

The Effects of Deep Brain Stimulation Amplitude
on Motor Performance in Parkinson's Disease

by

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ABSTRACT

The efficacy of deep brain stimulation (DBS) in Parkinson's disease (PD) has been convincingly demonstrated in studies that compare motor performance with and without stimulation, but characterization of performance at intermediate stimulation amplitudes has been limited. This study investigated the effects of changing DBS amplitude in order to assess dose-response characteristics, inter-subject variability, consistency of effect across outcome measures, and day-to-day variability. Eight subjects with PD and bilateral DBS systems were evaluated at their clinically determined stimulation (CDS) and at three reduced amplitude conditions: approximately 70%, 30%, and 0% of the CDS (MOD, LOW, and OFF, respectively). Overall symptom severity and performance on a battery of motor tasks – gait, postural control, single-joint flexion-extension, postural tremor, and tapping – were assessed at each condition using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and quantitative measures. Data were analyzed to determine whether subjects demonstrated a threshold response (one decrement in stimulation resulted in $\geq 70\%$ of the maximum change) or a graded response to reduced stimulation. Day-to-day variability was assessed using the CDS data from the three testing sessions. Although the cohort as a whole demonstrated a graded response on several measures, there was high variability across subjects, with subsets exhibiting graded, threshold, or minimal responses. Some subjects experienced greater variability in their CDS performance across the three days than the change induced by reducing stimulation. For several tasks, a subset of subjects exhibited improved performance at one or more of the reduced conditions. Reducing stimulation did not affect all subjects equally, nor did it uniformly affect each subject's performance across tasks. These results indicate that altered recruitment of neural structures can differentially affect motor capabilities and demonstrate the need for clinical consideration of the effects on multiple symptoms across several days when selecting DBS parameters.

To my wonderful husband Aaron,
who has encouraged and supported me over the years.

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CHAPTER 1

INTRODUCTION

Parkinson's disease (PD) is a progressive neurological disorder due to loss of cells in the substantia nigra which results in profound dopamine depletion in the striatum (Fearnley & Lees, 1991). This decrease of dopaminergic input disrupts the basal ganglia circuitry, which contributes to motor function. The primary symptoms of PD include tremor, muscular rigidity, bradykinesia, impaired postural reflexes, and associated disturbances in gait. Initially, these symptoms can be managed well with medication, but the side effects of medication are often problematic. When this occurs, deep brain stimulation (DBS) of the subthalamic nucleus may improve many symptoms of PD, reduce needed medication levels, and reduce medication-related side effects (Bakker et al., 2004; Marjama-Lyons & Koller, 2000).

After surgical installation, successful implementation of a DBS system requires the clinician to select an active contact(s) and a set of stimulation parameters (pulse amplitude, pulse width, and pulse frequency) from thousands of possible combinations. Furthermore, two sets of contacts and parameters must be chosen if the patient has a bilateral system, one for each hemisphere of the brain. Finalizing parameter selections requires multiple visits in the months following initial DBS system implantation, and most individuals also require periodic adjustments to continue to fine-tune stimulation.

The primary goal in tuning the DBS system is to maximize alleviation of symptoms while avoiding side-effects, and a secondary goal is to minimize battery power consumption. Even if the clinician chooses a typically effective starting point for pulse width and frequency, iteratively progressing through amplitude and contact combinations can be tedious and time-consuming, especially during the initial programming phase. Due to practical time constraints, clinicians often base their choices on symptoms that respond quickly to stimulation changes (Volkman, Herzog, Kopper, & Deuschl, 2002). This may result in choosing settings which, although optimal for one symptom, don't fully alleviate other symptoms. To minimize battery power consumption, it may also be important to understand whether improvements in symptoms continue to be clinically

relevant as amplitude is increased, or whether performance is essentially the same once a certain threshold is reached.

Another factor that complicates the programming process is that PD symptoms may vary substantially from day to day, with consecutive UPDRS measurements determined to vary by as much as 15%. Without a baseline measure, this may confound the ability to compare performance across days. However, this is often done in both clinical practice and also in research, with many DBS studies comparing assessments obtained on multiple days (Delwaide & Gonce, 1998; Plaha, Ben-Shlomo, Patel, & Gill, 2006).

Many studies have compared motor performance at clinically determined stimulation (CDS) settings, i.e., the settings considered by the clinician to currently be optimal, to performance with the DBS system turned off completely, but few have investigated motor performance at intermediate stimulation levels (Dafotakis, Fink, Allert, & Nowak, 2008; Diamond, Shahed, & Jankovic, 2007; Plaha, et al., 2006; Robertson, Horak, Anderson, Burchiel, & Hammerstad, 2001; Timmermann et al., 2008). Of those that have, one study examined the effects of different combinations of stimulation amplitude and electrode contact location (relative to the subthalamic nucleus) in people with PD. However, speech intelligibility was the main focus of the work, so effects on movement were only measured with a composite outcome (Tripoliti et al., 2008). In another study, frequency and stimulation amplitude were determined to be the most important factors to ameliorate tremor amplitude in people with essential tremor, while varying pulse width had little effect (Kuncel et al., 2006). Neither of these studies accounted for the different stimulation settings that had been prescribed for each subject, instead evaluating all subjects at the same set of amplitude values.

A third study investigated the effects of varying pulse width, frequency, and stimulation amplitude on tremor, bradykinesia, and rigidity (Moro et al., 2002). Similar to the study targeted toward people with essential tremor, this research also concluded that stimulation amplitude was the most important parameter to alleviate the parkinsonian symptoms. However, this study did not evaluate effects on posture or gait.

The long-term goal of this project is to enhance the efficacy of DBS systems by developing an improved procedure for selecting stimulation parameters. A pre-requisite for developing such a procedure, however, is an improved understanding of how changes in stimulation settings affect the various symptoms experienced by people with PD. Toward that end, the objective of this project was to characterize changes in several components of motor performance induced by changing stimulation amplitude. The specific aims of this study are as follows:

1. To determine if reducing the amplitude of stimulation from CDS to intermediate levels affects performance on specific motor tasks.
2. To determine if reducing stimulation has a similar effect across multiple tasks.
3. To assess the day-to-day variability in motor performance at the CDS condition and compare it to the degree of change induced by reducing stimulation amplitude.

To address these aims, the research reported here evaluated multiple components of motor performance – gait , postural control, single-joint flexion-extension, postural tremor, and tapping – in a population with PD. Based on the findings cited earlier, this work focused on changing stimulation amplitude only. Since CDS amplitude may vary widely across individuals, the amplitude settings were chosen with respect to each subject's CDS amplitude rather than applying the same choice of amplitude to all subjects. To avoid inducing stimulation-related adverse effects, the CDS amplitude was defined as the ceiling, since it is often set just below the threshold for adverse effects (Moro, et al., 2002). Performance was evaluated at CDS and the following three amplitude conditions: approximately 70%, 30%, and 0% of the CDS (MOD, LOW, and OFF, respectively). Overall performance was assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) as well as a battery of quantitative measures. This work also assessed motor performance at the CDS condition on each experiment day to provide a baseline for comparison with measurements of motor performance at an altered stimulation condition. The repeated assessments of motor performance on each of several days at the CDS condition also enabled characterization of day-to-day variability.

CHAPTER 2

BACKGROUND

The background material provided here lays the foundation for this project. Briefly, people with PD experience a variety of motor symptoms which can often be successfully treated with pharmaceuticals during the early stages of the disease. Although ablative surgery is an option when pharmaceuticals become less effective, deep brain stimulation (DBS) is usually preferred due to its reversible nature. Once the DBS system has been implanted, the clinician is charged with finding the optimal, or at least an acceptable, set of stimulation parameters. The clinical effect of DBS is influenced by the specific nature of the symptoms experienced by the individual, the underlying local neuronanatomy, the location of the electrode array and the selection of stimulation parameters. Given the complexity of the neural circuits and the multifactorial nature of the problem, multiple clinical visits are often required in order to choose acceptable stimulation parameters. This project is based on the idea that an improved understanding of how changes in stimulation affect the array of symptoms in an individual may increase the effectiveness of the DBS programming process.

Parkinson's Disease (PD)

First identified by James Parkinson in 1817, Parkinson's disease (PD) is a movement disorder caused by the loss of dopaminergic cells in the substantia nigra of the midbrain. In most cases, symptoms do not present until 60-80% of the dopamine-producing cells are dead. The four primary symptoms of PD are resting tremor, rigidity, bradykinesia, and postural instability. Secondary symptoms include loss of facial expression, hypophonia, micrographia, loss of smell, difficulty with fine motor tasks, depression, sleep disorders, and autonomic dysfunction. PD typically affects people over 50. While younger individuals are sometimes diagnosed, it is uncommon to find the disease in people under the age of 25 (Hauser & Zesiewicz, 1996).

Physiology and Pathophysiology of PD

There are five nuclei in the basal ganglia: caudate nucleus, putamen, globus pallidus, substantia nigra, and subthalamic nucleus. The caudate nucleus and putamen are collectively referred to as the striatum and receive all the input to the basal ganglia. The globus pallidus,

which is responsible for much of the basal ganglia's output, is divided into internal (GPi) and external (GPe) segments. The substantia nigra is also divided into two regions: pars compacta (SNpc) and pars reticulata (SNpr) (Carpenter, 1991; Heimer, 1983). The anatomical connections of these nuclei are depicted in Figure 2.1. As shown, the striatum receives glutamatergic (excitatory) inputs from the cerebral cortex and intralaminar thalamic nuclei, as well as dopaminergic inputs from the SNpc. The striatum in turn projects GABAergic (inhibitory) fibers topographically to SNpr and both portions of the globus pallidus. SNpr and GPi are the main output regions of the basal ganglia, sending inhibitory projections to the ventral thalamic nuclei and the brainstem. Finally, the STN receives inhibitory projections from GPe and sends excitatory ones to the output nuclei--GPi and SNpr. These connections can also be viewed as two pathways through the basal ganglia--one direct and one indirect (Carpenter, 1991; Heimer, 1983).

As depicted in Figure 2.2, the direct pathway connects the striatum immediately to the output nuclei, GPi and SNpr. The indirect pathway also connects the input and output stages, but by way of GPe and STN. The two pathways produce opposite results--the direct pathway inhibits the output stage, while the indirect pathway excites the output stage. Since the output stage inhibits thalamus, this means the direct pathway disinhibits thalamus and actually facilitates movement, while the indirect pathway inhibits thalamus and hinders movement. Although this model is a simplification of what occurs in the basal ganglia, it can be helpful in understanding movement disorders. Hyperkinetic disorders, such as Huntington's disease, result from a decrease in GPi/SNpr firing that causes excessive thalamic activation, and hence, excessive movements. Hypokinetic disorders, on the other hand, result from an increase in GPi/SNpr firing that overly inhibits the thalamus and therefore cortical activity as well. Figure 2.3 depicts how this thalamic inhibition results from the loss of dopaminergic cells in Parkinson's disease (Carpenter, 1991; Heimer, 1983).

A key feature of the anatomy of the basal ganglia, which may have particular relevance for deep brain stimulation, is depicted in Figure 2.4. The efferent projections from GPi to the ventral thalamic nuclei course through two fiber bundles--ansa lenticularis (AL) and lenticular fasciculus (LF). Fibers in AL originate primarily from the lateral portion of GPi, while fibers in LF

originate from medial GPi. AL courses anteriorly around the posterior limb of the internal capsule (IC) before entering the H Field of Forel. LF, also termed the H₂ Field of Forel, traverses the IC and joins with AL in the H Field of Forel. Now joined, they form the thalamic fasciculus, or H₁ Field of Forel (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004; Heimer, 1983).

PD Treatment Options

Pharmacology: levodopa, dopamine agonists, & anticholinergics. There are three main options to consider for pharmacological management of PD: (a) levodopa (L-dopa), (b) dopamine (DA) agonists, and (c) anticholinergics. L-dopa is the chemical precursor of DA, and unlike DA, it can cross the blood-brain barrier. L-dopa is foundational for treating the symptoms of PD. It is best for alleviating bradykinesia and rigidity, with inconsistent effects on tremor and no improvement in balance. Side effects include nausea and vomiting, orthostatic hypotension, confusion, hallucinations, delusions, and hypersexuality. Nausea and vomiting can be decreased by concurrent prescription of carbidopa. In addition, carbidopa both increases the half-life of L-dopa and decreases the needed dosage. L-dopa is available in a standard and controlled release form, the main difference being that the controlled release form tends to maintain a more stable level of DA (Hauser & Zesiewicz, 1996).

L-dopa therapy does raise some concerns: 1) the oxidative metabolism of DA may lead to increased neuronal degeneration through the production of free radicals and 2) fluctuating DA levels may cause dyskinesias--jerky movements often seen with chronic L-dopa use. Not only do DA agonists eliminate these concerns, they may even delay the onset of dyskinesias. Since they function by directly stimulating post-synaptic DA receptors, DA agonists are not oxidatively metabolized. Although effective as an alternative to L-dopa during the first few years of symptomatic therapy, disease progression usually requires the addition of L-dopa therapy. The agonists are often prescribed as an adjunct to L-dopa in later disease stages to smooth motor fluctuations. Examples of commonly prescribed agonists are bromocriptine, pergolide, lisuride, and apomorphine. Side effects are similar to those associated with L-dopa and include nausea, vomiting, orthostatic hypotension, nightmares, hallucinations, and psychiatric symptoms (Hauser & Zesiewicz, 1996).

Until recently, anticholinergic medications were the most prescribed drug family for PD. Providing little relief of bradykinesia and rigidity, they are best at reducing tremor. Side effects include confusion, hallucinations, dry mouth, dry eyes, ocular accommodation abnormalities, and tachycardia. Older individuals and those who are demented experience these side effects more than others. In addition, glaucoma is usually a contraindication. Anticholinergics are most effective in two cases: 1) tremor-dominant manifestation in the early stages of PD and 2) the alleviation of disabling tremor when bradykinesia and rigidity are under control. Common anticholinergics include trihexyphenidyl-HCl, bethropine mesylate, biperiden-HCl, and procyclidine-HCl (Hauser & Zesiewicz, 1996).

Surgery: ablation and DBS. Surgery is usually not considered until after a positive response to medication diminishes and dyskinesias become intolerable. Options include ablative therapy or deep brain stimulation of the following targets: 1) ventral intermediate thalamic nucleus, 2) subthalamic nucleus, and 3) internal portion of the globus pallidus. In ablative therapy, an electrode is placed stereotactically in the targeted nucleus, then a lesion is created using radiofrequency (RF) thermocoagulation. In deep brain stimulation, similar surgical techniques are used to implant a quadripolar electrode, (Walter & Vitek, 2004) then the targeted nucleus is electrically activated in a reversible manner. Although it alleviates parkinsonian tremor in more than 85% of individuals, thalamic lesioning is not usually recommended for people with PD, because it fails to improve the other cardinal symptoms and may even worsen speech and gait deficits (Kelly et al., 1987; Narabayashi, 1982; Selby, 1967; Speelman, 1991; Walter & Vitek, 2004). Pallidal lesioning, or pallidotomy, improves all cardinal parkinsonian symptoms while also decreasing dyskinetic episodes (Baron et al., 1996; Dogali et al., 1995; Vitek et al., 2003). However, there are mixed results regarding the longevity of the benefits, with gait and posture disorders often reverting after one year (Fazzini, Dogali, Sterio, Eidelberg, & Beric, 1997; Laitinen, Bergenheim, & Hariz, 1992; Lang et al., 1997; Vitek, et al., 2003). In addition, only unilateral pallidotomies are performed, since bilateral pallidotomies may cause severe cognitive and neuropsychological effects (De Bie, Schuurman, Esselink, Bosch, & Speelman, 2002; Favre, Burchiel, Taha, & Hammerstad, 2000). Subthalamotomy provides results similar to those of

pallidotomy. Both procedures have been considered as acceptable alternatives when DBS is too costly or requires too much follow-up to be feasible (Walter & Vitek, 2004).

Similar to VIM lesioning, stimulation of this nucleus is only effective at improving tremor in people with PD. This has limited its use as a target for DBS (Benazzouz et al., 2002; Walter & Vitek, 2004). GPi DBS provides the same improvements as GPi lesioning with an added benefit-- it can be used bilaterally without the risk of invoking speech deficits ("Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease," 2001; Durif, Lemaire, Debilly, & Dordain, 2002; Ghika et al., 1998; Walter & Vitek, 2004). The final target, the subthalamic nucleus, has become the most commonly utilized nucleus for PD. It improves all of the cardinal motor symptoms of PD and also allows for reduced levodopa dosage ("Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease," 2001; Limousin et al., 1998; Romito et al., 2002). Reduced dosing can reduce the amount of dyskinesias experienced and can prolong the time during which pharmaceutical treatment is effective. Those who have undergone STN stimulation have reported more instances of behavioral and cognitive side effects, but these are often related to location of the active contact and are reversible when the stimulation is turned off or another contact is chosen (Walter & Vitek, 2004).

Transplantation. Neural transplantation has been investigated as a PD treatment for several reasons including the following: 1) PD is characterized by a specific degeneration of dopamine (DA) neurons, 2) pharmaceutical DA replacement significantly improves clinical outcomes, and 3) there are defined targets for implantation (Olanow, Freeman, & Kordower, 2004). Rodent and primate studies in the 1970s and 1980s demonstrated promising results from transplantation of both species-specific and human fetal nigral cells (Brundin & Bjorklund, 1987; Mahalik, Finger, Stromberg, & Olson, 1985; Redmond et al., 1986). Results in human subjects, however, have been mixed. Although fetal cells have survived grafting and have even been shown to reinnervate the striatum, they have not provided significant clinical improvements compared to placebo surgeries. They have also induced severe off-medication dyskinesias in subjects, rendering transplantation a currently infeasible and unsafe treatment. Future work in this

area will focus both on increasing the number of surviving grafted neurons and increasing striatal innervation (Olanow, et al., 2004).

Deep Brain Stimulation

System components. The DBS system is composed of three elements: a DBS lead, extension wire, and implantable pulse generator (IPG). There are four platinum-iridium contacts at the distal end of the DBS lead that are spaced either 1.5 mm or 0.5 mm apart, depending on the model used (Models 3387 and 3389, Medtronic, Minneapolis). Two contacts are selected for bipolar stimulation, while one is selected for monopolar stimulation with reference to the IPG case (Volkman, et al., 2002). The extension wire, which is tunneled under the skin, connects the lead to the IPG power source. Normally implanted in the infraclavicular region, the IPG may be either a single- or dual-program model. Two single-program IPGs or one dual-program are required for bilateral stimulation (Lyons & Pahwa, 2004; Medtronic, 2003). Stimulation parameters are typically set to 1-3.5 V, 60-210 μ s pulse width, and 130-185 Hz pulse frequency (Moro, et al., 2002; O'Suilleabhain, Frawley, Giller, & Dewey, 2003; Rizzone et al., 2001; Volkman, et al., 2002).

Electrical stimulation of neural tissue. Model-based studies have been used to study the effect of electrical stimulation on neural tissue in DBS systems. The primary emphasis of these studies has been to study the differential effects of polarity, distance and stimulation waveform selection on electrical activation of various types of neural tissue. McIntyre and Grill modeled the effects of extracellular stimulation on fifty cells and fifty fibers randomly distributed about an electrode (2000). They determined that a monophasic *cathodic* stimulus selectively stimulated fibers over cells (70% vs 10%), while a monophasic *anodic* stimulus selectively stimulated cells over fibers (70% vs 25%). Due to the concerns of electrode corrosion and tissue damage associated with monophasic stimuli, they also investigated charge-balanced biphasic stimuli. Two asymmetrical waveforms, both characterized by a longer first pulse and shorter second pulse, were examined. In their model-based study, these waveforms demonstrated improved selectivity over the monophasic stimuli. *Anodic first, cathodic second* waveforms

selectively stimulated fibers over cells (70% vs 5%); *cathodic first, anodic second* waveforms selectively stimulated cells over fibers (70% vs 20%) (2000).

McIntyre and Grill also examined the relationship between cathodic stimulation and electrode-neural tissue distance (2000). They found that the current needed to excite both cells and fibers increased as the distance between the neural elements and the electrode increased.

Electrode geometry also affects the stimulation of neural tissue. Recall that the DBS system can be programmed in either a monopolar (with the case as the anode) or bipolar configuration. Because of the greater distance between the anode and cathode, the monopolar configuration produces a greater current spread than the bipolar (Kuncel & Grill, 2004; Sotiropoulos, 2005; Valenstein & Beer, 1961). Similarly, the current spread increases for bipolar configurations as the distance between the poles increases (2005). The larger current spread means that a monopolar geometry often requires a lower voltage setting than a bipolar geometry to produce the same clinical outcomes (Pollack, Benabid, Krack, Limousin, & Benazzouz, 1998). It also means that the smaller current spread produced by a bipolar setting may be less likely to stimulate adjacent structures and induce side effects (Volkman, et al., 2002). However, it is important to note that reducing current spread does not necessarily result in greater selectivity. Since neural elements may be activated at both the anode and the cathode, bipolar stimulation may actually be less selective than monopolar (2004). This assertion is supported by modeling studies which found almost equivalent fiber and cell recruitment by bipolar stimulation independent of inter-contact distance (McIntyre & Grill, 2000).

Tissue conductivity plays a role in the shape of the electric field generated by stimulation (Grill, 1999). While gray matter is isotropic, white matter is approximately 10 times more conductive in the direction parallel to fibers than in the direction perpendicular to fibers (Nicholson, 1965). Thus, current flow that is parallel to fibers is much more effective at activating the fibers compared with a perpendicular current flow (Ranck, 1975; Sotiropoulos, 2005). This relationship breaks down when the distance between the fibers and the electrode is very small, at which point fiber orientation does not seem to affect activation (2005).

Mechanism of action. Responses to stimulation depend upon the nucleus being stimulated. These differences may be related to differences in neuronal and synaptic distribution or to other properties of the target nucleus (Lozano, Dostrovsky, Chen, & Ashby, 2002). Regardless of the cause, the relationship between stimulated nucleus and stimulation effects limits the utility of comparing effects between different target nuclei. Therefore, this review will only examine STN stimulation with regards to mechanism. There are two general opposing beliefs concerning the effects of DBS: 1) DBS activates the stimulated nucleus and 2) DBS inhibits the stimulated nucleus. Each position is supported by evidence as demonstrated below.

Scalp potentials evoked by single and repeated stimuli to the STN can be recorded in human subjects with an implanted DBS system and the recorded activity increases with repeated stimuli (P. Ashby et al., 2001). The short chronaxie and refractory period of the neural structures imply the stimulated structures are large axons (Lozano, et al., 2002). Animal studies also provide evidence of stimulatory effects. Lee *et al.* reported that STN-HFS in rat slices *in vitro* increased firing rates while Garcia *et al.* recorded bursts of spikes in rat STN slices after HFS (Garcia, Audin, D'Alessandro, Bioulac, & Hammond, 2003; Lee, Chang, Roberts, & Kim, 2004; Lee, Roberts, & Kim, 2003). In addition, stimulating glutamatergic output neurons in the STN also causes excitatory activity in one of its target structures, the GPi (Feger, Hassani, & Mouroux, 1997; Hammond, Deniau, Rizk, & Feger, 1978; Nakanishi, Kita, & Kitai, 1991; Rinvik & Ottersen, 1993). It is important to remember the size difference between the electrode contacts used in human and animal studies when attempting to compare results across species. The smaller area of animal electrode contacts allow for much higher current densities, which can silence neurons (Asanuma & Arnold, 1975). Therefore, some researchers question the relevance of animal studies in explaining the mechanism of action of DBS in humans (P Ashby, 2001).

Long-duration HFS of the STN causes a period of neuronal silence lasting from several hundred milliseconds to as much as tens of seconds in both humans and animals (Beurrier, Bioulac, Audin, & Hammond, 2001; Filali, Hutchison, Palter, Lozano, & Dostrovsky, 2004; Lee, et al., 2004; Lozano, et al., 2002; Tai et al., 2003; Welter et al., 2004). Although it does not completely inhibit firing, Benazzouz *et al.* found that a 5-s HFS train depressed firing for 30-90 s

(Benazzouz et al., 2000). Several mechanisms have been proposed for the observed depression or blockage of firing, including neuronal energy depletion, synaptic failure, or the temporary depression of Na^+ and T-type Ca^{2+} currents (Beurrier, et al., 2001; Lozano, et al., 2002). HFS has also been shown to decrease metabolic activity in the targeted nucleus. A decrease of about 10-35% in STN metabolic activity was caused by long-term HFS in both control and lesioned rats (Salin, Manrique, Forni, & Kerkerian-Le Goff, 2002; Tai, et al., 2003). Finally, HFS of the STN caused mild firing rate depression in the GP of both control and lesioned rats (Burbaud, Gross, & Bioulac, 1994).

There are four basic hypotheses to explain the effects of DBS: (a) DBS creates a depolarization block (Beurrier, et al., 2001), (b) DBS inhibits synaptic activity (Dostrovsky et al., 2000), (c) DBS limits synaptic activity (Urbano, Leznik, & Llinas, 2002), and (d) DBS modulates pathologic activity (Montgomery & Baker, 2000). Depolarization block and synaptic inhibition are supported by many studies listed above and would explain how both lesioning and DBS provide therapeutic benefit in PD. However, they do not allow for the possibility that efferent axons are activated independently of somatic suppression, as suggested by theoretical models (McIntyre, Grill, Sherman, & Thakor, 2004). The possibility that somatic and axonal activity are decoupled is supported by considering the effects of extracellular stimulation. Namely, action potentials are initiated in the axon and trans-synaptic inputs are activated. Although somatic firing is inhibited, axonal initiation of action potentials leads to the production of patterns of efferent activity (Dostrovsky, et al., 2000; McIntyre & Grill, 1999; Nowak & Bullier, 1998a, 1998b).

This once again raises the question of how therapy that causes efferent output results in clinical outcomes that are comparable to those of an ablative lesion. One explanation is that neurotransmitter depletion (synaptic depression) in the activated neurons prevents them from maintaining activity at a high frequency (Urbano, et al., 2002). However, other studies indicate just the opposite--that transmitter release actually increases during HFS (Hashimoto, Elder, Okun, Patrick, & Vitek, 2003; Windels et al., 2003). Thus, the fourth hypothesis is the only one consistent with all available data on stimulation effects (McIntyre, Savasta, Kerkerian-Le Goff, & Vitek, 2004). Of course, since the activity produced by DBS is not in itself normal, it is not

possible to explicitly link DBS results to therapeutic mechanisms (McIntyre, Savasta, et al., 2004). Garcia *et al.* agree with this hypothesis, proposing that the modulation induced by HFS includes not only removing the pathological rhythm but also replacing it with a new pattern that is time-locked to the stimulation (2005). This is similar to the prokinetic high-frequency rhythm posited by Brown and Marsden to explain the therapeutic effects of L-dopa (1998). STN oscillatory activity in people with PD and primate models increases from 11-30 Hz to more than 70 Hz after treatment with L-dopa (Brown et al., 2001; Williams et al., 2002).

Electrode Location

Optimal electrode placement. There are still many questions regarding optimal electrode location. Although the STN is known to be an effective stimulation site for treating PD, the optimal location within its borders is still undetermined. Most surgeons target the ventral-posterior STN border so as many contacts as possible are within the STN (Lanotte et al., 2002; Simuni et al., 2002; Zonenshayn et al., 2000). However, Voges and colleagues found the most clinically effective site near the anatomically defined dorsal border of the STN (2002). Zonenshayn and colleagues compared the distance between the dorsal STN border and the center of clinically effective active contacts to locate the best position (2004). They found the active contact was usually located at the anterior, dorsal, and lateral STN border. It was often just outside the atlas-defined STN, supporting the idea that the fiber tracts are more involved with stimulation effects than the neurons in the STN (Morel, Magnin, & Jeanmonod, 1997; Schaltenbrand & Wahren, 1977). Optimal clinical benefits were elicited by monopolar stimulation at the anterior dorsolateral STN border approximately 13 mm lateral to the midcommissural point (2000).

Voges and colleagues investigated the relationship between clinical improvement, energy use, and electrode location (2002). They found that although the most distal contact was usually positioned in the STN as intended, the best therapeutic results were produced by contacts several mm above this one. In addition, correlating motor improvements with stimulus intensity revealed the best results were elicited by active contacts projecting onto white matter dorsal to the STN. Similarly, Littlechild and colleagues also found that proximal contacts were chosen more

often than distal ones, corresponding to a location just dorsal to the STN in the S-W atlas (2003). This further supports the assertion that fiber tracts mediate stimulation effects more than do STN neurons (Voges, et al., 2002). Saint-Cyr and colleagues determined that electrodes placed in the anterior-dorsal STN and/or the FF/zi produced the greatest clinical effects with the least side effects (2002). Similarly, Patel and colleagues experienced more success with lesions that extended into the FF/zi (2003). Electrodes placed on the border between the STN and the region where the FF/zi and STN projections are contained relieved rigidity with the least voltage (Hamel et al., 2003). Finally, electrode contacts in the fiber tracts required less power than those in the STN to produce the same clinical benefit (Voges, et al., 2002).

Taken together, these results suggest that while contacts in the STN still produce clinical effects, the fiber tracts are a better option. However, Herzog and colleagues found just the opposite--fiber tract contacts were less effective than ones in the dorsolateral border zone (2004). These contradictory results and the uncertainty surrounding the structures responsible for clinical benefits of DBS can only be resolved through more thorough investigations of the relationships between electrode location, therapeutic motor effects, adverse side effects, and effects due to stimulation parameters (Kuncel & Grill, 2004).

Adverse effects. The STN is surrounded by fiber tracts and other nuclei whose stimulation may induce adverse effects. While some side effects may be tolerated when accompanied by antiparkinsonian motor improvement, others must be alleviated by decreasing stimulation amplitude, choosing a different contact, or relocating the electrode (Pollak et al., 2002). Stimulation of the corticobulbar tract, which runs anterior to the STN, may result in pharyngeal and laryngeal muscle contractions leading to speech deficits. Stimulation that spreads outside the lateral side of STN may activate the corticospinal tract, resulting in contralateral muscle contractions (Pollak, et al., 2002; Saint-Cyr, et al., 2002). Conversely, medially-placed electrodes may cause activation of the oculomotor nerve, resulting in adduction or upward or downward deviation (Pollak, et al., 2002). Medial electrodes may also stimulate the red nucleus (RN) causing proximal muscle contractions (Saint-Cyr, et al., 2002). In addition, RN lesions have

been known to induce tremor and gait ataxia (Felice, Keilson, & Schwartz, 1990; Vidailhet, Jedynak, Pollak, & Agid, 1998).

Behavioral complications sometimes result from DBS therapy of the STN. Stefurak and colleagues presented a case study in which bilateral stimulation produced unexpected results (2003). The left electrode, which was located in the inferior STN, elicited improvements in tremor and bradykinesia on the contralateral side. The right electrode, on the other hand, was located in the Fields of Forel/zona incerta (FF/zi), superior and lateral to the intended STN target. Stimulation using this electrode induced a severe dysphoric mood in the subject with little change in motor symptoms. The emotional response disappeared within four weeks, and the right electrode was re-implanted after six months to increase the therapeutic effect on motor symptoms. Bejjani and colleagues reported the case of a 65-year-old woman with bilateral STN stimulation (1999). They determined the locations of her electrode contacts on MRIs using the Schaltenbrand and Wahren atlas for assistance. The most distal contact (contact 0) of the left electrode was positioned in the central STN, including a portion of the pars compacta and pars reticulata, while contacts 1 and 2 were positioned in the STN. Stimulation of contact 0 induced an acute transient depression, while contact 2 improved motor symptoms.

Experimental Assessment of Functional Outcomes

Most experimental studies have used the UPDRS (Unified Parkinson's Disease Rating Scale) to assess functional outcomes. This is a subjective five-level (0-4) scale used to rate (a) mental ability and behavior, (b) activities of daily living, (c) motor function, and (d) complications of therapy. Although this test can be readily administered and provides a mechanism to assess clinical outcomes, its utility is limited by the subjective nature of the test and the sensitivity of the ordinal values used for individual measures. Stimulation through a particular contact does not necessarily affect all symptoms, and the uncertainty surrounding the structures responsible for clinical benefits of DBS can only be resolved through detailed studies of the relationships between electrode location, therapeutic motor effects, adverse side effects, and effects of changing stimulation parameters (Kuncel & Grill, 2004; Yelnik et al., 2003). The UPDRS scale may not be sensitive enough to discern substantive changes induced by modifying stimulation

parameters. Quantitative assessment could increase the power for detecting changes in individual symptom alleviation.

Partial reductions in stimulation amplitude. Since it has been established that DBS improves the cardinal symptoms of PD, it is important to understand how incremental changes in amplitude affect the efficacy of DBS (Kuncel & Grill, 2004; Limousin, et al., 1998; Romito, et al., 2002). Most of the studies that have investigated the effects of DBS were carried out in the following four conditions: 1) Medication OFF/Stimulation OFF, 2) Medication OFF/Stimulation ON, 3) Medication ON/ Stimulation OFF, and 4) Medication ON/Stimulation ON. Few have studied the effects of partial reductions in stimulation amplitude. Of those that have, not all have measured performance quantitatively but have measured it solely with the UPDRS (Tripoliti, et al., 2008). Others have only utilized short acclimation periods before assessing symptoms which may not be sufficient to see the effects of stimulation changes on all symptoms (Kuncel & Grill, 2004; Moro, et al., 2002).

Initiating and maintaining repetitive motions. People with PD have been shown to perform differently than controls in repetitive finger tapping, lip movement, and walking tasks. Several studies have shown that people with PD exhibit greater variability than controls for both self- and externally- paced tasks. In addition, people with PD demonstrated increased mean rates for lower cued frequencies and decreased mean rates for higher cued frequencies (J. S. Freeman, F. W. Cody, & W. Schady, 1993a; Konczak, Ackermann, Hertrich, Spieker, & Dichgans, 1997). Repetitive tasks have also elicited different responses in people with PD based upon their primary symptom. Yahalom and colleagues determined that both tremor-predominant and akinetic-rigid subtypes performed slower and exhibited more variability in a hand tapping task than other PD subtypes and controls (2004).

Many individuals with PD also present with gait deficits. Ferrarin and colleagues compared a PD cohort with bilateral subthalamic stimulation to age-matched controls (Ferrarin et al., 2002). The PD cohort demonstrated a significantly reduced mean gait velocity in the Stimulation OFF condition. Mean velocity as well as stride length increased significantly in the Stimulation ON condition. Hausdorff and colleagues found that stride-to-stride variability was

significantly increased in PD subjects with freezing of gait (FOG) compared to those without FOG (Hausdorff et al., 2003). This indicates that FOG impairs the ability to maintain a stable walking rhythm. Schaffsma and colleagues utilized stride time variability as a marker of fall risk in PD subjects (Schaafsma et al., 2003). They found that stride time variability was significantly higher in the fallers group than that of the non-fallers.

Postural control. Using qualitative measures, it has been reported that STN-DBS improved postural stability in the absence of anti-parkinsonian medication (Nilsson, Tornqvist, & Rehncrona, 2005). STN-DBS has been demonstrated to reduce postural sway to near normal values, whereas levodopa alone increased postural sway (Rocchi, Chiari, & Horak, 2002). Dynamic posturography has been used to demonstrate that STN stimulation in combination with levodopa reduced postural instability. Postural control is also affected indirectly by increased rigidity, which is typically observed in people with PD. Bartolic and colleagues reported that a PD cohort demonstrated improvements in postural stability after taking a dopaminergic agonist that reduced their rigidity (2005).

Summary

DBS is effective at improving the cardinal symptoms of PD, but its benefits are influenced by how the disease manifests itself in an individual, the location of the electrode array, and the selection of stimulation parameters. Choosing acceptable stimulation parameters is often time-intensive, and it may be difficult to optimize parameters to benefit all effects of PD. Understanding how different symptoms are affected by changes in stimulation may increase the effectiveness of the DBS programming process.

Table 2.1

Glossary of Abbreviations

STN	subthalamic nucleus
SN	substantia nigra
SNpc	substantia nigra pars compacta
SNpr	substantia nigra pars reticulata
Vim	ventral intermediate thalamic nucleus
GPi	globus pallidus internal portion
FF	fields of Forel
ZI	zona incerta
AC	anterior commissure
PC	posterior commissure
MCP	mid-commissural point
PPN	pedunculopontine nucleus
GABA	gamma-aminobutyric acid

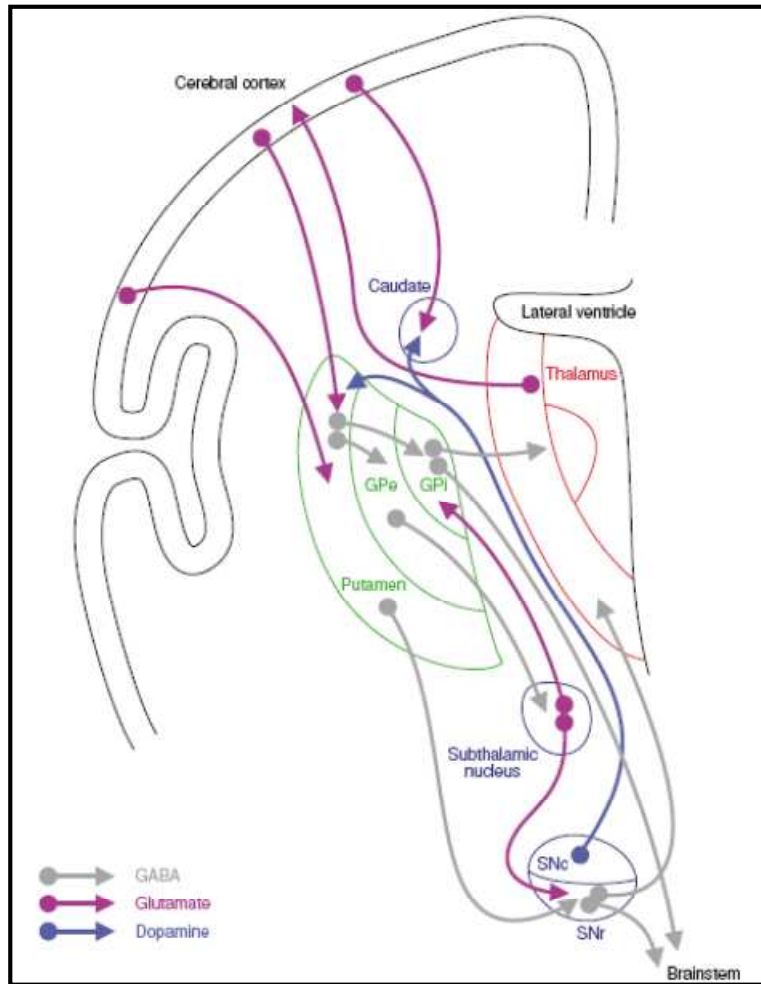


Figure 2.1. Connections of the basal ganglia. Please note connections from the caudate to GPe and SNr are not shown for reasons of clarity. Reproduced from Lewis, Caldwell, & Barker (2003).

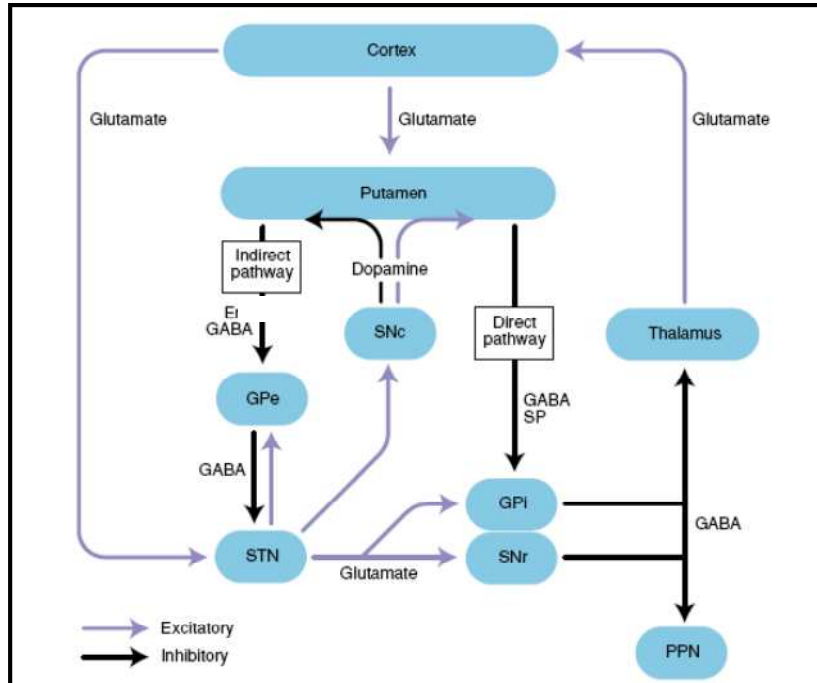


Figure 2.2. Basal ganglia pathways in normal conditions. PPN = pedunclopontine nucleus (located in brainstem). Modified from Lewis, Caldwell, & Barker (2003).

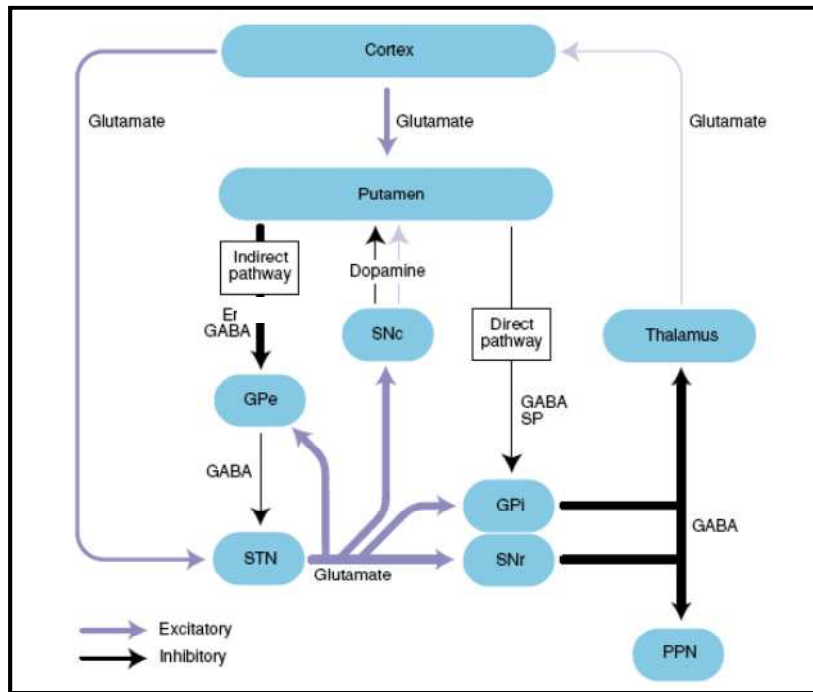


Figure 2.3. Basal ganglia pathways in Parkinson's disease. The decrease of striatal dopamine diminishes the direct pathway while increasing the indirect pathway. Arrow thickness represents the activation level of each connection. Modified from Lewis, Caldwell, & Barker (2003).

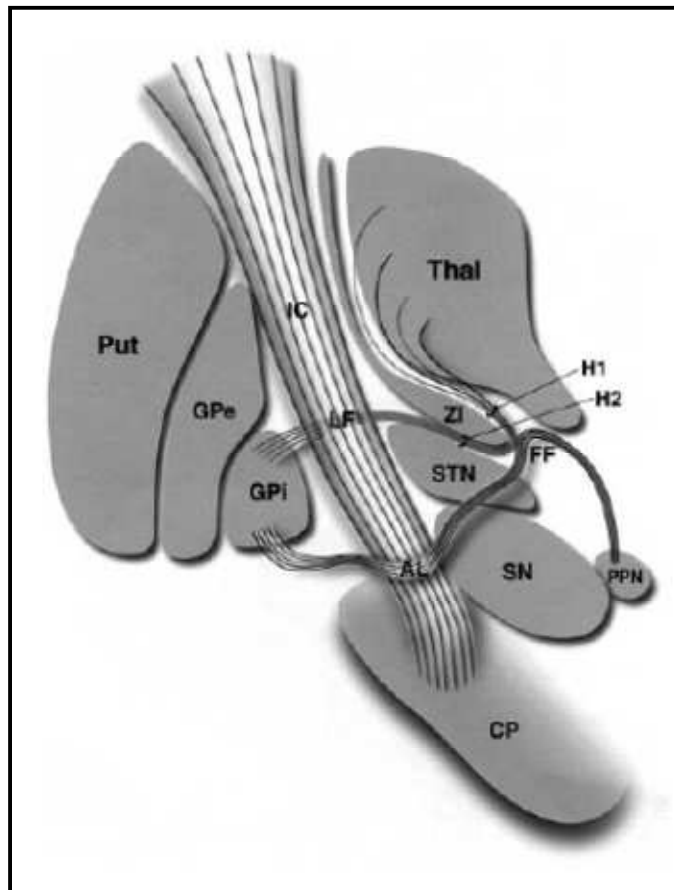


Figure 2.4. Depiction of several fiber tracts associated with STN. AL = ansa lenticularis, FF = Fields of Forel, IC = internal capsule, LF = lenticular fasciculus, ZI = zona incerta. Reproduced from Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano (2004).

CHAPTER 3

EFFECTS OF DEEP BRAIN STIMULATION AMPLITUDE ON MOTOR PERFORMANCE IN PARKINSON'S DISEASE

Abstract

Background. The efficacy of deep brain stimulation (DBS) in Parkinson's disease (PD) has been convincingly demonstrated in studies that compare motor performance with and without stimulation, but characterization of the stimulation dose-response curves has been limited.

Methods. In a series of case studies, eight subjects with PD and bilateral DBS systems were evaluated at their clinically determined stimulation (CDS) and at three reduced amplitudes, i.e., approximately 70%, 30%, and 0% of the CDS (MOD, LOW, and OFF, respectively). Performance was assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III), which includes subscores for tremor, bradykinesia, gait, posture, and tapping. The data at reduced settings were analyzed to determine if individual subjects demonstrated a threshold-like response, which was defined as a dose-response curve in which one decrement in stimulation accounted for $\geq 70\%$ of the maximum change observed. Day-to-day variability was assessed using the CDS data from the three different days.

Results. In the dose-response curves, two subjects exhibited a threshold-like response, four exhibited a graded change, and two did not exhibit substantial changes. For some subjects the variability in CDS performance across the three days exceeded the change observed when reducing amplitude to the MOD setting. Comparisons across this set of 8 subjects demonstrated that the mean UPDRS-III and all but one subscore significantly increased (performance degraded) when amplitude was reduced from CDS to the LOW and OFF conditions, but there were no significant changes when amplitude was reduced from CDS to the MOD condition.

Conclusions. Individual differences in the DBS dose-response curves may provide opportunities to optimize clinical performance. Day-to-day variability in motor performance cautions against the use of a single UPDRS measurement in clinical selection of DBS settings.

Introduction

For many people with PD, deep brain stimulation (DBS) of the subthalamic nucleus (STN) can alleviate many symptoms of PD, reduce prescribed medication levels, and reduce medication-related side effects (Bakker, et al., 2004; Krack et al., 1998; Limousin, et al., 1998; Obeso et al., 2001). Several studies have compared motor performance at patients' clinically determined stimulation (CDS) settings – the settings currently considered by the patient's clinician to be optimal for the patient – to performance with the DBS system turned off completely (Dafotakis, et al., 2008; Diamond, et al., 2007; Plaha, et al., 2006; Robertson, et al., 2001; Timmermann, et al., 2008). Although such studies demonstrate the benefits of using DBS, they do not provide much guidance to the clinician trying to select stimulation parameters that balance the tradeoffs between clinical effects and battery life. A more detailed understanding might help clinicians select more suitable stimulation parameters, but only a few studies have begun to investigate motor performance at intermediate stimulation settings. For example, one study investigated the effects of different combinations of contact location (relative to the STN) and amplitude in patients with PD. Given that the main focus was speech intelligibility, movement was only examined as a composite outcome (Tripoliti, et al., 2008). Another demonstrated that frequency and stimulation amplitude were the most important factors in alleviating tremor amplitude in patients with essential tremor, while varying pulse width had little effect (Kuncel, et al., 2006). In both studies, patients were evaluated at the same amplitude values regardless of the settings that had been prescribed specifically for each patient.

The effects of varying pulse width, frequency, and stimulation amplitude on tremor, rigidity, and bradykinesia have been investigated in one study (Moro, et al., 2002), but it did not evaluate effects on posture or gait. This report also concluded that varying pulse width did not have a clear effect on symptoms of PD, while stimulation amplitude was the most important factor in alleviating the parkinsonian triad.

In the series of case studies reported here, we evaluated five components of motor performance, i.e., tremor, bradykinesia, gait, posture, and tapping, in a population with PD. Based upon the reports cited above (Kuncel, et al., 2006; Moro, et al., 2002), we focused our

assessment on the effect of changing stimulation amplitude only. Motor performance was assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III). A UPDRS subscore was defined and assessed for each component. Given that the CDS amplitude setting can vary widely across individuals, we varied amplitude as a percentage of the CDS value to facilitate comparison across subjects. The CDS amplitude was defined as the ceiling, because stimulation amplitude is often set just below the threshold for adverse effects (2002).

Symptoms are known to vary daily in people with PD, with studies indicating that consecutive UPDRS measurements may vary by as much as 15%, yet many DBS studies have compared capabilities as assessed on different days (Delwaide & Gonce, 1998; Plaha, et al., 2006). Therefore, we also examined motor performance at the same stimulation condition over three different days to provide a daily baseline measurement.

Methods

Subjects. Subjects who met the following criteria were recruited from the Movement Disorders Clinic at Banner Good Samaritan Medical Center and Movement Disorder Specialists (Phoenix, AZ): age 18-80 years; diagnosis of idiopathic PD with bilateral symptoms; a Hoehn & Yahr (H&Y) stage ≤ 4 during the 'medication-on/stimulation-on' condition; bilateral DBS system implanted in the STN for more than 3 months; willingness to sign the informed consent document; and ability to understand and follow directions.

Subjects were excluded if they presented with any of the following: significant hepatic, renal, cardiovascular, endocrinological, respiratory or unstable neurological disease aside from PD; psychotic illness or chronic psychiatric disorder; history of drug dependence or intellectual impairment; history of cerebral insult (causing delayed secondary PD); an H&Y stage of 5 during the 'medication-on/stimulation-on' condition; Parkinson's plus syndrome; score ≥ 3 for UPDRS-II items 13-15 (falling unrelated to freezing, freezing when walking, and walking) during the 'medication-on/stimulation-on' condition; or score ≥ 4 during the 'medication-on/stimulation-on' condition for UPDRS III items.

Eight subjects (six males, two females) met the criteria and were enrolled in the study. The mean age at enrollment was 59.5 ± 8.9 years. Mean time since PD diagnosis was 12.6 ± 4.0

years, and mean time since the first DBS surgery was 46.8 ± 23.7 months. The median H&Y stage at enrollment was 2.0 with a range of 2.0-3.0 (Table 3.1). Seven of the subjects had previously been implanted with two Soletra[®] Model 7426 neurostimulators (Medtronic Inc., Minneapolis, MN), while one subject (subject 2) had previously been implanted with one dual-program Kinetra[®] Model 7428 neurostimulator (Medtronic Inc.). The surgical placement technique used for all subjects included the use of microelectrode recordings. All subjects had been implanted with Model 3387 macroelectrodes (Medtronic, Inc.) except subjects 4 and 8, who had been implanted with Model 3389 macroelectrodes (Medtronic, Inc.).

Experimental protocol. For each subject, data were collected during three separate sessions, with a 1-4 week period between sessions (actual mean time between sessions 16.6 ± 5.0 days). All sessions were conducted at the Clinical Neurobiology and Bioengineering Research Laboratory at Banner Good Samaritan Medical Center in Phoenix, AZ. All experimental procedures were approved by the center's institutional review board and conducted in accordance with the center's guidelines and the Declaration of Helsinki. Informed consent was obtained from all subjects before participating in this research.

The experimental sessions were conducted during subjects' 'medication-on' state in order to provide information about the dose-response characteristics of DBS as a supplement to prescribed medication. Although several studies have defined the 'medication-on' state as a suprathreshold dosage of levodopa, here the 'medication-on' state represented the subjects' daily living condition to simulate a clinically relevant situation and allow the results to be readily transferred to the clinic (Guehl et al., 2006). To ensure subjects were at the same point in their medication cycle, all three sessions occurred at the same time of day for each subject. The dosage of medication is reported as levodopa equivalent daily dose (LEDD) in Table 3.1 (Vingerhoets et al., 2002). Of note, one subject (subject 4) was not taking any antiparkinsonian medications throughout the course of the test sessions.

At each session, subjects were first evaluated at their currently programmed CDS settings and next with reduced amplitude stimulation settings. This provided a consistent assessment of change in the same direction (i.e., always from CDS to the altered condition) and

a consistent assessment of the CDS settings (i.e., it was always assessed before any changes to stimulation occurred. Reduced settings were always chosen relative to each subject's CDS amplitude on that day, therefore allowing performance at reduced settings to be compared with performance at the settings currently determined to be optimal by the patient's clinician. Subjects were given a 20-minute rest period after their DBS settings were reduced to allow any changes induced by the reduction to take full effect, which is equivalent to or longer than the calibration time in other studies that have evaluated motor performance at multiple stimulation settings (Kuncel, et al., 2006; Moro, et al., 2002; Tripoliti, et al., 2008; Waldau, Clayton, Gasperson, & Turner, 2011). This rest period also limited the effects of subject fatigue and/or changes in drug efficacy that might have occurred with longer rest periods. The reduced amplitude setting on a given day was one of three conditions: MOD (approximately 70% of the CDS), LOW (approximately 30% of the CDS) and OFF (DBS stimulation completely switched off). Given the limited resolution on the implanted pulse generator (IPG), stimulation conditions were selected to be as close as possible to the target percent condition. Across subjects, the order in which the reduced amplitude settings were tested was randomized.

The CDS and reduced amplitude values, rate, pulse width, and active contacts used for each subject during each test session are given in Table 3.1. The mean CDS, MOD, and LOW amplitudes were 3.4 ± 0.8 V, 2.4 ± 0.6 V, and 1.0 ± 0.3 V, respectively. The mean rate was 177 ± 17 Hz. The mean pulse width was 74 ± 16 μ s. Note that the study did not place any restrictions on changes in clinical prescription of medication or stimulation settings; those changes are noted in the table and in the following sections of the text. In order to limit the effect of such intersession changes, the study primarily uses intrasession differences (between CDS and the altered condition) to characterize the response to changes in stimulation amplitude.

A trained DBS system operator queried the IPG using a Model 8840 N'Vision™ clinician programmer (Medtronic Inc., Minneapolis, MN), recorded the current stimulation settings, and changed the stimulation settings. A researcher trained to administer the UPDRS evaluated items 18-31 (the motor examination section) during all experimental sessions.

Outcome measures. Outcome measures included the total UPDRS III motor score (maximum 108) along with several motor subscores. Note that on this scale, a higher score indicates worse performance. For individual subjects, a change of five points in the total UPDRS III motor score (4.6% of the maximum score) was considered to be a minimal clinically important change, as defined by Schrag and colleagues (for patients in H&Y stages 1-3) (2006).

All of the subscores except for tapping were based on definitions used in previous studies: (a) tremor = items 20-21 assessed only at the hands (maximum 16) (Hamani, Richter, Schwalb, & Lozano, 2005; Wider, Pollo, Bloch, Burkhard, & Vingerhoets, 2008), (b) bradykinesia = items 23-26, 31 (maximum 36) (Bartels et al., 2003), (c) gait = item 29 (maximum 4) (Visser-Vandewalle et al., 2005), and (d) posture = items 28, 30 (maximum 8) (Krause, Fogel, Mayer, Kloss, & Tronnier, 2004). The tapping subscore was defined as item 23 (maximum 8). The differences in mean scores obtained at the CDS and reduced amplitudes were calculated for each outcome measure and normalized by the maximum possible score for that particular measure to facilitate comparison across different measures. For each of the subscores, we have identified which measures exhibited a change > 25% of the maximum possible score.

Dose-response characteristics. To characterize the nature of the response to stimulation, dose-response curves were produced for the overall UPDRS III and for each of the subscores. In these plots, dosage is reported as stimulation condition, which was normalized by the CDS amplitude for each subject. The response is reported as the change in the UPDRS score (or subscore) recorded at each altered stimulation amplitude with respect to the score (or subscore) recorded at the CDS condition of stimulation on that day.

The linearity of the dose-response curves for each subject was assessed by calculating the slopes of each of the segments. If the response to stimulation was graded and linear, each decrement in stimulation would account for 30-40% of observed maximum change in outcome measure (30% for MOD, 40% for LOW, and 30% for OFF). If the response exhibited a purely threshold (on/off) effect, one of the decrements in stimulation would account for 100% of the change in outcomes. In this analysis a subject was characterized as having a 'threshold' dose-response characteristic if one decrement in stimulation accounted for $\geq 70\%$ of the maximum

performance change observed, which is the amount of change expected from two decrements. Otherwise, the subject was characterized as having a 'graded' dose-response characteristic.

Statistical analysis. Statistics were performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL). For each outcome measure, the two-tailed Wilcoxon signed rank test was used to compare the values measured at each session's CDS amplitude with the values measured at that same session's reduced amplitude. Performance at each session's CDS amplitude was treated as a baseline measure for performance at the associated reduced amplitude to account for minor changes in medication or CDS settings over the course of all three test sessions. Unless otherwise noted, summary data is reported as mean \pm 1 standard deviation, and a *P* value < 0.05 was considered to be statistically significant.

Results

Dose-response characteristics. Although the mean dose-response curves for the subscores (Figure 3.1) were nearly linear, there was high variability across subjects. Applying the linearity criterion described above to the total UPDRS III motor score, four subjects exhibited a graded dose-response characteristic (3, 4, 6, and 7) and two exhibited a threshold response (1 and 2). The two subjects (5 and 8) who showed very small overall change in the UPDRS III score were not included in this characterization of the dose-response curve.

Comparison across stimulation conditions. When amplitude was reduced from the CDS to the MOD condition, only four subjects experienced a clinically important decrease in performance, and two of these decreases were only borderline, defined as 5-7 points (Figure 3.2, Table 3.2). However, all eight subjects experienced a clinically important change (\geq 5 points) when amplitude was reduced from the CDS to the LOW condition (three designated as borderline changes). When amplitude was reduced to the OFF condition, six subjects showed clear deterioration in performance with increases in the total UPDRS III motor score ranging from 13-59 points. Interestingly, two of the subjects (5 and 8) who only experienced borderline changes in the LOW condition did not experience a clinically important change in the OFF condition.

For the subscores, none of the subjects experienced change > 25% of the maximum score at the MOD condition, but half of the subjects experienced a change > 25% of the

maximum score for at least one subscore at the LOW or OFF conditions. The other four subjects (3, 4, 5, and 8) did not experience a change > 25% of the maximum score in any condition.

When the subjects were examined as a group, none of the mean outcomes degraded significantly when amplitude was decreased from the CDS to the MOD condition (Figure 3.3). However, all mean outcomes except one significantly degraded when amplitude was decreased from the CDS to the LOW and OFF conditions (gait and posture, respectively).

Repeatability at CDS condition. Each subject had three scores obtained at the CDS condition, one from each data collection session (Table 3.2). For the total UPDRS III motor score, the difference in CDS measurements was calculated to determine if there were any clinically important changes between days. Subjects 3, 5, 6, and 7 experienced a clinically important change between at least two sessions. For the subscores, the range of these three measurements was calculated to characterize the variability in each subject's results (Figure 3.1). Compared with the maximum possible score for each subscore, subjects 1, 2, and 8 experienced low variability for all of the subscores. Subjects 3, 4, 6, and 7 experienced low variability on all but one subscore, and subject 5 experienced high variability for two subscores.

The range of CDS values was also compared to the change in score from the CDS condition to each reduced amplitude condition. The mean change in score from the CDS to the MOD condition was comparable with the mean CDS range for the total UPDRS III score as well as for the tremor, bradykinesia, and tapping subscores, but the mean changes in score from the CDS to the LOW and OFF conditions were greater than the mean CDS range. However, for the gait and posture subscores, the mean change in score from the CDS to the MOD condition was half the size of the mean CDS range, and the mean change in score from the CDS to the LOW condition was equal to the mean CDS range. For these two subscores, only the mean change in score from the CDS to the OFF condition was greater than the mean CDS range.

When examined for each subject, the change in score from the CDS to the MOD condition was greater than the CDS range for subjects 2 and 7 for the total UPDRS III score as well as the majority of the subscores. For the rest of the subjects, the change in score from the CDS to the MOD condition was comparable with or less than the CDS ranges for the total

UPDRS III score and the majority of the subscores. In contrast, the change in score from the CDS to the LOW condition exceeded the CDS range for the total UPDRS III score for all subjects except subject 5 and for at least half of the subscores for subjects 1, 2, 4, 6, and 7.

Discussion

Individual subject measures. Subjects 1 and 2 were both characterized as having a threshold in the dose-response curve. In addition, neither exhibited clinically significant day-to-day variability in the CDS measures. However, subject 2 experienced a greater change in score when amplitude was reduced to the MOD condition compared with the range of scores experienced during different CDS sessions, while subject 1 did not. This difference may be explained by the location of the thresholds for the two subjects. The threshold for subject 1 was located between the MOD and LOW conditions, with little difference observed between CDS and MOD. The threshold for subject 2, however, was located between CDS and MOD and a reduction in stimulation amplitude of 30% accounted for more than 80% of the total observed change in score.

Subjects 3, 6, and 7 were all characterized as having a graded dose response curve and all exhibited some clinically significant variability in the CDS outcomes. For these subjects, the graded response characteristic may be responsible for observed day-to-day variability as well as the sensitivity to changes in stimulation. The characteristics of these subjects demonstrate that at least some patients may benefit from fine-tuning of the stimulation level and possibly may benefit from a system that allows for daily adjustments to stimulation level either in an automated or patient-selected manner. However, subject 4 was also characterized as having a linear dose-response curve but did not exhibit clinically significant variability in the CDS outcomes. This observation may be due to the fact that the total effect of stimulation was low in this subject and this was the only subject in the study that was not taking antiparkinsonian medications. Subjects 5 and 8 demonstrated less sensitivity to the degree of stimulation reduction compared with the other subjects, with the largest observed changes in the total UPDRS III score at less than 10.

DBS dose-response characteristics. Several studies have demonstrated the value of DBS by assessing motor function with and without stimulation, but very few have investigated

more subtle changes in stimulation values. By assessing motor function at 4 different amplitudes, we have been able to characterize the dose-response curves for individual subjects. With only 4 data points, this is a very coarse characterization of the dose-response curve, but does enable classification of different response characteristics that may have implications for clinical adjustments to stimulation settings.

A linear dose-response curve would suggest that the effect of DBS could be precisely regulated by adjusting stimulation amplitude. Although the group means for the total UPDRS III score and each of the subscores all exhibited linear dose-response curves, the data demonstrated a high degree of variability across the set of subjects. These data reflect the variability observed clinically in the effects of PD on motor performance and the variability in the reported on/off effects of DBS. Although a wide range of response characteristics was demonstrated across symptoms, six of the eight subjects could be grouped into one of two categories, comprising those who exhibited a threshold, i.e., an all-or-none type of response to stimulation, and those who exhibited a graded response that was approximately linear.

The two classes of dose-response characteristics that were observed may be due to differences in the nature and/or stage of PD or may be due to differences in electrode location. If this classification scheme were to be confirmed in a larger study, the results could lead to the development of alternative parameter selection procedures for use in the clinic: those exhibiting graded responses could have stimulation levels iteratively adjusted to improve performance while those that exhibit threshold-like responses could have stimulation adjusted to just above their threshold in order to reduce battery power consumption. Perhaps more importantly, a larger study could also characterize electrode location to determine the degree to which dose-response classification is determined by surgical placement.

Comparison across stimulation conditions. Reducing the stimulation to the MOD condition caused a clinically important decrease in performance for half of the subjects, but further reductions (to the LOW and/or OFF setting) caused clinically important changes for all subjects. The lack of observed change at the MOD condition may truly reflect a lack of clinical effect or it may indicate a failure to detect the effect due to insufficient sensitivity in measurement

procedures. Although the UPDRS III has been found to be reliable and valid, it has been criticized for placing too much emphasis on severe manifestations of symptoms and not enough on milder presentations such as might be seen if stimulation amplitude was reduced by only 30% (Vieregge, Stolze, Klein, & Heberlein, 1997). In addition, the scale measures symptoms that are not experienced by every patient, which decreases its overall sensitivity (Visser, Marinus, Stiggelbout, & van Hilten, 2006). However, if there was indeed no significant change in performance at the MOD condition for some of the subjects, then stimulation amplitude could be reduced by at least 30% for these subjects and performance would not degrade.

Although many subjects experienced similar increases in their total UPDRS III motor scores and several even had similar raw scores at each amplitude condition, their performance as measured by the subscores was very different. This may be explained by the differences in the subjects' primary symptoms. Previous reports (Gomez-Esteban et al., 2007) observed that although two patients may have the same UPDRS score, their quality of life may actually be very different depending on their prominent symptom(s), which suggests that adjusting stimulation parameters based on the total UPDRS III motor score alone may not always provide the most benefit for a patient's functionality.

In current clinical practice, stimulation amplitude is often chosen primarily based on the presentation of tremor, since tremor responds almost instantaneously to changes in stimulation. Unfortunately, tremor has been shown not to be correlated with other components of motor performance, to have little relation to functional disability, and to have little impact on patient quality of life (Gomez-Esteban, et al., 2007; Martinez-Martin et al., 1994; Stebbins & Goetz, 1998). It is possible that stimulation amplitude should be set based on the response of other components of motor performance. Bradykinesia, postural stability, gait, and rigidity ratings have been suggested to be the most dominant factors contributing to disability in patients with PD (1998).

Day-to-day variability. Across the three sessions, four of the subjects (1, 2, 4, 8) exhibited consistent UPDRS III motor scores at the CDS amplitude, and four subjects (3, 5, 6, 7) exhibited a range of CDS scores that exceeded the criterion for minimal clinically important

change. For comparison, the change in stimulation to the MOD condition produced a similar result: four subjects exhibited no clinically important change and four exhibited clinically important changes. The fact that half of the subjects exhibited clinically significant differences across days with the same stimulation settings indicates that day-to-day variability in motor performance is substantial and strongly cautions against the use of a single UPDRS reading in setting DBS parameters.

This study did not restrict changes in clinical prescription of stimulation or medication over the course of the subject's participation in the study, but it is important to note that these changes did not coincide with any of the observed clinically significant day-to-day variability in CDS scores. For subject 3 and 6, although there were no changes in the CDS levels between sessions 1 and 2, there were clinically significant changes in the total UPDRS III scores observed at the CDS settings (from 12 to 7 for subject 3; from 5 to 13 for subject 6). Between sessions 2 and 3, the CDS levels had been changed for both subjects (values reported in Table 3.1), but there was only a small change in UPDRS score (from 7 to 11 for subject 3; from 13 to 15 for subject 6). For subjects 1, 2 and 8, there were changes in the LEDD and/or stimulation settings across the set of sessions, but none of these changes coincided with clinically significant variability in the UPDRS scores measured at CDS.

Table 3.1

Subject Characteristics: LEDD and Stimulation Parameters at Each Test Session

Subj.	Age (yrs)	Sex	PD (yrs)	DBS (mos)	H&Y	LEDD	Rate (Hz)		Pulse width (µs)		Active contacts			MOD Test session		LOW Test session		OFF Test session	
							L	R	L	R	L	R		L	R	L	R	L	R
1	60	M	18	9	2	100 ^a	145 ^b	185	60	60	C+ 2-	3-	C+ 2-	Relative day ^f Amplitude (V)	21 3.7 (2.6) 3.0 (2.1)	0 3.6 (1.1) 2.4 (0.7)	35 3.7 (0) 3.0 (0)		
2	63	M	6	31	2	308	185	185	90	60	3+ 1-		C+ 7- ^d	Relative day Amplitude (V)	28 4.0 (2.8) 3.1 (2.2)	0 4.2 (1.5) 3.1 (1.0)	15 4.0 (0) 3.1 (0)		
3	52	M	8	33	2	341	185	170	60	60	C+ 3-		3+ 1-	Relative day Amplitude (V)	0 3.7 (2.6) 3.7 (2.6)	27 3.5 (1.1) 3.5 (1.1)	13 3.7 (0) 3.7 (0)		
4	60	F	14	61	3	0	145	185	60	60	C+ 2-		2+ 0-	Relative day Amplitude (V)	0 4.0 (2.8) 3.6 (2.5)	9 4.0 (1.3) 3.6 (1.1)	28 4.0 (0) 3.6 (0)		
5	79	M	11	52	3	525	185	185	90	90	1+ 3-		1+ 3-	Relative day Amplitude (V)	20 2.8 (2.0) 2.8 (2.0)	38 2.8 (0.8) 2.8 (0.8)	0 2.8 (0) 2.8 (0)		
6	55	M	14	41	2	150	135 ^e	185	90 ^f	60	C+ 1-		C+ 2-	Relative day Amplitude (V)	18 3.9 (2.8) 2.4 (1.7)	30 3.0 (0.9) 2.4 (0.7)	0 3.9 (0) 2.4 (0)		
7	51	F	14	60	2	254	185	185	90	90	3+ 1-		3+ 1-	Relative day Amplitude (V)	0 4.5 (3.2) 5.0 (3.5)	51 4.5 (1.4) 5.0 (1.5)	21 4.5 (0) 5.0 (0)		
8	56	M	16	87	2	854 ^g	185	185	60	90	2+ 3- ^h		C+ 2- 3-	Relative day Amplitude (V)	14 1.4 (1.0) 3.1 (2.2)	28 1.4 (0.5) 3.1 (0.9)	0 1.8 (0) 3.1 (0)		

Notes: PD, time since PD diagnosis (yrs); DBS, time since first DBS surgery (months); amplitude: CDS value in bold, reduced value in parentheses; ^a200 for LOW session, 50 for OFF session; ^b135 for LOW session; ^cday of session relative to first session (0); ^dcontact 7 is equivalent to contact 3 in Kinetra[®] dual-channel neurostimulator; ^e185 for LOW session; ^f120 for LOW session; ^g754 for LOW session, 708 for OFF session; ^h3+ 2- for OFF session.

Abbreviations: Subj, subject; PD, Parkinson's disease; DBS, deep brain stimulation; H&Y, Hoehn and Yahr stage; LEDD, levodopa equivalent daily dose; MOD, LOW and OFF, approximately 70%, 30% and 0% of clinically determined stimulation respectively; C, case.

Table 3.2

Subjects' UPDRS Part III Scores at the CDS, MOD, LOW, and OFF levels

Subject	MOD				LOW				OFF			
	CDS _M	MOD	Δ	% Δ	CDS _L	LOW	Δ	% Δ	CDS _O	OFF	Δ	% Δ
1	7	11	4	3.7	10	34	24	22.2	11	39	28	25.9
2	16	35	19	17.6	13	29	16	14.8	14	37	23	21.3
3	12	8	-4	-3.7	11	17	6	5.6	7	24	17	15.7
4	38	45	7	6.5	36	45	9	8.3	37	50	13	12.0
5	24	24	0	0.0	18	25	7	6.5	29	30	1	0.9
6	13	19	6	5.6	15	28	13	12.0	5	30	25	23.1
7	6	25	19	17.6	14	46	32	29.6	16	75	59	54.6
8	19	21	2	1.9	19	24	5	4.6	21	24	3	2.8
Mean ± SEM	16.9±3.7	23.5±4.3	6.6±3.0	6.1±2.7	17.0±2.9	31.0±3.6	14.0±3.4	13.0±3.1	17.5±3.9	38.6±6.0	21.1±6.4	19.6±6.0

Notes: CDS_M, CDS for MOD session; CDS_L, CDS for LOW session; CDS_O, CDS for OFF session; Δ, amount worsened; % Δ, amount worsened as % of max possible score (108).

Abbreviations: CDS, clinically determined stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MOD, LOW and OFF, approximately 70%, 30% and 0% of CDS respectively.

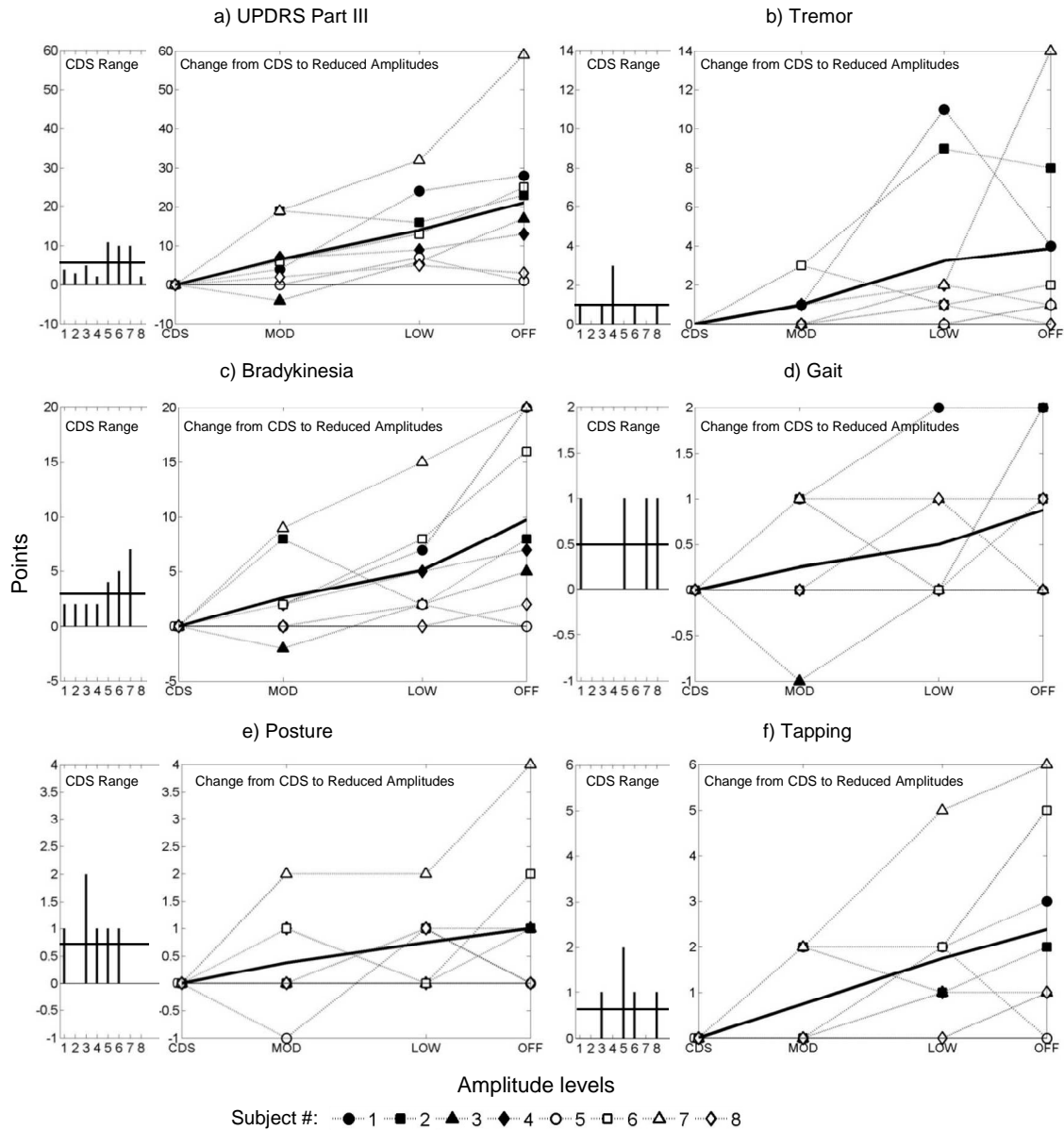


Figure 3.1. Day-to-day CDS variability compared to change in outcome measure from CDS to each reduced amplitude.

Notes: Left side of each lettered subplot represents each subject's range of CDS values over the three sessions for (A) UPDRS Part III score, (B) tremor subscore, (C) bradykinesia subscore, (D) gait subscore, (E) posture subscore, and (F) tapping subscore. The horizontal line represents the mean ($n = 8$ subjects), while the vertical bars represent each individual subject. Right side of each lettered subplot represents change in outcome measure from CDS to each reduced amplitude for (A-F). The black line represents the mean ($n = 8$ subjects), while the gray lines represent each individual subject.

Abbreviations: CDS, clinically determined stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

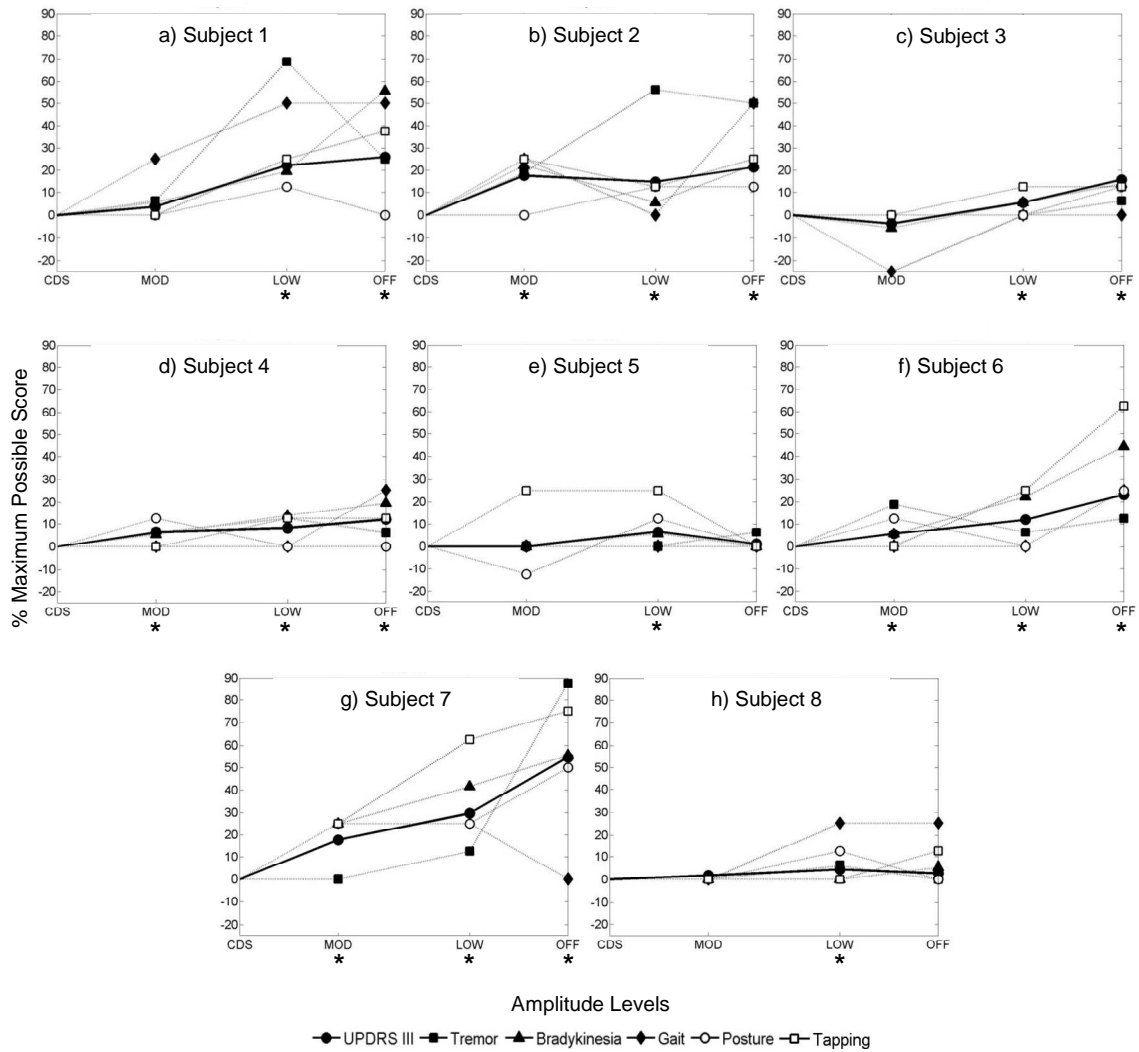


Figure 3.2. Change in outcome measure from CDS to each reduced amplitude as a percentage of the maximum possible score for that particular measure for each subject. Notes: The black line represents the UPDRS Part III score, while the gray lines represent each subscore. *Indicates clinically important changes in the UPDRS Part III scores observed at CDS and reduced amplitude during the same test session.

Abbreviations: CDS, clinically determined stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MOD, LOW and OFF, approximately 70%, 30% and 0% of CDS respectively.

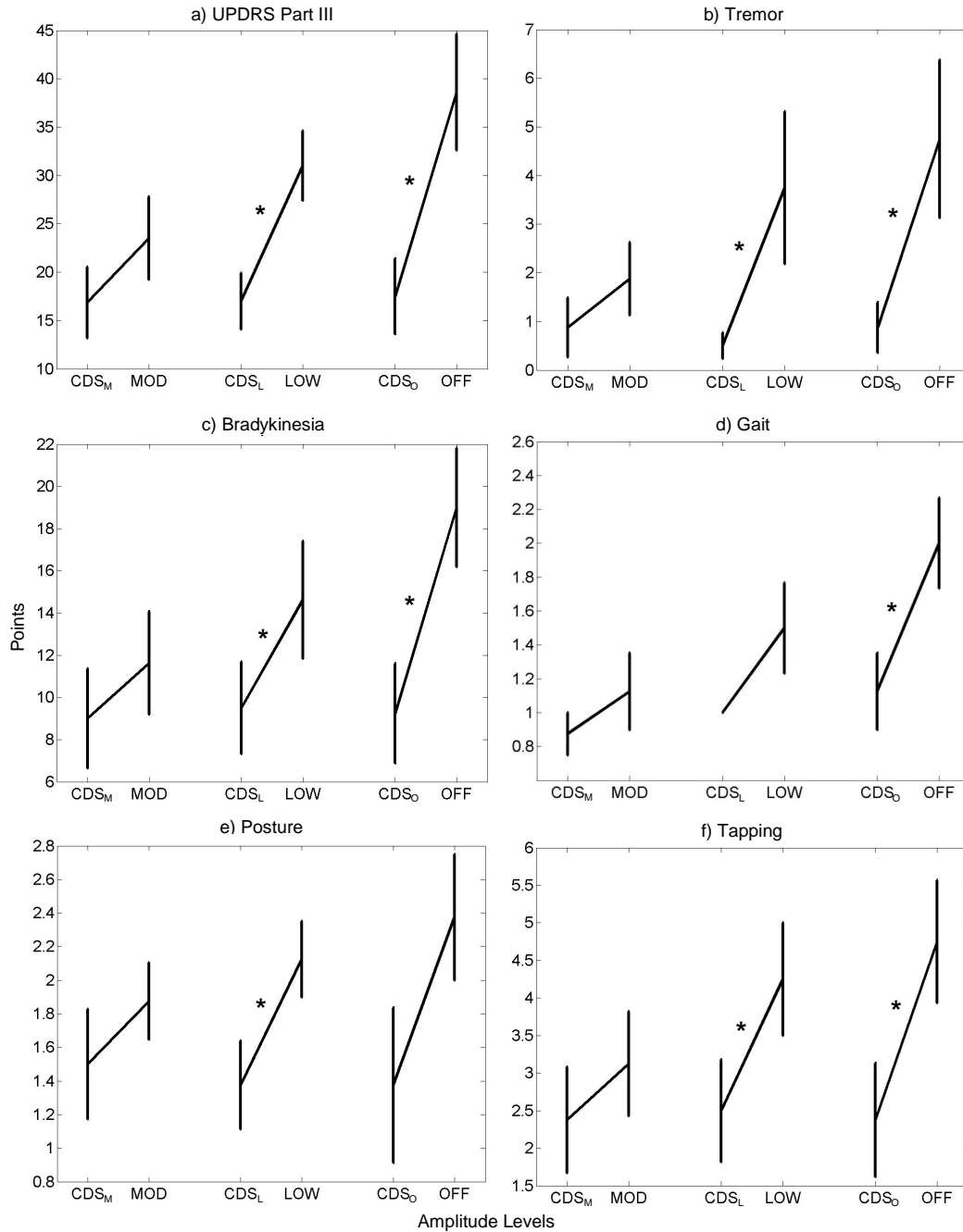


Figure 3.3. Changes in mean (\pm standard error of the mean) UPDRS score/subscores from the CDS condition for each amplitude level. *Indicates changes in mean across subjects of each outcome that were significant. (A) UPDRS Part III score, (B) tremor subscore, (C) bradykinesia subscore, (D) gait subscore, (E) posture subscore, and (F) tapping subscore.

Note: $n = 8$ subjects for each condition. CDS_M, CDS_L, and CDS_O: CDS amplitudes for the sessions in which amplitude was reduced to the MOD, LOW, and OFF levels, respectively.

Abbreviations: CDS, clinically determined stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MOD, LOW and OFF, approximately 70%, 30% and 0% of CDS respectively.

CHAPTER 4

POSTURAL TREMOR

Introduction

To better understand how deep brain stimulation (DBS) affects tremor in people with Parkinson's disease (PD), many studies have assessed individuals with their DBS systems set to the stimulation parameters determined by their physician and with their DBS systems turned off (Diamond, et al., 2007; Kumar et al., 1998; Plaha, et al., 2006; Sturman, Vaillancourt, Metman, Bakay, & Corcos, 2004). However, few have investigated parkinsonian tremor at intermediate stimulation settings.

In closely related research, Kuncel and colleagues examined the effects of varying pulse width, frequency, and stimulation amplitude on tremor amplitude in people with essential tremor (2006). Their work demonstrated that frequency and stimulation amplitude were the most important factors in alleviating tremor, while varying pulse width had little effect. Of note, all subjects were evaluated at the same stimulation amplitude values without regard to the physician-determined settings specifically prescribed. Moro and colleagues applied a similar approach to studying a PD population to examine the effects of varying pulse width, frequency, and stimulation amplitude on the parkinsonian triad of tremor, rigidity, and bradykinesia (2002). This study also concluded that varying pulse width did not have a clear effect on PD symptoms and identified stimulation amplitude as the most important factor in alleviating the parkinsonian triad. However, this research only examined a subset of possible amplitude settings, with the lowest level being only 39% less than the highest level (2.2-3.6 V).

Based upon the literature cited above (Kuncel et al. 2006; Moro et al., 2002), we focused this study to assess the effect of changing stimulation amplitude. Since the clinically determined stimulation (CDS) amplitude setting can vary widely across individuals, we varied amplitude as a percentage of the CDS value to facilitate comparison across subjects. The CDS amplitude was defined as the ceiling, since stimulation amplitude is often set just below the threshold for adverse effects (2002). In addition to evaluating postural tremor at CDS and 0% amplitude, this research evaluated it at two intermediate amplitude conditions to determine the effects of incrementally

altering stimulation amplitude on postural tremor in people with PD. Postural tremor was measured quantitatively using an accelerometer, and because the Unified Parkinson's disease rating scale (UPDRS) is the standard in clinical PD measurement tools, tremor was also assessed using tremor-specific questions from the motor section of the UPDRS (UPDRS III).

Methods

Subjects. Subjects were recruited as described in chapter 3. Please refer to Table 3.1 for subject characteristics, relative timing of each test session, and LEDD and stimulation parameters at each test session.

Experimental protocol. Please refer to the section titled "Experimental protocol" in chapter 3 for details on the daily protocol for changes in stimulation settings and UPDRS measurements. Briefly, in a given experimental session, subjects performed a series of tests at the CDS settings, underwent reduction of their stimulation level, and performed the same set of tests at the reduced amplitude. Each subject completed sessions on three different days to provide measurements at each of three reduced stimulation settings which were approximately 70%, 30%, and 0% of the CDS (MOD, LOW, and OFF, respectively). In addition to the UPDRS assessments described in chapter 3, subjects also participated in a quantitative postural tremor task for which a tri-axial accelerometer (Crossbow Technology CXL10LP3) was attached to the dorsum of each wrist using Velcro bands. The accelerometer was oriented with the x-axis lateral, the y-axis anterior/posterior, and the z-axis superior/inferior relative to the subject. While seated, the subject was asked to hold his or her arms outstretched with hands pronated and fingers abducted for 15 seconds. The right and left sides were evaluated separately. Three repetitions were performed with rest periods interspersed. The signals from the accelerometers were sampled at a rate of 100 Hz using a custom LabVIEW program and stored for further analysis.

Data analysis. The data from each trial consisted of the time series of three variables: acceleration along the x-axis, y-axis, and z-axis. After subtracting the zero g output from the raw data, the data was converted from volts to cm/s^2 and band-pass filtered from 0.5 Hz to 25 Hz. The acceleration along each axis was averaged across the three trials, and principal components

analysis was performed, transforming the data into the principal components space. A power spectrum was then performed using windows of 500 data points.

The spectra were categorized based on the frequency of the greatest peak and the percent power contained in different bandwidths. A trial was labeled as a parkinsonian tremor incident if its dominant frequency was ≥ 3 Hz but ≤ 7 Hz and at least 33% of its total power was contained in that same bandwidth (Figure 4.1). A trial was labeled as a physiological tremor incident if its dominant frequency was > 7 Hz but ≤ 12 Hz and at least 33% of its total power was contained in that same bandwidth (Edwards & Beuter, 1999).

Outcome measures. Tremor intensity was calculated as the rms of the filtered acceleration signal. Power dispersion was obtained by first sorting the discrete power spectrum from greatest power to least and then calculating the center of mass of the sorted spectrum (Edwards & Beuter, 1999). A one-sided UPDRS tremor subscore was calculated by adding the scores for items 20 and 21, assessed at only the right or left hand.

Statistical analysis. Statistics were performed using IBM SPSS Statistics software (SPSS Inc, Chicago, IL). For tremor intensity and power dispersion, the two-tailed Wilcoxon signed rank test was used to compare the values measured at each session's CDS amplitude to the values measured at that same session's reduced amplitude for all arms. For a subset of arms that experienced parkinsonian tremor incidents at both the LOW and OFF conditions, the values measured at the LOW condition were also compared to the values measured at the OFF condition. A P value ≤ 0.05 was considered statistically significant.

Results

Because tremor may affect only one side of a person, or affect the left and right sides to varying degrees, tremor incidents were evaluated separately for each arm (L and R will be used to denote the left and right arms of a subject). The change in power dispersion and intensity from CDS to each reduced amplitude is presented for all trials in Figure 4.2. As evidenced by the low intensity, some subjects did not experience tremor incidents at any amplitude condition, and some only experienced tremor incidents in one arm. Although neither mean power dispersion nor intensity changed significantly when amplitude was decreased from the CDS to the MOD

condition, both changed significantly when amplitude was decreased to the LOW condition and mean power dispersion also changed significantly when amplitude was further decreased to the OFF condition. When the power dispersion and intensity values at reduced amplitude conditions were compared, the only significant difference was between power dispersion at MOD and LOW.

To better understand how the characteristics of trials containing PD tremor incidents compare to those with physiological or no tremor incident, Figure 4.3 depicts each trial as a point defined by percent power contained in the PD bandwidth and dominant frequency. The dotted lines illustrate the intersection of dominant frequency and PD bandwidth power values defined to potentially contain PD tremor incidents. For the trials determined to actually contain PD tremor incidents, the dominant frequency and PD bandwidth power ranged from 4.4 to 7.0 Hz and from 33.3% to 88.2%, respectively.

As seen in Figure 4.4, an equal percentage of trials at the CDS and MOD conditions contained a physiological tremor incident (25%: 12 of 48 possible CDS trials; 25%: 4 of 16 possible MOD trials). Regarding parkinsonian tremor, reducing stimulation to the MOD condition decreased the number of tremor incidents to zero, although this was not significantly different from the number experienced at CDS. Further reducing stimulation to the LOW and OFF conditions decreased the number of physiological tremor incidents experienced to just 1 per condition, while it increased the number of parkinsonian tremor incidents to almost 50% of possible trials.

Figure 4.5 depicts power dispersion and intensity for the ten arms that experienced at least one parkinsonian tremor incident. Arm 8L only experienced parkinsonian tremor incidents at the CDS condition. Arms 6L and 2R each experienced only one parkinsonian tremor incident at the LOW and OFF conditions, respectively. Arms 4L and 4R both experienced parkinsonian tremor incidents at the CDS condition and at one reduced amplitude condition. The remaining five arms experienced a parkinsonian tremor incident only at the LOW and OFF conditions. Reducing amplitude from the LOW to the OFF condition seemed to exacerbate the tremor, causing overall trends toward more regular oscillations, as depicted by the decreased mean power dispersion and increased mean intensity.

Changes in intensity and power dispersion were examined in conjunction for each arm that experienced a parkinsonian tremor incident at both the LOW and OFF conditions (Figure 4.6). For the majority of the arms, intensity increased and power dispersion decreased when the amplitude was reduced from the LOW to the OFF condition. For arm 1L, however, the tremor characteristics behaved opposite compared to the rest of the group, and actually showed very little change in intensity between the two conditions.

Detection of both parkinsonian and physiological tremor incidents by measured assessment was compared to detection using UPDRS scores. Of note, UPDRS assessment detects tremor incidents in general and cannot be used to further classify those incidents as parkinsonian or physiological. A UPDRS-detected tremor incident was defined as a score of 2-4 for either item 20 (rest tremor) or item 21 (postural/action tremor) on the side of interest. Table 4.1 shows the concurrence between the measured and UPDRS assessments of tremor incidents at all amplitude conditions.

The UPDRS method never detected a tremor incident during the trials for which measured assessment detected physiological tremor incidents. In addition, the UPDRS method never detected a tremor incident for arm 4L, even though the measured assessment method detected two parkinsonian tremor incidents for this arm. The two methods agreed on the occurrence of a tremor incident for the majority of the trials at the CDS, MOD, and OFF conditions (CDS: 92%; MOD: 88%; OFF: 100%), while they concurred for only about two thirds (63%) of the trials at the LOW condition.

Figure 4.3 provides a way to visualize PD tremor incidents that were detected by one or both of the methods. This depiction illustrates that, in general, the trials determined by both methods to contain a PD tremor incident contained the greatest percentages of power within the PD bandwidth. Also, most of the PD tremor incidents detected solely by UPDRS (indicated with *) have dominant frequencies outside the PD bandwidth.

Discussion

It may seem surprising that so many physiological tremor incidents were identified in a group of people with PD. One might expect to still see parkinsonian tremor incidents even at the

higher amplitude CDS and MOD conditions, just with reduced intensity. However, previous work has demonstrated that DBS of the STN can modify both the amplitude and frequency of tremor in people with PD to be more similar to those of physiologic tremor (Sturman, et al., 2004). For subjects who experienced no tremor incidents, this may simply be an effect of tremor not being their primary PD symptom(s).

Previous work done in the study of tremor has indicated that multiple aspects of tremor should be examined when using a computerized method to first detect tremor incidents and to then discriminate between different types, such as physiological and pathological (Edwards & Beuter, 1999). Thus, the measured assessment of tremor in the current study relied on both frequency and power to differentiate between physiological, parkinsonian, and the absence of tremor incidents. In response to research which has shown the typical frequency ranges associated with parkinsonian and physiological tremors are often exceeded, the ranges were expanded to aid in tremor detection and prevent false negatives. Although parkinsonian tremor is expected to be concentrated in the 4-6 Hz range, and the frequency of physiological tremor is typically expected to lie in the 8-12 Hz range, the ranges were increased to 3 to 7 Hz for parkinsonian and 7 to 12 Hz for physiological tremor incidents (Edwards & Beuter, 1999; Elble & Koller, 1990).

Previous work has demonstrated that scores on tremor-related UPDRS items are improved at the CDS condition compared to the OFF condition (Diamond, et al., 2007; Moro, et al., 2002). Although different outcome measures were used which prevents a direct comparison, the current research supports the finding that tremor is worse at the OFF amplitude level compared to higher amplitude levels in both the quantity of parkinsonian incidents as well as the characteristics of those incidents.

Of the three arms that experienced parkinsonian tremor incidents at the CDS condition, 8L stands apart. While 4L and 4R each experienced a tremor incident at one CDS trial and at one reduced amplitude condition, 8L experienced parkinsonian tremor incidents at two CDS trials and not at any of the other reduced conditions. Subject 8 had previously experienced an injury to the left arm which may have altered the arm's performance on this test and may explain the

appearance of parkinsonian tremor at the CDS condition which was then not seen at any of the reduced conditions as would be expected with true parkinsonian tremor.

Arms that experienced parkinsonian tremor incidents at both the LOW and OFF conditions can be grouped based on the changes in intensity between the two amplitude conditions. As previously discussed, 1L showed little difference in intensity when the amplitude was reduced from LOW to OFF. Coupled with the small change in power dispersion between the three amplitude conditions, this raises the possibility that the CDS settings had no significant effect on the tremor experienced by the arm.

Although the minor change in intensity experienced by 1L was in the opposite direction of the change experienced by arms 1R and 2L, these arms can be grouped together since they all displayed little change in intensity from LOW to OFF. This may indicate that the amplitude at the LOW condition was not high enough to cause a change in the tremor presentation. The remaining two arms that experienced parkinsonian tremor at both LOW and OFF – 7L and 7R – both demonstrated a measuredly greater intensity at the OFF condition.

Examining the concurrence of parkinsonian tremor incident detection by the measured assessment and UPDRS methods demonstrates that the incidents detected by the UPDRS method but not by the measured assessment method were of lower intensity and higher power dispersion. The dominant frequency of these trials extended beyond the frequency range occupied by the incidents determined by both methods to be parkinsonian. Interestingly, the UPDRS method did not detect any of the physiological tremor incidents, all of which also had lower intensity and higher power dispersion.

The incidents detected by the measured assessment method but not by the UPDRS method fell within the same range of dominant frequencies and percent PD bandwidth power as the parkinsonian incidents detected by both methods. The characteristics of these incidents were more similar to the characteristics of the incidents detected by both methods than were the incidents detected solely by the UPDRS method.

Table 4.1

Concurrence between Detection Methods

		Measured	
		Tremor	No Tremor
UPDRS	Tremor	11 (all PD) ^a	5
	No Tremor	25 (7 PD, 18 Ph)	55

^aPD = parkinsonian, Ph = physiological

Note: n = 96 trials

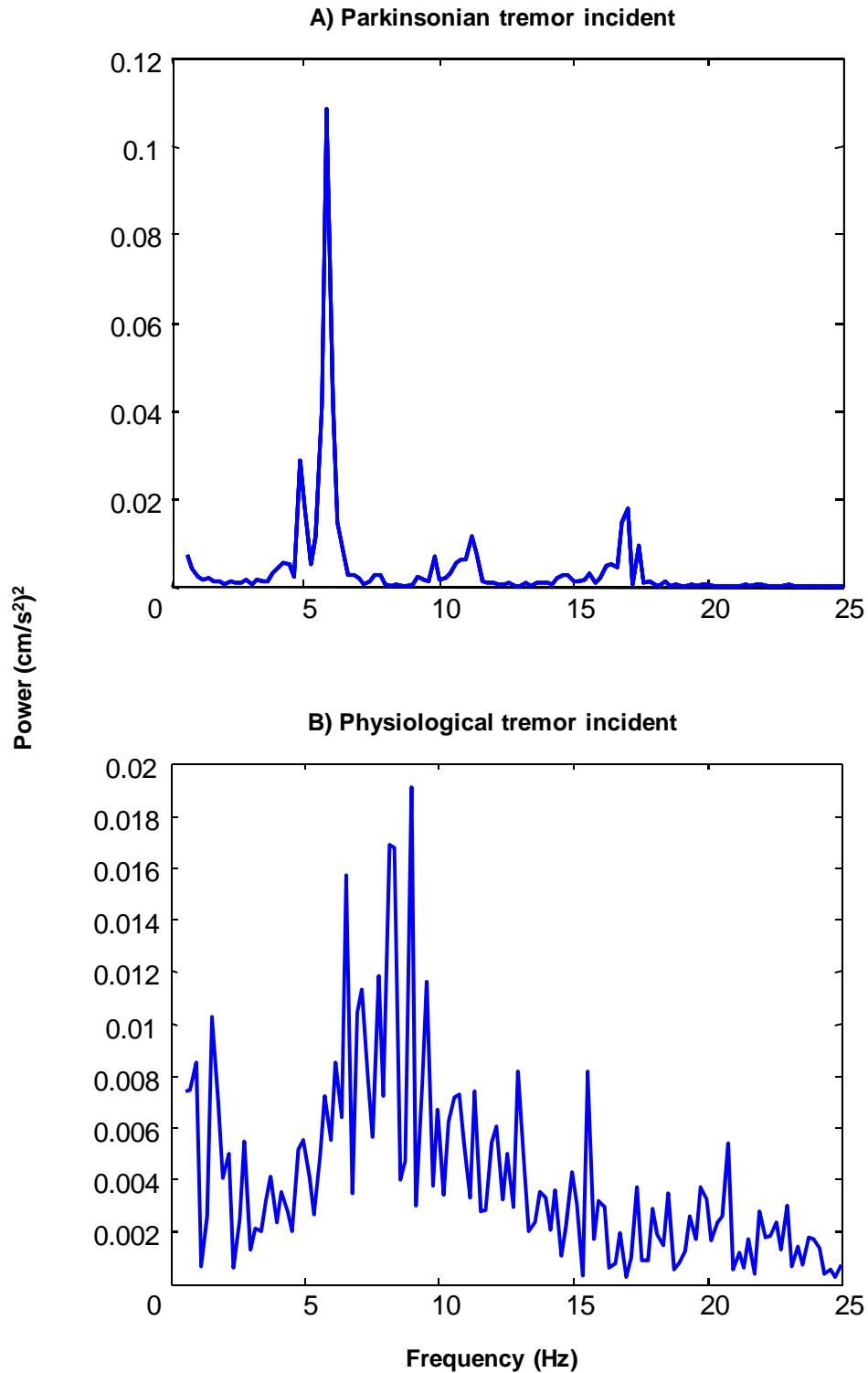


Figure 4.1. Tremor data after performing fast fourier transform analysis. Examples of spectra that were classified as **(A)** parkinsonian tremor incident (arm 1R at the OFF condition) and **(B)** physiological tremor incident (arm 6L at the CDS condition).

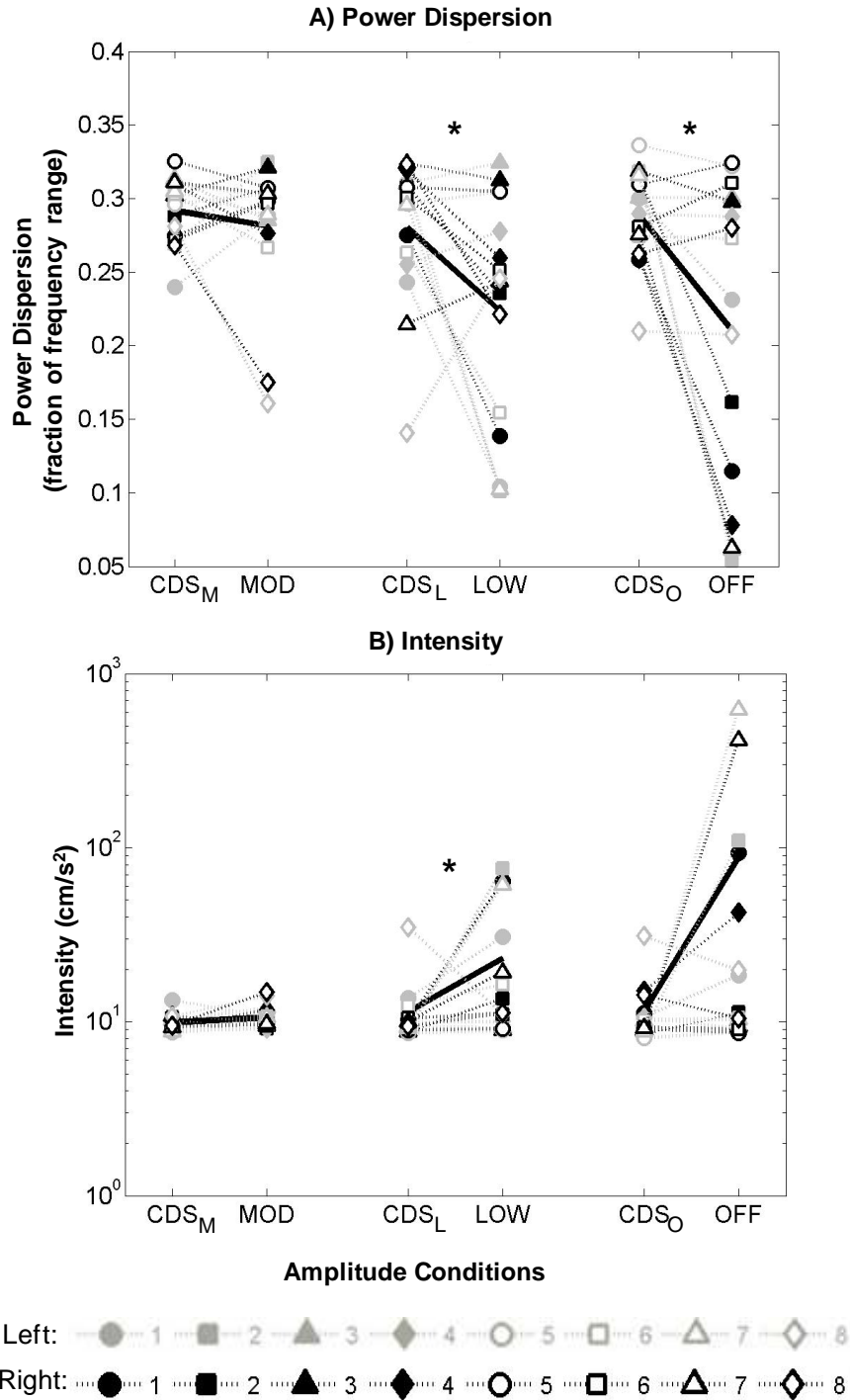


Figure 4.2. Change in (A) power dispersion and (B) intensity from the CDS condition to each reduced amplitude condition.

Notes: The solid black line represents the mean ($n = 16$: 8 subjects, both arms); the gray and black markers represent the subjects' left and right arms, respectively. *Indicates changes in mean that were significant.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

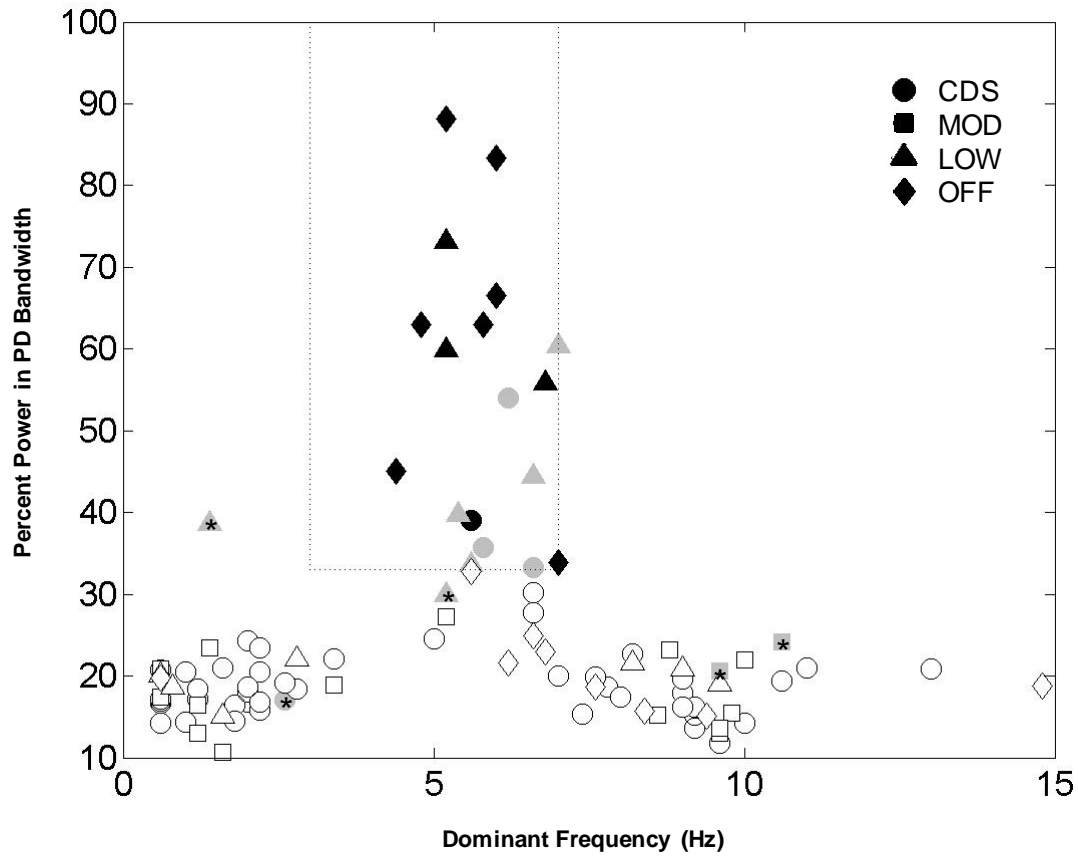


Figure 4.3. Each trial (96 trials: 8 subjects, both arms, 6 conditions) represented by the intersection of percent power within the PD bandwidth (3-7 Hz) and dominant frequency. Trials determined by both the measured assessment and UPDRS methods to contain parkinsonian tremor incidents are shaded black, trials determined by only one method to contain parkinsonian incidents are shaded gray (UPDRS-detected PD tremor incident denoted by *), and trials determined to contain no tremor incident are not shaded.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

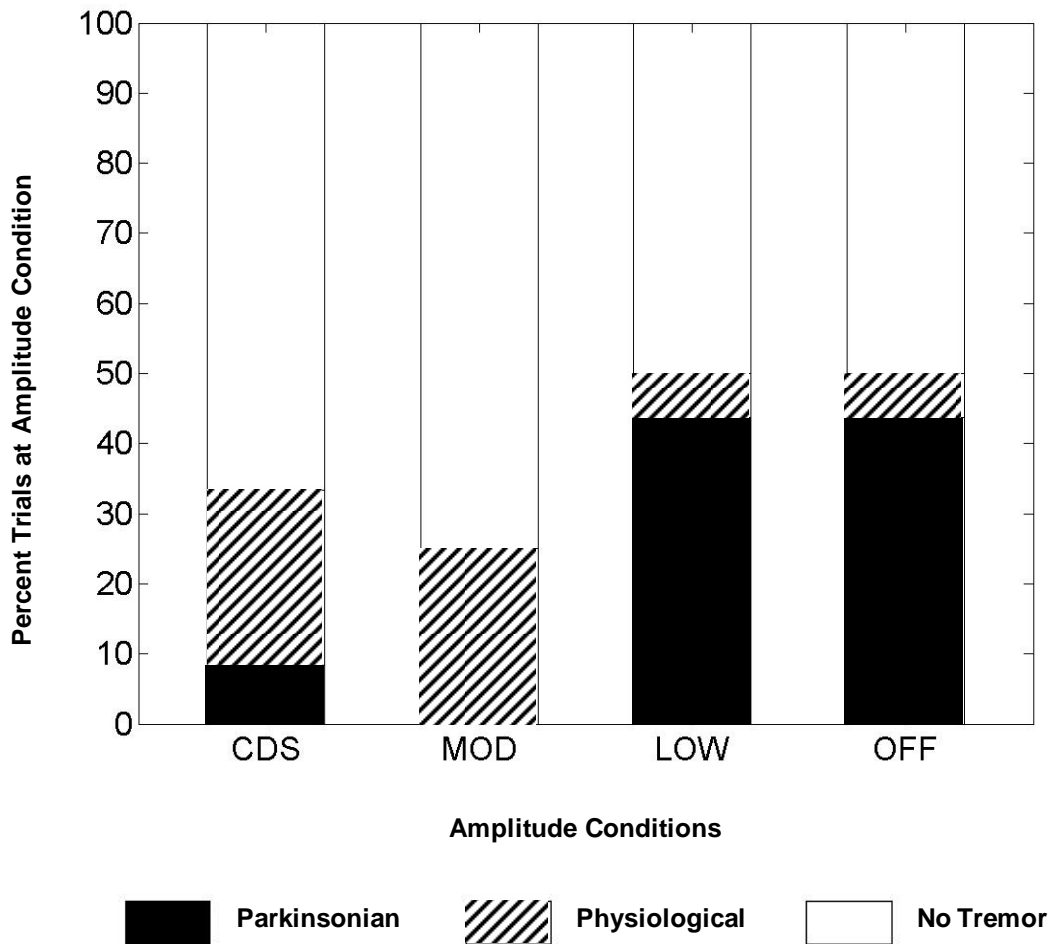


Figure 4.4. Percent trials that contained a parkinsonian, physiological, or no tremor incident at the MOD, LOW, and OFF conditions.

A trial was categorized as containing a parkinsonian tremor incident if its dominant frequency was ≥ 3 Hz but ≤ 7 Hz and at least 33% of its total power was contained in that same bandwidth. A trial was categorized as containing a physiological tremor incident if its dominant frequency was > 7 Hz but ≤ 12 Hz and at least 33% of its total power was contained in that same bandwidth.

Notes: $n = 48$ trials for CDS; $n = 16$ trials for MOD, LOW, and OFF.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

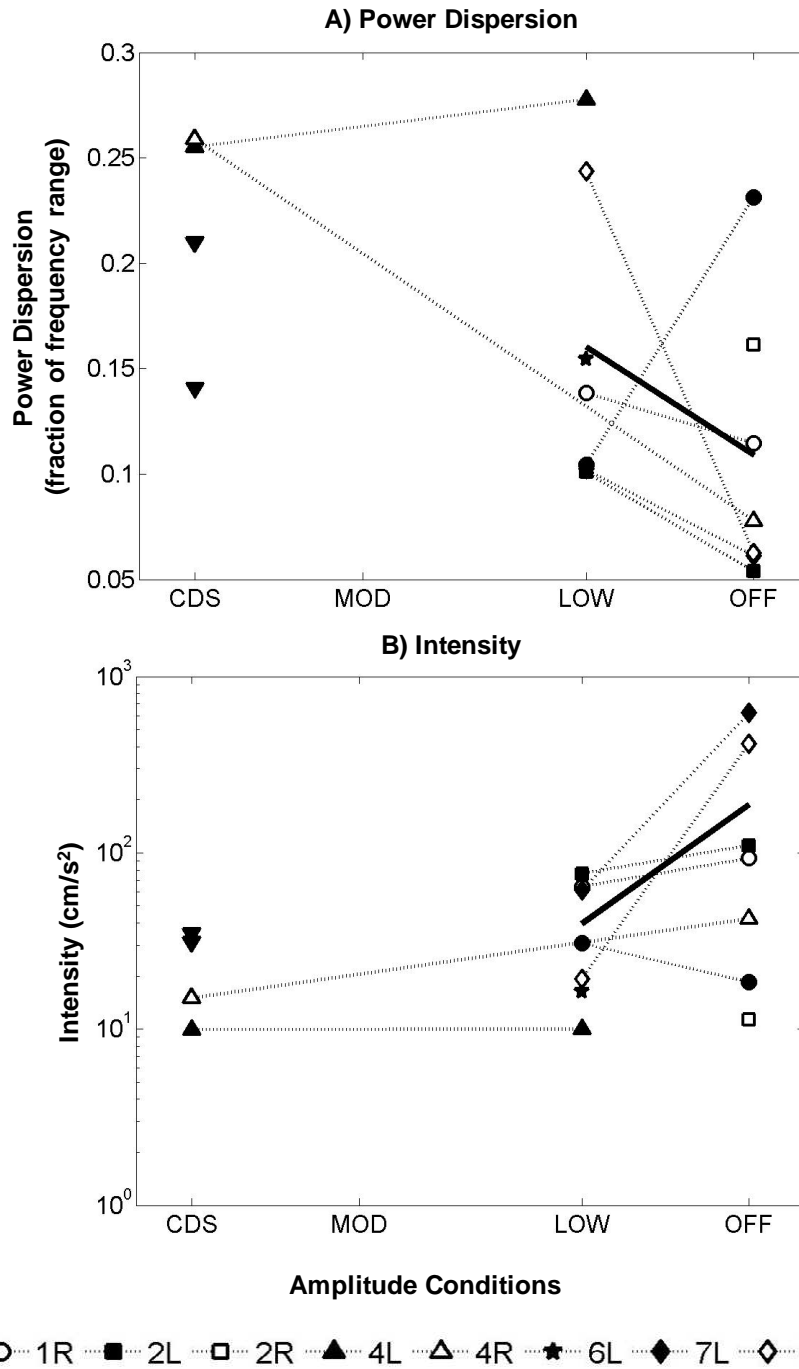


Figure 4.5. (A) Power dispersion and (B) intensity for every arm that experienced a parkinsonian tremor incident.

Notes: The solid black line represents the mean change ($n = 5$ arms) from the LOW to the OFF condition, while the markers represent each individual arm at all conditions.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

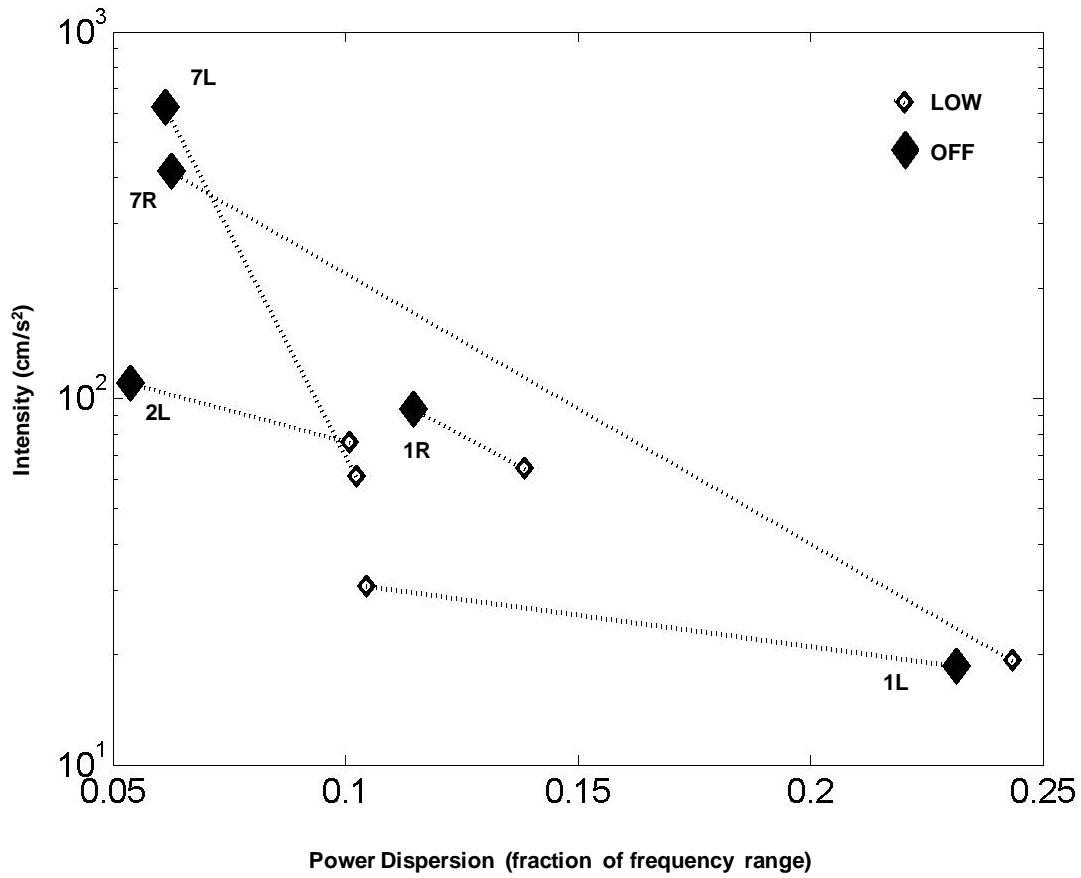


Figure 4.6. Intensity and power dispersion of parkinsonian tremor incidents for the five arms that experienced a parkinsonian incident at both the LOW and OFF conditions
 Abbreviations: CDS, clinically determined stimulation; LOW and OFF, approximately 30%, and 0% of CDS respectively.

CHAPTER 5

UPPER EXTREMITY SINGLE-JOINT TASKS

Introduction

Although the term technically only refers to slowness of movement, bradykinesia has been considered to comprise deficits in several areas related to movement execution including speed, amplitude, and rhythmicity (Heldman et al., 2011). In addition to being one of the cardinal symptoms of Parkinson's disease (PD), bradykinesia has been found to correlate with scores on the life satisfaction index (Adams, 1969; Dural, Atay, Akbostanci, & Kucukdeveci, 2003; Hoyt & Creech, 1983; Neugarten, Havighurst, & Tobin, 1961; Wood, Wylie, & Sheafor, 1969). The assessment and mitigation of bradykinesia can increase the independence and associated life satisfaction of people with PD, which is a primary goal for both people with PD and their families (Dural, et al., 2003).

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus has been shown to alleviate symptoms of bradykinesia (Dafotakis, et al., 2008; Kumar, et al., 1998; Limousin, et al., 1998; Romito, et al., 2002; Taylor Tavares et al., 2005). As discussed in chapters 2 and 3, many studies have demonstrated improvement of PD symptoms, including upper extremity (UE) bradykinesia, by comparing performance at DBS settings considered optimal by the clinician to performance with the DBS system turned off completely (Dafotakis, et al., 2008; Rissanen et al., 2011). However, few have evaluated intermediate stimulation settings and few have focused on bradykinesia. Two studies that did evaluate bradykinesia at various stimulation amplitudes only measured one aspect of UE bradykinesia for one arm of subjects, and effects were measured just two to three minutes after adjusting stimulation amplitude (T. Mera, Vitek, Alberts, & Giuffrida, 2011; Moro, et al., 2002).

Previous work has shown that people with PD tend to have decreased ability to perform fine motor control tasks requiring coordination of the wrist and fingers (Teulings, ContrerasVidal, Stelmach, & Adler, 1997). In fact, fine motor control deficits may be one of the earliest presenting motor symptoms associated with PD (Koop, Shivitz, & Bronte-Stewart, 2008; Taylor Tavares, et al., 2005). Although the motor section of the clinically accepted Unified Parkinson's Disease

Rating Scale (UPDRS-III) is useful for measuring function, it may not always identify mild deficits such as those seen in early-stage PD (2008), which is why many studies have used quantitative methods, such as elbow flexion-extension and finger tapping tasks, to evaluate fine motor control in people with PD (Brocker et al., 2013; Dafotakis, et al., 2008; Pal et al., 2001; Rissanen, et al., 2011; Taylor Tavares, et al., 2005; Vieregge, et al., 1997). In addition, quantitative methods allow clinicians to evaluate aspects of movement separately, whereas the UPDRS requires assessment of multiple characteristics of movement to be compressed into one score (Heldman, et al., 2011).

This research evaluated elbow flexion-extension, wrist flexion-extension, and finger tapping at four amplitude levels, each chosen with reference to the clinically determined stimulation (CDS) amplitude, or the amplitude currently considered to be optimal by the treating clinician. Changes in elbow and wrist flexion-extension were quantified using cycle period and peak velocity, and changes in finger tapping were quantified using inter-tap variability. Three tapping tasks were performed: tapping at a self-selected pace, tapping as fast as possible, and tapping to a 4-Hz auditory cue. Elbow flexion-extension, hand movements, and finger tapping have all previously been used to study UE bradykinesia (Dunnewold, Jacobi, & vanHilten, 1997; Rissanen, et al., 2011; Taylor Tavares, et al., 2005). Changes in performance were also assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) to provide a clinically accepted reference for the quantitative measures.

Earlier work has shown that tapping at a fast pace may lead to fatigue, resulting in the decision to also evaluate tapping at a self-selected pace (Aoki & Kinoshita, 2001; Arias, Robles-Garcia, Espinosa, Corral, & Cudeiro, 2012). Tapping to a steady auditory cue was assessed in response to research that has shown people with PD benefit from external cues.

Suteerawattananon and colleagues showed that visual and auditory cues improved stride length and gait cadence, respectively, in people with PD (2004). Similarly, Morris and colleagues found that visual cues increased stride length and, in conjunction with medication, enabled people with PD to demonstrate a stride length considered to be normal. Visual and auditory cues have also improved performance of movement sequences (Georgiou et al., 1994; Kritikos et al., 1995). For finger tapping specifically, auditory cues ranging from 1-5 Hz have improved rhythm maintenance

in people with PD, although the variability was in general still greater than that of healthy controls (J. S. Freeman, F. W. J. Cody, & W. Schady, 1993b).

Variability is a distinguishing characteristic of PD, with consecutive UPDRS measurements reported to vary by as much as 15% (Delwaide & Gonce, 1998; Plaha, et al., 2006). This research also assessed performance of single-joint tasks at the same stimulation amplitude (CDS) on multiple days in order to provide a daily baseline measurement.

Methods

Subjects. Subjects were recruited as described in chapter 3. Please refer to Table 3.1 for subject characteristics, relative timing of each test session, and LEDD and stimulation parameters at each test session.

Experimental protocol. Please refer to the section titled “Experimental protocol” in chapter 3 for details on the daily protocol for changes in stimulation settings and UPDRS measurements. Briefly, in a given experimental session, subjects performed a series of tests at the CDS settings, underwent reduction of their stimulation level, and performed the same set of tests at the reduced amplitude. Each subject completed sessions on three different days to provide measurements at each of three reduced stimulation settings, which were approximately 70%, 30%, and 0% of the CDS (MOD, LOW, and OFF, respectively). In addition to the UPDRS assessments described in chapter 3, subjects also participated in three single-joint tasks – elbow flexion-extension, wrist flexion-extension, and finger tapping – twice during each test session, once at CDS settings and next at reduced amplitude stimulation settings.

Elbow and wrist flexion-extension protocol and data analysis. The subject was seated in a standard height chair for both tasks, and data were recorded using a Nest of Birds™ electromagnetic tracking system (Ascension Technology Corporation, Burlington, VT). The signal from the sensor was sampled at a rate of 30 Hz using a custom LabVIEW program and stored for analysis. The subject performed ten cycles of each movement in one trial, unless fatigue prevented the completion of all ten cycles. The subject performed two trials each for the right and left sides with rest periods interspersed.

For both tasks, the sensor was oriented with the x-axis lateral, the y-axis anterior/posterior, and the z-axis superior/inferior relative to the subject. For elbow flexion-extension, the sensor was attached to the dorsal surface of the wrist and the subject flexed and extended the forearm at a comfortable pace, maintaining the brachium in a horizontal position at the level of the shoulder. For wrist flexion-extension, the sensor was attached to the dorsal surface of the hand and the subject flexed and extended the hand at a comfortable pace, maintaining the brachium in a horizontal position at the level of the shoulder.

Sensor position along the x-axis, y-axis, and z-axis was collected throughout the trial and used to calculate position in three-dimensional space. Position was calculated relative to the first data point and then filtered using a fourth order Butterworth low-pass filter with a cut-off frequency of 7 Hz. Velocity was calculated and used to determine the start of each movement cycle. Five movement cycles from each trial were analyzed, beginning with the third cycle to eliminate start-up effects. The five cycles from both trials were combined for a total of ten movement cycles per task.

Finger tapping protocol and data analysis. The subject was seated at a standard height table with the forearm and hand resting on the table. Similar to previous work, subjects were asked to tap the index finger with a comfortable amplitude on a touch-sensitive pad for 15 seconds (del Olmo, Arias, Furio, Pozo, & Cudeiro, 2006; Leijnse, Campbell-Kyureghyan, Spektor, & Quesada, 2008; Shimoyama, Ninchoji, & Uemura, 1990). Three tasks were tested: tapping at a self-selected pace (Comfortable), tapping as fast as possible (Fast), and tapping to a 4-Hz auditory cue (4 Hz). To avoid any potential lasting effects of the auditory cues, the self-initiated tasks were tested before the externally-cued task. If bradykinesia had been determined by the subject's clinician to be the primary PD symptom on one side, then the subject completed all trials using that arm. Otherwise, the dominant arm was used (2006). The subject performed two trials each of all three tasks with rest periods interspersed. The first trial was considered to be a practice trial, and only the second was analyzed.

For each trial, the time of each tap was recorded using a custom-designed data acquisition program, and the inter-tap intervals were calculated and analyzed off-line. The first

two seconds of data were discarded to eliminate any onset effects. The trials were filtered for false taps (e.g., instances when the subject dragged the finger across the touch-sensitive pad instead of removing it completely) by removing time points separated by < 50 ms. They were also filtered for undetected taps (e.g., the subject did not strike the touch pad with enough force to register a tap) by removing time points separated by > 1 s. Removing these invalid time points divided each trial into multiple segments. Inter-tap intervals (time between each tap) were then calculated between each valid time point within a segment.

Outcome measures. Outcome measures included cycle period and peak velocity for elbow and wrist flexion-extension, and inter-tap variability for finger tapping. Inter-tap variability was obtained by calculating the standard deviation of the inter-tap intervals. For elbow and wrist flexion-extension, the UPDRS-III bradykinesia subscore (items 23-26 and 31) (Bartels, et al., 2003) was assessed at the CDS condition for each side to clinically determine which side was more affected by PD. Based on these classifications, the more affected and less affected sides were compared for individual subjects as well as across the cohort. Since performance was evaluated at the CDS condition during each test session, each subject had three CDS values for each outcome measure. The variability of each subject's day-to-day performance was quantified by calculating the range of these three values.

Statistical analysis. Statistics were performed using IBM SPSS Statistics software (SPSS Inc, Chicago, IL). For each subject, the cycle period and peak velocity values obtained at each session's CDS amplitude were compared to the values obtained at that same session's reduced amplitude using the Mann-Whitney Test. The two-tailed Wilcoxon signed rank test was used to compare mean differences between outcome measures obtained at CDS and reduced amplitude across all subjects. Performance at each session's CDS amplitude was treated as a baseline measure for performance at the same session's reduced amplitude to account for minor changes in medication or CDS settings over the course of all three test sessions.

The differences in values obtained at the CDS and reduced amplitude conditions (deltas) were calculated for each outcome measure. The deltas for the UPDRS scores were compared to the deltas for each quantitative measure to determine if there was a relationship between the

UPDRS scores and the respective quantitative measures. Spearman's rho was calculated, and the correlation coefficients were evaluated using the same criteria as Brusse and colleagues: fair = 0.25–0.50, moderate to good = 0.50 –0.75, and excellent = 0.75-1.00.(Brusse, Zimdars, Zalewski, & Steffen, 2005) If an outlier was present in one of the data groups, Spearman's rho was calculated both including and excluding that point. Unless otherwise noted, a *P* value \leq 0.05 was considered to be statistically significant.

Results

Comparison across stimulation conditions. For the group as a whole, reducing stimulation amplitude induced several significant increases in the cycle period of both elbow and wrist flexion-extension (Figure 5.1). Wrist flexion-extension as performed by the more affected limb was the only task for which no significant changes were seen. Reducing stimulation amplitude also induced several significant decreases in the peak velocity of both elbow and wrist flexion-extension (Figure 5.2). At least one significant decrease was seen for every task.

For inter-tap variability, reducing amplitude to the MOD and OFF conditions did not cause a significant change in the mean value for any of the tasks (Figure 5.3). However, reducing amplitude to the LOW condition resulted in significantly increased inter-tap variability for the Fast tapping task. Although not significant changes, the group means followed the same pattern for the Fast and 4-Hz tasks – decreased inter-tap variability at the MOD condition and increased inter-tap variability at the LOW and OFF conditions.

Of note, subject 1 demonstrated several large changes in inter-tap variability, often in the opposite direction of the majority of the subjects (Figure 5.4). However, excluding subject 1 from the group mean did not alter the result that there were no significant changes from CDS to any of the reduced conditions.

As depicted in Figure 5.5, the groups of more and less affected limbs responded similarly to reduced stimulation, experiencing about the same percentage of statistically significant changes in both cycle period and peak velocity. In addition, both groups of limbs demonstrated substantially more degradations than improvements in performance.

Trials were also examined to determine whether reducing stimulation induced changes likely to be substantial, since statistically significant differences may not always translate to clinically significant differences. For this analysis, we defined a substantial change as one whose magnitude was $> 25\%$ of the performance measured at the CDS condition for that session. Figure 5.6 depicts the percentage of trials that contained substantial and clinically insignificant changes for cycle period, peak velocity, and inter-tap variability. More often than not, subjects demonstrated degraded rather than improved performance as amplitude was reduced, except for in the performance of Fast and 4-Hz tapping at the MOD condition.

DBS dose-response characteristics. As in chapter 3, dose-response curves were examined for each of the outcome measures, with a threshold response defined as one decrement in stimulation accounting for $\geq 70\%$ of the maximum change in performance observed (Figures 5.7-5.9). A good example of a graded dose-response was demonstrated by subject 7's more affected limb for elbow flexion-extension cycle period. A good example of a threshold response was demonstrated by subject 6's less affected limb for wrist flexion-extension cycle period.

Of the limbs determined to experience substantial changes in cycle period and peak velocity, Figure 5.10 summarizes the percentage which demonstrated graded characteristics, threshold characteristics, or didn't fit either category. Although trials in this last category technically included a change whose magnitude was $\geq 70\%$ with one decrement in amplitude, they didn't truly demonstrate threshold behavior, as they also included changes of comparable magnitude in the opposite direction.

Repeatability at CDS condition. For each outcome measure, there were subjects who consistently demonstrated larger or smaller range of changes at the CDS condition compared to the mean CDS range. However, these groups of subjects were different for each measure. Subject 5, who exhibited smaller changes than the mean CDS range for both cycle period and peak velocity, was the only instance of overlap.

The range of CDS values was also compared with the change experienced when the CDS amplitude was reduced to the MOD, LOW, and OFF conditions. For both cycle period and

peak velocity, the mean range of CDS values for the group was greater than the mean change seen when amplitude was reduced from CDS to the MOD condition. However, the mean change from CDS to the LOW and OFF conditions was greater than the mean range of CDS values more than half the time. For all three tapping tasks, the mean range of CDS values for the group was greater than the mean change seen when amplitude was reduced from CDS to any of the altered conditions.

As with the group as a whole, the individual subjects displayed a variety of responses. Some subjects required more than a 30% reduction in stimulation amplitude to induce a change in performance greater than the change they had exhibited on different days at the CDS condition. For some subjects, even turning the stimulation completely off did not induce a change greater than the change they experienced at the CDS condition.

Correlations. Spearman's rho was calculated to obtain a better understanding of how the UPDRS scores and quantitative measures might be related. There was only one statistically significant correlation for cycle period, between elbow flexion-extension performed by the less affected limb and the bradykinesia UPDRS subscore. None of the cycle period correlations were judged to be stronger than fair using the criteria developed by Brusse and colleagues.(Brusse, et al., 2005) However, peak velocity for all the tasks was significantly correlated with both the total UPDRS-III score and the bradykinesia subscore. In addition, all of the correlations were considered to meet the moderate to good criteria except for the correlation between the bradykinesia subscore and wrist flexion-extension performed by the less affected side.

Since subject 1 experienced several large changes in inter-tap variability, often in the opposite direction of the group measures, the correlations were calculated both including and excluding subject 1's scores. None of the correlations, either with or without subject 1, were statistically significant, and none were stronger than fair.

Discussion

In previous work, Dafotakis and colleagues found increases in both mean tapping frequency and mean peak velocity at the CDS condition compared to the OFF condition (2008). The current research demonstrated similar results for both wrist and elbow flexion-extension, with

lower mean cycle periods and higher mean peak velocities at the CDS condition compared to the reduced amplitude conditions. Rissanen and colleagues also examined elbow flexion-extension and found that subjects exhibited characteristics that were more similar to healthy control subjects at the CDS condition compared to the OFF condition (Rissanen, et al., 2011). Although these two previous studies did not examine intermediate amplitude levels, the overall trends in results are supported by the results of the current research.

The subjects often reacted very differently to amplitude reductions depending on the task being performed. For example, subject 7 demonstrated a clearly graded response to reduced stimulation, which was also substantially more dramatic compared to the rest of the subjects, when performing elbow flexion-extension with the more affected side. However, subject 7 demonstrated very little change compared to the other subjects when performing both Fast and Comfortable tapping, and the response for 4-Hz tapping, although larger compared to the other subjects, was far from meeting the graded criteria.

Across all tasks, substantial changes were experienced in less than 50% of the trials. Investigating the trials that did contain substantial changes revealed that there were clearly more degradations compared to improvements in performance with three exceptions. Comfortable tapping at the LOW condition and Fast tapping at the MOD condition induced an equal number of improvements and degradations, and 4-Hz tapping at the MOD condition actually induced more improvements than degradations. The overall number of substantial changes was also very similar for each of the reduced amplitude conditions. However, the number of substantial improvements seen at the MOD condition was substantially greater than the number seen at the LOW and OFF conditions.

It would appear that not all tasks are affected by stimulation in the same way. Although the CDS condition did produce the best performance for some tasks as might be expected, other tasks were best performed at a reduced amplitude condition, most notably the MOD condition. This translates to the clinical environment by supporting the idea that the stimulation settings chosen by a clinician may be dependent on the task being performed during the programming

session. It may be best to choose a stimulation amplitude that optimizes performance on a variety of tasks.

Although the group of limbs clinically determined to be more affected by PD was expected to show a greater number of statistically significant changes with reduced stimulation amplitude, the two groups of limbs actually experienced a very similar number of changes. In addition, the ratio of degradations to improvements was also very similar, with degradations substantially outnumbering improvements. This may indicate that PD had actually affected both sides of these subjects to a similar degree, or it may indicate that the tasks performed were not effective in distinguishing between the two groups of limbs.

Several subjects were unable to adequately perform one or more of the tapping tasks. The Comfortable task appeared to be the most difficult to perform, with successful completion of only half the trials. The Fast task appeared to be the easiest to perform, with successful completion of more trials than either the Comfortable or 4-Hz tasks. Attempting to tap at a rate slower than as fast as possible appears to have been difficult for this subject cohort, even with an auditory cue. In addition, inter-tap variability was not lower for the 4-Hz task compared to the Comfortable and Fast tasks, as would have been expected based upon previous work using auditory cues (Freeman, et al., 1993b).

Stimulation amplitude may have also played a role in subjects' abilities to execute the tasks, with the LOW condition appearing to be the most difficult at which to tap as directed. It was visually apparent during some of the testing sessions that subjects were experiencing difficulty controlling the tapping rate and producing a large enough amplitude, and these observations corresponded to trials they were unable to perform adequately. Investigating whether inter-tap variability was correlated to either of the UPDRS scores illustrated that UPDRS item 23 may not be a good measure of variability. However, the lack of correlation may also be due to the different tapping motion assessed by item 23 compared to that assessed quantitatively (thumb to index finger vs. single-joint index finger tapping). A consideration for future work would be to measure inter-tap variability for an alternate finger tapping test, as this task has been determined to potentially be a more sensitive tool for determining disease severity. (Ozen Barut et al., 2012)

Peak velocity may be a more sensitive parameter than cycle period for revealing differences in elbow and wrist flexion-extension induced by stimulation changes. About 50% more substantial changes were experienced for peak velocity compared to cycle period. In addition, peak velocity was significantly correlated with both the total UPDRS-III score and the bradykinesia subscore. Of the three tapping tasks, Fast tapping may be the best choice to use for people with PD. Although both Fast and 4-Hz tapping revealed more substantial differences than Comfortable tapping, the 4-Hz task appeared to be more difficult to perform, with fewer trials being successfully completed. In a clinical setting, where it's important to obtain as much information as possible in the least amount of time, Fast tapping would be the most efficient choice.

In general, motor performance degraded as stimulation amplitude was reduced, but there were some exceptions. These instances of improved performance at a reduced condition may indicate that a subject's CDS amplitude was set too high for optimal performance of that specific task. The responses of the individual subjects varied greatly, and they did not reflect the mean response exhibited by the group. This variability suggests that more than one approach to DBS programming may be required. Variability was also exhibited in subjects' CDS performance across days, suggesting that repeated evaluation of DBS settings may be necessary to confidently choose the optimal combination for any one individual.

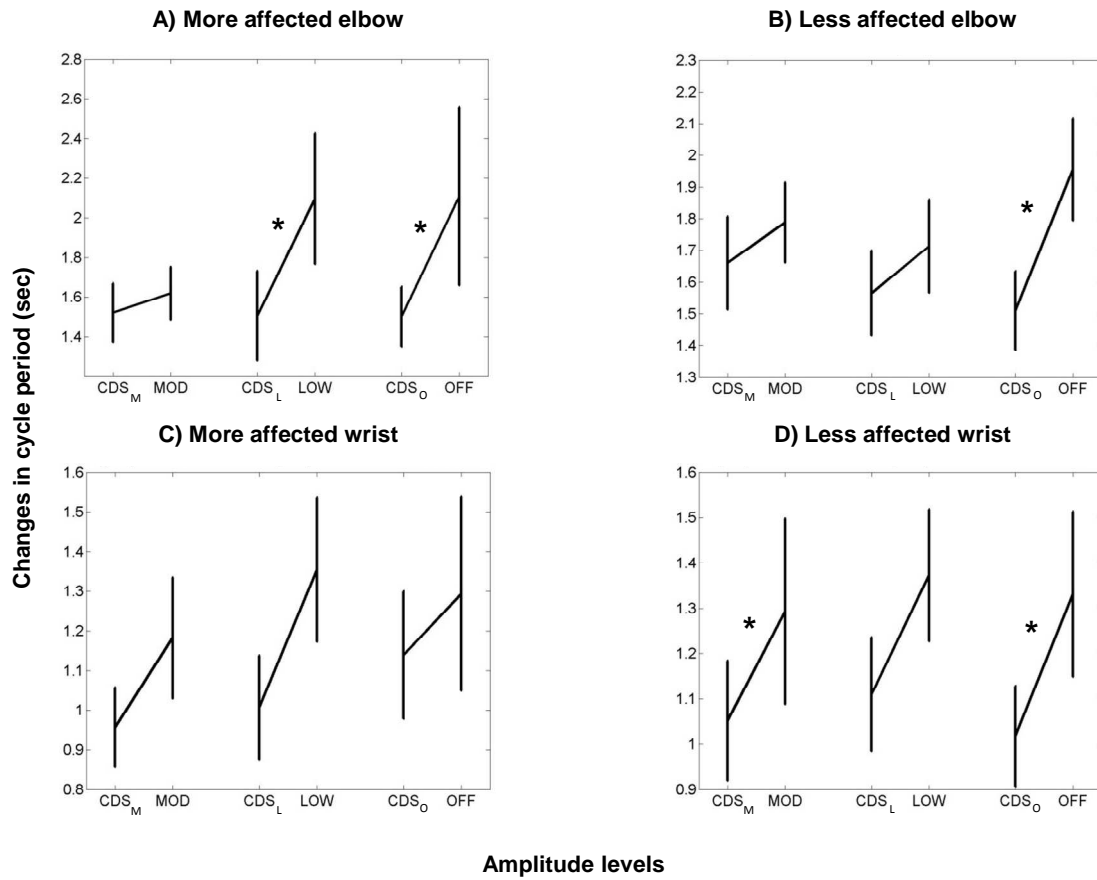


Figure 5.1. Changes in mean (\pm standard error of the mean) cycle period from the CDS condition to each reduced amplitude level. (A) More affected elbow, (B) Less affected elbow, (C) More affected wrist, and (D) Less affected wrist.

Notes: $n = 8$ subjects for each condition in each subplot. *Indicates changes in mean that were significant.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

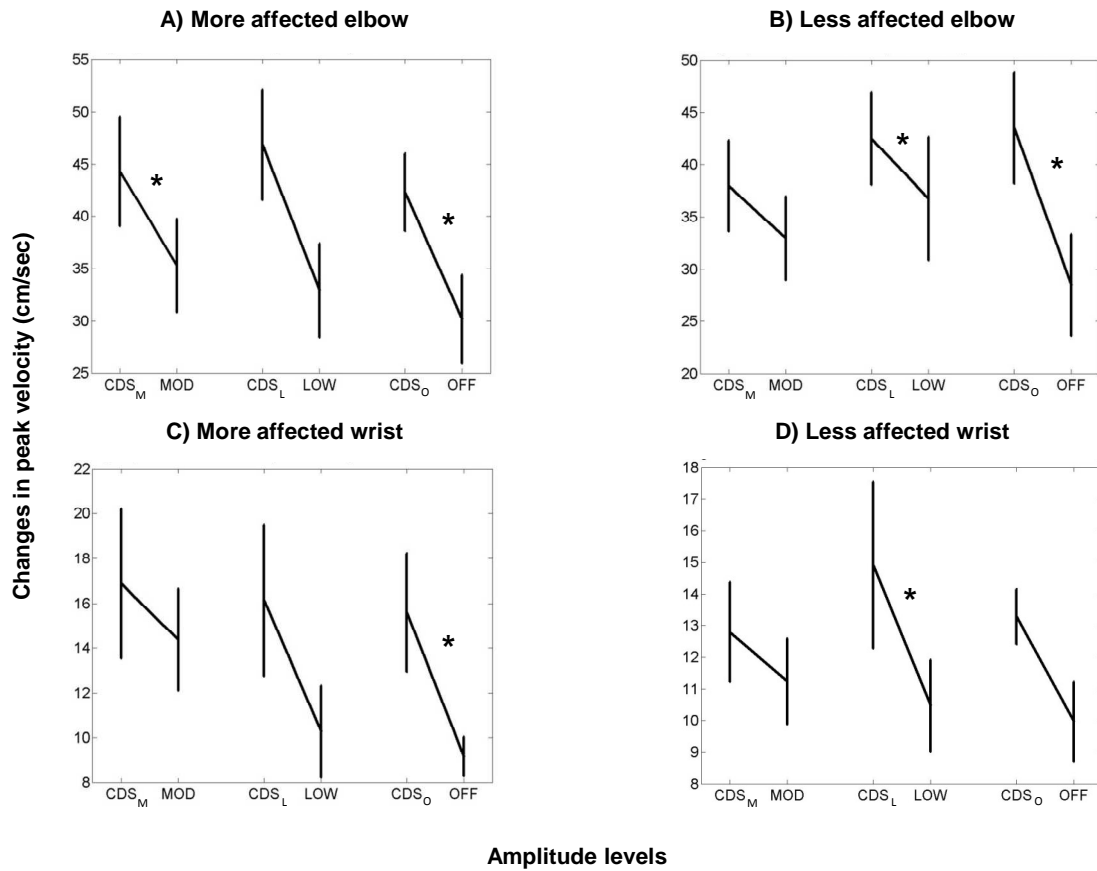


Figure 5.2. Changes in mean (\pm standard error of the mean) peak velocity from the CDS condition to each reduced amplitude level. (A) More affected elbow, (B) Less affected elbow, (C) More affected wrist, and (D) Less affected wrist.

Notes: $n = 8, 7,$ and 8 subjects for the MOD, LOW, and OFF conditions in each subplot, respectively. Subject 1 was excluded as an outlier from the LOW session. *Indicates changes in mean that were significant.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

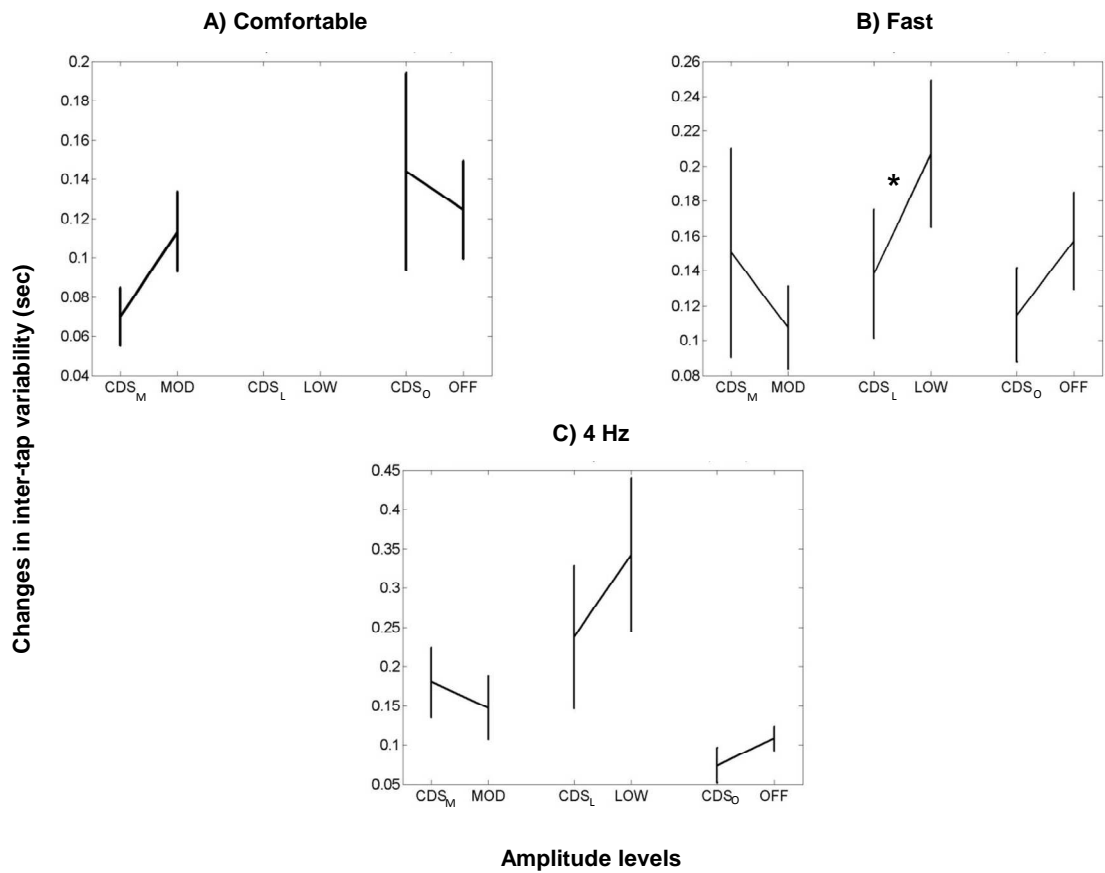


Figure 5.3. Changes in mean (\pm standard error of the mean) inter-tap variability from the CDS condition to each reduced amplitude level. **(A)** Comfortable, **(B)** Fast, and **(C)** 4 Hz. Notes: For the Comfortable task, $n = 5$ subjects for the MOD and OFF conditions; means for the LOW session were not calculated due to a low number of successfully completed tasks. For the Fast task, $n = 8, 5,$ and 6 subjects for the MOD, LOW, and OFF conditions, respectively. For the 4 Hz task, $n = 7, 4,$ and 5 subjects for the MOD, LOW, and OFF conditions, respectively. *Indicates changes in mean that were significant. Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

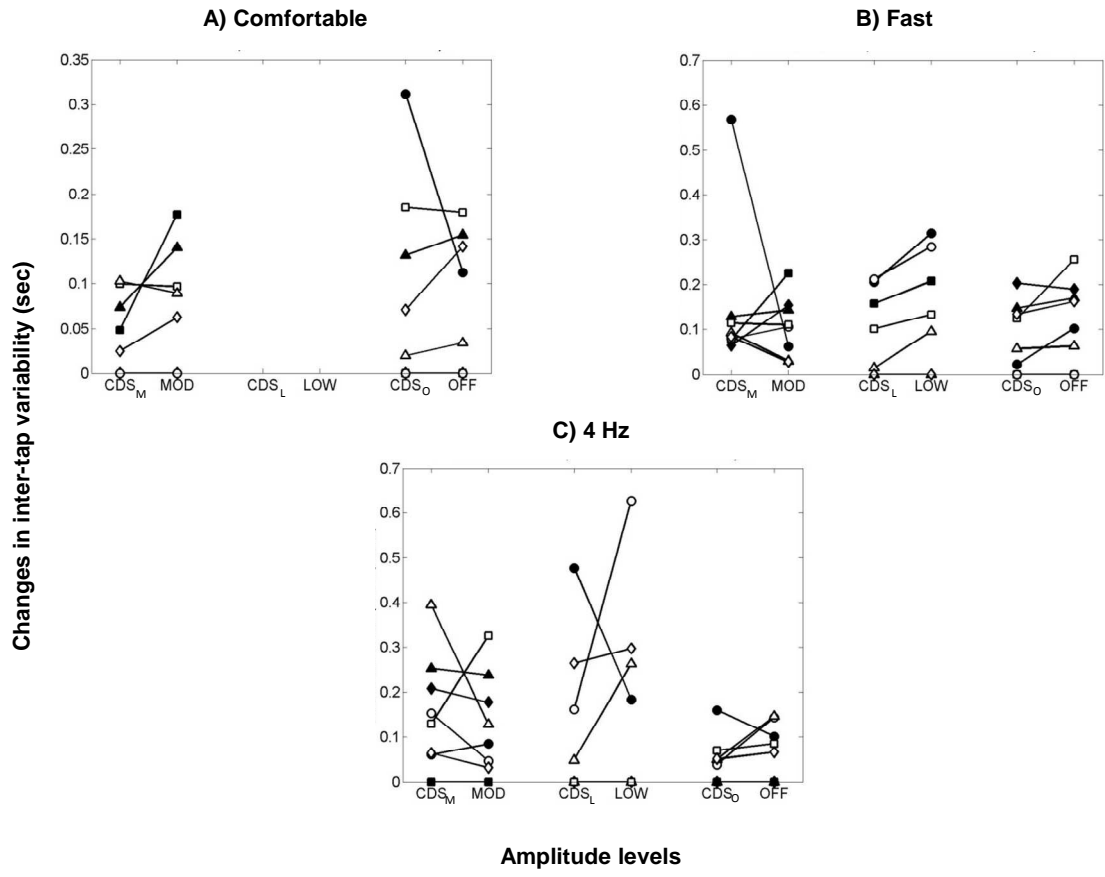


Figure 5.4. Changes in inter-tap variability from the CDS condition to each reduced amplitude level for each subject. (A) Comfortable, (B) Fast, and (C) 4 Hz. Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

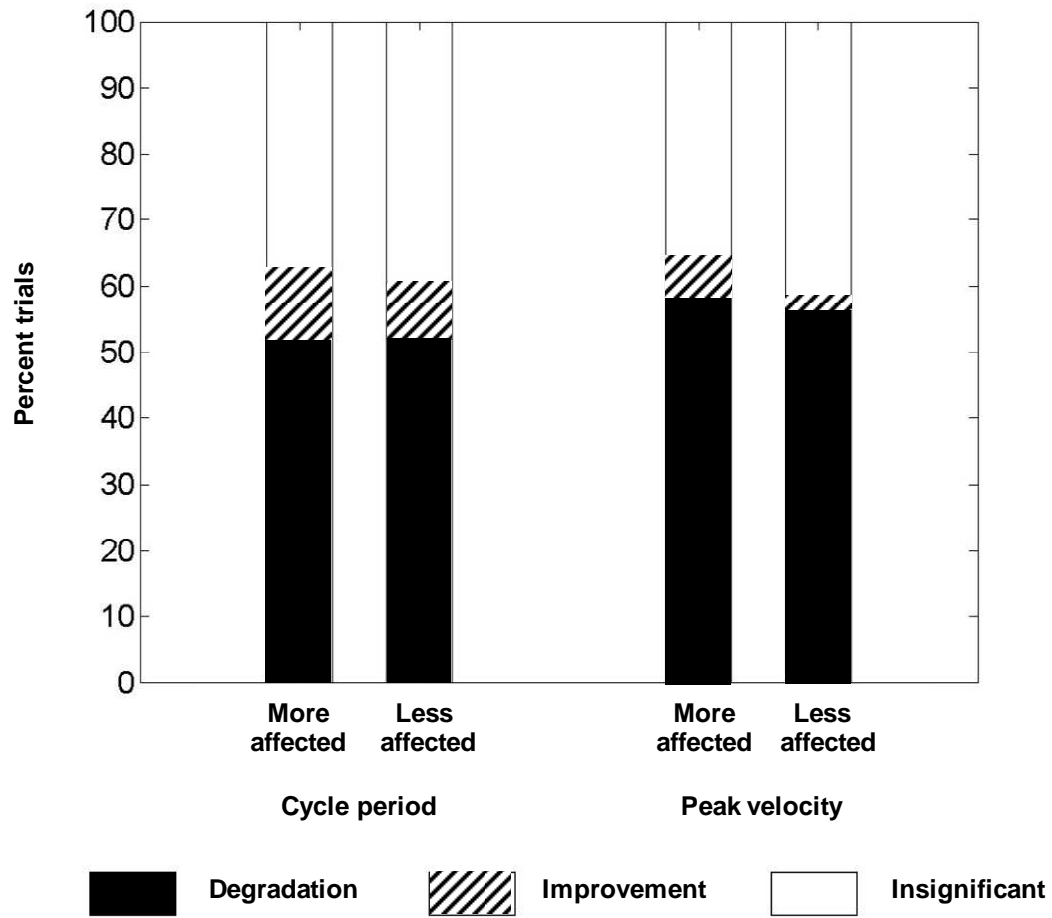


Figure 5.5. Percent trials with statistically significant degradations, statistically significant improvements, and insignificant changes in cycle period and peak velocity for both the more and less affected groups of limbs.

Notes: n = 48 trials for each column: 8 subjects, 2 single-joint tasks, 3 sessions.

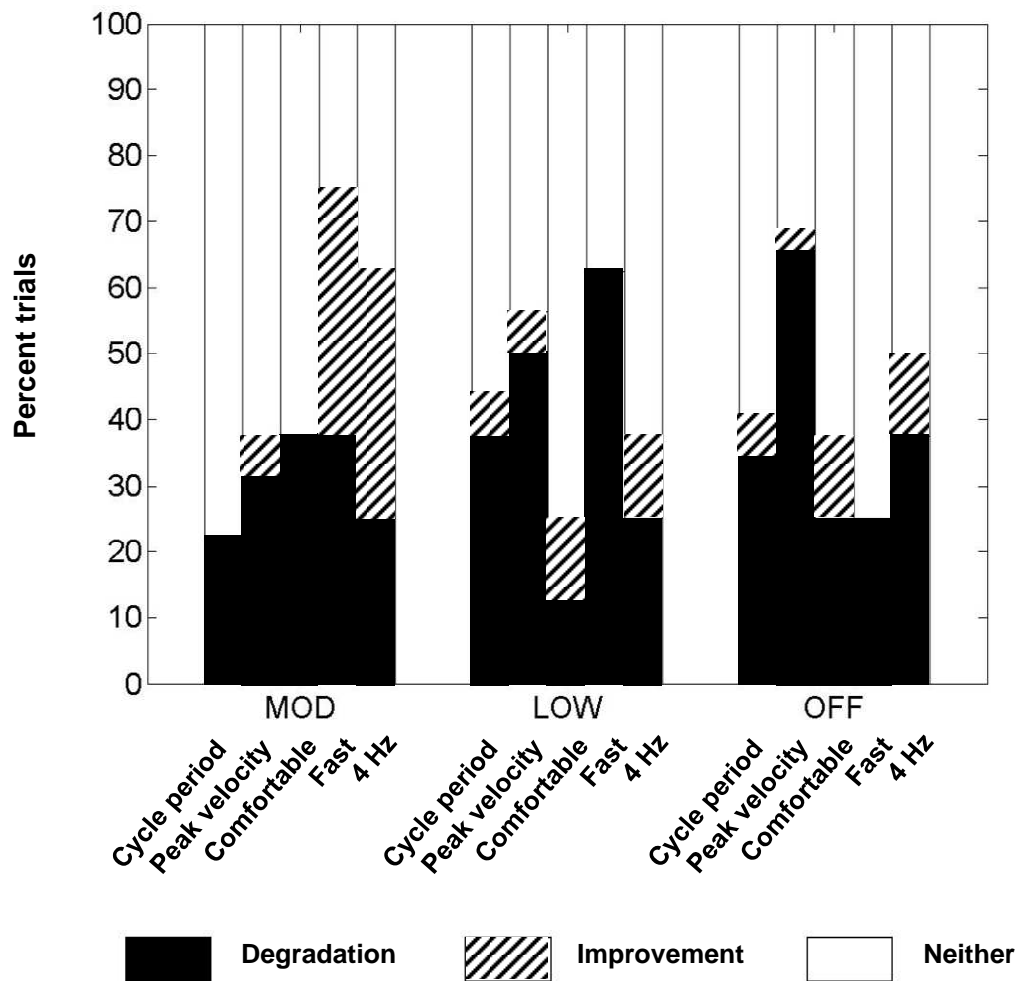


Figure 5.6. Percent trials with substantial degradations, substantial improvements, and changes that were not substantial at the MOD, LOW, and OFF conditions for cycle period, peak velocity, and inter-tap variability.

Notes: n = 32 trials for cycle period and peak velocity at each condition: 8 subjects, both arms, 2 single-joint tasks; n = 8 subjects for the Comfortable, Fast, and 4 Hz tasks.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

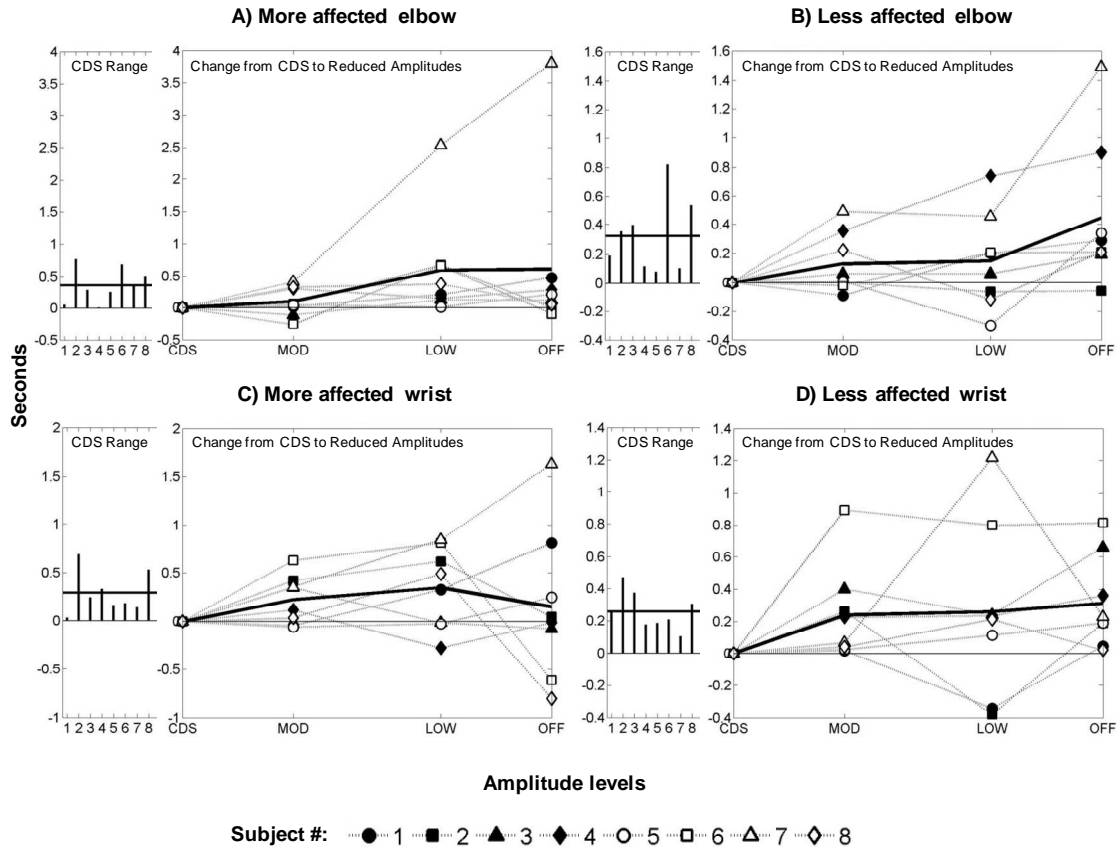


Figure 5.7. Day-to-day CDS variability compared to change in cycle period from CDS to each reduced amplitude level.

Notes: Left side of each lettered subplot represents each subject's range of CDS values over the three sessions when performing (A) elbow flexion-extension with the more affected limb, (B) elbow flexion-extension with the less affected limb, (C) wrist flexion-extension with the more affected limb, and (D) wrist flexion-extension with the less affected limb. The horizontal line represents the mean (n = 8 subjects), while the vertical bars represent each individual subject. Right side of each lettered subplot represents change in cycle period from CDS to each reduced amplitude for (A-D). The black line represents the mean (n = 8 subjects), while the gray lines represent each individual subject.

Abbreviations: CDS, clinically determined stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

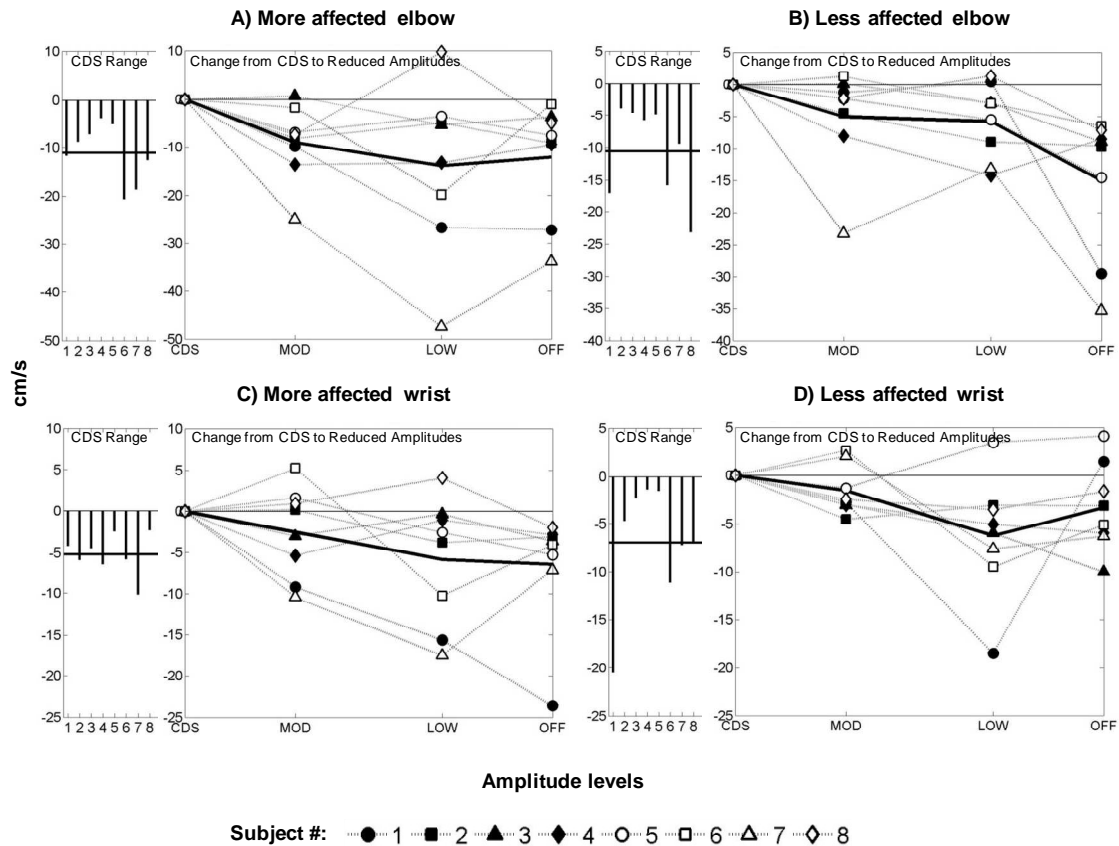


Figure 5.8. Day-to-day CDS variability compared to change in peak velocity from CDS to each reduced amplitude level.

Notes: Left side of each lettered subplot represents each subject's range of CDS values over the three sessions when performing (A) elbow flexion-extension with the more affected limb, (B) elbow flexion-extension with the less affected limb, (C) wrist flexion-extension with the more affected limb, and (D) wrist flexion-extension with the less affected limb. The horizontal line represents the mean (n = 8 subjects), while the vertical bars represent each individual subject. Right side of each lettered subplot represents change in peak velocity from CDS to each reduced amplitude for (A-D). The black line represents the mean (n = 8 subjects), while the gray lines represent each individual subject.

Abbreviations: CDS, clinically determined stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

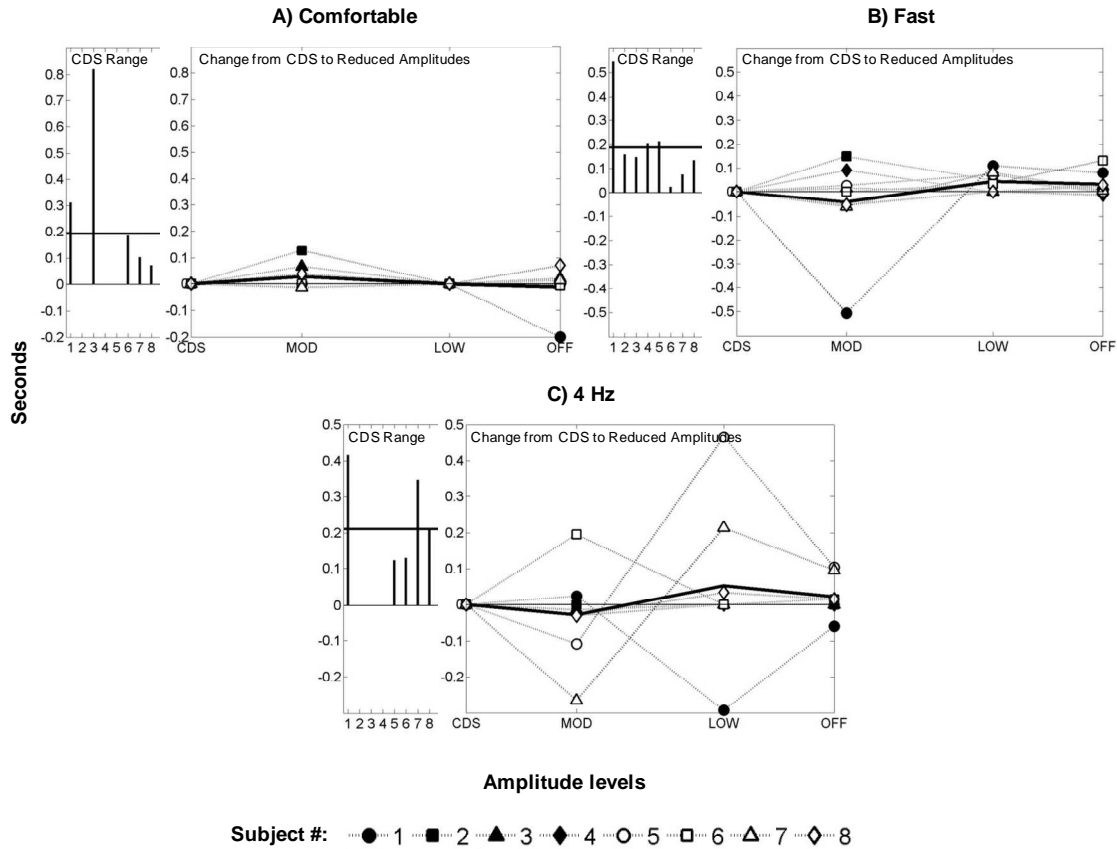


Figure 5.9. Day-to-day CDS variability compared to change in inter-tap variability from CDS to each reduced amplitude level. Notes: Left side of each lettered subplot represents each subject's range of CDS values over the three sessions when performing (A) tapping at a comfortable pace, (B) tapping at a fast pace, and (C) tapping at a 4-Hz pace. The horizontal line represents the mean, while the vertical bars represent each individual subject. Right side of each lettered subplot represents change in inter-tap variability from CDS to each reduced amplitude for (A-C). The black line represents the mean, while the gray lines represent each individual subject. For (A) and (C), $n = 5$ subjects for the means on the left and right sides of the subplot. For (B), $n = 8$ subjects for the means on the left and right sides of the subplot. For each task, subjects who only successfully completed one trial at CDS were excluded from the mean and CDS range calculations.

Abbreviations: CDS, clinically determined stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

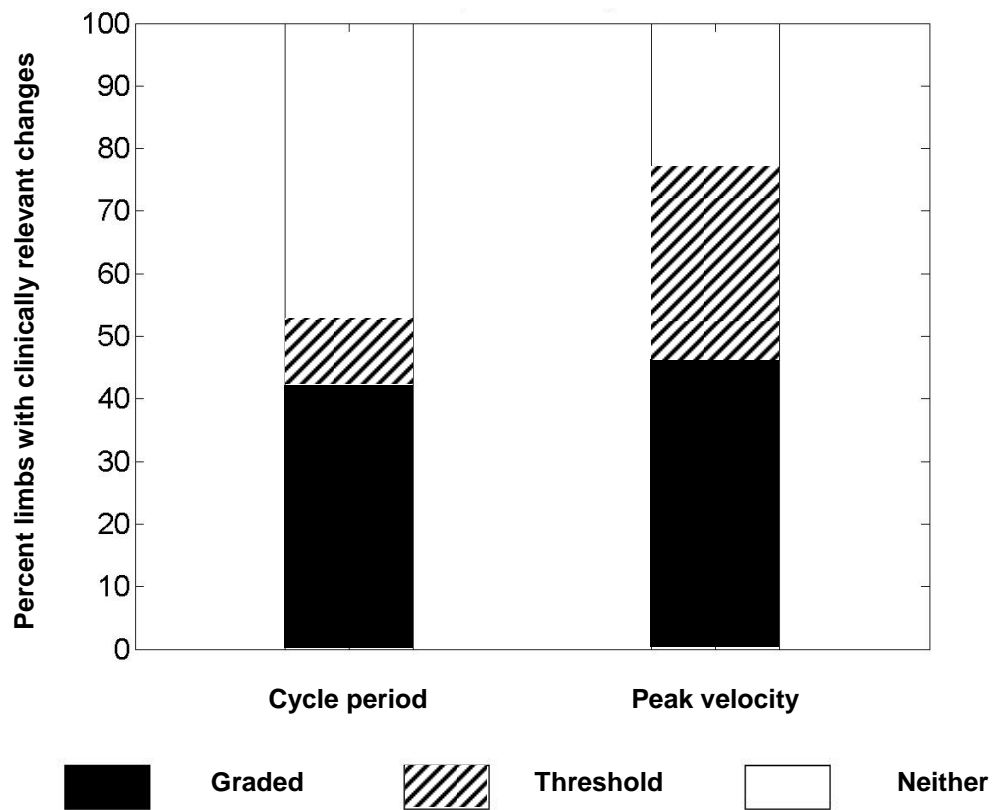


Figure 5.10. Of the limbs which experienced substantial changes, the percent that demonstrated graded, threshold, or neither characteristic for cycle period and peak velocity. Notes: n = 19 and 26 limbs with substantial changes for cycle period and peak velocity, respectively.

CHAPTER 6

GAIT AND LOWER EXTREMITY SINGLE-JOINT TASKS

Introduction

It has been suggested that people with Parkinson's disease (PD) may experience greater functional disability if their disease manifests as gait deficits rather than as tremor, underlining the importance of assessing and improving gait deficits in people with PD (Stebbins & Goetz, 1998). Bilateral deep brain stimulation (DBS) of the subthalamic nucleus has been shown to improve gait disability and also to result in a reduction in the dose of antiparkinsonian medication needed (Bakker, et al., 2004; Bastian, Kelly, Revilla, Perlmutter, & Mink, 2003; Kumar, et al., 1998; Larsh, Duker, Bhattacharya, & Revilla, 2011; McNeely & Earhart, 2013; McNeely et al., 2011; T. O. Mera et al., 2013; Rizzone et al., 2002). As discussed in chapters 2 and 3, many studies have demonstrated this improvement by comparing performance at DBS settings considered optimal by the clinician to performance with the DBS system turned off completely. However, few have studied intermediate stimulation settings, and those that have, did not document the effect on gait.

Lower-extremity (LE) bradykinesia has been shown to be related to aspects of gait, including reduced limb coordination and freezing of gait episodes (Morris, Iansek, & Galna, 2008; Winogrodzka, Wagenaar, Booij, & Wolters, 2005). Although LE bradykinesia has not been studied as thoroughly as upper extremity bradykinesia, its association with gait deficits demonstrates the value of investigating this PD symptom in greater detail (Kim et al., 2012).

The research reported here evaluated gait performance, seated hip flexion-extension, and seated dorsiflexion-plantar flexion at four amplitude levels, each level chosen as a percentage of the clinically determined stimulation (CDS) amplitude currently chosen by the clinician. Changes in gait performance were quantified using stride time variability, and changes in performance of the single-joint tasks were quantified using cycle period and peak velocity.

Changes in performance were also assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) to provide a clinically accepted reference for the quantitative measures. Other studies have also evaluated gait performance using the UPDRS

and quantitative means, and have reached opposing conclusions regarding whether changes in performance are reflected in both measures (Brusse, et al., 2005; Herman, Giladi, Gruendlinger, & Hausdorff, 2007; Martinez-Martin, et al., 1994; Vieregge, et al., 1997). Both Martinez-Martin and colleagues as well as Brusse and colleagues reported that gait speed did not correlate with UPDRS-III scores (Brusse, et al., 2005; 1994). Another reason to assess people with PD quantitatively and not solely with the UPDRS-III may be to uncover milder gait deficits. The UPDRS-III focuses on gait deficits seen at an advanced stage of PD, so it may be difficult to identify milder gait deficits using the scale (Vieregge, et al., 1997).

As PD is known to be a disease in which symptoms may vary substantially from day to day, this work also assessed gait performance and single-joint tasks at the same stimulation amplitude (CDS) on multiple days to provide a baseline measurement. It has been reported that consecutive UPDRS measurements vary by as much as 15% (Delwaide & Gonce, 1998; Plaha, et al., 2006).

Methods

Subjects. Subjects were recruited as described in chapter 3. Please refer to Table 3.1 for subject characteristics, relative timing of each test session, and LEDD and stimulation parameters at each test session.

Experimental protocol. Please refer to the section titled “Experimental protocol” in chapter 3 for details on the daily protocol for changes in stimulation settings and UPDRS measurements. Briefly, in a given experimental session, subjects performed a series of tests at the CDS settings, the stimulation level was reduced, and then the subjects performed the same set of tests at the reduced amplitude. Each subject completed sessions on three different days to provide measurements at each of three reduced stimulation settings which were approximately 70%, 30%, and 0% of the CDS (MOD, LOW, and OFF, respectively). In addition to the UPDRS assessments described in chapter 3, subjects also participated in a quantitative gait control task and two single-joint tasks twice during each test session, once at CDS settings and next at reduced amplitude stimulation settings.

Single-joint tasks protocol and data analysis. The subject was seated in a standard height chair for both tasks, and data were recorded using a Nest of Birds™ electromagnetic tracking system (Ascension Technology Corporation, Burlington, VT). The signal from the sensor was sampled at a rate of 30 Hz using a custom LabVIEW program and stored for analysis. The subject performed ten cycles of each movement in one trial unless fatigue prevented the completion of all ten cycles. The subject performed two trials each for the right and left sides with rest periods interspersed.

For both tasks, the sensor was oriented with the x-axis lateral, the y-axis anterior/posterior, and the z-axis superior/inferior relative to the subject. For hip flexion-extension, the sensor was attached to the anterior thigh and the subject tapped the foot on the floor, lifting the entire leg off the floor and then lowering it heel first, similar to item 26 on the UPDRS-III. For dorsiflexion-plantar flexion, the sensor was attached to the dorsal surface of the foot and the subject tapped the foot at a comfortable pace, keeping the heel on the floor (Kim, et al., 2012).

Sensor position along the x-axis, y-axis, and z-axis was collected throughout the trial and used to calculate position in three-dimensional space. Position was calculated relative to the first data point and then filtered using a fourth order Butterworth low-pass filter with a cut-off frequency of 7 Hz. Velocity was calculated and used to determine the start of each movement cycle. Five movement cycles from each trial were analyzed, beginning with the third cycle to eliminate start-up effects. The five cycles from both trials were combined for a total of ten movement cycles per task.

Gait control task protocol and data analysis. Sets of force sensitive resistors (FSRs) were fastened under the heel of each foot (Figure 6.1), and shoes were worn over the sensors. The FSRs were connected to a lightweight data logger (Crossbow Technology AD128) to enable continuous data collection. The data logger was positioned at the subject's waist, and its wires were secured around the subject's legs to ensure uninhibited walking. Although the subject walked unassisted, a member of the research staff lightly held a physical therapy belt that was

fastened around the subject to ensure safety. Two 80-m trials, each requiring a 180° turn were completed at a self-determined comfortable speed.

The gait data had been processed and measures of variability were calculated by other members of the research team and initial analysis has been previously reported (Krishnamurthi, Sitek, Mahant, Samanta, & Abbas, 2007). In that analysis, the data files for the FSRs attached to the left and right heels (Figure 6.2) were imported into a custom MATLAB program designed to semi-automatically extract the time of heel strike from the files (data for the left heel is presented). The two trials obtained at each amplitude condition were combined and then segmented into steady-state portions of data, excluding the first few steps and the 180° turn. After filtering with a fourth order Butterworth band-pass filter ($f_L = 3$ Hz, $f_H = 5$ Hz), the FSR data was inverted and a peak detection threshold appropriate to the subject's mass was chosen as a guideline to determine heel strikes. The resulting heel strikes were then visually confirmed, and stride time was calculated as the time difference between consecutive heel strikes (Figure 6.3).

Poincaré plots were created by plotting consecutive points in a time series; such analysis has been used to assess variability in physiological signals such as heart rate (Acharya, Joseph, Kannathal, Lim, & Suri, 2006; Karmakar, Khandoker, Gubbi, & Palaniswami, 2009; Toichi, Sugiura, Murai, & Sengoku, 1997). To measure stride time variability, each stride time value was plotted against the immediately preceding value. As demonstrated in Figure 6.4(A), the data marker lies along the diagonal line of identity when two consecutive stride time values are equal; the marker falls into the upper half of the plot when a stride time value is greater than the immediately preceding value; and the marker falls into the lower half of the plot when a stride time value is less than the immediately preceding value.

The plot was quantified by fitting an ellipse to the data, such that the minor axis indicates dispersion of values perpendicular to the line of identity and the major axis indicates dispersion parallel to the line of identity (Figure 6.4(B)). The semiminor (SD1) and semimajor (SD2) axes are calculated using equations (1) and (2), respectively.

$$SD1 = \text{std}(ST_n - ST_{n+1}) / \sqrt{2} \quad (1)$$

$n=1, \dots, N-1$

$$SD2 = \text{std}(ST_n + ST_{n+1}) / \sqrt{2} \quad (2)$$

$n=1, \dots, N-1$

SD1 measures short-term variability, or the variability of successive strides, while SD2 measures long-term variability, similar to the coefficient of variability (Brennan, Palaniswami, & Kamen, 2001; Karmakar, et al., 2009; Tulppo, Makikallio, Takala, Seppanen, & Huikuri, 1996).

Outcome measures. Outcome measures included Poincaré plot descriptors SD1 and SD2 as measures of stride time variability for the gait task and cycle period and peak velocity for the single-joint tasks.

For each subject, the UPDRS-III bradykinesia subscore (items 23-26 and 31) (Bartels, et al., 2003) was assessed at the CDS condition for each side to clinically determine which side was more affected by PD. Based on these classifications, the more affected and less affected sides were compared for individual subjects as well as across the cohort. Since performance was evaluated at the CDS condition during each test session, each subject had three CDS values for each outcome measure. The variability of each subject's day-to-day performance was quantified by calculating the range of these three values.

Statistical analysis. Statistics were performed using IBM SPSS Statistics software (SPSS Inc, Chicago, IL). For each subject, the cycle period and peak velocity values obtained at each session's CDS amplitude were compared to the values obtained at that same session's reduced amplitude using the Mann-Whitney Test. The two-tailed Wilcoxon signed rank test was used to compare mean differences between outcome measures obtained at CDS and reduced amplitude across all subjects. Performance at the CDS amplitude was treated as a baseline measure to account for day-to-day variations when assessing the effect of the change to a reduced stimulation amplitude.

The differences in values obtained at the CDS and reduced amplitude conditions (deltas) were calculated for each outcome measure. The deltas for the UPDRS scores were compared to the deltas for each quantitative measure to determine if there was a relationship between the UPDRS scores and the respective quantitative measures. Spearman's rho was calculated, and the correlation coefficients were evaluated using the same criteria as Brusse and colleagues: fair

= 0.25 - 0.50, moderate to good = 0.50 - 0.75, and excellent = 0.75 - 1.00 (2005). If an outlier was present in one of the data groups, Spearman's rho was calculated both including and excluding that point. Unless otherwise noted, a *P* value ≤ 0.05 was considered to be statistically significant.

Results

Comparison across stimulation conditions. For the group as a whole, reducing stimulation amplitude did not significantly change the mean cycle period of the single-joint tasks for either the more or less affected limbs (Figure 6.5). Reducing amplitude also did not change the mean peak velocity of either task for the group of more affected limbs (Figure 6.6). However, for the less affected limbs, reducing amplitude to the LOW and OFF conditions significantly decreased the mean peak velocity of hip flexion-extension. Also for the less affected limbs, reducing amplitude to the MOD condition significantly decreased the mean peak velocity of dorsiflexion-plantar flexion, but, reducing it further to the LOW and OFF conditions induced no significant difference from performance at CDS. Note that sensor interference prevented the collection of left dorsiflexion-plantar flexion data for subject 1 at the CDS condition of the LOW test session.

For stride time variability, reducing amplitude to the MOD or LOW condition did not cause a significant change in mean value for the group (Figure 6.7), but reducing amplitude from the CDS to the OFF condition resulted in a significant increase in stride time variability as measured by both SD1 and SD2.

Although mean cycle period across the set of subjects was not significantly affected by reducing amplitude, each subject experienced significant changes in cycle period at reduced amplitude conditions. For hip flexion-extension, reducing amplitude to the MOD and LOW conditions caused almost equal numbers of limbs to improve and decline, whereas reducing amplitude further to the OFF condition caused almost twice as many limbs to decline rather than improve. For dorsiflexion-plantar flexion, reducing amplitude to any of the three conditions resulted in about equal numbers of limbs improving and declining, but reducing it just to the MOD condition actually caused the greatest number of changes in total.

Each subject also demonstrated significant changes in peak velocity at reduced amplitude conditions. For hip flexion-extension, reducing amplitude to the MOD condition caused almost equal numbers of limbs to improve and decline, whereas reducing amplitude to the LOW and OFF conditions caused more than twice as many limbs to decline rather than improve. For dorsiflexion-plantar flexion, reducing amplitude to the MOD and LOW conditions resulted in substantially more declines, while reducing it further to the OFF condition induced a similar number of improvements and declines.

Examination of the stride time variability results for individual subjects as depicted in Figure 6.8 revealed that the significant increase in mean stride time variability between the CDS and OFF conditions was mainly due to the performance of subjects 1 and 7. Subject 7 also experienced much higher variability at the CDS condition for the majority of the sessions compared to the other subjects, and experienced much greater changes when stimulation amplitude was reduced to the MOD and OFF conditions compared to the LOW condition.

In general, stride time variability increased when stimulation amplitude was reduced from the CDS condition. However, some subjects experienced decreased variability at one or more reduced amplitude conditions. Subject 5 experienced the greatest decline in variability when the CDS condition was reduced to the MOD condition.

As depicted in Figure 6.9, the groups of more and less affected limbs responded similarly to reduced stimulation, experiencing about the same number of statistically significant changes in both cycle period and peak velocity.

Statistically significant differences may not always translate to clinically significant differences, however, so trials were also examined to determine whether reducing stimulation induced changes likely to be substantial. For this analysis, we defined a substantial change as one whose magnitude was > 25% of the performance measured at the CDS condition for that session. Figure 6.10 depicts how many trials exhibited substantial and less than substantial changes for cycle period, peak velocity, and the stride time variability measures. Subjects demonstrated more substantial changes in peak velocity and in the stride time variability measures than they did in cycle period. More often than not, subjects demonstrated degraded

rather than improved performance with reduced amplitude, with more than two-thirds of the substantial changes characterized as degradation in performance.

DBS dose-response characteristics. As in chapter 3, dose-response curves were examined for each of the outcome measures, with a threshold response defined as one decrement in stimulation accounting for $\geq 70\%$ of the maximum change in performance observed (Figures 6.11-6.13). Of the limbs determined to experience substantial changes in the outcome measures, Figure 6.14 summarizes the percentage which demonstrated graded characteristics, threshold characteristics, or didn't fit either category. Although trials in this last category technically included a change whose magnitude was $\geq 70\%$ with one decrement in amplitude, they didn't truly demonstrate threshold behavior, as they also included changes of comparable magnitude in the opposite direction.

Day-to-day variability. Compared to the mean range of CDS values for the group, the more affected limb of subject 4 demonstrated much smaller changes in cycle period at the CDS condition, while the more affected limb of subject 7 demonstrated much larger changes in cycle period at CDS. The peak velocity values demonstrated by subject 1 were more than twice the size of the range experienced by the group. The more affected limb of subject 6 demonstrated much less variability in both cycle period and peak velocity at CDS than the group mean.

The range of CDS values was also compared with the change experienced when the CDS amplitude was reduced to the MOD, LOW, and OFF conditions. The group results were similar for both single-joint tasks: for both cycle period and peak velocity, the mean range of CDS values for the group was greater than the mean change seen when amplitude was reduced from CDS to any of the three reduced amplitude conditions.

Some of the individual subjects reflected the response of the entire cohort, demonstrating a greater range in performance at the CDS condition than the effect of reducing amplitude from CDS. A less common response was for a subject to demonstrate greater changes in performance at every reduced amplitude than the range of CDS measures. A third response required amplitude to be reduced by 100% before a subject experienced a change in performance that was greater than the range experienced at the CDS condition. However, in the most common

response, an intermediate amplitude condition induced a greater change in performance than was experienced at the CDS condition, but reducing amplitude further induced less change than was experienced at CDS.

For the stride time variability measures, subjects 6 and 7 clearly experienced more day-to-day variability in SD1 than the group did, while subjects 5 and 7 experienced more variability for SD2. For SD1, the mean change in performance experienced when amplitude was reduced to both the MOD and OFF conditions exceeded the mean change in CDS performance experienced on different days. For SD2, only the mean change in performance experienced by reducing amplitude to the OFF condition exceeded the mean change in CDS performance observed on different days.

For SD1, most subjects experienced greater changes between their CDS performance on different days than they experienced when amplitude was reduced to the MOD condition, and some even experienced greater range at CDS than the magnitude of the change when amplitude was reduced to the LOW condition. However, all subjects except 3 and 6 experienced a greater change in SD1 when amplitude was reduced to the OFF condition compared to the range of CDS values.

For SD2, all subjects except 1 experienced about the same or even less change when amplitude was decreased to one or more of the reduced conditions than they experienced in their CDS performance on different days. However, most subjects experienced a greater change in SD2 when amplitude was reduced to the OFF condition compared to the range of CDS values.

Correlations. Spearman's rho was calculated to obtain a better understanding of how the UPDRS scores and quantitative measures might be related. There were no statistically significant correlations between cycle period of the single-joint tasks and the UPDRS scores, and there were no correlations judged to be stronger than fair using the criteria developed by Brusse and colleagues (2005). For peak velocity, however, both the total UPDRS-III score and the bradykinesia subscore were significantly correlated with hip flexion-extension on both the more and less affected sides. In addition, these four correlations were all considered to meet the moderate to good criteria.

Since subjects 1 and 7 experienced such large changes in the stride time variability measures when amplitude was reduced to the OFF condition, they were excluded from calculating the correlation. For the stride time variability measures, the only statistically significant correlation was between the UPDRS gait subscore and SD1, which was also categorized as a moderate to good correlation.

Discussion

Due to the high variability demonstrated by subjects when stimulation amplitude was reduced, very few significant effects were observed when the cohort was evaluated as a whole. However, similar to other work, some significant changes were seen for the single-joint movement tasks. DBS has been found to significantly increase the velocity of both ankle and hip flexion-extension (T. O. Mera, et al., 2013). Although only a few significant changes were found between reduced amplitude and CDS velocities in the current research, velocity tended to be greater at the CDS condition. In addition, there was a significant difference in both mean stride time variability measures between the OFF and CDS conditions, supporting previous work which found that stride time variability significantly increased when stimulation amplitude was reduced from the CDS to the OFF condition (Larsh, et al., 2011).

Although the limbs were separated into two groups based on which side was clinically determined to be more affected by PD, the two groups actually demonstrated very similar results. It was anticipated that the group of more affected limbs would demonstrate a greater number of significant changes with reduced stimulation than the group of less affected limbs. However, the two groups demonstrated almost the same number of changes for both cycle period and peak velocity. Further, the more affected limbs were expected to demonstrate more declines in performance than the less affected limbs, but the opposite actually occurred. It may be that this cohort included subjects for whom both sides were very similarly affected by PD, resulting in differences in the UPDRS bradykinesia subscore that were not substantial. It may also be that the bradykinesia subscore did not accurately designate which limbs were more and less affected, and another means of categorization would have been more effective.

There were many instances, both for individual subjects and across the whole cohort, when progressively greater reductions in amplitude did not result in progressively greater changes in the outcome measures. For subjects who experienced almost no change or even an improvement in performance when amplitude was reduced to the MOD condition, this may indicate that a 30% amplitude reduction was not great enough to induce a change in performance. It may also indicate that the subject experienced higher variability when performing that task, or that the task itself was not sensitive enough to detect changes.

Some subjects experienced significant changes at intermediate amplitudes when performing select tasks, but they did not experience any changes as amplitude was decreased further. In these cases, the intermediate amplitude condition may be the best setting to optimize the subject's performance of that specific task. However, this response may also reflect the inherent variability of PD in that the subject's symptoms may have responded more dramatically to amplitude reduction on the day LOW was tested.

As expected, subjects overall experienced more substantial degradations than improvements. However, some subjects actually performed better on select tasks at reduced amplitude conditions. This may indicate that their current stimulation parameters are set too high for optimal performance of that task. Stimulation may not affect each symptom equally and thus may not need to be set at the same level to optimize one aspect of motor performance compared to another. Stimulation parameters are often chosen primarily based on the response of tremor, but it may be more beneficial to determine settings based on the response of multiple symptoms. This may enable the clinician to determine a setting that balances tradeoffs in a manner that maximizes the clinical benefits of DBS for that individual.

Regarding the single-joint tasks, cycle period and peak velocity were expected to have an inverse relationship. However, some subjects demonstrated both increased cycle period and increased peak velocity or decreased cycle period and decreased peak velocity as amplitude was reduced. These responses would seem to indicate that there was greater variability in the velocity at which the single-joint tasks were performed at reduced amplitude levels. Although this might be

expected to correspond to increased variability in gait performance as well, this was not always the case.

Not all subjects were expected to experience substantial changes with every stimulation decrement, as it was thought that a 30% reduction in amplitude might not be enough to induce change in a subset of the subjects. However, it was expected that the subject cohort as a whole would experience more substantial changes as stimulation was decreased by a greater amount, but this was not the case. The number of substantial changes experienced at each amplitude condition was not related to the percentage of reduction from the CDS condition, but was fairly evenly distributed amongst the three reduced conditions.

Peak velocity and stride time variability may be more sensitive parameters than cycle period for revealing differences induced by stimulation changes. More than twice the percent of substantial changes were experienced in the peak velocity and stride time variability measures compared to cycle period. In other reports, overall gait velocity has been used as an indicator of gait function. However, in this study, many subjects needed to rest during the gait trials performed at the LOW and OFF conditions, which prevented the calculation of consistent and reliable measures of gait velocity.

Correlation analysis reinforced the previous finding that peak velocity and stride time variability may be better choices than cycle period to measure change induced by reducing amplitude. It also revealed that hip flexion/extension may be better measured by the UPDRS-III score than ankle dorsiflexion-plantar flexion, which is surprising in light of previous work which demonstrated that ankle dorsiflexion-plantar flexion was significantly correlated to the UPDRS-III score (Kim, et al., 2012). Regarding gait, this research supported previous findings that gait measures were not correlated with the UPDRS-III score (Brusse, et al., 2005; Martinez-Martin, et al., 1994). However, this research also demonstrated a significant correlation between gait measures and the UPDRS gait subscore, which was not evaluated in the previous studies. As short-term rather than long-term variability was correlated, this may indicate that visually evaluating gait facilitates comparison of successive strides rather than an overall assessment of variability throughout the trial.

Motor performance both for individual subjects and across the group generally degraded as stimulation amplitude was reduced. However, there were some exceptions in which improved performance was exhibited at a reduced condition. This may indicate that the subject's CDS amplitude was too high for optimal performance of that specific task. Although the group response was similar across tasks, the individual subjects varied greatly in their performance. They also demonstrated substantial variability in their CDS performance across days, and repeated evaluation of DBS settings may be necessary to offset this variability.

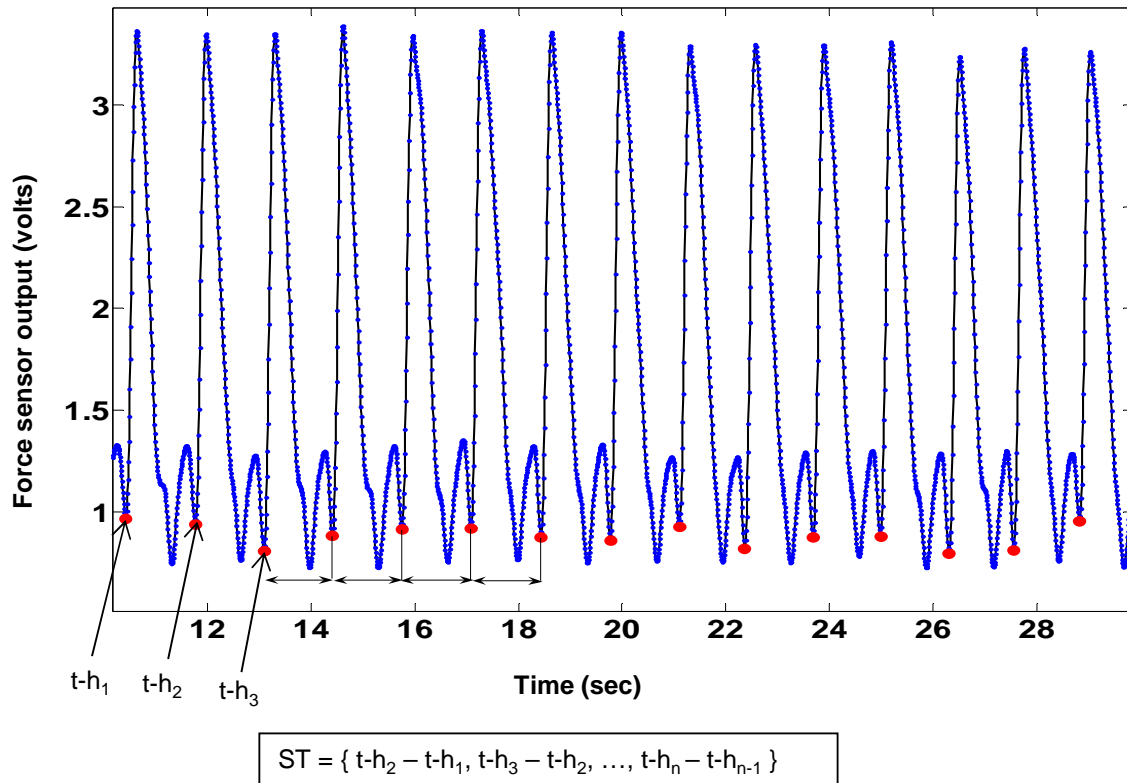


Figure 6.2. As described by Krishnamurthi, a force profile obtained from a single force sensor during a steady-state portion of a trial performed at the CDS condition (2007). The red dots indicate heel strikes. Stride time was calculated as the time difference between two successive heel strikes.

Abbreviations: $t-h_n$, time of heel strike n ; ST, stride time; sec, seconds; CDS, clinically determined stimulation.

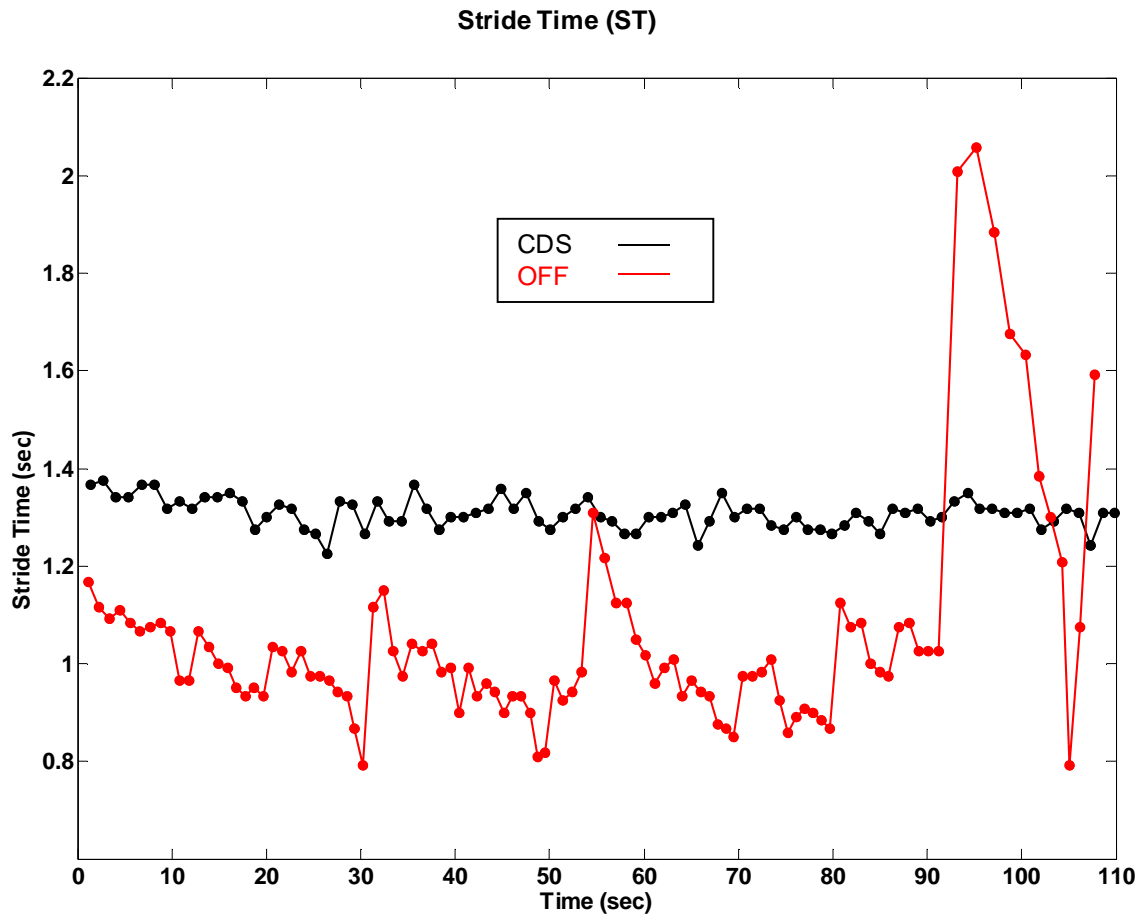


Figure 6.3. As described by Krishnamurthi, stride time measured during the CDS (black line) and OFF (red line) portions of one subject's OFF test session (2007).

Abbreviations: ST, stride time; CDS, clinically determined stimulation; OFF, 0% stimulation amplitude; sec, seconds.

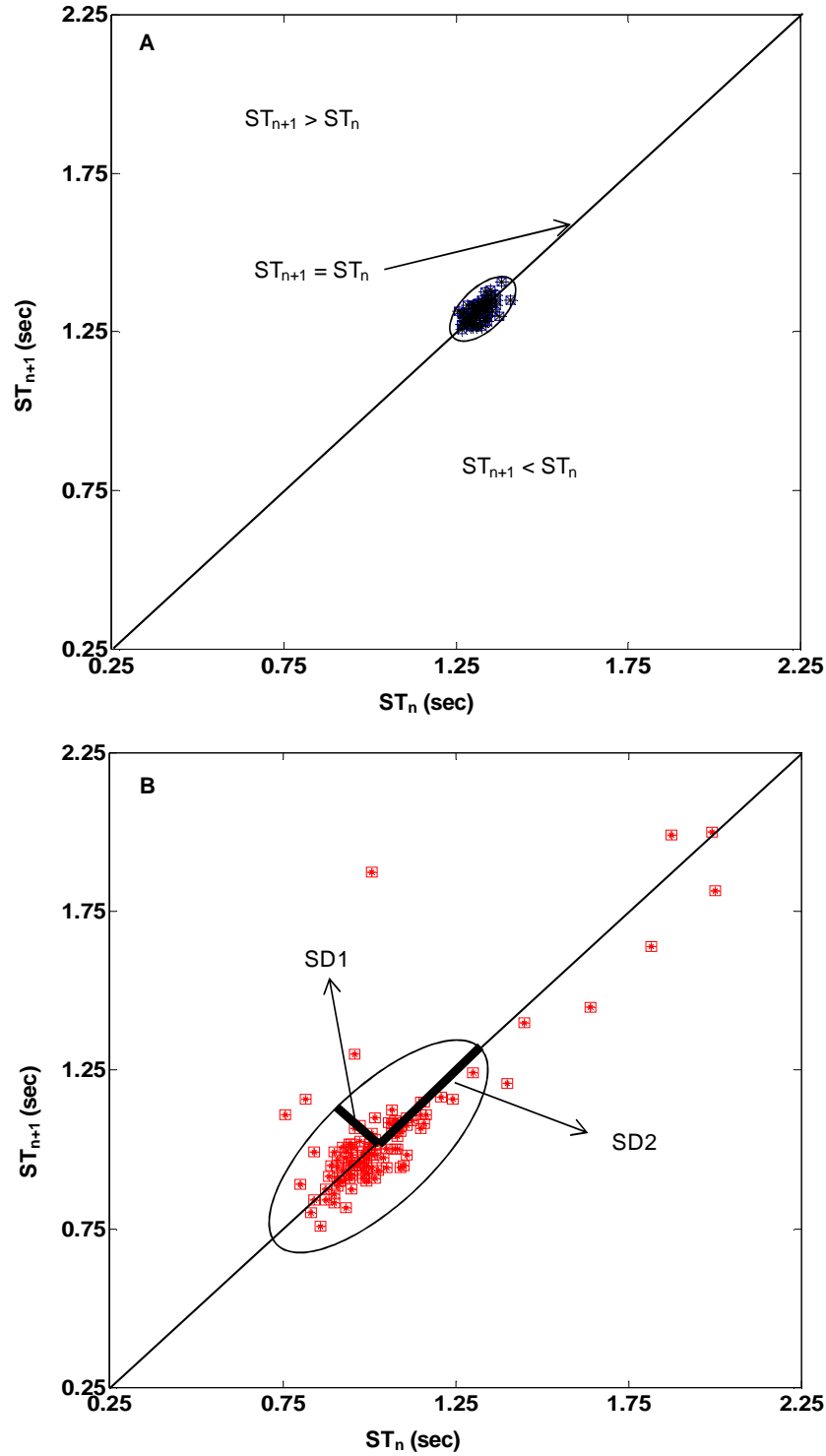


Figure 6.4. As described by Krishnamurthi, Poincaré plots for one subject created from data obtained during the CDS (A) and OFF (B) portions of the OFF test session (2007). Abbreviations: ST, stride time; SD1 and SD2, Poincaré plot descriptors; sec, seconds; CDS, clinically determined stimulation; OFF, 0% stimulation amplitude.

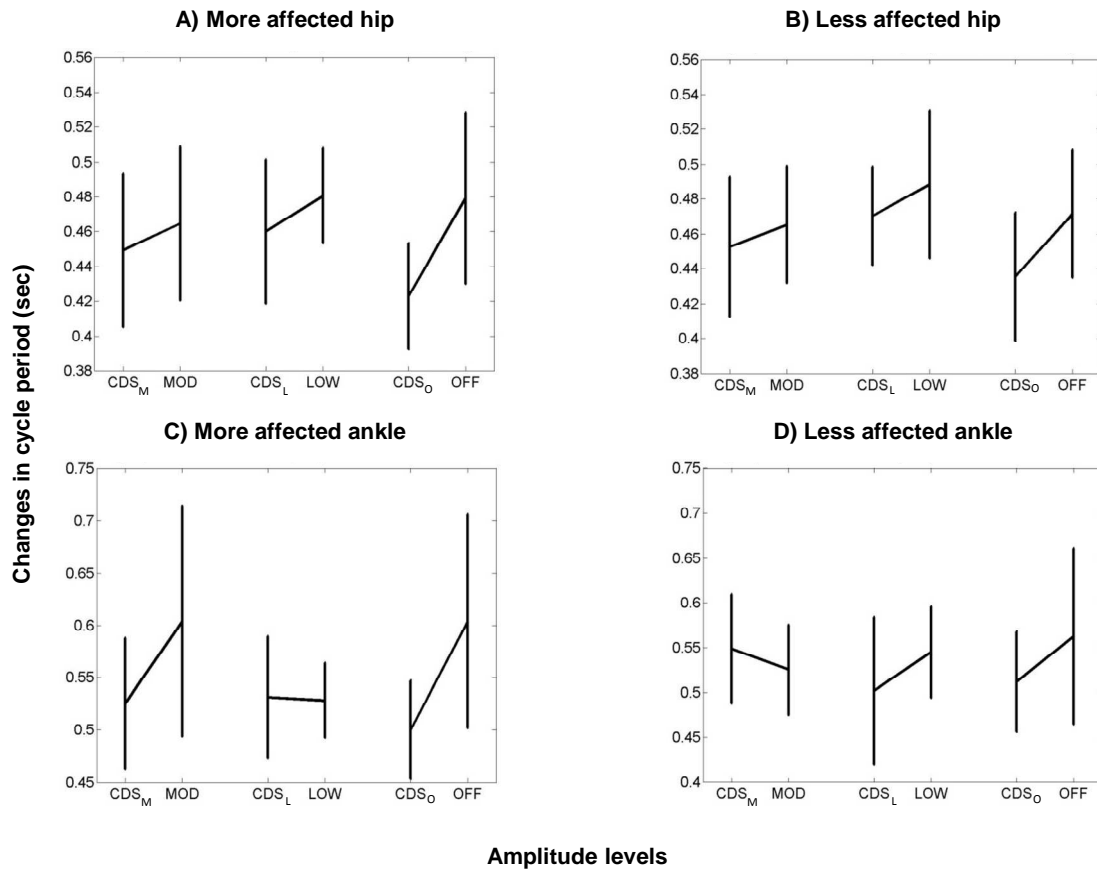


Figure 6.5. Changes in mean (\pm standard error of the mean) cycle period from the CDS condition to each reduced amplitude level. (A) More affected hip, (B) Less affected hip, (C) More affected ankle, and (D) Less affected ankle.

Notes: For (A-C), $n = 8$ subjects for each condition in each subplot. For (D), $n = 8, 7,$ and 8 subjects for the MOD, LOW, and OFF conditions, respectively. Subject 1 was excluded as an outlier from the LOW session. *Indicates changes in mean that were significant.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

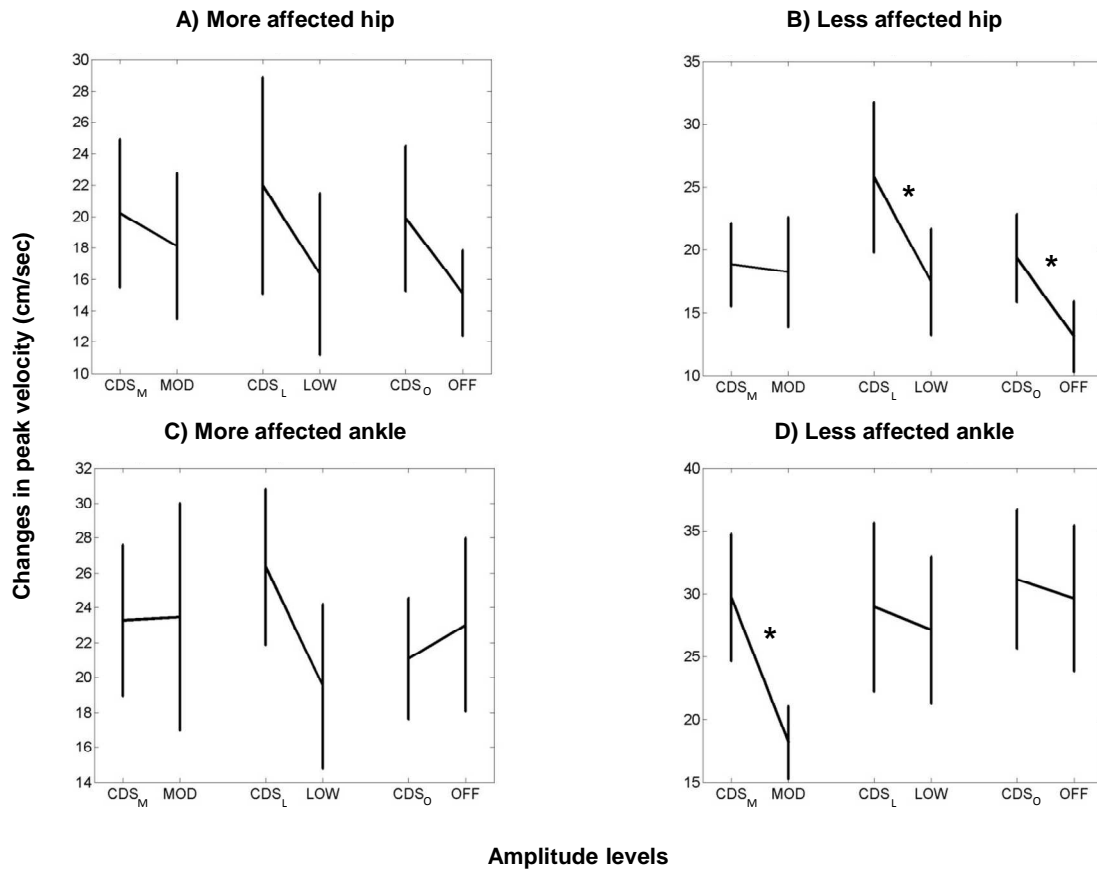


Figure 6.6. Changes in mean (\pm standard error of the mean) peak velocity from the CDS condition to each reduced amplitude level. (A) More affected hip, (B) Less affected hip, (C) More affected ankle, and (D) Less affected ankle.

Notes: For (A-C), $n = 8$ subjects for each condition in each subplot. For (D), $n = 8, 7,$ and 8 subjects for the MOD, LOW, and OFF conditions, respectively. Subject 1 was excluded as an outlier from the LOW session. *Indicates changes in mean that were significant.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively; cm/sec: centimeters per second.

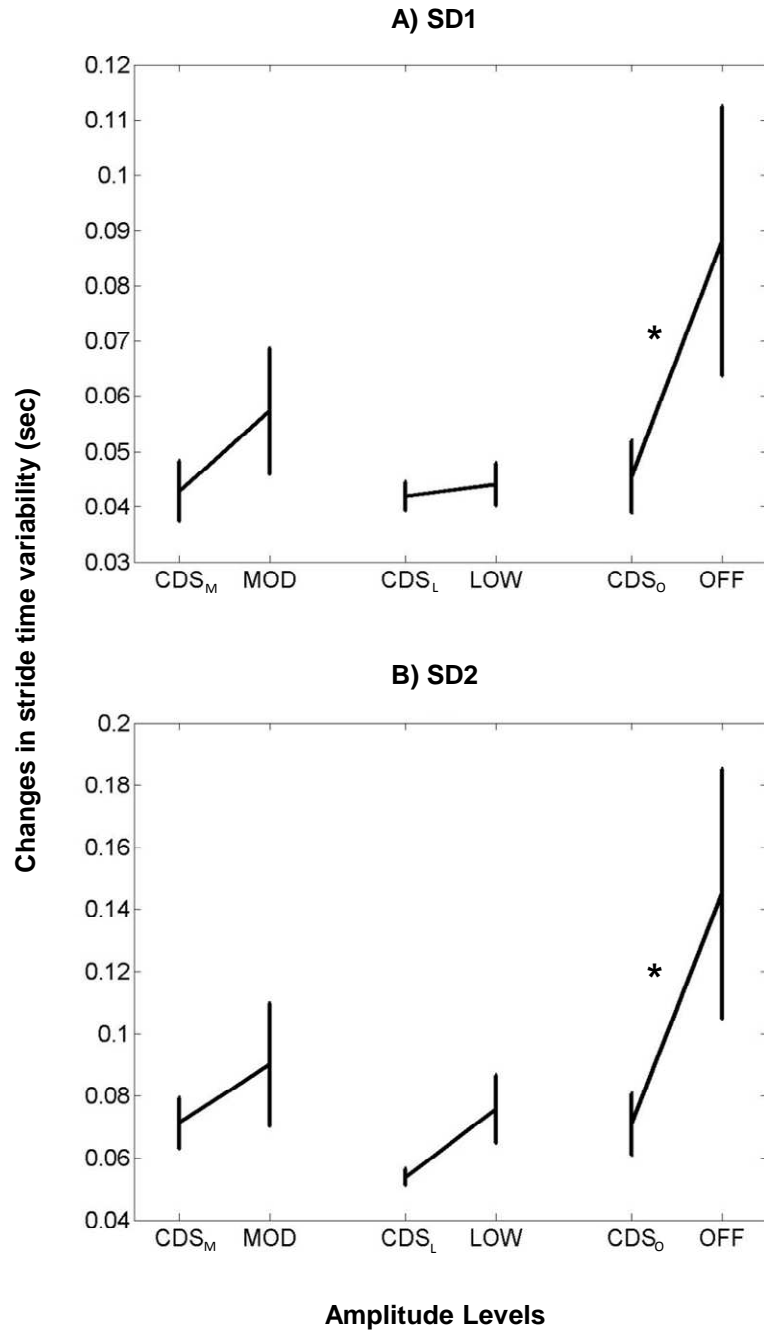


Figure 6.7. Changes in mean (\pm standard error of the mean) stride time variability from the CDS condition to each reduced amplitude level. (A) SD1 and (B) SD2.

Notes: $n = 8$ subjects for each condition in each subplot. *Indicates changes in mean that were significant.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively; SD1 and SD2: Poincaré plot descriptors.

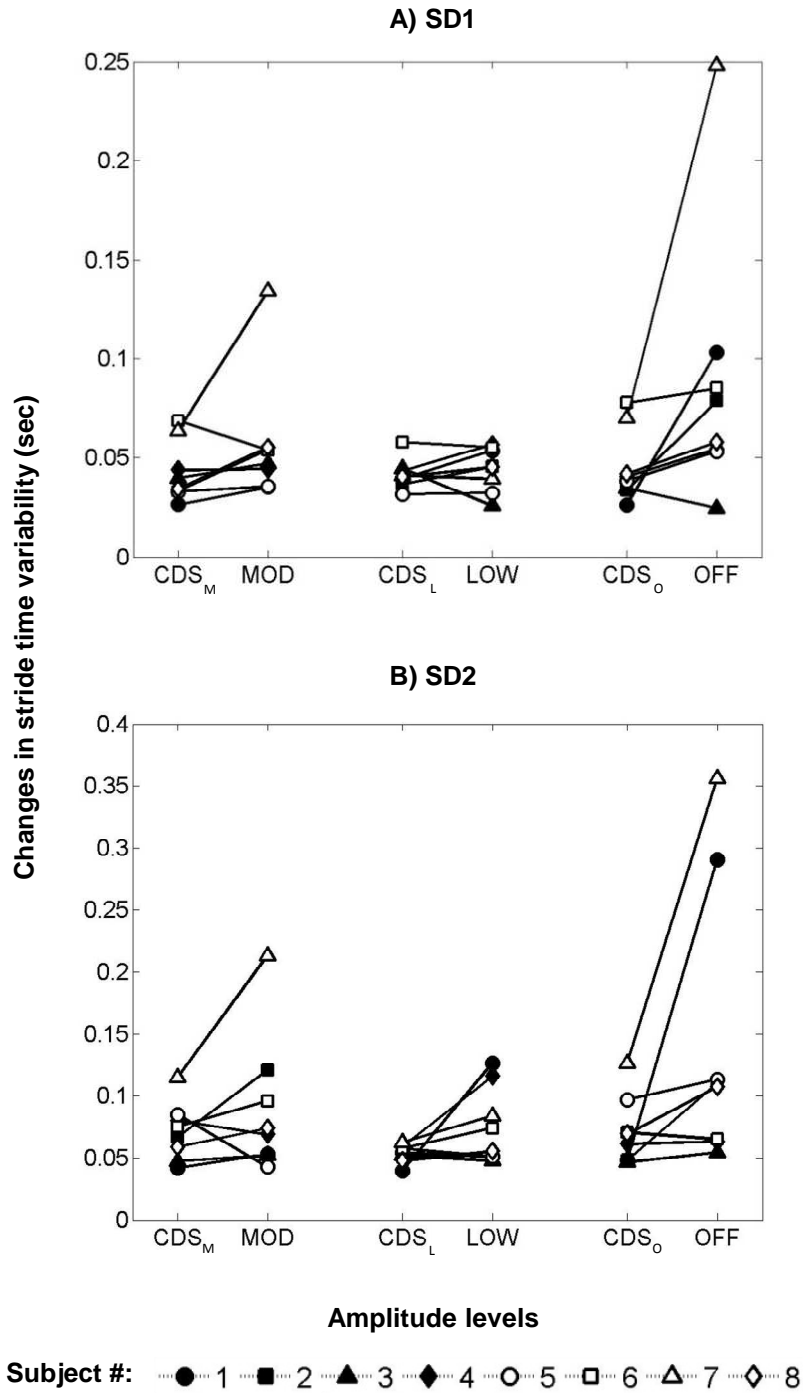


Figure 6.8. Changes in stride time variability from the CDS condition to each reduced amplitude level for each subject. (A) SD1 and (B) SD2.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively; SD1 and SD2: Poincaré plot descriptors.

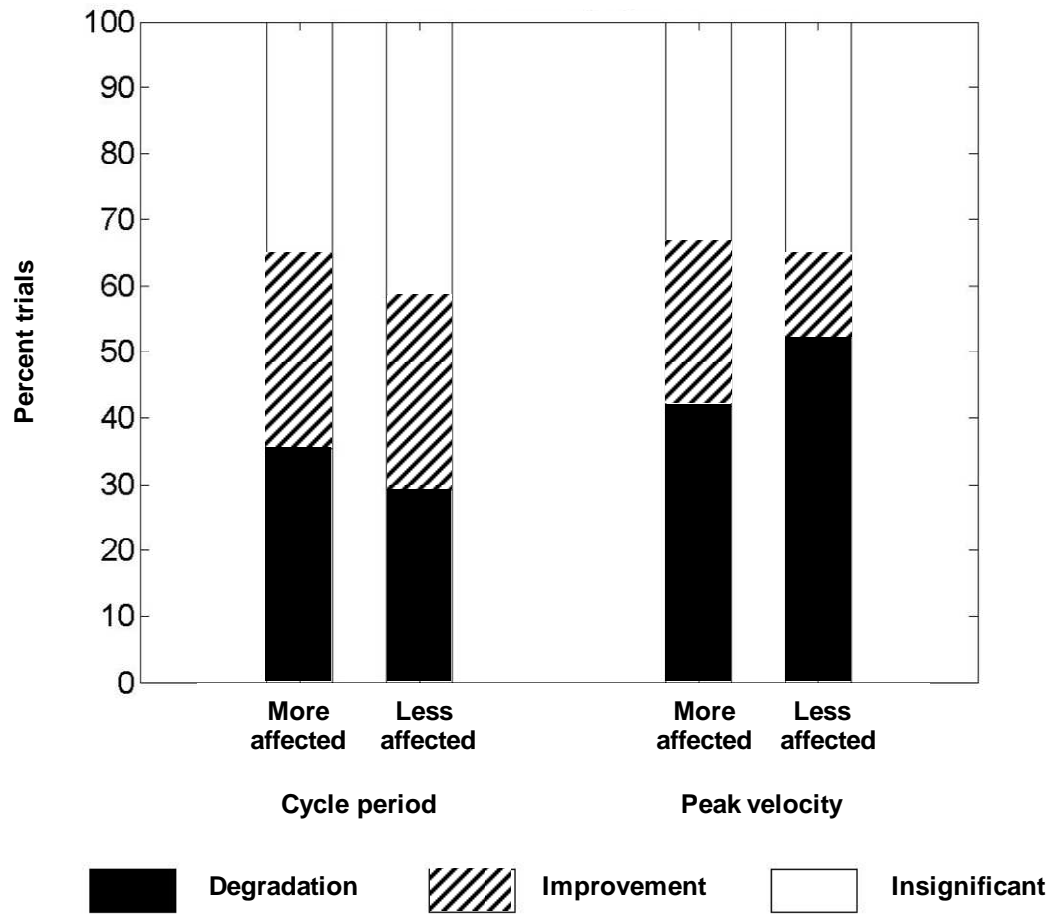


Figure 6.9. Percent trials with statistically significant degradations, statistically significant improvements, and insignificant changes in cycle period and peak velocity for both the more and less affected groups of limbs.

Notes: n = 48 trials for each column: 8 subjects, 2 single-joint tasks, 3 sessions.

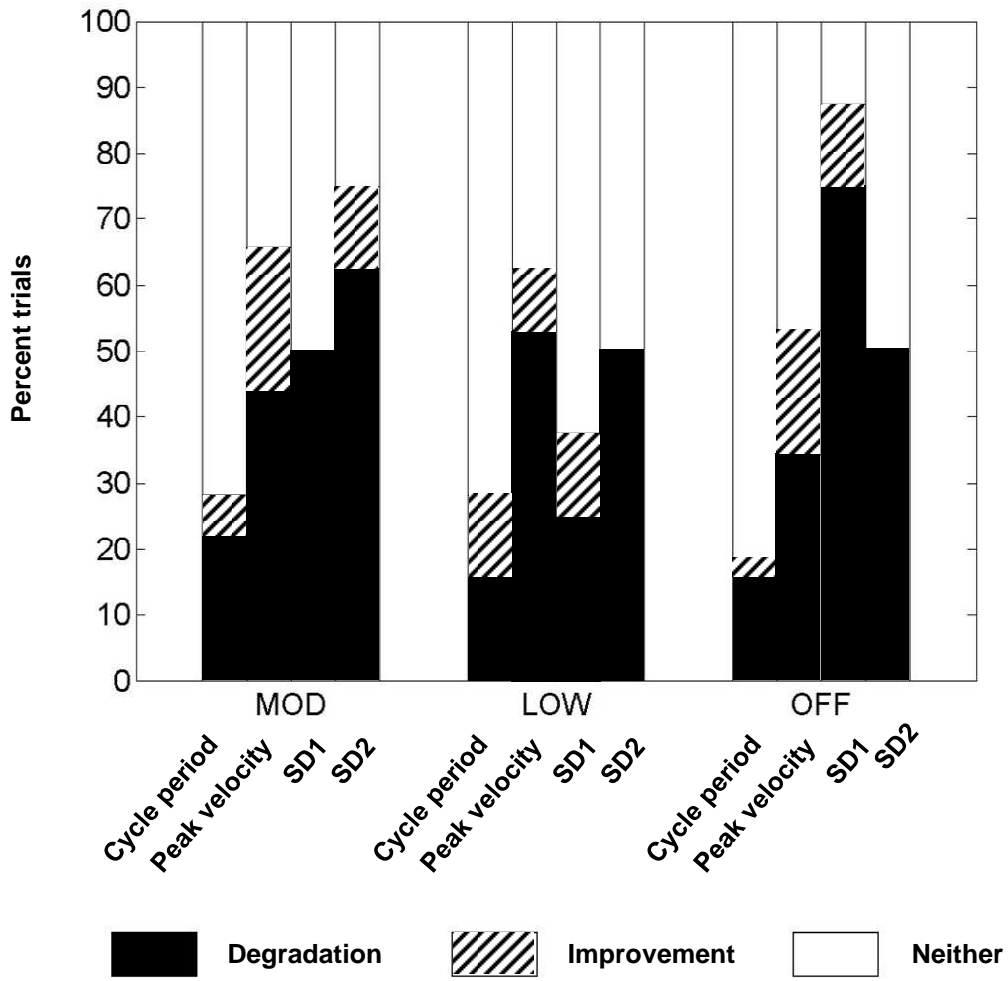


Figure 6.10. Percent trials with substantial degradations, substantial improvements, and changes that were not substantial at the MOD, LOW, and OFF conditions for cycle period, peak velocity, SD1, and SD2.

Notes: n = 32 trials for cycle period and peak velocity at each condition: 8 subjects, both arms, 2 single-joint tasks; n = 8 subjects for SD1 and SD2.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively; SD1 and SD2: Poincaré plot descriptors.

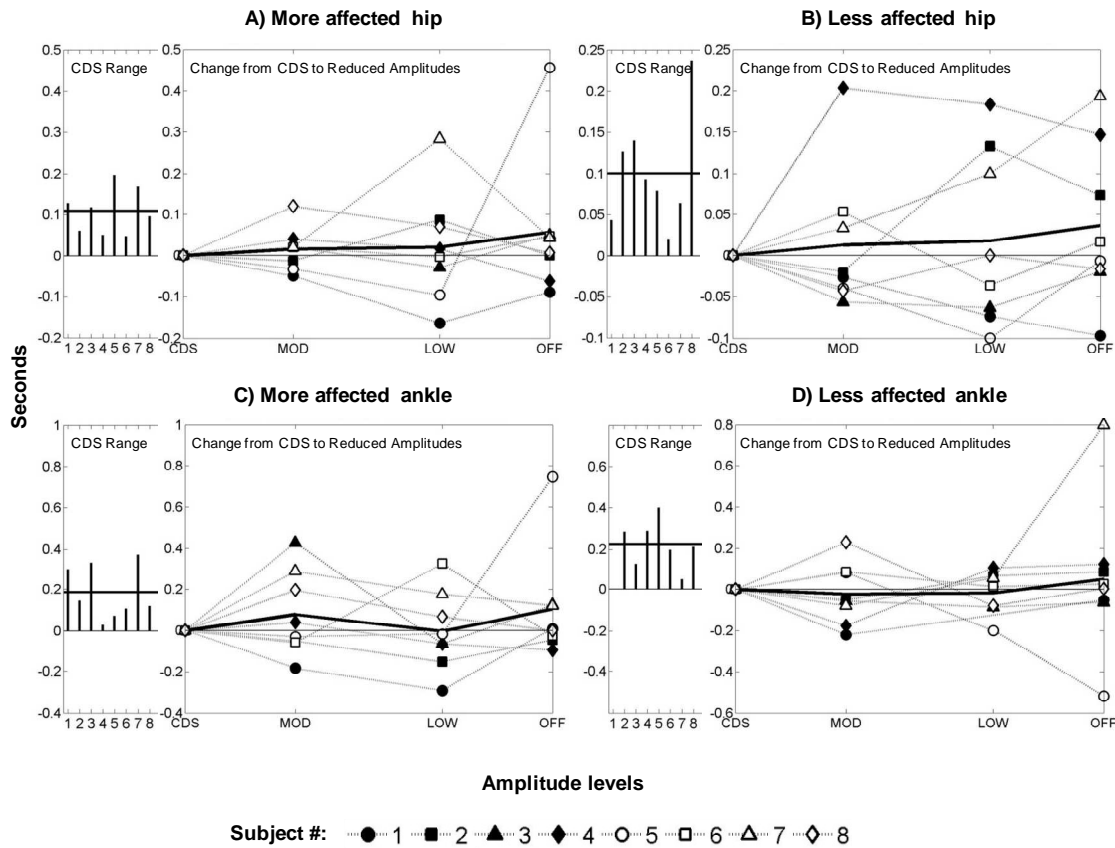


Figure 6.11. Day-to-day CDS variability compared to change in cycle period from CDS to each reduced amplitude level.

Notes: Left side of each lettered subplot represents each subject's range of CDS values over the three sessions when performing (A) hip flexion-extension with the more affected limb, (B) hip flexion-extension with the less affected limb, (C) dorsiflexion-plantar flexion with the more affected limb, and (D) dorsiflexion-plantar flexion with the less affected limb. The horizontal line represents the mean, while the vertical bars represent each individual subject. Right side of each lettered subplot represents change in cycle period from CDS to each reduced amplitude for (A-D). The black line represents the mean, while the gray lines represent each individual subject. For (A-C), $n = 8$ subjects for the means on the left and right sides of the subplot. For (D), $n = 7$ subjects for the means on the left and right sides of the subplot. Subject 1 was excluded as an outlier from the LOW session.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

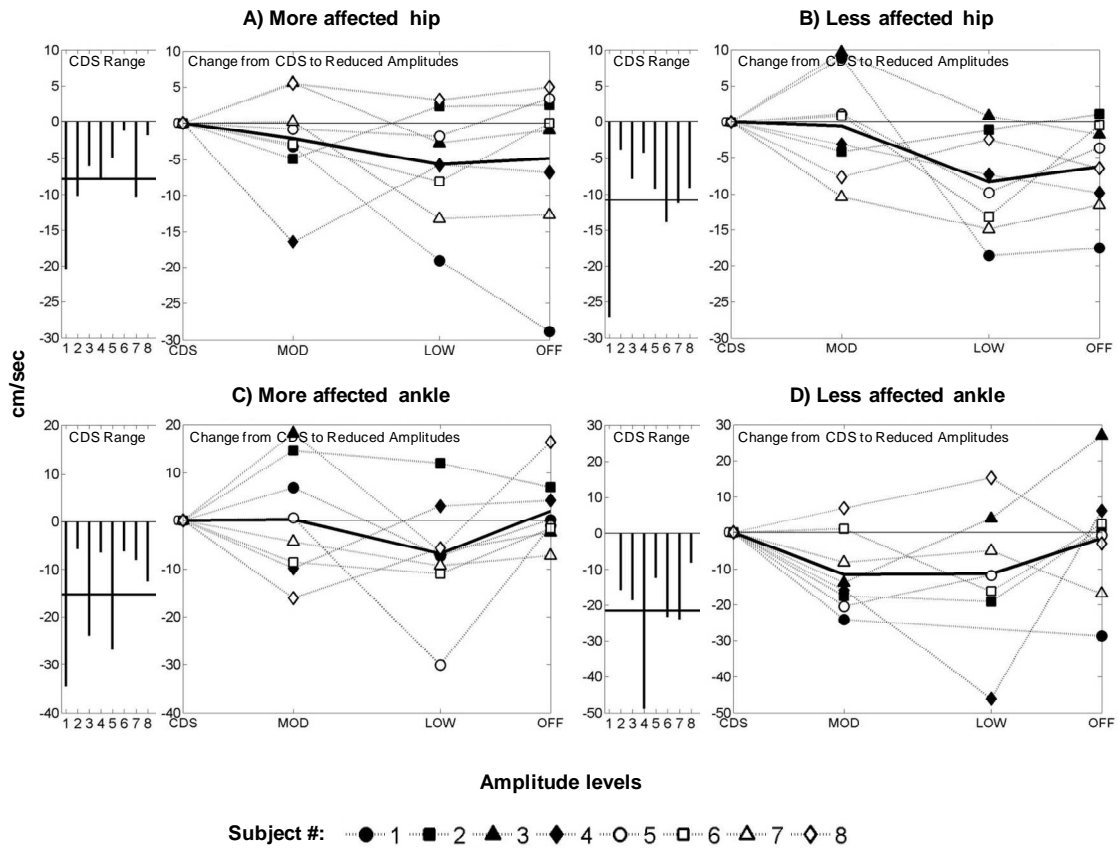


Figure 6.12. Day-to-day CDS variability compared to change in peak velocity from CDS to each reduced amplitude level.

Notes: Left side of each lettered subplot represents each subject's range of CDS values over the three sessions when performing (A) hip flexion-extension with the more affected limb, (B) hip flexion-extension with the less affected limb, (C) dorsiflexion-plantar flexion with the more affected limb, and (D) dorsiflexion-plantar flexion with the less affected limb. The horizontal line represents the mean, while the vertical bars represent each individual subject. Right side of each lettered subplot represents change in peak velocity from CDS to each reduced amplitude for (A-D). The black line represents the mean, while the gray lines represent each individual subject. For (A-C), $n = 8$ subjects for the means on the left and right sides of the subplot. For (D), $n = 7$ subjects for the means on the left and right sides of the subplot. Subject 1 was excluded as an outlier from the LOW session.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively; cm/sec: centimeters per second.

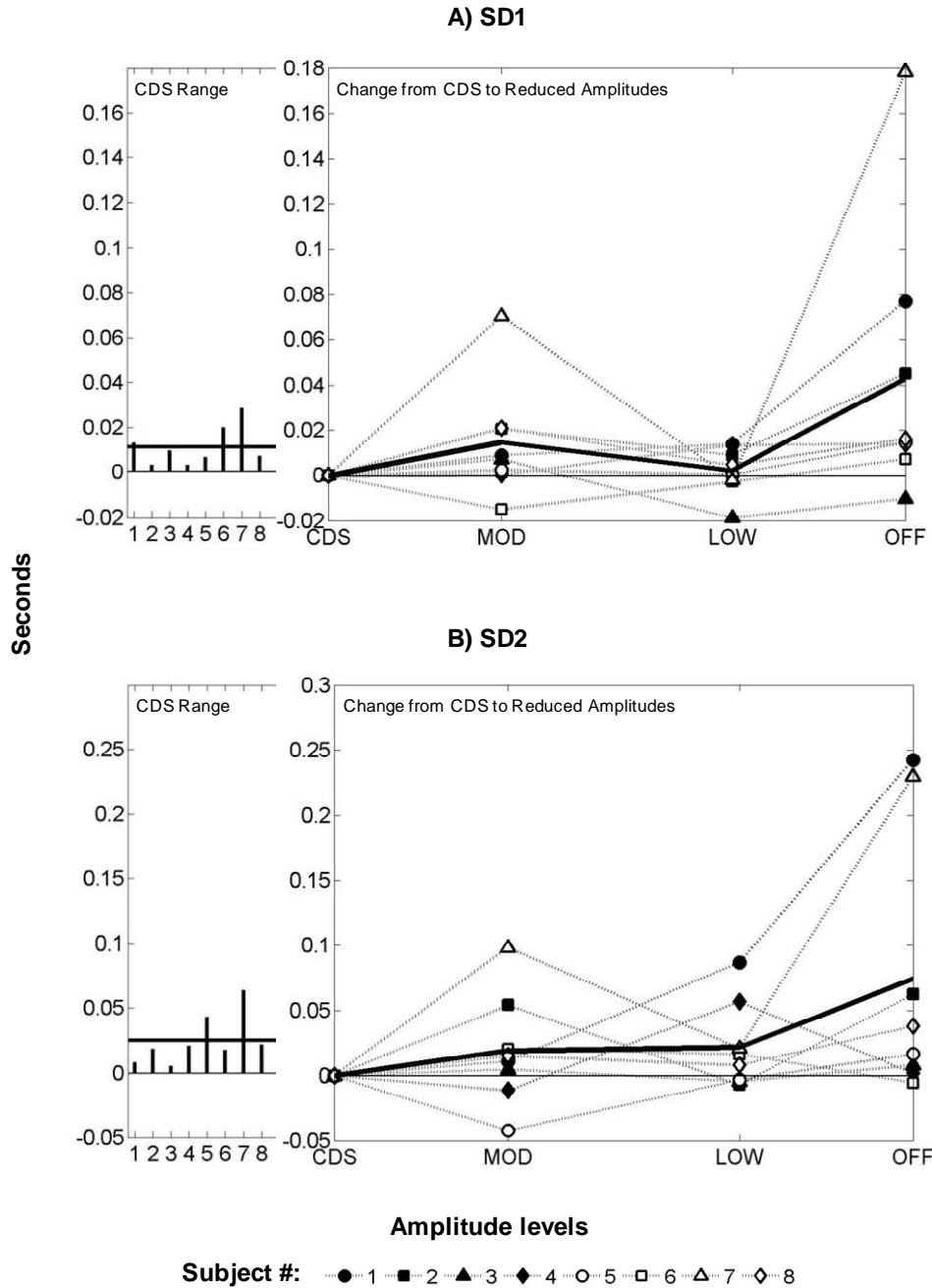


Figure 6.13. Day-to-day CDS variability compared to changes in SD1 and SD2 from CDS to each reduced amplitude level.

Notes: Left side of each lettered subplot represents each subject's range of CDS values over the three sessions for (A) SD1 and (B) SD2. The horizontal line represents the mean ($n = 8$ subjects), while the vertical bars represent each individual subject. Right side of each lettered subplot represents changes in SD1 and SD2 from CDS to each reduced amplitude for (A-B). The black line represents the mean ($n = 8$ subjects), while the gray lines represent each individual subject.

Abbreviations: CDS, clinically determined stimulation; SD1 and SD2: Poincaré plot descriptors; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

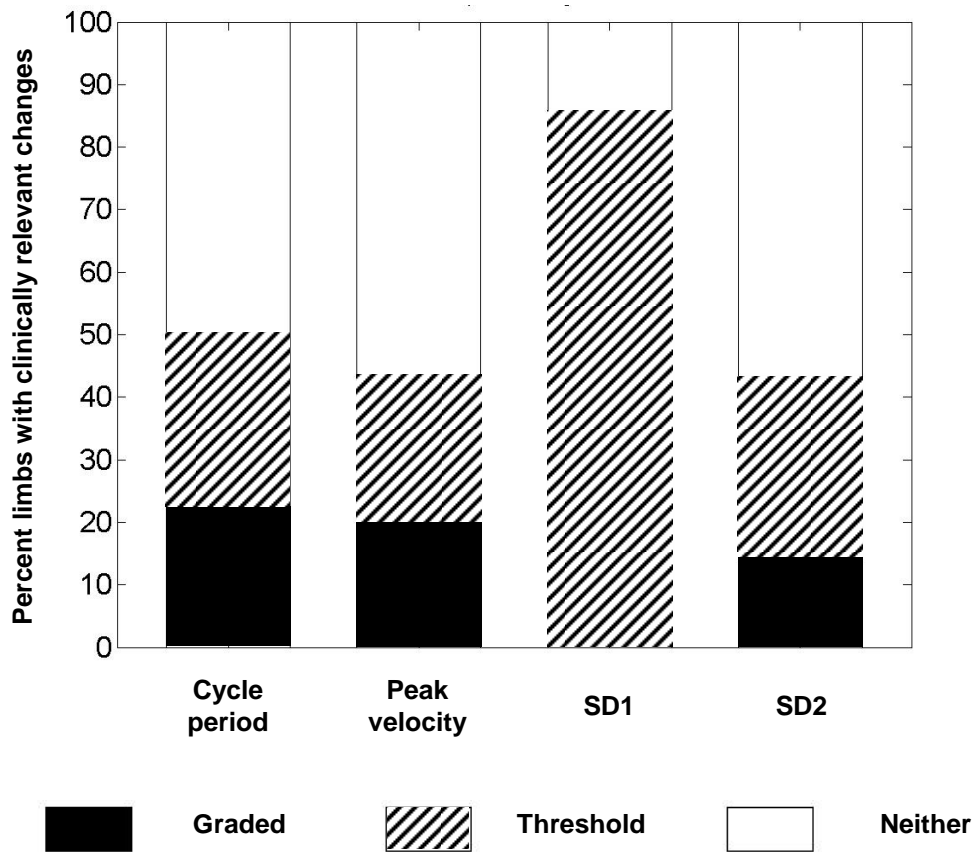


Figure 6.14. Of the limbs which experienced substantial changes, the percent that demonstrated graded, threshold, or neither characteristic for cycle period, peak velocity, SD1, and SD2.

Note: n = 18, 30, 7, and 7 limbs with substantial changes for cycle period, peak velocity, SD1, and SD2, respectively.

Abbreviations: SD1 and SD2: Poincaré plot descriptors.

CHAPTER 7

POSTURAL CONTROL

Introduction

Deficits in postural control can negatively impact the quality of life and propensity for falls in people with PD, particularly those at an advanced stage (Bloem, van Vugt, & Beckley, 2001; Robertson, et al., 2001). Bilateral deep brain stimulation (DBS) of the subthalamic nucleus has been shown to improve scores on the total motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) as well as for specific items related to posture (Bakker, et al., 2004; Bastian, et al., 2003; Kumar, et al., 1998; Limousin, et al., 1998; McNeely & Earhart, 2013; Rizzone, et al., 2002; St George et al., 2012). As discussed in chapters 2 and 3, many studies have demonstrated this improvement by comparing performance at DBS settings considered optimal by the clinician to performance with the DBS system turned off completely. However, few have studied intermediate stimulation settings, and those that have, did not document the effect on postural control.

Other work has shown that people with PD demonstrate decreased sway velocity and significantly different sway area compared to an elderly control group (Horak, Nutt, & Nashner, 1992; Mancini et al., 2012). Similar work indicated that people with PD also exhibited a slower velocity when voluntarily leaning forward and backward (Mancini, Rocchi, Horak, & Chiari, 2008). The dynamic postural control task utilized in the current research also involved voluntary forward leans, as well as voluntary left, right, and diagonal leans. A previous iteration of this task was used to study people with PD undergoing DBS therapy, and the results indicated that subjects experienced significant changes in velocity measures with changes in stimulation amplitude (Krishnamurthi, Mulligan, Mahant, Samanta, & Abbas, 2012). Based on these findings, the current research also focused on velocity as a measurement of changes in postural control.

The research reported here evaluated performance on a dynamic postural control task at four amplitude levels, each level chosen as a percentage of the clinically determined stimulation (CDS) amplitude currently chosen by the clinician. Changes in performance were quantified using peak velocities during different phases of the task. This type of dynamic task may address the

stated need for alternate methods of balance assessment to address possible limitations of the UPDRS in providing a comprehensive measure of mobility performance in people with PD (Brusse, et al., 2005; Qutubuddin et al., 2005). Changes in performance were also assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III), since it is a clinically accepted reference.

PD is known as a disease in which symptoms vary substantially from day to day, with consecutive UPDRS measurements reported to vary by as much as 15% (Delwaide & Gonce, 1998; Plaha, et al., 2006). To characterize this variability, this work also assessed performance on the dynamic postural control task at the same stimulation amplitude (CDS) on multiple days.

Methods

Subjects. Subjects were recruited as described in chapter 3. Please refer to Table 3.1 for subject characteristics, relative timing of each test session, and LEDD and stimulation parameters at each test session.

Experimental protocol. Please refer to the section titled "Experimental protocol" in chapter 3 for details on the daily protocol for changes in stimulation settings and UPDRS measurements. Briefly, in a given experimental session, subjects performed a series of tests at the CDS settings, the stimulation level was reduced, and then the subjects performed the same set of tests at the reduced amplitude. Each subject completed sessions on three different days to provide measurements at each of three reduced stimulation settings which were approximately 70%, 30%, and 0% of the CDS (MOD, LOW, and OFF, respectively). In addition to the UPDRS assessments described in chapter 3, subjects also participated in a dynamic postural control task twice during each test session, once at CDS settings and next at reduced amplitude stimulation settings.

For the dynamic postural control task, the subject stood on a force platform (Bertec Corp., Columbus, OH) with feet approximately hip-width apart. The subject wore a harness attached to an overhead support (LiteGait, Mobility Research, Inc.). The harness was intended to provide vertical support of the subject's body weight only if the subject were to lose balance. A software program provided real-time visual feedback of the subject's center of pressure (COP) via

a computer monitor placed at the subject's eye level. The trial began with the cursor at the center target, and the subject was instructed to move the cursor to the center of a new target that was presented as quickly and accurately as possible by shifting his weight without actually moving his feet (Figure 7.1). A target was considered to be successfully attained once the subject maintained the cursor within the target boundaries for two seconds. If the subject was unable to successfully attain the target within 10 seconds, a new target was presented.

Twenty targets were presented during each trial, alternating between the center target and one of five outer targets. The outer targets were located at 45° increments relative to the center target, and each was presented twice during each trial in a sequence that was varied across trials (Figure 7.2). Each outer target was equidistant from the center target, and the distance was customized for each subject based on anthropometric measurements and calculated limits of stability. Two trials of the dynamic task were performed at each amplitude condition with rest periods interspersed as needed.

Data analysis. The force platform data were imported into a custom MATLAB program to calculate the subject's COP. The target presentations from the two trials performed at each amplitude condition were combined for a total of 40 target presentations at each amplitude condition. The target presentations were grouped into three categories: (a) attained after one entry into the target area (Single Entry), (b) attained after multiple entries into the target area (Reentry), and (c) never attained (Missed). The missed targets were excluded from further analysis. As depicted in Figure 7.3(A), two phases were designated for all Single Entry targets: the movement phase (presentation of target through entry into target area) and the acquisition phase (entry into target area through attainment of target two seconds later). As depicted in Figure 7.3(B), three phases were designated for all Reentry targets: (a) movement phase (presentation of target through first entry into target area), (b) correction phase (first entry into target area through final entry into target area), and (c) acquisition phase (final entry into target area through attainment of target two seconds later). The peak velocity during each of these phases was calculated. The Single Entry and Reentry categories were also combined to form the Attained category to determine if this grouping resulted in any additional significant differences.

Outcome measures. Outcome measures included the peak velocities of the movement, correction (Reentry targets only), and acquisition phases. Since performance was evaluated at the CDS condition during each test session, each subject had three CDS values for each outcome measure. The variability of each subject's day-to-day performance was quantified by calculating the range of these three values.

Statistical analysis. Statistics were performed using IBM SPSS Statistics software (SPSS Inc, Chicago, IL). For each subject, the peak velocities calculated during each session's CDS amplitude were compared to the values obtained at that same session's reduced amplitude using the Mann-Whitney Test. The two-tailed Wilcoxon signed rank test was used to compare mean differences between outcome measures obtained at CDS and reduced amplitude across all subjects. Performance at the CDS amplitude was treated as a baseline measure to account for day-to-day variations when assessing the effect of the change to a reduced stimulation amplitude.

Results

Comparison across stimulation conditions. Across the group as a whole, the number of target presentations that were grouped into the Single Entry, Reentry, and Missed categories remained consistent across all amplitude conditions (Figure 7.4). For all conditions, the number of Single Entry target presentations was either equal to or slightly larger than the number of Reentry target presentations. The Missed category was consistently small across all conditions, and this category was almost completely composed of target presentations from trials for subjects 5 and 8.

The group as a whole did not experience any statistically significant changes in peak velocities for the Single Entry category of target presentations (Figure 7.5). However, significant changes were experienced at the LOW condition during the movement and correction phases for the Reentry target presentations. The Single Entry and Reentry target presentations were also combined to form the Attained category to determine whether this grouping resulted in additional significant differences. Similar to the Reentry target presentations, a significant change was experienced at the LOW condition during the movement phase. In addition, a significant change was also experienced at the OFF condition during the acquisition phase.

The data were also examined to determine whether the subjects experienced any changes likely to be substantial as amplitude was decreased, since statistically significant differences may not always translate to clinically significant differences. For this analysis, we defined a substantial change as one whose magnitude was > 25% of the performance measured at the CDS condition for that session. Both substantial increases and decreases in velocity were exhibited at the altered conditions compared to the respective session's CDS condition. Figure 7.6 depicts the results for one of the peak velocity measures: Single Entry targets during the movement phase. Note that a greater number of substantial differences were exhibited at the MOD condition compared to either the LOW or OFF conditions, and this same pattern was repeated across the other peak velocity measures as well.

Repeatability at CDS condition. For each peak velocity measure, subjects 1 and 5 consistently demonstrated a larger range of changes at the CDS condition compared to the mean CDS range (Figure 7.7). Other subjects also experienced a large range of CDS changes for some of the peak velocity measures, but none were as consistently high as subjects 1 and 5.

The range of CDS values was also compared with the change experienced when the CDS amplitude was reduced to the MOD, LOW, and OFF conditions. Across all the peak velocity measures, the mean range of CDS values for the group was either similar to or greater than the mean change seen when amplitude was reduced from CDS to any of the altered conditions. The changes from CDS to the LOW condition during the movement and correction phases for the Reentry target presentations were the only ones that were approximately the same as the mean CDS range.

As with the group as a whole, the individual subjects often experienced a greater range of change during the three CDS sessions than they did when amplitude was reduced to an altered condition. However, reducing amplitude induced at least one instance of a greater change in velocity for many of the subjects. When greater changes were experienced at reduced amplitude, they were distributed across the MOD, LOW, and OFF conditions.

Discussion

Based on the number of target presentations that were grouped into the Single Entry, Reentry, and Missed categories, it does not appear that reducing stimulation amplitude affected the subjects' ability to complete the dynamic postural control task. Subjects may actually have been able to better control their velocity at both the MOD and LOW conditions, as there was a small increase in the number of target presentations that were successfully attained after only one entry into the target zone. Even subjects 5 and 8, who were responsible for almost all of the missed target presentations, did not experience a great change in the number of targets they missed at the CDS condition compared to the reduced conditions (subject 5: 8 and 11 missed at CDS and altered, respectively; subject 8: 22 and 23 missed at CDS and altered, respectively).

Reducing stimulation amplitude also did not appear to consistently affect the peak velocity with which any of the phases were completed. Regardless of how the target presentations were grouped, very few statistical changes were experienced by the cohort. Of the four that were demonstrated, three occurred when amplitude was reduced to the LOW condition and only one when amplitude was reduced to the OFF condition, supporting the notion that performance does not always incrementally improve or degrade along the continuum of stimulation amplitude. As with other postural control research in people with PD, the statistically significant differences were decreases in velocity, rather than increases (Horak, et al., 1992; Mancini, et al., 2012). Although this is typically viewed as a sign of decreased postural control capabilities, it's difficult to determine whether decreased velocity corresponded to an improvement or degradation in performance for the current task. Increased sway velocity, or the ability to quickly manipulate the COP, is often viewed positively, since it may indicate decreased response time to a postural perturbation. However, increased velocity may have actually been detrimental to performing the current task and may be the reason why subjects moved into and out of the target zone before they were able to maintain their COP within the boundaries of the target.

Further supporting the idea that performance may be most affected by an intermediate stimulation amplitude, more subjects experienced substantial changes in peak velocity when

amplitude was reduced to the MOD condition than to either the LOW or OFF conditions. This pattern was demonstrated across all peak velocity measures, regardless of the phase. The inconsistent results demonstrated with reduced amplitude may indicate that DBS does not have a predictable effect on dynamic postural control, or it may indicate that the task chosen is not appropriate or not sensitive enough to detect changes experienced in postural control. Regardless, it emphasizes the importance of carefully selecting the tasks that are used to determine DBS stimulation parameters to ensure that all important symptoms are assessed.

In general, the group demonstrated decreased velocity as stimulation amplitude was reduced, but it not clear whether that corresponded to improved or degraded performance. Overall, performance on this task did not appear to be greatly affected by reducing stimulation amplitude. There was consistently greater variability in performance measured at the CDS condition than when amplitude was reduced to any of the altered amplitude conditions. This variability suggests that repeated evaluation of DBS parameters may be necessary to confidently choose the optimal combination for any one individual.

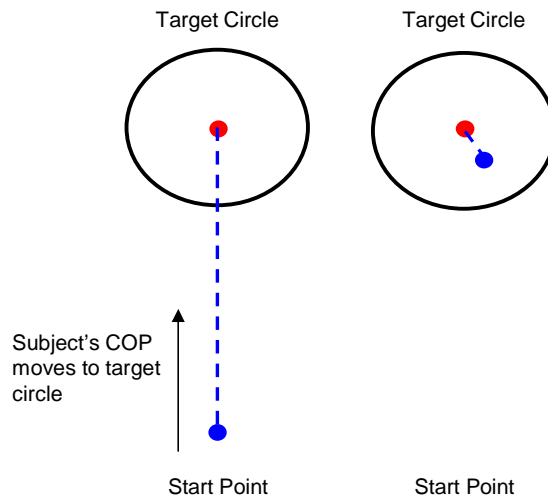


Figure 7.1. Target presentation and COP visual feedback.

Notes: The blue dot indicates the subject's COP, and the red dot indicates the center of the target.

Abbreviation: COP, center of pressure.

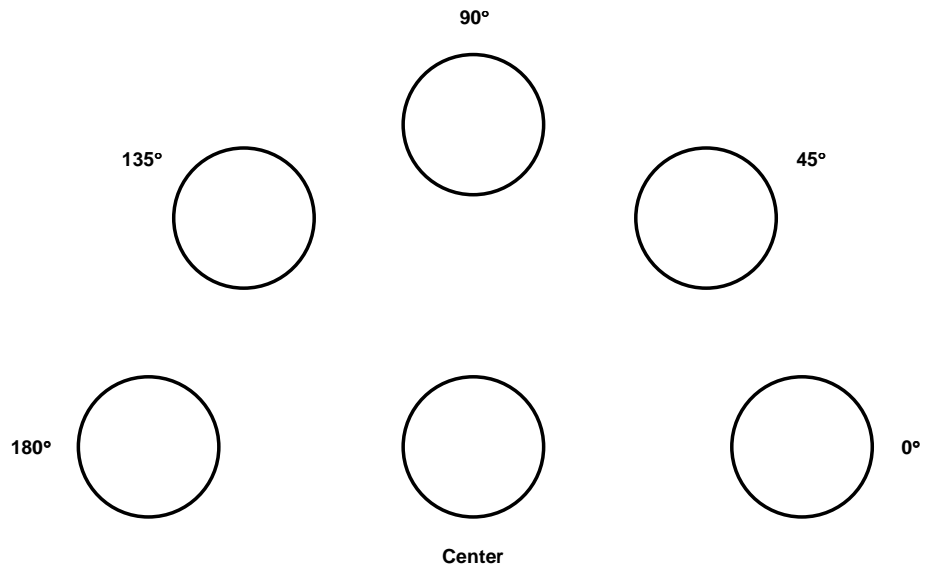


Figure 7.2. Locations of outer targets relative to center target.

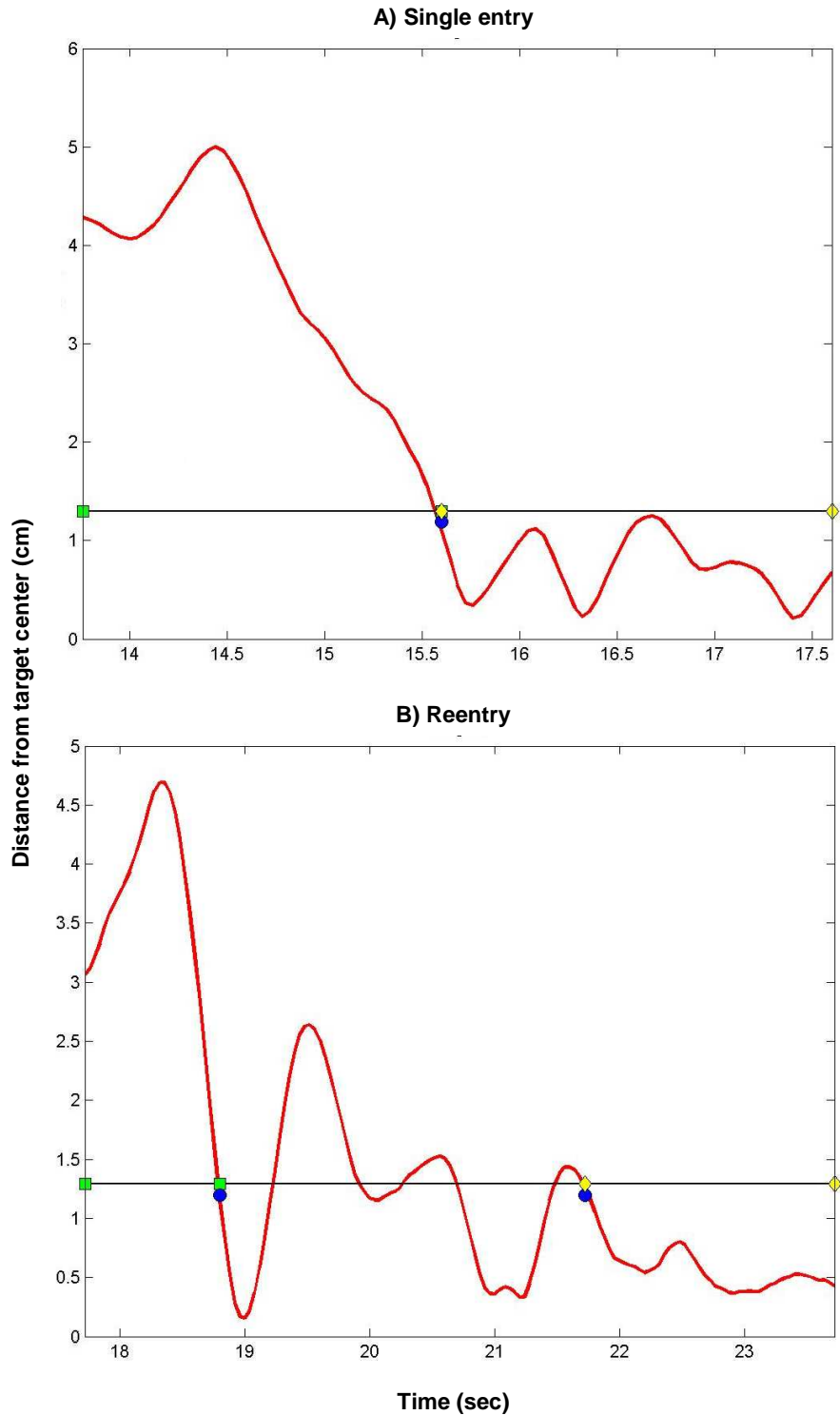


Figure 7.3. Examples of a subject's path to the presented target: **(A)** Single entry and **(B)** Reentry for subject 1 at the LOW condition.

Notes: The green squares mark the beginning and end of the movement phase, the blue circles mark the beginning and end of the correction phase, and the yellow diamonds mark the beginning and end of the acquisition phase.

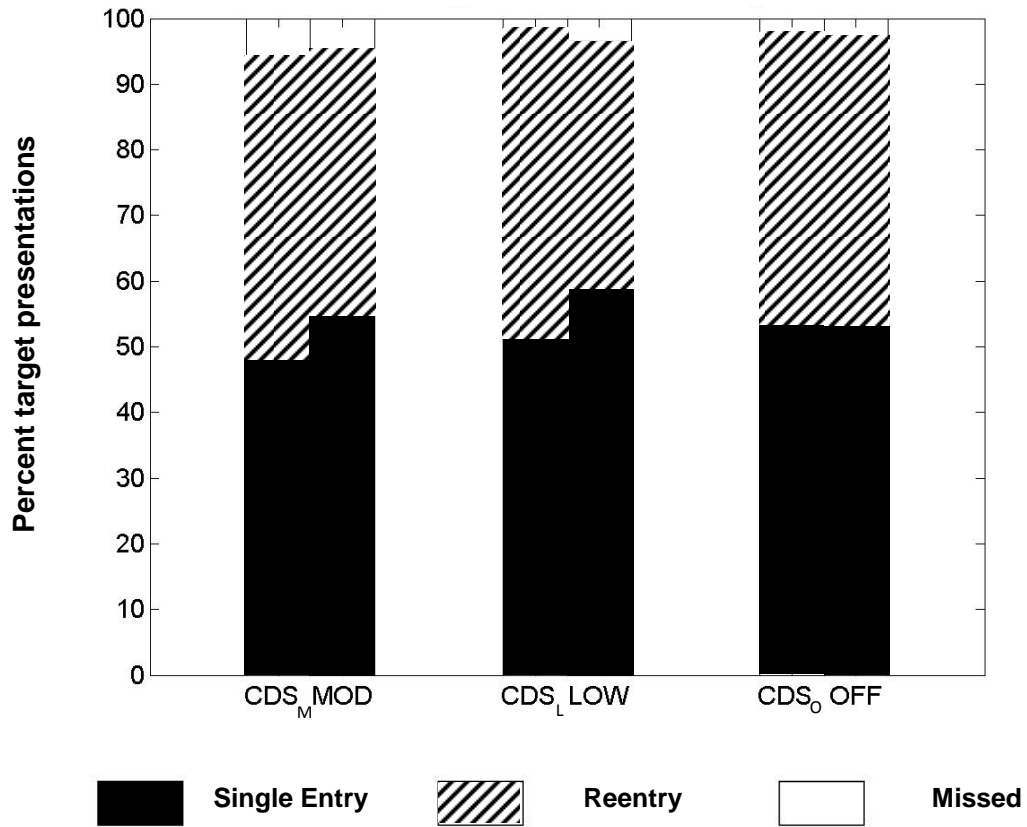


Figure 7.4. Percent target presentations categorized as Single Entry, Reentry, and Missed for each amplitude level.

Notes: n = 320 for each condition: 8 subjects, 40 target presentations.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

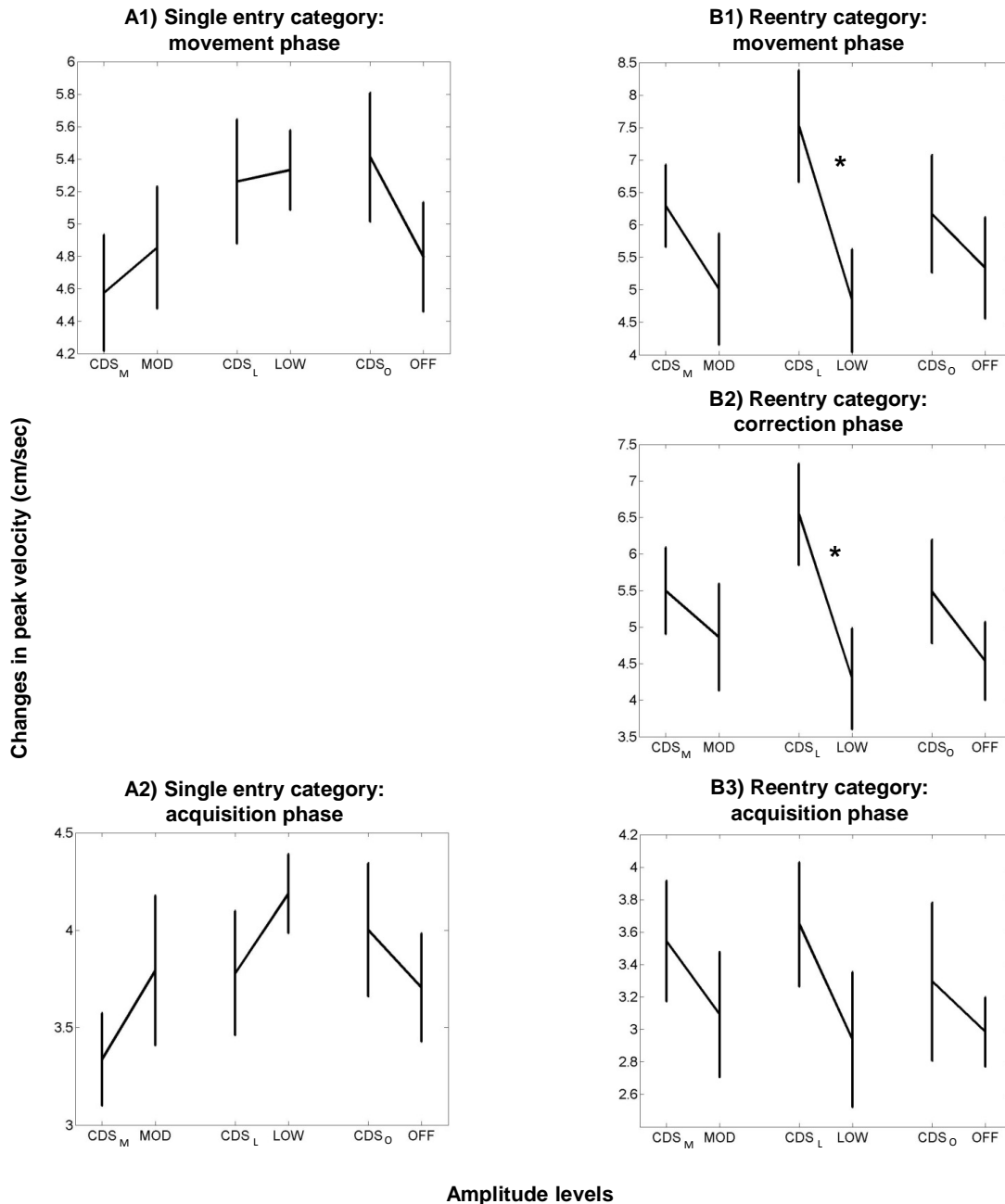


Figure 7.5. Changes in mean (\pm standard error of the mean) peak velocity from the CDS condition to each reduced amplitude level. **(A1)** Single entry category: movement phase, **(A2)** Single entry category: acquisition phase, **(B1)** Reentry category: movement phase, **(B2)** Reentry category: correction phase, and **(B3)** Reentry category: acquisition phase.

Notes: For **(A1)** and **(A2)**, $n = 8$ subjects for each session. For **(B1)**, $n = 7, 8,$ and 6 subjects for the MOD, LOW, and OFF sessions, respectively. For **(B2)** and **(B3)**, $n = 8, 8,$ and 7 subjects for the MOD, LOW, and OFF sessions, respectively. Subject 4 was excluded from **(B1-B3)** category OFF sessions due to a low number of Reentry target presentations in the CDS condition, and subject 8 was excluded as an outlier from the **(B1)** MOD and OFF sessions. *Indicates changes in mean that were significant.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

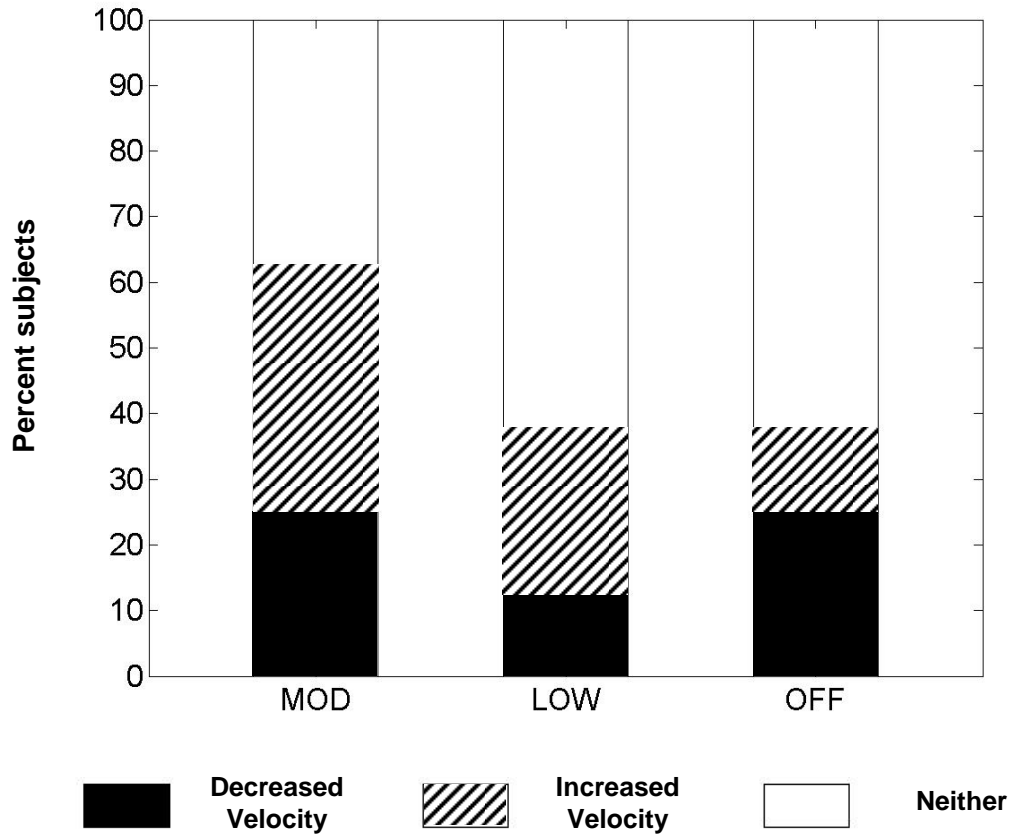


Figure 7.6. Percent subjects who experienced a substantial decrease, a substantial increase, or a change that was not substantial at the MOD, LOW, and OFF conditions for peak velocity in the movement phase (Single Entry target presentations only).

Notes: n = 8 subjects for each condition.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

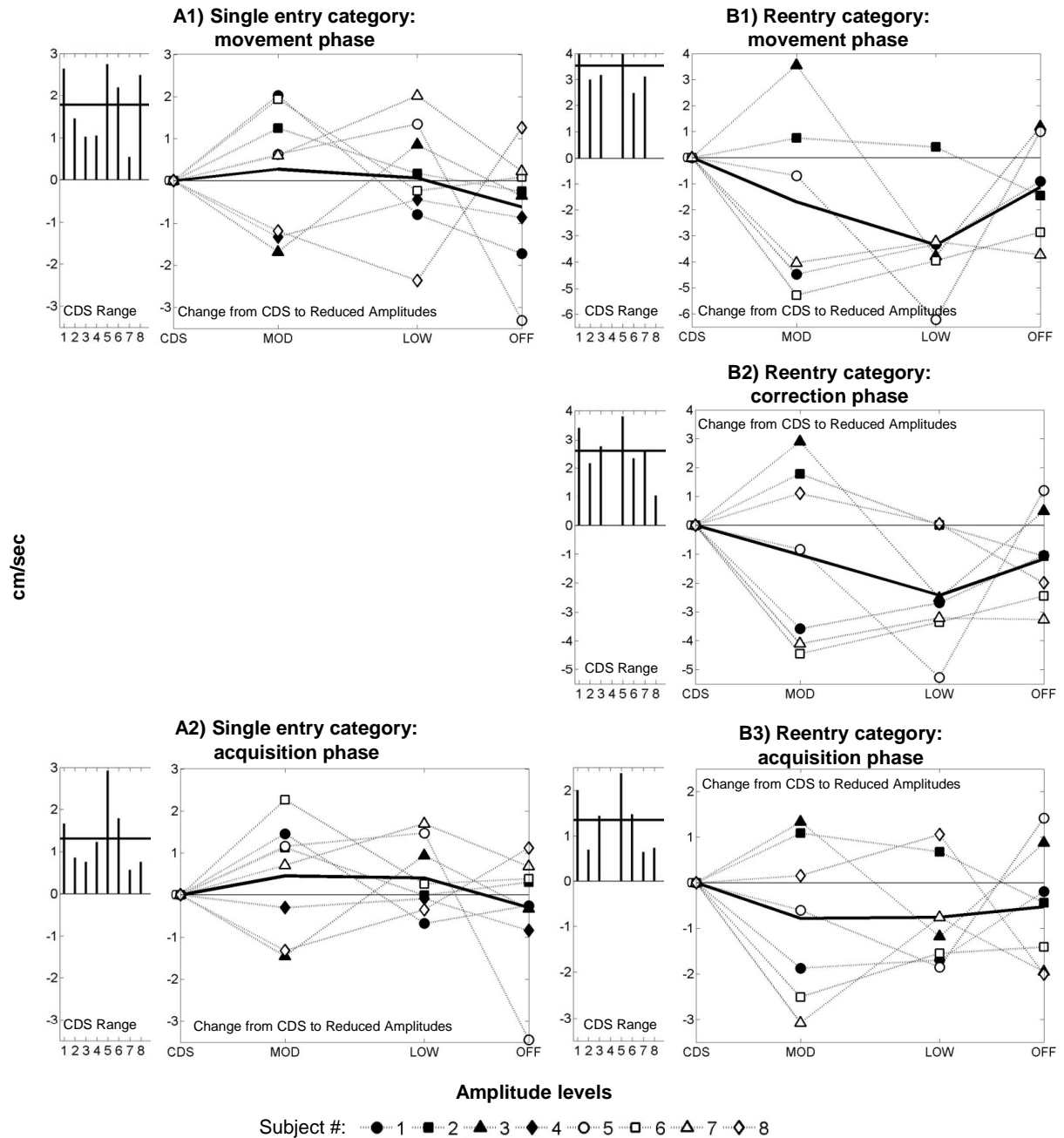


Figure 7.7. Day-to-day CDS variability compared to change in peak velocity from CDS to each reduced amplitude level.

Left side of each lettered subplot represents each subject's range of CDS values over the three sessions for (A1) single entry category: movement phase, (A2) single entry category: acquisition phase, (B1) reentry category: movement phase, (B2) reentry category: correction phase, and (B3) reentry category: acquisition phase. The horizontal line represents the mean, while the vertical bars represent each individual subject. Right side of each lettered subplot represents change in peak velocity from CDS to each reduced amplitude for (A1-B3). The black line represents the mean, while the gray lines represent each individual subject. Please refer to Figure 7.5 for the n values for each subplot.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively.

CHAPTER 8

CONCLUSIONS

The purpose of this research was to characterize the effects of changing DBS amplitude on multiple aspects of motor performance in people with PD. This work demonstrated that motor performance as assessed by the UPDRS-III score and quantitative measures was affected by altering stimulation amplitude, but it also demonstrated high inter- and intra-subject variability across all tasks.

In numerous instances across the battery of tasks, the mean performance of the cohort differed statistically at the LOW and OFF conditions compared to CDS, but there were very few instances when there was a statistical difference between performance at the MOD condition compared to CDS. With few exceptions, the group exhibited degraded performance as amplitude was reduced, and the response across conditions was typically graded. Even though the group's responses were very similar regardless of task, individual subjects' responses varied greatly. Most subjects demonstrated all three responses – graded, threshold, and minimal – depending on the task being assessed. For several tasks, a subset of subjects exhibited improved performance at one or more of the reduced conditions (Figure 8.1). However, these instances of improved performance occurred to a lesser degree as amplitude was reduced, while instances of degraded performance occurred to a greater degree as amplitude was reduced. In addition, the number of changes that were not substantial decreased as amplitude was reduced.

For both the group and the individuals, the variability in CDS performance across the three testing sessions was often substantial, sometimes exceeding the change induced by reducing stimulation. Although there were multiple examples of CDS variability exceeding the change exhibited at every reduced condition, it occurred most often for the MOD condition.

This research demonstrated that the mean response of a group of individuals with PD may be very different from the individual responses. For this cohort, the mean response was not representative of each subject's individual response, or even of the majority of the subjects. The variability seen in subjects' responses may indicate that they would also benefit from a varied approach to DBS programming. Understanding an individual's response to amplitude changes

could provide advance insight into whether continued iterative adjustments are likely to be beneficial, or whether a threshold will be reached, i.e., continued adjustments will yield little appreciable difference. Adapting programming procedures could thus increase their efficiency.

Currently available non-rechargeable neurostimulator batteries have a typical battery life of 3-6 years (Activa SC and PC), while the rechargeable Activa RC has a typical lifespan of 9 years (Medtronic Inc., Minneapolis, MN) ("Activa RC Neurostimulator: Features and Specifications," ; "Getting a Replacement - DBS Therapy, "). Since patients with abnormally high settings may require battery replacement sooner than the average times listed above, it may benefit patients who exhibit a threshold response to choose the amplitude setting just above their threshold amplitude.

The inter-subject variability demonstrated by this research may point to differences in the location of each subject's active contacts. There are contradictory findings regarding optimal contact location, with some work identifying the Fields of Forel as the best location and others indicating that the STN itself is the best location (Herzog, et al., 2004; Saint-Cyr, et al., 2002; Voges, et al., 2002). The intra-subject variability may indicate differences in the neural structures that were affected as stimulation amplitude was decreased. As indicated in Figure 8.2, many subjects demonstrated different behaviors across the battery of motor tasks as amplitude was decreased. For some tasks, subjects demonstrated a graded decrease in performance. This response could indicate that even the smallest sphere of stimulation generated at the LOW amplitude level still activated target structures, although not as strongly as when amplitude was at a greater value. For other tasks, no substantial difference was induced by any of the reduced amplitude levels. This may indicate that the target structures for that particular task were not stimulated at any amplitude level, even CDS.

As mentioned previously, subjects demonstrated improved performance on certain tasks as amplitude was decreased. This may actually mean that a smaller sphere of stimulation prevented the activation of neural structures that induced side effects that were counter-productive to performing the motor task. For some tasks, amplitude was reduced below the MOD amplitude level before any substantial difference was induced. This threshold response could

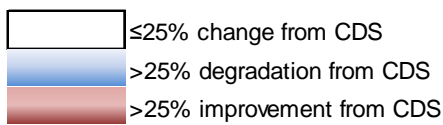
indicate that the sphere of stimulation induced at MOD activated essentially the same target structures as CDS, whereas the sphere induced at LOW and OFF was not adequate to activate these structures to the same degree.

Not every finding generated by this research has immediate implications, but certain aspects can be readily applied to current programming practices. Due to the varied responses of symptoms to changes in stimulation, this work cautions against setting DBS parameters based on the response of a single symptom. Accounting for multiple symptoms will enable stimulation to be optimized across symptoms. This work also cautions against choosing parameters because they produced a positive result during one session. As demonstrated repeatedly by this research, day-to-day variability may exceed the difference in performance experienced at two amplitudes. DBS programming procedures should be expanded to include assessment of multiple symptoms and repeated evaluation of parameter combinations. Although this could increase the length of programming sessions, the time commitment may be offset by the increased efficiency introduced by prospectively understanding individual responses to reduced stimulation.

In addition to applying the concepts discussed above, the results of this work could be confirmed with a larger cohort to see if subsets again emerged demonstrating graded, threshold, and minimal responses. Evaluation of a larger cohort could also provide insight into the underlying reasons for the different responses, e.g., electrode location, PD severity, or the primary symptoms manifested in each individual. Expanding the work to incorporate alteration of the active contacts in addition to amplitude could provide greater detail into understanding optimal electrode location.

Another benefit of performing a similar study with a larger group of subjects would be to confirm the ability of the quantitative measures to detect differences in performance at different amplitude conditions. Although some measures would need to be revised in order to be feasible in a clinical setting, i.e., require only readily-available equipment, quantitative measures may be a valuable supplement to the UPDRS assessments that are currently used in standard DBS programming procedures.

Reducing stimulation did not affect all subjects equally, nor did it uniformly affect each subject's performance across tasks resulting in mean responses that were not representative of individual subjects. The inter-subject variability may point to differences in the location of each subject's active contacts, and the intra-subject variability may indicate differences in the neural structures that were affected as stimulation amplitude was decreased. These results support the importance of recent advances in DBS technology that give the user the flexibility to choose from multiple programs depending on which aspect of motor performance they would like to optimize at a given time.

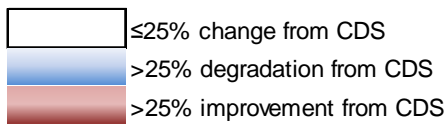


		Total UPDRS-III	Tremor Intensity - R	Inter-tap Variability - Fast	Gait - SD1	Max Movement Velocity - First Try	Elbow Peak Velocity - R	Hip Peak Velocity - R	
MOD	1			-89.1	33.8	-54.8			
	2	95		194	61.1	-27.5			
	3							-35.4	
	4	35	26.5	141.2		29.9	29.8	26.5	
	5			34					
	6	30					-55.2		
	7	95		-66.8	110.8		42.7		
	8		55.6	-66.4	60.9	26.8		32.6	
LOW	1	120	544.1	52.9	34.9		36.8	27.7	
	2	80	54.3	31			27.3		
	3	30		--	-42.4				
	4	45		--	30.8		48.8	45.1	
	5	35		34.2			-32.8		
	6	65		32.8			36.3	35.6	
	7	160	92	563.9			-62.1	77.1	83.6
	8			--		34.1			
OFF	1	140	729.4	360.7	294.3	27.1	44.6	59.5	
	2	115	32.8	--	133.8		30.5		
	3	85			-29.4				
	4	65	181.3		34.1		36.7	67.4	
	5			--	37.4	48.1		-59.6	
	6	125		105.2					
	7	295	4428		254.4		79.1	72.3	
	8		-26.3		38.4	-25.7		44.6	

Figure 8.1. Substantial differences in performance of multiple tasks grouped by amplitude condition.

A substantial difference was defined as a change in performance from CDS to a reduced amplitude that was $\geq 25\%$ of the value at CDS. Blue shading indicates substantial degradations in performance, while red indicates substantial improvements in performance. The degree of shading indicates the magnitude of the substantial difference. One representative outcome measure obtained from every motor task performed is listed in order to compare across motor tasks.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively; SD1, Poincaré plot descriptor; R, right.



		Total UPDRS-III	Tremor Intensity - R	Inter-tap Variability - Fast	Gait - SD1	Max Movement Velocity - First Try	Elbow Peak Velocity - R	Hip Peak Velocity - R
1	MOD			-89.1	33.8	-54.8		
	LOW	120	544.1	52.9	34.9		36.8	27.7
	OFF	140	729.4	360.7	294.3	27.1	44.6	59.5
2	MOD	95		194	61.1	-27.5		
	LOW	80	54.3	31			27.3	
	OFF	115	32.8	--	133.8		30.5	
3	MOD							-35.4
	LOW	30		--	-42.4			
	OFF	85			-29.4			
4	MOD	35	26.5	141.2		29.9	29.8	26.5
	LOW	45		--	30.8		48.8	45.1
	OFF	65	181.3		34.1		36.7	67.4
5	MOD			34				
	LOW	35		34.2		-32.8		
	OFF			--	37.4	48.1		-59.6
6	MOD	30				-55.2		
	LOW	65		32.8			36.3	35.6
	OFF	125		105.2				
7	MOD	95		-66.8	110.8		42.7	
	LOW	160	92	563.9		-62.1	77.1	83.6
	OFF	295	4428		254.4		79.1	72.3
8	MOD		55.6	-66.4	60.9	26.8		32.6
	LOW			--		34.1		
	OFF		-26.3		38.4	-25.7		44.6

Figure 8.2. Substantial differences in performance of multiple tasks grouped by subject. A substantial difference was defined as a change in performance from CDS to a reduced amplitude that was $\leq 25\%$ of the value at CDS. Blue shading indicates substantial degradations in performance, while red indicates substantial improvements in performance. The degree of shading indicates the magnitude of the substantial difference. One representative outcome measure obtained from every motor task performed is listed in order to compare across motor tasks.

Abbreviations: CDS, clinically determined stimulation; MOD, LOW, and OFF, approximately 70%, 30%, and 0% of CDS respectively; SD1, Poincaré plot descriptor; R, right.

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IRB APPROVAL LETTER



September 20, 2006

James Abbas, PhD
Attn: Helen Salisbury
Banner Good Samaritan Medical Center
Rehabilitation Institute
1111 E. McDowell Road
Phoenix, AZ 85006

RE: **BHRI # 04-0077-01 Effects of Deep Brain Stimulation on Locomotion Control in Parkinson's Disease**
iRIS submission reference: 001776
IRB Review and Approval – Revised Protocol (dated 8/17/06) including Study Title change,
Revised Data Collection Forms, Revised Informed Consent (dated 8/17/06), Revised Pamphlet
(dated 8/17/06)

Dear Dr. Abbas:

This letter serves to notify you that the revised Protocol, Data Collection Forms, Informed Consent and Pamphlet for the above referenced study were reviewed and approved by the Banner Health Institutional Review Board (BGSMC Panel) on September 14, 2006. A copy of this letter will be placed in the study file.

Thank you for your continued participation in research at Banner Health. If you have any questions, please contact Jane Hoverson, IRB Coordinator, at (602) 747-9735.

Sincerely,

Signature applied by Joseph J. Frank on 09/21/2006 05:20:14 PM

A handwritten signature in black ink that reads "Joseph J. Frank".

Joseph Frank, PhD, Chairman
Banner Health IRB (BGSMC Panel)

JF/jh

Enc: Stamped Informed Consent

APPENDIX B

APPROVAL TO USE PUBLISHED ARTICLE

All co-authors of the following published article have granted their permission to include it as

Chapter 3 of this dissertation:

Conovaloff A, Krishnamurthi N, Mahant P, Samanta J, Abbas J. Effects of deep brain stimulation amplitude on motor performance in Parkinson's disease. *J Parkinsonism RLS* 2012; 2: 73-83.

BIOGRAPHICAL SKETCH

A native of Phoenix, Arizona, Alison graduated from Valley Christian High School in 1997. She began the Bioengineering undergraduate program at Arizona State University later that fall, graduating Magna Cum Laude in May 2001. Alison remained at ASU and earned her Master of Science in Bioengineering in August 2003. Her project was titled "Development of an Inexpensive Upper-Extremity Prosthesis for Use in Developing Countries" and was completed under the direction of Gary Yamaguchi, PhD. Originally planning to further develop her work on the prosthetic arm project, Alison began her doctoral studies, also at ASU. However, Dr. Yamaguchi's departure from ASU caused her to change paths and embark on her current project under the direction of James Abbas, PhD. Having successfully completed her coursework and prospectus, Alison entered the field of clinical research in August 2008. She currently manages several endovascular graft clinical studies for Cook Medical. Alison is excited to have reached the end of her graduate studies and looks forward to spending more time with her husband and family.