	10 minutes	C1: 5 Hz	None	UPDRS-III sub-score	NR	NR
					UPDRS: Akinesia score	NR	NR
			C2: 10 Hz	None	UPDRS-III sub-score	↓	NR
					UPDRS: Akinesia score	↓	NR
			C3: 20 Hz	None	UPDRS-III sub-score	NR	NR
					UPDRS: Akinesia score	NR	NR
			C4: 45 Hz	None	UPDRS-III sub-score	NR	NR
					UPDRS: Akinesia score	NR	NR

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Tsang 2012	143.6 ± 22.0 Hz, 3.3 ± 0.1 V, 60.0 ± 0.0 µs / On (NR) & Off (0.0 ± 0.0 mg)	15 minutes	C1: 8.2 ± 2.0 Hz	7.2 ± 2.4 V (TEED lower than CS)	UPDRS: Hemi-body score	=	= C1-C6
					UPDRS: Axial score	=	= C1-C6
					Hand tapping test	↓	= C1-C6
			C2: 7.8 ± 2.0 Hz	7.1 ± 2.2 V (TEED lower than CS	UPDRS: Hemi-body score	=	= C1-C6
					UPDRS: Axial score	=	= C1-C6
					Hand tapping test	↓	= C1-C6
			C3: 22.7 ± 5.2 Hz	7.4 ± 2.6 V (TEED maintained)	UPDRS: Hemi-body score	=	= C1-C6
					UPDRS: Axial score	=	= C1-C6
					Hand tapping test	↓	= C1-C6
			C4: 24.1 ± 6.3 Hz	7.1 ± 2.6 V (TEED maintained)	UPDRS: Hemi-body score	=	= C1-C6
					UPDRS: Axial score	=	= C1-C6
					Hand tapping test	↓	= C1-C6
			C5: 55.9 ± 16.3 Hz	5.4 ± 1.3 V (TEED maintained)	UPDRS: Hemi-body score	=	= C1-C6
					UPDRS: Axial score	=	= C1-C6
					Hand tapping test	=	= C1-C6
			C6: 72.7 ± 1.2 Hz	4.7 ± 1 V (TEED maintained)	UPDRS: Hemi-body score	=	= C1-C6
					UPDRS: Axial score	=	= C1-C6
					Hand tapping test	=	= C1-C6

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Vallabhajosula 2015	CS (>129.0) Hz, 2.8 ± 0.4* V, 90.8 ± 9.3* μs / Off (0.0 ± 0.0 mg)	10 minutes	C1: 30 Hz	Increased (Maximum tolerable voltage)	UPDRS-III sub-score	=	=
					UPDRS: Tremor score	↓	↓ vs C2
					UPDRS: Bradykinesia score	=	=
					UPDRS: Posture score	=	=
					UPDRS: Gait score	=	=
					UPDRS: Balance score	=	=
					UPDRS: Rigidity score	=	=
					Swing leg step length	=	=
					Stance leg step length	=	=
					Swing leg step time	=	=
					Stance leg step time	=	=
					Swing leg step velocity	=	=
					Stance leg step velocity	=	=
					Spatiotemporal gait characteristics variability	=	=

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
			C2: 60 Hz	Increased (Maximum tolerable voltage)	UPDRS-III sub-score	=	=
					UPDRS: Tremor score	=	↑ vs C1
					UPDRS: Bradykinesia score	=	=
					UPDRS: Posture score	=	=
					UPDRS: Gait score	=	=
					UPDRS: Balance score	=	=
					UPDRS: Rigidity score	=	=
					Swing leg step length	=	=
					Stance leg step length	=	=
					Swing leg step time	=	=
					Stance leg step time	=	=
					Swing leg step velocity	=	=
					Stance leg step velocity	=	=
					Spatiotemporal gait characteristics variability	=	=

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	***Wash in time***	***Frequency Intervention***	***Voltage change***	***Outcome(s)***	***Vs CS***	***Vs Experimental condition(s) and Follow up times***
Wojtecki 2006	130.0 ± 0.0 Hz, 3.2 ± 0.5* V, 68.8 ± 14.9* µs / Off (0.0 ± 0.0 mg)	5 minutes	C1: 10 Hz	None	UPDRS-III sub-score	↓	NA
Wojtecki 2011	137.5 ± 15.4* Hz, 2.9 ± 0.5* V, 63.8 ± 13.0* µs / Off (0.0 ± 0.0 mg)	15 minutes	C1: 10 Hz	None	UPDRS-III sub-score	↓	NA
					Reaction time (finger taps)	=	NA

Table 5.2 continues on next page

Study	*CS Condition*	*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*Wash in time*	*Frequency Intervention*	*Voltage change*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s) and Follow up times*
Xie 2015	130.0 ± 0.0 Hz, RHS: 3.1 ± 0.4 V, LHS: 3.2 ± 0.4 V, RHS: 81.4 ± 14.6 µs, LHS: 90.0 ± 24.5 µs / On (1,007.0 ± 402.0 mg)	30 minutes	C1:	60 Hz	None	UPDRS-III sub-score	↑	= FU1
						UPDRS: Axial score	↑	= FU1
						UPDRS: Tremor score	=	= FU1
						FOG-Q	↑	= FU1
						SWS: FOG episodes during	↑	= FU1
						SWS: Time to complete	=	= FU1
		3 to 8 weeks	FU1:	60 Hz	None	UPDRS-III sub-score	NR	= C1
						UPDRS: Axial score	NR	= C1
						UPDRS: Tremor score	NR	= C1
						FOG-Q	NR	= C1
						SWS: FOG episodes during	NR	= C1
						SWS: Time to complete	NR	= C1

Abbreviations: ACC: Acceleration; **CS:** Chronic stimulation; **Cx:** Experimental condition x (range = 1 to 6); **EMG:** Electromyography; **FUx:** Follow-up assessment x (range = 1 to 3); **FOG**: freezing of gait; **FOG-Q**: freezing of gait questionnaire; **Hz:** Hertz (relating to frequency of stimulation); **LED**: Levodopa equivalent dose; **LHS**: Left-hand side; **LRT**: levodopa replacement therapy; **mg:** milligrams; **NA**: Not applicable; **NR**: Not reported in this study; **RHS**: Right-hand side; **SWS**: stand-walk-sit test; **TEED**: Total electrical energy derived; **UPDRS**: Unified Parkinson's Disease Rating Scale; **UPDRS-III**: Unified Parkinson's Disease Rating Scale (motor section); **UPDRS-IV**: Unified Parkinson's Disease Rating Scale (motor complication section); **V:** Voltage of stimulation: **µs:** microsecond (relating to pulse width).

Symbols: *: Mean and Standard Deviation (SD) calculated from reported participant values; ŧ: Mean and range reported; ⊽: Median and range; ●: Median and interquartile ranges.

Comparisons: =: No significant change; **↑:** Significant improvement; **↓:** Significant worsening.

While the majority of studies included in this review investigated the effects of varying frequency on the management of motor symptoms, 5 studies (23.8%) specifically focused on the effect of altering amplitude on the management of clinical symptoms (Table 5.3) (Fasano et al., 2011; Krishnamurthi, Mulligan, Mahant, Samanta, & Abbas, 2012; Moreau et al., 2008; Rissanen et al., 2015; Zwartjes, Heida, Van Vugt, Geelen, & Veltink, 2010). Of the included studies, those that sought only to alter the amplitude of stimulation (i.e. while maintaining the pulse width and frequency of stimulation at the chronic stimulation parameters) all employed constant-voltage systems. Within the five studies, there were seven experimental conditions investigated; five of which included lowering amplitude and two of which involved increasing amplitude. In studies reporting the effects of lowering amplitude relative to the chronic stimulation value, amplitudes were typically reduced; i) by 50% for one hemisphere (Fasano et al., 2011), ii) to approximately 80% (Zwartjes et al., 2010), 70% (Krishnamurthi et al., 2012), or 30% (Krishnamurthi et al., 2012) of the chronic stimulation values; or iii) to a level that was 0.3 V lower than chronic stimulation (Rissanen et al., 2015). In contrast, studies examining the effects of increasing amplitudes included experimental conditions that involved increasing amplitudes; i) to the highest level tolerable for each patient (Moreau et al., 2008); or ii) to a level that was 0.3 V higher than chronic stimulation (Rissanen et al., 2015).

Table 5.3: Studies that investigated changes in motor symptom severity following adjustment of the stimulation amplitude from chronic stimulation parameters. Note: Frequency and pulse width were unchanged during all experiments.

Study	CS Condition		Experimental condition(s)			Comparisons		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	UPDRS-III	Wash in time		Voltage Intervention	Outcome(s)	Vs CS	Vs Experimental condition(s)
Fasano 2011	170.0 ± 26.8* Hz, 3.2 ± 0.9* V, 61.2 ± 5.9* µs / Off (0.0 ± 0.0 mg)	NR	15 minutes	C1:	50% less than CS for hemisphere corresponding to leg with shorter step length	UPDRS-III sub-score	↓	= vs C2
						Gait velocity	=	= vs C2
						Cadence	=	↑ vs C2
						Stride length	=	↓ vs C2
						Step height	=	= vs C2
						Phase coordination index	↓	↓ vs C2
						Step time coefficient of variation	↓	↓ vs C2
						Step time asymmetry	↓	↓ vs C2
						FOG episodes during	=	NR
						Duration of FOG episodes during	↓	NR
				C2:	50% less than CS for hemisphere corresponding to leg with longer step length	UPDRS-III sub-score	↓	= vs C1
						Gait velocity	=	= vs C1
						Cadence	=	↓ vs C1
						Stride length	=	↑ vs C1
						Step height	=	= vs C1
						Step time coefficient of variation	↑	↑ vs C1
						Step time asymmetry	↑	↑ vs C1
						Temporal accuracy	↑	↑ vs C1
						FOG episodes during	↑	NR
						Duration of FOG episodes during	↑	NR

Table 5.3 continued on next page

Study	*CS Condition*		*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*UPDRS-III*	*Wash in time*	*Voltage Intervention*		*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s)*
Krishnamurthi 2012	170.6 ± 24.0* Hz, 3.8 ± 1.0* V, 82.5 ± 15.0* µs / On (390-2,450 mg)	NR	20 minutes	C1:	~70% of CS (2.7 ± 0.7* V)	UPDRS-III sub-score	=	= vs C2
						Path length	=	= vs C2
						Average sway velocity	↓	↓ vs C2
						Peak sway velocity	↓	↓ vs C2
						Targeting errors	=	= vs C2
						Unsteadiness	=	= vs C2
				C2:	~30% of CS (1.2 ± 0.3* V)	UPDRS-III sub-score	=	= vs C1
						Path length	=	= vs C1
						Average sway velocity	↓	↑ vs C1
						Peak sway velocity	↓	↑ vs C1
						Targeting errors	=	= vs C1
						Unsteadiness	=	= vs C1
Moreau et al., 2008	130.0 ± 0.0 Hz 3.0 (2.0-3.4) V● 60.0 ± 0.0 µs / Off (0.0 ± 0.0 mg)	26 (21–30)●	10 minutes	C1:	3.7 (3.5–4.5)●	SWS: Time to complete	↓	NA
						SWS: Steps to complete	↓	NA
						SWS: FOG episodes during	↓	NA

Table 5.3 continued on next page

Study	*CS Condition*		*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*UPDRS-III*	*Wash in time*		*Voltage Intervention*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s)*
Rissanen 2015	133.1 ± 14.4* Hz, 2.97 ± 0.4* V, 60.0 ± 0.0* µs / On (NR mg)	23.4 ± 7.6	5 minutes	C1:	0.3 V lower than CS	UPDRS: Resting tremor score	NR	NR
						UPDRS: Rigidity score	NR	NR
						Biceps brachii: EMG sample kurtosis	↓	NR
						Biceps brachii: EMG recurrence rate	↓	NR
						Biceps brachii: EMG correlation dimension	↓	NR
						Biceps brachii: EMG and ACC correlation	↓	NR
						Tibialis anterior: EMG sample kurtosis	=	NR
						Tibialis anterior: EMG recurrence rate	=	NR
						Tibialis anterior: EMG correlation dimension	=	NR
						Tibialis anterior: EMG and ACC correlation	=	NR

Table 5.3 continued

Study	*CS Condition*		*Experimental condition(s)*		*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*UPDRS-III*	*Wash in time*	*Voltage Intervention*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s)*
			C2:	0.3 V higher than CS	UPDRS: Resting tremor score	NR	NR
					UPDRS: Rigidity score	NR	NR
					Biceps brachii: EMG sample kurtosis	↓	NR
					Biceps brachii: EMG recurrence rate	↓	NR
					Biceps brachii: EMG correlation dimension	↓	NR
					Biceps brachii: EMG and ACC correlation	=	NR
					Tibialis anterior: EMG sample kurtosis	=	NR
					Tibialis anterior: EMG recurrence rate	=	NR
					Tibialis anterior: EMG correlation dimension	=	NR
					Tibialis anterior: EMG and ACC correlation	=	NR

Table 5.3 continued on next page

Study	*CS Condition*		*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*UPDRS-III*	*Wash in time*		*Voltage Intervention*	*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s)*
Zwartjes et al., 2010	CS Hz, CS V, CS µs / NR (NR mg)	NR	15-30 minutes	C1:	20% lower than CS	UPDRS: Resting tremor score	=	NA
						Quantitative (wearable sensors): Tremor	↓	NA
						UPDRS: Bradykinesia score	=	NA
						Quantitative (wearable sensors): Bradykinesia	=	NA

Abbreviations: ACC: Acceleration; **CS**: Chronic stimulation; **Cx**: Experimental condition x (range = 1 to 2); **EMG**: Electromyography; **FOG**: Freezing of gait; **Hz**: Hertz (relating to frequency of stimulation); **LED**: Levodopa equivalent dose; **LRT**: levodopa replacement therapy; **mg**: milligrams; **NA**: Not applicable; **NR**: Not reported in this study; **SWS**: stand-walk-sit test; **UPDRS**: Unified Parkinson's Disease Rating Scale; **UPDRS-III**: Unified Parkinson's Disease Rating Scale (motor section); **V**: Voltage of stimulation: **µs**: microsecond (relating to pulse width).
Symbols: *: Mean and Standard Deviation (SD) calculated from reported participant values; ●: Median and interquartile ranges.
Comparisons: =: No significant change; ↑: Significant improvement; ↓: Significant worsening.

The remaining two (9.52%) studies included in this review investigated changes in the management of motor symptoms in post-operative STN-DBS PD patients in response to shortening or lengthening the pulse width (Reich et al., 2015; Rissanen et al., 2015) (Table 5.4). Specifically, these studies evaluated the effect of shortening pulse widths to 20, 30, 40 and 50 μs (Reich et al., 2015) or lengthening pulse widths to 90 (Reich et al., 2015; Rissanen et al., 2015) or 120 μs (Reich et al., 2015). Of the two studies that investigated changes in pulse width, one employed a constant-current amplitude (Reich et al., 2015), while the other examined a constant-voltage system (Rissanen et al., 2015). Although our systematic search strategy identified a number of studies investigating the effect of different electrode polarities on the severity of motor symptoms in post-operative STN-DBS PD patients, all were excluded for not meeting one or more of the pre-defined inclusion criteria.

Table 5.4: Summary of the studies that investigated changes in motor symptom severity following adjustment of the pulse width from chronic stimulation parameters. Note: Frequency and voltage were unchanged in one study, but voltage was systematically increased in the other until the therapeutic window (defined as optimal therapeutic relief of stimulation without adverse side effects) was achieved.

Study	CS Condition		Experimental condition(s)			Comparisons		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	UPDRS-III	Wash in time	Pulse width Intervention		Outcome(s)	Vs CS	Vs Experimental condition(s)
Reich 2015	130.0 ± 0.0 Hz, 2.2 ± 1.6 mA, 60.0 ± 0.0 µs / Off (0.0 ± 0.0 mg)	24.8 ± 8.6	NR	C1:	20 µs	UPDRS: Rigidity score	NR	NA
				C2:	30 µs	UPDRS: Rigidity score	NR	NA
				C3:	40 µs	UPDRS: Rigidity score	NR	NA
				C4:	50 µs	UPDRS: Rigidity score	NR	NA
				C5:	90 µs	UPDRS: Rigidity score	NR	NA
				C6:	120 µs	UPDRS: Rigidity score	NR	NA

Table 5.4 continues on the next page

Study	*CS Condition*		*Experimental condition(s)*			*Comparisons*		
	Frequency, Voltage, Pulse Width / On or Off LRT (LED)	*UPDRS-III*	*Wash in time*	*Pulse width Intervention*		*Outcome(s)*	*Vs CS*	*Vs Experimental condition(s)*
Rissanen 2015	133.1 ± 14.4* Hz, 2.97 ± 0.4* V, 60.0 ± 0.0* µs / On (NR mg)	23.4 ± 7.6	5 minutes	C1:	90 µs	UPDRS: Resting tremor score	NR	NA
						UPDRS: Rigidity score	NR	NA
						Biceps brachii: EMG sample kurtosis	=	NA
						Biceps brachii: EMG recurrence rate	↓	NA
						Biceps brachii: EMG correlation dimension	↓	NA
						Biceps brachii: EMG and ACC correlation	=	NA
						Tibialis anterior: EMG sample kurtosis	=	NA
						Tibialis anterior: EMG recurrence rate	=	NA
						Tibialis anterior: EMG correlation dimension	=	NA
						Tibialis anterior: EMG and ACC correlation	=	NA

Abbreviations: ACC: Acceleration; **CS**: Chronic stimulation; **Cx**: Experimental condition x (range = 1 to 6); **EMG**: Electromyography; **Hz**: Hertz (relating to frequency of stimulation); **LED**: Levodopa equivalent dose; **LRT**: levodopa replacement therapy; **mg**: milligrams; **mA:** milliamps; **NA**: Not applicable; **NR**: not reported in the study; **UPDRS**: Unified Parkinson's Disease Rating Scale; **UPDRS-III**: Unified Parkinson's Disease Rating Scale (motor section); **V**: Voltage of stimulation: **µs**: microsecond (relating to pulse width of stimulation).
Symbols: *: Mean and Standard Deviation (SD) calculated from reported participant values
Comparisons: =: No significant change; ↓: Significant worsening.

5.4.3 Meta-analysis

To establish the effect of lower frequencies of stimulation on motor symptom severity, the results of six studies that reported the UPDRS-III sub-score for STN-DBS PD patients at high- (≈130 Hz) and low-frequency (60 Hz) stimulation were considered for inclusion in a meta-analysis (Khoo et al., 2014; Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Phibbs et al., 2014; Vallabhajosula et al., 2015; Xie et al., 2015). Where the studies' results were presented as medians, 95% confidence intervals and/or ranges, the corresponding authors were emailed to request the means and standard deviations for the required outcome. Following this process, data for 5 of the 6 eligible studies were acquired (Khoo et al., 2014; Moreau et al., 2008; Phibbs et al., 2014; Vallabhajosula et al., 2015; Xie et al., 2015), while the sixth study was excluded due to difficulties with obtaining the necessary mean and standard deviation data for inclusion (i.e. data were reported as medians and interquartile ranges) (Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011). Of the five studies included in the meta-analysis, two implemented a low-frequency stimulation strategy with an increased amplitude to maintain the chronic stimulation TEED (Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011), one study increased amplitude to optimise symptom management (Khoo et al., 2014), two studies maintained chronic stimulation amplitude (Phibbs et al., 2014; Xie et al., 2015) and one increased amplitude to the maximum level tolerable for each patient (Vallabhajosula et al., 2015). Analysis of the heterogeneity of the five studies (total n = 73 participants) returned a statistically significant outcome, suggesting significant variation among the studies, with respect to their reported results (Cochran's $\chi^2 = 34.50$, $p<0.00001$; $I^2 = 88\%$). On the basis of this heterogeneity, it seemed inappropriate and of limited clinical use to combine the data from the five studies (Fletcher, 2007). However, upon reviewing each of the studies, it was evident that much of this heterogeneity was likely attributable to whether researchers sought to alter the

amplitude to maintain the TEED after increasing or decreasing frequency. After sub-dividing the studies based on whether they adjusted amplitude or not, it was found that those studies that made an adjustment to stimulation amplitude returned a non-significant outcome for the test of heterogeneity, while those that did not adjust amplitude exhibited significant heterogeneity (Figure 5.2). On the basis of the GRADE evidence assessment of outcomes, the pooled evidence from the five studies was of very low quality due to risks of bias, inconsistency (presence of statistical heterogeneity) and imprecision.

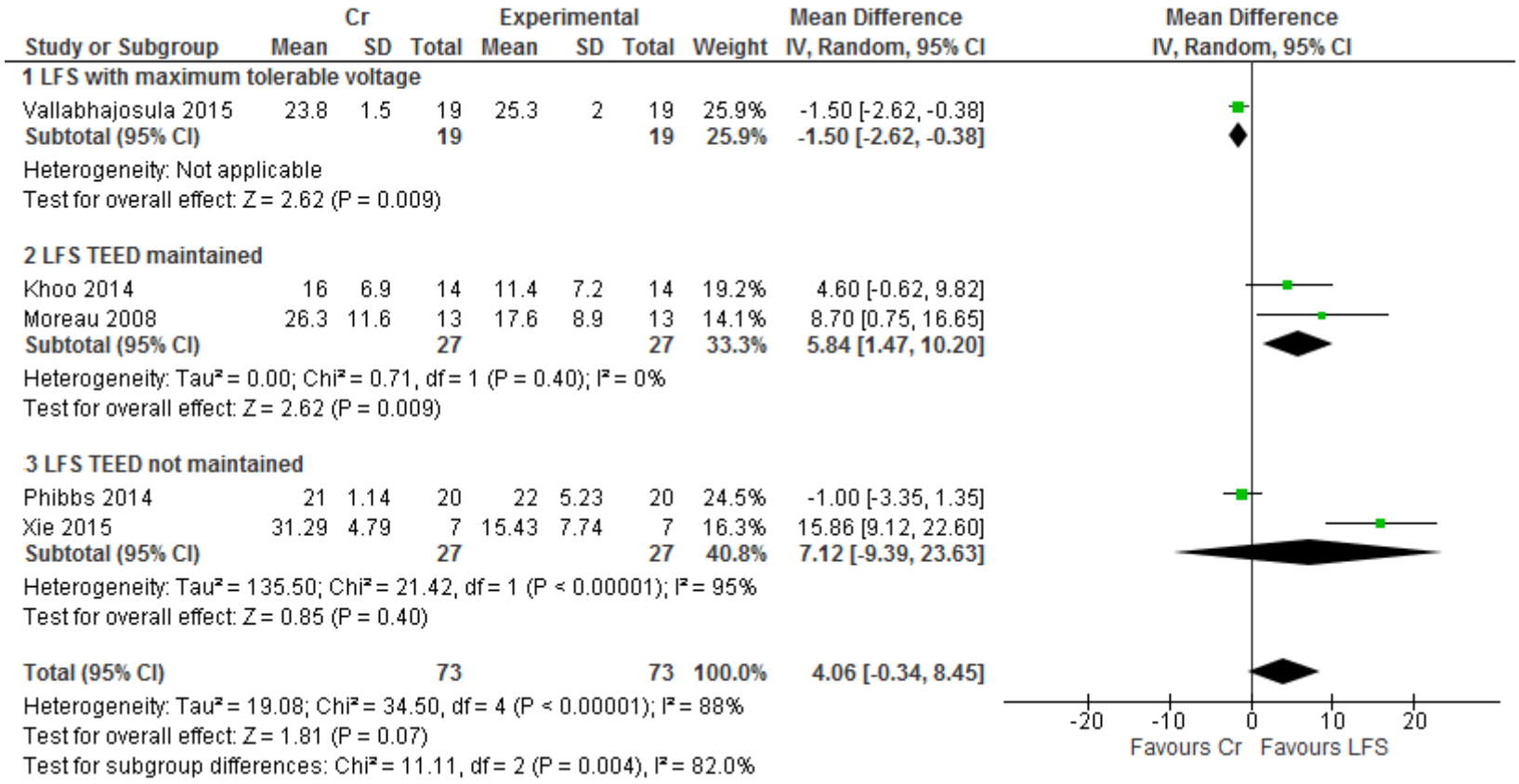

Figure 5.2: Motor sub-score of the Unified Parkinson's Disease Rating Scale (UPDRS-III) for the studies that reduced stimulation frequency to 60 Hz (LFS) compared to the chronic stimulation (CS) 130 Hz deep brain stimulation condition. Subgroups include; 1) studies that increased amplitude to a maximum tolerable level; 2) studies that increased amplitude to maintain the total electrical energy derived (TEED) at the CS level; and 3) studies that maintained amplitude at the CS level.

5.5 Discussion

The results of this review suggested that research concerning the potential utility of alternate STN-DBS parameters is an emerging field and that, for the most part, there has been a specific emphasis on determining the efficacy of low-frequency STN-DBS for managing PD motor symptoms. Synthesis of the available literature concerning low-frequency STN-DBS therapy for people with PD provides some promising results, especially relating to short-term improvements in gait outcomes without the inadvertent worsening of other motor symptoms (e.g. tremor). However, despite the promise of these preliminary findings, the assessment of methodological reporting quality identified a number of key areas that have traditionally been overlooked in the reporting of study designs and outcomes in this field of research.

On the basis of the Downs and Black tool, the overall methodological reporting quality of the included studies was largely of a moderate standard. In general, the reviewed studies scored poorly on items relating to the representativeness of their study populations (external validity), as many consecutively enrolled patients from clinics or hospital settings or investigated a specific sub-type of STN-DBS patients. Furthermore, others provided insufficient information to determine where their population was recruited from, which made it difficult to determine the potential for population bias in these studies. The potential for population bias was most notable in studies investigating the influence of low-frequency stimulation on the severity of motor symptoms in people with PD. Specifically, the populations targeted in these studies included patients with; i) tremor-dominant and non-tremor dominant symptoms (Stegemöller et al., 2013); ii) symptoms of dystonia (Merola et al., 2013); and iii) post-operative deficits in gait or axial function (Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Ricchi et al., 2012; Sidiropoulos et al., 2013). Another factor that contributed to the low to moderate methodological reporting quality

scores was the relatively small sample sizes included in these studies and the large number of studies (14 studies; 66.67%) that did not include a statement regarding an a-priori statistical power calculation or provide data to allow power to be estimated post-hoc. Due to the heavy emphasis placed on this component of the methodological reporting checklist, the omission of such a statement contributed significantly to the overall assessment of the methodological reporting quality for these studies Nevertheless, it is important to emphasise that, in spite of these shortcomings, the findings of such studies are still clinically useful and have provided important insights that have assisted with clinical practices and shaping the direction of future research.

Low-frequency STN-DBS conditions that increased amplitude

The studies that evaluated the influence of varying stimulation frequency exhibited considerable heterogeneity with respect to whether or not they made a compensatory change to the stimulation amplitude following their adjustments to stimulation frequency. Given that the TEED represents the product of stimulation frequency, amplitude, pulse width and biological impedance, any changes that are made to one of these parameters (e.g. lowering frequency) ultimately changes the TEED, unless a compensatory change is made to one of the other parameters (e.g. by increasing amplitude). The body of work that has been completed in this area represents a mixture of studies that have increased amplitude in response to a decrease in frequency and those that have not. For clarity, these two sub-groups are discussed separately.

The results of the systematic review highlighted that the outcomes reported by the included studies were almost exclusively based on well-established clinical scales. While these assessments are routinely used in clinical practice, other objective measures of postural stability and gait may provide further insight into the strengths and weaknesses of alternate patterns of

STN-DBS stimulation. For example, in spite of a trend toward improved motor symptom management with low-frequency STN-DBS, the results of the meta-analysis reported no significant improvement in motor symptom severity (as assessed via the UPDRS) with this alternate therapy. However, post-operative STN-DBS patients have been shown to complete a standardized gait assessment in a shorter amount of time with fewer steps while receiving low-frequency STN-DBS with the TEED maintained (Moreau et al., 2008; Ricchi et al., 2012), but not when the TEED was not maintained (Xie et al., 2015). Importantly, the improvements evident for low-frequency stimulation with TEED maintained were achieved without significantly influencing the severity of rigidity, resting tremor or dyskinesias (Merola et al., 2013; Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Ricchi et al., 2012). Furthermore, low-frequency stimulation had a positive effect on akinesia (Ricchi et al., 2012), which is a symptom potentially exacerbated in some STN-DBS patients at 130 Hz (Fleury et al., 2016). Collectively, these findings suggest low-frequency stimulation may offer short-term benefits for managing the motor symptoms of PD, but the efficacy of this approach is influenced by whether a compensatory increase in amplitude is made. The meta-analysis illustrates a trend towards improved motor symptom management with low-frequency STN-DBS that is combined with an increase in amplitude; however, the optimal amplitude adjustment is likely to vary across patients. Therefore clinicians are encouraged to use specific clinical outcomes (e.g. complete suppression of contralateral rigidity (Reich et al., 2015)) to guide the titration of alternate stimulation parameters and tailor the therapy to each individual's needs.

Despite the growing evidence for short-term improvements in axial symptoms with low-frequency STN-DBS, the long-term efficacy of this therapy for these symptoms may be no better than high-frequency STN-DBS treatment (Ricchi et al., 2012; Sidiropoulos et al., 2013).

Furthermore, in the three studies that reported long-term follow-up data for patients receiving low-frequency STN-DBS therapy with TEED maintained, 73% (Sidiropoulos et al., 2013), 50% (Merola et al., 2013), and 18% (Ricchi et al., 2012) of the patients requested to revert back to high-frequency stimulation due to negative changes in their tremor, gait patterns and/or rigidity. Interestingly, those patients who continued to receive low-frequency STN-DBS experienced continued therapeutic benefits with respect to the management of tremor and rigidity after 12- (Merola et al., 2013) or 15-months (Ricchi et al., 2012) of chronic stimulation. Furthermore, patients with dyskinesia showed sustained improvements in the severity and duration of dyskinesia after 12-months of low-frequency STN-DBS therapy (Merola et al., 2013). Collectively, these long-term follow-up data suggest that low-frequency STN-DBS may not benefit all patients in the same way; highlighting the need for improved strategies for determining the potential benefits of non-routine stimulation parameters for patients with sub-optimal responses to routine parameters.

Experimental STN-DBS conditions that did not maintain TEED

While a small number of studies in this area have sought to maintain TEED during their experimental conditions, a large number of experiments have not maintained this parameter. As a percentage of these studies evaluated the effects of very low-frequencies of STN-DBS (e.g. 5, 20, 50 Hz), it was not always possible for these research teams to account for the marked drop in stimulation frequency with adjustments to other stimulation parameters (Fogelson et al., 2005; Little et al., 2012; Timmermann et al., 2004; Tsang et al., 2012; Vallabhajosula et al., 2015; Wojtecki et al., 2011; Wojtecki, Timmermann, Jörgens, et al., 2006). In such studies, STN-DBS at 10 Hz was reported to result in significantly worse symptom severity (based on the UPDRS-III sub-score) (Timmermann et al., 2004; Wojtecki et al., 2011; Wojtecki, Timmermann, Jörgens, et al., 2006), slower upper limb movements (Fogelson et al., 2005;

Tsang et al., 2012; Wojtecki, Timmermann, Jörgens, et al., 2006), and increased wrist rigidity (Little et al., 2012) compared with high-frequency STN-DBS. Even after the amplitude was increased to the maximum level tolerable for the patients, a 30 Hz stimulation frequency remained inadequate to manage symptoms of tremor, despite some improvements in the total UPDRS-III sub-score and spatiotemporal gait characteristics (Vallabhajosula et al., 2015). Overall, these findings suggested that the frequency of stimulation plays an important role in managing symptoms of tremor and that very low-frequency stimulation may be unsuitable for the ongoing post-operative management of PD motor symptoms.

Mixed results were reported for those studies assessing the effects of low-frequency STN-DBS while not maintaining the TEED. For example, some reported improvements in axial symptoms (based on the UPDRS) (Xie et al., 2015) and symptoms of freezing of gait (FOG) (Xie et al., 2015), while others observed no significant improvement in spatiotemporal gait characteristics (Phibbs et al., 2014) or rigidity, bradykinesia, and gait scores (Stegemöller et al., 2013) compared with high-frequency STN-DBS. Furthermore, the specific benefits of low-frequency STN-DBS for managing the axial symptoms and gait difficulties associated with PD may begin to diminish in as little as eight weeks (Xie et al., 2015) and the reduced efficacy of this therapy for symptoms of tremor (Phibbs et al., 2014; Rissanen et al., 2015; Stegemöller et al., 2013) would typically require an increase in oral medications (Xie et al., 2015). Interestingly, however, one study found that low-frequency stimulation, when combined with amplitudes ≥5.1 V (i.e. higher than the ≈3 V clinical recommendation), significantly improved standardized gait test performances for a group of patients with gait disorders compared with chronic stimulation STN-DBS parameters (Moreau et al., 2008). Importantly, these stimulation parameters were only tolerated by 11 of the 13 patients (84.6%) and required an increased daily dose of levodopa to counteract the re-emergence of other motor symptoms, including tremor

(Moreau et al., 2008). However, given that a separate study reported no significant improvement in postural sway or gait outcomes when low frequencies of STN-DBS stimulation were combined with higher amplitudes (Vallabhajosula et al., 2015), these outcomes should be carefully considered.

In addition to evaluating the effect of alternate stimulation frequencies on the management of motor symptoms in post-operative STN-DBS PD patients, this review also considered the effect of experimentally altering amplitude on motor symptoms. The findings of the reviewed studies demonstrated that increasing STN-DBS amplitude to a level above chronic stimulation (e.g. >3 V) led to muscle activation patterns that reflected a worse disease state (Rissanen et al., 2015). Interestingly, however, one study reported that patients completed the Stand-Walk-Sit test in less time and with fewer number of steps and freezing episodes when STN-DBS amplitude was increased above the chronic stimulation level, suggesting that higher amplitudes may be beneficial for managing gait-related difficulties (Moreau et al., 2008). In contrast, a separate study indicated that lowering amplitude by 50% for the hemisphere corresponding to the patients' legs that exhibited the longer step length (i.e. compared with the contralateral limb), significantly reduced the frequency and duration of freezing episodes without introducing any measurable changes in velocity, stride length, or cadence (Fasano et al., 2011). However, these improvements in freezing of gait came at the cost of a re-emergence of other PD motor symptoms (Fasano et al., 2011); a finding that is commensurate with the outcomes of separate studies examining the potential benefits of lower STN-DBS amplitude (Fasano et al., 2011; Krishnamurthi et al., 2012; Moreau et al., 2008; Rissanen et al., 2015; Zwartjes et al., 2010). Furthermore, reducing STN-DBS amplitude to approximately 30% of the chronic stimulation value were shown to contribute to poorer performances during posturography assessments in a small group of three participants (Krishnamurthi et al., 2012).

Collectively these findings demonstrate the apparent sensitivity of PD-related motor symptoms to changes in stimulation amplitude.

Compared to frequency and amplitude, substantially fewer studies investigated the effects of changing pulse width or electrode polarity on the management of motor symptoms in post-operative STN-DBS PD patients. With respect to the small number of studies that have investigated the effects of varying pulse width, longer pulse widths (e.g. 90 μs) were shown to significantly reduce STN-DBS efficacy (Reich et al., 2015; Rissanen et al., 2015), while shorter pulse widths (e.g. 30 μs) were shown to improve the therapeutic window up to twofold (Reich et al., 2015). Simply, the therapeutic window describes the range of amplitudes that offer relief from motor symptoms and is limited when amplitude changes induce dysarthria or impaired motor skills. Therefore, shorter pulse widths led to an increased range of amplitudes that offered therapeutic benefit, while also decreasing the total charge per pulse required (Reich et al., 2015). Collectively, these findings highlight the potential value of investigating the effects of shorter pulse width on the management of motor symptoms in post-operative STN-DBS PD patients.

Limitations

The findings of this review should be considered in light of a number of potential limitations. First, the meta-analysis found a large degree of heterogeneity across studies, which may be attributed, at least in part, to differences in patient characteristics for the cohorts of the respective studies. Specifically, the five studies included in the meta-analysis reported investigating cohorts that included patients who experienced; i) severe gait disorders (Moreau et al., 2008); ii) freezing of gait with 130 Hz stimulation and dopaminergic medication (Xie et al., 2015); or iii) multiple changes in their gait including balance, freezing, and festination (Phibbs et al., 2014). The remaining two studies reported not specifically targeting STN-DBS

patients who experience gait impairments (Khoo et al., 2014; Vallabhajosula et al., 2015). Second, the collection of terms used in our systematic search did not specifically cover studies that investigated the effect of different stimulation configurations (e.g. interleaving) on the efficacy of STN-DBS treatment. Given there have been a number of studies that have investigated this topic recently (Ramirez-Zamora, Kahn, Campbell, DeLaCruz, & Pilitsis, 2015), future research may seek to establish a consensus from this literature to guide the potential use of this approach for therapeutic purposes. Third, the results of the meta-analysis were limited to reporting on the acute effects of low-frequency STN-DBS (10 to 60 minutes following the change) on the severity of motor symptoms in people with PD. However, research has shown that the severity of motor symptoms can continue to worsen up to four hours after the cessation of STN-DBS therapy (Temperli et al., 2003). Given the studies included in this review involved a change in stimulation parameters, rather than the complete cessation of treatment, future research should consider assessing the efficacy of alternate stimulation parameters after a longer wash-in period. Lastly, the clinical implications of this review are limited to evaluating the efficacy of STN-DBS for the management of motor symptoms other than speech in people with PD. It is known that one's capacity for speech is heavily influenced by both motor and cognitive factors (Parsons, Rogers, Braaten, Woods, & Troster, 2006). Given the complex interaction that seems to exist between high-frequency STN-DBS, cognitive function and speech, a systematic review aimed at establishing the effects of STN-DBS therapy on speech-related outcomes should be considered for future research. To improve the scientific rigor of research in this area, there is a clear need for consensus regarding the importance of maintaining the TEED when assessing the influence of alternate stimulation profiles. Furthermore, scientists are encouraged to further examine the effects of alternate STN-DBS therapies (e.g. shorter pulse widths) on symptom management in people with PD and to ensure that patient samples are representative of the wider STN-DBS PD population.

5.6 Conclusions

The results of this systematic review identified significant heterogeneity amongst the included studies, which emphasized the need for a more uniform approach to examining the potential benefits of alternate patterns of STN-DBS. Nevertheless, the presented findings suggested that low-frequency STN-DBS may provide short-term benefits for patients who experience significant axial motor symptoms (postural stability and gait difficulties) and/or who respond sub-optimally to routine high-frequency STN-DBS. However, there is a need for appropriate techniques to identify patients who will most likely benefit from this non-routine stimulation strategy, as evidence suggests that low-frequency STN-DBS is unlikely to provide the same therapeutic benefits as high-frequency STN-DBS for patients who present with tremor-dominant symptoms. As such, the results of this systematic review and meta-analysis do not support a change to the currently recommended routine stimulation parameters for STN-DBS patients, but rather suggest that non-routine stimulation strategies may offer a viable alternative to be considered for patients whose symptoms are sub-optimally managed with routine therapies.

CHAPTER 6: METHODOLOGY OF THE EXPERIMENTAL STUDIES

6.1 Population

6.1.1 Recruitment

Prospective participants were randomly recruited via two streams; a Brisbane-based neurology clinic and a local DBS support group. By adopting a randomised recruitment strategy, this research addresses one of the short coming of previous research in that many of the reviewed studies (Study 1) consecutively enrolled participants from clinic or hospital settings or investigated a specific sub-type of people with PD and STN-DBS. The specific recruitment strategies were,

i) Brisbane-based neurology clinic: People with PD who had undergone STN-DBS and who had elected to be contacted regarding relevant research projects. These individuals were sent a participant information sheet by the neurology clinic staff, that outlined what the study involved and what potential benefits and risks may be associated with participation (Appendix B). In total, 133 people from this Brisbane-based neurology clinic were sent an invitation to participate letter.

ii) Local DBS support group: Members of this DBS support group were emailed an invitation to participate. The invitation outlined the requirements of participation and the potential benefits and risks of participation (Appendix C). Interested persons were encouraged to contact the student researcher via phone or email for initial screening and to receive the full-length participant information sheet and/or to ask any questions. In total, 140 people from this support group were emailed regarding this research.

After considering participant information sheet, interested individuals were encouraged to call the student researcher directly via phone or email. As part of this initial conversation, prospective participants were asked specific questions about any known medical conditions and their physical activity capacity to determine their eligibility for inclusion.

6.1.2 Inclusion criteria

People clinically-diagnosed with idiopathic PD (Hughes et al., 1992) who had undergone bilateral STN-DBS surgery no less than 12-months earlier were recruited for the research. The rationale for only involving participants who had been receiving STN-DBS therapy for at least 12-months was guided by the understanding that axial symptoms of PD may initially improve during the 12-months following the procedure, but tend to deteriorate between 12- and 36-months (St George et al., 2010). Furthermore, to limit the risk of prospective participants having conditions that may have affected their capacity to complete the movement tasks and/or provide written informed consent (World Medical Association., 2011), participants were considered for inclusion if they were;

i) Aged between 50 and 75 years
ii) Independently living within the community
iii) Able to stand and ambulate without assistance
iv) Free of significant visual disorders that were not corrected with prescription lens (Salive et al., 1994)
v) Free of any medical conditions and/or significant musculoskeletal problems that could adversely affect their postu
vi) ral stability or mobility
vii) Free of signs of dementia based on the Standardised Mini-Mental State Examination (score >24) (Molloy, Alemayehu, & Roberts, 1991; Vertesi et al., 2001) (Appendix D).
viii) Not taking medications (other than their anti-parkinsonian medications) that would adversely affect their performance on the assessments of postural stability or mobility.

A check list was completed over the phone or via email to determine the participants' initial eligibility for inclusion (Appendix E).

6.1.3 Sample size justification

Given the lack of existing data concerning the movement patterns of the head and trunk segments for people who have undergone STN-DBS surgery, an *a priori* sample size estimate was derived from data collected for optimally-medicated people with PD. Specifically, symmetry of head and trunk movements during walking were used to derive a sample size estimate. Based on these data, it was determined that a minimum of 12 participants was required to detect changes in the harmonic ratio, one of the primary outcomes of this dissertation (discussed in section 6.3.1.1), between different stimulation parameters (Effect Size≥0.82, Power=0.8, p=0.05). As such, a target sample of 24 participants was deemed adequate to not only ensure statistical power but also accommodate an attrition rate of up to 50%. The rationale for allowing for such a high attrition rate was guided by previous research, which has highlighted that people with PD whose primary motor symptom is resting tremor are more likely not to be able to tolerate low-frequency stimulation (Moreau et al., 2008; Xie et al., 2015).

6.2 Data collection

People who agreed to participate were invited to attend a single testing session held within a dedicated research space at a specialist neurology clinic in Spring Hill, Brisbane. Participants were assessed following overnight withdrawal of their anti-parkinsonian medications (≥12 hours) to minimise the potential risk of fluctuations in the efficacy of pharmacological therapies influencing the measures of gait stability (Pelicioni et al., 2018).

6.2.1 Questionnaires

Participants complete a series of paper-based questionnaires that included:

i) A demographics and health questionnaire, which collected basic demographic details (e.g. date of birth, years of education), medical history (e.g. date of

diagnosis, date of surgery, medications) and the number of falls experienced in the previous 12-months (Appendix F).

ii) The 6-item Activities-specific Balance Confidence scale (ABC-6), which was used to evaluate balance confidence (Peretz, Herman, Hausdorff, & Giladi, 2006). This short-form version has been shown to have good agreement with the original 16-item scale and is reported to be an independent predictor of recurrent falls in people with PD (Cole, Rippey, Naughton, & Silburn, 2016). This questionnaire is scored as the average of the participant's responses to 6 questions, which are each appraised on a scale of 0 to 100%. Each question asks participants "*How confident are you that you will not lose your balance or become unsteady*" while performing a range of everyday tasks (e.g. standing on tiptoes and reaching). Scores closer to 100% represent greater balance confidence (Appendix G).

iii) The Revised Freezing of Gait Questionnaire, which is a reliable tool for assessing the extent to which people with PD experience symptoms of freezing of gait (Nieuwboer et al., 2009). The questionnaire includes a single question that asks people with PD whether they have experienced freezing of gait during the past month. If participants answer 'yes', they are asked to answer 8 further questions (scored on a Likert scale) that seek to determine the extent to which these symptoms impact their day to day lives. Higher scores represent a greater severity of freezing of gait (Appendix H).

iv) The 8-item Parkinson's disease Questionnaire (PDQ-8), which is a PD-specific quality of life measure that assesses the impact of PD symptoms on an individual's ability to perform common activities of daily living (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997a). The short-form questionnaire was developed from the original 39-item version and has been shown to be a valid and reliable disease-

specific quality of life measure (Hagell & Nygren, 2007; Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997b). Higher scores are representative of poorer quality of life (Appendix I).

These questionnaires were administered while the participant's STN-DBS parameters were programmed to chronic stimulation, as recommended by their treating neurologist. Where applicable, details were cross checked with medical records.

6.2.2 STN-DBS parameters

During the single testing session, participants were assessed under two stimulation conditions, with data collection taking between 5 and 6 hours (including enforced rest breaks). On arrival, participants were asked to produce their completed and signed informed consent form and questioned about their last administration of anti-parkinsonian medication to ensure an overnight withdrawal (≥12 hours) had taken place. If participants had not undertaken the required overnight withdrawal of their antiparkinsonian medication, their data were not included in subsequent analyses and another testing session date was offered. For those who had undertaken the overnight withdrawal, a specialist DBS nurse acquired information about the participant's stimulation parameters, including the biological impedance for the DBS device. This was done by using a handheld programmer that wirelessly communicated with the implanted pulse generator through the skin. Using this information, the nurse determined the TEED for each participant at their chronic (high-frequency) stimulation (Equation 6.1). Specifically, the TEED was calculated by determining the product of the voltage amplitude, stimulation frequency, pulse width and biological impedance for each participant (Koss et al., 2005).

$$\text{TEED}_{1\text{ second}} = \frac{\text{Voltage}^2 \times \text{ frequency} \times \text{ pulse width}}{\text{impedance}} \times 1\text{ second}$$

Equation 6.1

A double-blinded randomised cross-over study design, using a one-to-one allocation ratio, was employed to investigate the effects of two stimulation conditions on managing symptoms of postural instability and gait difficulties. To facilitate randomisation, a member of the research team who had no direct involvement in the assessment of participants prepared a computer-generated randomisation sequence to determine the order of stimulation conditions for each participant. This list was subsequently provided to the DBS nurse only, as she was responsible for checking and adjusting the stimulation parameters for each participant. Both the participant and the student researcher conducting the data collection sessions were blinded to the order of stimulation conditions. Where a change of STN-DBS parameters was not required, for example, if the first testing condition was high-frequency (usual chronic) stimulation, the nurse would conduct a "mock" change. Data analyses were performed by the student researcher using the blinded data, with the group classifications only re-identified after the statistical procedures were completed. The two stimulation conditions were:

(i) *High-frequency stimulation:* STN-DBS electrodes bilaterally active with the high-frequency stimulation (>100 Hz) that the participant's received during chronic stimulation.

(ii) *Low-frequency stimulation:* STN-DBS electrodes being bilaterally set to 60 Hz (Figure 6.1) with the voltage increased to maintain the TEED of their high-frequency stimulation condition; as per the TEED calculation. A worked through example can be found in Appendix J.

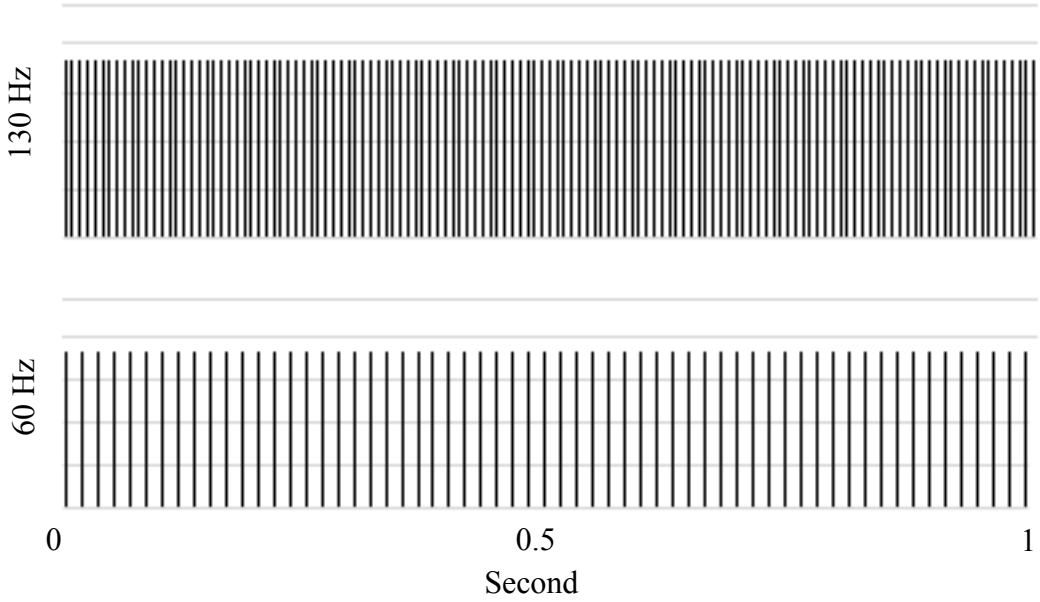

Figure 6.1: Representation of frequency of stimulation over one second for the high-frequency (top) and low-frequency (bottom) conditions. Note that each vertical line depicts the timing of each stimulation delivered to the active electrodes for the two therapeutic states.

After the participants had completed all of the assessments under the first stimulation condition, they were required to take a one-hour break to consume lunch and to minimise the risk of fatigue (Table 6.1). This break also ensured adequate time for the change in stimulation parameters to take full effect (i.e. wash in) and limited the risk of any carry-over effects between stimulation conditions (Moro et al., 2002). At the completion of the day's testing, participants were allowed to take any prescribed anti-parkinsonian medications and were changed back to their clinically programmed STN-DBS parameters by the DBS nurse before leaving the clinic. To ensure that both the participant and the student researcher remained blinded to the order of testing, the DBS nurse made this final change to the participant's stimulation parameters, regardless of whether it was necessary (i.e. the change was simulated if the participant finished with their usual high-frequency stimulation).

Table 6.1: Timeline overview of single testing session.

Elapsed Time (*hh:mm*)	**Role**
-12:00	Anti-parkinsonian medication withdrawal
00:00	Participant arrived, introduction to the study, consent form signature, paper-based questionnaires.
00:20	DBS nurse calculated the TEED for the participant's high-frequency stimulation
00:40	DBS nurse changed (or not) the participant's STN-DBS parameters based on the established randomised allocation. An enforced 1-hour wash in took place with equipment preparation being done while the participant was seated.
01:50	Symptom severity assessment (See section 6.2.3)
02:10	Walking (see section 6.2.4) and standing (see section 6.2.6) assessments
02:40	DBS nurse changed STN-DBS parameters for the other condition. An enforced 1-hour wash in took place while the participant ate lunch.
03:50	Symptom severity assessment (See section 6.2.3)
04:10	Walking (see section 6.2.4) and standing (see section 6.2.6) assessments
04:40	DBS nurse changed (or not) the participant's STN-DBS parameters back to their high-frequency stimulation.
05:00	Conclusion of day and debrief with participant

Abbreviations: **DBS:** Deep brain stimulation; **STN-DBS:** Deep brain stimulation of the subthalamic nucleus; **TEED:** Total electrical energy delivered.

6.2.3 Symptom severity assessment

To clinically assess changes in symptom severity to the different stimulation conditions, an experienced movement disorder scientist who was blinded to the participants' stimulation condition administered the Movement Disorders Society-Sponsored Revision of the UPDRS. The UPDRS comprises four sub-sections that evaluate; i) changes in behaviour, mood and mentation; ii) difficulties with activities of daily living; iii) motor symptoms; and iv) complications associated with therapy (Goetz et al., 2008). Importantly, the UPDRS has been shown to have high internal consistency, validity and reliability (Goetz et al., 2008). Given this dissertation aimed to investigate how motor symptoms responded to changes in STN-DBS, only Part III of UPDRS (motor sub-scale) was used. The motor sub-scale includes items that are each assessed on a 5-point Likert scale (scores range from 0-4). The scores for each item were

summed to yield the total score, with greater scores being representative of greater motor symptom severity. This assessment is routinely used in clinical practice and clinical research.

6.2.4 Walking tasks

Following completion of the questionnaires and the clinical assessments, participants completed a series of barefoot gait tasks that are common to activities of daily life. A stopwatch was used to record the time taken to complete each task, while a 30-second rest period was enforced for between attempts. The specific walking tasks included:

i) Comfortable walking: Participants performed two straight line walking trials at a self-selected comfortable pace along a 14-metre long, level walkway. This was performed for the quantification of gait stability (see Section 6.3.1.1).

ii) 6-metre walk test: Participants were timed with a stopwatch as they walked as quickly as possible along a straight 6-metre long walkway, in accordance with the test's established procedures (Hubble, Silburn, Naughton, & Cole, 2016). Participants performed this task twice, with the average time for the two 6-metre walks used for the analyses.

iii) The 6-metre Timed Up and Go Test: Participants started in a seated position with their feet flat on the floor, knees at 90 degrees, their back flat against the backrest, and their arms resting on the armrests. Following the instruction of "GO", participants stood and walked at a brisk, but comfortable pace to a line on the floor six metres away, turned 180° and returned to the seated position. The average time taken to complete the course during two separate attempts was used for the analyses. Performance on the Timed Up and Go test has been shown to differentiate prospective PD fallers from non-fallers (Kerr et al., 2010).

6.2.5 Head and trunk movement

Assessments of head and trunk movement during walking were completed using two light-weight tri-axial accelerometers (21 x 16 x 7.5 mm) (Noraxon Inc., Scottsdale, AZ) that were firmly affixed to a headband positioned over the occipital protuberance of the skull (Figure 6.2) and to the skin overlying the spinous process of the 10th thoracic vertebra (Cole et al., 2017; Cole et al., 2014; Hubble et al., 2018). During the comfortable walking task, accelerations were recorded at 1500 Hz and were wirelessly telemetered to a Telemyo DTS unit connected to a laptop computer running the MyoResearch XP (v1.08) software. Acceleration data for each trial were truncated to include 8 complete gait cycles (i.e. 4 right/4 left).

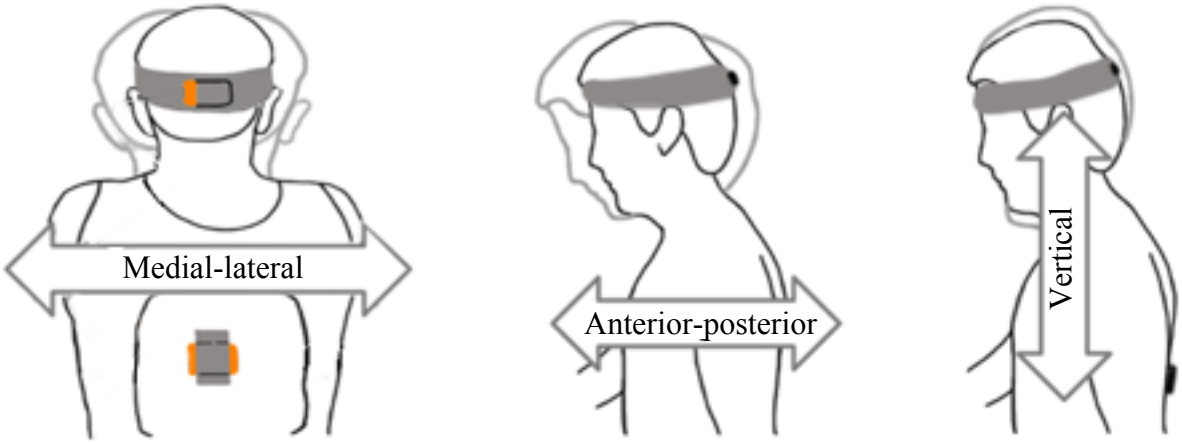

Figure 6.2: Illustration depicting the specific positioning of the tri-axial accelerometers on the head and trunk and the directions in which accelerations are captured.

6.2.6 Standing postural stability

Participants completed two 30-second trials that involved standing barefoot on a portable force plate (Advanced Mechanical Technology, Watertown MA, USA) with their hands at rest by their sides and their feet 10 cm apart with their eyes open (Figure 6.3). The location of the participants feet was marked on the force plate for consistency between trials. Participants were asked to focus their gaze on a point situated 10 meters directly in front of

them and to refrain from talking, unless necessary. For any trials where the participant was unable to stand quietly (e.g. they spoke, coughed, sneezed), the task was repeated. COP data were collected at 200 Hz.

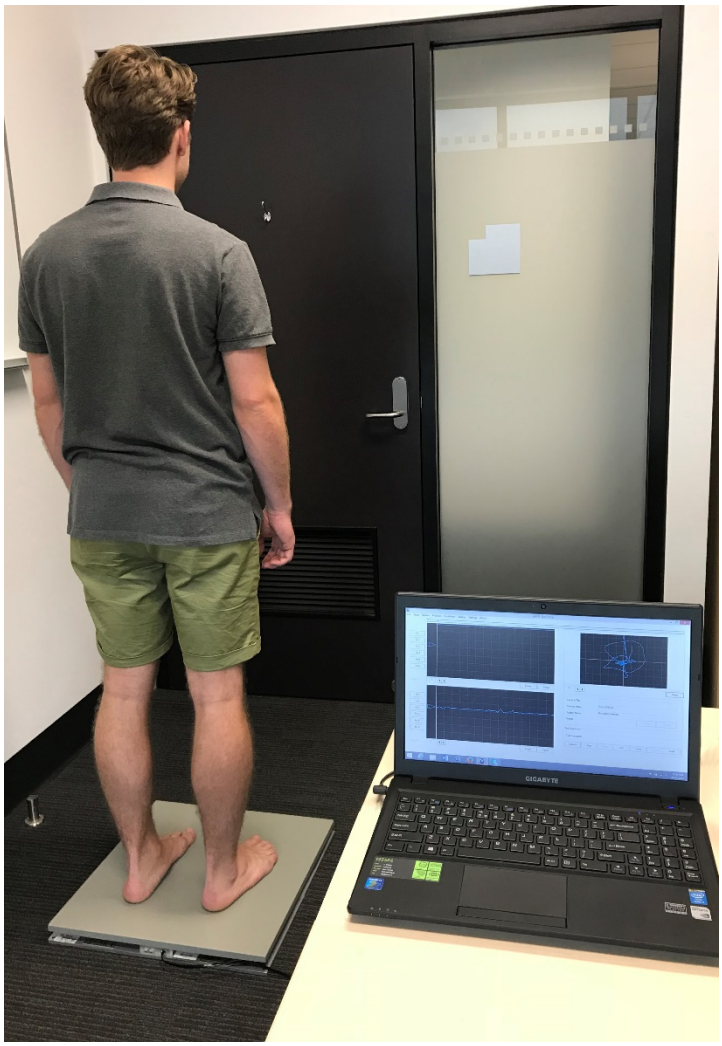

Figure 6.3: Photograph of the force plate set-up for the capture of centre of pressure data during the assessment of standing postural stability. Image printed with permission.

6.2.7 Medical imaging

In line with standard clinical practice, all participants had preoperative magnetic resonance imaging scans taken prior to undergoing STN-DBS to aid the neurologist with identifying the ideal targets for the electrodes. Additionally, postoperative computed

tomography scans were performed to confirm the final positions of the two implanted electrodes. Following receipt of the participants' consent, these pre- and post-operative images were acquired so that electrode location could be determined for this dissertation. These images were acquired from the neurosurgical team that performed the STN-DBS surgery.

6.3 Data analysis

6.3.1 Acceleration signal

Due to the nature via which tri-axial accelerometers collect data, the raw three-dimensional accelerations recorded by these units included both accelerations relating to movement and gravitational acceleration. To separate the movement-related accelerations from the acceleration due to gravity (constant value of -9.81 m/s^2), a previously described and extensively used rotational algorithm was employed (Kavanagh, Barrett, & Morrison, 2005; Kavanagh, Barrett, & Morrison, 2004; Kavanagh, Morrison, et al., 2005; Kavanagh, Morrison, James, & Barrett, 2006). In short, this procedure uses an extension of trigonometry to mathematically rotate (transform) the three-dimensional accelerations collected by the wearable devices to ensure that gravitational acceleration is only represented along the vertical axis. Following this process, it was possible to subtract the gravitational constant and analyse the movement-related accelerations separately.

Following transformation of the data and the removal of the gravitational component, accelerations were low-pass filtered using a fourth-order Butterworth filter with a cut-off frequency of 30 Hz; consistent with research (Kavanagh et al., 2004; Sejdic, Lowry, Bellanca, Redfern, & Brach, 2014). The continuous acceleration data were subsequently divided into individual gait cycles (i.e. data from one-foot contact with the ground to the subsequent foot contact with the ground for the same foot) using a peak-identification algorithm (Figure 6.4).

Similar algorithms have been used in previous research (Cole et al., 2017; Hubble et al., 2018; Hubble et al., 2016) and are based on the understanding that the peaks in vertical trunk accelerations coincide with the timing of individual heel contacts during unconstrained gait (Henriksen, Lund, Moe-Nilssen, Bliddal, & Danneskiod-Samsoe, 2004; Lowry, Lokenvitz, & Smiley-Oyen, 2012; Lowry et al., 2009).

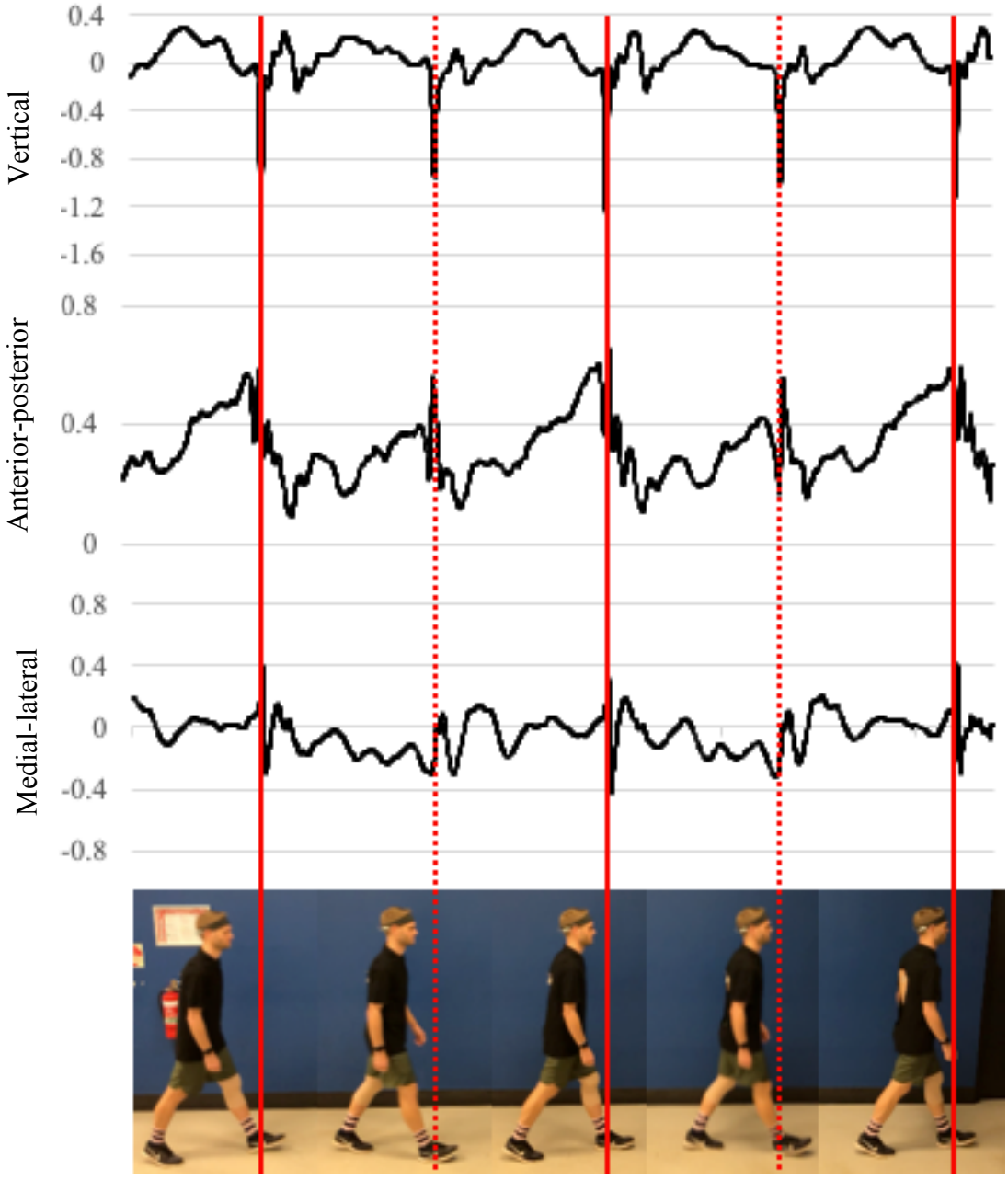

Figure 6.4: Acceleration signal for each axis with vertical lines for left (solid) and right (dotted) heel contacts. Image printed with permission.

6.3.1.1 Gait stability

To provide insight into gait stability, the harmonic ratios of the head and trunk accelerations were calculated. Using the filtered accelerations for each individual gait cycle, the harmonic ratio was calculated for the anterior-posterior, medial-lateral and vertical directions, respectively. To do so, after the accelerations had been segmented into individual gait cycles, accelerations were analysed in the frequency domain using the Fourier series (Oppenheim & Willsky, 1997). The Fourier series identifies any periodic function defined between two time points, which was defined as the time between subsequent foot contacts of the same foot, that are continuously repeated to be expressed as an infinite sum of sinusoids and cosines (Zill, Wright, & Cullen, 2011). By defining a single gait cycle between two time points, a Fourier series can be calculated for each gait cycle; this process is often referred to as the Discrete Fourier Transformation in the literature (Bellanca et al., 2013b). Via this process, the harmonic coefficients (referred to as harmonics) for each acceleration component are identified and extracted (Figure 6.5) (Bellanca et al., 2013b), with stride duration representing the fundamental frequency (Smidt, Arora, & Johnston, 1971). While walking at a cadence of 60 steps/min or above, the majority of the power in walking-related accelerations occurs at or below 10 Hz (Bellanca et al., 2013b; Kavanagh, Morrison, et al., 2005); hence, the harmonic ratio was calculated using the first 20 harmonics (i.e. 10 odd and 10 even) (Bellanca et al., 2013b; Kavanagh, Barrett, et al., 2005; Kavanagh, Morrison, et al., 2006; Lowry et al., 2010; Lowry et al., 2012; Smidt et al., 1971).

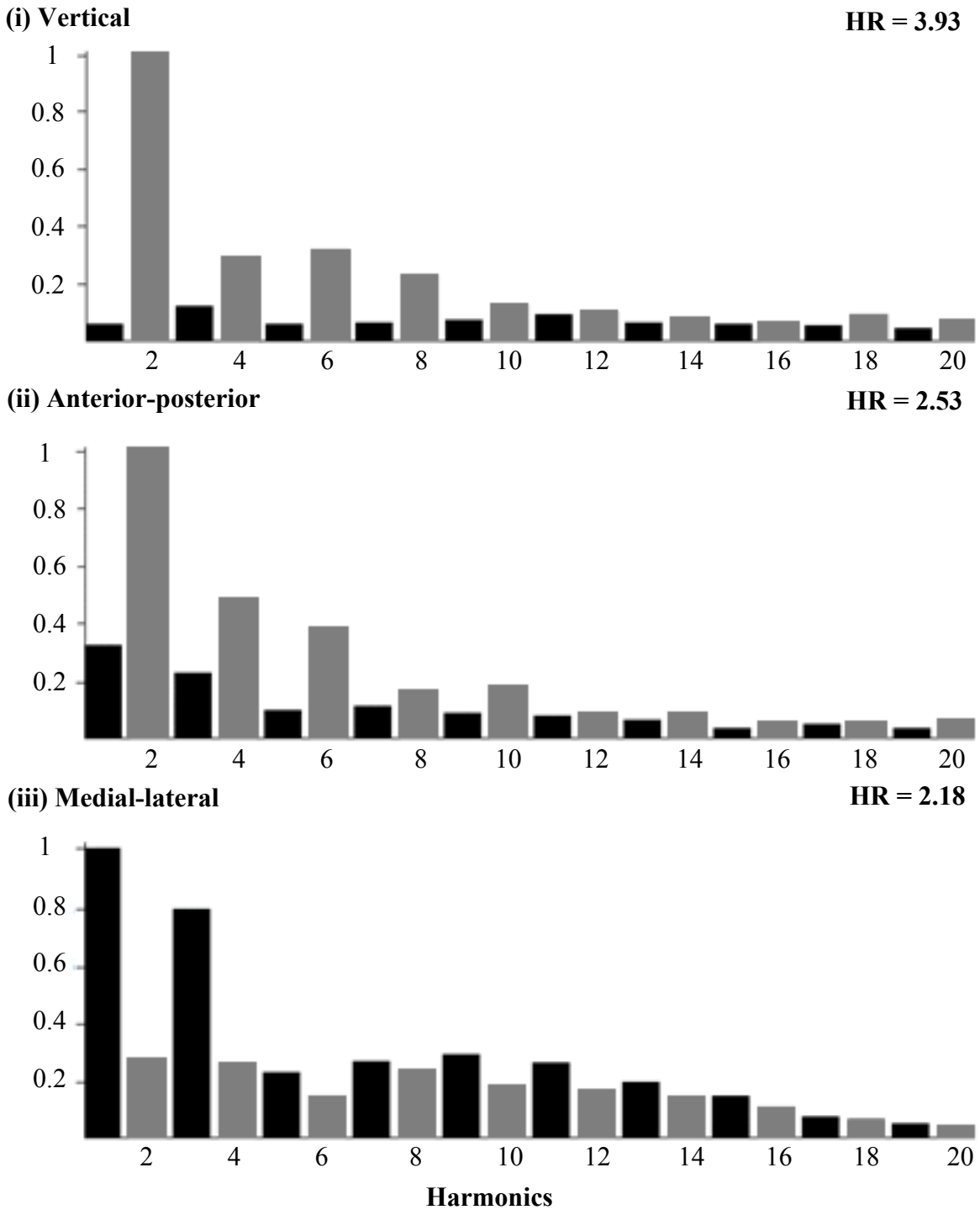

Figure 6.5: Exemplar harmonics of the (i) vertical, (ii) anterior-posterior and (iii) medial-lateral acceleration signals with even harmonics in grey and odd harmonics in black. Note that the magnitude of the harmonics is expressed as an arbitrary unit normalised to 1.

During gait, the accelerations in both the anterior-posterior and vertical directions comprise two major peaks that coincide with the left and right steps in any given gait cycle. Given anterior-posterior and vertical accelerations occur in pairs during walking, the even harmonics (i.e. harmonics 2, 4, 6, etc) in the frequency domain are considered to represent the in-phase components of the signal, while the odd harmonics (i.e. harmonics 1, 3, 5, etc) represent the out-of-phase components (Latt et al., 2009; Lowry et al., 2010; Menz, Lord, & Fitzpatrick, 2003a, 2003b; Yack & Berger, 1993). On the basis of this understanding, the anterior-posterior (Equation 6.2) and vertical harmonic ratios (Equation 6.3) were calculated by dividing the sum of the first 10 in-phase (even) harmonics by the sum of the first 10 out-of-phase (odd) harmonics (Smidt et al., 1971) to provide insight into the participants' gait stability.

$$\textit{Anterior-posterior harmonic ratio} = \Sigma \textit{ Even harmonics} / \Sigma \textit{ Odd harmonics}$$

Equation 6.2

$$\textit{Vertical harmonic ratio} = \Sigma \textit{ Even harmonics} / \Sigma \textit{ Odd harmonics}$$

Equation 6.3

In contrast to the anterior-posterior and vertical components, which are characterised by pairs of acceleration peaks during each gait cycle, the medial-lateral component is characterised by a single peak that coincides with the body being accelerated toward the contralateral side to the supporting limb. Given medial-lateral accelerations peak only once during each gait cycle, the odd harmonics represent the in-phase components of the movement while the even harmonics characterise the out-of-phase components. Therefore, to calculate the medial-lateral harmonic ratio (Equation 6.4), the sum of the first 10 odd (in-phase) harmonics was divided by the sum of the first 10 even (out-of-phase) harmonics (Menz et al., 2003b).\

$$\textit{Medial-lateral harmonic ratio} = \Sigma \textit{ Odd harmonics} / \Sigma \textit{ Even harmonics}$$

Equation 6.4

In all cases, higher harmonic ratios were considered to represent greater movement symmetry within a stride (Bellanca et al., 2013b). Of the research that has utilised acceleration-based measures to evaluate gait stability in people with PD, the harmonic ratio is reported to be one of the most commonly-used and sensitive measures (Hubble et al., 2015). All procedures for the calculation of harmonic ratios were completed using a custom script developed in MATLAB (Version 7.13, The MathWorks, USA).

6.3.1.2 Movement amplitude

To provide insight into the amplitude of head and trunk movements (i.e. accelerations) relative to zero in the anterior-posterior, medial-lateral and vertical directions, the root mean square was calculated separately for each axis (Menz et al., 2003b). Root mean square accelerations were calculated for the same gait cycles used for the harmonic ratio calculations, but used the time-series data, rather than their frequency transformations (Equation 6.5).

$$\textit{Root Mean Square Acceleration } (m/s^2) = \sqrt{[(a^2_0 + a^2_1 + \cdots a^2_n)/ N]}$$

Equation 6.5

All procedures for the calculation of root mean square accelerations were completed using a custom script developed in MATLAB (Version 7.13, The MathWorks, USA).

6.3.1.3 Temporal measures

Given that the peaks in vertical trunk accelerations coincide with individual heel contacts during unconstrained gait (Henriksen et al., 2004; Lowry et al., 2012; Lowry et al., 2009), temporal measures were calculated by identifying the timing of foot contact using a peak detection technique that was applied to the vertical trunk acceleration data (Cole et al., 2017; Hubble et al., 2018; Hubble et al., 2016).

- Cadence (steps/min): A step was defined as the time elapsed between two consecutive vertical peaks in the vertical trunk acceleration data. Cadence was calculated by dividing the number of steps taken during each trial by the time taken (in minutes) to complete the trial.
- Step time (seconds): Step time was defined as the elapsed time between two consecutive peaks in the vertical trunk acceleration data.
- Step time variability (milliseconds): This was calculated as the standard deviation of the step times collected during a trial. Greater variability values were considered to represent a less rhythmic walking pattern (Roemmich et al., 2012).

6.3.2 Force plate derived

6.3.2.1 Quiet standing

For this project, measures of standing postural stability were derived from the COP data collected by the portable force plate (section 6.2.8) using the BioAnalysis software (Advanced Mechanical Technology, Watertown MA, USA) (Figure 6.6). Measures included;

- Anterior-posterior sway range (mm): Linear distance between the most anterior and posterior positions of the COP during each 30-second trial.
- Medial-lateral sway range (mm): Linear distance between the left-most and right-most positions of the COP during each 30-second trial.

- Variability of anterior-posterior sway (mm): Standard deviation of the anterior-posterior COP data.
- Variability of medial-lateral sway (mm): Standard deviation of the medial-lateral COP data.
- Average velocity (cm/second): COP path length, measured in centimetres, divided by the duration of the trial, assessed in seconds.
- Sway area (mm^2): 95^{th} percentile of an ellipse fitted to the overall COP trace.

These measures have been used to find differences in sway characteristics between people with PD compared to age-matched controls (Blaszczyk & Orawiec, 2011; Ickenstein et al., 2012; Qiu et al., 2013). Furthermore, it has been found that greater PD severity resulted in an increased extent of sway (Frenklach et al., 2009) and PD fallers having more sway than non-fallers (Kerr et al., 2010).

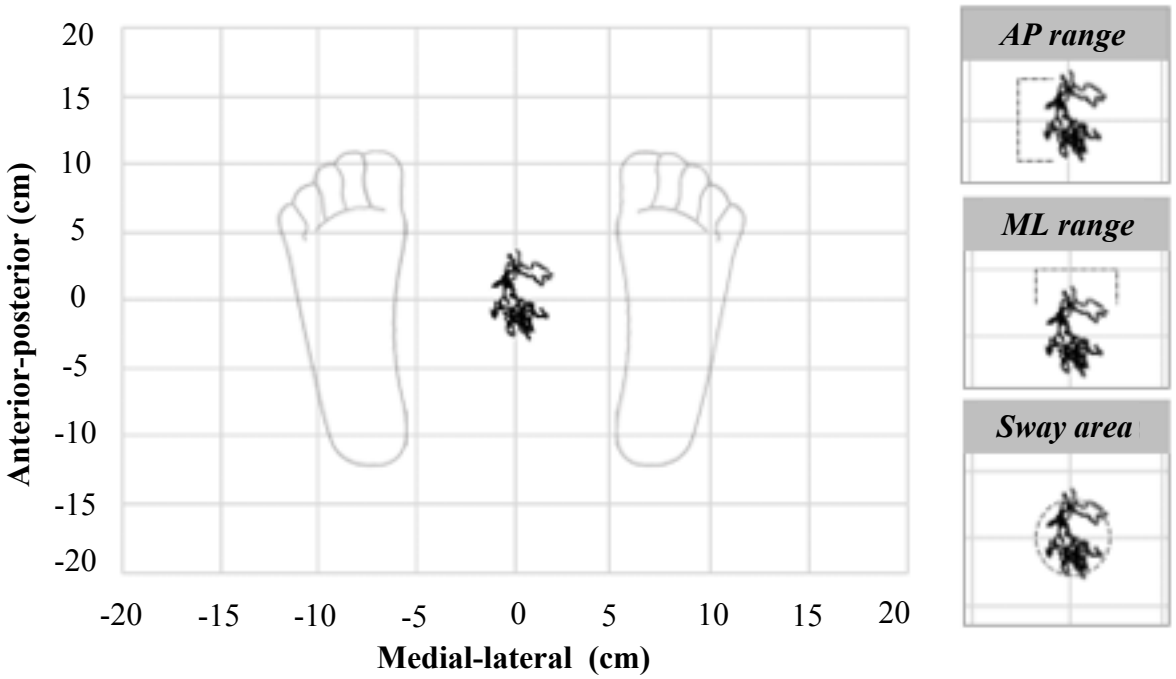

Figure 6.6: Exemplar centre of pressure data, with illustrations of the feet's position and the described outcomes included for clarity.

Entropy analysis is a measure of regularity providing a number between zero and two that indicates the likelihood of predicting future data based on knowledge of past data from the same time series (Pincus, 1991). Richman and Moorman refined the approximate entropy formula to develop the sample entropy as a measure of both complexity and regularity for the application of human cardiovascular physiology (2000). Across a time series, data with a high degree of regularity (i.e. predictability) would result in an entropy value closer to zero, while values closer to two would suggest greater irregularity in the time series (Pincus, 1991; Richman & Moorman, 2000) (Figure 6.7). The sample entropy measure has been applied to many other physiological and biomechanical sources, including COP data collected during quiet stance. It has been suggested that a more regular COP pattern (low entropy) is indicative of a more rigid system (Donker, Ledebt, Roerdink, Savelsbergh, & Beek, 2008); that is, a system that is less able to react to unexpected perturbations (Borg & Laxaback, 2010). This is exemplified in populations who exhibit a decline in postural stability, including aging populations (Choy, Brauer, & Nitz, 2003) and people with neurological diseases (Donker et al., 2008), for whom postural sway has been documented to be more regular. To provide insight into the regularity of postural sway in people with PD following STN-DBS during the two stimulation conditions, sample entropy analysis was conducted. To facilitate this process, the instantaneous velocities of anterior-posterior and medial-lateral COP data were used, and the resulting sample entropies were expressed on a scale from zero to two (increased values corresponded with a less regular sway pattern). For the calculation of sample entropy, the input parameters of m=2 and r=0.30 were used, in accordance with research (Ramdani, Seigle, Lagarde, Bouchara, & Bernard, 2009).

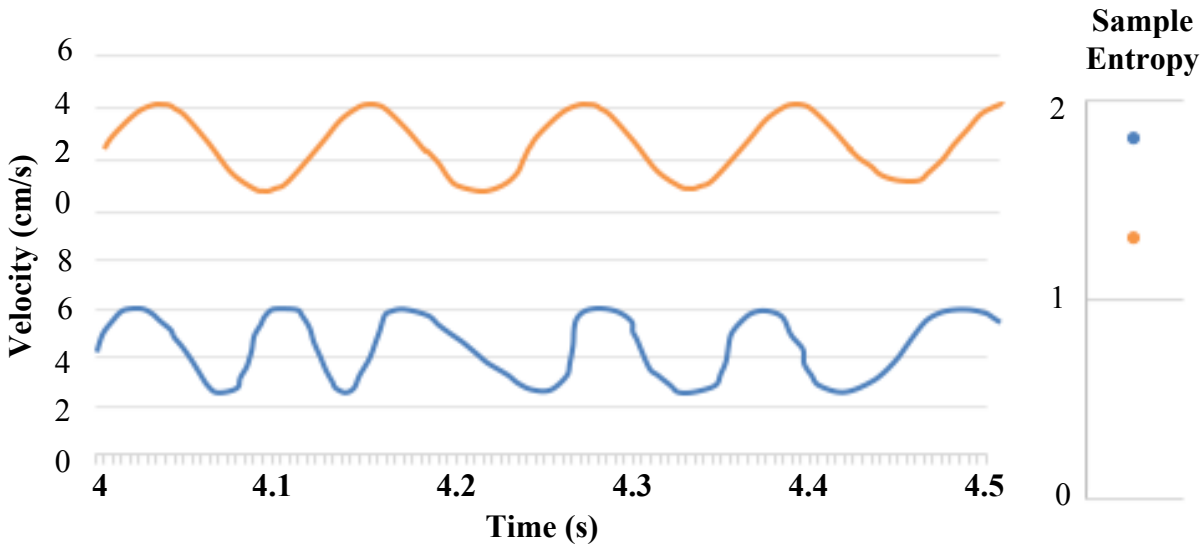

Figure 6.7: Exemplar centre of pressure velocity data illustrating, more regular sway velocity (orange) which corresponds to higher sample entropy and a less regular sway velocity (blue) which corresponds to lower sample entropy.

6.3.2.2 Gait initiation

Measures of the gait initiation were derived from COP data collected during the participants' initiation of the walking tasks. COP data were divided into two phases; i) the postural phase; and ii) the locomotion phase, based on research (Breniere & Do, 1991). The postural phase included all data between the start of the trial and the point at which the COP reached its maximum posterior and lateral displacement (Figure 6.8) (Elble, Moody, Leffler, & Sinha, 1994). In contrast, the locomotion phase included all COP data between the end of the postural phase and the point at which the trailing leg (the stance leg during the initial step) left the force plate (i.e. the participant was no longer in contact with the force platform) (Elble et al., 1994). During each phase, anterior-posterior sway (mm), medial-lateral sway path length (mm), COP path length (cm), average velocity (cm/seconds) and sway area (mm^2) were derived (Section 6.3.2.1 for previous description). The calculation of these outcomes for both the

postural and locomotion phases was completed using a custom script developed in Microsoft Excel.

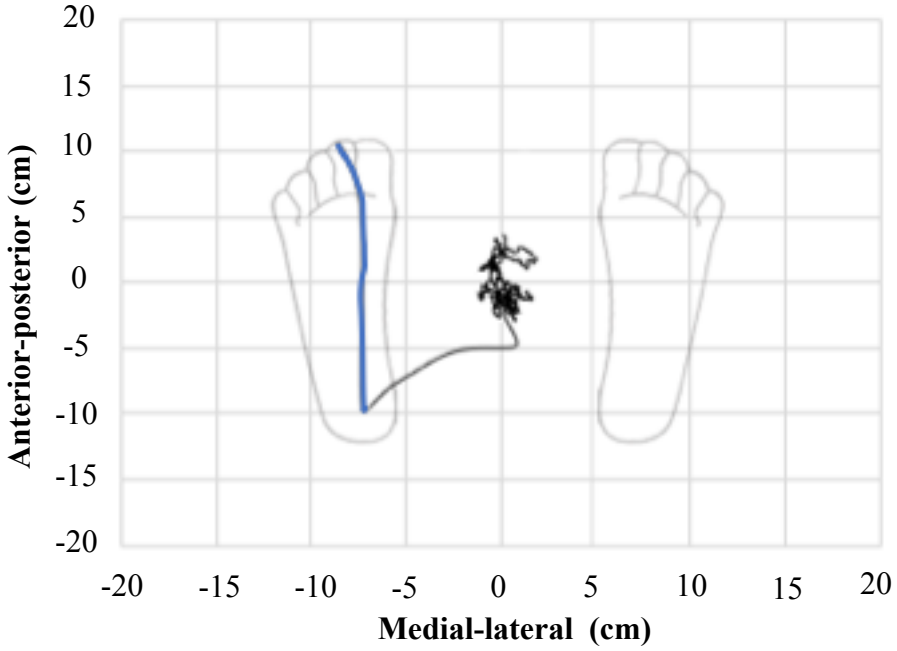

Figure 6.8: Centre of pressure trace to identify the postural phase (black) and locomotion phase (blue). Note: Trial illustrates typical data for a walking trial initiated with a right step.

6.3.3 Electrode location

Individual DBS electrodes were identified by merging the postoperative computed tomography scans with the preoperative magnetic resonance imaging using 3D Slicer v4.11 to manually mark the mid-point appearing as hyperintense voxels due to metallic artefact (Figure 6.9) (Fedorov et al., 2012). Images were aligned along the Anterior and Posterior Commissures to normalise brain orientation using acpcdetect v2.0 (NeuroImaging Tools & Resources Collaboratory, https://www.nitrc.org). The three-dimensional coordinates for the ideal neurosurgical target within each STN were determined separately for each hemisphere of the brain by an experienced neurologist (Dembek et al., 2019). It is worth noting that the marking of both the ideal target in the STN and the DBS electrode is a manual process, and thus,

encompasses confounds such as bias and inter-operator variability. In an attempt to limit the risk of these potential confounds, these processes were completed by the same experienced neurologist and experienced data analyst for all the DBS electrodes; consistent with recent work (Sinclair et al., 2018). These data were subsequently used to calculate the distance (in millimetres) between the midpoint of each electrode and the ideal target. The difference between the ideal and actual location of the active electrode was expressed in the form of X (negative = more medial), Y (negative = more posterior) and Z (negative = more inferior) distances, which were combined to provide a Euclidean distance. All distance calculations were performed automatically using a custom script written in Python v3.7 (Python Software Foundation).

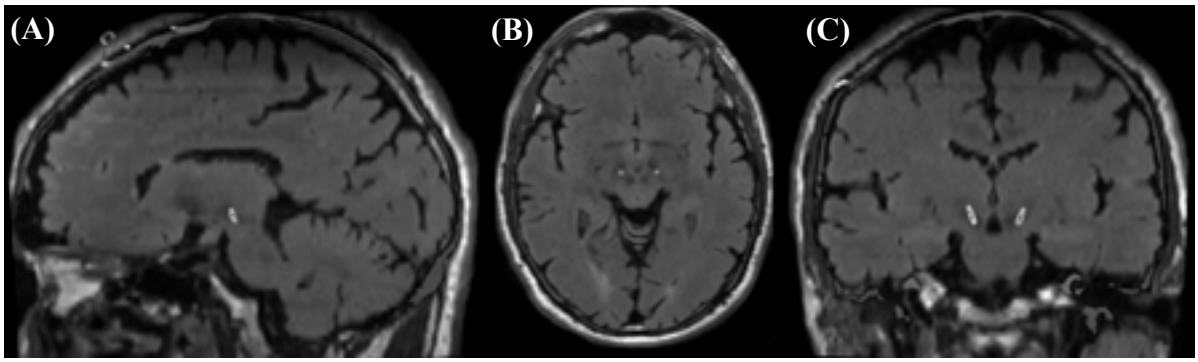

Figure 6.9: Merged magnetic resonance imaging and computed tomography scans depicting the (A) sagittal, (B) axial, and (C) coronal images used to classify electrode positions. The hyperintense voxels due to metallic artefact correspond with the implanted electrodes into the STN.

6.4 Statistical analysis

Although each of the experimental studies had its own specific aims, there are certain aspects of the statistical procedures that can be discussed together. As the specific aims of this research did not require the study cohort to be divided into specific sub-groups (e.g.

retrospective fallers vs. non-fallers), demographic data were reported as aggregate means and standard deviations for the entire group.

To determine the suitability of using parametric statistical procedures to compare the different stimulation conditions, the Shapiro-Wilk test was used to assess the normality of the continuous outcome measures. In situations where the test of normality returned a p-value that was less than 0.05, the data were not considered to be normally distributed. For Study 2, which used correlation statistics to establish the relationship between common clinical measures of postural stability and gait and more novel accelerometer-based measures, the non-parametric Spearman's Rho test was used in place of the Pearson's correlation coefficient, as some of the clinical scales were subject to ceiling or floor effects that impacted their normality. In addition to the correlation analyses, linear regression was performed to examine whether clinical measures could explain a significant proportion of the variance in head and trunk harmonic ratios during walking.

To examine differences between high- and low-frequency stimulation conditions with respect to the clinical assessments, accelerometer-based and force plate measures (Studies 3 and 4), linear mixed model analyses were used. Compared with other repeated measures approaches (e.g. repeated measures analysis of variance), linear mixed model analyses are considered to be more flexible for use with datasets that include missing values and/or an uneven number of observations for different participants (Barton & Peat, 2014). As highlighted in the sample size justification (section 6.1.3), it was anticipated that not all of the randomly recruited participants would tolerate low-frequency stimulation (Moreau et al., 2008; Xie et al., 2015). As such, this statistical procedure was considered to be better suited for accommodating any participants who were unable complete some of the assessments under both stimulation

conditions. Repeated factors were added to include different stimulation condition (2 levels; high-frequency, low-frequency) and, where applicable, walking task. To maximise the ecological validity of the studies' findings, walking speed was not constrained in this study; that is, participants were asked to walk at their own self-selected and comfortable speed. However, given that variations in walking speed are known to influence the magnitude of segmental accelerations (Menz et al., 2003b), walking speed was included as a covariate in each of the linear mixed model analyses. As such, estimated marginal means and standard errors derived from these models are reported in these studies. All statistical analyses were conducted using the Statistical Package for the Social Sciences (Version 25, New York, USA) and the level of significance for all statistical tests was set at $p < 0.05$.

CHAPTER 7: STUDY II - Gait Stability in Parkinson's Disease who have STN-DBS: Do Objective Measures Add Insight?

7.1 Preface

The systematic review (Study I) suggested that research concerning the potential utility of alternate STN-DBS parameters reported outcomes almost exclusively based on clinical measures. While these measures are well-established and routinely used in clinical practice to monitor changes in symptom severity, assessments such as the 'pull test', are ultimately subjective in nature. Objective measures of postural instability derived from wearable sensors may provide supplemental insight into postural stability in people with PD who have STN-DBS. Study II aimed to determine whether objective measures of gait stability derived from segmental accelerations can provide unique information that complements the clinical measures of symptom severity, postural stability, balance confidence and mobility that are traditionally used to monitor people with PD who have STN-DBS.

7.2 Introduction

STN-DBS has become a common procedure for the ongoing management of PD symptoms (Thevathasan & Gregory, 2010). However, in response to the uncertainty regarding the effectiveness of STN-DBS for managing postural instability (Fasano et al., 2010), recent studies have shown STN-DBS with alternate stimulation parameters (Conway et al., 2019) can improve performance on established clinical scales measuring gait and postural instability (Khoo et al., 2014; Xie et al., 2015). While clinical measures have their shortcomings, they do benefit from being easy to administer in busy clinical and hospital settings and, importantly, have been shown to provide insight into complex postural stability dysfunction in optimally-medicated PD populations (Hubble et al., 2016). There is however the potential to use objective measures, such as those derived from wearable sensors such as accelerometers, to confirm research findings and to aid in the management of postural instability and gait difficulties with STN-DBS.

Of the research that has utilized acceleration-derived measures in people with PD (without STN-DBS), the harmonic ratio has been found to be one of the most commonly-used measures (Hubble et al., 2015). The harmonic ratio is a measure that quantifies step-to-step symmetry and provides unique information regarding gait stability in PD (Bellanca et al., 2013b; Buckley et al., 2015). However, it is unknown whether these clinical measures are similarly useful for evaluating the severity of axial motor symptoms in STN-DBS PD populations. This study aimed to determine whether objective measures of gait stability provide unique and additional information to that already captured by clinical measures of symptom severity, postural instability, balance confidence and mobility in those with PD who have STN-DBS. It was hypothesised that clinical measures of mobility, gait difficulty, postural stability

and balance confidence would be predictive of the objective measure of gait stability, the harmonic ratio.

7.3 Methods

Prospective participants were randomly recruited via both a Brisbane-based neurology clinic and local support groups via letters of invitation and an online advertisement, respectively. Interested participants were considered eligible for inclusion if they; i) were clinically-diagnosed with idiopathic PD; ii) were aged between 50 and 75 years; iii) had undergone bilateral STN-DBS surgery no less than 12-months earlier; iv) were independently living within the community; v) were able to stand and ambulate without assistance; vi) were free of significant musculoskeletal injuries or medical conditions (other than PD) that would adversely affect their balance or mobility; and vii) were free of dementia (score of >25 on the Standardized Mini-Mental State Examination during the session) (Molloy et al., 1991). This study was approved by the University's Human Research Ethics Committee (2017-155H) and volunteers provided written informed consent.

7.3.1 Data collection

Participants completed a battery of clinical measures to determine their symptom severity, balance confidence, postural stability and mobility. These clinical measures included:

(i) The motor sub-section (Part III) of the UPDRS-III, which was used to establish motor symptom severity (Goetz et al., 2008).

(ii) The retropulsion test (item 12 of the UPDRS-III), which is used in clinical scenarios to diagnose postural instability. Specifically, this test involves participants standing erect with eyes open and their feet comfortably separated and parallel to each other. The examiner provides a fast, unexpected, and forceful backwards pull on the

participant's shoulders to perturb their stability. The participant's response to the perturbation is subsequently rated on a 5-point Likert scale (0 to 4).

(iii) The ABC-6 was used to evaluate balance confidence (Peretz et al., 2006). This assessment averages the participants' self-reported confidence (expressed as a percentage) that they would not overbalance or fall during the performance of 6 different everyday tasks. Scores closer to 100% represent greater balance confidence and is an independent predictor of recurrent falls in optimally-medicated PD participants (Cole, Rippey, et al., 2016).

(iv) The 6-metre timed up and go test, where participants, started in a seated position and following the instruction of "GO", stood and walked at a brisk, but comfortable pace to a line on the floor six metres away, turned 180° and returned to the seated position. The average time taken to complete the course during two separate attempts was used for the analyses. Performance on the timed up and go test has been shown to differentiate prospective PD fallers from non-fallers (Kerr et al., 2010).

In addition to these clinical measures, participants were asked to complete a series of walking trials while wearing two tri-axial accelerometers to objectively assess gait stability. These walking tasks involved participants completing two trials of walking barefoot at a self-selected comfortable pace along a level 14-metre long walkway. One accelerometer (1500 Hz; Noraxon Inc., Scottsdale, AZ) was firmly fitted within a headband, such that the accelerometer was positioned over the occipital protuberance of the skull (Cole et al., 2017). The second accelerometer was firmly affixed to the skin overlying the spinous process of the 10th thoracic vertebra using double-sided tape (Cole et al., 2014). During these trials, accelerations were

wirelessly telemetered to a Telemyo DTS unit connected to a laptop computer running the MyoResearch (v3.6) software.

7.3.2 Data Analysis

Using a developed algorithm, peak vertical trunk accelerations were used to identify the individual foot contacts and to truncate the walking trials to include data for 8 consecutive gait cycles only (Cole et al., 2017). To allow movement-related accelerations to be separated from gravitational acceleration (constant -9.81 m/s^2), the data were rotated using a previously described method to ensure that the vertical axis of each accelerometer was aligned with the line of gravity (Cole et al., 2017). Data were then low-pass filtered using a fourth-order Butterworth filter with a cut-off frequency of 30 Hz and subsequently analysed in the frequency domain using the Fourier series technique (Oppenheim & Willsky, 1997) with the fundamental frequency of the signal derived from stride duration (Smidt et al., 1971). Harmonic ratios were calculated for the head and trunk separately along the anterior-posterior, medial-lateral, and vertical by dividing the sum of the in-phase harmonics by the sum of out-of-phase harmonics using the first 20 harmonic coefficients (Bellanca et al., 2013b; Kavanagh et al., 2004). Higher harmonic ratios represented greater in-phase harmonics relative to out-of-phase harmonics and, hence, were considered to represent greater movement symmetry and gait stability (Bellanca et al., 2013b). All processing and analysis of the acceleration data were performed using custom programs developed in MATLAB (v7.13, The MathWorks, USA).

7.3.3 Statistical Analysis

To establish the relationship between the outcomes of the clinical measures and the accelerometer-based measures, simple correlation and linear regression analyses were performed. To determine the suitability of parametric procedures, the Shapiro-Wilk test was

used to assess the normality of the continuous outcome measures. When the test of normality returned a p-value of less than 0.05, normality could not be assumed; hence, the non-parametric Spearman's Rho test was used in place of the Pearson's correlation coefficient. Linear regression analyses were performed to examine whether clinical measures could explain a significant proportion of the variance in head and trunk harmonic ratios during walking. An a-priori sample size calculation determined that 13 participants were required to examine the relationships between the clinical measures and the harmonic ratios (Power = 80%, $\rho H_1 = 0.7$, $p<0.05$). Statistical analyses were conducted using the Statistical Package for the Social Sciences (Version 25, New York, USA) and the level of significance for all statistical tests was set at $p < 0.05$.

7.4 Results

Sixteen people with PD and bilateral STN-DBS completed the data collection session (Table 7.1). The Shapiro-Wilk test identified several measures were not normally distributed, therefore the Spearman's Rho test was used to assess the relationships between the clinical and objective measures. The linear regression analyses indicated that, although the time taken to complete the timed up and go test significantly predicted medial-lateral head harmonic ratio (p=0.049), the remaining clinical outcomes were not predictive of the accelerometer-based stability measures (Table 7.2). In contrast, the scores derived from many of the clinical measures were found to be correlated with and predictive of one another. Specifically, the UPDRS-III significantly predicted the retropulsion test (p=0.005) and timed up and go test (p=0.015). Similarly, the retropulsion test was also a significant predictor of the ABC-6 (p=0.003).

Table 7.1: Demographic information, clinical outcome measures, and accelerometer-based harmonic ratios for the people with PD and STN-DBS. Data represent mean (±1 standard deviation) or absolute numbers (percentage sample)[a].

	n =16
Demographics	
Gender (Male)[a]	14 (87.50%)
Age (years)	68.58 (7.48)
Height (m)	1.77 (0.09)
Mass (kg)	82.56 (14.44)
Neurological Examination	
Disease duration (years)	12.06 (5.63)
Time since STN-DBS (years)	3.75 (2.24)
N-FOG	17.83 (9.80)
Freezers[a]	6 (37.50%)
PDQ-8	26.56 (15.14)
No anti-parkinsonian medications[a]	7 (43.75%)
Levodopa dose (mg/day)	168.75 (227.94)
Retrospective faller[a]	9 (56.00%)
Retrospective falls	3.33 (2.17)
Clinical measures	
UPDRS-III	32.44 (9.95)
Retropulsion test (UPDRS-III, Item 12)	1.31 (1.25)
ABC-6	56.33% (24.04%)
Timed up and go time (s)	18.82 (5.25)
Objectives measures	
Head anteroposterior harmonic ratio	1.96 (0.66)
Head medial-lateral harmonic ratio	2.27 (0.59)
Head vertical harmonic ratio	2.61 (0.71)
Trunk anteroposterior harmonic ratio	1.90 (0.54)
Trunk medial-lateral harmonic ratio	1.95 (0.58)
Trunk vertical harmonic ratio	2.98 (0.90)

Abbreviations: **ABC-6:** 6-item Activities-specific Balance Confidence scale; **N-FOG**: New Freezing of Gait questionnaire; **PD:** Parkinson's disease; **PDQ-8:** 8-item Parkinson's Disease Questionnaire; **STN-DBS**: Deep brain stimulation of the subthalamic nucleus; **UPDRS-III:** Motor subscale of the Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

Table 7.2: Results of the linear regression and correlation analyses for the clinical outcomes and the accelerometer-based measures collected for the people with PD who have STN-DBS.

	Unstandardised beta	Standardised beta	Spearman's Rho	p-value
UPDRS-III				
Retropulsion Test	**0.12**	**0.60**	**0.62**	**0.005***
ABC-6	**-1.91**	**-0.54**	-0.39	0.069
Timed Up and Go Time	**0.42**	**0.55**	**0.58**	**0.015***
Head AP harmonic ratios	0.01	-0.05	0.14	0.312
Head ML harmonic ratios	-0.02	-0.51	**-0.55**	**0.017***
Head VT harmonic ratios	-0.03	-0.42	-0.34	0.109
Trunk AP harmonic ratios	-0.01	-0.27	-0.17	0.26
Trunk ML harmonic ratios	-0.01	-0.2	-0.11	0.339
Trunk VT harmonic ratios	-0.03	-0.36	-0.3	0.13
Retropulsion Test				
UPDRS-III	**3.08**	**0.60**		
ABC-6	**-12.67**	**-0.69**	**-0.65**	**0.003***
Timed Up and Go Time	0.8	0.2	0.36	0.105
Head AP harmonic ratios	0.06	0.12	-0.01	0.49
Head ML harmonic ratios	-0.02	-0.06	-0.13	0.323
Head VT harmonic ratios	-0.05	-0.09	-0.11	0.344
Trunk AP harmonic ratios	0.03	0.07	0.03	0.454
Trunk ML harmonic ratios	0.11	0.28	0.07	0.401
Trunk VT harmonic ratios	0.01	0.01	-0.09	0.374
ABC-6				
UPDRS-III	**-0.15**	**-0.54**		
Retropulsion Test	**-0.04**	**-0.69**		
Timed Up and Go Time	-0.06	-0.28	-0.21	0.241
Head AP harmonic ratios	0.01	-0.07	-0.01	0.492
Head ML harmonic ratios	0.01	0.22	0.25	0.182
Head VT harmonic ratios	0.01	0.41	0.39	0.077
Trunk AP harmonic ratios	0.01	-0.14	-0.12	0.336
Trunk ML harmonic ratios	0.01	0.07	0.26	0.17
Trunk VT harmonic ratios	0.01	0.17	0.21	0.217
Timed up and go time				
UPDRS-III	**0.72**	**0.55**		
Retropulsion Test	0.05	0.2		
ABC-6	-1.28	-0.28		
Head AP harmonic ratios	0.01	0.12	0.04	0.443
Head ML harmonic ratios	**-0.05**	**-0.56**	**-0.48**	**0.049***
Head VT harmonic ratios	-0.05	-0.4	-0.37	0.108
Trunk AP harmonic ratios	0.01	0.06	0.14	0.318
Trunk ML harmonic ratios	-0.02	-0.23	-0.17	0.287
Trunk VT harmonic ratios	-0.06	-0.4	**-0.62**	**0.009***

Abbreviations: **ABC-6** = 6-item Activities-specific Balance Confidence scale, **AP**: anterior-posterior, **ML**: Medial-lateral; **UPDRS-III**: Motor subscale of the Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, **VT**: Vertical.
Symbols: ***** = Significant correlation.

7.5 Discussion

This study aimed to determine whether the harmonic ratio, an objective measure that quantifies step-to-step rythmicity provides unique and additional insight into gait stability that are complementary to clinical measures of symptom severity, postural instability, balance confidence and mobility in people with PD and STN-DBS. The results of this study did not support the hypothesis, as most of the clinical outcomes were not predictive of the harmonic ratios. The only exception to this was the time taken to complete the timed up and go test, where longer times were predictive of less rhythmic medial-lateral head movements (i.e. lower harmonic ratios). Although more relationships between the different measures were hypothesised, it is perhaps not surprising that performance on the timed up and go test, an assessment that includes components that place demands on gait stability (i.e. sit-to-stand, turning), was predictive of the harmonic ratio, an objective measure of step-to-step rhythmicity. Nevertheless, this finding should be considered with caution, as the bivariate relationship between the two measures was moderate (ρ=-0.48, p=0.049) and the regression analysis indicated that performance on the timed up and go time accounted for only 31% of the variance in medial-lateral head harmonic ratio.

In work involving people with PD without STN-DBS, balance confidence was shown to be predictive of vertical head harmonic ratios (Hubble et al., 2016). However, the outcomes presented in the current study suggest that the relationship between balance confidence and harmonic ratios is not present in a STN-DBS PD cohort. For people with PD without STN-DBS, poor balance confidence is strongly associated with postural instability (Adkin, Frank, & Jog, 2003; Mak & Pang, 2009) and future falls (Cole, Rippey, et al., 2016). However, in spite of the improved balance confidence following STN-DBS, falls are no less prevalent following

STN-DBS (Nilsson et al., 2011). Our data adds evidence that activity-specific balance confidence does not predict gait stability for people with PD who have STN-DBS.

The UPDRS-III is widely utilised in day-to-day clinical practice and has been shown to correlate with objective measures of static postural stability (e.g. COP measures) in people with PD, including those with DBS (Matinolli et al., 2007; Perera et al., 2018). While the UPDRS-III is known to be associated with walking speed (Tan, Danoudis, McGinley, & Morris, 2012), in this study, it does not appear to provide insight into gait stability. A rationale for this may be the specificity of the harmonic ratio measure to gait stability compared to the broad range of symptoms the UPDRS-III assesses (e.g. tremor, rigidity, rising from chair, gait, postural stability). The UPDRS-III was shown however to be a significant predictor of the retropulsion test, ABC-6 and timed up and go test. This finding supports the continued use of the UPDRS-III and suggests that this measure of overall motor symptom severity provides valuable insight into facets of balance confidence and mobility in the day-to-day lives of people with PD who have STN-DBS.

Similarly, greater scores on the retropulsion test was found to be related to greater motor symptom severity (greater UPDRS-III score) and poorer balance confidence (lower ABC-6 score). This reflects the association between impaired postural stability (Adkin et al., 2003; Mak & Pang, 2009) and increased motor symptom severity (van der Heeden et al., 2016). However, despite its widespread use in clinical practice, the retropulsion test appears to lack the sensitivity to predict future falls in people with PD (Bloem, Grimbergen, et al., 2001) and has subsequently been suggested as a poor test for confirming the efficacy treatments (Thevathasan et al., 2011). The results of previous research (Hubble et al., 2016) and of the current study lend support to this notion, as performance on the retropulsion test was not

predictive of the accelerometer-based measures of gait stability. A possible explanation is that the retropulsion test is performed during bipedal quiet stance, while the accelerometer-based measures were collected during walking.

A possible limitation of the current study was the relatively small sample size. Although the number of participants assessed exceeded the minimum group size determined in our a-priori sample size calculation, confirmation of these study findings in a larger STN-DBS PD cohort is warranted and would allow sub-group analyses (i.e. retrospective fallers vs. non-fallers) to be performed. Additionally, it should be noted that three of the participants' chronic stimulation parameters were low-frequency STN-DBS stimulation, rather than the more typical high-frequency stimulation. There is some evidence to suggest that, for certain people with PD, this stimulation strategy may have a beneficial effect on measures of postural stability (Conway et al., 2019) and, hence, may have influenced the homogeneity of the sample.

Nonetheless, easily administered clinical measures, such as the timed up and go test, are likely to continue to be the mainstay of clinical appraisals and contribute to the battery of outcome measures in clinical research. In research investigating alternate STN-DBS stimulation strategies, the time taken to complete walking tasks have been used to quantity the efficacy of these alternate strategies (Conway et al., 2019). Therefore, the results of the current study seem to support the growing opinion that acceleration measures may provide unique information about one's gait (Buckley, Galna, Rochester, & Mazza, 2018) and suggest that wearable sensors provide information that could aid clinical decision making.

7.6 Conclusion

This study found that, for an STN-DBS PD cohort, currently used clinical measures of motor symptom severity, postural stability, balance confidence and mobility were not predictive of accelerometer-based measures of gait stability. As such, the results indicated that objective measures derived from relatively inexpensive and unobtrusive wearable sensors provide unique information concerning the gait stability of those with PD following STN-DBS. Researchers and clinicians should consider incorporating objective gait outcomes into their assessments for additional information of gait stability when managing people with PD who have STN-DBS.

CHAPTER 8: STUDY III - Low-Frequency STN-DBS for Standing and Gait Initiation in Parkinson's Disease: A Double-Blinded Randomised Control Trial

8.1 Preface

The results of the systematic review and meta-analysis (Study I) suggested that in response to the apparent inefficacy of high-frequency STN-DBS for managing symptoms of postural instability in people with PD, low-frequency stimulation may better manage such symptoms. However, much of the available evidence concerning the potential utility of low-frequency STN-DBS has been based on outcome measures derived from well-established clinical measures (e.g. Berg balance scale) and investigations are focused on overall symptom severity or freezing of gait occurrences (Study I). Extending from this, Study III employed a double-blinded randomised cross-over design to evaluate the effect of low-frequency STN-DBS on objective measures of postural stability during standing and gait initiation in people with PD. This was quantified using postural stability measures derived from a force plate (referred to as posturography).

8.2 Introduction

STN-DBS has become a common procedure for improving symptoms of PD, such as resting tremor and limb stiffness, that are refractory to pharmacological treatments (Deuschl, Schade-Brittinger, et al., 2006; Weaver et al., 2009). However, postural instability, a symptom strongly associated with falling in people with PD (Bloem, van Vugt, et al., 2001), is reported to decline following STN-DBS (St George et al., 2010). The deterioration of postural stability following STN-DBS is considered to be a contributing factor to the increased falls rate reported for people who are more than one year post-surgery (Rizzone et al., 2014). Postural stability is commonly evaluated by measuring the COP on a force plate (referred to as posturography) to provide insight into the movements of one's COM and, hence, their postural sway.

Assessments of postural stability have traditionally focused on postural stability during static (i.e. standing) or steady-state dynamic (i.e. walking) tasks, with a growing number of studies investigating the transition phase between these static and dynamic states (i.e. gait initiation) (Crenna et al., 2006; Hass, Waddell, Fleming, Juncos, & Gregor, 2005; Muniz et al., 2010). Gait initiation includes two distinct phases that are respectively referred to as the postural phase and the locomotion phase (Breniere & Do, 1991). During the postural phase, there is a shift in COM towards the stance leg which results in a concomitant and proportional change in position of the COP. During the locomotion phase of gait initiation, the COM is projected forward in the direction of travel, which is reflected by a simultaneous change in the trajectory of the COP (Elble et al., 1994).

Despite the improvements reported for symptoms of limb tremor and rigidity, people with PD continue to experience declines in postural stability during gait initiation following STN-DBS surgery (Rocchi et al., 2012). Such findings have led to suggestions that conventional

STN-DBS stimulation strategies may be inadequate for managing PD symptoms that affect postural stability and may contribute to an increased falls risk post-operatively (Fasano et al., 2015). Outcomes from research investigating the effects of alternate stimulation parameters (e.g. voltage amplitude or stimulation frequency) on the post-operative management of postural stability has produced inconsistent findings (Conway et al., 2019). Specifically, low-frequency stimulation (60-80 Hz) has been shown to both improve (Khoo et al., 2014; Xie et al., 2015) and not change clinical measures of postural stability (Moreau et al., 2008; Phibbs et al., 2014; Sidiropoulos et al., 2013). Though most research has focused on the effect of low-frequency stimulation on steady state walking (Conway et al., 2019); there is a need for further research to assess the potential benefits of alternate stimulation parameters, such as low-frequency STN-DBS for improving postural stability during standing and gait initiation. This study employed a double-blind randomized cross-over design to evaluate the effect of low-frequency STN-DBS on objective measures of postural stability during standing and gait initiation in people with PD. It was hypothesized that low-frequency stimulation would significantly improve postural stability compared to the usual high-frequency stimulation.

8.3 Methods

8.3.1 Participants

Participants were randomly recruited from a private neurology clinic and local support groups via a letter of invitation that outlined the study's requirements and the potential benefits and risks of participation. Volunteers were accepted into the study if they were; clinically-diagnosed with idiopathic PD; aged between 50 and 75 years; had undergone bilateral STN-DBS surgery no less than 12-months earlier; independently living within the community; able to stand and ambulate without assistance; free of any significant musculoskeletal or medical conditions (other than PD); were not taking any non-antiparkinsonian medications that would

adversely affect their postural stability or mobility; and free of any signs of dementia (Standardized Mini-Mental State Examination score >25) (Molloy et al., 1991). This study was approved by the Australian Catholic University's Human Research Ethics Committee (2017-155H) and volunteers provided written informed consent prior to participation. Given the lack of reported data concerning posturographic outcomes with low-frequency STN-DBS, sample estimate was based on posturographic data collected while investigating a similar group with and without high-frequency DBS (Liu et al., 2006). It was determined that a minimum of 11 participants was required to detect differences between high- and low-frequency stimulation with respect to the to the COP outcomes (Effect Size≥0.49, Power=0.8, p=0.05).

The location of DBS electrodes were identified by merging the postoperative CT scans with the preoperative MRI using 3D Slicer v4.11 (Fedorov et al., 2012). Images were aligned along the anterior and posterior commissures to normalise brain orientation using acpcdetect v2.0 (NeuroImaging Tools & Resources Collaboratory, https://www.nitrc.org). The three-dimensional coordinates for the ideal neurosurgical target within each STN (Dembek et al., 2019) were determined separately for each hemisphere of the brain by an experienced neurologist. These data were subsequently used to calculate the distance (in millimetres) between the midpoint of each electrode and the ideal target. The difference between the ideal and actual location of the active electrode was expressed in the form of X (negative = more medial), Y (negative = more posterior) and Z (negative = more inferior) distance, which were combined to provide a Euclidean distance. All distance calculations were performed automatically using a custom script written in Python v3.7 (Python Software Foundation).

8.3.2 STN-DBS Interventions

Following overnight withdrawal of anti-parkinsonian medications (≥12 hours), participants attended a single testing session to complete measures of postural stability during both high- and low-frequency STN-DBS. Testing was completed within a dedicated research space at their usual neurology clinic. On arrival, a nurse specialised in the post-operative management of people with PD who have STN-DBS and who was blinded to the participants' assessments determined the electrode impedance of the DBS device and calculated the TEED for the participants' chronic stimulation. The TEED was determined by using the product of the voltage amplitude, stimulation frequency, pulse width and biological impedance for each participant (Koss et al., 2005). The order in which the high- and low-frequency stimulation conditions were applied was randomised, with the order determined using a computer-generated randomisation sequence conducted by a team member who had no direct involvement in data collection or analysis. Using a randomised one-to-one allocation ratio, the DBS nurse programmed the STN-DBS electrodes to one of two therapeutic conditions; i) high-frequency; or ii) low-frequency stimulation. Specifically, the high-frequency condition involved the STN-DBS electrodes being bilaterally active with the high-frequency stimulation (>100 Hz) that the participants were receiving as part of their usual chronic therapy. In contrast, low-frequency stimulation involved the STN-DBS electrodes being bilaterally set to a lower frequency (60 Hz) with the voltage increased to maintain the TEED at a level consistent with the participant's high-frequency stimulation. To limit the risk of any carry-over effects between the high- and low-frequency (or vice versa) conditions, a one-hour wash-in period was enforced between testing conditions (Moro et al., 2002). To limit the risk of bias, only the DBS nurse responsible for adjusting the stimulation parameters was aware of the STN-DBS parameters for each condition; hence, both the participant and the researchers administering the assessments were blinded to the stimulation state.

8.3.3 Procedures

Participants were asked to complete a series of questionnaires to acquire their medical history, medication use, and balance confidence. Furthermore, during each therapeutic condition, symptom severity was assessed by the same trained movement scientist using part three (motor sub-section) of the Movement Disorders Society-Sponsored Revision of the UPDRS-III. The total score and item 12 (retropulsion test) of the sub-section were reported, with higher scores for these outcomes representing greater symptom severity and/or poorer postural stability, respectively. Following the clinical assessment, participants were asked to complete two 30-second standing trials on a portable force plate (Advanced Mechanical Technology Inc., USA). During these trials, participants stood barefoot with their hands at rest by their sides, their feet 10 cm apart, and their eyes open. Participants were asked to focus their gaze on a point situated 10 meters directly in front of them and to refrain from talking, unless necessary. For any trials where the participant was unable to stand quietly (e.g. they spoke, coughed, sneezed), the task was repeated. Following this, participants were asked to complete two barefoot walking trials along a 14-metre long level walkway at a self-selected comfortable pace starting from a standing position on the force plate. During both the standing and walking tasks, COP data were captured by the force plate at 200 Hz.

8.3.4 Standing postural stability

For this project, measures of postural stability were derived from the COP data using the BioAnalysis software (Advanced Mechanical Technology, Watertown MA, USA). Specifically, these measures included the range of both the anterior-posterior (distance between the most anterior and posterior COP positions) and medial-lateral (distance between the left- and right-most positions of the COP trajectory), the variability of both the anterior-posterior and medial-lateral sway patterns (as determined using the standard deviation), 95% elliptical

sway area (cm^2), sway velocity (cm/s). These measures have been used to evaluate the efficacy of non-invasive interventions in people with PD (Hubble, Silburn, Naughton, & Cole, 2019) and have been shown to worsen with increased disease severity (Frenklach et al., 2009). Additionally, the sample entropy measure was used to determine the regularity of the sway patterns in both the anterior-posterior and medial-lateral directions separately (Ramdani et al., 2009). This procedure used the instantaneous velocity of the anterior-posterior and medial-lateral COP data and expressed the regularity of the time-series on a scale from zero to two (higher values correspond with less regular sway patterns). For the calculation of sample entropy, the input parameters of m=2 and r=0.30 were used, in accordance with research (Ramdani et al., 2009).

8.3.5 Gait initiation

Measures of the anticipatory postural adjustments that precede gait initiation were derived from the COP data collected during the moments preceding the participants' comfortable walking trials. To facilitate these analyses, the COP data were divided into two phases. The first was the postural phase, which included all data between the start of the trial and the point at which the COP reached its maximum posterior and lateral displacement. The second was the locomotion phase, which included all data from the end of the postural phase through until the point where the trailing leg was no longer in contact with the force plate. During each of these phases, outcome measures that included the anterior-posterior sway path length, medial-lateral sway path length, average velocity. The calculation of these outcomes for both the postural and locomotion phases was completed using a custom program developed in Microsoft Excel.

8.3.6 Statistical Analysis

Demographic data were reported as aggregate means and standard deviations for the entire group. To examine differences between high- and low-frequency stimulation conditions, during standing and gait initiation, linear mixed model analyses with 1 repeated factor (stimulation, 2 levels) were used. All statistical procedures were conducted using the Statistical Package for the Social Sciences (Version 22, SPSS Inc., USA), with the estimated marginal means and standard errors considered against a $p<0.05$ level of significance. Following completion of all data analyses, the two therapeutic conditions were re-identified to allow appropriate interpretation and discussion of the outcomes.

8.4 RESULTS

8.4.1 Study Population

Between March and August 2018, 31 people with PD who have STN-DBS expressed interest to participate in the study. Of these people, 26 were deemed to be eligible following initial screening and scheduled to attend the data collection session (Figure 8.1). Of the five participants who were not recruited, two were unable to be contacted again after they had made initial contact and three were deemed to be ineligible, as their STN-DBS surgery was either <1 year ago (n = 2) or their age was <50 years (n = 1). Of the 26 participants recruited into the study, four withdrew prior to their scheduled assessment and one participant was excluded as they were unable to stand or ambulate following overnight withdrawal from their medication. The remaining 21 participants underwent the study. Following data collection, data for five participants were excluded because they took their anti-parkinsonian medication on the morning of testing (n = 3) or because their typical chronic stimulation was already low-frequency stimulation (n = 2). Data for the remaining 16 participants (Table 1) were included in the subsequent analyses.

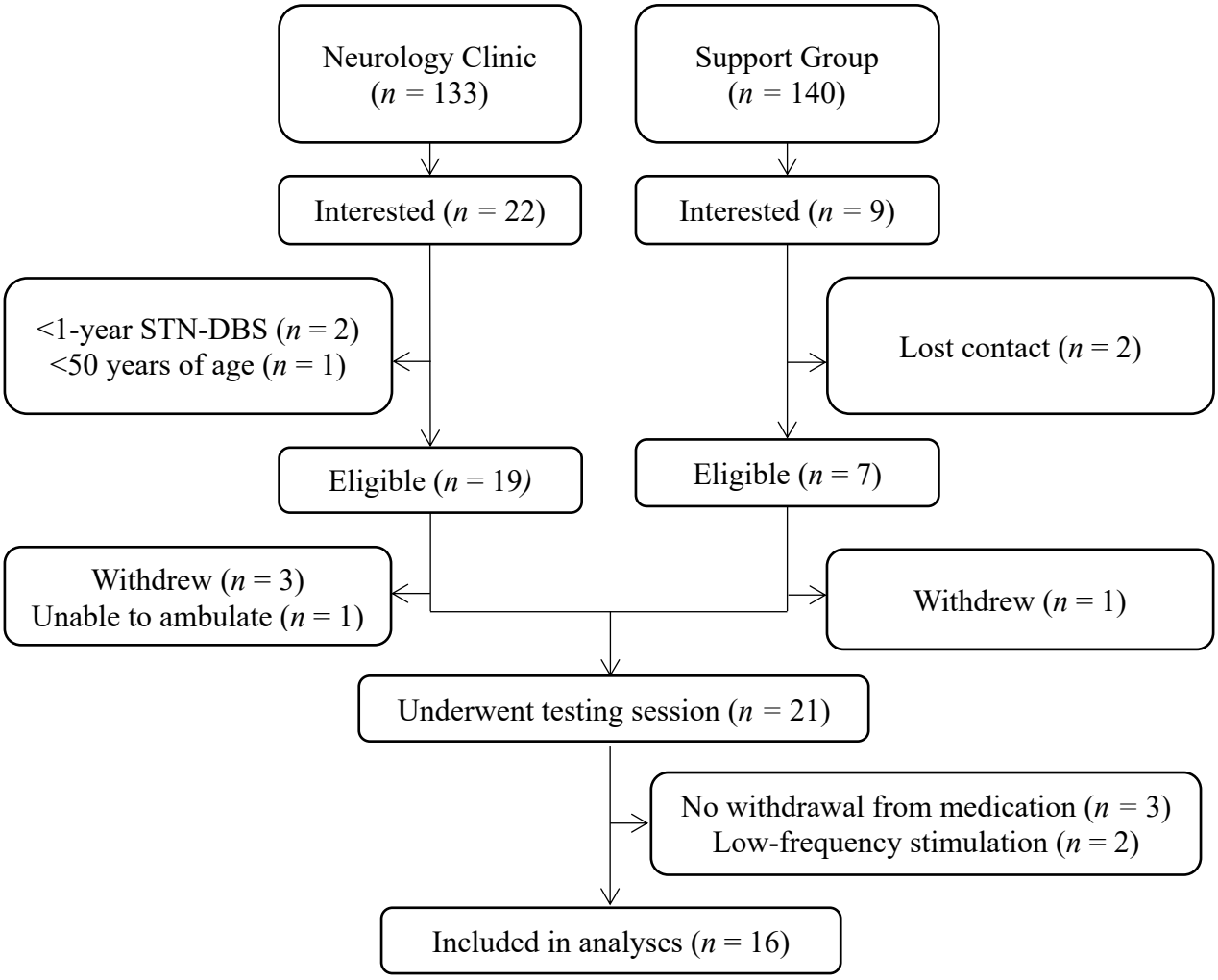

Figure 8.1: Study flow chart.

Table 8.1: Demographic information, disease-specific characteristics and surgical information for the people with PD and STN-DBS as well as clinical measures and stimulation paraments for chronic high-frequency stimulation and low-frequency stimulation. Data represent mean (±1 standard deviation), absolute numbers (percentage of sample)[a] or mean (range)[b].

	HFS (n = 14)	**LFS** (n = 12)
Demographics		
Gender (male)[a]	12.0 (75.0%)	-
Age (years)	69.9 (7.5)	-
Height (meters)	1.72 (0.1)	-
Mass (kg)	80.1 (14.6)	-
Falls history and fear of falls		
Retrospective faller[a]	9.0 (56.25%)	-
ABC-6	49.0% (26.1%)	-
Neurological Examination		
Disease duration (years)	12.4 (6.6)	-
UPDRS-III	33.2 (10.0)	32.7 (10.9)
Freezers[a]	5.0 (31.3%)	-
New Freezing of Gait Questionnaire	19.0 (5.5)	-
PDQ-8	27.7 (14.9)	-
No anti-parkinsonian medications[a]	7.0 (43.8%)	-
Levodopa dose (mg/day)	297.2 (112.1)	-
Dopamine agonists[a]	5.0 (45.5%)	-
Clinical measures		
Retropulsion test	1.6 (1.4)	1.5 (1.4)
Comfortable 6m walk test (s)	5.9 (2.4)	6.3 (3.3)
Quick 6m walk test (s)	4.1 (1.0)	4.1 (0.9)
Timed up and go (s)	18.9 (5.7)	17.4 (3.4)
DBS information		
Time since STN-DBS (years)	4.1 (2.3)	-
Euclidean distance[b]	2.36 (0.32 to 5.17)	-
X distance (negative = medial)[b]	-0.90 (-3.17 to 1.72)	-
Y distance (negative = posterior) [b]	-0.35 (-1.80 to 3.45)	-
Z distance (negative = inferior) [b]	-0.74 (-4.33 to 2.68)	-
Frequency (Hz)	127.2 (14.9)	60.0 (0.0)
Amplitude (V)	3.3 (0.6)	4.7 (1.1)
Pulse width (μs)	62.5 (5.5)	62.5 (5.5)

Abbreviations: **ABC-6:** 6-item Activities-specific Balance Confidence scale; **HFS:** high-frequency stimulation; **LFS**: low-frequency stimulation; **PDQ-8**: 8-item Parkinson's Disease Questionnaire; **UPDRS-III:** Motor subscale of the Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

8.4.2 Standing postural stability

Linear mixed model analyses returned a significant effect for stimulation (high- vs. low-frequency) for sway velocity and anterior-posterior and medial-lateral sample entropy (Table 2). Sway velocity was significantly reduced during low-frequency stimulation and this change was independent of electrode location and motor symptom severity. Similarly, during the low-frequency stimulation condition, the regularity of anterior-posterior and medial-lateral sway was also reduced (i.e. lower sample entropy values) relative to the high-frequency stimulation state. While the lower values for medial-lateral sway regularity were independent of electrode placement, TEED and motor symptom severity, the differences in anterior-posterior sway regularity were negated after accounting for differences in electrode placement.

Table 8.2: Force plate derived measures during standing postural stability for the HFS and LFS STN-DBS conditions. Data represent means (±1 standard deviation).

Measures	HFS (n = 14)	LFS (n = 12)	Covariates						
			None	**ED (2.318)**	**X (-0.831)**	**Y (0.533)**	**Z (-0.360)**	**TEED (105.50)**	**UPDRS-III (32.69)**
Medial-lateral range (cm)	1.75 (0.85)	1.59 (0.59)	ns	ns	ns	ns	ns	ns	ns
Anterior-posterior range (cm)	2.99 (1.1)	3.12 (1.09)	ns	ns	ns	ns	ns	ns	ns
Variability of medial-lateral sway (cm)	0.37 (0.23)	0.32 (0.12)	ns	ns	ns	ns	ns	ns	ns
Variability of anterior-posterior sway (cm)	0.64 (0.27)	0.64 (0.26)	ns	ns	ns	ns	ns	ns	ns
Sway area (cm^2)	4.13 (3.38)	3.42 (1.86)	ns	ns	ns	ns	ns	ns	ns
Sway velocity (cm/s)	4.19 (3.39)	3.77 (0.98)	**0.016**	**0.027**	**0.028**	**0.028**	**0.028**	**0.016**	**0.011**
Medial-lateral sample entropy	1.31 (0.27)	1.18 (0.34)	**0.023**	**0.025**	**0.024**	**0.025**	**0.024**	**0.023**	**0.02**
Anterior-posterior sample entropy	0.99 (0.32)	0.78 (0.28)	**0.010**	ns	ns	ns	ns	**0.011**	**0.02**

Abbreviations: **ED:** Euclidian distance; **HFS:** High-frequency stimulation; **LFS:** Low-frequency stimulation; **TEED:** Total Electrical Energy Delivered; **UPDRS-III:** Motor sub-scale (Part III) of the Unified Parkinson's Disease Rating Scale; **X, Y, Z:** Difference between the ideal and actual location of the active electrode in the X (negative = more medial), Y (negative = more posterior) and Z (negative = more inferior) directions.

8.4.3 Gait initiation

The statistical analyses identified no significant differences between high- and low-frequency for any of the postural stability measures derived from the postural phase of gait initiation. However, during the locomotion phase of gait initiation, low-frequency stimulation led to increased medial-lateral range, sway area and average velocity compared to high-frequency STN-DBS. The difference observed for sway area was independent of electrode location, while the changes in both medial-lateral range and average velocity appeared to be explained by variations in electrode location (Table 8.3).

Table 8.3: Force plate derived measures for the high-frequency stimulation and low-frequency stimulation STN-DBS conditions during gait initiation. Data represent means (±1 standard deviation).

Measures	HFS (n = 14)	LFS (n = 12)	Covariates						
			None	ED (2.318)	X (-0.831)	Y (0.533)	Z (-0.360)	TEED (93.46)	UPDRS-III (31.60)
Postural									
Medial-lateral range (cm)	4.49 (10.74)	4.39 (13.23)	ns	ns	ns	ns	ns	ns	ns
Anterior-posterior range (cm)	2.2 (9.42)	2.63 (12.72)	ns	ns	ns	ns	ns	ns	ns
Sway area (cm^2)	4.31 (5.59)	6.05 (9.04)	ns	ns	ns	ns	ns	ns	ns
Average velocity (cm/s)	2.44 (6.49)	3.02 (15.04)	ns	ns	ns	ns	ns	ns	ns
Locomotion									
Medial-lateral range (cm)	1.19 (6.49)	1.59 (8.37)	**0.031**	ns	ns	ns	ns	**0.031**	**0.037**
Anterior-posterior range (cm)	5.58 (14.51)	5.95 (17.32)	ns	ns	ns	ns	ns	ns	ns
Sway area (cm^2)	3.66 (17.99)	7.04 (40.20)	**0.000**	**0.000**	**0.001**	**0.000**	**0.000**	**0.001**	**0.001**
Average velocity (cm/s)	10.99 (33.77)	13.88 (55.56)	**0.030**	ns	ns	ns	ns	**0.042**	**0.034**

Abbreviations: **ED:** Euclidian distance; **HFS:** High-frequency stimulation; **LFS:** Low-frequency stimulation; **TEED:** Total Electrical Energy Delivered; **UPDRS-III:** Motor sub-scale (Part III) of the Unified Parkinson's Disease Rating Scale; **X, Y, Z:** Difference between the ideal and actual location of the active electrode in the X (negative = more medial), Y (negative = more posterior) and Z (negative = more inferior) directions.

8.4.4 Symptoms severity and clinical measures

There were no significant differences in any of the clinical measures of mobility (6-metre walk, Timed Up and Go) or symptom severity (UPDRS-III, retropulsion test) between the high- and low-frequency stimulation conditions. While five of the participants reported freezing of gait symptoms, no freezing episodes took place during data collection. Of the 16 participants who completed assessments under high-frequency stimulation, 10 experienced worsening symptoms of resting tremor with low-frequency stimulation. Six of these participants were able to complete the assessments without difficulty, but the remaining four were unable to complete the assessments while receiving low-frequency stimulation. Secondary analyses that included only those participants who were able to complete the assessments under both therapeutic conditions confirmed that the reported findings were not biased by the four participants who were unable to complete the low-frequency STN-DBS condition. There was no difference in age, disease duration, time since surgery or electrode location for those who were unable to complete the low-frequency STN-DBS condition.

8.5 Discussion

This study employed a double-blind randomised cross-over design to evaluate the effect of low-frequency STN-DBS on objective measures of stability during standing postural stability and gait initiation in people with PD. In accordance with our hypotheses, we found low-frequency STN-DBS (60 Hz) with a commensurate voltage increase to maintain the TEED at the participants' high-frequency stimulation level significantly improved postural stability during standing and gait initiation in people with PD who have STN-DBS. However, this alternate stimulation strategy was not tolerated by all participants and, in some cases, the gait improvements came at the cost of re-emerged limb tremor. With respect to clinical measures, there were no significant differences for the retropulsion test between the high- and low-

frequency stimulation conditions. Similar findings have been reported in separate studies that evaluated the efficacy of low-frequency stimulation on largely subjective assessments of postural stability (Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Phibbs et al., 2014; Sidiropoulos et al., 2013; Vallabhajosula et al., 2015). It is possible that clinical measures of postural stability lack the sensitivity to detect subtle changes evident in people with PD with STN-DBS. A battery of tests, including objective force plate-measures of postural stability might be best suited to assessing postural stability in this clinical population (Tan et al., 2018).

In response to the reported declines in postural stability with high-frequency STN-DBS (Fasano et al., 2015; St George et al., 2010), research investigating the potential benefits of low-frequency STN-DBS for improving postural stability in people with PD has provided inconsistent findings, with some reporting improvements (Khoo et al., 2014; Xie et al., 2015) and others describing no difference (Moreau et al., 2008; Phibbs et al., 2014; Sidiropoulos et al., 2013). The current study extends on this earlier research by incorporating objective force plate-measures to further examine the effects of low-frequency STN-DBS therapy on objective measures of postural stability. Our findings are potentially important, as research has shown that, in spite of its capacity to alleviate medication-induced postural instability (Rocchi, Chiari, & Horak, 2002), high-frequency STN-DBS has only a limited capacity for improving symptoms of postural instability in people with PD (Visser et al., 2008).

To our knowledge, this is the first study to evaluate the regularity of standing postural stability following STN-DBS using the sample entropy measure. Our results show that low-frequency stimulation resulted in more regular sway patterns (i.e. lower sample entropies) than high-frequency stimulation. It has been suggested that more regular sway patterns were

indicative of better standing postural stability, as younger adults exhibited more regular sway than elderly fallers and non-fallers (Borg & Laxaback, 2010). However, more recent investigations have proposed more regular sway may be reflective of a postural control system that has reduced flexibility and, hence an impaired capacity to adapt to different conditions. Support for this notion is provided by studies that report more regular sway for community-dwelling older adults who fall compared with non-fallers (Zhou, Habtemariam, Iloputaife, Lipsitz, & Manor, 2017) and more regular sway for people with PD compared to controls (Pelykh, Klein, Botzel, Kosutzka, & Ilmberger, 2015). Considering these collective findings, it seems that sample entropy may provide unique insight into the impact of disease on postural stability and/or the effect of different therapies on symptom management. However, further research is warranted to clarify the extent to which sway regularity can be used to determine the efficacy of treatment on one's risk of falls and other adverse events.

During gait initiation, low-frequency stimulation had no significant impact on sway measures during the postural phase of gait initiation. However, during the locomotion phase of gait initiation, medial-lateral range, sway velocity and sway area were all significantly increased. Given that reduced sway area is known to correspond with increased symptom severity in people with PD (Hass et al., 2005), and worsens with high-frequency STN-DBS (Rocchi et al., 2012), the greater sway area observed with low-frequency stimulation during the locomotion phase was considered to reflect improved gait initiation. Furthermore, the increased sway velocity exhibited by participants with low-frequency STN-DBS during the locomotion phase, was indicative of a more dynamic movement pattern during this transition period between standing postural stability and steady-state walking. These findings suggest that low-frequency stimulation might be a useful alternative strategy for improving postural stability and mobility during gait initiation. This finding is consistent with recent systematic evidence that

shows that, compared to high-frequency stimulation, low-frequency STN-DBS improves gait patterns in people with PD (Conway et al., 2019).

Given the lack of differences between high- and low-frequency STN-DBS during the postural phase of gait initiation, our findings suggest that the mechanisms responsible for controlling postural stability during standing and locomotor tasks (e.g. gait) may differ. Although we are unable to compare these improvements with a pre-surgical state, our results indicate that low-frequency STN-DBS therapy that is administered with a voltage change that serves to maintain the TEED improved gait initiation in people with PD who have STN-DBS. These findings potentially provide evidence for the utility of alternate STN-DBS stimulation parameters for people with PD who experience significant gait impairment following the procedure. It must be noted that this alternate stimulation was not tolerated by all and, in some cases, the gait improvements came at the cost of a re-emerged limb tremor. Specifically, six participants experienced re-emerged tremor symptoms but were still willing and able to complete the assessments with low-frequency stimulation. A further four participants were unable to complete the assessments at the alternate frequency due to a re-emergence of tremor. A similar re-emergence of tremor was reported in a separate study evaluating the effects of low-frequency STN-DBS (Phibbs et al., 2014); potentially highlighting the need for careful selection of those likely to benefit.

Limitations

It is arguable that a longer wash-in period (i.e. more than the 60 minutes used in this study) may have been needed to improve therapeutic efficacy. Though the 60-minute wash-in/wash-out period was commensurate with studies that have adopted similar methodologies (Khoo et al., 2014; Moro et al., 2002). Nevertheless, the relatively short time period between

one stimulation condition and the other means that the results presented in this paper should be considered to represent the participants' acute responses to low-frequency stimulation. Longitudinal studies are required to determine the long-term efficacy of low-frequency stimulation for people with PD following STN-DBS. A second potential limitation of this research is that participants were assessed following overnight withdrawal from their anti-parkinsonian medications, meaning that even during high-frequency stimulation condition for 50% of the participants (i.e. those who usually took medication) was not reflective of their best therapeutic state. However, by removing the potential influence of anti-parkinsonian medications from our assessments of standing postural stability and gait initiation, we felt that we could better attribute any changes in outcome to the specific stimulation conditions. These limitations should be considered when interpreting the implications of this study's outcomes.

8.6 Conclusions

During low-frequency STN-DBS, people with PD exhibited improved postural stability during standing and gait initiation compared to their chronic high-frequency STN-DBS treatment. However, low-frequency stimulation was not well tolerated by all participants, as some experienced a re-emergence of resting tremor. Furthermore, low-frequency stimulation resulted in more regular sway patterns, though what this means postural stability and falls risk requires further research.

CHAPTER 9: STUDY IV - Low-Frequency STN-DBS For Gait in Parkinson's Disease: Double-Blinded Randomised Cross-over Trial

9.1 Preface

Extending from the findings in Study III, which showed that low-frequency STN-DBS improved the more dynamic aspect of gait initiation compared to high-frequency stimulation, Study IV adopted a double-blinded randomised cross-over trial design to investigate the effects of low-frequency STN-DBS on gait stability. For the purposes of this study, gait stability was quantified using the harmonic ratio; an objective acceleration-derived measure.

This Chapter of the PhD thesis is currently under review for publication at *Brain Stimulation* and the full citation for this work is as follows:

Conway, Z. J., Silburn, P. Thushara, P. O'Maley, K., Thevathasan, W., & Cole, M. H. (*Under Review*). Low-Frequency STN-DBS for gait in Parkinson's disease: Double-blinded randomised cross-over trial. *Brain Stimulation.*

9.2 Introduction

STN-DBS has become a common procedure for improving symptoms of PD, such as resting tremor and limb stiffness, that are refractory to pharmacological treatments (Deuschl, Schade-Brittinger, et al., 2006). However, postural instability, a symptom strongly associated with falling in those with PD (Bloem, van Vugt, et al., 2001), declines following STN-DBS (St George et al., 2010) and subsequently has been considered a contributing factor to the increased falls rate reported for those who are more than one year post-surgery (Rizzone et al., 2014). Such research has led to suggestions that high-frequency STN-DBS stimulation may be inadequate for managing symptoms of postural instability in PD populations. Due to this potential shortcoming of the therapy, people with PD who are receiving STN-DBS would likely exhibit an increased falls risk following surgery (Fasano et al., 2015).

In response to the documented decline in gait, postural stability and subsequent falls risk, researchers have investigated whether alternate stimulation parameters (e.g. voltage amplitude or stimulation frequency) may improve the post-operative management of such symptoms. Studies have found low-frequency stimulation (60-80 Hz) was shown to improve axial motor symptoms (e.g. postural stability) with no significant adverse effects on the management of limb tremor (Khoo et al., 2014; Xie et al., 2015). While the use of low-frequency STN-DBS seems beneficial for improving axial symptoms when compared to high-frequency stimulation (Xie et al., 2017), the exact therapeutic mechanism for this improvement remains unconfirmed. Furthermore, to date, the reported changes in motor symptoms in response to alternate STN-DBS stimulation strategies have been based almost exclusively on well-established, though often subjective, clinical scales or spatial-temporal measures (2019). However, recent research involving optimally-medicated people with PD has provided evidence to suggest that inexpensive and unobtrusive wearable sensors can provide important

insight into changes in postural stability (Hubble et al., 2019) and gait stability (Cole et al., 2017; Conway, Blackmore, Silburn, & Cole, 2018; Hubble et al., 2018) in this population; potentially adding value to current clinical practices.

Of the research that has utilized acceleration-derived measures in optimally-medicated people with PD, the harmonic ratio is the most commonly reported measure of gait stability (Hubble et al., 2015). The harmonic ratio uses gait-related accelerations to provide a unique measure of one's gait rhythmicity and gait stability (Bellanca, Lowry, VanSwearingen, Brach, & Redfern, 2013a; Buckley et al., 2015; Cole et al., 2017; Latt et al., 2009; Lowry et al., 2012; Lowry et al., 2009; Yack & Berger, 1993). Less rhythmic gait patterns are exhibited by people that have greater difficulty adjusting to the small postural challenges often associated with walking. This difficulty is reflected by lower harmonic ratios and research has shown that lower harmonic ratios discriminate people with PD who experience falls from those who do not (Cole et al., 2017; Latt et al., 2009). Although this objective measure has been extensively used in the literature (Hubble et al., 2015), to date, no study has used the harmonic ratio understand gait-related changes in people with PD and STN-DBS or the effect of alternate stimulation parameters on gait stability. This study employed a double-blinded randomised cross-over design to investigate the effects of low-frequency STN-DBS on objective measures of gait stability in people with PD. It was hypothesized that low-frequency stimulation would significantly improve gait stability compared to the usual high-frequency stimulation.

9.3 Methods

9.3.1 Participants

Participants were randomly recruited from a neurology clinic and local support groups and were accepted into the study if they were; clinically-diagnosed with idiopathic PD; aged

between 50 and 75 years; had undergone bilateral STN-DBS surgery no less than 12-months earlier; independently living within the community; able to stand and ambulate without assistance; free of any significant musculoskeletal or medical conditions (other than PD); not taking non anti-parkinsonian medications that would adversely affect their postural stability; and free of any signs of dementia (Standardized Mini-Mental State Examination score <24) (Molloy et al., 1991). This study was approved by the Australian Catholic University's Human Research Ethics Committee (2017-155H) and volunteers provided written informed consent prior to participation. Given the lack of data concerning harmonic ratios for people with PD following STN-DBS, gait rhythmicity measures collected for optimally-medicated people with PD were used to derive an *a priori* sample size estimate. It was determined a minimum of 12 participants was required to detect differences between high- and low-frequency stimulation (Effect Size≥0.82 Power=0.8, p=0.05).

9.3.2 STN-DBS Interventions

Following overnight withdrawal of anti-parkinsonian medications (≥12 hours), participants attended a testing session held in a dedicated research space within a neurology clinic. On arrival, a registered nurse who specialised in the management of those with STN-DBS determined the DBS electrode impedance and calculated the TEED for the participants' chronic stimulation (Koss et al., 2005). Using a one-to-one allocation ratio, the DBS nurse, informed by a computer-generated randomisation sequence, programmed the STN-DBS electrodes to one of two therapeutic conditions; i) high-frequency; or ii) low-frequency stimulation. Specifically, the high-frequency condition involved the STN-DBS electrodes being bilaterally active at the high-frequency stimulation (>100 Hz) that the participants routinely received. Low-frequency stimulation involved electrodes being bilaterally set to a lower frequency (60 Hz) with the voltage increased to maintain the TEED consistent with the

participant's chronic high-frequency stimulation. A one-hour wash-in period was enforced between high-frequency and low-frequency conditions to limit the risk of any carry-over effects (Moro et al., 2002). To limit the risk of bias, only the DBS nurse was aware of the STN-DBS parameters; hence, both the participant and the researchers administering the assessments were blinded.

9.3.3 Procedures

Prior to attending the session, participants completed a series of questionnaires to establish their medical history, medication use, freezing of gait history (Nieuwboer et al., 2009) and balance confidence (Cole, Rippey, et al., 2016). Then during each therapeutic condition, symptom severity was assessed by a movement scientist using part three (motor sub-section) of the Movement Disorders Society-Sponsored Revision of the UPDRS-III. The total score for this sub-section and the result for item 12 (retropulsion test) were both reported, with higher scores representing greater symptom severity and poorer postural stability, respectively. Following the clinical assessment, participants were asked to complete four barefoot walking trials at a self-selected and comfortable pace along a flat and level 14-metre walkway while looking straight ahead. The time taken to traverse the central 6-metre distance was recorded using a handheld stopwatch; in accordance with the protocol for the 6-Metre Walk Test. Participants were then asked to complete two modified 6-metre Timed Up and Go assessments.

9.3.4 Outcomes

Commensurate with research, tri-axial accelerometers (1500 Hz; Noraxon Inc., Scottsdale, AZ) were firmly affixed to a headband positioned over the occipital protuberance of the skull and to the participant's spine overlying the spinous process of the 10^{th} thoracic vertebra (Cole et al., 2017; Cole et al., 2014; Hubble et al., 2018) (Figure 9.1). During the

walking tasks, accelerations were wirelessly telemetered to a Noraxon Telemyo DTS unit connected to a laptop computer running the MyoResearch XP (v1.08) software. Raw accelerations for each trial were subsequently truncated to include 8 continuous gait cycles (i.e. 4 right/4 left) in the middle of the walking trial. Given the raw accelerations are known to comprise both movement-related and gravitational (constant -9.81 m/s^2) accelerations, a previously-described rotational algorithm was used to isolate the movement-related component (Kavanagh et al., 2004). Data were then low-pass filtered using a fourth-order Butterworth filter with a cut-off frequency of 30 Hz and subsequently analysed in the frequency domain using the well-established Fourier series technique (Oppenheim & Willsky, 1997) with the fundamental frequency of the signal derived from stride duration (Smidt et al., 1971). The harmonic ratio was then calculated separately along the anterior-posterior, medial-lateral, and vertical axes for the head and trunk by dividing the sum of in-phase harmonics by the sum of out-of-phase harmonics using the first 20 harmonic coefficients (Bellanca et al., 2013a; Kavanagh et al., 2004) (Figure 9.2). Higher harmonic ratios represented more in-phase harmonics relative to out-of-phase harmonics and, hence were considered to represent greater gait rhythmicity and gait stability (Bellanca et al., 2013a). From the recorded acceleration signals, the root mean square (RMS) amplitude of the time-series data was also calculated to provide insight into the magnitude of head and trunk accelerations in the anterior-posterior, medial-lateral, and vertical directions (Cole et al., 2017). The RMS amplitude of the segmental accelerations provided insight into the magnitude of movement exhibited by the head and trunk during the walking tasks.

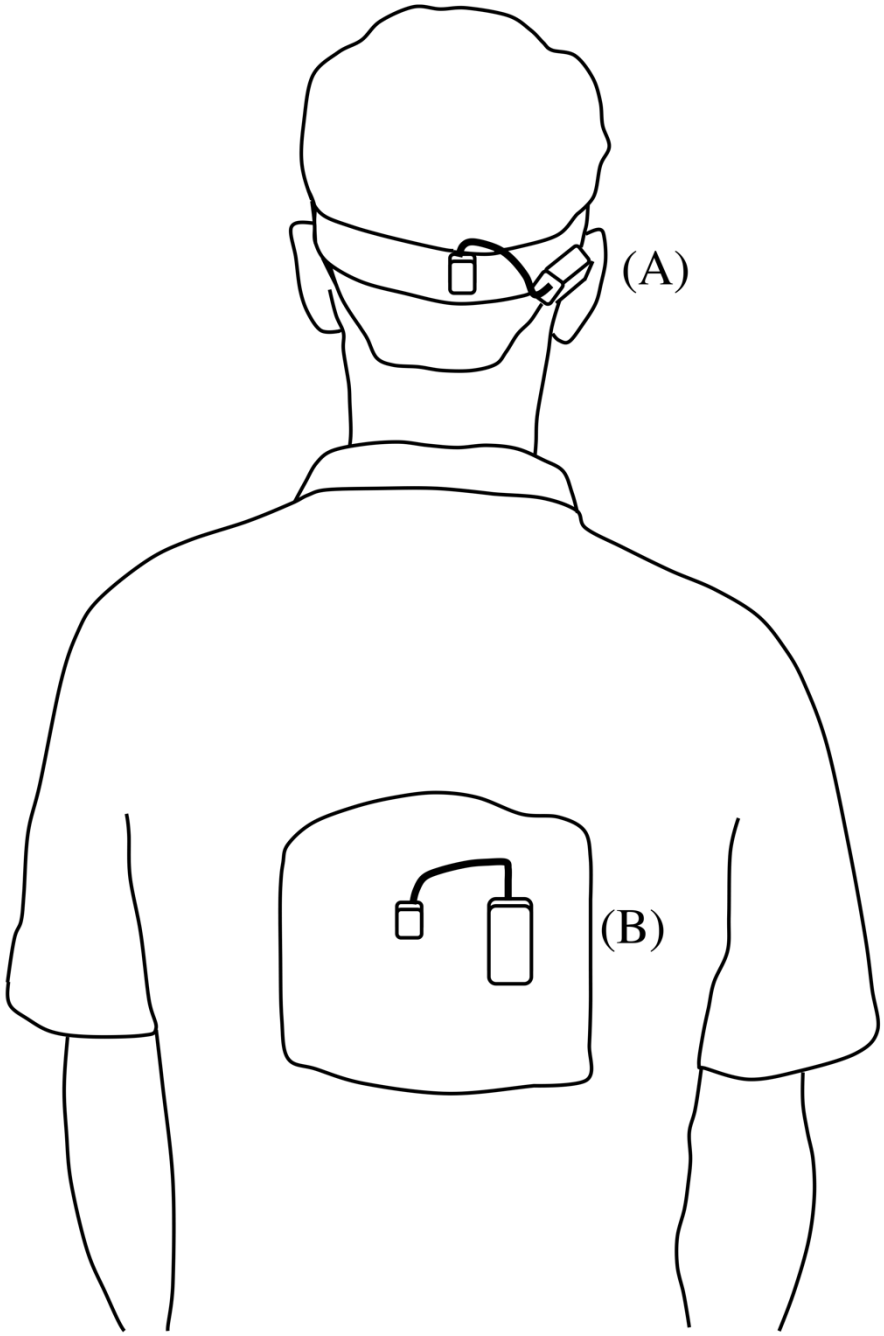

Figure 9.1: Illustration of tri-axial accelerometers affixed (A) to a headband over the occipital protuberance and (B) to the participant's back overlying the spinous process of the 10th thoracic vertebra.

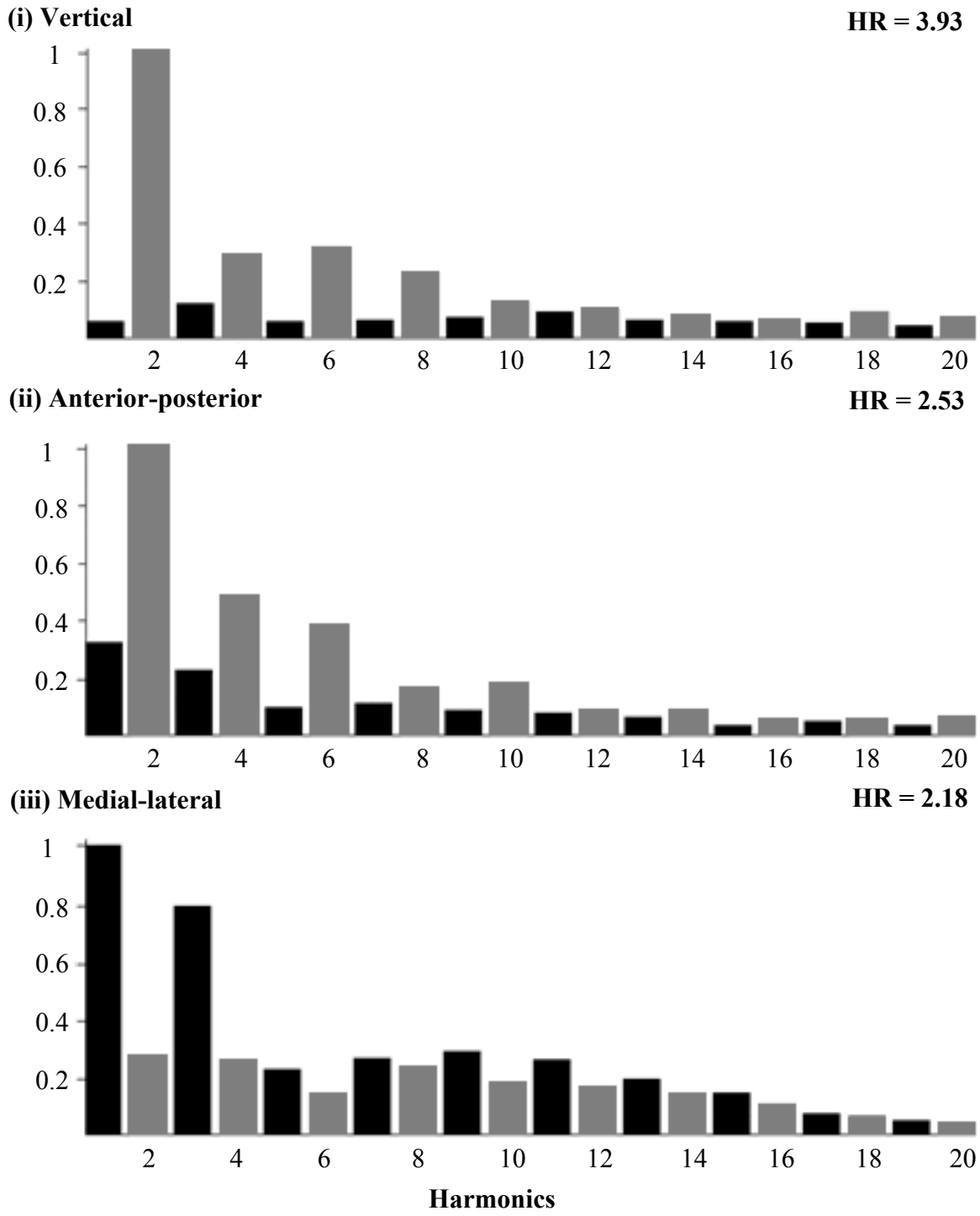

Figure 9.2: Exemplar harmonics of the (i) vertical, (ii) anterior-posterior and (iii) medial-lateral acceleration signal with even harmonics in grey and odd harmonics in black. Note that the magnitude of the harmonics is expressed as an arbitrary unit normalised to 1.

Trunk accelerations were also used to derive several temporal gait measures, by identifying the timing of foot contacts using peak vertical trunk accelerations (Cole et al., 2017). By summing the number of steps taken by each participant during each walking trial and dividing this by the time taken in minutes, it was possible to determine cadence (steps/min). Similarly, by determining the time that had elapsed between two successive steps, it was possible to calculate the average step time for each participant (seconds) and step timing variability (standard deviation of the step times, recorded in milliseconds). All accelerometer-based analyses were performed using a custom developed MATLAB program (v7.13, The MathWorks, USA).

Individual DBS electrodes were identified by merging the postoperative computed tomography scans with the preoperative magnetic resonance imaging using 3D Slicer v4.11 (Fedorov et al., 2012). Images were aligned along the Anterior and Posterior Commissures to normalise brain orientation using acpcdetect v2.0 (NeuroImaging Tools & Resources Collaboratory, https://www.nitrc.org). The three-dimensional coordinates for the ideal neurosurgical target within each STN were determined separately for each hemisphere of the brain by an experienced neurologist (Dembek et al., 2019). These data were subsequently used to calculate the distance (in millimetres) between the midpoint of each electrode and the ideal target. The difference between the ideal and actual location of the active electrode was expressed in the form of X (negative = more medial), Y (negative = more posterior) and Z (negative = more inferior) distance, which were combined to provide a Euclidean distance. All distance calculations were performed automatically using a custom script written in Python v3.7 (Python Software Foundation).

9.3.5 Statistical Analysis

Demographic data were reported as aggregate means and standard deviations for the entire group. To examine differences between high- and low-frequency stimulation conditions with respect to the clinical assessments and the accelerometer-based measures of gait, linear mixed model analyses with a repeated factor of stimulation (2 levels) were used. Given that walking speed has been shown to influence segmental accelerations (Menz et al., 2003b) and was not constrained in this study, it was included as a covariate in each of the linear mixed model analyses. Linear mixed model analyses were performed with walking speed and each of the following entered separately as covariates; the Euclidean distance; X distance; Y distance; Z distance; the TEED, and the UPDRS-III. Furthermore, to determine whether the difference between the ideal and actual location of the active electrode significantly influenced head and trunk harmonic ratios, simple linear regression was used. All statistical procedures were conducted using the Statistical Package for the Social Sciences (SPSS) (Version 25, SPSS Inc., USA), with the estimated marginal means and standard errors considered against $P < 0.05$ level of significance. Following completion of all data analyses, the principal investigator was unblinded to the order of participant testing to allow the study's outcomes to be appropriately interpreted and discussed.

9.4 Results

9.4.1 Study Population

Between March and August 2018, 31 people with PD and STN-DBS expressed interest to participate in the study. Of these people, 26 were deemed to be eligible following initial screening and scheduled to attend the data collection session (Figure 9.3). Of the 5 participants who were not recruited, 2 were unable to be contacted again after they had made initial contact and 3 were deemed to be ineligible, as their STN-DBS surgery was either <1 year ago (n = 2)

or their age was <50 years (n = 1). Of the 26 participants recruited into the study, 4 withdrew prior to their scheduled assessment and a further 3 were excluded as they were unable to ambulate following overnight withdrawal from their medication. The remaining 19 participants attended the testing session and completed the objective walking assessments and the clinical assessments for symptom severity. Following data collection, data for 5 participants were excluded due to the participants either reporting that they had taken their anti-parkinsonian medication on the morning of testing (n = 3) or because their chronic stimulation was already low-frequency stimulation (n = 2). Data for the remaining 14 participants (Table 9.1) were included in the subsequent analyses.

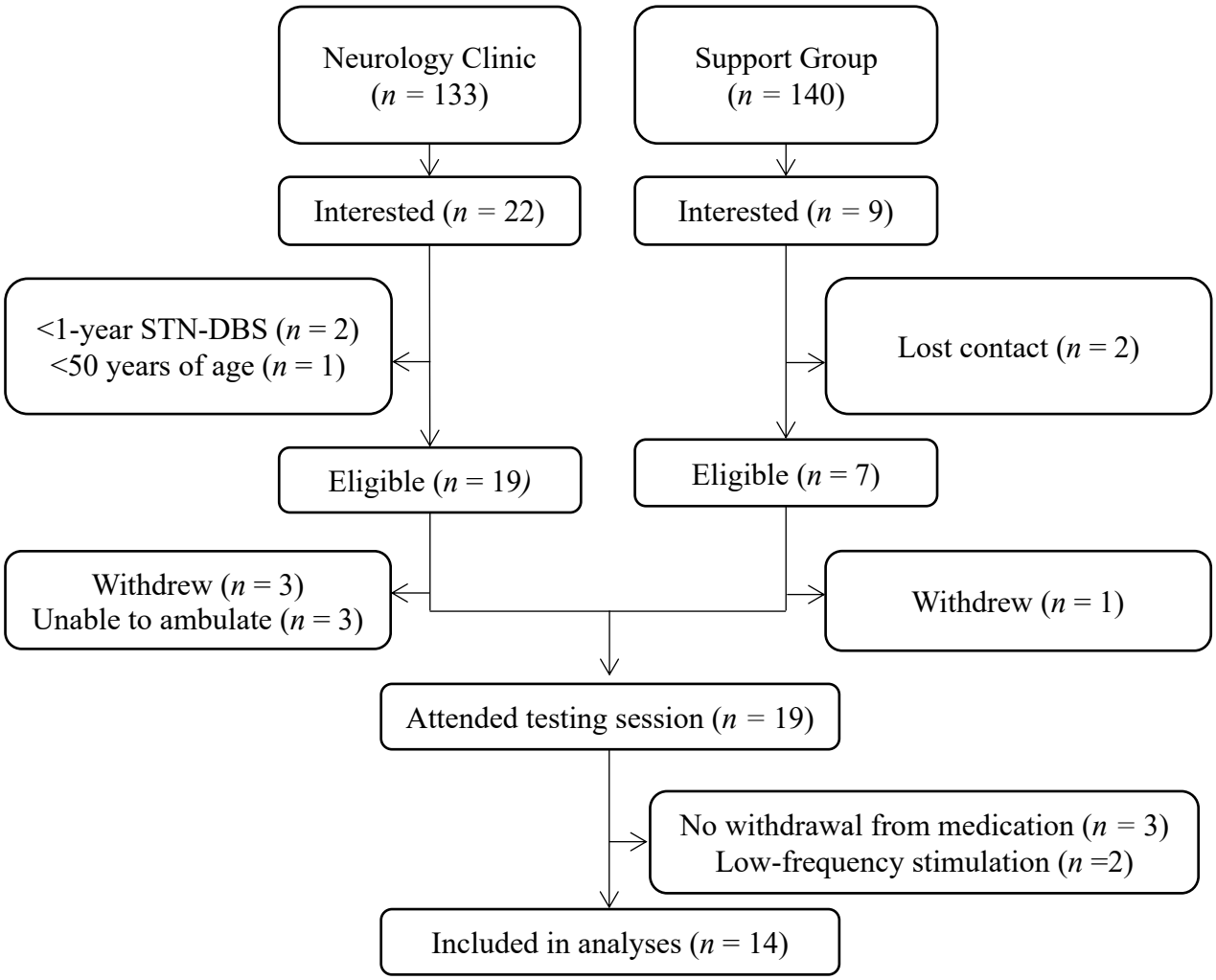

Figure 9.3: Study Flow chart.

Table 9.1: Demographic information and disease-specific characteristics for the people with PD and STN-DBS. Data represent mean (±1 standard deviation), absolute numbers (percentage of sample)[a] or mean (range)[b].

	n = 14
Demographics	
Gender (male)[a]	12.0 (85.7%)
Age (years)	69.6 (7.5)
Height (m)	1.8 (0.1)
Mass (kg)	81.3 (15.1)
Falls history and fear of falls	
Retrospective faller[a]	7.0 (50.0%)
ABC-6	53.8 % (23.6%)
Neurological Examination	
Disease duration (years)	12.0 (6.2)
UPDRS-III	32.7 (10.7)
Freezers[a]	5.0 (35.7%)
New Freezing of Gait Questionnaire	19.8 (5.8)
PDQ-8	27.7 (15.9)
No anti-parkinsonian medications[a]	7.0 (50.0%)
Levodopa dose (mg/day)	271.5 (115.0)
Dopamine agonists[a]	4.0 (28.6%)
Monoamine oxidase type B inhibitors[a]	0.0 (0.0%)
Catechol-o-methyl transferase inhibitors[a]	0.0 (0.0%)
DBS information	
Time since STN-DBS (years)	4.0 (2.4)
Euclidean distance[b]	2.36 (0.32 - 5.17)
X distance (negative = medial)[b]	-0.90 (-3.17 - 1.72)
Y distance (negative = posterior) [b]	-0.35 (-1.80 – 3.45)
Z distance (negative = inferior) [b]	-0.74 (-4.33 – 2.68)

Abbreviations: **ABC-6:** 6-item Activities-specific Balance Confidence scale; **PD:** Parkinson's disease; **PDQ-8**: 8-item Parkinson's Disease Questionnaire; **STN-DBS**: Deep brain stimulation of the subthalamic nucleus; **UPDRS-III:** Motor subscale of the Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

9.4.2 Gait stability

Linear mixed model analyses that controlled for walking speed, returned a significant main effect for stimulation (low- vs. high-frequency), for medial-lateral and vertical harmonic ratios of the trunk (Table 9.2). For each of these components, the harmonic ratios were significantly higher during the low-frequency stimulation condition, compared with the high-frequency stimulation state. Linear mixed model analyses that controlled for both walking speed and the Euclidean distance returned a significant main effect only for medial-lateral harmonic ratios of the trunk, which did not change when controlling for the X, Y, and Z distances of the active electrodes or the TEED. When controlling for symptom severity, a significant main effect was found for anterior-posterior, medial-lateral and vertical harmonic ratios of the trunk. Simple linear regression analyses showed that, during the high-frequency stimulation condition, having more ventrally located active electrodes was predictive of lower medial-lateral (B = 0.19, $P = 0.030$), and vertical (B = 0.40, $P = 0.017$) harmonic ratios of the trunk. Only the magnitude of vertical trunk movement was found to be significantly increased with low-frequency stimulation compared with high-frequency.

Table 9.2: Temporal and accelerometer-based measures of gait for PD participants receiving high-frequency stimulation and low-frequency stimulation during self-selected and comfortable walking. Data represent the mean (±1 standard deviation). Linear mixed model analyses were performed with walking speed and each of the following entered separately as covariates; the Euclidean distance; X distance; Y distance; Z distance; the total electrical energy derived, and the UPDRS-III.

	HFS (n = 14)	**LFS** (n = 10)	**Speed (1.08 m/s)**	**Speed (1.09 m/s) & ED (2.31 mm)**	**Speed (1.09 m/s) & X (-0.76)**	**Speed (1.09 m/s) & Z (-0.18)**	**Speed (1.09 m/s) & Y (0.72)**	**Speed (1.08 m/s) & TEED (92.40)**	**Speed (1.08 m/s) & UPDRS-III (31.70)**
Temporal measures									
Walking Speed (m/s)	1.08 (0.15)	1.08 (0.19)	ns	ns	ns	ns	ns	ns	ns
Cadence (steps/minute)	126.69 (9.06)	126.66 (11.74)	ns	ns	ns	ns	ns	ns	ns
Step time (seconds)	0.53 (0.04)	0.53 (0.05)	ns	ns	ns	ns	ns	ns	ns
Step time variability (ms)	24.5 (14.22)	22.76 (17.26)	ns	ns	ns	ns	ns	ns	ns
Harmonic ratios									
Head AP	1.83 (0.51)	2.04 (0.63)	ns	ns	ns	ns	ns	ns	ns
Head ML	2.25 (0.54)	2.39 (0.69)	ns	ns	ns	ns	ns	ns	ns
Head VT	2.57 (0.78)	2.96 (0.8)	ns	ns	ns	ns	ns	ns	ns
Trunk AP	1.78 (0.43)	2.06 (0.44)	ns	ns	ns	ns	ns	ns	**0.046**
Trunk ML	1.81 (0.5)	2.23 (0.61)	**0.005**	**0.012**	**0.011**	**0.010**	**0.011**	**0.010**	**0.002**
Trunk VT	2.9 (1.01)	3.34 (1.11)	**0.048**	ns	ns	ns	ns	ns	**0.044**
Movement Amplitude									
Head AP	1.18 (0.53)	1.20 (0.41)	ns	ns	ns	ns	ns	ns	ns
Head ML	1.07 (0.23)	1.02 (0.2)	ns	ns	ns	ns	ns	ns	ns
Head VT	2.07 (0.32)	2.09 (0.46)	ns	ns	ns	ns	ns	ns	ns
Trunk AP	0.91 (0.16)	0.92 (0.21)	ns	ns	ns	ns	ns	ns	ns
Trunk ML	1.23 (0.35)	1.18 (0.29)	ns	ns	ns	ns	ns	ns	ns
Trunk VT	2.28 (0.31)	2.33 (0.47)	**0.006**	**0.027**	**0.028**	**0.027**	**0.027**	**0.004**	**0.018**

Abbreviations: AP: Anteroposterior; **ED:** Euclidean distance; **HFS:** High-frequency stimulation; **LFS:** Low-frequency stimulation; **ML:** Medial-lateral; **ms:** Milliseconds; **m/s:** metres per second; **TEED**: the total electrical energy derived; **UPDRS-III:** Motor sub-section of the Unified Parkinson's Disease Rating Scale; **VT:** Vertical.
Symbols: ns = no significant differences.

9.4.3 Temporal gait outcomes and clinical assessments

There were no significant differences in walking speed, cadence, step time or step time variability between the high- and low-frequency conditions. Furthermore, there were no differences reported for any of the clinical mobility measures (6-metre walk or Timed Up and Go test) or symptom severity measures (UPDRS-III or retropulsion test) between the low- and high-frequency stimulation conditions (Table 9.3). While 5 of the investigated population had reported freezing of gait symptoms, no freezing episodes took place during data collection.

Table 9.3: Clinical measures and stimulation paraments for high-frequency stimulation and low-frequency stimulation during self-selected comfortable and quick walking speeds. Data represent the mean (±1 standard deviation).

	HFS Mean (SD)	**LFS Mean (SD)**	***Sig.***
Clinical measures			
UPDRS-III	32.7 (10.7)	30.9 (9.8)	0.675
Retropulsion test	1.4 (1.3)	1.1 (1.2)	0.623
Comfortable 6m walk test (s)	5.3 (0.9)	5.4 (1.2)	0.809
Quick 6m walk test (s)	4.1 (0.8)	4.1 (0.9)	0.837
Timed up and go (s)	18.9 (5.7)	17.4 (3.4)	0.513
Stimulation parameters			
Frequency (Hz)	126.1 (12.3)	60.0 (0.0)	**<0.001**
Amplitude (V)	3.3 (0.7)	4.7 (1.1)	**<0.001**
Pulse width (μs)	62.1 (5.5)	62.1 (5.5)	1.000

Abbreviations: **HFS**: High-frequency stimulation; **LFS**: Low-frequency stimulation; **UPDRS-III:** Motor subscale of the Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

Of the 14 participants who completed the assessments, 10 experienced worsening symptoms of resting tremor with low-frequency stimulation. Six of these participants were able to complete the assessments without difficulty, but the remaining 4 were unable to complete the assessments while receiving low-frequency stimulation. Secondary analyses that included only those participants who were able to complete the assessments under both therapeutic

conditions confirmed that the reported findings were not biased by the four participants who were unable to complete the low-frequency STN-DBS condition. There was no difference in age, disease duration, time since surgery or electrode location for those who were or were not unable to complete the low-frequency STN-DBS condition.

9.5 Discussion

This study employed a double-blinded randomised cross-over design to evaluate the effect of low-frequency STN-DBS on objective measures of gait stability in people with PD. The study's hypothesis was supported in that we found low-frequency STN-DBS (60 Hz) with a commensurate voltage increase to maintain the TEED at the participants' usual chronic high-frequency stimulation level significantly improved gait stability in people with PD following STN-DBS compared to high-frequency stimulation. However, this alternate stimulation strategy was not tolerated by all participants and, in some cases, the gait improvements came at the cost of re-emerged limb tremor.

Rather than investigating the effect of low-frequency stimulation for alleviating freezing of gait, a symptom that is known to respond well to this stimulation strategy (Xie et al., 2017), this study explored in greater detail it's impact on gait stability during straight line walking. Of the published studies investigating alternate patterns of STN-DBS stimulation, the outcomes regarding postural stability reported were almost exclusively based on well-established, albeit largely subjective, clinical scales (Conway et al., 2019). While these measures have provided important information regarding the potential efficacy of alternate STN-DBS parameters, it was considered that objective measures of gait rhythmicity may offer additional and unique insight into such alternate approaches. Considering higher harmonic ratios represent improved gait patterns, the higher values recorded with low-frequency stimulation suggest that this strategy

may be an effective means for improving a participant's gait stability. This notion is supported by research which has shown that people with PD exhibit less rhythmic movements (i.e. lower harmonic ratios) than age-matched controls during unconstrained walking (Lowry et al., 2009). Similarly, in separate research, PD fallers who have not undergone STN-DBS were shown to exhibit significantly poorer head (medial-lateral, vertical) and trunk (anterior-posterior, medial-lateral, vertical) rhythmicities compared with PD non-fallers (Cole et al., 2017), which were determined to be reflective of reduced gait stability in these people. To our knowledge this is the first study to evaluate gait stability in people with PD following STN-DBS using the accelerometer-based harmonic ratio measure. Our results indicate that low-frequency STN-DBS therapy that is administered with a voltage change to maintain the TEED was effective at improving gait stability in most post-operative people with PD. Although we are unable to compare improvements with a pre-surgical state, these findings provide evidence for the utility of alternate STN-DBS stimulation parameters for people with PD who experience gait complications with high-frequency STN-DBS.

It has been highlighted in a small number of studies that compared with their pre-surgery state, some people experience a decline in postural stability with high-frequency STN-DBS (Fasano et al., 2015; St George et al., 2010). Interestingly, our results showed that participants who have more ventrally located electrodes were more likely to experience deficits in gait stability during high-frequency stimulation. This finding was complementary to research that found ventral stimulation had a significant detrimental effect on temporal-spatial measures compared to dorsal (Johnsen, Sunde, Mogensen, & Ostergaard, 2010). High-frequency stimulation at more ventrally located electrodes may have undesired effects on areas immediately inferior to the target, such as the substantia nigra pars reticulata and the pedunculopontine area. Both of these areas are considered to be involved in posture control

(Tommasi et al., 2007) and are known to respond well to low-frequency stimulation (Thevathasan et al., 2018; Valldeoriola et al., 2019). Interestingly, while high-frequency stimulation at more ventrally located electrodes may have undesired effects, participants with more ventrally positioned electrodes experience greater improvements with low-frequency STN-DBS (Khoo et al., 2014).

To our knowledge, this is the first double-blinded randomised trial to statistically account for differences in active electrode location to explore whether the efficacy of low-frequency stimulation for gait stability was influenced by the location of the active electrode. The results suggest that, despite a range of active electrode locations, low-frequency stimulation significantly improved gait compared to high-frequency stimulation for the investigated population. While the exact therapeutic mechanism of low-frequency stimulation remains unclear, there is evidence to suggest that the improvements observed with low-frequency stimulation may result due to the diminished effect that this alternate therapy has (compared with high-frequency stimulation) on the neuronal tissues surrounding the STN. However, the results of the current study suggest that these improvements were independent of electrode location and that other mechanisms may also be responsible. For example, the independent improvement in gait stability may lend support to a previously identified mechanism, which suggests that a stimulation frequency of 60 Hz, as used in this study, may override the pathological neuronal oscillation in PD and boost the prokinetic gamma band activity (Brown, 2003; Xie et al., 2017). However, while this mechanism may be pertinent for explaining the alleviation of freezing of gait symptoms, it is unclear whether a similar mechanism is responsible for improvements in gait stability with low-frequency STN-DBS compared to high-frequency stimulation. As such, this area warrants further investigation.

It must be noted that this alternate stimulation was not tolerated by all and, in some cases, the gait improvements came at the cost of a re-emerged limb tremor. Specifically, six participants experienced tremor symptoms but were still willing and able to complete the assessments with low-frequency stimulation. A further four participants were unable to complete the assessments at the alternate frequency due to a re-emergence of tremor. A similar re-emergence of tremor was reported in a separate study evaluating the effects of low-frequency STN-DBS (Phibbs et al., 2014); potentially highlighting the need for careful selection of those likely to benefit. Nonetheless, the current study's findings show that low-frequency stimulation improves gait stability, regardless of electrode placement. With advances in adaptive DBS technology (Little et al., 2016), it may become feasible to deliver low-frequency stimulation for the improvement of gait stability, while also having a high-frequency stimulation policy to initiate when symptoms of tremor reappear.

Unlike objective gait stability, there were no differences between stimulation conditions for the recorded temporal gait measures. Although these outcomes were commensurate with one study (Vallabhajosula et al., 2015), they were in contrast to most other research, which has reported improvements in walking speed with low-frequency STN-DBS (Khoo et al., 2014; Moreau et al., 2008; Ricchi et al., 2012; Xie et al., 2015). The apparent disparity between the current study's findings and earlier studies may reflect the largely heterogeneous populations. For example, research has found that low-frequency stimulation significantly improved gait speed and reduced step frequency in those who exhibited significant gait disability with high-frequency STN-DBS (Moreau et al., 2008). Furthermore, the parameters used by different studies when programming the low-frequency STN-DBS adjustment to voltage (Conway et al., 2019) were highly variable, with some making changes to frequency only, while others also made a concomitant adjustment to voltage (Conway et al., 2019).

Similar to other studies investigating the effect of 60 Hz stimulation on valid, clinically feasible, although largely subjective assessments of postural stability (Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destée, et al., 2011; Phibbs et al., 2014; Sidiropoulos et al., 2013; Vallabhajosula et al., 2015), no significant differences were noted for the retropulsion test between the high- and low-frequency stimulation conditions. While this may be due to the retropulsion test focusing more on stability under static conditions, the similar lack of differences for the clinical mobility assessments seems to suggest that subtle changes in stability and/or gait function are not easily captured with these tools (Tan et al., 2018). Given this point, it seems reasonable to suggest that the incorporation of wearable technology into routine clinical practice may provide additional and unique information about gait dysfunction in people with PD (Buckley et al., 2018).

Limitations

Participants were required to wait a minimum of 60-minutes before each stimulation condition to allow adequate wash-in time. While it could be argued that a longer wash-in period may have been needed to gauge therapeutic efficacy, the 60-minute wash-in/wash-out period was in line with studies that have adopted similar methodologies (Khoo et al., 2014; Moro et al., 2002; Temperli et al., 2003). Nevertheless, the relatively short time period between stimulation conditions means that the results presented in this paper should be considered to represent the participants' acute responses. Longitudinal studies are required to determine the long-term efficacy of low-frequency stimulation for people with PD and STN-DBS. A second potential limitation is that participants were assessed following overnight withdrawal from their anti-parkinsonian medications, meaning that, for participants that usually would take anti-parkinsonian medications, the high-frequency stimulation condition would not have been

reflective of their best therapeutic state. Nonetheless, similar research involving a non-DBS PD population who presented with primary symptoms of postural instability has shown that, levodopa replacement therapy has varied effects on gait stability and at times, detrimental (Pelicioni et al., 2018).

9.6 Conclusions

This double-blinded randomised cross-over study found that low-frequency STN-DBS improved gait stability in people with PD compared with high-frequency stimulation. While the exact underlying therapeutic mechanism remains unconfirmed, the improvement was independent of the anatomical placement of the active electrode, symptom severity and TEED. However, low-frequency stimulation was not well tolerated by all participants, as some experienced a marked increase in resting tremor, while others were unable to tolerate the alternate stimulation. For these people, it may be advisable to promote alternate forms of therapy, such as exercise-based interventions (Hubble et al., 2018; Hubble et al., 2019), to complement high-frequency STN-DBS and improve gait stability. Nonetheless, the results of this study provide evidence for the potential efficacy of low-frequency stimulation to improve gait stability for people with PD who have STN-DBS.

CHAPTER 10: GENERAL DISCUSSION & FINDINGS

It is well understood that high-frequency STN-DBS is ineffective for managing symptoms of postural instability in people with PD (Fasano et al., 2010; Zibetti et al., 2011). Given this apparent shortcoming, this program of research addressed a series of questions concerning the post-operative management of people with PD who have STN-DBS by investigating the effects of low-frequency stimulation on postural stability compared to high-frequency stimulation. Postural stability was objectively assessed during both standing, walking and the transition between the two (i.e. gait initiation). The results presented in this dissertation provided evidence that low-frequency stimulation with an increase in voltage to maintain the TEED of high-frequency STN-DBS, improved postural stability during standing and dynamic tasks compared to high-frequency stimulation.

During standing, low-frequency STN-DBS reduced the sway velocity of participants COP movement compared to high-frequency STN-DBS (Figure 10.1). While there were no differences for the range that the COP travelled, the reduced sway velocity during low-frequency STN-DBS means that the COP moved at a slower rate within the range covered (Figure 10.2). This reduction in sway velocity is considered to be reflective of improved postural stability, as people with PD without STN-DBS exhibit increased sway velocity compared to aged-matched healthy controls (Menant et al., 2011). In response to the reported declines in postural stability with high-frequency STN-DBS (Fasano et al., 2015; St George et al., 2010), research investigating low-frequency stimulation has provided inconsistent findings, with some reporting improvements (Khoo et al., 2014; Xie et al., 2015) and others describing no difference in postural stability (Moreau et al., 2008; Phibbs et al., 2014; Sidiropoulos et al., 2013). However, such research has been conducted with outcomes almost exclusively based on well-established, albeit largely subjective, clinical scales (Conway et al., 2019). This dissertation extends on this body of research by incorporating objective force plate measures to

examine the effects of low-frequency STN-DBS on standing postural stability. The reported improvements in objective force plate measures of postural stability during the low-frequency stimulation condition provides evidence for its utility. Similar changes in sway velocity have been reported following exercise-based interventions aimed at improving postural stability in people with PD (Hubble et al., 2019). As such, it seems reasonable to suggest that based on sway measures, it is possible to improve standing postural stability with low-frequency STN-DBS compared to high-frequency.

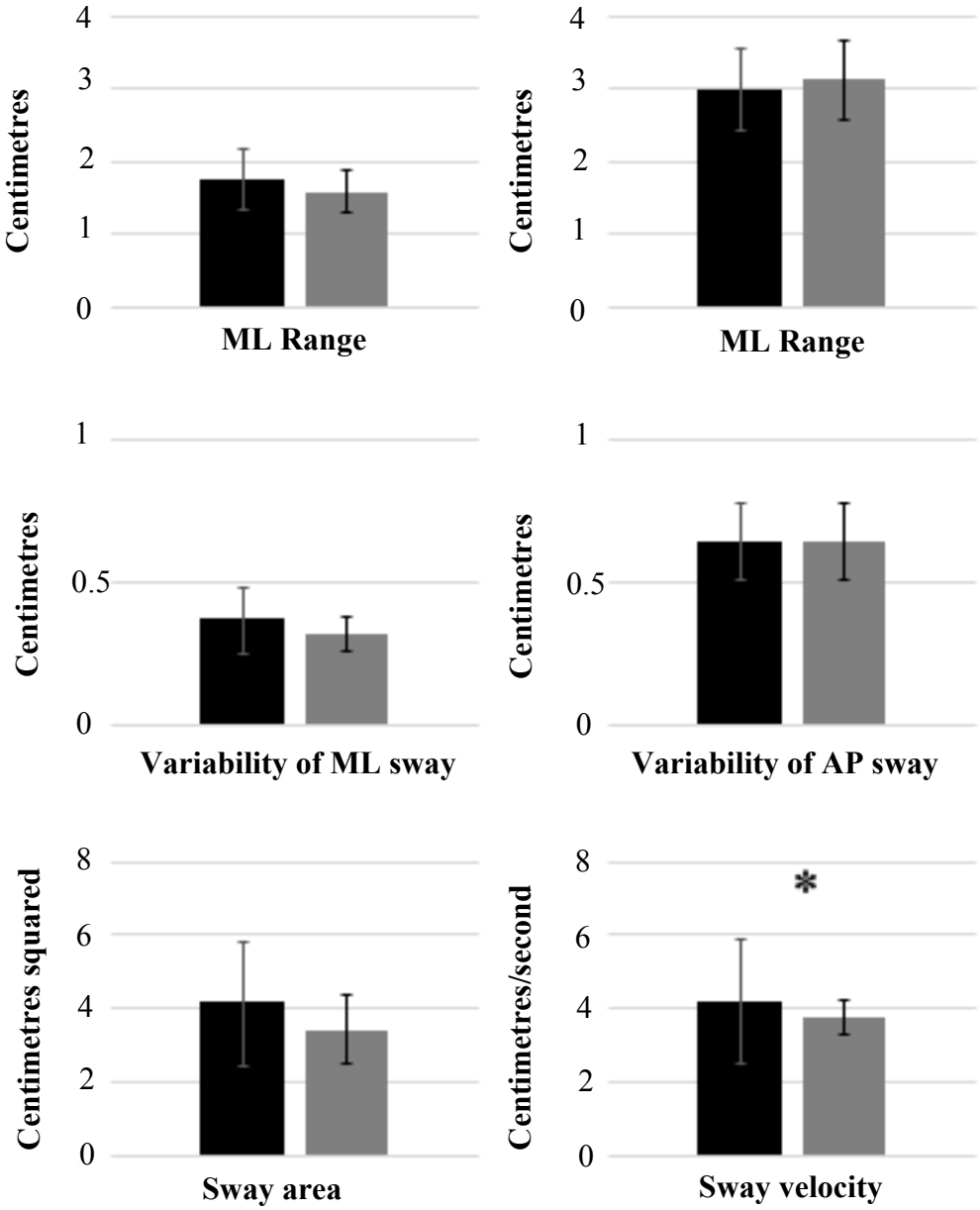

Figure 10.1: Group means for the time-series measures of standing postural stability derived from the centre of pressure data collected using a force-plate during the high-frequency stimulation (black) and low-frequency stimulation (grey) conditions. AP: anterior-posterior, ML: medial-lateral.∗ denotes p <0.05 between conditions.

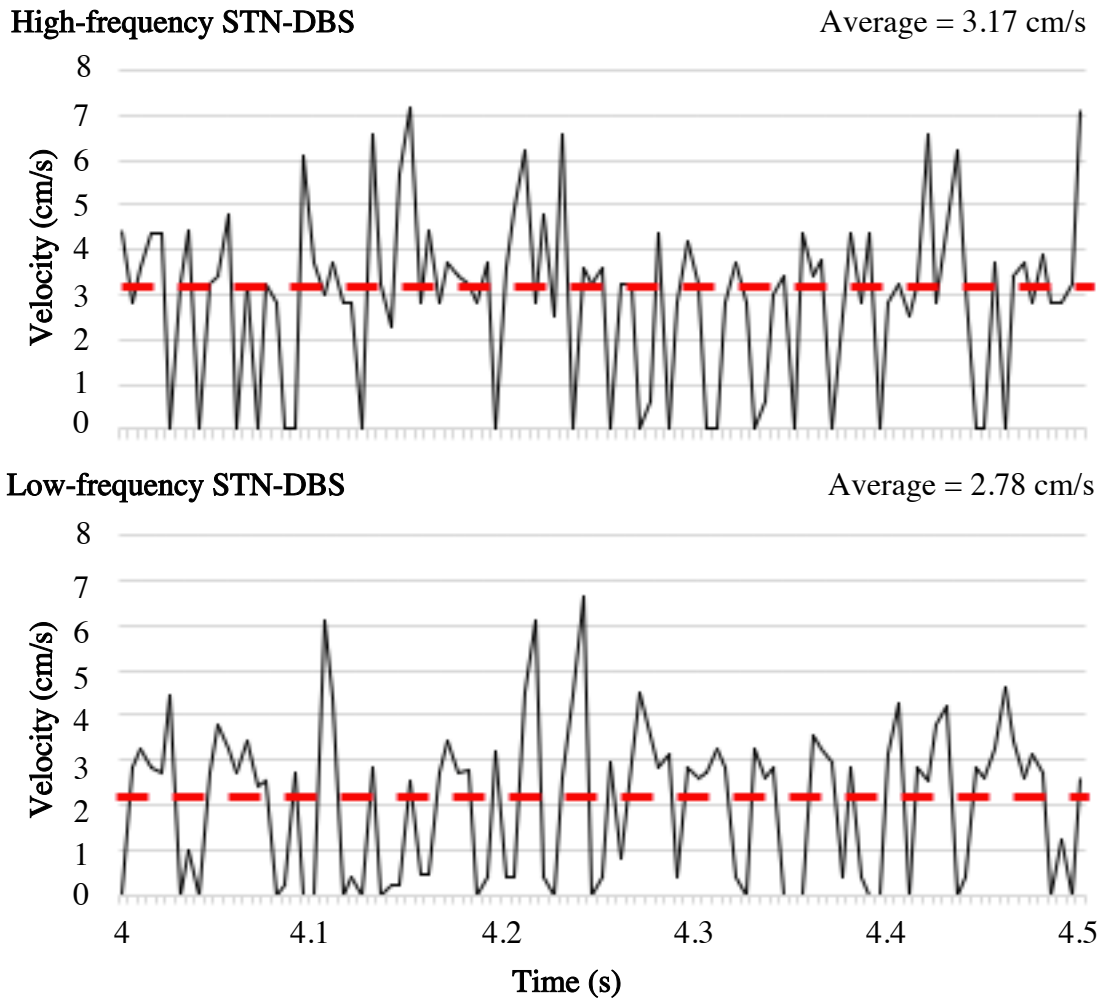

Figure 10.2: Exemplar COP velocity data for one participant's (n = 1) high- and low-frequency STN-DBS with the average of the data visually represented by the dotted line.

This was the first research to examine the regularity of COP sway using the sample entropy measure in people with PD with STN-DBS. During low-frequency STN-DBS, participants demonstrated slower sway velocities and a more regular sway pattern (i.e., more predictable) compared to high-frequency stimulation (Figure 10.3). These differences in sample entropy suggest that measures of sway regularity may provide unique insight into standing postural stability and the efficacy of different STN-DBS parameters for people with PD who have STN-DBS. However, given there has been little research using this measure, there is currently a lack of consensus regarding how best to interpret the meaning of the more regular

sway patterns (i.e. lower sample entropies) observed with low-frequency STN-DBS. For example, in some research, a more regular sway pattern has been suggested to be indicative of better postural stability. This assertion has been based on earlier work, which showed that younger adults exhibited more regular sway patterns than elderly fallers and non-fallers (non-PD population) (Borg & Laxaback, 2010). In contrast, more recent investigations have offered an alternate interpretation, suggesting that more regular sway patterns may reflect a postural control system that has reduced flexibility and, hence an impaired capacity to adapt to different conditions. This argument has stemmed from studies that reported more regular sway patterns for community-dwelling older adults who fall compared with their age-matched counterparts who do not fall (Zhou et al., 2017) and more regular sway patterns for people with PD compared to non-PD populations (Pelykh et al., 2015). With the latter interpretation in mind, our findings may suggest that the more regular sway patterns during low-frequency stimulation may reflect an unwanted effect of this stimulation strategy on standing postural stability. However, as this is the first research to use sample entropy in a STN-DBS PD cohort, there is a need for further research to clarify the relationship between sway regularity to the risk of falling and other adverse events.

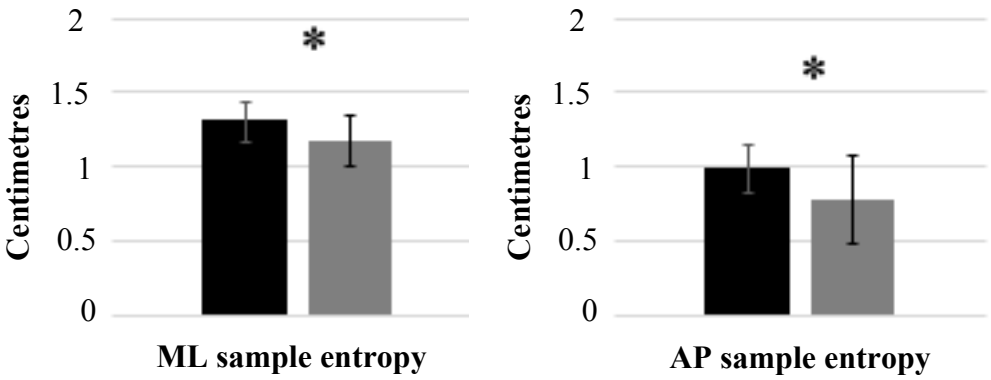

Figure 10.3: Mean sample entropy data for medial-lateral (ML) and anterior-posterior (AP) sway during the high-frequency stimulation (black) and low-frequency stimulation (grey) conditions.∗ denotes p <0.05 between conditions.

With regards to investigating postural stability during the transition from standing to gait, referred to as gait initiation, low-frequency STN-DBS improved postural stability during the locomotion phase compared to high-frequency stimulation. During the locomotion phase, participants had a greater sway area (i.e. overall COP trace) with low-frequency STN-DBS, which was underpinned by an increased medial-lateral sway range. The increased medial-lateral sway range illustrates that during low-frequency STN-DBS, participants moved a greater distance side-to-side, as reflected by the increased COP medial-lateral range and sway area. This increase in side-to-side movement is considered an improvement as increased COP displacement during this task indicates better postural stability (Hass, Waddell, Wolf, Juncos, & Gregor, 2008; Liu et al., 2006). Importantly, improvements in medial-lateral range, sway area and average sway velocity were noted during the locomotion phase which has been shown to worsen with increased symptom severity (Hass et al., 2005). Furthermore, average sway velocity also increased (improve) during gait initiation, which has been shown to worsen following high-frequency STN-DBS compared to pre-surgery (Rocchi et al., 2012). Research has highlighted that rehabilitation strategies to improve sway range laterally may be beneficial for improving postural stability during gait initiation (Hass et al., 2008). Therefore, findings of the investigation into gait initiation supports the positive effect of low-frequency STN-DBS compared to high-frequency STN-DBS for postural stability during dynamic tasks.

Following STN-DBS, most falls occur during steady-state walking (Nilsson et al., 2011), highlighting the elevated risk associated with the performance of this task. Throughout this dissertation, changes in gait-related (dynamic) postural stability were assessed using the harmonic ratio, in which higher harmonic ratios were deemed to be representative of improved gait stability (Bellanca et al., 2013a; Cole et al., 2017; Lowry et al., 2009). People who exhibit less rhythmic gait patterns are suggested to have greater difficulty adjusting to the small postural

challenges that characterise walking in real world environments (Cole et al., 2017). Therefore, the higher harmonic ratios (i.e. more rhythmic gait patterns) observed during the trials completed with low-frequency stimulation provided evidence that this stimulation strategy may be an effective means for improving a participant's gait stability compared to high-frequency (Figure 10.4). The results of this dissertation also provide evidence that may aid in the advancement of new technologies, such as adaptive DBS, suggesting that during periods of dynamic movement, low-frequency stimulation is beneficial (Little et al., 2013). While the exact underlying therapeutic mechanism for these improvements remains unconfirmed, the apparent benefits of the lower frequency was independent of the anatomical placement of the active electrode, symptom severity and TEED.

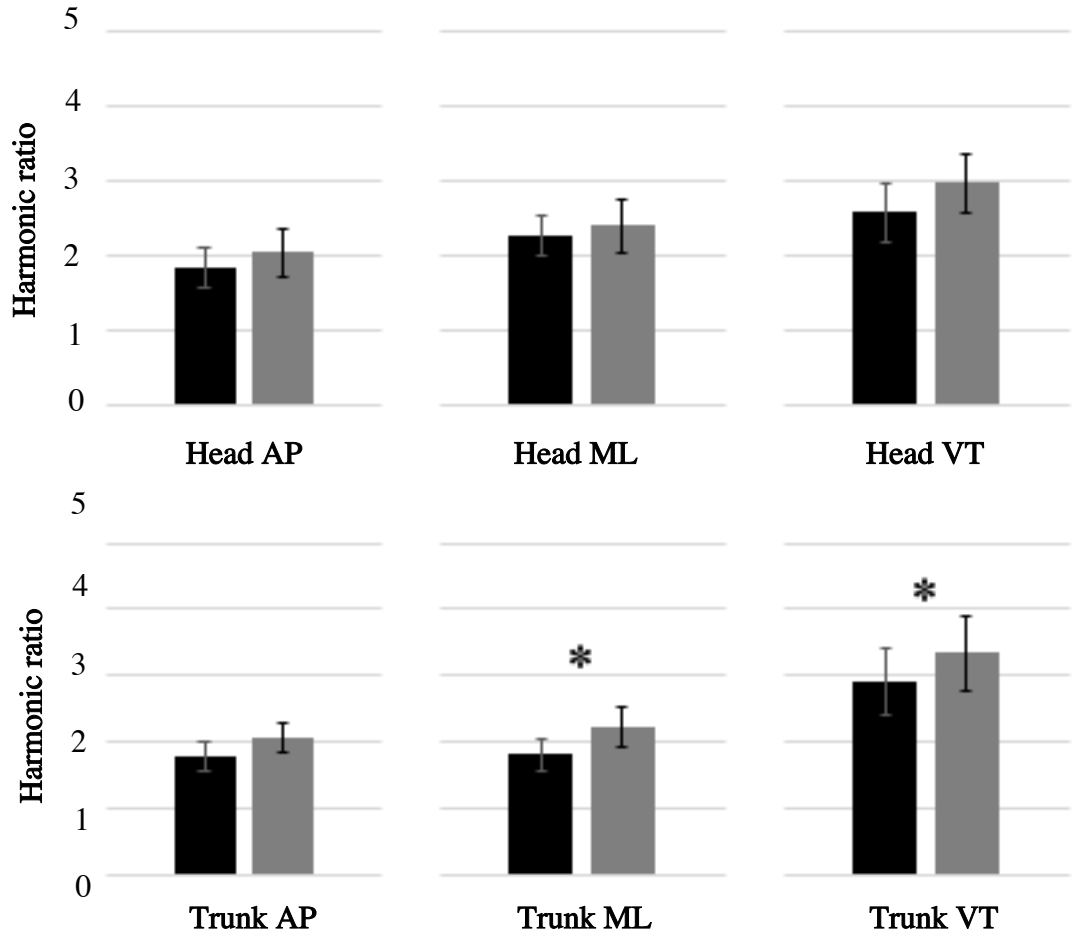

Figure 10.4: Mean harmonic ratios for the head and trunk segments during walking trials with high-frequency stimulation (black) and low-frequency stimulation (grey). AP: anterior-posterior, ML: medial-lateral, VT: vertical.

To explore the underlying therapeutic mechanism for these improvements, the electrode placement data were included in regression analyses of the gait stability measures. Participants whose active contacts were more ventrally located were found to be more likely to experience deficits in gait stability during high-frequency stimulation. This finding adds important information to the body of evidence surrounding the importance of electrode placement and may prove to be useful for surgical teams who are seeking to maximise postural stability outcomes for people with PD receiving high-frequency STN-DBS. The relationship between a more ventrally located active contact and the poorer postural stability outcomes may be due to

the electrical current spreading to neural areas located immediately inferior to the STN (e.g. substantia nigra pars reticulata, pedunculopontine area), which are believed to be involved in posture control (Tommasi et al., 2007). Given these areas are known to respond well to low-frequency stimulation when targeted via DBS (Thevathasan et al., 2018; Valldeoriola et al., 2019), it is perhaps unsurprising that postural stability outcomes improved with low-frequency STN-DBS. This is similar to research that found participants with more ventrally positioned electrodes experience greater improvements in motor symptoms with low-frequency STN-DBS (Khoo et al., 2014). This is the first study to statistically account for differences in active electrode location to explore whether the efficacy of low-frequency stimulation for postural stability is influenced by the location of the active electrode. Despite a range of active electrode locations, low-frequency stimulation improved postural stability during both the locomotion phase of gait initiation and steady-state walking. While the exact therapeutic mechanism remains unconfirmed, the independent improvement in gait stability may lend support to the notion that low-frequency stimulation (e.g. at 60 Hz) overrides the pathological neuronal oscillations evident in PD and boost the prokinetic gamma band activity. Ultimately, this boost in the prokinetic gamma band activity would facilitate movement and promote the successful execution of daily tasks (Brown, 2003; Xie et al., 2017). Nevertheless, while this mechanism may be pertinent for explaining the alleviation of freezing of gait in people with PD, it is unclear whether a similar mechanism is responsible for the reported improvements in gait stability observed in the current cohort during the low-frequency STN-DBS condition. As such, this area warrants further investigation.

While the efficacy of low-frequency stimulation for improving postural stability has been highlighted, the potential utility of this alternate stimulation strategy may be limited due to the noted adverse effects. In this program of studies, no differences were found between the

high- and low-frequency stimulation conditions with respect to the total UPDRS score. Furthermore, due to risks of bias, presence of statistical heterogeneity and imprecision amongst the results presented in the existing literature (Conway et al., 2019), it was not deemed appropriate to include the UPDRS-III in the meta-analysis performed in Study 1. However, despite the lack of significant change in UPDRS-III sub-scores between the two therapeutic conditions, it seemed that low-frequency stimulation resulted in a re-emergence of tremor for some participants. Of the participants included in this program of research, eight participants experienced increased tremor severity during the low-frequency STN-DBS condition. Of these participants, 4 were able to complete the assessments without difficulty, while the remaining 4 were unable or unwilling to complete the assessments with the low-frequency stimulation. When considering the characteristics of the participants who could not complete the assessments with low-frequency STN-DBS, there were no differences for age, disease duration, time since surgery or electrode location. A similar re-emergence of tremor at lower STN-DBS frequencies has been reported (Phibbs et al., 2014), while others have reported no significant adverse effects with respect to the management of limb tremor (Khoo et al., 2014; Xie et al., 2015). Given high-frequency STN-DBS is believed to reduce tremor severity by reducing STN local field potentials associated with tremor severity (Beudel et al., 2015), lower stimulation frequencies may be associated with higher STN local field potentials and, hence, increased tremor severity. It is also possible that the re-emergence of tremor symptoms during low-frequency stimulation may be a result of increased coupling in cortico-striato-STN circuitry, which is considered to play a role in tremor severity (Blumenfeld et al., 2017). Considering the data presented in this dissertation and the existing literature, it seems that compared to high-frequency stimulation, low-frequency may be effective at improving symptoms of postural stability, but careful selection of those likely to benefit would be necessary to ensure these improvements do not come at the cost of exacerbating other potentially disabling symptoms.

People with PD who present with primarily tremor-dominant symptoms pre-surgery are more likely to experience a re-emergence of tremor with low-frequency STN-DBS, suggesting they should not be considered for low-frequency STN-DBS (Moreau et al., 2008; Ricchi et al., 2012; Xie et al., 2015). The data collected as a part of this dissertation supports this, with four participants not tolerating low-frequency STN-DBS due to the re-emergence of tremor. While sub-group analyses were underpowered, comparison of the patients who could and could not tolerate low-frequency STN-DBS highlighted no significant differences between the patients for symptom severity, or clinical or objective measures of postural stability during the high-frequency STN-DBS condition. Therefore, the dissertation could not add further information to the existing literature to inform the selection of people with PD who have STN-DBS that can tolerate low-frequency. Nonetheless, for those able to tolerate low-frequency STN-DBS, the data collected as a part of this dissertation builds on the existing evidence concerning its potential utility to improve postural stability for people with PD who have STN-DBS.

Table 10.1: Participant demographics.

Age / Gender	PDQ-8	ABC-6	RFOG	Disease / DBS Duration	High-frequency stimulation			Low-frequency stimulation			Comments
					Parameters			Parameters			
					V	F	PW	V	F	PW	
70.0 / Male	3.1	85	-	14.9 / 8.3	3.1	130	75	4.5	60	75	
76.3 / Male	46.9	38	26	9.8 / 3.0	2.7	110	60	3.7	60	60	
73.8 / Female	25.0	32	20	8.3 / 4.3	3.2	120	60	4.5	60	60	
74.0 / Male	6.3	77	-	7.5 / 3.4	3.9	130	60	5.8	60	60	
71.5 / Male	18.8	13	14	8.5 / 1.3	3.9	130	60	5.7	60	60	
64.9 / Male	59.4	65	-	29.3 / 2.9	2.3	115	60	3.1	60	60	
62.2 / Female	18.8	65	-	7.0 / 1.7	2.6	120	60	3.2	60	60	Tremor re-emerged with LFS
78.4 / Male	18.8	75	-	9.5 / 3.6	3.5	130	60	5.2	60	60	Tremor re-emerged with LFS
50.3 / Male	21.9	78	-	7.8 / 2.0	3.9	110	60	5.2	60	60	Tremor re-emerged with LFS
69.2 / Male	40.6	38	-	9.4 / 3.9	2.9	115	60	4.0	60	60	Tremor re-emerged with LFS
71.4 / Male	21.9	28	25	17.4 / 9.4	3.8	155	75	5.6	60	75	Unable to tolerate LFS
66.9 / Male	28.1	80	-	18.4 / 5.4	2.6	140	60	3.9	60	60	Unable to tolerate LFS
76.7 / Male	46.9	45	-	10.5 / 2.4	2.7	130	60	3.9	60	60	Unable to tolerate LFS
69.3 / Male	31.3	33	14	9.9 / 4.4	4.6	130	60	6.8	60	60	Unable to tolerate LFS
72.1 / Female	31.3	28	15	23.6 / 6.6	3.5	160	70	5.6	60	70	Non-ambulatory
71.9 / Female	25.0	2	-	6.9 / 2.9	3.3	110	60	4.5	60	60	Non-ambulatory

Abbreviations: **ABC-6:** 6-item Activities-specific Balance Confidence scale; **DBS**: Deep Brain Stimulation; **F**: Frequency; **LFS**: low-frequency stimulation; **M:** Male; **PDQ-8:** 8-item Parkinson's Disease Questionnaire; **PW**: Pulse width; **RFOG:** New Freezing of Gait Questionnaire; **V**: Voltage.

This dissertation found that for the studies investigating alternate patterns of STN-DBS stimulation, the outcomes reported were almost exclusively based on well-established, albeit largely subjective, clinical scales (Conway et al., 2019). This dissertation is the first to evaluate people with PD who have STN-DBS using the harmonic ratio measure for an insight into gait stability. It was found that the harmonic ratio delineated between high- and low-frequency stimulation conditions despite no differences in the UPDRS-III score, retropulsion pull test and tests of mobility (Figure 10.5). It should be noted that the *a priori* sample size estimate performed for this research was based on the harmonic ratio, and therefore, the lack of differences reported for clinical measures may be attributable to insufficient participant numbers. These findings are consistent with research also reporting a similar lack of differences between high- and low-frequency stimulation (Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destée, et al., 2011; Phibbs et al., 2014; Sidiropoulos et al., 2013; Vallabhajosula et al., 2015). There were also no differences in the temporal gait measures (e.g. step time) between the high- and low-frequency stimulation conditions. Collectively, this seems to add to the body of evidence suggesting that subtle changes in postural stability may not be easily captured with existing clinical tools (Buckley et al., 2018; Tan et al., 2018). The capacity of the harmonic ratio measure to delineate stimulation condition highlights the measure's utility to provide unique insight into the effects of STN-DBS stimulation strategies that are otherwise not captured by clinical measures and gait characteristics.

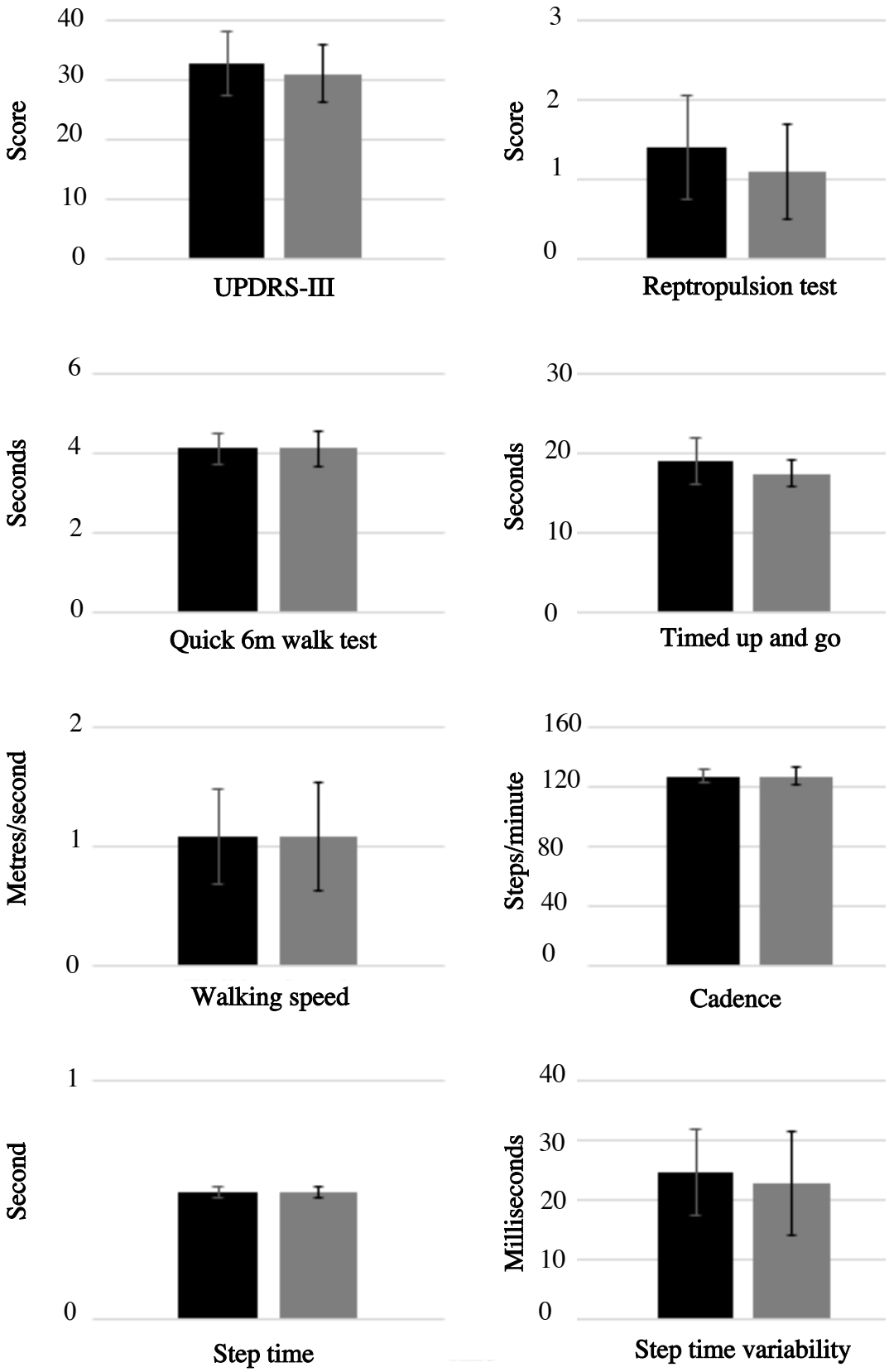

Figure 10.5: Mean scores for the clinical measures of symptom severity and mobility while receiving high-frequency stimulation (black) and low-frequency stimulation (grey).

Limitations

This dissertation was not without limitations. Firstly, although the number of participants assessed exceeded the minimum group size determined in our a-priori sample size calculation, the small sample size potentially limits the generalizability of the reported findings to the broader population. Future research involving a larger STN-DBS PD cohort is warranted and would allow more detailed sub-group analyses (e.g. retrospective fallers vs. non-fallers) to be performed. Additionally, a larger participant cohort would add evidence for those who would likely benefit from the alternate therapy and those who would likely experience debilitating side effects. For example, research has shown that those who present with primarily non-tremor dominant symptoms are more likely to tolerate low-frequency stimulation (Zibetti et al., 2016). In contrast, people with PD who present primarily tremor-dominant symptoms pre-surgery are more likely to experience a re-emergence of tremor with low-frequency STN-DBS, necessitating their return to high-frequency stimulation (Moreau et al., 2008; Ricchi et al., 2012; Xie et al., 2015). While this dissertation may have benefited from recruiting those more likely to tolerate low-frequency stimulation, the randomised recruitment strategy was adopted in response to Study I's findings, which highlighted that the wider spread implications of previous studies may have been limited by the lack of representativeness of their populations (Conway et al., 2019). This was attributed to many of the study populations being consecutively enrolled from clinics or hospital settings, or studies targeting a specific sub-type of people with PD who have STN-DBS, such as those who exhibited post-operative deficits in gait or axial function (Moreau et al., 2008; Moreau, Pennel-Ployart, Pinto, Plachez, Annic, Viallet, Destee, et al., 2011; Ricchi et al., 2012; Sidiropoulos et al., 2013). Therefore, the randomised recruitment strategy adopted for this dissertation meant that the investigated sample was more likely to be representative of the broader STN-DBS PD population.

A further limitation of this research was that the experimental investigations took place following the participants' overnight withdrawal from their anti-parkinsonian medications. This meant that for those who would usually take anti-parkinsonian medications (50% of the investigated population), the high-frequency stimulation condition was not reflective of their best therapeutic state. However, the decision to assess participants following overnight withdrawal from anti-parkinsonian medications was guided by the need to limit the effects of any medication-induced 'on/off fluctuations' on the reported outcomes. Specifically, 'on/off fluctuations' in medication effectiveness over the drug cycle can lead to variable motor symptom severity, such as increased tremor, and/or drug-induced dyskinesias (Ahlskog & Muenter, 2001; Schrag & Quinn, 2000). Furthermore, the effects of anti-parkinsonian medications on postural stability and gait stability are known to be more varied (Pelicioni et al., 2018). Therefore, it was considered appropriate to assess the participants following an overnight withdrawal of anti-parkinsonian medications due to its potential to influence the effects of the stimulation conditions. Due to this withdrawal, it is unknown whether those that could not tolerate low-frequency STN-DBS due to tremor re-emergence may have tolerated it if they had not completed an overnight withdrawal from their anti-parkinsonian medications. This is of potential interest for future research to investigate the interaction between anti-parkinsonian medication and low-frequency STN-DBS for the ongoing management of people with PD.

It should be noted that the chosen low-frequency strategy of 60 Hz was not only informed by previous research, but the level at which the voltage was increased to was limited to the resources available. Specifically, due to a limited time available for a DBS nurse to administer the changes to the participants DBS, the increase in voltage was standardised to maintain the TEED of their chronic (high-frequency) stimulation condition. This method was

adopted, as selecting an appropriate voltage via a traditional titration process can take significant time to identify the best parameters for alleviating the clinically recognisable symptoms. If this study had employed a more traditional titration process while introducing the alternate therapy, it is possible that the re-emergence of tremor experienced by some of the participants with low-frequency STN-DBS could have been avoided. Furthermore, the adoption of a titration-based approach may have made it possible to include those whose chronic stimulation was low-frequency stimulation to get an appropriate and comparable high-frequency stimulation condition.

Future research

This dissertation found that low-frequency STN-DBS improved gait stability, based on the harmonic ratio, compared to high-frequency. However, currently, there is no published data using the harmonic ratio comparing a participant's pre- and post-surgery state. Therefore, it was not possible to draw conclusions regarding the effects of low-frequency STN-DBS relative to the participant's pre-operative state; highlighting a potentially important area for future research. Such future investigations comparing pre-operative state would allow researchers to determine whether low-frequency STN-DBS improves gait stability in PD or rather alleviates possible high-frequency stimulation induced symptoms (Fasano et al., 2015; St George et al., 2010). In doing so, such investigations would build on the understanding of the effect of STN-DBS on postural stability and assist with determining the therapeutic mechanism(s) of low-frequency STN-DBS. Furthermore, there is also an ongoing need for research aimed at better understanding the mechanisms underlying the reported increase in falls for people with PD who have STN-DBS compared with those receiving traditional pharmacological treatment (Rizzone et al., 2014; Weaver et al., 2009).

This the first research to use sample entropy to investigate the regularity of postural sway during standing in people with PD who have STN-DBS. Although the presented findings suggest that this outcome may provide unique insight into therapy-induced changes in postural sway, further research is warranted to clarify the specific relationship between these changes and other measures of physical function and falls risk.

While there was an adequate time to allow for stimulation wash-in/wash-out, (Khoo et al., 2014; Moro et al., 2002; Temperli et al., 2003), it should be noted that the participants were only receiving the alternate (low-frequency) stimulation for a relatively short time period prior to completing the clinical and instrumented assessments of symptom severity, postural stability and gait stability. Therefore, the results presented in this dissertation should be considered to represent the participants' acute responses to the alternate stimulation strategy. The findings presented in this dissertation provide important information regarding the short-term benefits of low-frequency STN-DBS, but previous research suggests that the efficacy of this alternate therapy may diminish over extended timeframes (Sidiropoulos, 2015). Therefore, longitudinal studies are required to determine the long-term efficacy of low-frequency stimulation for the reported improvements in static and gait stability measures.

Future research is needed to investigate the effects of pulse width on postural stability. Research has found that while longer pulse widths (e.g. 90 μs) reduce the efficacy of STN-DBS (Reich et al., 2015; Rissanen et al., 2015), shorter pulse widths (e.g. 30 μs) improve the therapeutic window (Bouthour et al., 2018; Dayal et al., 2018; Reich et al., 2015; Steigerwald et al., 2018). This may aid clinicians when stimulation side effects take place due to diffusion to other neuronal structures evidenced by improvements in those with stimulation-induced dysarthria (Dayal et al., 2019). While these studies highlight the potential value of shorter pulse

widths for improving the management of motor symptoms in people with PD who have STN-DBS, there are currently no studies that have reported postural stability as an outcome. Therefore, future research should investigate whether narrowing the pulse width has a significant impact on postural stability in this population.

Conclusions

This dissertation builds on the existing evidence concerning the potential utility of low-frequency stimulation to improve the current post-operative management of people with PD who have STN-DBS. Results of the double-blinded randomised cross-over trials indicate that low-frequency STN-DBS with a voltage increase that maintains the TEED of chronic high-frequency stimulation was effective at improving postural stability compared to high-frequency stimulation, independent of electrode location. Despite these positive findings, low-frequency stimulation STN-DBS may not be suitable for all participants, as some participants experienced the re-emergence of limb tremor during the low-frequency condition. This work provides clinicians with objective evidence concerning the utility of low-frequency STN-DBS for people with PD and highlights the potential benefits from incorporating objective measures of standing and walking stability into their daily clinical practices. Such measures have the potential to provide additional and unique insights into the strengths and weaknesses of alternate patterns of STN-DBS for people with PD and may assist with monitoring subtle changes in therapeutic needs.

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APPENDICES

Appendix A. Search strategy

To identify potentially relevant papers, these databases will be systematically searched using the following nested search procedure:

Population:

parkins*[Title/Abstract]

Therapy:

((((((deep brain stimulation[Title/Abstract]) OR DBS[Title/Abstract]) OR neurosurgery[Title/Abstract]) OR stimulation[Title/Abstract]) OR neurostimulation[Title/Abstract]) OR stereotactic[Title/Abstract]) NOT transcranial*[Title/Abstract]

Intervention:

((((((voltage[Title/Abstract]) OR parameter*[Title/Abstract]) OR pulse[Title/Abstract]) OR frequenc*[Title/Abstract]) OR setting*[Title/Abstract]) polar*[Title/Abstract]) OR amplitude*[Title/Abstract]

Outcomes:

(((((((((((((((motor[Title/Abstract]) OR axial[Title/Abstract]) OR balance[Title/Abstract]) OR postur*[Title/Abstract]) OR gait[Title/Abstract]) OR walk*[Title/Abstract]) OR stab*[Title/Abstract]) OR freez*[Title/Abstract]) OR FOG[Title/Abstract]) OR tremor[Title/Abstract]) OR rigid*[Title/Abstract]) OR hypokin*[Title/Abstract]) OR hyperkin*[Title/Abstract]) OR bradykin*[Title/Abstract]) OR UPDRS[Title/Abstract]) OR Unified*[Title/Abstract]) OR appendicular[Title/Abstract])

Appendix B. Invitation letter

PARTICIPANT INFORMATION LETTER

TITLE OF PROJECT:	Optimizing the post-operative management of Parkinson's disease patients with deep brain stimulation
CHIEF INVESTIGATOR:	Dr Michael Cole
CO-INVESTIGATORS:	Professor Peter Silburn, Karen O'Maley, Professor Geraldine Naughton
STUDENT RESEARCHER:	Zachary Conway

Dear Sir/Madam,

You are invited to participate in the research project described below.

What is the project about?

The purpose of this research is to enhance the post-operative management of people with Parkinson's disease following deep brain stimulation by seeking to improve symptoms affecting the limbs, trunk and neck via the optimization of stimulation parameters. The information gathered via this project is essential for developing a set of targeted post-operative procedures to ensure that patients whose symptoms are primarily managed with deep brain stimulation therapy receive the best outcomes from this procedure. By ensuring that Parkinson's disease symptoms are optimally-managed via this therapy, it may be possible to reduce the risk of falls in this population; ultimately improving their quality of life. To facilitate this research, we are inviting people diagnosed with Parkinson's disease who have elected to undergo deep brain stimulation surgery and who have no history of recurrent musculoskeletal problems (e.g. chronic low back pain) to volunteer their time to participate in this study. Participants will be asked to attend a maximum of three 3-hour long testing sessions that will be spread over a 7-month period and a brief description of the tests involved is provided below. We would like to thank you for considering being a part of this study.

Who is undertaking the project?

This research forms the basis of Zachary Conway's Doctor of Philosophy project and is being conducted under the supervision of Dr Michael Cole and Professor Geraldine Naughton from the Australian Catholic University. During this program of research, Zachary will also be supported by Professor Peter Silburn and Ms Karen O'Maley from Neurosciences Queensland. All data collection sessions will be conducted by Zachary who is a trained Exercise Scientists with experience working with people with Parkinson's disease. Dr Cole has more than 10 years' experience working as a movement disorders researcher and is specifically focused on better understanding the mechanisms of postural instability and gait disability in people with Parkinson's disease. Professor Silburn is a Brisbane-based neurologist with over 20 years' experience and who is internationally recognised as an expert in the treatment and research of Parkinson's disease, related neurodegenerative disorders and deep brain stimulation. Ms. O'Maley is a Nurse Consultant for Movement Disorders and has more than 25 years' experience as a specialist in neurology and neurosurgery nursing.

Are there any risks associated with participating in this project?

Participation in this research will require individuals to voluntarily forego their usual anti-parkinsonian medications for a 12-hour period (i.e. overnight); hence some participants may experience mild worsening of symptoms in the absence of their medication. Similarly, during data collection, participants will be asked to complete a series of assessments pre- and post-operatively without their usual treatment (i.e. medication and/or deep brain stimulator therapy) and with the parameters of their deep brain stimulation therapy slightly adjusted. Given this point, there is a possibility that the benefits of the medications and/or deep brain stimulation therapy may be temporarily reduced; further increasing the risk of mild changes in symptom severity (e.g. tremor) for some participants. However, it should be emphasised that any re-emergence of symptoms will be temporary, and the full clinical benefit of the therapies will be restored upon completion of each testing session when deep brain stimulation therapy and oral medications are recommenced. At this time, it is important to note that the planned stimulation parameter changes have all been previously assessed in people with Parkinson's disease and are known to have no long-lasting or significant adverse effects. Nevertheless, it is foreseeable that some participants may experience mild discomfort due to changes in their symptom severity; hence, participants are encouraged to contact their neurologist to discuss any concerns.

To assist with quantifying each participant's performance, a series of wearable sensors will be affixed to their skin using double-sided wig tape. To maximise data quality and ensure adequate adhesion, the areas of skin overlying the regions of interest (see page 6) will be cleaned using a latex free exfoliating paste and isopropyl alcohol. While these products are hypoallergenic, some participants may experience mild skin irritation related to these procedures; although the risk of this is no greater than that in similar routines of everyday life. If a participant experiences an adverse reaction, data collection will immediately cease to minimise the risk of further discomfort. While wearing the light-weight sensors, participants will be asked to perform a series of tests that may involve short bouts of standing, walking or maximal voluntary muscle contraction, which may cause some fatigue and/or discomfort. To ameliorate this risk, participants will be given rest breaks between tests and may ask for additional breaks if required. Furthermore, participants will be encouraged to do the tests at their own pace and a member or the research team will be close by during the tests to ensure that they are safe at all times. During the longer rest periods, participants will be provided with lunch, which will help to break the testing session up and to maintain the participant's energy levels.

What will I be asked to do?

If you agree to participate in this research, your balance, gait and falls risk will be assessed under the therapeutic conditions described below using both questionnaires and physical assessments: -

1. **Pre-operative assessment**
   To assist with determining the efficacy of the deep brain stimulation surgery, participants will be invited to complete pre-operative assessments of symptom severity, balance and mobility up to 4 weeks prior to their scheduled surgery. These pre-operative assessments will be completed under 2 conditions; i) after overnight withdrawal from any medications; and ii) 30-minutes after the resumption of usual treatment.
2. **Conditions of deep brain stimulation programming:**
   This study requires participants to consent to having their current deep brain stimulation parameters adjusted by a registered nurse specialised in the post-operative management of deep brain stimulation patients (Karen O'Maley). Specifically, participants will be assessed with their stimulators bilaterally active and with the pattern of stimulation slightly adjusted. The proposed adjustment is well within the ranges used in clinical treatment and have

previously been used in various projects around the world. At the conclusion of each day, each participant's stimulation parameters will be returned to their usual state before returning home. Unfortunately, due to the study's aims, there are no alternatives to the outlined therapeutic changes; hence participants who are unable to provide written consent will be ineligible.

3. **Questionnaires & Clinical Assessments:**
   Prior to and during the assessment, participants will be asked to complete a series of questionnaires to collect information about current medications, falls history, balance confidence, symptom severity, freezing of gait and quality of life. Participants will be asked to complete some of these questionnaires at home prior to the testing session (10-15 minutes), while the remainder will be completed during the face-to-face assessment (15-20 minute). Clinical assessments of symptom severity will be assessed by a trained Exercise Scientist (Zachary Conway) using assessments that are common in clinical practice.
4. **Physical Function Assessment:**
   In addition to the questionnaire-based assessments, participants will be asked to complete a series of common assessments aimed at evaluating mobility and lower limb muscle strength. These tests are similar to those used in routine clinical practice, but will incorporate commercially-available measuring equipment to improve the measurement accuracy. Participants will be encouraged to complete these tests at their own pace and a member of the research team will always be close by to ensure their safety. A more detailed description of the physical function assessments is provided on the final pages for those who may be interested in learning more about what will be required.

How much time will the project take?

To participate in this research, participants will be asked to attend no more than three one-on-one face-to-face testing sessions with a trained Exercise Scientist (Zachary Conway) who has experience working with people with Parkinson's disease. Each testing session will take approximately three hours to complete and will include plenty of time to accommodate rest breaks and refreshments. The first of the three sessions will be scheduled up to 4 weeks prior to the surgery (i.e. 3-hr commitment pre-operative), while the second and third sessions will be completed 6-months following the procedure (i.e. 6-hr commitment post-operative). To minimise the potential for inconvenience, participants will be given the option to complete sessions at either Spring Hill or Banyo.

What are the benefits of the research project?

Although the personal benefits of participation may be limited to having the opportunity to be assessed by an exercise scientist and a nurse who specializes in the post-operative management of deep brain stimulation patients, the results of this project are expected to benefit the wider community. Particularly, this research will aid in future treatment of people with Parkinson's disease whose symptoms are primarily managed with deep brain stimulation therapy. Those who participate in this study will be assisting us to improve our understanding of the balance and gait difficulties experienced by people with Parkinson's disease and will help form a scientific basis for developing tools to improve the post-operative management of deep brain stimulation patients.

Can I withdraw from the study?

Taking part in this project is entirely voluntary and we will ask all participants to sign a written consent form to confirm that they agree to participate. However, it is important to know that participants are free to withdraw consent before, during, or after the experiment without comment or penalty. Under no circumstances will you be prejudiced as a result of your actions;

your participation or withdrawal of consent will not influence your present or future care or your relationship with the research staff at the Australian Catholic University. Should a participant elect to withdraw from the study prior to, during or after data collection, any data collected may be used for the purposes of this and any future studies.

If, at any time, there are concerns about a participant's safety and/or well-being, the research team will immediately terminate the testing session and return the participant's stimulators to their clinically optimised state. Furthermore, if, over the course of this study, new significant findings are reported that are considered to alter the outlined risks and/or benefits associated with this research, all participants will be informed.

Will anyone else know the results of the project?

All data will be kept at the Australian Catholic University, in a locked filing cabinet and/or on password-protected computers within the University. To prevent against the potential for data loss, back-up copies of all electronic data will also be held on a portable hard-drive for storage off-site. The researchers will take every care to ensure that individually identifying material will be removed from the data as soon as it is possible, in order to ensure the privacy and confidentiality of the participants. You should be aware that your identity will not be disclosed in the reporting of the research. Following completion of data collection, the results from the study will be summarised and presented in the form of scientific publications. It is important however, to reiterate that the outcomes of this research will focus on the averaged data from all participants and will not identify individual participants in any way.

Will I be able to find out the results of the project?

Each individual who takes part in this research will be offered verbal feedback on their performance at the end of the testing session and, if consent is provided, a summary of their results can be forwarded to their treating physician to assist with the ongoing management of their health. Furthermore, participants will be given the option to receive a summary of the overall findings of the research following its completion to help them better understand what they have contributed to.

Compensation or treatment for injury

In the event of any injuries that may be sustained by participants as a direct result of their involvement in this project, it should be noted that the Australian Catholic University will be providing the research team with protection during the conduct of this Clinical Trial. Participants who feel that they have a claim to compensation for any adverse event or injury that has been documented during the testing sessions should contact the research team.

Who do I contact if I have questions about the project?

If you have any questions regarding this study or you require any further information about it, please do not hesitate to contact a member of the research team at the Australian Catholic University in Brisbane:

Name:	Zachary Conway	Dr Michael Cole
Telephone:	07 3623 7385	07 3623 7674
Email:	zachary.conway@acu.edu.au	michael.cole@acu.edu.au
Postal Address:	School of Exercise Science Australian Catholic University P.O. Box 456 Virginia QLD 4014	School of Exercise Science Australian Catholic University P.O. Box 456 Virginia QLD 4014

Additional costs

There are no financial costs associated with participation in this study. For each of the two days of testing, the research team will be covering the costs of parking at St Andrew's Place or the costs of a taxi or public transport up to the value of $45 per day. Additionally, the research team will be providing both the participants and their companions (if in attendance) with lunch, refreshments and light reading materials (e.g. newspaper) on each testing day to help pass the time between sessions and to ensure all volunteers are well nourished.

What if I have a complaint or any concerns?

The study has been reviewed by the Australian Catholic University's Human Research Ethics Committee (approval #2017-155H). If you have any complaints or concerns about the conduct of the project, you may write to the Manager of the Human Research Ethics Committee care of the Office of the Deputy Vice Chancellor (Research).

Manager, Ethics
c/o Office of the Deputy Vice Chancellor (Research)
North Sydney Campus
P.O. Box 968
North Sydney NSW 2059
Telephone: 02 9739 2519
Facsimile: 02 9739 2870
Email: res.ethics@acu.edu.au

Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

I want to participate! How do I sign up?

If you agree to participate in this project, **please contact Zachary Conway** or another member of the research team (details provided above) to indicate your interest in participating. Thank you for taking the time to consider this research and we look forward to discussing this research with you soon.

Yours sincerely,

Zachary Conway
School of Exercise Science
Australian Catholic University
1100 Nudgee Road, Banyo, QLD, 4014
4014
Telephone: 07 3623 7385
E-mail: zachary.conway@acu.edu.au

Dr Michael Cole
School of Exercise Science
Australian Catholic University
1100 Nudgee Road, Banyo, QLD,

Telephone: 07 3623 7674
E-mail: michael.cole@acu.edu.au

Appendix C. Flyer

What is the project about?
This project is a part of Zachary Conway's Doctor of Philosophy degree, which aims to enhance the post-operative management of people with Parkinson's disease following deep brain stimulation. Specifically, the outcomes of this research will clarify the effect on symptoms relating to walking ability and balance.

Am I eligible?
We are inviting people with Parkinson's disease who have previously undergone deep brain stimulation surgery to kindly volunteer your time to contact us.

What are the benefits of the project?
Through your participation in this project, we anticipate that the knowledge gained will have significant implications for improving the physical capabilities, independence and overall quality of life of people with PD. Additionally, as a part of your own participation in this study, we hope to provide you with more information relating to your own walking ability and balance.

What will you be asked to?
Participation will require at least 1 face-to-face testing session (no more than four hours including rest times during). During this session your balance and falls risk will be assessed using both questionnaires and walking tasks that are common to clinical practices. If willing you will also be invited back to a second day that will replicate the first session however will take no more than three hours. During these sessions, refreshments will be provided.

Who is undertaking the project?
This research forms the basis of Zachary Conway's Doctor of Philosophy project and is being conducted under the supervision of Dr Michael Cole and Professor Geraldine Naughton from the Australian Catholic University. During this program of research, Zachary will also be supported by Professor Peter Silburn and Ms Karen O'Maley from Neurosciences Queensland.

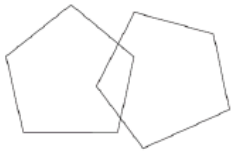
Who do you contact if you have questions about the project?
We would like to thank you for considering being a part of this study. If you would like to be involved, have any questions or you require any further information, please contact Zachary Conway.

Name: Zachary Conway

Telephone: 07 3623 7385

Email: zachary.conway@acu.edu.au

Appendix D. Standardized mini-mental state examination

	QUESTION	TIME ALLOWED	SCORE
1	a. *What year is this?*	10 seconds	/1
	b. *Which season is this?*	10 seconds	/1
	c. *What month is this?*	10 seconds	/1
	d. *What is today's date?*	10 seconds	/1
	e. *What day of the week is this?*	10 seconds	/1
2	a. *What country are we in?*	10 seconds	/1
	b. *What province are we in?*	10 seconds	/1
	c. *What city/town are we in?*	10 seconds	/1
	d. *IN HOME – What is the street address of this house?* *IN FACILITY – What is the name of this building?*	10 seconds	/1
	e. *IN HOME – What room are we in? IN FACILITY – What floor are we on?*	10 seconds	/1
3	SAY: *I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.* Say the following words slowly at 1-second intervals - **ball/ car/ man**	20 seconds	/3
4	*Spell the word WORLD. Now spell it backwards.*	30 seconds	/5
5	*Now what were the three objects I asked you to remember?*	10 seconds	/3
6	SHOW wristwatch. ASK: *What is this called?*	10 seconds	/1
7	SHOW pencil. ASK: *What is this called?*	10 seconds	/1
8	SAY: *I would like you to repeat this phrase after me: No ifs, ands or buts.*	10 seconds	/1
9	SAY: *Read the words on the page and then do what it says.* Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	10 seconds	/1
10	HAND the person a pencil and paper. SAY: *Write any complete sentence on that piece of paper.* (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/1
11	PLACE design, eraser and pencil in front of the person. SAY: *Copy this design please.*  Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.	1 minute	/1
12	ASK the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. SAY: *Take this paper in your right/left hand* (whichever is non-dominant), *fold the paper in half once with both hands and put the paper down on the floor* . Score 1 point for each instruction executed correctly. Takes paper correctly in hand Folds it in half Puts it on the floor	30 seconds	/1 /1 /1
	TOTAL TEST SCORE		**/30**

Appendix E. Eligibility check

Name: _____

Residential & Postal Address: _____

_____ **Phone number:** _____

Eligibility Criteria

Inclusion criteria	*Exclusion criteria*
☐ Aged 50 years and over	☐ Is the participant medically unstable or presents with another medical condition that would confound physical function testing?
☐ Diagnosed with PD	☐ Does the participant have a significant visual, cognitive or sensory deficits confirmed via clinical assessment?
☐ Able to walk greater than 50m with not more than minimal assistance	☐ Is the participant unable to stand or ambulate unaided?
☐ Ability to understand written and spoken English	☐ Is the participant unable to understand instructions with no carer available?
☐ Has the participant been enrolled in deep brain stimulation (DBS) surgery?	☐ Has the participant had a recent or recurrent history of musculoskeletal injury or surgery that affects balance or mobility? (E.g. Lower back problems)
☐ Targeted for STN stimulation only	

Circle: **ELIGIBLE / INELIGIBLE**
If ineligible, is the person interested in being contacted regarding future research projects?:
Yes / No

Carpark details: **Participant Plate number:**_____ **Model of Car:**_____
Carpark space booked? □

	Date	Venue	Time of arrival	Q's sent	Booked
Day 1					
Day 2:					
Day 3:					

Will a friend/carer/spouse be present during the assessment?_____

Appendix F. Demographics and health questionnaire

The following questions ask about your health, medications, and balance confidence. Please fill in both sides of the page and answer each question as accurately as you can. If you are unsure of the answer, please provide your best guess.

1. **When were you <u>FIRST</u> diagnosed with Parkinson's disease (i.e. month and year)?**

_____/_____
(Month) (Year)

2. **When are you scheduled to undergo Deep Brain Stimulation surgery?**

_____/_____/_____
(Date) (Month) (Year)

3. **Name of treating Neurologist?**:_____

4. **What medication are you currently taking for <u>Parkinson's disease</u>?** ☐ **No medications**

	Medication Name	Frequency Per Day	Number of Tablets/Doses	Dosage (e.g. 100/25)
1.				
2.				
3.				
4.				
5.				
6.				
7.				

5. **What other medications are you currently taking?** ☐

	Medication Name	Frequency Per Day	Number of Tablets/Doses	Dosage
1.				
2.				
3.				
4.				
5.				
6.				

5. How many falls did you have in the past year? _____ falls

6. What was the most severe injury sustained due to a fall in the past 12 months?

[ ] Not applicable
[ ] No injury
[ ] Minor injury not requiring medical attention
[ ] Minor injury requiring medical attention
[ ] Severe injury (e.g. fracture)

7. If you have fallen in the previous 12 months, please describe the circumstances of your most recent fall:

Time of fall: AM / PM

Location of fall: Inside the home / Outside the home / In the community

Direction of fall: Left / Right / Forward / Backward / Down / Can't Remember /

Other

If other, please describe:

_____

_____

Cause of fall: Trip / Slip / Loss of balance / Knees gave way / Feeling dizzy or giddy / Fainted / Fell out of bed / Alcohol or meds / Unknown

Injuries (if any):

_____

_____

Appendix G. 6-Item Activities-Specific Balance Confidence

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

0% 10 20 30 40 50 60 70 80 90 100%
No confidence Completely confident

How confident are you that you will not lose your balance or become unsteady when you…

1. …stand on your tiptoes and reach for something above your head? ____%
2. …stand on a chair and reach for something? ____%
3. …are bumped into by people as you walk through the mall? ____%
4. …step onto or off an escalator while you are holding onto a railing? ____%
5. …step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? ____%
6. …walk outside on icy sidewalks? ____%

Source: Peretz, C., Herman, T., Hausdorff, J. M., Giladi, N. (2006). Assessing fear of falling: Can a short version of the activities-specific balance confidence scale be useful? *Movement Disorders, 21*(12), 2101-2105.

Appendix H. Revised freezing of gait questionnaire

Part I: Determining 'Freezer' or 'Non-Freezer' over the past month

1. Did you experience "freezing episodes" over the past month?
Freezing is the feeling that your feet are transiently glued to the floor while trying to initiate walking, making a turn or when walking through narrow spaces or in crowded places? Sometimes it can be accompanied with trembling of the legs and small shuffling steps.

[ ] I have not experienced such a feeling or episode over the past month
↳ **Thank you for completing this questionnaire**

[ ] I have experienced such a feeling or episode over the past month
↳ **Please complete Parts II and III below**

Part II: Freezing severity

2. **How frequently do you experience freezing episodes**?

[ ] Less than once a week
[ ] Not often, about once a week
[ ] Often, about once a day
[ ] Very often, more than once a day

3. How frequently do you experience freezing episodes during turning?

[ ] Never → GO TO QUESTION 5
[ ] Rarely, about one a month → GO TO QUESTION 4
[ ] Not often, about once a week → GO TO QUESTION 4
[ ] Often, about once a day → GO TO QUESTION 4
[ ] Very often, more than once a day → GO TO QUESTION 4

4. How long is your longest freezing episode during turning?

[ ] Very short - 1 second
[ ] Short - 2 to 5 seconds
[ ] Long - 5 and 30 seconds
[ ] Very long - unable to walk for more than 30 seconds

Please continue to the next page.

5. How frequently do you experience episodes of freezing when initiating the first step?

[ ] Never → GO TO QUESTION 7
[ ] Rarely, about one a month → GO TO QUESTION 6
[ ] Not often, about once a week → GO TO QUESTION 6
[ ] Often, about once a day → GO TO QUESTION 6
[ ] Very often, more than once a day → GO TO QUESTION 6

6. How long is your longest freezing episode when initiating the first step?

[ ] Very short - 1 second
[ ] Short - 2 to 5 seconds
[ ] Long - 5 and 30 seconds
[ ] Very long - unable to walk for more than 30 seconds

Part III: Freezing impact on daily life

7. How disturbing are the freezing episodes for your daily walking?

[ ] Not at all
[ ] Very little
[ ] Moderately
[ ] Significantly

8. Do the freezing episodes cause feelings of insecurity and fear of falling?

[ ] Not at all
[ ] Very little
[ ] Moderately
[ ] Significantly

9. Are your freezing episodes affecting your daily activities?

Rate the impact of freezing on daily activities only, not the impact of the disease in general

[ ] Not at all - I continue doing things as normal
[ ] Mildly - I avoid only a few daily activities
[ ] Moderately - I avoid a significant number (about half) of daily activities
[ ] Severely - I am very restricted in carrying out most daily activities

Source: Nieuwboer, A., Rochester, L., Herman, T., Vandenberghe, W., Emil, G. E., Thomaes, T., & Giladi, N. (2009). Reliability of the new freezing of gait questionnaire: Agreement between patients with Parkinson's disease and their carers. *Gait and Posture, 30*(4), 459-463.

Appendix I. 8-item Parkinson's disease Questionnaire

Please place a tick or cross in <u>one</u> box for each question

Due to having Parkinson's disease, how often <u>during the last month</u> have you…	Never	Occasionally	Sometimes	Often	Always *or cannot do at all*
1 Had difficulty getting around in public?	☐	☐	☐	☐	☐
2 Had difficulty dressing yourself?	☐	☐	☐	☐	☐
3 Felt depressed?	☐	☐	☐	☐	☐
4 Had problems with your close personal relationships?	☐	☐	☐	☐	☐
5 Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
6 Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
7 Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
8 Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐

Source: Jenkinson, C., Fitzpatrick, R., Peto, V., Greenhall, R., & Hyman, N. (1997). The PDQ-8: Development and validation of a short-form Parkinson's disease questionnaire. *Psychology & Health, 12*(6), 805-814.

Appendix J. TEED worked through calculation

Chronic stimulation parameters

Voltage = 4

Frequency = 130

Pulse width 60

Impedance = 1000

Chronic stimulation TEED

$$\text{TEED}_{1\text{ second}} = \frac{Voltage^2 \cdot frequnecy \cdot pulse\ width}{impedence} \cdot 1\ second$$

$$= \frac{4^2 \cdot 130 \cdot 60}{1000} \cdot 1\ second$$

$$= 124.8$$

Voltage for LFS

$$\text{Voltage} = \sqrt{(Cr\ TEED \text{ x } Impedance)/(\ Frequency \text{ x } Pulse\ Width))}$$

$$= \sqrt{((124.8 \text{ x } 1000)/(60 \text{ x } 60))}$$

$$= 5.89 \text{ Volts}$$

LFS parameters

Voltage = 5.89

Frequency = 60

Pulse width = 60

RESEARCH PORTFOLIO

Published works of the thesis

The studies outlined below were conducted during this PhD and make up the presented thesis; each paper has been published following peer review.

Study I (Chapter 5)

Conway, Z. J., Silburn, P. A., Thevathasan, W., O'Maley, K., Naughton, G. A., & Cole, M. H. (2019). Alternate Subthalamic Nucleus Deep Brain Stimulation Parameters to Manage Motor Symptoms of Parkinson's Disease: Systematic Review and Meta-analysis. *Movement Disorders Clinical Practice*, *6*(1), 17-26.

Zachary Conway, Peter Silburn, Wesley Thevathasan, Karen O'Maley, Geraldine Naughton, Michael Cole contributed to 60, 3, 3, 2, 2 and 30% respectively to this paper. Author roles included:

Zachary Conway:	1A, 1B, 1C, 2A, 2B, 2C, 3A
Peter Silburn:	1A, 3B, 4A
Wesley Thevathasan:	1A, 3B, 4A
Karen O'Maley:	1A, 3B
Geraldine Naughton:	1B, 3C, 4A
Michael Cole:	1A, 1B, 1C, 2A, 2B, 2C, 3B, 4A

1) Research project: **A**. Conception, **B**. Organization, **C**. Execution;

2) Statistical Analysis: **A**. Design, **B**. Execution, **C**. Review and Critique;

3) Manuscript: **A**. Writing of the first draft, **B**. Review and Critique.

4) Other: **A.** Study supervision

Movement Disorders
CLINICAL PRACTICE

REVIEW

Alternate Subthalamic Nucleus Deep Brain Stimulation Parameters to Manage Motor Symptoms of Parkinson's Disease: Systematic Review and Meta-analysis

Zachary J. Conway,[1]* Peter A. Silburn,[2,3] Wesley Thevathasan,[4,5,6] Karen O' Maley,[3] Geraldine A. Naughton,[7] Michael H. Cole[1]*

ABSTRACT: **Background:** The use of alternate frequencies, amplitudes, and pulse widths to manage motor symptoms in Parkinson's disease (PD) patients with subthalamic nucleus deep brain stimulation (STN-DBS) is of clinical interest, but currently lacks systematic evidence.
Objective/Hypothesis: Systematically review whether alternate STN-DBS settings influence the therapy's efficacy for managing PD motor symptoms.
Methods: Systematic searches identified studies that; involved bilateral STN-DBS PD patients; manipulated ≥ 1 STN-DBS parameter (e.g., amplitude); assessed ≥ 1 motor symptom (e.g., tremor); and contrasted the experimental and chronic stimulation settings. A Mantel-Haenszel random-effects meta-analysis compared the UPDRS-III sub-scores at low (60-Hz) and high frequencies (≥ 130 Hz). Inter-study heterogeneity was assessed with the Cohen's χ^2 and I^2 index, while the standard GRADE evidence assessment examined strength of evidence.
Results: Of the 21 included studies, 17 investigated the effect of alternate stimulation frequencies, five examined alternate stimulation amplitudes, and two studied changes in pulse width. Given the available data, meta-analyses were only possible for alternate stimulation frequencies. Analysis of the heterogeneity amongst the included studies indicated significant variability between studies and, on the basis of the GRADE framework, the pooled evidence from the meta-analysis studies was of very low quality due to the significant risks of bias.
Conclusions: The meta-analysis reported a very low quality of evidence for the efficacy of low-frequency STN-DBS for managing PD motor symptoms. Furthermore, it highlighted that lower amplitudes lead to the re-emergence of motor symptoms and further research is needed to understand the potential benefits of alternate STN-DBS parameters for PD patients.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) has become one of the most prominent therapies for managing motor symptoms associated with Parkinson's disease (PD).[1] Studies have reported that patients may experience improvements in tremor, stiffness (rigidity), and slowness (akinesia) of movement for a number of years following STN-DBS, which has significant implications for their independence and overall quality of life.[2,3] However, symptoms of postural instability and gait disability (particularly gait freezing) can benefit less from STN-DBS therapy.[4] Some research has reported (1) no

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Keywords: DBS, low-frequency stimulation, STN, UPDRS.
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Unpublished Works of the Thesis

The studies outlined below were conducted during this PhD and make up the presented thesis; each paper has been published following peer review.

Study II (Chapter 7)

Gait stability in Parkinson's disease who have STN-DBS: Do objective measures add insight?

Zachary J. Conway, Peter A. Silburn, Karen O'Maley, Michael H. Cole contributed to 60, 5, 5 and 30% respectively to this paper. Author roles included:

Zachary J. Conway:	1A, 1B, 1C, 2A, 2B, 2C, 3A
Peter A. Silburn:	1A, 3B, 4A
Karen O'Maley:	1A, 3B
Michael H. Cole:	1A, 1B, 1C, 2A, 2B, 2C, 3B, 4A

1) Research project: **A**. Conception, **B**. Organization, **C**. Execution;

2) Statistical Analysis: **A**. Design, **B**. Execution, **C**. Review and Critique;

3) Manuscript: **A**. Writing of the first draft, **B**. Review and Critique.

4) Other: **A.** Study supervision

Study III (Chapter 8)

Low-frequency STN-DBS for static postural stability and gait initiation in Parkinson's Disease: A double-blinded randomised control trial

Zachary Conway, Peter Silburn, Liam Johnson, Thushara Perera, Karen O'Maley, Wesley Thevathasan, Michael Cole contributed to 60, 5, 5, 5, 5, 5 and 15% respectively to this paper. Author roles included:

Zachary Conway:	1A, 1B, 1C, 2A, 2B, 2C, 3A
Peter Silburn:	1A, 3B, 4A
Liam Johnson	3B, 4A
Thushara Perera:	2A, 2B, 3B
Karen O′Maley*:*	1A, 3B
Wesley Thevathasan:	1A, 3B, 4A
Michael Cole:	1A, 1B, 1C, 2C, 3B, 4A

1) Research project: **A**. Conception, **B**. Organization, **C**. Execution;

2) Statistical Analysis: **A**. Design, **B**. Execution, **C**. Review and Critique;

3) Manuscript: **A**. Writing of the first draft, **B**. Review and Critique.

4) Other: **A.** Study supervision

Study IV (Chapter 9)

Low-frequency STN-DBS for gait in Parkinson's Disease: A double-blinded randomised control trial

Zachary Conway, Peter Silburn, Thushara Perera, Karen O'Maley, Wesley Thevathasan, Michael H. Cole contributed to 60, 5, 5, 5, 5 and 20% respectively to this paper. Author roles included:

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Michael Cole:	1A, 1B, 1C, 2C, 3B, 4A

1) Research project: **A**. Conception, **B**. Organization, **C**. Execution;

2) Statistical Analysis: **A**. Design, **B**. Execution, **C**. Review and Critique;

3) Manuscript: **A**. Writing of the first draft, **B**. Review and Critique.

4) Other: **A.** Study supervision

Co-authors signed statement(s) of contributions.

Professor Peter Silburn

In his role(s) of research project conception, manuscript review and critique and study supervision, Professor Peter Silburn contributed 2% (Study I), 5% (Study II), 5% (Study III) and 5% (Study IV) to the respective studies.

I acknowledge that my contributions to the above papers are 2%, 5%, 5% and 5%.

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In his role(s) of statistical analysis design, statistical analysis execution, and manuscript review and critique, Thushara Perera contributed 5% (Study III) and 5% (Study IV) to the respective studies.

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In her role(s) of research project conception, manuscript review and critique, Karen O′Maley contributed 3% (Study I), 5% (Study II), 5% (Study III) and 5% (Study IV) to the respective studies.

I acknowledge that my contributions to the above papers are 3%, 5%, 5% and 5%.

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In his role(s) of research project **c**onception, research project organization, research project execution, statistical Analysis review and critique, manuscript **r**eview and critique, and study supervision, Michael Cole contributed 30% (Study I), 30% (Study II), 15% (Study III) and 20% (Study IV) to the respective studies.

I acknowledge that my contributions to the above papers are 30%, 30% 15% and 20%.

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