EFFECTS OF TACTILE CUEING ON FUNCTIONAL MOVEMENT MODULATION IN PARKINSON'S DISEASE

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A Dissertation

Presented to

The Faculty of the Department

Of Health and Human Performance

University of Houston

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In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

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By

Vladimir Ivkovic

December, 2012

EFFECTS OF TACTILE CUEING ON FUNCTIONAL MOVEMENT MODULATION

IN PARKINSON'S DISEASE

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ABSTRACT

Parkinson Disease (PD) is the second most prevalent neurodegenerative disorder in the United States. The symptoms include decreased movement automaticity, greater reliance on external sensory cues and attention-dependent (executive) motor control. Visual and auditory cueing have been shown to transiently improve motor-cognitive performance in PD patients. However audiovisual processing shares many cognitive resources used for attention-dependent situational awareness. Conversely, tactile cues are processed faster, with minimal attentional demand, and may be more efficient means for modulating motor-cognitive performance.

To date, no studies systematically investigated the efficacy and limitations of tactile cueing (TC) in modulating motor-cognitive performance in PD and healthy individuals. The objectives of this study were to investigate the efficacy and characterize the functional limitations of TC in: (1) modulating simple (heel tapping) and complex (straight line walking) motor tasks over a range of cueing intervals; (2) improving gait performance; (3) improving motor-cognitive performance on complex functional gait tasks (walking and turning while carrying tray with cups of water).

The study was performed on 10 PD patients (71 ± 9 years) and 10 healthy individuals (69 ± 7 years). TC was delivered through a smart phone controlled by a custom-developed application. The results indicate that (1) PD patients and healthy individuals were able to use TC to effectively modulate performance on simple (seated heel tapping) and complex (straight line walking) motor tasks; (2) increase in task complexity and decrease in TC intervals reduce synchronized motor performance accuracy – PD patients are able to modulate performance at a

narrower range of cueing intervals than healthy individuals; (3) TC improves PD patients' turn cadence and turn times in dual tasks; (4) PD patients use TC opportunistically when their motor-cognitive resources are highly challenged (turning while carrying a tray with cups of water); (5) TC is a useful method for improving motor-cognitive integration for PD patients performing challenging tasks.

This study provides novel insight about the role of TC in PD movement modulation and the mechanisms of motor-cognitive integration in PD patient population. The custom-developed TC smart phone application was validated and represents a new addition in the repertoire of available walking aids.

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None of this would have been possible without the unconditional love and support of my entire family – Carmen, Eli, Dragor, Suzi, Petra, Samir, Lana, Sven, and especially my mom Vesna, late granddad Augustin, dad Branko, and Aja – you are with me always.

I am thankful to all my dear friends for sticking with me through thick and thin – Igor, Laki, Lo, Janus, Alma, Mary, Nina, Nikica, Niksa, Minda, Frane, Peki, Zaki, Zac, Maja, Dajana, Botis, Katey, Chiaki, Laura, Lance, Colleen, Sheryl, Mark, Shanna, Guillaume S., Marius, Gordon, Julie, Ashley, Guillaume D., Rolf, Eylem, Stacy, Billy, …

For the time we spent together, the calls we responded to, and for all those we have yet to respond – I am most proud of my brothers and sisters firefighters and first responders of the Nassau Bay Fire Department and Nassau Bay Emergency Medical Services – we will continue to run in when all others run out.

My deepest gratitude goes to Bill Paloski – an advisor, a friend and a model scientist – for being there, for pushing me when I needed to be pushed, and supporting me when I needed the support… and for brewing the Bird Brain Ale.

Special thanks go to Martin Castaneda, Stanley Fisher, Tom Krouskop, Adam Paloski, Angie Robertson, Nirja Shah, Ankur Sharma, Pallavi Sharma, Cheri Triplett, and the members of my dissertation committee for their invaluable help in designing and conducting these studies.

If you wish to understand the secrets of the Universe,
think of energy, frequency and vibration.

Nikola Tesla

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CHAPTER I

Introduction

Parkinson Disease (PD) ranks as the second most prevalent neurodegenerative disease in the United States (NINDS 2004) and affects more than 4 million people worldwide (Dorsey et al. 2007). PD is characterized by motor and cognitive decrements caused by the progressive loss of dopaminergic neurons in substantia nigra, and consequently, in the basal nuclei (BN), resulting in decreased movement automaticity, increased reliance on external sensory inputs for movement timing, and a shift towards prefrontally-mediated, executively-driven motor control.

These changes induce gait difficulties and increase the risk of falls and related injuries. Due to its progressive nature, PD symptoms are exacerbated over the course of the disease. While no cure exists today, pharmacological treatments offer relief of motor and cognitive symptoms; but, they come at a cost of physical, cognitive, and emotional side effects and addiction to medication. External visual and auditory cueing has been shown to transiently improve PD gait and motor-cognitive integration (Baker et al. 2007, 2008; Hausdorff et al. 2007; Howe et al. 2003; Morris et al. 1994, 1996; Rochester et al. 2005). However, application of audiovisual cues increases the burden on executive control and attention, since both sensory modalities are central to maintaining spatial orientation and situational awareness (Azulay et al. 2006; Malapani et al. 1994).

Cueing via alternate sensory modalities that are not central to maintaining spatial orientation and situational awareness may improve PD symptoms without

the burden on executive control and attention. Tactile cueing (TC) is a modality that has shown promise (Nieuwboer et al. 2007, 2009a; Rochester et al. 2007, 2010; van Wegen et al. 2006), but has not been extensively explored. Thus, the focus of this dissertation was to explore the efficacy and effectiveness of TC in movement modulation and expand understanding of the underlying neurocognitive mechanisms relating PD-induced changes in basal nuclei to reorganization of motor-cognitive integration.

1.1 MOTIVATION

Current models of PD neuropathology (e.g. Redgrave et al. 2010) suggest that dysfunctional dopaminergic input into BN causes dysfunctional posterior BN output. Since posterior BN mediate timing of motor activity (Freeman et al. 1993; Merchant et al. 2008; Rodriguez-Oroz et al. 2009), their dysfunctional output results in decreased motor automaticity, festination, or slowness of movement, and reliance on executive control for motor-cognitive integration (Dubuois & Pillon 2002; Hallet 2008; Jones et al. 2008, 2011; Jahanshahi et al. 2010). The progressive deterioration of BN function causes a reorganization of motor-cognitive processing away from BN-mediated automatic processing (via the lateral system), and towards pre-frontally-mediated, goal –directed, executively-driven processing (via the ventromedial system; Georgiou et al. 1993; Hallet 2008).

The shift in motor-cognitive integration impairs motor performance, and increases the burden on executive control which translates to slower attention shifting, longer processing times, and ultimately results in higher incidence of falls and fall related injuries (Bloem et al. 2001; Keus et al. 2007; Niino et al. 2000). In this

dissertation, changes in motor-cognitive integration refer to changes in motor performance characteristics when the primary motor task (e.g. heel tapping or walking) is performed with or without a secondary motor task (e.g. holding / carrying a tray with cups of water), or is compounded by additional performance demands (e.g. turning around obstacles) – all of which require increased executive control and attention allocation.

One of the most widely used research paradigms for studying timing of motor performance and motor-cognitive integration is the synchronization paradigm (Wing & Kristofferson 1973a, b) wherein the subject synchronizes a repetitive activity (e.g. finger tapping) to external sensory stimuli (e.g. auditory cues). The paradigm tests the ability to entrain neuromotor responses to external stimuli and the functionality of participant's internal timing mechanisms for maintenance of rhythmic performance; it has been used in seminal studies (e.g. Freeman et al. 1993; Harrington et al. 1998; etc.) that demonstrated impairments of motor timing in PD patients with dysfunctional BN.

While a number of studies investigated the effects of sensory (auditory) cueing on timing synchronization of simple finger tapping tasks (e.g. Ivry & Hazeltine 1995), only one study (Chen et al. 2006) compared the synchronized performance of simple heel tapping and more complex stepping-in-place tasks in healthy individuals. However, no randomized controlled TC synchronization studies comparing simple lower limb motor tasks (e.g. heel tapping) to more complex walking tasks have been reported in healthy, nor in PD patients. Since lower limb motor control and integration into gait directly translate to control of gait and posture – and unlike simple tapping, likely also involve sub-pyramidal spinal central pattern generation

(Dobkin 2003) – understanding the lower-limb motor control and responses to TC in healthy and PD patients may provide unprecedented insight into TC efficacy and mechanisms of healthy and PD-impaired sensorimotor integration. Therefore, one of the aims of this study was to investigate the ability of healthy individuals and PD patients to synchronize simple heel tapping and complex gait tasks to TC delivered at a range of tactile cueing intervals (TCI) above and below the comfortable stepping interval (CSI).

Previously reported studies on external visual and auditory cueing indicated promising effects on short-term improvement of motor symptoms. Auditory and visual cues were demonstrated to modulate spatial and temporal gait parameters, resulting in increased gait speed, cadence and step length, decreased turn times, and reduced freezing of gait (FOG) episodes (Baker et al. 2007, 2008; Hausdorff et al. 2007; Howe et al. 2003; Morris et al. 1994, 1996; Nieuwboer et al. 2007; Nieuwboer et al. 2009a; Rochester et al. 2005, 2009, 2010; Willems et al. 2006). While some studies (e.g. Willems et al. 2006) report increased step length with longer cueing intervals and slower cadence, others (e.g. Hausdorff et al. 2007) report decreased step length and variability – possibly due to reliance on mechanics of leg swings – with shorter cueing intervals.

As reported by Willems et al. (2006), changes in gait parameters diminish at cueing intervals below and above ±10% of the comfortable stepping intervals, indicating breakdown of motor-cognitive integration beyond these intervals. As TC provides temporal cues, one of the objectives of this dissertation is to resolve this confusion in the literature by examining the limits of PD patients' abilities to tap

their foot and walk in synchrony with a range of cueing intervals above and below their comfortable stepping intervals (CSI).

Auditory and visual cues have also been shown to facilitate motor-cognitive integration on dual gait tasks by improving temporal and spatial gait parameters during performance of secondary motor-cognitive tasks (Nieuwboer et al. 2009a; Rochester et al. 2010). Since external sensory cues are thought to be processed by the ventromedial system (Elsinger et al. 2006; Redgrave et al. 2010), they may (i) relieve the executive control burden on the prefrontal areas, (ii) increase neuromotor control of posture and gait, and (iii) reduce the risk of falls and fall related injuries.

The improvements associated with auditory and visual cueing in gait performance with secondary motor-cognitive tasks appear to be highly dependent on the amount of attention allocated to cue entrainment (Morris et al. 1994, 1996; Nieuwboer et al. 2009a). However, allocating attention to sensory cueing could interfere with the use of sensory modalities for other purposes – e.g. spatial orientation and situational awareness – which could additionally burden the executive control resources. Furthermore, as progressive reliance on executive control for simple motor tasks diminishes the PD patients' ability to provide adequate motor-cognitive responses to challenging situations – such as attention shifting to maintain situational awareness or adequate reaction times (Dobkin 2003) – any benefits of audiovisual cues may be short-lived and only effective in patients at earlier stages of the disease.

On the other hand, tactile sensory inputs enable extremely rapid (~85ms) postural stabilization and reestablishment of spatial orientation after exposure to

destabilizing or disorienting visual, vestibular, and proprioceptive stimuli (Lackner & DiZio 2005). Contribution of tactile sensory modality to spatial orientation overrides the otherwise dominant visual (Rabin et al. 2004, 2008) and proprioceptive (Lackner et al. 2000) inputs, and is processed subconsciously (Johansson & Westling 1984) at approximately three times the speed of visual processing (Rabin et al. 2006). Thus, tactile sensory modality seems to play the primarily corrective role for spatial orientation and situational awareness, and as such, unlike the orientation-dominant visual inputs, requires virtually no cognitive processing.

To date, however, only a few studies (van Wegen et al. 2006; Nieuwboer et al. 2007, 2009a; Rochester et al. 2007, 2010) have investigated the efficacy of tactile cueing in modulating gait performance or motor-cognitive integration in PD. Van Wegen et al. (2006) found that provision of rhythmic vibrotactile cues reduced cadence and increased step length in PD patients walking on a treadmill, Nieuwboer et al. (2007) demonstrated that three-week in-home TC training increases gait speed, step length and reduces freezing of gait, and later (Nieuwboer et al. 2009) TC improved the speed of functional turns. Finally, Rochester et al. (2007; 2010) found that tactile cueing increased walking speed and step length during performance of single and dual motor tasks.

Although the results of these studies suggest that TC modulates spatial and temporal gait parameters, and results in improved gait performance, the methodologies in these studies were inconsistent, none of the studies involved healthy control participants, and none of the overground studies explored effects of different cueing intervals which may reflect differential ability to organize adequate neuromotor output within longer or shorter performance intervals as required by

the particular task. Thus, the objectives of this dissertation are to investigate the efficacy and effectiveness of TC for movement modulation in PD patients performing increasingly complex motor-cognitive tasks, over a range of cueing intervals, as well as TC-modulated motor performance differences between healthy and PD patients.

1.2 Problem Statement

Despite limited evidence of TC efficacy for movement modulation and motor-cognitive integration in PD (van Wegen et al. 2006; Nieuwboer et al. 2009a; Rochester et al. 2007, 2010), no studies have systematically investigated its functional benefits and limitations. As a result, there remain knowledge gaps that lead to the principal research questions addressed by this dissertation:

Question #1: How well can PD patients use TC to modulate performance of simple motor task (seated heel tapping) over a range of cueing intervals?

Question #2: How well can PD patients use TC to modulate performance of complex motor tasks (straight line walking) over a range of cueing intervals?

Question #3: How well can PD patients use TC to modulate highly complex motor tasks (straight line walking and turning) over a range of cueing intervals?

Question #4: To what extent does a secondary motor task (carrying tray with two cups of water) interfere with the ability of PD patients to use TC to modulate increasingly complex motor tasks (seated heel tapping, straight line walking, and turning corners) over a range of cueing intervals?

1.3 Research Objectives

Three research objectives were developed to address the stated questions, and three experiments were conducted to accomplish the three objectives. The participants were 10 patients (aged 71.08 ± 8.16 years) with moderate PD (Hoehn-Yahr motor disability score 2.8 ± 0.48) and high level of cognitive function (Mini Mental State Exam score 29.05 ± 1.09), and 10 sex-, age- (69.27 ± 7.42 years) and activity-matched healthy individuals (MMSE 30.0 ± 0). In order to characterize TC modulation effects on motor performance, TC was delivered at a range of cueing intervals above and below their comfortable stepping interval (CSI).

In Experiment #1 – designed to answer Questions #1 and #4 – TC efficacy in modulating temporal parameter – inter tap intervals (ITI) – were investigated in a seated heel tapping task with and without TC delivered at a range of cueing intervals above and below the comfortable stepping interval (CSI; Objective #1). Each trial consisted of three continuously executed phases: (1) Pre-synchronization (30 heel taps; TC OFF); (2) synchronization (30 heel taps, TC ON); (3) continuation (30 heel taps, TC OFF). Data were analyzed only from synchronization phase as the participants tapped in response to TC. One trial was conducted at comfortable stepping interval with a secondary motor-cognitive task (holding tray with 2 cups of water) to assess TC effects on motor-cognitive integration.

In Experiment #2 – designed to answer Questions #2 and #4 – TC efficacy in modulating temporal gait parameter – inter step intervals (ISI) – was investigated in a straight-line walking task with and without TC delivered at a range of cueing intervals above and below the comfortable stepping intervals (CSI; Objective #2). Each trial consisted of three continuously executed phases: (1) pre-synchronization

(30 steps, TC OFF); (2) synchronization (30 steps, TC ON); and (3) continuation (30 steps, TC OFF). Data were analyzed only from synchronization phase as the participants tapped in response to TC. One trial was conducted at CSI, with a secondary motor-cognitive task (carrying tray with 2 cups of water) in order to assess TC effects on motor-cognitive integration.

In Experiment #3 – designed to answer Questions #3 and #4 – TC efficacy in modulating temporal (cadence, turn time, and task completion time) and spatial (step length) gait parameters, and its effects on dual task performance was investigated during execution of single and dual gait tasks with and without TC delivered at a range of cueing intervals above and below CSI (Objective #3). Each trial consisted of three continuously executed segments: (1) walking in a straight line; (2) performing a 180^{o} turn around a pylon, (3) walking back in a straight line to the starting position.

1.4 Research Hypotheses

Based on the stated research questions and objectives, four research hypotheses were tested in the proposed experiments.

Hypothesis #1: Healthy and PD participants were expected to be able to modulate performance of heel tapping and straight line walking to TC, wherein performance variability was expected to be higher in PD patients.

Hypothesis #2: Modulated performance on motor tasks was expected to be worse in PD patients due to dysfunctional BN-modulated internal timing mechanisms.

Hypothesis #3: Healthy participants and PD patients were expected to modulate motor task performance in response to modulation of TC interval duration wherein modulation efficacy was expected to be higher in simpler tasks and at longer cueing intervals and overall higher for healthy participants.

Hypothesis #4: Provision of TC was expected to improve motor performance of the highly complex gait tasks in the presence of the secondary motor task.

1.5 Dissertation Outline

Chapter 1, *Introduction* – introduces the reader to the topic of this dissertation – i.e. the general state of knowledge, problems and potential solutions through application of tactile cueing;

Chapter 2, *Literature Review* – provides a detailed overview of the current state of knowledge, existing gaps in knowledge, and potential problems in closing the identified gaps about tactile cueing effects on motor performance and of motor-cognitive integration in healthy individuals and PD patients;

Chapter 3, *Manuscript I: Tactile Cueing Modulation of Simple and Complex Motor Tasks – Implications for Contemporary Models of Basal Nuclei Function in Parkinson's Disease* – describes changes in performance of simple (seated heel tapping task) and more complex (straight-line walking) motor tasks in response to TC delivered through a range of cueing intervals. The results indicate that both PD patients and healthy individuals synchronize simple heel taping task performance to TC at all tested cueing intervals. However, the ability to synchronize to TC diminishes with increased task complexity (straight-line walking), and even further with introduction of a secondary motor task (holding/carrying tray with two cups of

water). While healthy participants can synchronize through ~10% shorter (i.e. faster) cueing intervals, PD patients' ability to synchronize is severely diminished beyond comfortable cueing. Introduction of a secondary task significantly slows down PD patient's performance of complex tasks;

Chapter 4, *Manuscript II: Tactile Cueing – An Opportunistic Gait Aid for Parkinson's Disease Patients Performing Highly Complex Gait Tasks* – describes changes in PD patients' and healthy individuals' performance of a highly complex functional gait task in response to TC delivered through a range of cueing intervals. The results indicate that TC is more effective in functionally significant modulation of cadence and performance times during most complex motor-cognitive tasks consisting of performance of functional turns while carrying a tray with two cups of water. PD patients achieved greatest cadence and task completion time improvements when cued at ~10% shorter (i.e. faster) cueing intervals. Healthy individuals modulated cadence and task completion time most when cued at ~20% shorter (i.e. fastest) cueing intervals. These findings are discussed in detail;

Chapter 5, *Summary, Future Directions and Limitations* – this chapter combines the results from the two manuscripts and discussed these findings in a common context of the efficacy of TC in modulation of motor performance and implications for understanding of underlying motor-cognitive integration mechanisms in PD and healthy individuals. In addition, design and implementation limitations of the conducted research project are discussed in this chapter, and implications for future studies are presented.

Chapter 6, *Appendices* – a list of supplementary materials and methods.

Chapter 7, *References* – provides information on the literature sources cited.

1.6 Potential Contributions

The effects of TC on performance of simple and complex motor tasks in healthy individuals and PD patients remain incompletely understood. Comparative investigation of healthy individuals' and PD patients' ability to modulate motor performance in response to TC, and the characteristics of modulated motor performance in simple and complex motor tasks – as performed in this research project - provide unprecedented insight into the mechanisms of motor-cognitive integration, and should thus advance development of long-term TC-based performance aids for alleviation of PD motor symptoms. The use of TC-based aids could further reduce injury risks associated with impaired gait in the affected population. Experimental validation of a custom developed TC application for commercially available smart phones could result in an easily accessible and user friendly TC walking aid.

1.7 Definitions of Important Terms and Abbreviations

BN – Basal Nuclei; *CSI* – Comfortable Stepping Interval; *DLPFC* – Dorsolateral Prefrontal Cortex; *EF* – Executive Function; *FOG* – Freezing of Gait; *ITI* – Inter Tap Interval; *ISI* – Inter Step Interval; *MCI* – Mild Cognitive Impairment; *PC* – Parietal Cortex; *PD* – Parkinson's Disease; *PIGD* – Postural Instability and Gait Difficulty; *PFC* – Prefrontal Cortex; *PMC* – Premotor Cortex; *RE* – Relative Error; *SMC* – Supplementary Motor Cortex; *TC* – Tactile Cueing; *TCI* – Tactile Cueing Interval.

CHAPTER II

Literature Review

As the second most prevalent neurodegenerative disorder in the United States (NINDS 2004) that affects more than 4 million people worldwide (Dorsey et al. 2007), Parkinson's disease presents a significant public health issue. Since the available treatment options offer only transient alleviation of symptoms, intermediate methods for movement modulation – such as TC – may improve PD patients' motor performance, disease management, and increase their overall quality of life. The aim of this dissertation, therefore, was development and validation of TC-based movement modulation aid that would reduce the impact of progressive PD symptoms in a subset of the patient population.

In the following sections, the motor and cognitive functions related to basal nuclei and PD-related neurophysiologic changes are reviewed in the context of motor-cognitive integration and potential modulating role of TC. In the opening section, PD neuropathology and its impact on BN function are discussed within the framework of current models of sensorimotor (re)integration and TC-based movement modulation. In the following sections, current knowledge on the effects of sensory cueing – auditory, visual and tactile – on modulation of movement in PD is reviewed. In the final section the interaction of motor and cognitive processes on performance is discussed in the context of TC's predicted advantage over alternative sensory cueing modalities. The chapter ends with a brief summary of the reviewed literature and the overall aims of this dissertation.

2.1 Parkinson's Disease Neuropathology and Assessment

Clinical symptoms of PD include slowness of movement (bradykinesia), tonic rigidity, postural instability, resting tremor followed by postural instability and gait difficulty (PIGD), impaired kinesthesia, cognitive impairments (CI) and affective disorders (Braak et al. 2003; Burn et al. 1994; Gelb et al. 1999; Jankovic et al. 1990; Jankovic et al. 2002; Perlmutter 2010). The prevalence of PD increases with increasing age, and is higher in men than in women (Jankovic et al. 2002). Although a number of environmental, genetic, occupational, and life style factors have been implicated in PD, its specific etiology remains unknown (Au et al. 2005).

Neurophysiologically, PD begins with an asymptomatic preclinical period (generally ranging between 2.8 to 6.5, and up to 40–50 years; Au et al. 2005; Braak et al. 2003) during which α-synuclein protein agglomerations – Lewy bodies (LB) and/or Lewy neurites (LN) – accumulate in the brain, resulting in disruption of regular dopaminergic neural signal transmission and cell cycles (Braak et al. 2003; Halliday & McCann 2010; Tanner et al. 2002). Infiltration of α-synuclein starts in the nigrostriatal dopaminergic neurons and subsequently progresses to organizationally higher structures of the brain, ultimately affecting the entire neocortex (Braak et al. 2003; Halliday & McCann 2010).

PD symptoms progress over the course of the disease; however the loss of striatal dopamine varies greatly between individual patients – from 1.7% to 13.1% per year (Nurmi et al. 2000). Motor symptoms are associated with earlier stages of the disease and the Lewy body infiltration of brain stem and basal nuclei, while cognitive impairments and dementia are associated with infiltration into prefrontal and frontal cortical structures.

In spite of the great variability in PD and PD-related symptoms, Braak et al. (2003) and Halliday & McCann (2010) identified three major PD phenotypes (Figure 2.1) – typical (idiopathic) PD, PD with Dementia (PDD) and Dementia with Lewy Bodies (DLB). Progression of LB infiltration and related symptoms is slowest in idiopathic PD, and increases in PDD and DLB. In addition to LB infiltration, PDD and DLB phenotypes are also marked by concurrent infiltration of brain stem, cortical and subcortical structures by large protein plaques. Onset of PD is earliest in idiopathic PD, followed by DLB and PDD (Halliday & McCann 2010). Idiopathic PD is the most common phenotype and is also marked by least comorbid motor-cognitive impairments. Early idiopathic PD symptoms are most commonly unilateral, become bilateral with disease progression, and ultimately result in severe disability.

With disease progression, there is exacerbation of postural instability and gait difficulty (PIGD), including reduced gait speed, step length, cadence, and impaired ability to perform functional turns (Baker et al. 2007; Elble 2002). Motor symptoms may overlap with cognitive impairments. One of the cardinal cognitive impairments associated with PD is the dysexecutive syndrome (PDDS) – i.e. impaired formulation, planning, attention to, and execution of goal-directed tasks (Dubuois & Pillon 2002; Lezak 1983). Combination of complex postural, gait and cognitive symptoms further increases the incidence of falls and fall-related injuries (Bloem et al. 2001b; Keus et al. 2007; Niino et al. 2000). Progression of PD motor-cognitive symptoms presents a diagnostic challenge and requires the use of specialized assessment tools.

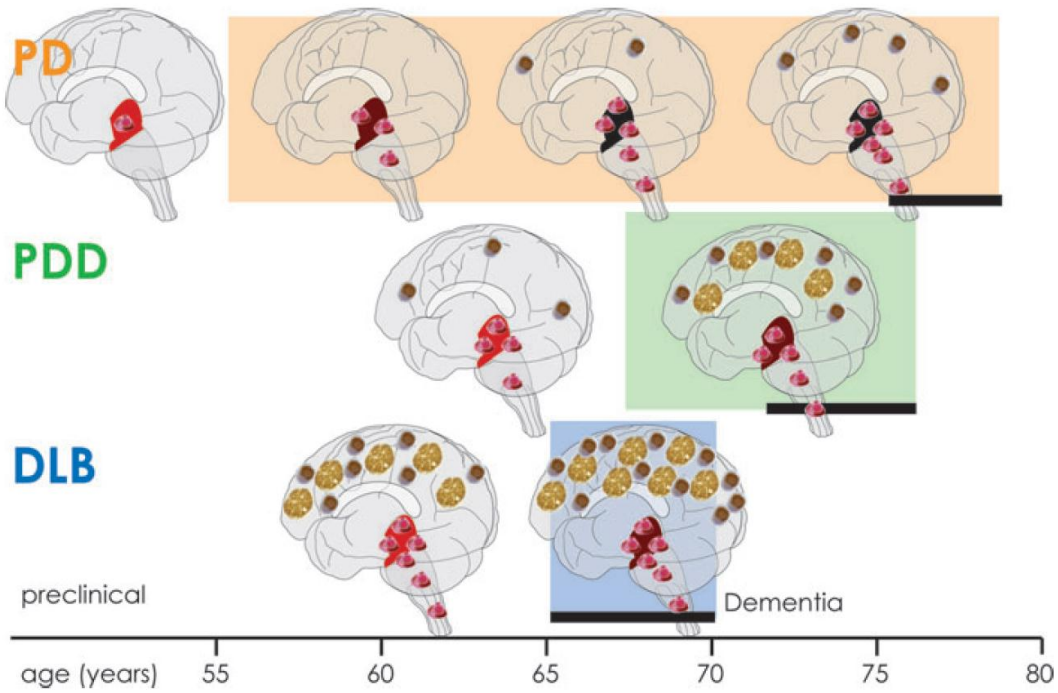


Figure 2.1: Pathological progression of PD in the three main clinical phenotypes – idiopathic PD (PD), PD dementia (PDD) and dementia with Lewy bodies (DLB). Loss of dopaminergic neurons in substantia nigra shown in solid color – darker colors indicate greater cell loss over time. Progressive infiltration of the Lewy bodies (pink), cortical Lewy bodies (brown), and cortical plaques (light brown) depicted over the course of years; Adopted from Halliday & McCann (2010).

The progress of PD motor symptoms and disability has been traditionally assessed by the Hoehn-Yahr scale (Hoehn & Yahr 1967) comprising five ranks of clinical motor symptoms – starting with unilateral disease (stage 1), progressing over bilateral disease (stage 2-3) and severe disability (stage 4), and ending in wheelchair-bound / bedridden patient (stage 5). The H-Y stage 2 indicates bilateral involvement with no impairment of balance, H-Y stage 3 indicates mild to moderate bilateral involvement with balance impairment, and H-Y stage 4 indicates severe bilateral involvement with balance impairment. The bilateral symptomatic involvement, which is clinically observable in H-Y stages 2 – 4, contributes to impairments of gait and locomotion (Goetz et al. 2004). Therefore, patients staged 2 – 4 on H-Y scale are considered appropriate candidates for inclusion in studies involving ambulation.

The most commonly used assessment tool for cognitive function in PD is the Mini Mental State Examination (MMSE; Folstein et al. 1975) which has been validated as a screening method for assessment of cognitive function and indication of cognitive impairments in Parkinson disease (Marder 2010; Oh et al. 2010). The MMSE is an 11-item questionnaire that tests orientation, registration, attention and calculation, recall, and language. With the maximum score of 30, cognitive impairment is indicated for scores below 27 (Jones 2008, 2011; Oh et al. 2010).

The primary clinical PD motor and cognitive assessment scale is the Unified Parkinson Disease Rating Scale (UPDRS) which assesses motor and cognitive disability through a series of four subscales – (1) mentation, behavior, mood; (2) activities of daily living; (3) motor manifestations; (4) complications in treatment (Goetz et al. 2007; Perlmutter 2010). UPDRS scale 3 will therefore be used in this study to verify the level of motor functionality and dopaminergic medication efficacy.

Currently, a variety of PD therapeutic approaches are being used or developed. As Jankovic (2002) states, these can be divided into several groups: (a) dopaminergic (enhancing transmission of dopamine); (b) nondopaminergic (enhancing nondopaminergic neurotransmission); (c) symptomatic (treatment of specific symptoms); (d) neuroprotective (protecting remaining unaffected neurons); (e) surgical; and (f) preventive (based on understanding PD etiology). The most effective therapeutic "gold-standard" approach for partial – but transient and prone to side effects – longer term amelioration of PD symptoms, is dopaminergic levodopa (L-DOPA) / carbidopa (e.g. *Lodosyn*) treatment (duodopa, e.g. *Sinemet*; Abbott 2010).

Due to high prevalence of PD, its progressive nature, the resulting decrements in patient quality of life, the associated healthcare costs, and the current lack of cure, the need to develop non-invasive treatments for alleviation of PD symptoms has been recognized by the National Institutes of Neurological Disorders and Stroke (the New Strategic Vision for NINDS); as well as the November 2004 NINDS report *Parkinson's Disease: Challenges, Progress and Promise* (National Institutes of Neurological Disorders and Stroke – NINDS 2004). While a combination of pharmacological, physiotherapeutic and neurosurgical methods are used to treat PD and its associated symptoms, no cure exists at this time (Dibble et al. 2010). Development of methods for reduction of PD symptoms on motor-cognitive performance and related injuries may increase levels of physical activity PD patients engage in, and improve the quality of their lives.

2.1.1 Basal Nuclei and Parkinson's Disease

The normal function of basal nuclei is based on two distinct neuroanatomical pathways (Kandel et al. 2003; Redgrave et al. 2010): the excitatory direct pathway leading from striatal input nuclei (caudate, putamen) towards globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr); and the inhibitory indirect pathway leading from the striatal input nuclei towards globus pallidus externa (GPe) and subthalamic nucleus (STN). However, the normal functions of both pathways are further modulated by dopamine released from substantia nigra pars compacta (SNc; Redgrave et al. 2010; Figure 2.2 a, b). Activity of the direct pathway – inhibition of inhibitory control of thalamus and brainstem allowing movement execution – is

modulated by the excitatory D1 dopamine receptors which produce the net result of facilitating thalamic excitation and subsequent movement execution.

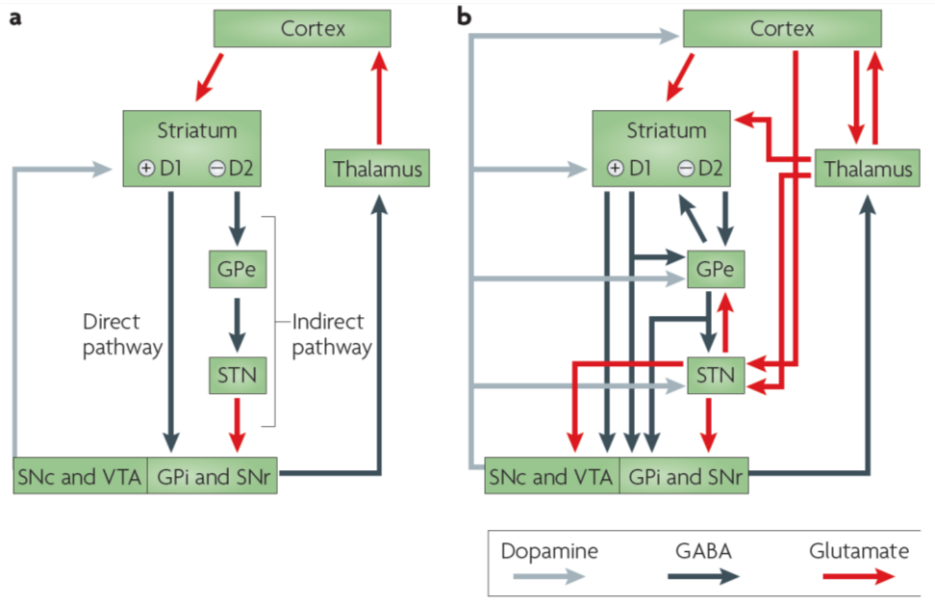


Figure 2.2: A schematic representation of the basal nuclei connections. (a) The basic BN model wherein BN output is governed by the balance between the direct and indirect pathways. (b) A new BN model based on recent neuroanatomical studies, presenting a more complex, interactive relationship between BN element inputs and outputs. BN elements described in the figure include GPe (globus pallidus pars externa); GPi (globus pallidus pars interna); SNr (substantia nigra pars reticulata); adopted from Redgrave et al. 2010.

Activity of the indirect pathway – maintaining thalamic and brain stem inhibition and consequent inhibition of movement execution – is modulated by the inhibitory D2 dopamine receptors which inhibit thalamic excitation and inhibit movement execution. Therefore, reduced dopaminergic activity in PD inhibits the direct pathway (i.e. inhibits movement execution) and facilitates the indirect pathway (i.e. facilitates movement inhibition). However, due to a complex network of interactions between excitatory and inhibitory pathways, and concurrent activity of antagonistic neurotransmitters such as dopamine, gama-aminobutyric-acid (GABA), glutamate and acetylcholine (ACh) deregulation of dopaminergic activity in

BG may result in hypokinetic and/or hyperkinetic symptoms (Redgrave et al. 2010; Figure 2.2b).

Apart from the basic direct / indirect pathway model, recent research produced evidence of very complex interactions between intrinsic and extrinsic neural connections that govern basal nuclei function (Redgrave et al. 2010). An important feature of basal nuclei functional architecture is based on homologous topographic organization of afferent cortical projections, such that cortical areas associated with sensorimotor processing project into dorsal lateral striatum, those associated with emotional processing project into ventral medial striatum, and those associated with cognitive processing in between ventral medial and dorsal lateral striatum (Redgrave et al. 2010).

This topographic organization also reflects on the functional divisions of the basal nuclei structures which are now considered to include the limbic (emotional / motivational), associative (cognitive), and sensorimotor divisions (Balleine et al. 2009a, 2009b; Redgrave et al. 2010; Figure 2.3). These functional divisions are based on neuroanatomical distinctions where dorsolateral striatum processes sensorimotor functions, the medial striatum influences associative / cognitive functions, and the ventral medial (limbic) striatum contributes to motivational functions (Nakano et al. 2000; Scholz et al. 2000; Gerardin et al. 2003; Romanelli et al. 2005).

Although a complex network of projections to and from basal nuclei and cortical, subcortical and pontine structures has been identified, of most importance for this study are the ascending dopaminergic fibers from the SNc and ventral tegmental area (VTA) that innervate dorsal, medial and ventral striatum (Bjorklund &

Dunnett 2007) which are associated with sensorimotor associative and motivational processing respectively.

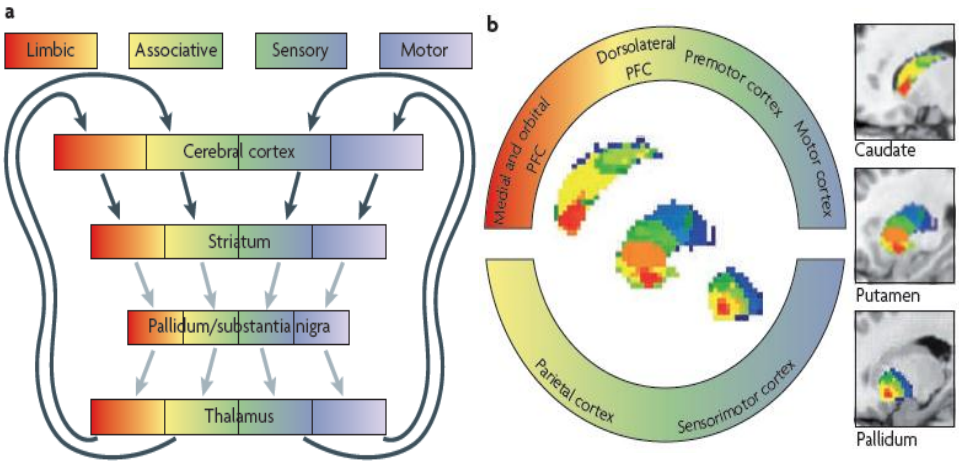


Figure 2.3: Corticobasal nuclei-cortical pathways in humans and animals. (a) Cortico-BN pathways run in parallel and functionally connect limbic (red), associative (yellow/green) and sensorimotor (blue/white) outputs. Cortical functional organization is preserved in the BN and corresponding thalamic pathways, and allows modulation of activity within the pathway by external signals. Glutamatergic (black arrows) and GABAergic (grey arrows) projections indicate the pathway direction. (b) Projection of the cortical regions onto caudate, putamen and pallidum in the human in sagittal plane; adopted from Redgrave et al. 2010.

Within that framework, PD-related loss of dopaminergic activity affects all three functional components of basal nuclei architecture (Marsden 1994; Rodriguez-Oroz et al. 2009). However, seminal studies by Fearnley and Lees (1991) indicated that PD-related loss of dopaminergic innervation occurs primarily in the posterior putamen and ventrolateral SNc, respectively. Later functional studies corroborated these findings and indicated that dopaminergic metabolism is significantly reduced in the caudal regions of the striatum (Morrish et al. 1995). These findings suggested that the loss of sensorimotor processing in posterior putamen is the primary contributing factor in development of early motor PD symptoms.

Furthermore, as suggested by Redgrave et al. (2010) the associative pathways control goal directed (i.e. performing an action to achieve a desired goal / outcome) behaviors while sensorimotor pathways control the stimulus–response (i.e. entrained, automatic activities requiring little or no cognitive guidance) behaviors. At cortical and brain stem levels, both pathways converge and exert interactive effects on the motor behavior output. Increased reliance on goal directed processing in PD is thought to result from the loss of dopaminergic innervation from sensorimotor regions in the basal nuclei and the related dysfunctional output from these regions. Goal directed behaviors are likely impeded by the dysfunctional inhibitory output from sensorimotor areas.

The functional reorganization of motor-cognitive processing from BN-modulated automatic, to frontally-modulated goal-directed is supported by neuroimaging evidence indicating the existence of the ventromedial and lateral sensorimotor integration systems (Elsinger et al. 2006; Jahanshahi et al. 2010; Redgrave et al. 2010; Kojovic et al. 2012). The lateral system includes the supplementary motor area (SMA) and the BN (particularly posterior caudate), and is implicated in performance of internally-paced and motivated actions, while the ventromedial system includes the premotor cortex (PMC), parietal cortex (PC), thalamus and the cerebellum, and is implicated in performance of movements elicited in response to environmental sensory cues. Since the lateral system relies on BN function, PD-induced dysfunction of BN in turn causes the dysfunction of the lateral system.

2.2 Sensorimotor Function in Parkinson's Disease

Current models of neuropathologic changes in BN and the related reorganization of motor-cognitive integration presented in previous sections suggest that TC may be a feasible means of improving integrated motor-cognitive performance. However, exploiting TC potential is dependent on functionality of patients' sensorimotor processing, their ability to entrain temporally-mediated cues, and finally, the ability to modulate functional movements in response to TC. A review of relevant literature on sensorimotor, timing and gait impairments in PD is presented in the following sections.

2.2.1 Sensorimotor and Timing Impairments in Parkinson's Disease

Impaired proprioception and timed motor performance in PD patients have been traced to impairments of central sensorimotor integration at the level of BN (Abbruzzese & Berardelli 2003; Maschke et al. 2003). Thus, in the context of using TC for movement modulation, it is particularly important to consider the potential effects of PD neuropathology on tactile sensorimotor integration. Recent studies indicate that tactile afference is not impaired in PD (Rabin et al. 2010), and that tactile sensory integration at the level of BN improves with improved dopamine availability (Nelson et al. 2012) – i.e. in line with contemporary models of BN that postulate unbalanced motor output from direct and indirect pathways that combine with externally driven sensory input mediated by the ventromedial system (Redgrave et al. 2010).

To assess the effects of tactile input on impaired proprioception in PD, Rabin et al. (2010) investigated the accuracy of arm-matching movements in 9 PD patients

(aged 58.67±6.59 years) off medication, and 9 age-matched healthy controls (demographic data not reported). The participants' task was to match the elevation of the forearms while their elbows rested on a stable surface. The difference in angular elbow/wrist displacement was calculated between the "cue arm" and the "control" arm in eight test conditions during which the "cue arm" proprioception was alternately manipulated by biceps vibrations, dynamic and passive finger tip cues. The results indicate that PD patients have overall lower arm-matching accuracy (angular matching error of 6.18°±0.98° vs. 4.93°±0.31°), which was however attenuated by tactile cues (angular matching error < 5°). Arm drift was also found to be greater in PD patients (9.99°±2.28) than healthy participants (5.62°±4.27°) when biceps vibrations were introduced, but this detrimental effect was again attenuated when "cue arm" finger touched a stationary surface. The same corrective patterns were observed in healthy individuals, and suggest that although proprioception is impaired, tactile sensorimotor integration is not disrupted in PD.

On the other hand, aiming to further elucidate the tactile sensorimotor integration in PD, Nelson et al. (2012) investigated changes in tactile sensitivity of PD patients on and off dopaminergic medication. In this study, PD patients (H-Y 2 – 3) and age matched healthy individuals performed a task wherein the perceived order of tactile stimulation of 2^{nd} and 3^{rd} digits was measured on and off medication, with and without synchronous vibration of the digits ahead of the tactile stimuli. The results indicate that synchronous vibration impaired tactile acuity in healthy individuals and PD patients off medications, but not PD patients on medications, suggesting that dopaminergic medication increases tactile sensitivity. Since BN has been known to play a prominent role in sensorimotor integration (Redgrave et al.

2010), these results further indicate that combined pharmacological and TC-based treatments may produce synergistic effects on movement modulation in PD.

Except for their role in sensorimotor integration, it has been well established that the BN play a central role in temporal modulation of movements. The BN have thus been described as internal clock for initiation (Freeman et al. 1993; Merchant et al. 2008) and synchronization of movements to external sensory cues (Ivry & Hazeltine 1995; Jones et al. 2008, 2011; Jahanshahi et al. 2010). PD-induced disruption of BN function is reflected in disrupted performance of self-paced movements and their synchronization to external cues – particularly at short auditory cueing intervals (≤250ms; Nakamura et al. 1978; Peters 1989).

However, the results of synchronization studies on comparative performance accuracy of PD patients and healthy individuals are inconsistent, with some reporting that PD patients' performance lags after the cues (Pastor et al. 1992), others reporting they lead ahead of the cues (leading; O'Boyle et al. 1996), and yet others that there is no difference in performance (Spencer & Ivry 2005). Although Spencer and Ivry (2005) found no changes in performance variability, most other synchronization studies (e.g. Harrington et al. 1998; Jahanshahi et al. 2010; O'Boyle et al. 1996; Pastor et al. 1992) indicate that PD patients' performance is more variable than that of healthy individuals.

In finger-tapping studies employing auditory cueing, O'Boyle et al. (1996), Harrington et al. (1998), and Ivry and Keele (1989) found that PD patients tended to tap at a faster rate than a control group at intervals between 300 and 600ms. However, Pastor et al. (1992) reported that PD patients tapped slower than healthy individuals when cued at 400ms-500ms intervals. In line with these divergent

findings, Logigian et al. (1991) and Pastor et al. (1992) reported unimpaired synchronization performance by PD patients at intervals ≥476ms and 666ms, respectively.

A recent neuroimaging study (Jahanshahi et al. 2010) that employed the synchronization-continuation (S-C) paradigm in a finger tapping task – wherein subjects synchronized finger tapping to external sensory stimuli, and were then asked to continue performing the activity at the same rate after the synchronizing stimuli were removed – found that variability was greater in continuation phase for both PD and healthy participants, and that in continuation phase, all participants performed ahead (leading) of the auditory cues delivered at 1000ms intervals. By analyzing the blood-oxygen level dependent (BOLD) changes in cortical activity, they also found differential cortical activation during both S-C phases: PD patients showed greater activation of the cerebellum, thalamus, and substantia nigra (i.e. the ventromedial system), while healthy individuals showed greater activation of medial prefrontal cortex (PFC), hippocampus, posterior cingulate, and caudate (i.e. the lateral system). During continuation phase both groups had increased activation of the dorsolateral prefrontal cortex (DLPF; implicated in volitional, internally generated behavior). These activation patterns suggest greater reliance of PD patients on external sensory stimuli (modulated by the ventromedial system) and of healthy individuals on internally generated cues (modulated by the lateral system) for timing of motor performance.

Several recent studies (Jones et al. 2008, 2011) investigated motor performance in synchronization and continuation phases over a broader range of auditory cueing intervals (250ms-2000ms). Their findings indicate that during the

synchronization phase at a short cueing interval (250ms) PD patients lead ahead of cues while healthy individuals lag behind them; this error difference was amplified during the continuation phase. At longer intervals (≥500ms) both groups were able to entrain to the stimulus during the synchronization phase, but led ahead of the stimulus in continuation phases. The systematic leading at intervals ≥500ms may indicate a systemic underestimation of the cued intervals (Aschersleben 2002; Flach 2005), while error difference at 250ms interval may indicate the difference between controlled performance of the healthy participants – resulting in lagging error – and uncontrolled (i.e. inhibited inhibition of motor output) performance of PD patients – resulting in leading error (Jones et al. 2011; Peters 1989).

When considering performance variability as another aspect of cue entrainment, Jones et al. (2011) report that PD patients and healthy individuals show increased variability at intervals ≥ 500ms, wherein variability during the continuation phase diverges from the performance variability during the synchronization phase with shorter cueing intervals. Also, as reported by Yahalom et al. (2004) – who tested PD patients and healthy individuals during finger tapping at their comfortable rate – performance variability in the synchronization task does not appear to be impaired in PD patients, and is lowest for PD patients and healthy individuals at 500ms interval. These findings further support the proposition that ~500ms interval has a special physiologic significance.

The convergent data on synchronization accuracy and variability suggests that the point at which the accuracy of repetitive tapping is compromised in PD is somewhere between 250ms and 500ms, designating this cueing interval range as one of particular significance in understanding motor timing behavior. Considering

the fact that all of the reported studies involved very limited and simple upper extremity tasks (e.g. finger tapping, wrist flexing) the neurophysiologic origins of synchronized motor timing in simple and more complex motor tasks – particularly in PD patients – remain incompletely understood. In their seminal study, Ivry & Hazeltine (1995) suggested that timed movement production and perception do not involve common neurophysiologic mechanisms. This notion is congruent with the proposed partial dissociation of sensorimotor integration via BN-modulated lateral system (internally driven), and sensory-cue-modulated ventromedial system (externally driven). More specifically, Ivry and Hazeltine (1995) have shown that repetition of external cues establishes an internal reference interval that may then be used for synchronization and reproduction of corresponding motor performance intervals.

Based on this notion, ability to entrain to, and effectively use external sensory cues to modulate intervals of motor performance, relies initially on the ventromedial system (for sensorimotor integration of externally cued intervals), and then on the lateral system (for establishment of internal representation of, and reproduction of time intervals). Since BN is thought to play a role in the latter part of the process, it should be expected that PD patients should exhibit decrements in synchronization and reproduction of timed intervals, as well as increased performance variability. Furthermore, due to inherent increase in sensorimotor integration times associated with increasing biomechanical and cognitive complexity of target tasks, it should be expected that increasing task complexity would detrimentally affect cueing synchronization and variability – particularly in PD patients.

A study reported by Chen et al. (2006) supports these propositions – albeit in healthy individuals. In the study investigating synchronization and correction of timed unilateral and bilateral heel tapping, upright bilateral heel tapping, and stepping in place, they demonstrated that synchronization accuracy was markedly higher in seated tasks (exceeding 80%) than in-place stepping tasks (where accuracy was under 40%), while synchronization variability was markedly higher during performance of bilateral tasks. As suggested by Chen et al. (2006), the reasons for the marked loss of synchronization accuracy and increased variability are the biomechanical task constraints including control of balance in upright stance, bilateral coordination, and dynamic spatial orientation – all of which slow down sensorimotor and motor-cognitive integration. The combined effects of neuromuscular and cognitive task complexity should therefore be expected to synergistically deteriorate motor-cognitive integration – particularly in the compromised PD patients.

Yet, there is still a lack of studies exploring the neuromotor and cognitive correlates of observed accuracy and variability changes in PD patients. Thus, increasing the motor task complexity level and the range of cueing intervals around the comfortable stepping interval could yield better systemic understanding of the underlying neurophysiologic mechanisms that govern motor timing, as well as their limitations in healthy individuals and PD patients. In that sense, application of TC for modulation of simple heel tapping and increasingly complex gait tasks was expected to yield novel insight, and provide new means of managing PIGD symptoms.

2.2.2 Gait Impairments in Parkinson's Disease

Gait represents a complex series of interlinked motor commands that control the stance and swing phase dynamics. The repetitive pattern of body segments and limb displacements during gait is typically presented as a gait cycle (Winter 2005) comprising of stance and swing phases (Figure 2.4). During the stance phase, comprising approximately 60% of the gait cycle, the leg that is in contact with the ground, carries the weight of the entire body. Conversely, during the swing phase (~40% of the gait cycle), the leg is swung from the hip in order to establish a new position for the subsequent stance phase. The swing phase is defined by the initial toe-off and the subsequent heel strike. Investigation of gait is based on kinematic analysis of gait characteristics which relies on successful determination of step / gait cycle events. As demonstrated by Aminian et al. (2002) and Salarian et al. (2004), heel strikes and other step cycle events can precisely be determined from thigh angular velocity profiles of the thighs and shanks.

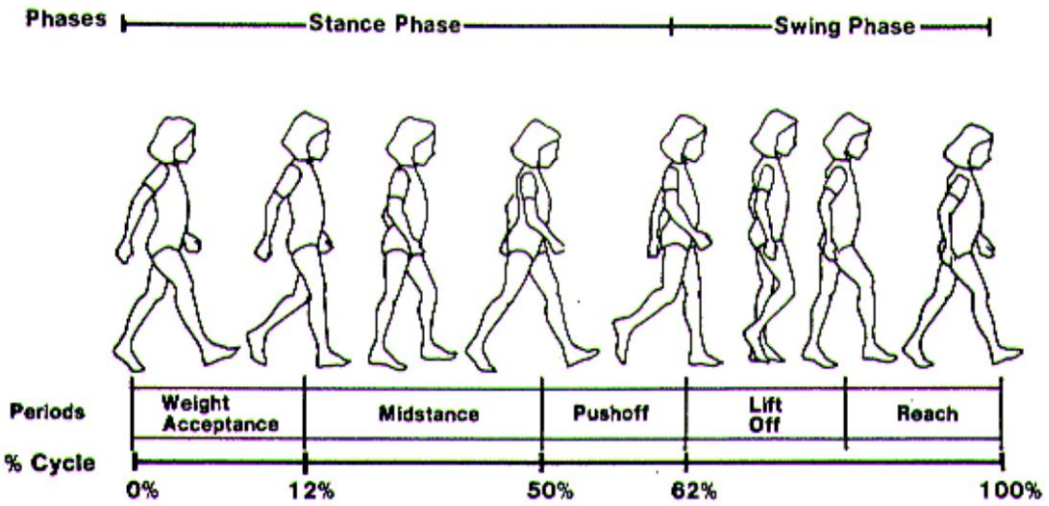


Figure 2.4: Phases of a gait cycle in a healthy individual. Adopted from course notes by Dr. Adam Thrasher, based on Winter (2005).

While healthy gait is performed as a rhythmic repetitive behavior with little active cognitive control, gait of PD patients with mild to severe symptoms of PD (H-Y 2 – 4) is characterized by bradykinesia, hypokinesia, decreased stride and step length (also known as “shuffling gait”; Stolze et al. 2001), and concomitantly decreased cadence (Azulay et al. 2006; Hausdorff et al. 2003, 2007; Morris et al. 1996; van Wegen et al. 2006).

In a seminal study performed on 10 idiopathic PD patients (H-Y 3 – 4; aged 61.5 ± 7.8 years) and 10 healthy individuals (aged 63.6 ± 10.5 years), Salarian et al. (2004) found that the PD patients had on average 52% lower stride velocity, 60% shorter stride length, and consequently 40% longer gait cycles than their neurologically intact counterparts. In these trials, the participants walked in a straight line over a 20 meter walkway. Participants’ gait cycles were analyzed by means of inertial sensors located on the wrists, thighs, and shanks of participants, assuming a five-link inverted pendulum model gait. This was a modification of a gait analysis method proposed by Zijlstra and Hof (2003) based on a three-link model.

The combined results of these studies suggest that PD patients walk on average slower than healthy individuals with shorter step lengths and lower cadence. Furthermore, spatiotemporal gait parameters most affected by PD – gait cadence, step length and gait speed – have also been found to be more variable in PD patients than healthy individuals, and have been further linked to increased risk of falls (Hausdorff et al. 2001; Hausdorff et al. 2003; Maki 1997; Nakamura et al. 1996; Schaafsma et al. 2003). The mechanisms of increased gait variability in PD have been linked to impaired automaticity in motor performance due to dysfunctional BN sensorimotor integration processes (Hausdorff et al. 1998; Stolze et

al. 2001). This model of PD gait is supported by findings of Schaafsma et al. (2003) who demonstrated that administration of Levodopa to PD patients reduces their gait variability and increases their gait velocity, thus further implicating dysfunctional BN-controlled sensorimotor integration mechanisms as the likely sources of PIGD.

Frenkel-Toledo et al. (2005) suggested that the observed variability in spatiotemporal parameters of PD gait may originate from different sources – while stride dynamics may be governed by an automatic rhythmic stepping mechanism, the swing phase dynamics may be governed by active balance control mechanisms modulated by BN. In their study, 36 idiopathic PD patients (H-Y 2 – 2.5; aged 61.2 ± 9 years; MMSE 27.9 ± 1.2) and 30 healthy individuals (aged 57.7 ± 7 years; MMSE 27.9 ± 1.9) walked at their individual comfortable speed and at a relative slow speed. The results indicate that at their comfortable speed PD patients walked ~15% slower, and with a ~10% shorter strides than healthy individuals. Compared to comfortable speed, slow speed of healthy individuals was 17% slower (average stride length was 7% shorter, and stride time 10% shorter) while slow speed of PD patients was 17% slower (average stride length was 7% shorter, and stride time 12% shorter).

They also found that gait variability in PD increased at higher gait speeds, while it decreased at lower gait speeds. These results support the notion that PD-induced impaired motor-cognitive integration at the level of BN reduces the ability of PD patients to adapt their motor performance to increasingly challenging motor integration tasks – such as excursions from preferred walking speeds towards either faster or slower gait. It may be inferred that walking at higher speeds may be more challenging since it imposes shorter processing time constraints. Due to compensatory sensorimotor reorganization and a shift from rapid PD-modulated

automatic processing, toward slower prefrontally-modulated processing, PD patients may be unable to process the required motor-cognitive commands in the short time interval imposed by the high gait speed.

In a related study, Ivkovic and Kurz (2011) investigated the effects of auditory-cued leg swing frequency on variability of angular displacements of the leg. They demonstrated that with increasing swing frequencies (i.e. shorter intervals) PD patients exhibit greater variability in leg swing intervals and angular kinematics than healthy young and elderly individuals. Although the motor task they investigated was a simplified model of swing phase dynamics, these results are in accordance with those reported by Frenkel-Toledo et al. (2005) suggesting increased variability in PD patients' gait at higher speeds is attributable to impaired BN-modulated motor-cognitive integration.

In the context of PIGD symptoms – marked by lower cadence, stride length and gait speed – the goal of TC should be to increase these gait parameters and reduce the executive control burden in challenging motor-cognitive tasks. Since increased gait speed may result from increased cadence, increased step length, or a combined increase of these gait parameters, application of temporally-modulated TC may result in increased cadence and consequently gait speed, while reducing the overall burden on the prefrontally-modulated control of swing phase dynamics. However, due to comparatively long swing times compounded by prolonged central processing in PD, it is expected that changes in gait parameters in response to TC plateau at shorter cueing intervals without reaching the level of change corresponding to shortest TC interval. Further discussion on sensory cueing effects on movement modulation is provided in the following sections.

2.3 Sensory Cueing & Movement Modulation in Parkinson's Disease

In a seminal study, Martin (1967) opened a promising line of research on sensory cueing as a source of movement modulation in BN disorders. In the past 40 years, visual and auditory sensory cueing has been shown to ameliorate PIGD symptoms and improve motor learning in PD patients (Azulay et al. 2002; Dibble et al. 2004; Dobkin 2003; Hallet 2008; Maschke et al. 2003; Suteerawattananon et al. 2004; Rochester et al. 2004; Nieuwboer et al. 2009b; Rochester et al. 2010). The mechanisms behind improved motor performance through sensory cueing in PD are based on the afferent cerebello-nigro-thalamic-cortical pathways that constitute the ventromedial system and are preserved in PD (Chuma et al. 2006; Marsden and Obeso 1994; Redgrave et al. 2010; see section 2.1.1; Figure 2.5). To date, the vast majority of sensory cueing studies were done using auditory and visual cues, with only a small minority of studies investigating the tactile sensory modality.

One of the reasons for a research emphasis on visual and auditory sensory cueing modalities may have been due to PD-related neurophysiologic changes in the BN causing PD patients to increasingly rely on visual and auditory sensory modalities for performance of motor tasks and spatial orientation (Hallet 2008; Rabin et al. 2010; Rochester et al. 2010). Due to the increased reliance on visual and auditory sensory modalities, the use of cues may increase demand for executive processing and attention shifting between environmental awareness and movement modulation, and in that way increase the burden on motor-cognitive integration. As van Wegen et al. (2009) suggest, except for their reliance on executive cognitive resources, the practical application of audiovisual cueing modalities may be further restricted by noisy or bright lit environments.

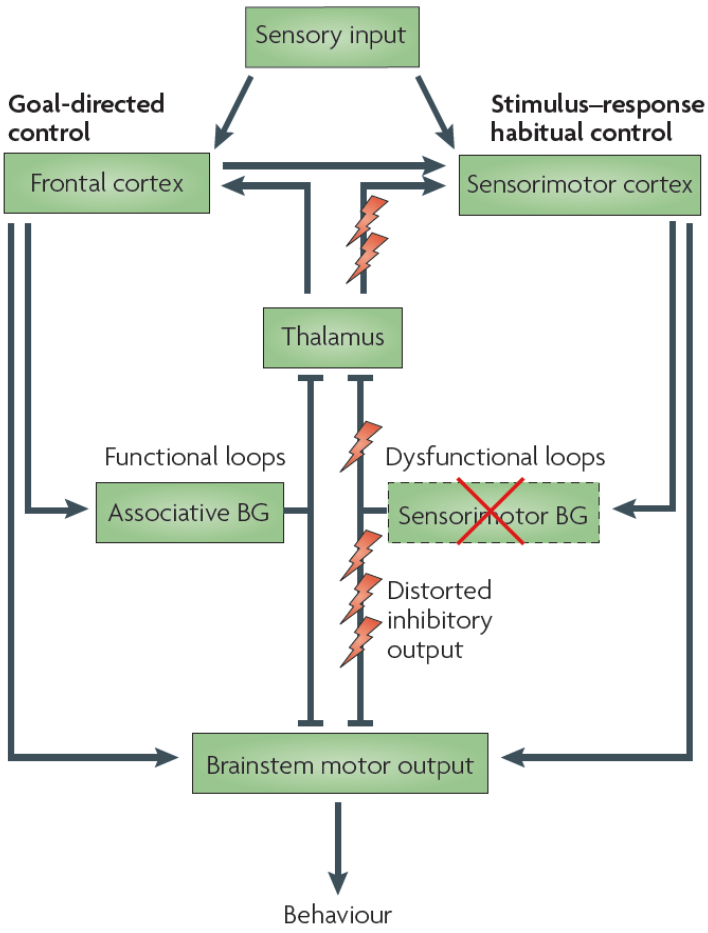


Figure 2.5: Affected and non-affected basal nuclei pathways in PD. Associative pathways control goal directed behaviors; sensorimotor pathways control stimulus–response behaviors. At the level of the cortex and brain stem both pathways converge and modulate motor output. Increased reliance on goal directed processing in PD likely results from the loss of dopaminergic innervation from sensorimotor regions in the basal nuclei (red X) and the related dysfunctional output from these regions and the related pathways (lightning). Goal directed behaviors are likely impeded by the dysfunctional inhibitory output from sensorimotor areas; adopted from Redgrave et al. 2010.

In more recent studies (Baker et al. 2007, 2008; Nieuwboer et al. 2009; Rochester et al. 2010), the combined attentional, auditory, visual and tactile cueing strategies have been shown to have different effects on spatial and temporal gait parameters in PD patient population. In the remainder of this chapter, the effects of

different cueing modalities are discussed in the context of PD movement modulation, and motor-cognitive integration.

2.3.1 Auditory Cueing

The effects of auditory cueing on functional movement modulation have been extensively studied in PD. Since auditory cues are delivered in the temporal domain as are tactile cues, the reported modulating effects of auditory cues are highly relevant to the proposed TC application.

For example, Howe et al. (2003) investigated the effects of different intervals of auditory cues on gait in PD patients whose spatial and temporal gait parameters were assessed as they performed a simple walking task while being exposed to auditory cues at 85%, 92.5%, 107.5% and 115% of their preferred stepping intervals. Cadence and gait speed increased when cued at 107.5% and 115%, and decreased when cued at 85%. However, stride length was not affected by changes in cueing intervals. These results indicate that auditory cues drive cadence without inducing changes in the spatial gait parameters.

In a similar study by Suteerawattananona et al. (2004), the effects of combining visual and auditory cues on the gait pattern of PD patients were compared to the effects of these cues applied individually. The auditory cues consisted of a metronome beat 25% faster than the subject's self-determined fastest stepping intervals. The visual cue consisted of bright parallel lines along the walkway at intervals equal to 40% of a subject's height. Visual cueing improved stride length, auditory cueing improved cadence, but their combination induced no improvement in gait parameters. These results corroborate the findings of Howe et al. (2003), and

suggest that changes in spatial parameters are driven by environmental visual cues (i.e. spatial domain), while changes in temporal parameters are driven by auditory cues (delivered in temporal domain).

However, the findings of Willems et al. (2006) stand in contrast to those reported by Howe et al. (2003) and Suteerawattananona et al. (2004). The authors of this study investigated the effect of auditory cues on gait in PD patients with and without freezing of gait (FOG), and healthy individuals. The participants performed simple walking tasks while cued by an auditory stimulus at their comfortable stepping interval, and at cueing intervals 10% and 20% slower and faster than that. Here, auditory cueing induced gait speed changes in all participants, but also increased stride length in PD patients at 10% longer (i.e. slower) cueing intervals. Conversely, when cued at the 10% shorter (i.e. faster) intervals, PD patients with FOG showed a decrease in stride length, while non-FOG patients showed an increase in stride length, potentially indicating different underlying mechanisms of sensorimotor integration in FOG and non-FOG patients.

Furthermore, these findings were supported by Hausdorff et al. (2007) who investigated the changes in PD patients' and healthy individuals' spatial and temporal gait parameter variability during a simple walking task while exposed to auditory cues administered at preferred stepping intervals and 10% shorter (i.e. faster) intervals. While cued at the preferred stepping intervals, PD patients increased their gait speed, stride length, and swing time, but cueing did not affect variability which was higher than in healthy individuals. When cued at 10% shorter intervals, gait speed, stride length and swing time increased, while variability decreased. Conversely, gait variability increased at both cueing intervals in healthy

participants. These results indicate – contrary to earlier findings of Frankel-Toledo et al. (2005) – that auditory cues may facilitate automatized movements and at the same time reduce stride-to-stride variability in PD patients. They also question central motor-cognitive integration of external stimuli: namely, seemingly better ability of PD patients to exploit external cueing than healthy individuals. A plausible explanation is that compensatory sensorimotor reorganization in PD patients and their greater reliance on external sensory input for movement modulation creates a damped attentional response to novel stimuli, while the same stimuli interfere with motor modulation in healthy individuals.

The role of attention in sensory integration of auditory stimuli is further demonstrated as ameliorative effects of cueing on gait performance seem to diminish when dual or multiple motor-cognitive tasks are performed. This marked change probably reflects impaired ability of PD patients to adequately respond to greater motor-cognitive integration demands during such tasks.

Baker et al. (2007) investigated the effects of auditory, attentional, and combined auditory-attentional cues on gait in PD patients during performance of single and dual motor-cognitive tasks. The cueing strategies included a rhythmic auditory cue (walking in time to a metronome beat), attention to stepping (focusing on taking big steps), and a combined auditory-attentional cue (walking in time to the metronome beat while taking big steps). The single task involved walking at comfortable speed, while dual task included walking while carrying a tray with two cups of water. PD patients' gait speed and step length increased in both single and dual task trials when cued by attentional and combined auditory-attentional strategy. When cued by attentional cues only, PD patients' cadence was reduced in

both single and dual task trials, but when exposed to attentional-auditory cues, their cadence was reduced in dual tasks. Exposure only to auditory cues did not change any of the investigated gait parameters. Thus, in contrast to the above reported studies by Howe et al. (2003), Hausdorff et al. (2007) and Willems et al. (2006), this study suggest limited efficacy of auditory cues in improving motor-cognitive integration, and emphasize the importance of executive attentional control.

In a follow up study, Baker et al. (2008) investigated the attentional cost of three cueing strategies – auditory, auditory-attentional, and attentional – by examining their effect on gait variability under single and dual gait tasks. The results indicate that PD patients' gait variability was reduced with all cues – but the most consistent reduction was found in the combined auditory-attentional strategy. While these changes were prominent in PD patients, they were negligible in healthy individuals. Although less prominent than the effects of combined cueing, the impact of auditory cueing is important since it may elicit functionally significant improvements in gait without increasing the executive processing demands.

The reported results point to the complexity of motor-cognitive integration in the context of dysfunctional executive processing and emphasize the role of attention in sensory cueing efficacy. Due to inherently overused executive function in PD – resulting from the functional reorganization of motor-cognitive integration from BN-modulated automatic control, to pre-frontally modulated executive control (Redgrave et al. 2010) – the efficacy of any cueing modality may depend on the amount of attention its processing requires – the less, the better. Thus, TC – a temporally driven, low-attention stimulus – may be a more feasible cueing modality than auditory cueing since it may require less attention and executive control, and

therefore be a more efficacious movement modulator in increasingly complex activities of daily living. However, the lack of systematic, methodologically comparable investigations resulted in divergent findings. In contrast to the reviewed studies, application of TC and its effects on motor-cognitive integration were investigated in a series of three integrated experiments which provided comprehensive data on the effects of TC on PD movement modulation in tasks with varying levels of motor and cognitive complexity.

2.3.2 Visual Cueing

Although visual sensory information is most heavily relied on for spatial orientation and motor control in the healthy population (Kandel et al. 2000), PD patients depend even more than healthy individuals on ongoing visual information for sensorimotor integration (Morris et al. 1994, 1996). The intimate neurophysiologic relationship between dopaminergic dysfunction and sensorimotor integration in PD has been demonstrated by the finding that administration of dopaminergic treatment makes PD patients less dependent on ongoing visual sensory inputs (Abbruzzese & Berardelli 2003). Thus, while provision of visual cues may be beneficial due to great reliance of PD patients on visual sensory inputs, it may also interfere with highly active visual sensory processing.

As demonstrated by (Morris et al. (1994), PD patients are able to shift attention, adjust cadence and gait speed when following external visual cues, even if they are not able to do so when relying on internally generated movement cues. In a follow-up study, Morris et al. (1996) demonstrated that training with both visual and attentional cues could maintain normal gait for up to two hours. However, in trials

where dual tasks were performed, as well as in trials when participants were unaware of being observed, their stride lengths reverted to the baseline. Although PD patients were able to generate normal spatial gait patterns, the effects of sensory cueing were thus shown to be highly affected by the allocated attention.

To compare the effects of visual and auditory cues on PD gait in increasingly complex motor-cognitive tasks, Rochester et al. (2005) conducted a study in which PD patients and healthy individuals performed a gait task that included walking from one room into another room (single task), picking up a tray with two cups of water and walking back to the starting position (dual task), and depositing the tray on a table. The task was performed with and without external auditory and visual cues. The results indicate that using auditory cues – but not visual cues – during performance of the dual motor-cognitive task reduced the task's interference of motor-cognitive integration and increased PD patients step length by 19%. Ameliorative effects of temporally-delivered auditory cues, and not spatially-delivered visual cues could be explained by PD patients' increased reliance on visual processing which in turn reduces the available executive resources in visual perceptual domain.

Presented evidence on the effects of auditory, visual, attentional and combined cueing modalities indicate that temporally delivered auditory cues primarily affect temporal gait parameters such as cadence, while spatially delivered visual cues primarily affect spatial gait parameters such as step length. Overlap of effects where auditory cues caused changes in step length, while visual cues caused changes in cadence, point to an interaction of central processing mechanisms that govern sensory-motor integration and biomechanics of cued gait.

Although auditory and visual cues modulate gait performance of PD patients, these effects seem to be highly dependent on allocated attention – particularly in dual tasks where the effects of cueing are improved when actively attended to. Overall, temporal cues seem to elicit better responses in dual tasks. Based on these observations, TC cues delivered in temporal domain and not actively used in spatial orientation should modulate movements in single and dual motor-cognitive tasks better than auditory or visual cues.

2.3.3 Tactile Cueing

Increased understanding of the sensory cueing potential for PIGD amelioration, as well as mounting research evidence suggesting that the positive effects of audiovisual cueing are limited by their interference with executive processing, resulted in recent increased interest in the use of TC for movement modulation. Contribution of TC to motor-cognitive integration has been dramatically demonstrated by McGrath et al. (2004) who outfitted pilots of high performance aircraft and helicopters with an instrumented flight vest (TSAS – Tactical Situational Awareness System) that provided vibrotactile stimuli conveying 3D information on aircraft orientation. Deprived of all visual inputs and relying exclusively on tactile cues for orientation, the pilots were able to adapt to the novel sensory modality within minutes, perform high performance maneuvers in flight, and land the aircraft. Application of TC could therefore be a feasible means of improving gait in PD patients while simultaneously reducing the burden on the patients' executive control resources.

In an early TC study, van Wegen et al. (2006) investigated whether 17 PD patients (aged 63.4 ± 10.3 years, H-Y 2.5 ± 0.9, MMSE ≥ 24) could adapt their treadmill walking pattern using rhythmic auditory cues to changing walking speeds and the presence of distracting visual flow. All participants performed systematic walking speed manipulations with and without cueing and distracting visual flows. The cueing rhythm was delivered at the wrist in 400ms bursts at stepping intervals 10% slower than their individual comfortable stride intervals for each of the four speed conditions tested: 0.6 m/s, 1.4 m/s, 2.2 m/s, 3.0 m/s, 3.8 m/s. Speed conditions lasted for 1 minute and were delivered consecutively from lowest to highest and from highest to lowest.

Walking with TC resulted in lower cadence and longer step lengths, regardless of walking speed. The presence of visual flow did not impair the use of tactile cueing suggesting that TC may be more resistant to interference from visual sensory modality and therefore a more robust cueing modality. Although the obtained results demonstrate that TC is a viable modality for modulation of cadence and step length, the findings cannot be well generalized to potential effects of TC in overground walking since treadmill ambulation produces proprioceptive cueing through the continuous movement of the belts and in that way affect production, timing and length of stepping.

In a study performed by Rochester et al (2007), changes in gait performance in 153 PD patients (ages 40 – 80, H-Y 2 – 4, MMSE ≥ 24) in response to using three rhythmical cues – auditory, visual and tactile, delivered at the comfortable stepping intervals – were measured during a single walking task and a dual walking task that were performed in the patients' homes. Spatiotemporal gait parameters of – gait

speed, step length and cadence – were collected by accelerometers. Single task consisted of walking in a straight line, while dual task included walking while carrying a tray with two cups of water. Interference effect between the single and the dual task was calculated to assess the extent to which the combined effects of task and cues interact in modulation of gait.

The results indicate that in single task, visual and tactile cueing reduced gait cadence and gait speed, while auditory cueing only reduced cadence. However, in dual tasks, tactile and auditory cues increased gait speed and step length but reduced cadence, while visual cues decreased gait speed and cadence but increased step length. The calculated interference effects indicated that in spite of the ameliorative effects of sensory cueing, there was a significant decrease of step length and gait speed in dual vs. single task. The reported effects were dependent on cue modality such that improvements for auditory cues were the greatest, while all cued trials improved the spatiotemporal gait parameters. While auditory cues yielded greatest improvements, tactile cueing yielded better effects than visual cueing. These findings further indicate that TC may facilitate motor-cognitive integration by facilitating attention shifting during complex motor tasks.

In a following study, Nieuwboer et al. (2009) investigated the effect of visual, auditory and tactile cueing – delivered at the comfortable stepping interval – on the duration of a functional turns in 133 PD patients (H-Y 2-4, MMSE 28.1 ± 2.9) who experienced FOG episodes (n = 68) and those who did not (n = 65). Since turning has been associated with instability, falls, and freezing in PD, the effect of the three cueing modalities on functional turning performance was investigated. The trials involved a 180 degree turn while picking up a tray with two glasses of water. All

three cueing modalities increased the speed of turn in all subjects. While auditory cues sped up turning more than visual cues, tactile cues increased turning speed even more than auditory cues. These results further support the proposition that TC – a low cognitive demand cueing modality – enhances motor performance during complex turning tasks by reducing the motor-cognitive integration load and facilitating attention shifting.

Although these results suggest that tactile cueing might achieve similar results as auditory cueing, the understanding of TC effects on modulation of simple movements and complex functional gait tasks remain incomplete. The use of different tasks (e.g. treadmill vs. overground walking; single vs. multiple cueing intervals), data collection settings (laboratory vs. home), and different study populations (e.g. with / without healthy control group) contribute to overall low external validity of thus reported studies. The methodological inconsistencies also contribute to incomplete understanding of the role of attention in TC movement modulation and motor-cognitive integration. Based on the reviewed studies and identified knowledge gaps, the series of integrated experiments in this dissertation for the first time systematically investigated TC efficacy and effectiveness in modulating simple and complex motor tasks over a range of functionally relevant cueing intervals, and in tasks requiring various levels of biomechanical and cognitive integration. Finally, as a common thread to auditory, visual and tactile cueing, the role of attention, executive function and competition for cognitive resource in the context of motor-cognitive integration are discussed in the following section.

2.3.4 Attention, Executive Function and Dual Tasking

It has been well documented that PD patients' ability to concurrently engage in multiple task performance is impaired (Canning et al. 2005, 2008; Giladi et al. 2007; Morris et al. 1996; Redgrave et al. 2010; Rochester et al. 2005) due to attentional overload and inability to rely on automatic movement control (Wu et al. 2010). In their study involving visual and attentional cueing, Morris et al. (1996) determined that constant attentional monitoring was required for attentional strategies to maintain their effectiveness in improving motor-cognitive performance – because exposure to interfering attentional task diminished the ameliorative effects of cueing.

As defined by Ward (2006), the executive cognitive function (a) optimizes performance in situations requiring operation of multiple cognitive processes; (b) controls / supervises non-automatic processes; (c) coordinates working memory (implicit / explicit) and controls manipulation of information. Current theoretical understanding of the executive processes center on the capacity-sharing theory, the bottleneck theory, the multiple resource models theory, and the cross-talk theory – all of which bear relevance to results of previously reported sensory cueing studies.

The capacity-sharing theory posits that attentional resources are limited in capacity, and so the performance of two attention-demanding tasks will cause deterioration of at least one of the tasks. When time between presentations of two or more stimuli is reduced, the processing time increases because of the limitations of the shared capacity (Rogers 2006). Thus, the performance of an additional task during walking alters gait, or the execution of the second task, or both. Similarly, the bottleneck theory proposes that if two tasks are processed by the same neural

processor or networks, a bottleneck is created in the processing of information. The processing of the second task will be delayed until the processor is free from processing the first task. According to this theory, performance of another task during walking might result in a slowed gait or delayed performance of the second cognitive task, but only if the neural networks involved in the two processes overlap (Ruthruff et al. 2001).

The multiple resource models suggest that processing may need a number of resources (Schmidt & Lee 2005) indicating that if any two tasks do not share common resources, dual task interference will not occur. Conversely, the cross-talk theory posits that if both tasks are from a similar domain and use the same neuronal populations, they will not disturb each other (Schmidt & Lee 2005).

Neuroimaging studies demonstrate that during dual tasking activity is found in the anterior cingulate cortex and prefrontal areas including the inferior frontal gyrus which are also involved in executive processing (Collette et al. 2005). Simultaneous performance of two attention-demanding tasks not only causes a competition for attention, it also challenges the brain to prioritize between the two tasks. Two areas of the brain are commonly mentioned in connection with the process of prioritization, the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC). Activation of both areas has been well documented when subjects perform dual tasking (Collette et al. 2005).

Consistent with this idea, when healthy adults performed a cognitive task while walking, quality of the task declined, but the gait pattern and gait stability did not, perhaps in order to avoid falling which suggests that appropriate prioritization of gait in healthy adults may be contrasted to the response to dual tasking in patient

populations. Patients with Parkinson's disease thus seem to use a "posture second" strategy and unnecessarily exacerbate their risk of falling in dual tasking situations (Yogev et al. 2008).

As demonstrated by studies of Rochester et al. (2005) and Nieuwboer et al. (2009) performance of concurrent gait-cognitive tasks resulted in PD patients walking at reduced gait speed and with shorter step lengths. Decreased executive function in PD patients was strongly implicated in reduction of gait speed during performance of the functional gait tasks. Thus, the research evidence supports the proposition that dysfunction of striatal automatic control and frontostriatal pathways in PD (Redgrave et al. 2010; Wu & Hallet 2010) increases the reliance of patients on goal directed behaviors, while at the same time impairs the executive function.

In a study that reiterated the significant role that attention has on the interplay of sensorimotor and cognitive processes in generation of gait, O'Shea et al. (2002) investigated the effects of the type of secondary task – motor or cognitive – on the extent of the task's interference with the primary task performed by PD patients. PD patients had lower stride length, cadence and gait speed than the healthy individuals during single task performance. While performing dual tasks, stride length and gait speed were decreased in the healthy participants, and decreased even further in PD patients who also exhibited a further decrease in cadence. However, the type of secondary task (motor or cognitive) was not found to be related to the extent of interference or performance decrement.

Within the context of PD-related impairments in sensorimotor integration, it is likely that the prominent PIGD symptoms, exacerbated during performance of dual

motor-cognitive tasks, are related to dysfunctional motor-cognitive integration modulated by BN and prefrontal regions. Thus, systematic manipulation of motor task complexity (i.e. simple – seated heel tapping; complex – straight line walking; highly complex – walking and turning; with and without secondary task) over a range of functionally relevant cueing intervals should require increased modulation of executive function and attention allocation. Since experimental protocols in the current research project were tested in two population samples – PD and healthy – with distinctly different motor-cognitive integration capacities, the resulting data provide unprecedented insight into the effects of TC on combined modulation of motor and cognitive function.

2.4 SUMMARY

PD symptoms are caused by disruption of basal nuclei function and result in decreased movement automaticity, increased reliance on external sensory inputs, and a shift towards frontally-mediated executively-driven motor control. These changes induce gait difficulties and increase the risk of falls and related injuries. By exploiting the increased reliance on external sensory inputs for motor control, visual and auditory cueing have been used to transiently improve gait performance and motor-cognitive integration in PD. In this context, tactile cueing (TC) may present an alternative sensory cueing modality that is not as heavily implicated in executive control, and may thus be a more efficient means for improving gait and motor-cognitive integration in PD. The incomplete understanding of TC efficacy and effectiveness in PD movement modulation and motor-cognitive integration stems from the lack of systematic controlled investigations of these phenomena.

CHAPTER III

Manuscript I: Tactile Cueing Modulation of Simple and Complex Motor Tasks – Implications for Contemporary Models of Basal Nuclei Function in Parkinson's Disease

3.1 INTRODUCTION

Current models of Parkinson's disease (PD) neuropathology (e.g. Redgrave et al. 2010) suggest that reduced dopamine availability to basal nuclei (BN) causes dysfunctional posterior BN output. Since posterior BN mediate timing of motor activity (Freeman et al. 1993; Merchant et al. 2008; Rodriguez-Oroz et al. 2009), decreased dopamine availability results in decreased motor automaticity, slowness of movement or festination, and reliance on executive control for motor-cognitive integration (Dubuois & Pillon 2002; Hallet 2008; Jones et al. 2008, 2011; Jahanshahi et al. 2010). The progressive deterioration of BN function causes a reorganization of motor-cognitive processing away from BN-mediated automatic processing (via the lateral system), and towards pre-frontally-mediated, goal –directed, executively-driven processing (via the ventromedial system; Georgiou et al. 1993; Hallet 2008).

The shift in motor-cognitive integration increases the burden on executive control which translates to slower attention shifting, longer processing times, and ultimately results in higher incidence of falls and fall related injuries (Bloem et al. 2001; Keus et al. 2007; Niino et al. 2000). Here, changes in motor-cognitive integration refer to changes in motor performance characteristics when the primary motor task (e.g. heel tapping or walking) is performed with or without a secondary motor task (e.g. holding / carrying a tray with cups of water), or is compounded by

additional performance demands (e.g. turning around obstacles) – all of which require increased executive control and attention allocation.

In a seminal study, Martin (1967) opened a promising line of research on sensory cueing as a source of movement modulation in BN disorders. Since then, visual and auditory sensory cueing has been shown to ameliorate PIGD symptoms and improve motor learning in PD patients (Azulay et al. 2002; Dibble et al. 2004; Dobkin 2003; Hallet 2008; Maschke et al. 2003; Suteerawattananon et al. 2004; Rochester et al. 2004; Nieuwboer et al. 2009b; Rochester et al. 2010). The mechanisms behind improved motor performance through sensory cueing in PD are thought to be based on the afferent cerebello-nigro-thalamic-cortical pathways that constitute the ventromedial system which is preserved in PD (Chuma et al. 2006; Marsden and Obeso 1994; Redgrave et al. 2010).

While most of sensory cueing studies to date have used auditory and/or visual cues, a few recent studies have begun investigating the tactile sensory modality, as the positive effects of audiovisual cueing are limited by their interference with executive processing. For example, Van Wegen et al. (2006) found that rhythmic vibrotactile cues reduced cadence and increased step length in PD patients walking on a treadmill. Also, Nieuwboer et al. (2007, 2009) demonstrated that three-week in-home TC training increased gait speed and step length, reduced freezing of gait, and improved the speed of walking around turns. Finally, Rochester et al. (2007; 2010) found that tactile cueing increased walking speed and step length during dual motor tasks. The evidence form these studies provide support for the hypothesis that TC modulates the timing of motor performance.

Tactile sensory inputs enable rapid (~85ms) postural stabilization and reestablishment of spatial orientation after exposure to destabilizing or disorienting visual, vestibular, and proprioceptive stimuli (Lackner & DiZio 2005). Tactile inputs to spatial orientation override the otherwise dominant visual (Rabin et al. 2004, 2008) and proprioceptive (Lackner et al. 2000) inputs, and are processed subconsciously (Johansson & Westling 1984) at approximately three times the speed of visual processing (Rabin et al. 2006). McGrath et al. (2004) demonstrated the functional utility of TC to spatial orientation and motor-cognitive integration by outfitting pilots of high performance aircraft and helicopters with an instrumented vest that provided vibrotactile stimuli conveying 3D information on aircraft orientation.

Deprived of all visual inputs and relying exclusively on tactile cues for orientation, the pilots were able to adapt to the novel sensory modality within minutes, perform high performance maneuvers in flight, and land the aircraft. Thus, the tactile system seems to play a primarily early warning / detection role for spatial orientation and situational awareness, and requires virtually no cognitive processing. Application of TC could therefore be a feasible means of improving gait in PD patients while simultaneously reducing the burden on the patients' executive control resources.

One of the most widely used research paradigms for studying timing of motor performance and motor-cognitive integration is the synchronization paradigm (Wing & Kristofferson 1973a, b) wherein the subject synchronizes a repetitive activity (e.g. finger tapping) to external sensory stimuli (e.g. auditory cues). This paradigm tests the participant's ability to entrain neuromotor responses to external stimuli and the functionality of the participant's internal timing mechanisms for maintenance of

rhythmic performance; it has been used in seminal studies (e.g. Freeman et al. 1993; Harrington et al. 1998; etc.) that demonstrated impairments of motor timing in PD patients with dysfunctional BN.

While a number of studies investigated the effects of sensory (auditory) cueing on timing synchronization of simple finger tapping tasks (e.g. Ivry & Hazeltine 1995), only one study (Chen et al. 2006) compared the synchronized performance of simple heel tapping and more complex stepping-in-place tasks in healthy individuals. Their findings suggest that combined effects of neuromuscular and cognitive task complexity synergistically deteriorate motor-cognitive integration. However, no randomized controlled studies have been reported in healthy, nor in PD patients comparing TC synchronization in simple lower limb motor tasks (e.g. heel tapping) to more complex walking tasks. Unlike simple heel tapping, lower limb motor control and integration into gait likely involve sub-pyramidal spinal central pattern generation (Dobkin 2003), and are subject to biomechanical and cognitive task constraints including control of balance in upright stance, bilateral coordination, and dynamic spatial orientation (Chen et al. 2006). The combined effects of neuromuscular and cognitive task complexity should therefore be expected to synergistically deteriorate motor-cognitive integration – particularly in the compromised PD patients.

Thus, understanding PD patients' and healthy individuals' ability to use TC for movement modulation in increasingly complex tasks could provide insight into the underlying mechanisms of PD-impaired and unimpaired motor-cognitive integration. Three principle research questions will be addressed by this manuscript: (1) How well can PD patients and healthy individuals use TC to modulate performance of a

simple motor task (seated heel tapping) over a range of cueing intervals? (2) How well can PD patients and healthy individuals use TC to modulate performance of more complex motor tasks (straight line walking) over a range of cueing intervals? (3) To what extent does a secondary motor task (carrying tray with two cups of water) interfere with the ability of PD patients to use TC to modulate increasingly complex motor tasks?

Therefore, the general aim of this study was to investigate differences between the ability of healthy individuals and PD patients to synchronize increasingly complex motor control tasks to rhythmic tactile cues delivered over a range of cueing intervals. Two experiments were conducted to answer the research questions. In the first, TC efficacy in modulating temporal parameters of motor performance were investigated in seated heel tapping. In the second, TC efficacy in modulating temporal gait parameters was investigated in straight-line walking. In both, participants were tested with TC delivered above and below their individual comfortable stepping intervals.

It was expected that (1) Healthy and PD participants would be able to modulate performance of heel tapping and straight line walking to TC, wherein performance variability was expected to be higher in PD patients; (2) Healthy participants and PD patients would be able to modulate motor task performance in response to modulation of TC interval duration wherein modulation efficacy would be higher in simpler tasks and at longer cueing intervals, and would be overall higher for healthy participants; (3) TC would improve performance in the presence of a secondary motor task.

3.2 METHODS

3.2.1 Participants

Two groups of participants were recruited for this study: a PD group and a healthy control group. Participants recruited into the PD group were diagnosed with idiopathic PD by a neurologist member of the investigator team, were on stable regimen of anti-Parkinsonian medication, and were able to independently walk and follow directions. Healthy participants were recruited from the general population by a flyer [*Appendix A*], and were sex-, age- (± 2 years), and activity-matched to PD participants. The study was conducted in compliance with the Federal and University of Houston (UH) policies regulating conduct with, and protection of human subjects in research; the study protocol was reviewed and approved by the UH Committees for the Protection of Human Subjects (CPHS). Each participant provided written, informed consent prior to participating [*Appendix B*].

3.2.1.1 Inclusion Criteria

All participants were free of significant medical conditions and cognitive impairments that could affect participation in the study (except for idiopathic PD), and were able to complete a 90-step continuous walk along a straight line. Age range for inclusion in this study was 55 – 85 years based on the Braak (2003) PD classification scale indicating higher incidence of idiopathic PD above 55 years of age. Potentially younger PD patients were excluded to reduce possible effects of aging on the results. Age, height and weight information were collected during the initial scripted interview [*Appendix C*] and verified after arrival to the test site.

Overall physical health and readiness to participate in the study were determined by the modified Physical Activity Readiness Questionnaire (PAR-Q;

Canadian Society for Exercise Physiology (2002); [*Appendix D*]) wherein eligible participants reported no significant medical conditions or limitations. Only individuals who engaged in minimal to moderate physical activity during the month prior to the study –determined by 0-3 score on the Self-Reported Physical Activity Questionnaire (SRPA-Q; Jackson et al. 1990; [*Appendix E*]) – were eligible to participate. PD patients staged 2 – 4 on the Hoehn-Yahr motor disability scale (Hoehn-Yahr 1968) were eligible to participate in the study if they were also high functioning individuals – determined by a score of 27 or higher on the Mini-Mental State Examination (MMSE; Folstein et al. 1975; [*Appendix F*]).

3.2.1.2 Exclusion Criteria

Potential participants were excluded from the study if they presented with a history of brain surgery or placement of a deep brain stimulator for Parkinson's disease, history of head trauma that resulted in loss of consciousness within 6 months prior to participation, any previous exposure to sensory cueing, and cognitive impairment preventing participants from following procedural instructions as determined by the PAR-Q, MMSE, and the H-Y scale (for PD patients).

3.2.2 Equipment

3.2.2.1 Tactile Cues

TC was administered using a standard commercial smart phone (MyTouch-3G™ HTC, Bellevue, Washington) weighing 0.16 Kg affixed to the lateral aspect of the less affected upper arm in contact with humero-radial joint (Myles & Binseel 2007; Weinstein 1968) by a Velcro strap. TC were provided using the embedded vibrator which oscillates at 100 Hz. TCs were generated by triggering 100ms vibration pulses

(Gemperle et al. 2003) through a custom-developed touch screen interface developed for Android™.

The baseline tactile cueing interval (TCI) for each participant was determined from that participant's average comfortable step interval (CSI) while walking over ground at their comfortable speed (Bilney et al. 2003; Menz et al. 2004; Webster et al. 2005). Based on the comfortable step interval (CSI), two shorter (i.e. faster), and two longer (i.e. slower) TCIs were established. For the purpose of relating TCI nomenclature to cued task performance, TCI durations are referred to in terms of performance speed (i.e. slower, faster than CSI; Table 3.1). Thus, the two slower intervals were determined by adding 55ms ("Slower") and 125ms ("Slowest") to the comfortable stepping interval, respectively. The two faster intervals were determined by subtracting 55ms ("Faster") and 125ms ("Fastest") from the comfortable step interval, respectively.

The ±55ms and ±125ms intervals have been established based on the time differences corresponding to ±10% and ±20% from comfortable stepping intervals reported in analogous auditory cueing studies, wherein synchronized gait performance was found to break down at ±20% from comfortable (Hausdorff et al. 2007; van Wegen et al. 2006; Willems et al. 2006; Zijlstra & Hof 2003). Table 3.1 describes the nomenclature and duration of tested tactile cueing intervals (TCIs).

Table 3.1: Nomenclature and durations of the investigated TCIs; comfortable step interval (CSI) was used as the base TCI. Tactile cueing intervals (TCI) are expressed as millisecond means and min/max of 95% confidence intervals (CI).

TCI Condition Names	***Slowest*** *CSI+125ms*	***Slower*** *CSI+55ms*	***Comfortable*** *CSI*	***Faster*** *CSI-55ms*	***Fastest*** *CSI-125ms*
PD TCIs (ms)	*0.70* *-0.70, +0.71*	*0.63* *-0.63, +0.64*	*0.58* *-0.57, +0.58*	*0.52* *-0.52, +0.53*	*0.45* *-0.45, +0.46*
Healthy TCIs (ms)	*0.66* *-0.65, +0.66*	*0.59* *-0.58, +0.59*	*0.55* *-0.54, +0.55*	*0.48* *-0.47, +0.48*	*0.41* *-0.40, +0.41*

3.2.2.2 Gait Assessment

Kinematic data were collected using four triaxial inertial orientation trackers (Model MTx, Xsens Technologies B.B., Netherlands). Using flexible Velcro straps, one of these sensors was attached near the subject's center of mass (on the midline, just above the sacrum), two others were attached on the lateral aspects of subject's left and right thighs, and one was attached to the TC emitting phone (to record TC vibrations and serve as an event marker during cued trials, allowing the operator to turn on / off TC by tapping on the phone screen).

The MTx sensors were connected to a portable data logger (Xbus Master B, Xsens Technologies B.V., Netherlands) affixed to the participants' lower back by an elastic Velcro belt. The data logger digitized the triaxial accelerometer, rate gyroscope, and earth-magnetometer data from each MTx sensor at a rate of 100 Hz and processed these signals using a Kalman filter (XKF-3, Xsens Technologies B.V., Netherlands), which corrected for drift in gyroscope measurements of angular velocity. Thus corrected three-dimensional linear acceleration, angular velocity and angular displacement data were stored for later analyses. The MTx sensor outputs were aligned to a common reference frame before each experimental trial.

A GAITRite instrumented walkway (Model #4.7.0, CIR Systems Inc., Peekskill, NY) was used to determine stepping intervals and cadence (steps/min) at each subject's comfortable walking speed.

3.2.3 Procedures

3.2.3.1 Medication Intake, Sensor Fitting and TC Familiarization

To ensure that PD patients participated in the study during the "on" phase of their PD medication, they took their medication upon arrival at the test facility. During the next 45 minutes their anthropometric measures were recorded, they were fitted with the inertial sensors and the TC emitting phone, and they were familiarized with tactile cues by rhythmically tapping their foot in cadence with TC while seated for up to one minute. After 45 min the "on" state was verified by self-report and items 3.1 – 3.10 of UPDRS, and the MMSE was administered to determine the level of cognitive function. The "On" state was verified if patients reported they were functional to a level of 9 on a 10 point scale, and if they were able to complete all UPDRS tasks including bilateral rhythmic finger snapping, heel tapping, and straight line walking. The healthy individuals followed a similar timeline (without taking any medication) and were administered the MMSE at the same time as the PD participants. "On" states were reconfirmed in the middle of the protocol, and after completing the protocol (Nieuwboer et al. 2000).

3.2.3.2 Baseline Gait Parameters

Baseline gait parameters were established in three walking trials at participants' comfortable walking speed over a straight 15m X 1.5m walkway. The 5 m long GAITRite pressure mat used to determine gait baseline parameters was located in the middle of the walkway. GAITRite and MTx data were collected simultaneously throughout each trial – starting 5 seconds prior to the start of walking, and terminated 5 seconds after the end of walking. Step interval, step length, cadence, and gait speed were calculated immediately by the GAITRite system

and used to calculate comfortable base TC intervals. The same parameters were calculated off-line from the Xsens data for quality control and calibration purposes. At the beginning of each trial, the participants were instructed to walk at their comfortable speed throughout the trial. A one min break was given after each trial.

3.2.3.3 Experiment #1 – Seated Heel Tapping

In the seated heel tapping experiment, the participants were seated comfortably in a chair, with feet on the ground, knees bent at approximately 90^{o}, and back straight and relaxed leaning against the back rest. The arm to which the smart phone was attached, rested comfortably on a padded table surface to minimize motion and/or discomfort (Figure 3.1), except during dual-tasking trials, when both arms were used to stabilize a tray holding two full water cups.

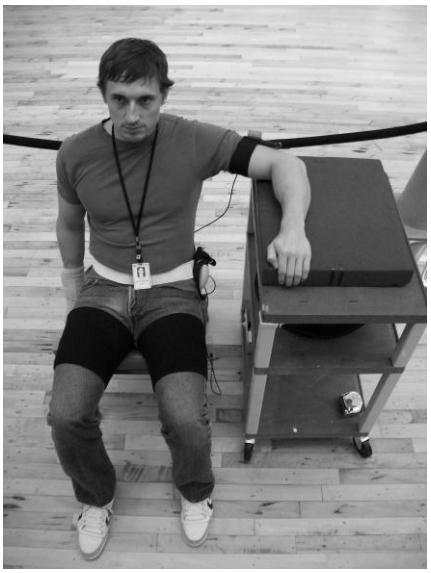


Figure 3.1: Setup for data collection during the heel-tapping procedures in Experiment #1.

The aim of this experiment was to investigate the ability of PD patients and healthy individuals to modulate simple heel tapping movements in response to TC, by characterizing temporal movement parameters with TC delivered at the comfortable stepping interval (CSI), two slower TC intervals (CSP+55ms, CSP+125ms),

and two faster TC intervals (CSI-55ms and CSI-125ms), which were previously found to be at the limits of auditory cued synchronized gait (Hausdorff et al. 2007; van Wegen et al. 2006; Willems et al. 2006; Zijlstra & Hof 2003).

Each participant completed a total of six trials. Two of the six trials were cued at CSI. One of the two CSI trials was conducted with a secondary motor-cognitive task (holding a tray with two cups of water) in order to assess TC effects on motor-cognitive integration. The four remaining trials were cued at faster and slower intervals respectively. The order of trials was randomized. Participants were given a three minute break after each trial.

During each trial the participants were required to tap their heel (while keeping their toe in contact with the floor) 90 times without interruption. During the first 30 taps (Pre-synchronization) the participants tapped at their self-selected comfortable cadence without TC. Following the 30^{th} tap, the operator initiated TC, and for the subsequent 30 taps (Synchronization), the participant attempted to tap in cadence to TC. Following the 60^{th} tap, TC was automatically stopped, and for the final 30 taps (Continuation) the participant attempted to maintain the tapping cadence previously provided by the TC.

3.2.3.4 Experiment #2 – Straight Line Walking

The straight line walking experiment was procedurally identical to the heel tapping experiment, with the only difference being that participants walked, instead of tapped. Here, participants walked along a straight 150m X 4m hallway (Figure 3.2). The hallway was cleared of pedestrians while the test was in progress, and supporting instrumentation was wheeled along behind the subject.

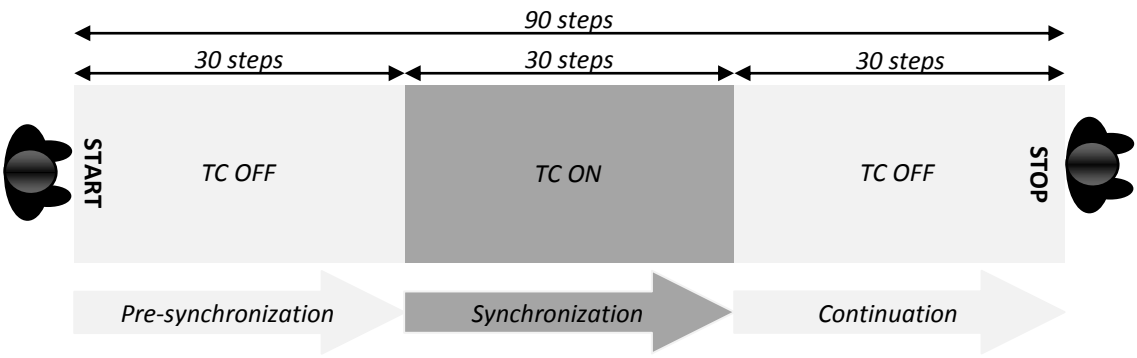


Figure 3.2: Schematic representation of the 90 step walkway used in Experiment #2. Arrows indicate direction of walking; not drawn to scale.

The aim of this experiment was to investigate the ability of PD patients and healthy individuals to modulate straight line gait in response to TC, by characterizing temporal movement parameters with TC delivered at the comfortable stepping interval (CSI), two slower intervals (CSI+55ms, CSI+125ms), and two faster intervals (CSI-55ms and CSI-125ms) – as described in previous sections.

Each participant completed a total of six trials. Two of the six trials were cued at CSI. One of the two CSI trials was conducted with a secondary motor-cognitive task (holding a tray with two cups of water) in order to assess TC effects on motor-cognitive integration. The four remaining trials were cued at faster and slower intervals respectively. The order of trials was randomized. Participants were given a three minute break after each trial.

During each trial the participants were required to walk in a straight line without interruption, until they completed 90 steps. During the first 30 steps (Pre-synchronization) the participants stepped at their self-selected comfortable cadence without TC. Following the 30th step, the operator initiated TC, and for the subsequent 30 steps (Synchronization), the participant attempted to step in cadence to TC. Following the 60th step, TC was automatically stopped, and for the final 30

steps (Continuation) the participant attempted to maintain the stepping cadence previously provided by the TC.

3.2.3.5 Data Reduction

The primary outcome measures for assessment of TC movement modulation in Experiments #1 and #2 were inter-tap interval (ITI) and inter step interval (ISI), respectively. TC effects on movement modulation were assessed by comparing ITIs and ISIs during synchronization phases at different TC intervals. ITIs and ISIs were calculated as the time difference between consecutive heel taps / heel strikes (designating steps) [*please refer to Equation A1 in Appendix G*].

Heel taps and heel strike times were manually identified using a custom script developed in Matlab (v.7.9.529, The Mathworks Inc., Natick, MA). Inter tap intervals (ITIs) were determined from superior-inferior linear acceleration of the thigh during the seated heel tapping task [*please refer to Figure A1 in Appendix G*]. The onsets of heel taps were visually identified as the minimum preceding the linear acceleration peak, and marked by cursor. The algorithm stored the time corresponding to cursor entries as times of heel taps. ITIs were then calculated for consecutive taps during each trial.

Inter step intervals (ISIs) were determined from anterior-posterior angular velocity profiles of the thighs [*please refer to Figure A2 in Appendix G*]. Heel strikes were visually identified as the first local minima after mid swing (designated by peak angular velocities and marked by cursor. The algorithm stored the cursor entry times as heel strike times. Inter step intervals were then calculated for all steps during a trial from consecutively recorded heel strikes. The procedure was repeated for all step cycles of both legs.

3.2.3.6 Statistical Analyses

Individual participant ITI and ISI data in all interval conditions were normalized to the individual comfortable step interval (CSI) through division of individual tap/step intervals by the comfortable step interval. All subsequent statistical analyses were then performed on thus normalized data. Statistical analyses of TC interval modulation effects on performance of simple (seated heel tapping) and complex motor tasks (straight line walking) in PD and healthy participants were performed by mixed design ANOVAs. The mixed design was defined by a within subjects factor "Interval" containing 5 levels (Slowest (CSI+125ms), Slower (CSI+55ms), CSI, Faster (CSI-55ms), Fastest (CSI-125ms)) and a between subjects grouping factor "Group" containing 2 levels (PD, Healthy).

Statistical analyses of task difficulty on performance of simple (seated heel tapping) and complex motor tasks (straight line walking) in PD and healthy participants were performed by mixed design ANOVAs. The mixed design was defined by a within subjects factor "Task" containing 2 levels (Single, Dual) and a between subjects grouping factor "Group" containing 2 levels (PD, Healthy). Differences between groups' accuracy were done by pairwise comparisons within the mixed ANOVA design. Analyses of synchronization accuracy in single and dual tasks were done by conducing paired samples and independent samples t-tests comparing normalized ITI and ISI data to the corresponding target CSIs, and comparing PD to healthy participants' data respectively, and calculating the lines of best fit across TCI conditions.

Analyses of main effects, interactions and pairwise comparisons were performed; Bonferroni adjustment for multiple comparisons were applied in all

analyses, while significance level was set to $\alpha = 0.05$. Since Mauchly's tests of sphericity were found to be significant in all performed analyses, the Greenhouse-Geisser corrections were applied to all reported results, and the data are presented as mean and 95% confidence interval (CI) minima and maxima (-, +). Statistical analyses were performed in SPSS v. 20 (IBM Corp., Somers, NY).

3.3 RESULTS

Twenty individuals were recruited to participate in this study (Table 3.2). PD group consisted of 10 patients with moderate PD and high level of cognitive function. The Healthy group consisted of 10 healthy individuals with high level of cognitive function who were sex-, age- and activity-matched to PD participants.

Table 3.2: Participants' demographic characteristics.

Group	*Age*	*N*	*Sex*	*Weight*	*BMI*	*H-Y*	*MMSE*	*SRPA-Q*
PD	*71.1*	*10*	*F 4*	*76.9*	*26.0*	*2.80*	*29.0*	*2.7*
	± 8.2		*M 6*	*± 14.1*	*± 3.6*	*± 0.48*	*± 1.1*	*± 0.7*
Healthy	*69.3*	*10*	*F 4*	*76.8*	*25.3*		*30.0*	*30.0*
	± 7.4		*M 6*	*± 15.9*	*± 3.4*		*± 0.00*	*± 0.0*

3.3.1 Effects of TC Intervals and Task Complexity on Motor Performance

In this manuscript, temporal parameters were analyzed only for the Synchronization phase of heel tapping and straight line walking experiments.

3.3.1.1 Seated Heel Tapping

In the seated heel tapping task, both PD patients and healthy individuals were able to effectively modulate heel tapping cadence to match TC cadence over the full range of TC intervals tested (CSI+125ms to CSI-125ms). While the main effect of Interval was significant ($F(3.8,1866.1) = 1008.1$; $p < 0.001$), the interaction of Interval X Group was not ($F(3.8,1866.1) = 1.0$; $p = 0.387$), indicating that both PD and

healthy participants were able to modulate their heel tapping in response to changing TC intervals in a similar manner. Figure 3.3 depicts the PD group's ITI responses to different cueing intervals. The healthy group exhibited similar performance, albeit with somewhat lower variability.

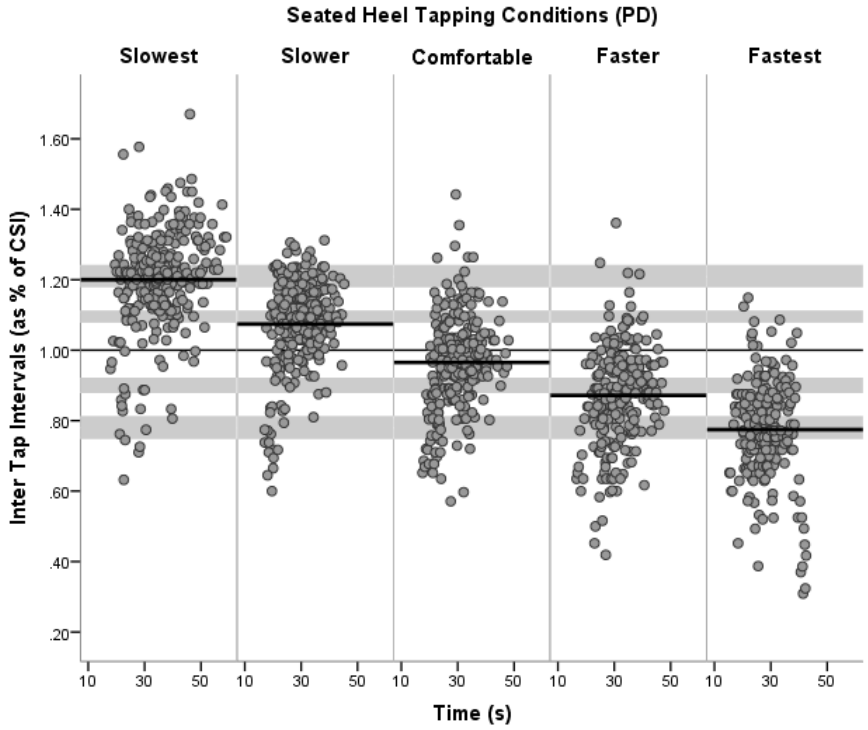


Figure 3.3: PD patients' ITIs during Synchronization segment (30 taps per participant) of the seated heel tapping experiment, normalized to CSI. The five panels depict ITIs over the five tested interval conditions (from Slowest to Fastest), with the time duration displayed on the X-axis for each panel/condition separately. Horizontal thin black line at 1.00 indicates mean cued CSI. Horizontal gray lines above CSI indicate mean CSI+55ms and CSI+125ms TCI conditions, respectively. Horizontal gray lines below CSI indicate mean CSI-55ms and CSI-125ms TCI conditions, respectively; the width of the gray line indicates the range of TC CSI. Solid bold black lines indicate ITI means in each TCI condition.

Overall, modulation of TC intervals from slowest (CSI+125ms) to fastest (CSI-125ms) resulted in shorter ITIs (i.e. faster tapping) in consecutive interval conditions for both groups of participants (Figure 3.4, top). As indicated by the lines of best fit and the corresponding R^2 values, both the PD (R^2 = 0.99) and the healthy (R^2 = 0.99) individuals were able to modulate heel tapping over the tested range of TCIs. As

indicated by the pairwise comparison, PD patients' synchronization accuracy was lower than healthy participants' – i.e. PD patients tapped faster than cued (festination) – so that the error difference between PD and healthy was approximately $\Delta = 2.6 \pm 0.01\%$ ($p < 0.001$).

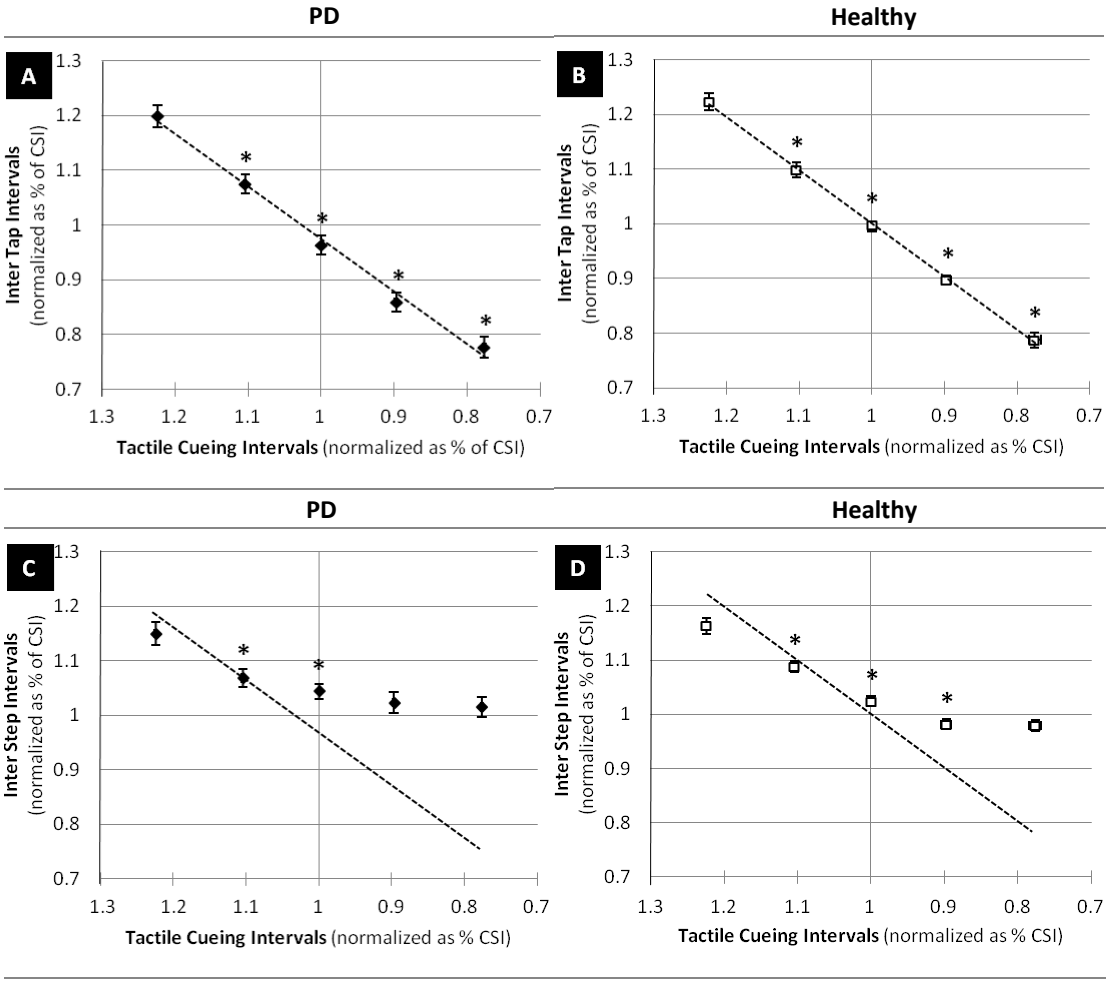


Figure 3.4: Inter tap/step intervals for PD (A, C) and healthy (B, D) participants normalized to, and expressed as % of comfortable step interval (CSI), across all TCI conditions. Top: seated heel tapping; Bottom: straight line walking. Horizontal lines indicate CSI, CSI±55ms, and CSI±125ms. All data expressed as means and 95% CIs. Dotted line of best fit plotted across all TCI conditions in A and B. For comparison, the same dotted lines are recreated in C and D. *denotes significant differences ($p < 0.05$) between consecutive tactile interval cue (TCI) conditions.

The finding indicates perseverance of the underlying PD-induced festination on the millisecond scale (arguably caused by reduced BN inhibitory control of the thalamus)

in spite of effective synchronization to TC. Tapping variability of PD patients was consistently higher than healthy participants' across all interval conditions (Figure 3.4, top).

3.3.1.2 Straight Line Walking

Unlike in the simple heel tapping task, in the more complex straight line walking task, PD patients were not able to modulate stepping beyond comfortable interval (CSI), while the healthy participants were not able to modulate stepping beyond faster interval (CSI-55ms; Figure 3.4, bottom). Here, the main effect of Interval was significant ($F(3.5,1448.7) = 187.5$; $p < 0.001$) as well as the interaction of Interval X Group ($F(3.5,1448.7) = 8.6$; $p < 0.001$), suggesting that PD modulated stepping in response to TC differently from the healthy participants.

There was a noted difference in the ability of PD patients and healthy individuals to modulate stepping in response to TCIs (Figure 3.4, bottom). While healthy individuals were able to modulate stepping from slowest (CSI+125ms) to faster (CSI-55ms) TCIs, PD patients were only able to modulate stepping between slowest (CSI+125ms) and comfortable (CSI) TCIs. However, as indicated by the lines of best fit and the corresponding R^2 values, the ability of both the PD ($R^2 = 0.56$) and the healthy ($R^2 = 0.84$) individuals to synchronize to TCI were dampened – i.e. both groups stepping lagged behind target TCI – with PD patients being able to synchronize over a narrow range of TCIs.

During straight line walking, relative to their respective target TCIs, PD participants overall stepped slower than healthy participants ($\Delta = 1.3 \pm 0.01$; $p = 0.009$), indicating a functional shift from festination in heel tapping, to lagging in straight line walking task. Inspection of inter step intervals (Figure 3.4, bottom)

indicates that PD patients' slower stepping relative to target TC intervals started occurring at comfortable (CSI), while for healthy participants it started at faster (CSI-55ms) TCIs. The noted shift from PD patients' festination to lagging (albeit on millisecond scale) suggests that increasing demands for neuromuscular control as well as motor-cognitive integration associated with more complex walking tasks delay motor performance in response to TC and ultimately diminish its efficacy.

3.3.2 Effects of TC on Dual Task Performance

3.3.2.1 Seated Heel Tapping

To further assess the relative contributions of neuromuscular and cognitive components of task complexity, performance of PD and healthy participants were compared in single and dual heel tapping and straight line walking tasks, as participants were cued at CSI. The results suggest that addition of a secondary motor task – holding a tray with two cups of water – slowed down seated heel tapping of PD and healthy participants (Figure 3.5, left) suggesting that the effects of the secondary task affected PD and healthy participants in a similar manner (main effect of Task ($F(1,544) = 11.15$; $p = 0.001$), Task X Group interaction ($F(1,544) = 0.37$; $p = 0.545$)). Dual tasking slowed down PD patients' tapping by 3.1% (-0.8, +6.0; $t = -2.4$; $df = 258$; $p = 0.019$) and healthy individuals by 2.2% (-0.9, +4.3; $t = -2.4$; $df = 286$; $p = 0.019$). More precisely, PD patients tapped 3.2% (-4.8, +1.6; $t = -4.4$; $df = 273$; $p < 0.001$) faster than cued (festination) in the single task, but they tapped on cue in the dual task. On the other hand, healthy participants tapped on cue in the single task, but slowed down to tap 1.7% (-0.4, +3.1; $t = 2.7$; $df = 286$; $p = 0.006$) slower than cued, in the dual task.

The noted slowing down of tapping should be considered in the context of synchronization accuracy – i.e. the magnitude of % difference between target cueing intervals and ITIs. When performing the single heel tapping task (Figure 3.5, left), PD participants were 3.2% (-5.1, +1.3) less accurate than healthy participants (t = -3.4; df = 273; p = 0.001). However, when performing dual task, the difference in synchronization accuracy diminished to 2.2% (-4.5, +0.2) between the two groups (t = -1.8; df = 260; p = 0.067).

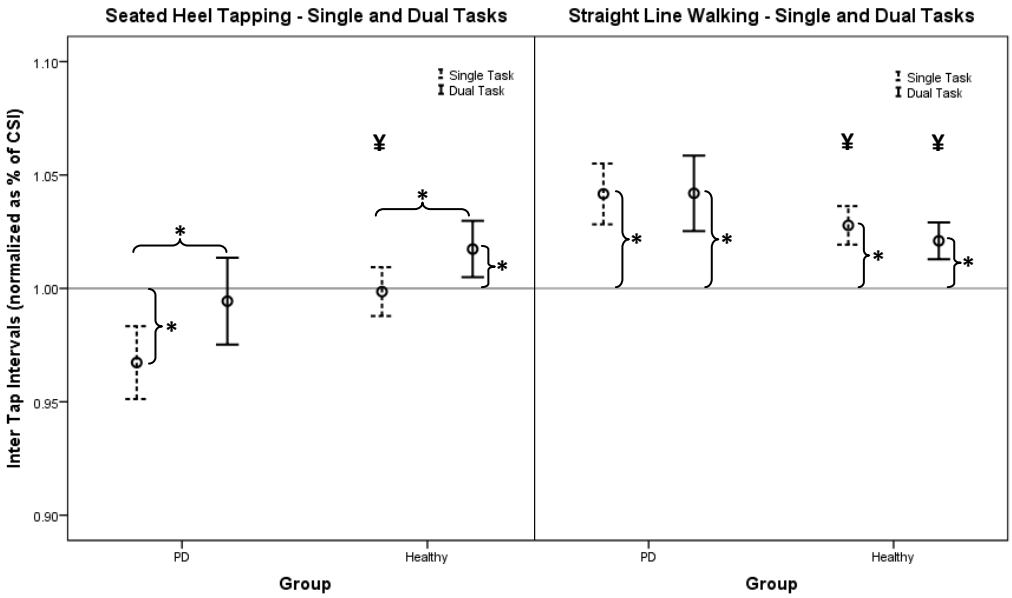


Figure 3.5: Inter tap/step intervals in single (dotted error bars) and dual (solid error bars) tasks normalized to comfortable step interval (CSI) during seated heel tapping (left panel) and straight line walking (right panel) experiments. Horizontal solid gray line indicates CSI. Significant difference ($p < 0.05$) between PD and Healthy groups within heel tapping and straight line walking experiments are designated by "¥"; all other significant differences ($p < 0.05$) designated by "*".

In the context of both groups' performance slowing down in dual tasks, these findings suggest that dual tasking slows down PD patients' ITIs more than healthy individuals'. However, since the pattern of change was similar in both groups, the results also indicate that in this simple heel tapping task, with low biomechanical and cognitive demand, and while being cued at comfortable intervals, the effects of TC

do not attenuate the negative effects of dual task on motor-cognitive integration which reflect in slower ITIs.

3.3.2.2 Straight Line Walking

Unlike in the heel tapping task, addition of the secondary motor task to straight line walking did not induce noticeable changes in stepping of PD nor of the healthy participants (Figure 3.5, right; main effect of Task ($F(1,494) = 0.4$; $p = 0.527$), Task X Group interaction ($F(1,494) = 0.5$; $p = 0.493$)). Since all tasks were performed while being cued at participants' comfortable intervals, these results could also indicate different effects of TC on motor-cognitive integration in simple (i.e. seated heel tapping) and more challenging (i.e. straight line walking) tasks.

Support for this proposition also comes from the analyses of synchronization accuracy showing that heel tapping accuracy profiles are different to those found in straight line walking: namely, there was a uniform decrease in synchronization accuracy in straight line walking (Figure 3.5, right), so that PD patients stepped 4.2% (-2.8, +5.5; $t = 5.9$; $df = 222$; $p < 0.001$) slower than cue target (lagging) in the single task, and 4.2% (-2.5, +5.9; $t = 5.0$; $df = 214$; $p < 0.001$) in the dual task. Also, healthy participants stepped 2.3% (-1.4, +3.3; $t = 6.4$; $df = 283$; $p < 0.001$) slower than cued in the single task, and 2.5% (-1.5, +3.5; $t = 5.2$; $df = 284$; $p < 0.001$) in the dual task. Overall, PD participants were 1.8% (-0.1, +3.4) less accurate than healthy participants ($t = 2.7$; $df = 222$; $p = 0.039$) in single tasks, and 1.8% (-0.1, +3.5) in dual task ($t = 2.1$; $df = 214$; $p = 0.042$). Comparison of the cued heel tapping and cued straight line walking indicates that cued straight line walking reduces synchronization accuracy (i.e. delays response to synchronizing cues), and attenuates the negative effects of dual tasking.

3.4 DISCUSSION

The results from the heel tapping and straight line walking experiments support our hypotheses that (1) PD patients can modulate heel tapping and straight line walking cadences to TC over a range of cueing intervals; (2) increased levels of integration required by a task limit the range of TC intervals over which PD patients can modulate performance; (3) TC improves PD patients' performance in the presence of a secondary motor task.

Overall, both PD and healthy participants were able to modulate simple heel tapping and more complex straight line walking performance in response to TC. Increases in task complexity – from heel tapping to walking – limited the range of efficacious TC intervals: while healthy participants were able to modulate their stepping up to ~10% faster than their comfortable stepping intervals, PD patients were not able to use TC to modulate their stepping beyond their comfortable stepping intervals. Finally, introduction of a secondary motor task and performance of the more complex straight line walking task slowed down the cued tapping / stepping rate in PD patients. The relative change in cued dual task performance from single to dual task was negative, indicating that the effects of TC may be more useful at increasingly challenging motor-cognitive tasks.

In the seated heel tapping tasks of Experiment #1, which presented a low motor-cognitive integration and performance challenge, both PD and healthy participants were able to accurately modulate their performance in response to TC intervals – from slowest (CSI+125ms) to fastest (CSI-125ms) TCIs. PD participants tended to festinate, tapping at a rate that was faster than cued, while healthy participants tended to lag, tapping at a rate slower than cued. These findings for PD

patients could be explained by the dysfunctional internal timing and sensory integration at the level of BN (Harrington et al. 1998) where the common motor output of BN comprises of disinhibited excitatory output from posterior putamen resulting in festination ("inhibited inhibition"), and TC-modulated, ventromedially-dependent output from the anterior putamen (Redgrave et al. 2010).

At long TC intervals, external sensory input may dampen the festinating signal from posterior putamen and result in relative low festination. Decreasing TC interval however, decreases the dampening and ultimately results in net increase of festination (Jahanshahi et al. 2010; Jones et al. 2011). Since heel tapping requires low-level motor-cognitive integration and limited neuromusculature, festination resulting from dysfunction of central BN processing should increase with decreasing TC intervals. The heel tapping data for PD patients (Figure 3.4, top left) suggests an increasing trend in festination with decrease of TC interval, and thus supports the previously reported results by Jahanshahi et al. (2010) and Jones et al. (2011).

Conversely, in straight line walking tasks of Experiment #2, which presented higher motor-cognitive integration and performance challenge, PD and healthy participants were able to partially synchronize their performance to TC at longer intervals, and less so at shorter intervals. More specifically, PD patients were able to modulate their stepping rate in response to TC at 20% and 10% slower and at the comfortable stepping interval, but not at TC intervals shorter than that. Healthy participants, on the other hand were able to modulate their stepping rate in response to TC at 20% and 10% longer, comfortable and 10% shorter intervals. In addition, healthy participants stepped at a faster rate than cued, while PD patients stepped slower than cued.

These results are congruent with the notion that more complex motor tasks (i.e. straight line walking vs. seated heel tapping) require higher level motor-cognitive integration, as well as control of more complex neuromusculature (Chen et al. 2006; Ivry & Hazeltine 1995). Thus, in the more complex straight line walking task, festination of PD patients was expected to turn into lagging due to more complex neuromusculature and sensory demands involved in task performance requiring higher motor-cognitive integration. Due to dysfunctional BN and increased reliance on pre-frontal loops, PD patients may not be able to process the required motor outputs at shorter time intervals – particularly at shorter cueing interval conditions (Redgrave et al. 2010). Therefore, changes in PD participants' ITI performance (i.e. from festination to lagging) observed in the straight line walking task seem to support the proposed mechanisms of action.

These findings suggests that the dampening effects of long-interval TC combined with increasing motor-cognitive integration requirements and processing times, result in PD patients' performance shift from festination to lagging that was not observed in the simple heel tapping task. While healthy participants' performance follows a similar pattern same pattern as PD patients', it may be noteworthy that they festinated less, and lagged more than PD patients, further pointing to the underlying difference in BN functionality – i.e. controlled output from BN in healthy individuals opposed to disinhibited output in PD patients.

The results of comparisons of single and dual task performance in the heel tapping and straight line walking experiments provide additional insight into relative contribution of cognitive task demands on motor-cognitive integration. Namely, in the simple heel tapping task, introduction of a secondary task (holding a cup with

two cups of water) slowed down motor performance of both PD and healthy participants in spite of TC (Figure 3.5, left). However, while PD patients festinated compared to healthy participants in the single task, their festination was decreased in the dual task suggesting the role of attention in slowing down of disinhibited BN motor performance.

However, in the more complex straight line walking task, PD patients performed at a slower rate than cued, but this time, there was no difference between the single and dual task performance (Figure 3.5, right). There were also no effects of dual task on performance of healthy participants. Thus, since addition of a secondary motor task during performance of a simple motor task slows down motor performance, it should be expected that addition of a secondary task to an even more complex task (i.e. straight line walking) should introduce an even greater relative slowing down of performance. Yet, while overall performance of PD patients was slower in the more complex straight line walking task, the relative change of timed performance between single and dual task was lower. A similar pattern was also observed in healthy participants. These results suggest that TC may play an important role in dampening the detremental effects of increased task complexity on motor-cognitive integration.

In the light of current knowledge, increased task complexity – i.e. walking vs. heel tapping – as well as dual tasking, should additively delay synchronized motor performance. Thus the observed delayed response in the single task may be explained by the increased neuromuscular and sensorimotor processing required to perform a walking task as opposed to a seated heel tapping task.

By the same token, however, it should be expected that performance of dual straight line walking task would (a) further delay stepping / decrease synchronization accuracy, and (b) exacerbate the difference between single and dual tasks accuracy. However, the results indicate that, compared to single task, there was no further synchronization delay. In summary, while the expected delaying effects of neuromuscular task complexity were found, the expected delaying effects of dual task were not found, suggesting the role of TC in attenuating detrimental effects of dual tasking on the cognitive component of motor-cognitive integration.

Based on current neurophysiologic models, tactile cueing is presumed to be processed, at least partially, by the ventromedial sensorimotor integration system which only minimally involves pre-frontal executive control areas, but relies on external sensory cues. Thus, in conditions in which cognitive resources (primarily executive control of attention) are not challenged to performance limits, it is expected that TC sensorimotor integration be allocated some portion of attention, which may in turn cause interference, and delay motor-cognitive integration.

However, since executive control of attention is thought to be involved in prioritization of attention allocation based on perceived importance of stimuli/processes, the attention allocated to TC may be reduced or diminished altogether when executive control resources are challenged by task demands (e.g. spatial orientation, balance, secondary task). This may in turn reduce the relative contribution of the pre-frontal, and increase the relative contribution of the ventromedial processing of TC, resulting in faster motor-cognitive integration.

Thus, in the least demanding, single heel tapping task, relative contribution of TC may be lower compared to more demanding dual heel tapping task. Respectively,

in the more demanding walking task, contribution of TC should be greater still, while it should be greatest in dual walking task. The observed attenuation of dual task effects in straight line walking may be interpreted as a result of TC engagement: in the most complex of the tested conditions, the executive resources may have been challenged to their limit by the motor-cognitive integration demands, which may have in turn minimized/eliminated attention allocated to TC, while maintaining ventromedial sensorimotor integration of TC into performance of the primary motor task – i.e. cued straight line walking. The finding that PD patients had consistently lower synchronization accuracy than healthy participants supports the assumption that PD affected motor-cognitive integration relies to a greater extent on pre-frontally mediated executive control, resulting in relative longer processing times.

In this context it is important to consider that the functional reorganization of motor-cognitive processing from BN-modulated automatic, to pre-frontally-modulated goal-directed, is supported by neuroimaging evidence indicating the existence of the ventromedial and lateral sensorimotor integration systems (Elsinger et al. 2006; Jahanshahi et al. 2010; Redgrave et al. 2010; Kojovic et al. 2012). The lateral system includes the supplementary motor area (SMA) and the BN (particularly posterior caudate), and is implicated in performance of internally-paced and motivated actions, while the ventromedial system includes the premotor cortex (PMC), parietal cortex (PC), thalamus and the cerebellum, and is implicated in performance of movements elicited in response to environmental sensory cues. Since the lateral system relies on BN function, PD-induced dysfunction of BN in turn causes the dysfunction of the lateral system.

Discussion of the relative motor performance changes in single and dual tasks – that seem to be attenuated by TC – should be done in the context of PD patients' impaired ability to concurrently engage in multiple task performance (Canning et al. 2005, 2008; Giladi et al. 2007; Morris et al. 1996; Redgrave et al. 2010; Rochester et al. 2005) due to attentional overload and inability to rely on automatic movement control (Wu et al. 2010). In their study involving visual and attentional cueing, Morris et al. (1996) determined that constant attentional monitoring was required for attentional strategies to maintain their effectiveness in improving motor-cognitive performance – because exposure to interfering attentional task diminished the ameliorative effects of cueing. However, the results indicating negative relative changes in motor performance with cueing in more complex – compared to simpler motor tasks – may suggest that unlike other sensory cueing modalities that require constant executive monitoring and attention, TC may elicit ameliorative effects on motor-cognitive performance of complex tasks. Within that context, these results provide further support to functional significance of TC and the motor-cognitive integrative role of the ventromedial system.

Finally, ITI variability was higher for PD participants – primarily in the simple motor task. Although all patients performed tasks on medication, sub-optimal dopaminergic neurotransmission is a plausible source of the inherently higher variability in motor performance of PD patients in both tasks (Frankel-Toledo et al. 2005). Furthermore, the higher variability found in the simple heel tapping task in PD patients may indicate changes in motor modulation based on the level of motor-cognitive integration required to perform the specific task.

Namely, in PD, due to dysfunction of automatic BN function, motor-cognitive integration is increasingly relegated to active, goal-directed prefrontal processing (Redgrave et al. 2010). However, with increasing motor task complexity – e.g. from heel tapping to straight line walking – motor control expands to involve central active (prefrontally-modulated) and automatic (BN-modulated), and sub-pyramidal automatic (spinal central pattern generation) processes, as well as the mechanics of the swaying leg (Frankel-Toledo et al. 2005; Hausdorff et al. 2007; Schmidt & Lee 2005). As performance of complex gait tasks involves distributed central and peripheral processing – which may effectively reduce the relative contribution of active common BN motor output – the variability of motor performance may be reduced in complex gait tasks wherein a combination of neuromotor and biomechanical mechanisms contribute to motor output. These data are further congruent with Harrington et al. (1998) and Jahanshahi et al. 2010 who indicate that PD patients' performance is more variable than that of healthy individuals.

In conclusion, TC was shown to modulate simple motor performance of PD patients and healthy individuals over a range of tested intervals. Increasing task complexity limits the efficacious range of TC intervals, wherein healthy individuals are able to modulate complex task performance at shorter TC intervals than PD patients. TC improves performance of complex tasks in the presence of a secondary motor task. TC may effectively be used to improve simple and complex motor performance in PD patients.

CHAPTER IV

Manuscript II: Tactile Cueing – Opportunistic Gait Aid Modality for Parkinson's Disease Patients

4.1 INTRODUCTION

Parkinson Disease (PD) ranks as the second most prevalent neurodegenerative disorder in the United States (NINDS 2004) and affects more than 4 million people worldwide (Dorsey et al. 2007). PD is characterized by motor and cognitive decrements caused by the progressive loss of dopaminergic neurons in substantia nigra of the basal nuclei (BN) involved in motor control. The result of this cell death is decreased movement automaticity, increased reliance on external sensory cues for movement timing, and a shift towards prefrontally-mediated, executively-driven motor control. The functional consequences of these changes include gait difficulties and increased risk of falls and fall related injuries. Due to its progressive nature, PD symptoms are exacerbated over the course of the disease. While no cure exists today, pharmacological treatments offer relief of motor and cognitive symptoms, but, they come at a cost of physical, cognitive, and emotional side effects and addiction to the medication (Jankovic 2002).

External visual and auditory cueing has been shown to transiently improve gait and motor-cognitive integration in moderately impaired PD patients by modulating spatial and temporal gait parameters, resulting in increased gait speed, cadence and step length, decreased turn times, and reduced freezing of gait (FOG) episodes (Baker et al. 2007, 2008; Hausdorff et al. 2007; Howe et al. 2003; Morris et al. 1994, 1996; Nieuwboer et al. 2007; Nieuwboer et al. 2009a; Rochester et al. 2005,

2009, 2010; Willems et al. 2006). While some studies (e.g. Willems et al. 2006) report increased step length with longer cueing intervals and slower cadence, others (e.g. Hausdorff et al. 2007) report decreased step length and variability – possibly due to reliance on mechanics of leg swings – with shorter cueing intervals. As reported by Willems et al. (2006), changes in gait parameters diminish at cueing intervals below and above ±10% of the comfortable walking speed, indicating breakdown of motor-cognitive integration beyond these cueing intervals. The beneficial motor-cognitive integrative effects of sensory cueing are thought to originate from sensory processing by the ventromedial system (Elsinger et al. 2006; Redgrave et al. 2010) they may (i) relieve the executive control burden on the prefrontal areas, (ii) increase neuromotor control of posture and gait, and (iii) reduce the risk of falls and fall related injuries.

The improvements associated with auditory and visual cueing in gait performance with secondary motor-cognitive tasks appear to be highly dependent on the amount of attention allocated to cue entrainment (Morris et al. 1994, 1996; Nieuwboer et al. 2009a). However, allocating attention to auditory and visual sensory cueing could additionally burden the executive control resources. As progressive reliance on executive control for simple motor tasks diminishes the PD patients' ability to provide adequate motor-cognitive responses to challenging situations – such as attention shifting to maintain situational awareness or adequate reaction times (Dobkin 2003) – any benefits of audiovisual cues may be short-lived and only effective in patients at earlier stages of the disease.

Cueing via alternate sensory modalities that are not central to maintaining spatial orientation and situational awareness may improve PD symptoms without

the burden on executive control and attention. Tactile cueing (TC) is a modality that has shown promise (Nieuwboer et al. 2007, 2009a; Rochester et al. 2007, 2010; van Wegen et al. 2006), but has not been extensively explored. Thus, the focus of this research effort was to explore the efficacy and effectiveness of TC in movement modulation and expand understanding of the underlying neurocognitive mechanisms relating PD-induced changes in basal nuclei to reorganization of motor-cognitive integration.

Due to direct anatomical connections, resulting from very early ontogenetic development of the tactile sensory system (McGrath 2000; Turner & Bateson 1988), its inputs enable extremely rapid (~85ms) postural stabilization and reestablishment of spatial orientation after exposure to destabilizing or disorienting visual, vestibular, and proprioceptive stimuli (Lackner & DiZio 2005). Furthermore, tactile sensory inputs to spatial orientation override the otherwise dominant visual (Rabin et al. 2004, 2008) and proprioceptive (Lackner et al. 2000) inputs, and are processed subconsciously (Johansson & Westling 1984) at approximately three times the speed of visual processing (Rabin et al. 2006).

To date, however, only a few studies (van Wegen et al. 2006; Nieuwboer et al. 2007, 2009a; Rochester et al. 2007, 2010) have investigated the efficacy of tactile cueing in modulating gait performance or motor-cognitive integration in PD. Van Wegen et al. (2006) found that rhythmic vibrotactile cues reduced cadence and increased step length in PD patients walking on a treadmill, Nieuwboer et al. (2007) demonstrated that three-week in-home TC training increased gait speed, step length and reduced freezing of gait, and later Nieuwboer et al. (2009) showed that TC improved the speed of functional turns. Finally, Rochester et al. (2007; 2010) found

that tactile cueing increased walking speed and step length during single and dual motor tasks. However, the methodologies in these studies were inconsistent, none of the studies involved healthy control participants, and none of the overground studies explored the effects of different cueing intervals which may reflect differential ability to organize adequate neuromotor output within longer or shorter time intervals as required by the particular task.

As a result, there remain knowledge gaps that lead to the principal research questions addressed by this study: (1) How well can PD patients and healthy individuals use TC to modulate performance of increasingly complex motor tasks – straight line walking, and turning corners – over a range of tactile cueing intervals (TCI)? (2) To what extent does a secondary motor task (carrying tray with cups of water) interfere with the ability of PD patients and healthy individuals to use TC to modulate the tasks – over a range of tactile cueing intervals?

An experiment was designed that, for the first time, systematically investigated TC efficacy in modulating increasingly complex motor tasks over a range of functionally relevant intervals by PD and healthy individuals. TC efficacy was investigated during single and dual (carrying tray with two cups of water) gait tasks with and without TC delivered at a range of cueing intervals above and below the individual's comfortable stepping intervals (CSI).

TC was expected to improve motor performance on all tasks, but particularly the highly complex tasks in the presence of the secondary motor task. Modulation of TC intervals was expected to modulate gait parameters so that greater modulation efficacy would be achieved at longer TC intervals. Healthy participants were

expected to perform better on all cued and non-cued tasks over the range of tested TC intervals.

4.2 METHODS

4.2.1 Participants

Two groups of participants were recruited for this study: a PD group and a healthy control group. Participants recruited into the PD group were diagnosed with idiopathic PD by a neurologist member of the investigator team, were on stable regimen of anti-Parkinsonian medication, and were able to independently walk and follow directions. Healthy participants were recruited from the general population by a flyer [*Appendix A*], and were sex-, age- (± 2 years), and activity-matched to PD participants. The study was conducted in compliance with the Federal and University of Houston (UH) policies regulating conduct with, and protection of human subjects in research; the study protocol was reviewed and approved by the UH Committees for the Protection of Human Subjects (CPHS). Each participant provided written, informed consent prior to participating [*Appendix B*].

4.2.1 .1 Inclusion Criteria

All participants were free of significant medical conditions and cognitive impairments that could affect participation in the study (except for idiopathic PD), and were able to complete a 90-step continuous walk along a straight line. Age range for inclusion in this study was 55 – 85 years based on the Braak (2003) PD classification scale indicating higher incidence of idiopathic PD above 55 years of age. Potentially younger PD patients were excluded to reduce possible effects of aging on

the results. Age, height and weight information were collected during the initial scripted interview [*Appendix C*] and verified after arrival to the test site.

Overall physical health and readiness to participate in the study were determined by the modified Physical Activity Readiness Questionnaire (PAR-Q; Canadian Society for Exercise Physiology (2002); [*Appendix D*]) wherein eligible participants reported no significant medical conditions or limitations. Only individuals who engaged in minimal to moderate physical activity during the month prior to the study –determined by 0-3 score on the Self-Reported Physical Activity Questionnaire (SRPA-Q; Jackson et al. 1990; [*Appendix E*]) – were eligible to participate. PD patients staged 2 – 4 on the Hoehn-Yahr motor disability scale (Hoehn-Yahr 1968) were eligible to participate in the study if they were also high functioning individuals – determined by a score of 27 or higher on the Mini-Mental State Examination (MMSE; Folstein et al. 1975; [*Appendix F*]).

4.2.1.2 Exclusion Criteria

Potential participants were excluded from the study if they presented with a history of brain surgery or placement of a deep brain stimulator for Parkinson's disease, history of head trauma that resulted in loss of consciousness within 6 months prior to participation, any previous exposure to sensory cueing, and cognitive impairment preventing participants from following procedural instructions as determined by the PAR-Q, MMSE, and the H-Y scale (for PD patients).

4.2.2 Equipment

4.2.2.1 Tactile Cues

TC was administered using a standard commercial smart phone (MyTouch-3G™ HTC, Bellevue, Washington) weighing 0.16 Kg affixed by a Velcro strap to the lateral aspect of the less affected upper arm in contact with humero-radial joint (Myles & Binseel 2007; Weinstein 1968). TC were provided using the embedded vibrator which oscillates at 100 Hz. TCs were generated by triggering 100ms vibration pulses (Gemperle et al. 2003) through a custom-developed touch screen interface developed for Android™.

The baseline tactile cueing interval (TCI) for each participant was determined from that participant's average comfortable step interval (CSI) while walking over ground at their comfortable speed (Bilney et al. 2003; Menz et al. 2004; Webster et al. 2005). Based on the comfortable step interval (CSI), two shorter (i.e. faster), and two longer (i.e. slower) TCIs were established. For the purpose of relating TCI nomenclature to cued task performance, TCI durations are referred to in terms of performance speed (i.e. slower, faster than CSI; Table 4.1). Thus, the two slower intervals were determined by adding 55ms ("Slower") and 125ms ("Slowest") to the comfortable stepping interval, respectively. The two faster intervals were determined by subtracting 55ms ("Faster") and 125ms ("Fastest") from the comfortable step interval, respectively.

The ±55ms and ±125ms intervals have been established based on the time differences corresponding to approximately ±10% and ±20% from comfortable stepping intervals reported in analogous auditory cueing studies, wherein synchronized gait performance was found to break down at ±20% from comfortable

(Hausdorff et al. 2007; van Wegen et al. 2006; Willems et al. 2006; Zijlstra & Hof 2003). The nomenclature, duration and corresponding variability for PD and healthy participants' tactile cueing intervals (TCI) over the five tested conditions is provided in Table 4.1 below.

Table 4.1: Nomenclature and durations of the investigated TCIs; comfortable step interval (CSI) was used as the base TCI. Tactile cueing intervals (TCI) are expressed as millisecond means and min/max of 95% confidence intervals (CI).

TCI Condition Names	***Slowest*** *CSI+125ms*	***Slower*** *CSI+55ms*	***Comfortable*** *CSI*	***Faster*** *CSI-55ms*	***Fastest*** *CSI-125ms*
PD TCIs (ms)	*0.70* *-0.70, +0.71*	*0.63* *-0.63, +0.64*	*0.58* *-0.57, +0.58*	*0.52* *-0.52, +0.53*	*0.45* *-0.45, +0.46*
Healthy TCIs (ms)	*0.66* *-0.65, +0.66*	*0.59* *-0.58, +0.59*	*0.53* *-0.53, +0.54*	*0.48* *-0.47, +0.48*	*0.41* *-0.40, +0.41*

4.2.2.2 Gait Assessment

Kinematic data were collected using four triaxial inertial orientation trackers (Model MTx, Xsens Technologies B.B., Netherlands). Using flexible Velcro straps, one of these sensors was attached near the subject's center of mass (on the midline, just above the sacrum), two others were attached on the lateral aspects of subject's left and right thighs, and one was attached to the TC emitting phone (to record TC vibrations and serve as an event marker during cued trials, allowing the operator to turn on / off TC by tapping on the phone screen).

The MTx sensors were connected to a portable data logger (Xbus Master B, Xsens Technologies B.V., Netherlands) affixed to the participants' lower back by an elastic Velcro belt. One MTx sensor was attached midline above the sacrum, two on the lateral aspects of left and right thighs, and one on the TC emitting phone by flexible Velcro straps (Figure 4.1). The sensor attached to the phone was used to record TC vibrations and served as a TC event marker during cued trials, allowing the

operator to turn on / off TC by tapping on the phone screen. The data logger digitized the triaxial accelerometer, rate gyroscope, and earth-magnetometer data from each MTx sensor at a rate of 100 Hz and processed these signals using a Kalman filter (XKF-3, Xsens Technologies B.V., Netherlands), which corrected for drift in gyroscope measurements of angular velocity. Thus corrected three-dimensional linear acceleration, angular velocity and angular displacement data were stored for later analyses. The MTx sensor outputs were aligned to a common reference frame before each experimental trial.

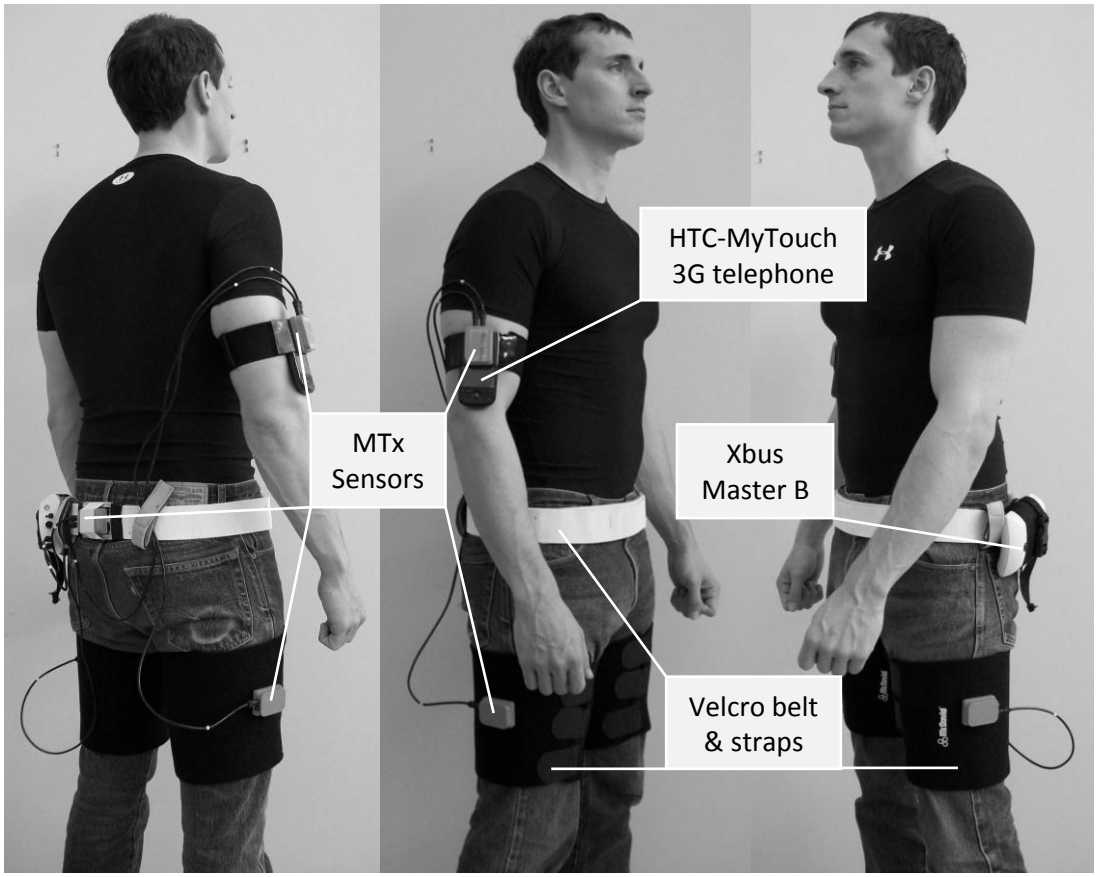


Figure 4.1: Locations of MTx inertial sensors, Xbus Master B portable data logger, and the TC emitting HTC-MyTouch-3G phone on the participant's body.

A GAITRite instrumented walkway (Model #4.7.0, CIR Systems Inc., Peekskill, NY) was used to determine step time and cadence (steps / min) at each subject's comfortable walking speed.

4.2.3 Procedures

4.2.3.1 Medication Intake, Sensor Fitting and TC Familiarization

To ensure that PD patients participated in the study during the "on" phase of their PD medication, they took their medication upon arrival at the test facility. During the next 45 minutes their anthropometric measures were recorded, they were fitted with the inertial sensors and the TC emitting phone, and they were familiarized with tactile cues by rhythmically tapping their foot in cadence with TC while seated for up to one minute. After 45 min the "on" state was verified by self-report and items 3.1 – 3.10 of UPDRS, and the MMSE was administered to determine the level of cognitive function. The "On" state was verified if patients reported they were functional to a level of 9 on a 10 point scale, and if they were able to complete all UPDRS tasks including bilateral rhythmic finger snapping, heel tapping, and straight line walking. The healthy individuals followed a similar timeline (without taking any medication) and were administered the MMSE at the same time as the PD participants. "On" states were reconfirmed in the middle of the protocol, and after completing the protocol (Nieuwboer et al. 2000).

4.2.3.2 Baseline Gait Parameters

Baseline gait parameters were established in three walking trials at participants' comfortable walking speed over a straight 15m X 1.5m walkway. The 5m long GAITRite pressure mat used to determine gait baseline parameters was located in the middle of the walkway. GAITRite and MTx data were collected simultaneously throughout each trial – starting 5 seconds prior to the start of walking, and terminated 5 seconds after the end of walking. Step time and length, cadence, and gait speed were calculated immediately by the GAITRite system and

used to calculate TC intervals. The same parameters were calculated off-line from the Xsens data for quality control and calibration purposes. At the beginning of each trial, the participants were instructed to walk at their comfortable speed throughout the trial. A one min break was given after each trial.

4.2.3.3 Functional Gait Task – Walking and Turning

All experimental trials were performed on a 9 meter bidirectional walkway (Figure 4.2). A rectangular pylon (0.5 X 0.5 X 2.4m) was located at one end of the walkway. A digital timer controlled by two pairs of IR photoelectric sensors placed 1m in front/behind the pylon, was used to measure turn times around it. The sensors were positioned on aluminum tripods at the height of 0.5m.

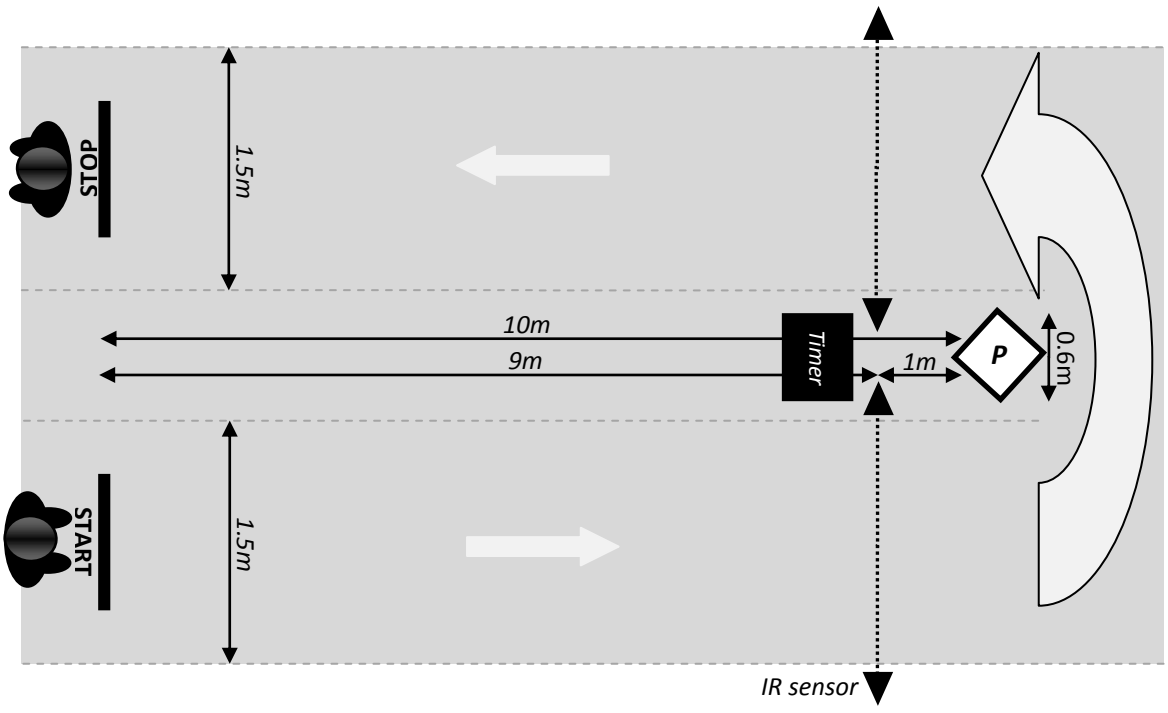


Figure 4.2: Schematic representation of the walkway used in the experiment. Pylon (P) is located at one end of the walkway, with timer-controlling IR sensors located 1m in front / behind the pylon; not drawn to scale.

Changes in spatial and temporal gait parameters in response to TC were assessed in a series of 24 gait trials around this course, tactile cueing at five different intervals, and two task difficulty levels. Four baseline trials without TC were

performed – two at each task difficulty level. Each trial consisted of three continuously executed segments: (1) walking 9 m in a straight line; (2) performing a 180^{o} turn around a pylon, (3) walking 9 m in a straight line back to the starting position. Two trials per condition were performed.

At the beginning of each non-cued trial, the participants were instructed to walk at their comfortable walking speed throughout the trial. At the beginning of each cued trial, the participants were instructed to step in cadence with the vibrations – one step for each vibration – throughout the trial. Two blocks of 12 single and 12 dual trials were performed. Each 12 trial block consisted of 6 blocks of 2 trials. The order of blocks of trials was randomized. After completing a trial, the participants were given a one minute break

4.2.3.4 Data Reduction

The primary outcome were stepping cadence, turn time and total task completion time and step length. Stepping cadence and step length were calculated for two straight line walking segments. Cadence was also calculated for the turn segment. Turn and task completion times were recorded by event markers and IR-sensor triggered timers respectively.

Step-by-step gait parameters were obtained from the angular velocity data captured by the lower extremity MTx sensors using a custom analysis algorithm developed in Matlab (v.7.9.529, The Mathworks Inc., Natick, MA) based on the method proposed by Aminian et al. (2002) and Salarian et al. (2004). For each trial, every heel strike was visually identified as the first local minima after mid swing and was marked by a cursor - *please refer to Figure A.3 (top) in Appendix G.* The corresponding pitch angles of each thigh at the exact time of the heel strike were

then retrieved and used to compute angular displacement from the baseline (i.e. vertical stance, 0 degrees) [*please refer to Figure A.3 (bottom) in Appendix G*].

4.2.3.5 Gait Modulation

Step lengths were then calculated based on modifications of a three-link model step cycle analysis methods proposed by Zijlstra & Hof (2003) and Salarian et al. (2004) [*please refer to Figure A.4 in Appendix G*]. The model assumes that a step cycle consists of a swing and a stance phase. A step begins with a swing phase marked by a toe-off from the preceding step. The end of the swing phase – which is also the beginning of the stance phase – is marked by a heel-strike. The most consistent step length is achieved at the instant of the heel strike which was therefore used as the measure of step length (Aminian et al. 2002; Gard & Childress 1999; Gard et al. 2004; Salarian et al. 2004).

4.2.3.6 Turn Time and Task Completion Time

Turn and task completion times were recorded by event markers and IR-sensor triggered timers respectively.

4.2.3.7 Statistical Analyses

Assessment of the effects of TC interval modulation was done by analyzing performance differences in cued and non-cued, single and dual tasks. All cued data were first normalized to non-cued baseline condition to assess the relative effects of cueing. Thus normalized cued data over the range of intervals were compared to the non-cued baseline. Then, to assess the relative effects of interval modulation on performance, all interval conditions were compared to the comfortable (CSI) condition. These analyses steps were performed for single and dual tasks.

Kolmogorov-Smirnov tests of normality were performed on all gait parameter data, and were found to be significant, thus indicating non-normal distribution of data and warranting the use of non-parametric statistical tests. The Wilcoxon signed-rank test was used for comparisons of pairs of related samples, the Mann-Whitney U test was used for comparisons of pairs of independent samples, and the Friedman's ANOVA was used for comparisons of multiple related samples. Statistical analyses were performed in SPSS v. 20 (IBM Corp., Somers, NY). Statistical significance was accepted for $p < 0.05$. Data are presented as median and 95% confidence interval (CI) minima and maxima (-, +). Statistical analyses were performed in SPSS v. 20 (IBM Corp., Somers, NY).

4.3. RESULTS

Twenty individuals were recruited to participate in this study (Table 3.2). PD group consisted of 10 patients with moderate PD and high level of cognitive function. The Healthy group consisted of 10 healthy individuals with high level of cognitive function who were sex-, age- and activity-matched to PD participants. Due to their persistent atypically fast performance of experimental protocol, two healthy participants (aged 72 and 77 years, respectively) were removed from data analyses.

Table 4.2: Participant demographic characteristics.

Group	*Age*	*N*	*Sex*	*Weight*	*BMI*	*H-Y*	*MMSE*	*SRPA-Q*
PD	*71*	*10*	*F 4*	*77*	*26*	*2.8*	*29*	*2.7*
	± 8		*M 6*	*± 14*	*± 3.6*	*± 0.5*	*± 1*	*± 0.7*
Healthy	*69*	*8*	*F 3*	*78*	*25*		*30*	*3.0*
	± 7		*M 5*	*± 18*	*± 3.4*		*± 0.0*	*± 0.0*

4.3.1 Gait Differences Between PD and Healthy Participants

Differences between PD and healthy participants at comfortable walking speed without / with TC (at CSI), and without / with secondary motor task are depicted in Figure 4.3. As expected, healthy participants were able to complete the full course (Figure 4.3 A), the straight segments (Figure 4.3 B), and the corner (Figure 4.3 C) more quickly than the PD participants for all conditions. But, surprisingly, no significant effects of task difficulty or TC (at CSI) were found on total task completion time (Figure 4.3 A) or straight line time (Figure 4.3 B). Dual tasking was shown to increase turn times (Figure 4.3, C) and decrease cadence (Figure 4.3, F) of PD patients, while TC was found to counteract these effects by reducing their turn times and increasing cadence. PD patients' gait was worse than that of healthy individuals.

Analyses of total task completion times (Figure 4.3, A) indicate that PD patients took on average 12.1s (42%) longer to complete single non-cued task than healthy participants ($p = 0.001$), and 14.6s (46%) longer to complete the dual non-cued task ($p < 0.001$). Also, it took PD patients 13.7s (46%) longer to complete single task cued at CSI than healthy participants ($p = 0.001$), and 11.9s (39%) longer to complete dual task cued at CSI ($p = 0.001$).

PD patients also took 9.1s (41%) longer to traverse straight line walking segments (Figure 4.3., B) than healthy participants in single non-cued task ($p = 0.001$), and 9.7s (43%) longer in dual non-cued task ($p = 0.012$). PD patients also took longer to traverse the straight line segments when cued at CSI in single ($\Delta = 12.5$s (50%); $p < 0.001$) and dual tasks ($\Delta = 9.2$s (40%); $p = 0.001$). It also took PD patients longer to complete functional turns than healthy participants in all four task / cueing conditions (Figure 4.4, C): single non-cued task ($\Delta = 1.54$s (26%); $p < 0.001$); dual non-

cued task (Δ = 4.0s (48%); $p < 0.001$); single cued task (Δ = 2.0s (44%); $p = 0.001$); and dual cued task (Δ = 3.54s (41%); $p = 0.001$). An increase in dual task non-cued turn time, and a subsequent decrease in turn time in the cued condition were noted in PD patients, suggesting possible effects of task difficulty and cueing on turn time.

Step lengths on the straight line segments were analyzed to assess their relative contribution to observed differences in task completion times between PD and healthy participants (Figure 4.3, D). The results indicate that PD patients' steps were shorter in all four conditions: single non-cued (Δ = 0.26m (33%); $p = 0.004$); dual non-cued (Δ = 0.28m (34%); $p = 0.001$); single cued (Δ = 0.28m (40%); $p < 0.001$); and dual cued (Δ = 0.27m (35%); $p < 0.001$). Analyses of cadence over straight line segment of the walkway (Figure 4.3, E), indicated no significant difference in cadence of PD patients and healthy participants in single and dual cued and non-cued tasks.

While analyses of cadence during the turn segment (Figure 4.3, F) indicate no difference between turn cadences of PD patients and healthy participants in single non-cued task; addition of the secondary motor task resulted in lower cadence of PD patients in non-cued condition (Δ = 15 steps/min (8%); $p = 0.006$). Yet, when performing single task while being cued at CSI, turn cadence was marginally lower for PD patients (Δ = 6 steps/min (5%); $p = 0.055$); but was no different during cued dual task ($p = 0.762$). Since functional turns are comparably, the most complex segments of the gait task, these results suggest that combined effects of task difficulty and secondary motor task cause significant motor-cognitive integration interference that reflects in decreased cadence (and as noted earlier – longer turn times) for PD patients. Restoration of cadence (and reduction of turn time) with TC, suggests potential ameliorative effects of TC on motor-cognitive integration.

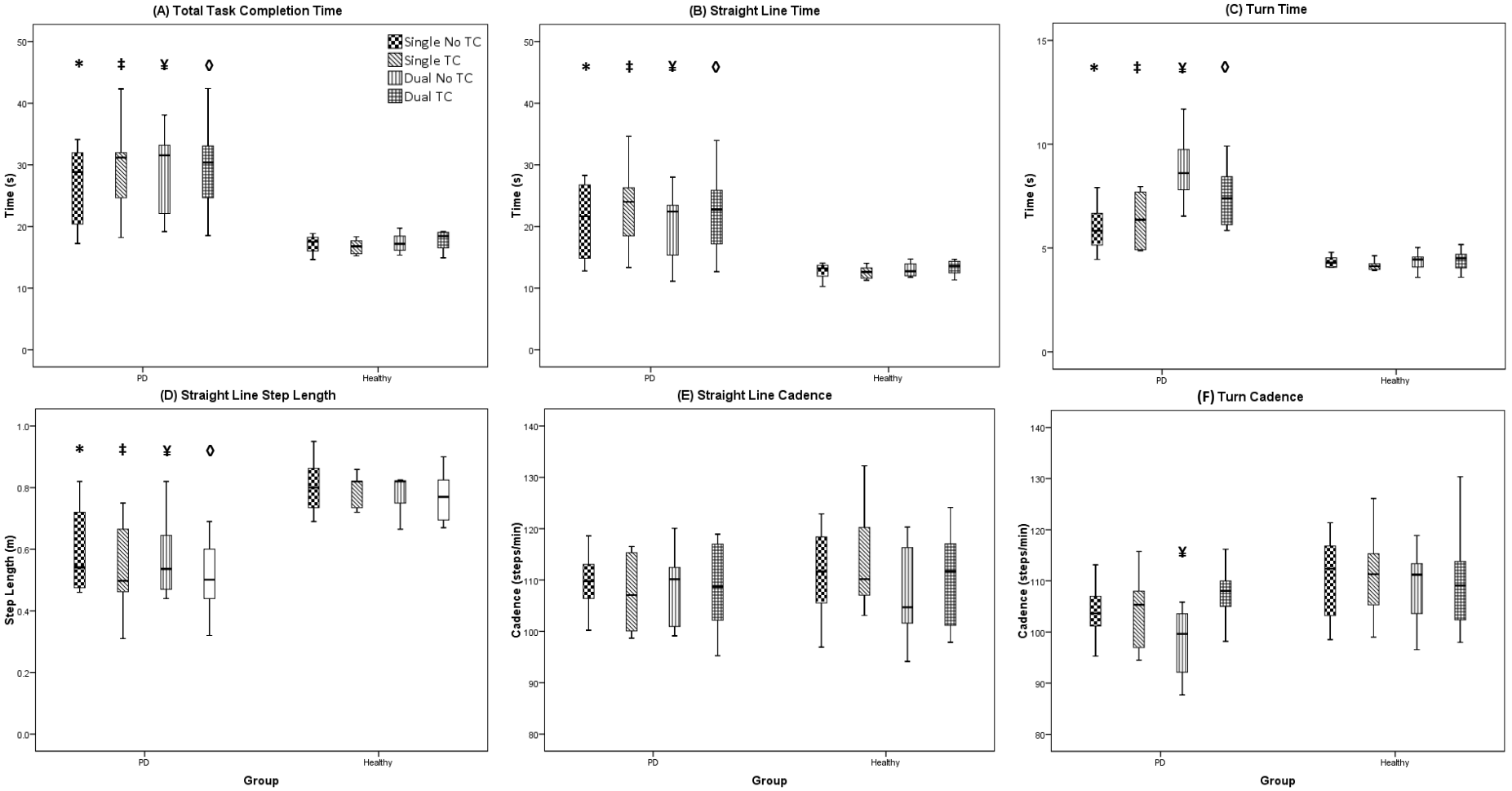


Figure 4.3: Gait parameters of PD and Healthy in Single NoTC, Single TC, Dual NoTC, Dual TC conditions: (A) Total task completion time, (B) Straight line time, (C) Turn time, (D) Straight line step length, (E) Straight line cadence, (F) Turn cadence. Significant differences between PD and healthy participants in specific conditions are depicted by following symbols: * Single NoTC; ‡ Single TC; ¥ Dual NoTC; ◊ Dual TC.

4.3.2 Effects of Tactile Cueing and Task Difficulty on Gait

Turn time differences across comfortable walking speed single, dual, cued and non-cued conditions were found in PD patients (χ^2 (3) = 18.60, p < 0.001), but not in healthy participants (χ^2 (3) = 4.05, p = 0.256). Cueing did not affect PD patients' turn times in single tasks (p = 0.114). However, in dual tasks, PD patients completed turns in less time when they were cued (7.6s, -6.3 +8.8) than when they were not cued (NoTC (8.5s, -7.2 +10.2); Z = -2.599, p = 0.009).

Turn cadence differences across comfortable walking speed single, dual, cued and on-cued conditions were found in PD patients (χ^2 (3) = 13.32, p = 0.004), but not in healthy participants (χ^2 (3) = 1.35, p = 0.717). Cueing did not affect PD patients' turn cadence in single tasks (p = 0.445). However, in dual tasks, PD patients turned at higher cadence when they were cued (108 steps/min, -100 +110) than when they were not cued (NoTC (96 steps/min, -91 +103); Z = -2.395, p = 0.017).

4.3.2.1 Relative Effects of Tactile Cueing (TC)

To assess the relative effects of tactile cueing on turn times (Figure 4.4, left) and turn cadence (Figure 4.4, right), the data in cued single and cued dual tasks were normalized to the baseline non-cued single condition. The results indicate that TC did not affect PD patients' turn times in single tasks, but that it significantly reduced them in dual tasks (p = 0.005); TC was also shown to be more effective in dual tasks than in single tasks (p = 0.005). As expected, the observed changes in turn times were driven by changes in turn cadence. Comparison of the relative effects of TC on PD turn cadence (Figure 4.4, right) shows that TC did not affect PD patients' turn cadence in single tasks, but that it significantly increased it in dual tasks (p = 0.017); again, TC was also shown to be more effective in dual than in single tasks (p = 0.013).

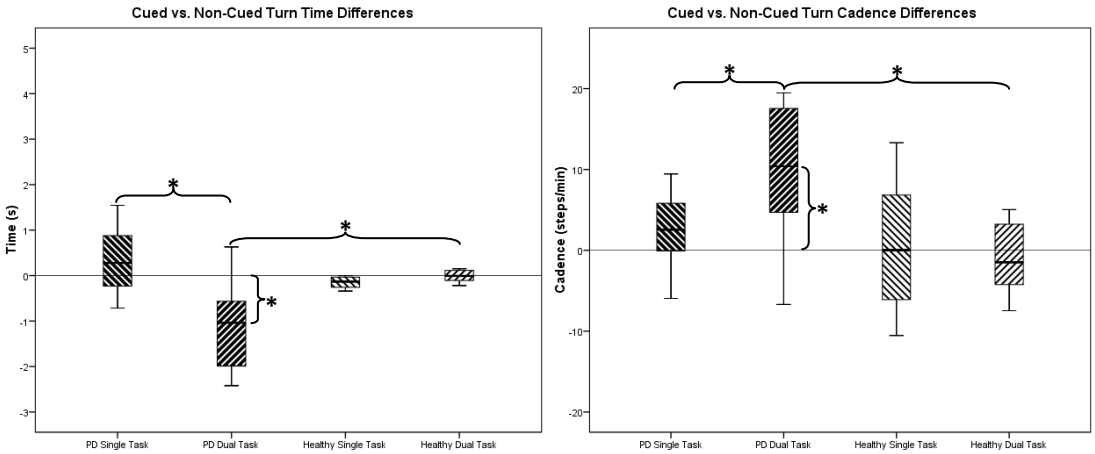


Figure 4.4: Differences in turn time (left) and turn cadence (right) between cued and non-cued conditions; Solid horizontal lines at 0 indicate non-cued single task turn time (left) and turn cadence (right), respectively; * indicate $p < 0.005$.

While there was no difference in TC effects on single task turn times of PD and healthy participants ($p = 0.173$), TC was shown to reduce PD patients' dual task turn times while not affecting those of healthy participants' ($p = 0.002$; Figure 4.4, left). Similarly, while there was no difference in TC effects on single task turn cadence of PD and healthy participants ($p = 0.173$), TC increased PD patients' turn cadence in dual tasks compared to healthy participants ($p = 0.034$; Figure 4.4, right).

4.3.2.2 Relative Effects of Task Difficulty

To assess the relative effects of task difficulty on turn times (Figure 4.5, left) and turn cadence (Figure 4.5, right), the data in dual non-cued and dual cued tasks were normalized to the non-cued single task condition. The results indicate that difficulty significantly increased PD patients' turn time ($p = 0.005$), but that this effect was significantly attenuated by introduction of TC ($p = 0.005$); However, in spite of the ameliorative effects of TC, PD patients' cued dual tasks took longer than non-cued single tasks ($p = 0.037$). Compared to non-cued single task (Figure 4.5, right), there was a relative decrease of turn cadence in non-cued dual task ($p = 0.013$), but

application of TC resulted in a significant increase of turn cadence in the cued dual task (p = 0.017). Thus, the negative effects of dual tasking on cadence were shown to be attenuated by introduction of TC (p = 0.013).

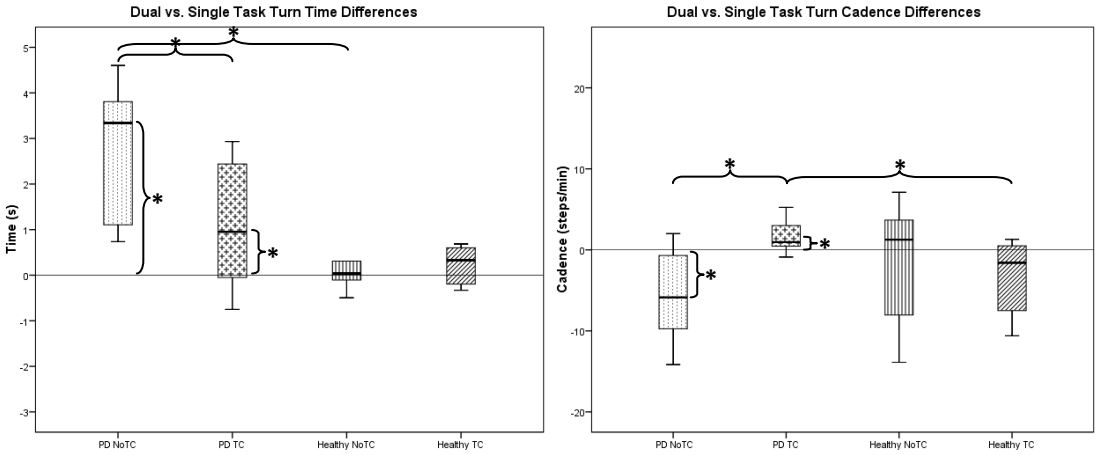


Figure 4.5: Differences in turn time (left) and turn cadence (right) between single and dual task conditions; Solid horizontal lines at 0 indicate non-cued single task turn time (left) and turn cadence (right), respectively; * indicate p < 0.005.

The delay in turn time introduced by dual task was greater for PD patients performing non-cued single task than healthy participants (p = 0.001), but when TC was applied, turn time difference between PD and healthy participants diminished (p = 0.146; Figure 4.5, left). Conversely, there was no difference in the effects of task difficulty on non-cued turn cadence between PD and healthy participants (p = 0.897). However, the marked increase in PD patients' cued dual task turn cadence was not found in healthy participants' data (p = 0.043; Figure 4.5, right), which suggests the effects of task difficulty are attenuated by TC in PD patients, but not the healthy.

4.3.3 Effects of TC Intervals and Task Difficulty on Gait

Since each trial contained two straight line walking segments, analyses of straight line segment data were first analyzed separately and compared to one

another. Since no differences were found in any of the tested parameters between the two segments, the data were averaged, and those averages were then used for all subsequent statistical analyses. No significant effects were found for straight line segment of the task. No effects of task difficulty (assessed in single vs. dual task) were found for these parameters. However, both TC intervals and task difficulty were found to affect turn cadence, turn time, and consequently – total task completion time. Thus, the interpretation of results will focus on performance of single and dual tasks in the turn segment of the task.

4.3.3.1 Single Task Performance

In single tasks (Figure 4.6), PD patients were able to modulate turn cadence to TC ranging from slowest (CSI+125ms) to faster (CSI-55ms) TC intervals, but were not able to modulate it to fastest TC (CSI-125ms). Consequently, their turn and total task completion times were affected by slowest (CSI+125ms) and slower (CSI+55ms), but not by faster (CSI-55ms) TC intervals.

Compared to non-cued turn cadence (102.91,-98.8 +108.0), PD patients' turn cadence (Figure 4.6, A) in response to slowest TC was reduced (CSI+125ms; $p = 0.013$) and it was increased in response to faster TC (CSI-55ms; $p = 0.007$). Compared to CSI (105.3,-99.6 +109.2) interval modulation effects were found in slowest TC ($p = 0.005$).

Compared to non-cued turn time (Figure 4.6, B; 5.83,-5.2 +6.8) PD patients slowed turns in response to slowest (CSI+125ms; $p = 0.022$) and slower TC (CSI+55ms; $p = 0.037$). Compared to CSI (6.4,-5.5 +7.3) interval modulation effects were greatest with slowest (CSI+125ms; $p = 0.009$) and fastest TC (CSI-125ms; $p = 0.005$). Total task times (Figure 4.6, C) were longer at slowest (CSI+125ms; $p = 0.005$),

and slower TC (CSI+55ms; p = 0.005) compared to non-cued (29.58,-22.2 +31.4) and CSI (31.18,-31.17,-24.1 +34.2) cued conditions.

Healthy participants were able to modulate their cadence over the entire range of TC intervals, but, similar to PD patients, plateaued at faster TCIs. However, their turn and completion times followed a linear pattern in response to TC interval modulation.

Compared to non-cued turn cadence (112.37,-103.5 +117.7), healthy participants' turn cadence (Figure 4.6, D) in response to TC delivered at slowest TC was reduced (CSI+125ms; p = 0.05) and it was increased in response to faster (CSI-55ms; p = 0.017) and fastest TC (CSI-125ms; p = 0.012). Compared to CSI (111.31,-103.8 +118.5) interval modulation effects were also found at these TC intervals (CSI+125ms, p = 0.036; CSI-55ms, p = 0.036; CSI-125ms, p = 0.012).

Compared to non-cued turn time (Figure 4.6, E; 4.3,-4.2 +4.6) healthy participants slowed turns in response to slowest (CSI+125ms; p = 0.025) and sped them up in response to CSI (p = 0.012), CSI-55ms (p = 0.012), and CSI-125ms (p = 0.012). Compared to CSI (4.1,-4.0 +4.3) interval modulation effects were greatest with slowest (CSI+125ms; p = 0.012), faster (CSI-55ms; p = 0.012), and fastest (CSI-125ms; p = 0.012) TC.

Total task times (Figure 4.6, F) were longer at slowest TC (CSI+125ms; p = 0.017), shorter at faster (CSI-55ms; p = 0.025) and fastest TC (CSI-125ms; p = 0.012) compared to non-cued (17.52,-15.9 +18.4) and CSI (16.78,-15.7 +17.7) cued conditions.

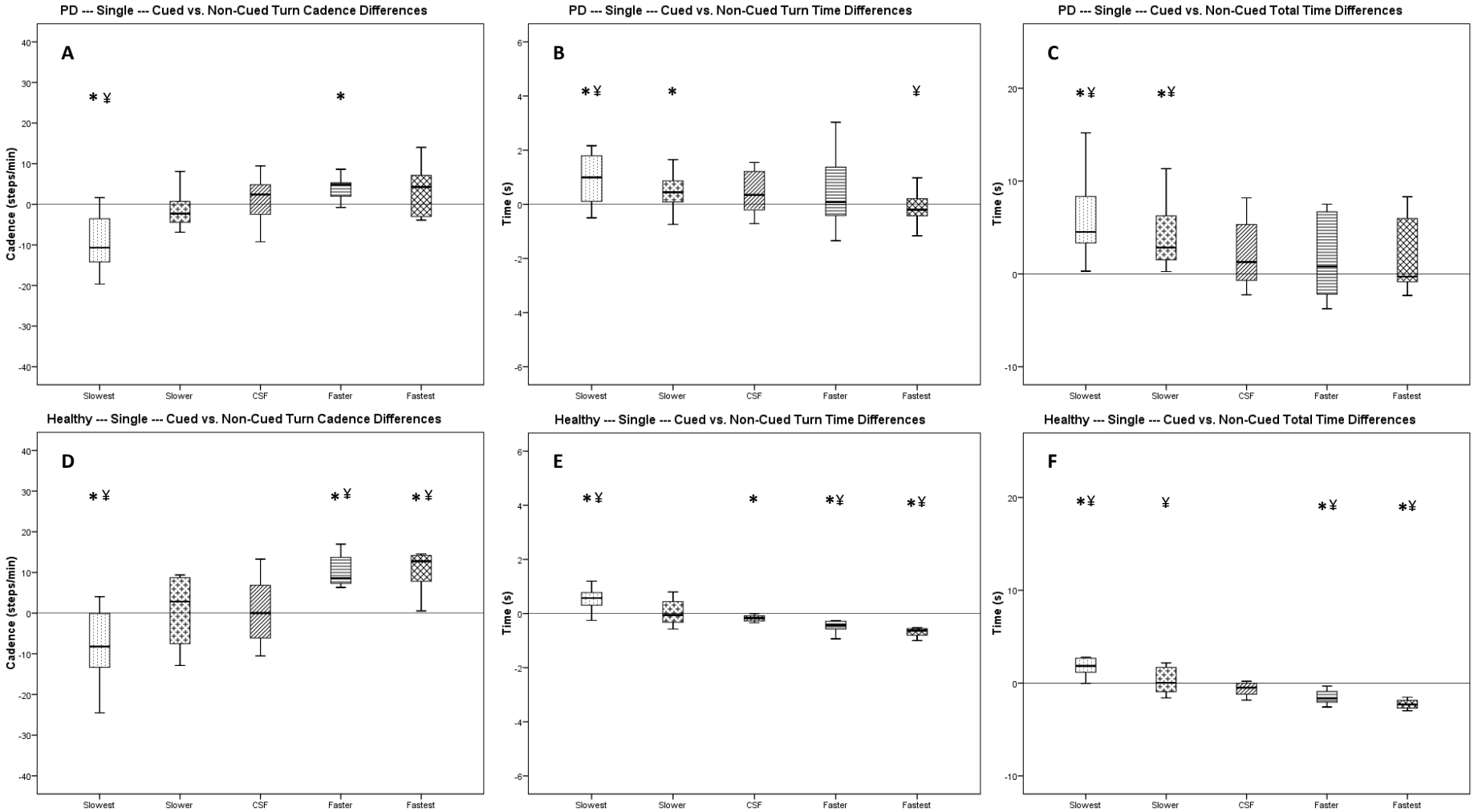


Figure 4.6: Effects of TC (NoTC = horizontal line at 0) on: turn cadence (A, D), turn time (B, E), total time (C, F); in PD (top) and healthy (bottom) participants, over a range of TC intervals in SINGLE tasks. * $p < 0.005$, Δ to non-cued (0 line); ¥ $p < 0.005$, Δ to CSI (middle box plot) condition.

4.3.3.2 Dual Task Performance

In the more challenging dual tasks (Figure 4.7), PD patients' cadence was positively affected by TC – most notably at comfortable (CSI) and faster (CSI-55ms) intervals. Also, PD patients were able to modulate their cadence to TC in the range between slowest (CSI+125ms) and faster (CSI-55ms) intervals, but were not able to maintain fastest TC (although positive cueing effects were evident even at fastest TC). These strong effects of TC suggest its efficacy may be amplified opportunistically when performing more challenging motor-cognitive tasks. Consequently, the turn and completion times were similarly affected, with turn times following a linear descending pattern until the fastest (CSI-125ms) condition. Effects of turn cadence were attenuated in total task time, but these were also found to follow a general linear pattern in response to TC interval modulation.

Compared to non-cued turn cadence (99.6, -93.0 +102.5), PD patients' turn cadence (Figure 4.7, A) was increased in response to TC delivered at CSI ($p = 0.017$), faster (CSI-55ms; $p = 0.007$), and fastest TC (CSI-125ms; $p = 0.005$). Compared to CSI (108.0,-102.8 +112.7) interval modulation effects were found slowest (CSI+125ms; $p = 0.005$), slower (CSI+55ms; $p = 0.022$), and faster (CSI-55ms; $p = 0.005$) TC conditions. Compared to non-cued turn time (8.6,-7.6 +9.8) PD patients sped up their turns in response to CSI ($p = 0.009$; Figure 4.7, B), faster (CSI-55ms; $p = 0.009$), and fastest TC (CSI-125ms; $p = 0.017$). Compared to CSI (7.4,-6.6 +8.5) interval modulation effects were noted with slowest (CSI+125ms; $p = 0.009$) and faster TC (CSI-55ms; $p = 0.022$).

While no differences between PD patients' cued and non-cued (31.55,-24.3 +33.4) total task times (Figure 4.7, C) were noted, comparison with CSI (30.35,-24.7

+37.3) condition revealed a interval modulation effect was found at the fastest TC condition (CSI-125ms, p = 0.005). It should be noted that very high variability in PD patients' total task times may reflect overall motor-cognitive integration challenges encountered during performance of a complex gait task such as this one.

Healthy participants were able to modulate their cadence over the entire range of TC intervals, suggesting – similar to PD patients – greater efficacy of TC in dual tasks. Both their turn and completion times followed a linear pattern in response to TC interval modulation.

Compared to non-cued turn cadence (111.21,-102.9 +115.1), healthy participants' turn cadence (Figure 4.7, D) in response to TC delivered at slowest TC was reduced (CSI+125ms; p = 0.025); it was increased in response to faster (CSI-55ms; p = 0.036) and fastest TC (CSI-125ms; p = 0.017). Compared to CSI (109.1,-101.3+118.5) interval modulation effects were greatest with slowest TC (CSI+125ms; p = 0.036), and fastest TC (CSI-125ms; p = 0.025).

Compared to non-cued turn time (Figure 4.7, E; 4.5,-4.0 +4.7) healthy participants slowed turns in response to slowest (CSI+125ms; p = 0.017) and sped them up in response to fastest TC (CSI-125ms; p = 0.036). Compared to CSI (4.5,-4.0 +4.9) interval modulation effects were noted with slowest (CSI+125ms; p = 0.017), faster (CSI-55ms; p = 0.03) and fastest TC (CSI-125ms; p = 0.012).

Total task times (Figure 4.7, F) were longer at slowest (CSI+125ms; p = 0.012), and slower TC (CSI+55ms; p = 0.05), and were shorter at faster (CSI-55ms; p = 0.05) and fastest TC (CSI-125ms; p = 0.017) compared to non-cued (17.20,-16.1 +18.6) and cued CSI (18.43,-18.4 +16.3) conditions.

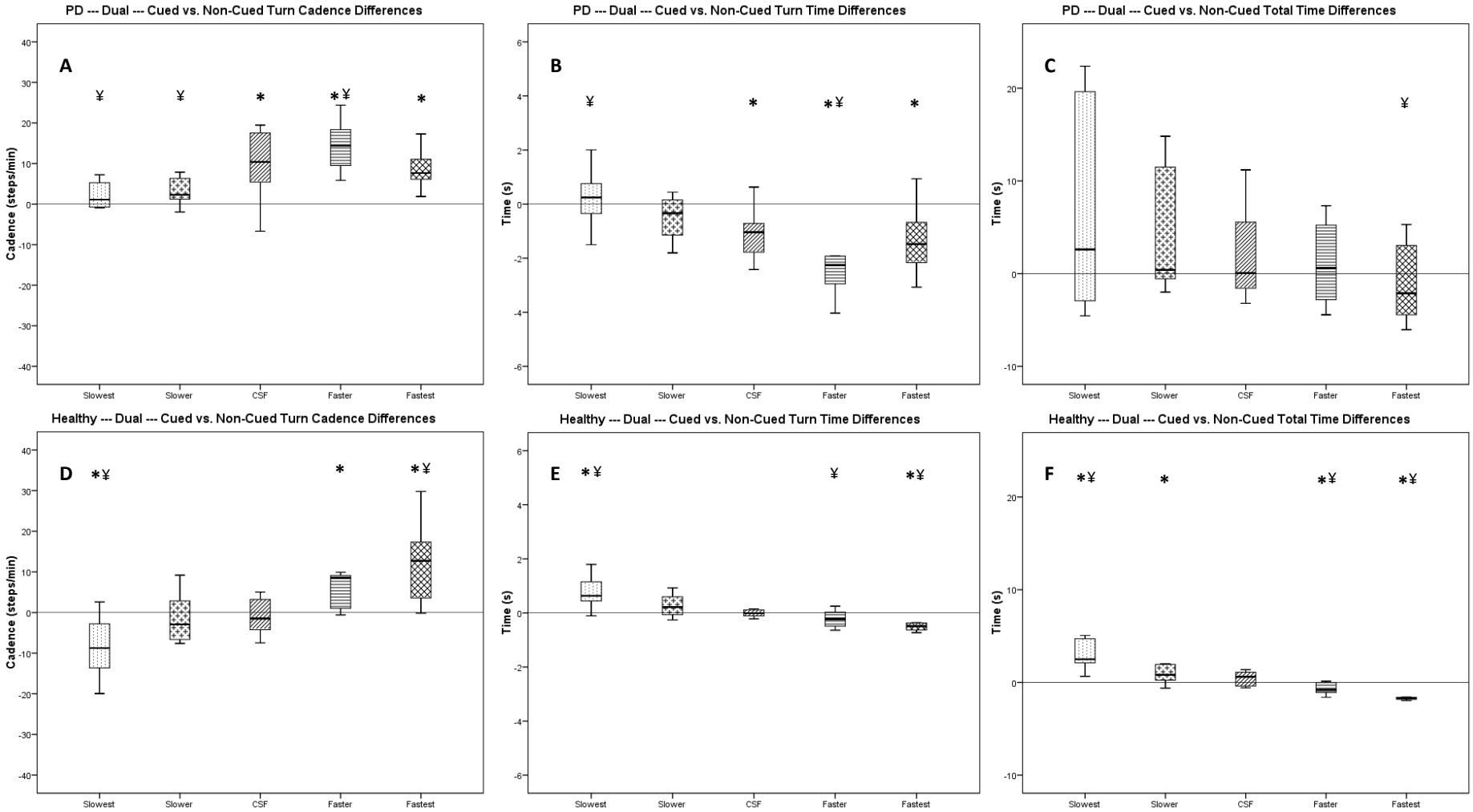


Figure 4.7: Effects of TC (NoTC = horizontal line at 0) on: turn cadence (A, D), turn time (B, E), total time (C, F); in PD (top) and healthy (bottom) participants, over a range of TC intervals in DUAL tasks. * $p < 0.005$, Δ to non-cued (0 line); ¥ $p < 0.005$, Δ to CSI (middle box plot) condition.

4.4 Discussion

The results support our hypotheses and indicate that: (1) TC improved motor-cognitive integration and performance – i.e. turn cadence, turn time, total task time – in the complex task segment (functional turns) performed with a secondary motor task; (2) modulation of TC intervals modulated motor performance (primarily turn cadence) which was reflected in turn and total task times that were longer when cued at slower TC intervals, and were shorter when cued at faster TC intervals; (3) TC efficacy in improving motor-cognitive integration was most prominent in PD patients' performance of complex dual task functional turns; (4) TC efficacy in modulating motor performance of PD patients was found at slowest, slower, comfortable and faster intervals, where the effects plateaued; (5) TC efficacy in modulation of motor performance was higher in healthy participants over the range of tested TC intervals but its relative effects on motor-cognitive integration were greater in PD patients performing dual turns at faster (CSI-55ms) interval.

These results indicate TC is a useful motor-cognitive performance aid particularly efficacious in improving motor performance and motor-cognitive integration of PD patients in the most challenging task conditions. The use of TC was related to the level of task difficulty so that its efficacy increased with the increase in motor-cognitive integration challenge. TC was used opportunistically when executive control capacities were challenged to their performance limits. Therefore, these results also indicate that PD patients – most likely due to impairments of BN function – increasingly rely on external sensory cues for movement modulation. Since highest TC efficacy was found at most challenging motor-cognitive conditions, TC likely

augments the missing or disrupted BN internal motor timing cues without significantly increasing the burden on executive control resources.

4.4.1 Group Differences in Gait Parameters

As expected (Frankel-Toledo et al. 2005), marked differences between PD and healthy participants' performance were found so that PD patients performed baseline non-cued, as well as cued (at CSI) single and dual tasks at longer total completion times (Figure 4.5 (A), including straight line (B) and turn times (C)), and had shorter step lengths than healthy participants (Figure 4.5, D). While straight line and turn cadence (Figure 4.5, E, F) were overall not different for PD and healthy participants, PD patients did performed dual non-cued turns at a lower cadence than healthy participants, which was a first indicator of the effects of dual tasks on PD patients' performance of the most complex experimental condition – i.e. performing a functional turn while carrying a tray with two cups of water. It should also be noted that variability was overall higher for PD patients than for healthy participants in total task time and its component times, as well as straight line step length (Figure 4.5). However, variability of straight line cadence and turn cadence were not different between PD and healthy participants.

These findings are congruent with previously published data reflecting the differences between PD and healthy gait (Frankel-Toledo et al. 2005; Hausdorff et al. 2007; Salarian et al. 2004; Zijlstra & Hof 2003, etc.) suggesting that PD patients walk on average slower than healthy individuals with shorter step lengths and lower cadence, as a result of decaying neuromuscular control due to increasingly dysfunctional BN control and coordination of motor and cognitive activity.

Consequently – and also in line with the findings of the current study – cadence and step length – have also been found to be more variable in PD patients than healthy individuals, and associated with increased risk of falls (Hausdorff et al. 2001; Hausdorff et al. 2003; Maki 1997; Nakamura et al. 1996; Schaafsma et al. 2003). The mechanisms of increased gait variability in PD have been linked to impaired automaticity in motor performance due to dysfunctional BN sensorimotor integration processes (Hausdorff et al. 1998; Stolze et al. 2001). This model of PD gait is supported by findings of Schaafsma et al. (2003) who demonstrated that administration of Levodopa to PD patients reduces their gait variability and increases their gait velocity, thus further implicating dysfunctional BN-controlled sensorimotor integration mechanisms as the likely sources of PIGD. Since all participants in the current study performed all activities while in the "on" state of their PD medication, it should be expected that their non-medicated performance would have been additionally impaired.

Based on these findings and in the broader context of PIGD symptoms – marked by lower cadence, stride length and gait speed – the goal of TC-based intervention was to improve the disrupted gait parameters and reduce the executive control burden in challenging motor-cognitive tasks. Based on the applied research paradigm, it was expected that application of temporally-modulated TC will result in increased cadence and consequently shorter performance times.

The results of performed experiments investigating overall efficacy of TC in modulating single and dual tasks is therefore discussed in the following sections. Since preliminary analyses of baseline cued and non-cued data indicated that total task completion times, straight line cadence, and step length were not affected by

TC nor by task difficulty (congruent with earlier findings of Howe et al. 2003; Suteerawattananona et al. (2004)), further analyses focused on turn cadence and turn time which were found to decrease and increase, respectively, with introduction of a secondary (dual) task, but reverted when TC was applied (Figure 4.5 E, F), thus indicating potential effects of task difficulty and TC.

4.4.2 Effects of TC & Tasks Difficulty on Motor Cognitive Integration

Turn times of PD patients were affected both by TC (Figure 4.6, left) and by task difficulty (Figure 4.6, right). When PD patients performed dual task turns, their turn times became ~ 3s longer compared to single task turns. But, when the same tasks were performed with TC (delivered at CSI), turn times were only ~1s longer than single tasks (Figure 4.6, right), indicating a significant improvement due to cueing. These findings suggest that PD patients were not able to compensate for increased motor-cognitive demands introduced by the secondary motor task, but that administration of TC significantly improved their motor cognitive integration in challenging dual tasks (as evidenced by ~ 2s shortening of turn tasks with TC). The findings replicate the findings of Rochester et al. (2007) who found that while auditory and tactile cueing improved cadence and speed in dual straight line gait tasks performed by PD patients, they were not able to restore performance to the level of single task. The results are also congruent with findings of Nieuwboer et al. (2009) suggesting that auditory and TC delivered at the comfortable stepping interval reduced turn times in PD patients.

Analyses of turn cadence indicated that the noted differences in PD patients' turn times were driven primarily by cadence. Notably while no TC effects on turn

cadence were found in single task, introduction of the secondary task reduced turn cadence by approximately 6 steps per minute (Figure 4.7, right). However, application of TC increased dual task turn cadence by approximately 10 steps per minute (Figure 4.7, left) – i.e. a significant improvement compared to single and non-cued dual tasks, as well as compared to TC effects on healthy participants' turn cadence. Again, these findings further support the notion that PD patients were not able to compensate for increased motor-cognitive demands introduced by the secondary motor task, but that administration of TC significantly improved their motor cognitive integration in challenging dual tasks which was reflected in increased cadence in response to TC administration in dual tasks.

On the other hand, no effects of TC (delivered at CSI; Figure 4.6, left) nor task difficulty (i.e. adding a secondary motor task to performing functional turns; Figure 4.6, right) were found in healthy participants' turn time performance, thus indicating that they were able to compensate for increased motor-cognitive demands introduced by the secondary motor task (i.e. carrying a tray with two cups of water), but also that administration of TC did not introduce untoward burden on motor-cognitive performance. Analyses of turn cadence corroborated these findings – i.e. no effects of TC (Figure 4.7, left) or task difficulty were found on healthy participants' turn cadence. A point of interest, however, was a noted (albeit insignificant) downward skewing trend (Figure 4.7, right) of dual task cadence, potentially indicating a mild detremental effect of dual tasking on healthy participants' cadence. While seemingly well compensated, this effect is further pointed to by a reduction in turn cadence variability in cued, compared to non-cued dual task.

Overall comparison of TC and task difficulty effects on turn time and cadence suggest that PD patients' performance is negatively affected by increasing task difficulty (i.e. increasing motor-cognitive integration challenges), but is, at the same time, positively affected by administration of TC in most challenging task conditions (i.e. performing functional turns while carrying a tray with two cups of water). Since these findings were not replicated during performance of less challenging single tasks, they indicate that PD patients – unlike healthy participants – opportunistically use TC in situations in which their motor-integration resources are functionally strained or tested close to their performance limits. The noted susceptibility of PD patients to task difficulty decrements in performance as well as responsiveness to TC in challenging motor-cognitive conditions – not found in healthy participants – is congruent with current model of BN dysfunction in PD (Redgrave et al. 2010).

Based on the model, due to progressive loss of BN function, a functional reorganization of motor-cognitive processing from BN-modulated automatic, to frontally-modulated goal-directed control occurs, and results in some of the observable PD symptoms such as bradykinesia, dysexecutive syndrome, etc. (Kojovic et al. 2012). Support for the current model also comes from recent neuroimaging evidence indicating the existence of the ventromedial and lateral sensorimotor integration systems (Elsinger et al. 2006; Jahanshahi et al. 2010; Redgrave et al. 2010; Kojovic et al. 2012). The lateral system includes the supplementary motor area (SMA) and the BN (particularly posterior caudate), and is implicated in performance of internally-paced and motivated actions, while the ventromedial system includes the premotor cortex (PMC), parietal cortex (PC), thalamus and the cerebellum, and is implicated in performance of movements elicited in response to environmental

sensory cues. Since the lateral system relies on BN function, PD-induced dysfunction of BN in turn causes the dysfunction of the lateral system, which forces greater reliance on the function of ventromedial system.

Thus, the observed inability of patients to adequately respond to a challenging dual turning task, may be explained by their increased concurrent reliance on frontally-mediated executive control of attention and goal direction for performance of the primary (i.e. turning) and secondary (tray carrying) tasks. Conversely, intact BN function of healthy participants may provide a "performance advantage" in such complex dual tasks, allowing executive coordination and control to be performed on-line without concurrent engagement in performance of the primary motor task of walking and turning that is mediated by the functional BN loops and the lateral system. Further support for the lateral vs. ventromedial engagement comes from the observed different response to TC by PD patients and healthy participants. While PD patients used TC opportunistically – i.e. in their most challenging task condition – the healthy participants did not seem to respond to TC in the four comfortable pace conditions (cued and non-cued, single, dual) conditions, since they never reached their performance threshold and thus did not require TC.

It may be argued that due to different motor-cognitive integration thresholds of PD and healthy participants, TC was used opportunistically by PD patients when overburdened executive resources were not capable of allocating additional attention and control required to maintain performance in given task conditions. Thus, by relying on ventromedial sensory integration, it is argued that TC was seamlessly used as a substitute for missing internal BN motor timing cues, and was

thus able to modulate cadence without adding to already limited motor-cognitive integration loads.

In the light of Jahanshahi et al. (2010) finding of greater reliance of PD patients on external sensory stimuli (modulated by the ventromedial system), and of healthy individuals on internally generated cues (modulated by the lateral system) for timing of motor performance, the lack of effect of task difficulty and TC on straight line cadence, time and step length, may be explained by (a) overall high performance of PD and healthy participants, (b) testing of PD patients in the "on" phase of medication, and (c) possibly too low task difficulty of the straight line walking segment of the task. To further assess the functional limitations of TC and challenge the performance thresholds of PD and healthy participants, the results of TC interval modulation on performance are discussed in the following section.

4.4.3 Effects of TC Interval Modulation and Task Difficulty on Motor Cognitive Integration

Assessment of the effects of TC interval modulation was done over a range of intervals around comfortable stepping interval (CSI), ranging from slowest (CSI+125ms) and slower (CSI+55ms), to faster (CSI-55ms) and fastest (CSI-125ms). Cued performances were compared to non-cued baseline performances, in single and dual task paradigms.

In single tasks, PD patients effectively modulated their turn cadence to TC between slowest and faster intervals (Figure 4.8, A). The greatest effect of interval modulation was found in the slowest TC condition. Although a trend to increased cadence was found at shortest TC interval, the variability in this condition was

greater than in preceding interval condition so that turn cadence in this condition was not different from non-cued nor from faster TCI conditions. This finding suggests that PD patients were not able to adjust their turn cadence to fastest TC, resulting in an apparent breakdown of cadence resulting in a relative decrease in turn cadence compared to the preceding (faster) cueing condition. Since cadence was shown to be the gait parameter most affected by TC, the pattern of turn cadence modulation in response to TC was reflected in PD patients' turn and completion times which were longer in cued conditions (Figure 4.8, B and C). These results are congruent with the findings of Howe et al. (2003) who found that cadence and gait speed of PD patients increased when cued at 107.5% and 115% of their comfortable walking speed, and decreased when cued at 85%, suggesting the motor-cognitive performance threshold for PD patients lay in the range between 10% and 20% below and above comfortable gait.

On the other hand, healthy participants were able to modulate their cadence over the entire range of TC intervals, but seemed to plateau between faster and fastest intervals (Figure 4.8, D). Yet, unlike PD patients, the variability in shortest interval was comparably smaller to that in slowest, slower and CSI conditions, while its median was significantly higher compared to non-cued condition. These findings suggest that although healthy participants were not apparently able to increase cadence beyond shorter TC interval, they were able to maintain coherent motor-cognitive performance even at the fastest TC condition. This notion was further reflected in healthy participants performance on turn (Figure 4.8, E) and total completion times (Figure 4.8, F) followed a linear decreasing pattern in response to faster TC intervals.

In more challenging dual tasks, PD patients' cadence was strongly affected both by TC and by TC interval modulation – most notably at comfortable and faster (Figure 4.9, A) – but not at slower intervals. PD patients effectively modulated their cadence to TC between comfortable and faster TC intervals, but, were unable to achieve the target cadence in the slowest, slower and fastest TC. In slowest and slower TCI conditions, their cadence was higher than targeted. However, at the fastest TC condition they stepped at lower cadence compared to the targeted as well as preceding (faster) condition, but their cadence was still higher than in non-cued baseline condition. This finding further supports the proposition that TC is used opportunistically by PD patients when motor-cognitive integration performance limits are reached. Furthermore, in dual task conditions, turn cadences were more affected by TC interval modulation than in single conditions – as evidenced by greater inter-condition differences (Figure 4.9, A).

This finding suggests TC efficacy may be greater when performing more challenging tasks wherein greater reliance on ventromedial system is reflected in greater responsiveness to TC interval modulation. The noted changes in turn cadence were translated in turn (Figure 4.9, B) and total completion times (Figure 4.9, C) were similarly affected. Turn times followed a linear pattern, with strong TC and modulation effects found in the fastest TC condition (arguably reaching the limits of motor-cognitive integration capacity). Consequently, turn time at the fastest TC was lower than in non-cued condition, but was no different from cued CSI condition, indicating partial breakdown of motor-cognitive integration. Effects of turn cadence were attenuated in total task time, with very high variability precluding any conclusions about a mild linear pattern of decreasing total completion time in

response to shorter (i.e. faster) TC interval. A potential source of high variability in total completion times – particularly at slowest and slower interval conditions – may originate from a combination of variable gait parameters including step lengths, cadence, and gait trajectories as well as the overall motor-cognitive integration challenges encountered during performance of a complex gait task. These findings are congruent with those reported by Hausdorff et al. (2007), who have shown that when cued at their comfortable walking speed PD patients increased their gait speed, stride length, and swing time, but not variability of these parameters. However, when cued at ~10% faster intervals, gait speed, stride length and swing time increased, while variability decreased.

In dual tasks, healthy participants were able to modulate their cadence over the entire range of TC intervals (Figure 4.9, D), suggesting greater efficacy of TC in dual than single tasks. Both their turn (Figure 4.9, E) and total completion times (Figure 4.9, F) followed a linear pattern in response to TC interval modulation. It should be noted that turn cadence variability was lower across all conditions of dual task compared to single task, except for the fastest condition in which variability was higher in the dual task. Also, while they were not able to achieve the targeted cadence in the fastest TC condition in single task paradigm, healthy participants were able to effectively modulate turn cadence to the shortest TC interval in the dual task paradigm.

These overall results support the notion proposed by Frankel-Toledo at al. (2005) and Willems et al. (2006), that PD-induced impaired motor-cognitive integration at the level of BN reduces the ability of PD patients to adapt their motor performance to increasingly challenging motor integration tasks – including

performance of a secondary task and excursions from preferred towards either faster or slower performance speeds. Thus, it is inferred that walking at fastest TC interval was more challenging since it imposed shorter processing time limits. On the other hand, walking at slowest TC interval was more challenging since it required monitoring and control of limb movement with minimal reliance on limb inertial properties (as would be the case at comfortable or faster gait), which arguably was expected to increase executive control of movement.

In this context, PD patient's lower efficacy to modulate cadence to slowest and fastest TC intervals in dual task condition may be explained by the current model of BN function PD (as described in earlier sections (Jahanshahi et al. 2011; Redgrave et al. 2010)), wherein due to compensatory sensorimotor reorganization and a shift from rapid BN-modulated automatic processing, toward slower prefrontally-modulated processing, PD patients may be unable to process the required motor-cognitive commands in the short time intervals imposed by the fastest TCI condition, or, conversely, due to increased executive control of limb movement – in the slowest TC interval condition.

Therefore, prefrontal executive control seems to be at the crux of defining motor-cognitive integration limits because, based on the obtained results, it is precisely those limits that determine the efficacy of TC – particularly in PD patients and particularly in complex dual task conditions. The role of executive control and attention in motor-cognitive interactions and their functional effects on motor performance have been well demonstrated by Baker et al. (2007) who found attentional (i.e. focusing on taking long steps) cues reduced cadence in single and dual gait tasks, while combined attentional and auditory (metronome beat) cueing

reduced cadence in dual tasks only, thus suggesting executive interference in a simpler task caused by dual cueing modalities, and an opportunistic efficacy of the same dual modality in a more challenging dual task. Further support for such interpretation of obtained results comes from studies by Rochester et al. (2005) and Nieuwboer et al. (2009) who demonstrated that performance of concurrent gait-cognitive tasks resulted in PD patients walking at reduced gait speed and with shorter step lengths. Decreased executive function in PD patients was strongly implicated to reduction of gait speed during performance of the functional gait tasks.

Impairments of PD patients' ability to concurrently engage in dual task performance have been well documented (Canning et al. 2005, 2008; Giladi et al. 2007; Morris et al. 1996; Redgrave et al. 2010; Rochester et al. 2005), and the current models of BN dysfunction implicating executive / attentional overload and inability to rely on automatic movement control have been proposed as mechanistic explanations of the observed motor-cognitive integration detriments (Collette et al. 2005; Jahanshahi et al. 2011; Redgrave et al. 2010; Wu et al. 2010).

The reduced ability of PD patients to modulate cadence to fastest and faster TC intervals, as well as the apparently opportunistic manner in which TC is employed by PD patients in most challenging motor-cognitive task conditions, may be well explained in the context of executive capacity-sharing (Rogers 2006) and bottleneck (Ruthruff et al. 2001) concepts. Namely, both motor and executive processes, as well as their integration, rely on prefrontal processing. PD patients also rely on these processes more than healthy individuals due to loss of BN function and the resulting compensatory reliance on executive control of movements. Increase of motor-integration demands brought about by task conditions (single vs. dual tasks,

excursions of performance intervals away from comfortable, etc.) respectively increase the burden on the prefrontally-mediated executive processes. In that manner, multiple independent motor-integrative processes rely on the same neural capacities, which, as a result of their limited capabilities, become a motor-integration bottleneck. While provision of TC – which is thought to be processed by the ventromedial system that bypasses the prefrontal executive resources – increases overall motor-integrative potential, the effective modulation of behavior may remain limited by the inherent bottleneck of the prefrontal executive control.

In conclusion, this study has revealed that PD patients are capable of using TC in an opportunistic manner to improve their motor-cognitive integration in simple and dual tasks when performance task conditions require function at the limits of motor-cognitive integration capacity. Furthermore, TC was shown to effectively modulate complex motor task performance over a range of intervals. In addition, while the range of intervals was narrowed when dual task paradigm was applied, the efficacy of TC in modulating motor performance was relatively higher compared to single paradigm, suggesting a positive correlation between motor-cognitive integration challenge and TC efficacy. Healthy participants were generally better able to entrain motor performance to TC, but the relative effects of TC were somewhat lower than in PD patients – likely due to intact BN function and lateral sensorimotor integration. These results establish TC as an effective gait aid for PD patients that can be used in highly challenging motor-cognitive situations. The findings of this study also provide the foundation for further development and external validation of AuTact application as the next steps in its evolution into an easily accessible, user friendly gait aid for PD patient population.

CHAPTER V

Summary, Limitations and Future Directions

5.1 SUMMARY

The results of this study provide novel insight into the role of tactile cueing in movement modulation and the mechanisms of motor-cognitive integration in PD patients and healthy individuals. The custom-developed tactile cueing smart phone application – AuTact – has been validated in controlled laboratory conditions, which represents the initial step towards development of a new, user friendly, freely available walking aid for PD and related movement disorders.

The results presented in Manuscript I (Chapter III), show that (1) PD patients and healthy individuals were able to effectively modulates performance on simple (seated heel tapping) and complex (straight line walking) motor tasks in in response to TC over a range of cueing intervals; (2) increases in task complexity and TC intervals reduce synchronized motor performance accuracy, wherein PD patients are able to modulate performance at a narrower range of intervals than healthy individuals. Thus TC may effectively be used to improve simple and complex motor performance in PD patients.

The results presented in Manuscript II (Chapter IV), show that (1) TC improves PD patients' turn cadence and turn times in dual tasks; (2) PD patients use TC opportunistically when their motor-cognitive resources are challenged to performance limits (i.e. turning while carrying a tray with 2 cups of water); (3) TC is a useful method for improving motor-cognitive integration for PD patients performing highly challenging motor-cognitive tasks so that PD patients use TC opportunistically

to improve their motor-cognitive integration when task conditions require performance at the limits of motor-cognitive integration capacity.

In single tasks, TC effectively modulated functional task performance over a range of intervals from slowest to faster. While the range of intervals was narrowed when dual task paradigm was applied, the efficacy of TC in modulating motor performance was relatively higher compared to single paradigm, suggesting a positive correlation between motor-cognitive integration challenge and TC efficacy. Healthy participants were better able to synchronize motor performance to TC, but the relative effects of TC were lower than in PD patients.

5.2 LIMITATIONS

Several limitations of this study have been identified. First, the amplitude of tactile cues provided by the smart phone vibrator could not be adjusted – i.e. amplified or dampened. During pilot trials, several participants reported losing the sensation of TC while performing walking tasks cued at faster (CSI-55ms) and fastest (CSI-125ms) intervals. The participants who reported this limitation had more adipose tissue, which was identified as the most probable reason for the lack of cutaneous sensitivity to vibrations. Vibration sensitivity was effectively increased in all participants by tightening the Velcro strap used to secure the smart phone to participants' arm. While no participants reported loss of TC sensation, nor any discomfort associated with tightening of the Velcro strap in experimental trials, it is possible that increased amplitude of TC might have increased overall effectiveness of TC in movement modulation. Development of future versions of the AuTact software will include exploration of amplitude modulation in different smart phone platforms.

A second limitation of the study might have been the number of participants – particularly in Experiment #3 (reported in Manuscript II) – where two healthy participants had to be excluded due to their atypical performance on experimental tasks. The omission of these participants reduced the overall statistical power. Since performance variability of PD patients was repeatedly found to be higher than healthy individuals', increasing the number of participants could have amplified the effect size of TC and the interactions with PD or healthy physiology. This may have reflected particularly on the effects of interval modulation in straight line walking segment where data trends suggested the effects of cueing interval modulation, but statistical significance was not reached.

A third limitation of the study may be related to task difficulty. Namely, the results indicate that the limit of functional motor-cognitive integration was reached in the turn segments of dual tasks performance of functional tasks. Since TC was shown to be used opportunistically in those situations, it remains possible that TC might have also been used more effectively by PD patients in straight line segments had the motor-cognitive task (carrying tray with cups of water) been more difficult.

5.3 Future Directions

The reported studies should be performed on PD-cognitively impaired populations. Further validation of AuTact software in home and clinical settings is required to increase external validity of the reported results. Current Android version of AuTact should be expanded to include functionality on iPhone platforms. AuTact user data base should be developed for assessment of its long-term effects.

CHAPTER VI

Appendix A

Health & Human Performance

DOES RHYTHMIC VIBRATION IMPROVE YOUR WALKING AND THINKING?

HEALTHY ADULTS NEEDED FOR A SENSORY CUEING STUDY

- You should be healthy and older than 55 years of age
- You should be able to walk unassisted for at least 90 steps
- Experience state of the art sensory cueing technology
- Participate in a study that may help Parkinson's disease patients
- Test session completed in approximately 3.5 hours
- Study performed at Texas Medical Center in Houston

For information on participating in this study, please contact us at
713 748 8973 or **vivkovic@mail.uh.edu**
This project has beenreviewed by the University of Houston Committee for the Protection of Human Subjects (713) 743-9204.

Appendix B

UNIVERSITY OF HOUSTON
CONSENT TO PARTICIPATE IN RESEARCH

PROJECT TITLE: **Effects of Tactile Cueing on Functional Movement Modulation in Parkinson Disease**

You are being invited to participate in a research project conducted by Mr. Vladimir Ivkovic, Dr. William Paloski and Dr. Stanley Fisher from the University of Houston Center for Neuromotor and Biomechanics Research, the Department of Health and Human Performance at the University of Houston, and the Methodist Neurological Institute. Mr. Martin Castaneda is also participating in the study as a student research assistant. This study is being conducted as a part of Mr. Ivkovic's doctoral dissertation research project.

NON-PARTICIPATION STATEMENT
Your participation is voluntary and you may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. You may also refuse to answer any questions. A decision to participate or not will have no effect on your medical care or your relationship with the University of Houston Center for Neuromotor and Biomechanics Research, the Department of Health and Human Performance at the University of Houston, or the Methodist Neurological Institute.

PURPOSE OF THE STUDY
The purpose of this study is to investigate how touch cues might be used to improve walking skills and attention during walking in Parkinson disease patients. The findings of this study could add valuable knowledge about how our brains keep us from falling as well as how our attention allows us to make split second decisions. This knowledge could be used to design better methods to protect vulnerable people from injuries caused by falling and to improve management of Parkinson disease symptoms.

PROCEDURES
You must complete three short questionnaires that help us assess your health and eligibility to participate in the study. You will be required to wear a comfortable pair of pants, a comfortable t-shirt and a pair of fitness running shoes. If you are a Parkinson's disease patient, you will be required to take your L-dopa medication in the laboratory.

During this study, you will be required to wear a smart phone that we will be attached to your arm, just above the elbow, by an elastic Velcro strap. During some trials, the phone will emit vibration cues to help you maintain your stepping cadence. We will also attach a lightweight sensor to the smart phone, two other sensors to your thighs by elastic Velcro straps, and one more to your lower back by a Velcro waist belt. These sensors will be connected by wires to a lightweight recording device also attached to the Velcro waist belt.

First, you will be asked to walk twice along a 9 meter (30 foot) long padded walkway. Then you will be asked to sit in a chair and try out the vibration cues by tapping your heel on the floor in cadence with the vibrations delivered through the smart phone.

Then we will ask you to perform a number of short walking trials. During some of these trials, you will be asked to walk around obstacles while carrying a tray with two glasses of water on it. During some of these trials, the vibrations will be turned on and you will be asked to step in tune with the vibration cues.

In six walking trials you will be asked to walk in a straight line for 90 steps. Then, in the following 24 trials, you will be asked to walk along a 9 meter walkway, and walk around a pylon on the ground. Altogether you will complete 30 walking trials with 1-3 minute breaks between consecutive trials. A longer, 15 minute break, will be given after the sixth walking trial.

One test session will be required to complete the entire research protocol. It will last approximately 3.5 hours. A total of 20 volunteers will be recruited to participate in this study.

CONFIDENTIALITY

Your participation in this project will be confidential. The information collected from you during this study will be combined with information collected from the other participants. Your data will be identified only by a unique code number. There will be no way for anyone to identify your data without this code.

RISKS / DISCOMFORTS

The tasks that we will ask you to perform are similar to a moderate exercise protocol, with minimal risks associated with their performance. You may become tired during walking trials. To prevent fatigue we will allow you a one to three minute rest period between trials. Two five minute and one 15 minute break will be provided if necessary.

Other possible discomforts include fatigue or heat buildup from wearing the sensors or cueing equipment. To prevent these discomforts, you will be allowed a minimum of one minute rest between trials. During all breaks, you will be able to rest in an armchair.

In the unlikely event of unexpected events/problems during data collection, the principal investigator will immediately stop the protocol, assess the need for medical attention and if determined necessary notify emergency medical services (EMS) and remain with you until arrival of EMS. In the event you will not need medical attention, the principal investigator will assist you to recover and exit the study. The principal investigator will immediately report the incident to the appropriate University of Houston authorities. In the event of any harm resulting from your participation in this study, the University of Houston does not provide any financial compensation including costs for medical treatment.

TIME COMMITMENT
The experimental protocol will require up to three and a half hours of your time.

BENEFITS
There are no known benefits to you for participating in this study.

INCENTIVES / REWARDS
We do not offer any incentives or rewards for your participation. However, any cost you incur parking during the study will be covered.

ALTERNATIVES
The only alternative is not to participate in the study.

PUBLICATION STATEMENT
The results of this study may be published in professional and/or scientific journals. They may also be used for educational purposes or for professional presentations. However, you will not be identified by name.

SUBJECT RIGHTS

1. I understand that informed consent is required of all persons participating in this project.

2. All procedures have been explained to me and all my questions have been answered to my satisfaction.

3. Any risks and/or discomforts have been explained to me.
4. Any benefits have been explained to me.

5. I understand that, if I have any questions, I may contact Vladimir Ivkovic (Principal Investigator) at 713-748-8973 or Dr. William Paloski (Faculty Sponsor) at 713-743-9272

6. I have been told that I may refuse to participate or to stop my participation in this project at any time before or during the project. I may also refuse to answer any question.

7. ANY QUESTIONS REGARDING MY RIGHTS AS A RESEARCH SUBJECT MAY BE ADDRESSED TO THE UNIVERSITY OF HOUSTON COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS (713-743-9204). ALL RESEARCH PROJECTS THAT ARE CARRIED OUT BY INVESTIGATORS AT THE UNIVERSITY OF HOUSTON ARE GOVERNED BY REQUIREMENTS OF THE UNIVERSITY AND THE FEDERAL GOVERNMENT.

8. All information that is obtained in connection with this project and that can be identified with me will remain confidential as far as possible within legal limits.

Information gained from this study that can be identified with me may be released to no one other than the principal investigator. The results may be published in scientific journals, professional publications, or educational presentations without identifying me by name.

I HAVE READ (OR HAVE HAD READ TO ME) THE CONTENTS OF THIS CONSENT FORM AND HAVE BEEN ENCOURAGED TO ASK QUESTIONS. I HAVE RECEIVED ANSWERS TO MY QUESTIONS. I GIVE MY CONSENT TO PARTICIPATE IN THIS STUDY. I HAVE RECEIVED (OR WILL RECEIVE) A COPY OF THIS FORM FOR MY RECORDS AND FUTURE REFERENCE.

Study Subject (print name):_____

Signature of Study Subject: _____

Date: _____

I HAVE READ THIS FORM TO THE SUBJECT AND/OR THE SUBJECT HAS READ THIS FORM. AN EXPLANATION OF THE RESEARCH WAS GIVEN AND QUESTIONS FROM THE SUBJECT WERE SOLICITED AND ANSWERED TO THE SUBJECT'S SATISFACTION. IN MY JUDGMENT, THE SUBJECT HAS DEMONSTRATED COMPREHENSION OF THE INFORMATION.

Principal Investigator (print name and title):_____

Signature of Principal Investigator:_____

Date:_____

Appendix C

Project Title: Effects of Tactile Cueing on Functional Movement Modulation in Parkinson Disease

PARTICIPANT PHONE CALL SCRIPT

The initial interview will be conducted by the principal investigator. During the initial phone interview, the prospective participant will be given an overview of the study. The prospective participants will then be interviewed to determine eligibility to participate based on the stated inclusion and exclusion criteria.

Eligibility of participants to participate in the study will be based on the PAR-Q and SRPA-Q questionnaires. If the answer to any question will indicate breach of inclusion / exclusion criteria, the prospective participant will be advised they are not eligible to participate, thanked for their time and answered any questions they may have in relation to the study. Alternatively, the prospective participant will be offered to make an appointment to participate in the study.

Activity	Detail & Purpose	Stop / Go
PI introduce himself	Position: PhD candidate at UH/HHP/CNBR Research interests: Neuromotor / neurocognitive control Qualifications: MSc. Biology; MSc. Space Studies	
Prospective participant prompted for questions they may have	Inform participant about the PI's qualifications; address potential concerns	
PI provides overview of the study	Background: tactile and auditory cueing as a novel method of movement modulation Significance: Understanding neurocognitive control of movement in PD Methodology: Tactile and auditory cueing through mobile telephone Expected time commitment: 2 hours Potential discomforts: mild fatigue Participant rights: terminate participation at any time Benefits: participation in novel research	
Prospective participant prompted for questions they may have	Inform participant about the study; address potential concerns	
PI asks the participant to state their age, height and weight	Determine eligibility to participate in the study based on age (50 -85 years of age eligible to participate); healthy participants age-, height, weight matched to PD, PD-CI participants	
PI administers PAR-Q (reads instructions, marks answers)	Determine eligibility to participate in the study based on general health status and potential injuries or medical diagnoses	

Prospective participant prompted for questions	Inform participant about the PAR-Q; address any concerns	
PI administers SRPA-Q (reads instructions, marks answers)	Determine eligibility to participate in the study based on the level of physical activity during 30 days prior to the interview	
PI proposes scheduling data collection appointments	Participation in the study	
Exchange of contact information with the participant	Ability to contact the participant (reminders, scheduling changes, etc.)	

This project has been reviewed by the University of Houston Committee for the Protection of Human Subjects (713) 743-9294.

Appendix D

Participant ID:

Date:

MODIEFIED PHYSICAL ACTIVITY READINESS QUESTIONNAIRE (PAR-Q)

For most people physical activity should not pose any problem or hazard. PAR-Q has been designed to identify the small number of adults for whom physical activity might be inappropriate or those who should have medical advice concerning the type of activity most suitable for them. Common sense is your best guide in answering these few questions. Please read them carefully and mark the yes or no opposite the question as it applies to you.

Yes__	No__	Can you walk at a comfortable steady pace for 4-5 minutes without stopping?
Yes__	No__	Has a physician ever said you have a heart condition and you should only do physical activity recommended by a physician?
Yes__	No__	When you do physical activity, do you feel pain in your chest?
Yes__	No__	When you were not doing physical activity, have you had chest pain in the past month?
Yes__	No__	Do you ever lose consciousness or do you lose your balance because of dizziness?
Yes__	No__	Do you have any problems of the circulatory system (e.g. problems with veins)? If so, specify:
Yes__	No__	Do you have a joint or a bone condition or problems with your feet? If so, specify:
Yes__	No__	Do you have insulin dependent diabetes or related conditions? If so, specify:
Yes__	No__	Do you have any breathing difficulties or suffer from asthma?
Yes__	No__	Do you suffer from epilepsy?
Yes__	No__	Do you have any neurological conditions? If so, specify:
Yes__	No__	Do you use (have been recommended to use) corrective lenses? If so, specify:
Yes__	No__	Is a physician currently prescribing medications? If so, specify which medication and for which condition(s):
Yes__	No__	Have you had a major operation? If so, specify (what, when):
Yes__	No__	Do you suffer from any other medical conditions? If so, specify:
Yes__	No__	Do you know of any other reason you should not exercise or increase your physical activity?

Appendix E

Participant ID:

Date:

MODIFIED SELF-REPORTED PHYSICAL ACTIVITY QUESTIONNAIRE FOR THE PAST 30 DAYS (SRPA-Q)

Please circle the appropriate number (0-7) that best describes your general activity level (*based on provided descriptions in italics*) for the previous month

You do not participate regularly in programmed recreation, sport, or heavy physical activity

0 Avoid walking or exertion, e.g., always use elevator, ride whenever possible instead of walking.

1 Walk for pleasure, routinely use stairs, occasionally exercise sufficiently to cause heavy breathing or perspiration.

You participate regularly in recreation or work requiring modest physical activity, such as gymnastics, horseback riding, calisthenics, table tennis, softball, baseball, weight lifting, yard work.

2 Spend 10 to 60 minutes per week in these types of physical activity.

3 Spend over 1 hour per week in these types of physical activity.

You participate regularly in heavy physical exercise, e.g., running or jogging, swimming, cycling, rowing, jumping rope, or engaging in vigorous aerobic activity type exercise such as tennis, basketball, soccer, or other similar sports activities.

4 Run less than 1 mile per week or spend less than 30 minutes per week in comparable physical activity.

Appendix F

Participant ID:

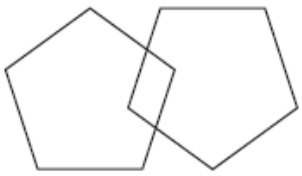
Date:

Used by permission of the Hartford Institute for Geriatric Nursing, Division of Nursing, New York University; available at: www.hartfording.org

The Mini-Mental State Exam

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used by permission.

Appendix G

TC effects were assessed by comparing inter tap / step intervals (it is) during synchronization phases at different TC intervals. ITIs were calculated as the time difference between consecutive heel taps / steps, as described by Equation A.1:

$$ITI = t_{Ti} - t_{Ti-1} \quad \textbf{Equation A.1}$$

where t_{Ti} and t_{Ti-1} denote heel tap or heel strike times.

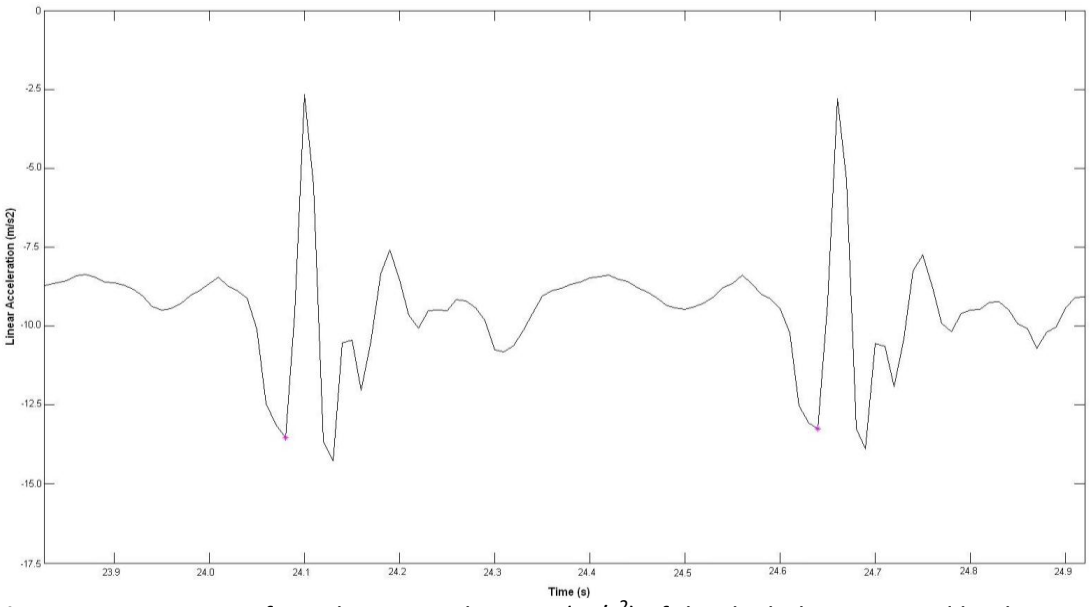


Figure A.1: Superior-inferior linear acceleration (m/s^2) of the thigh during seated heel tapping task. Visually identified onsets of heel tapping thigh movements (pink asterix) identified by the PI or collaborator and recorded by the heel tap/step finder algorithm.

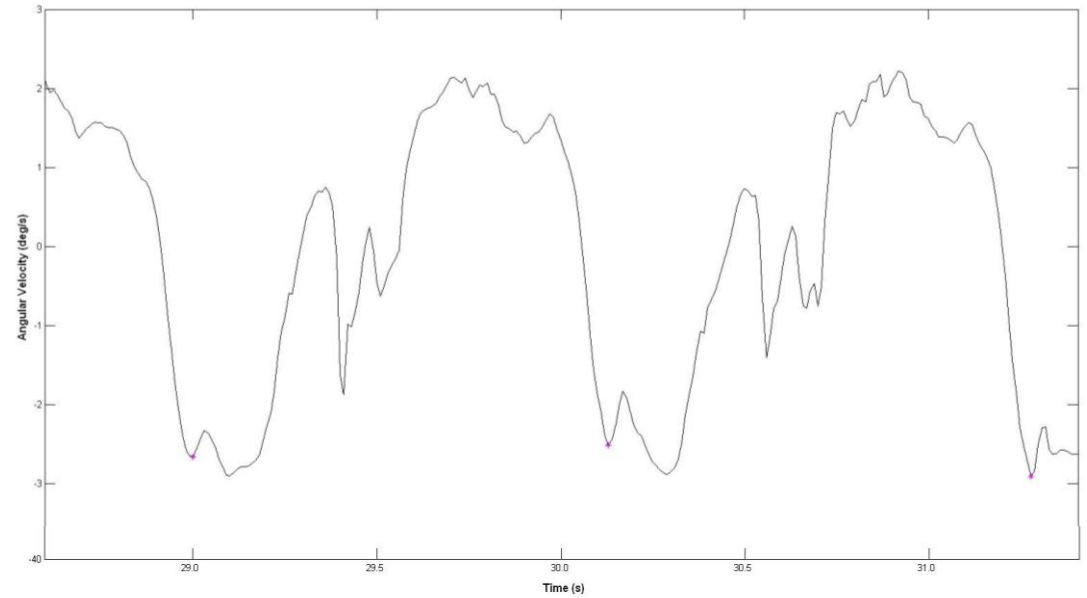


Figure A.2: Anterior-posterior angular velocity ($^o/s$) of the thigh; visually identified heel strikes (pink asterix) recorded by the heel tap/step finder algorithm.

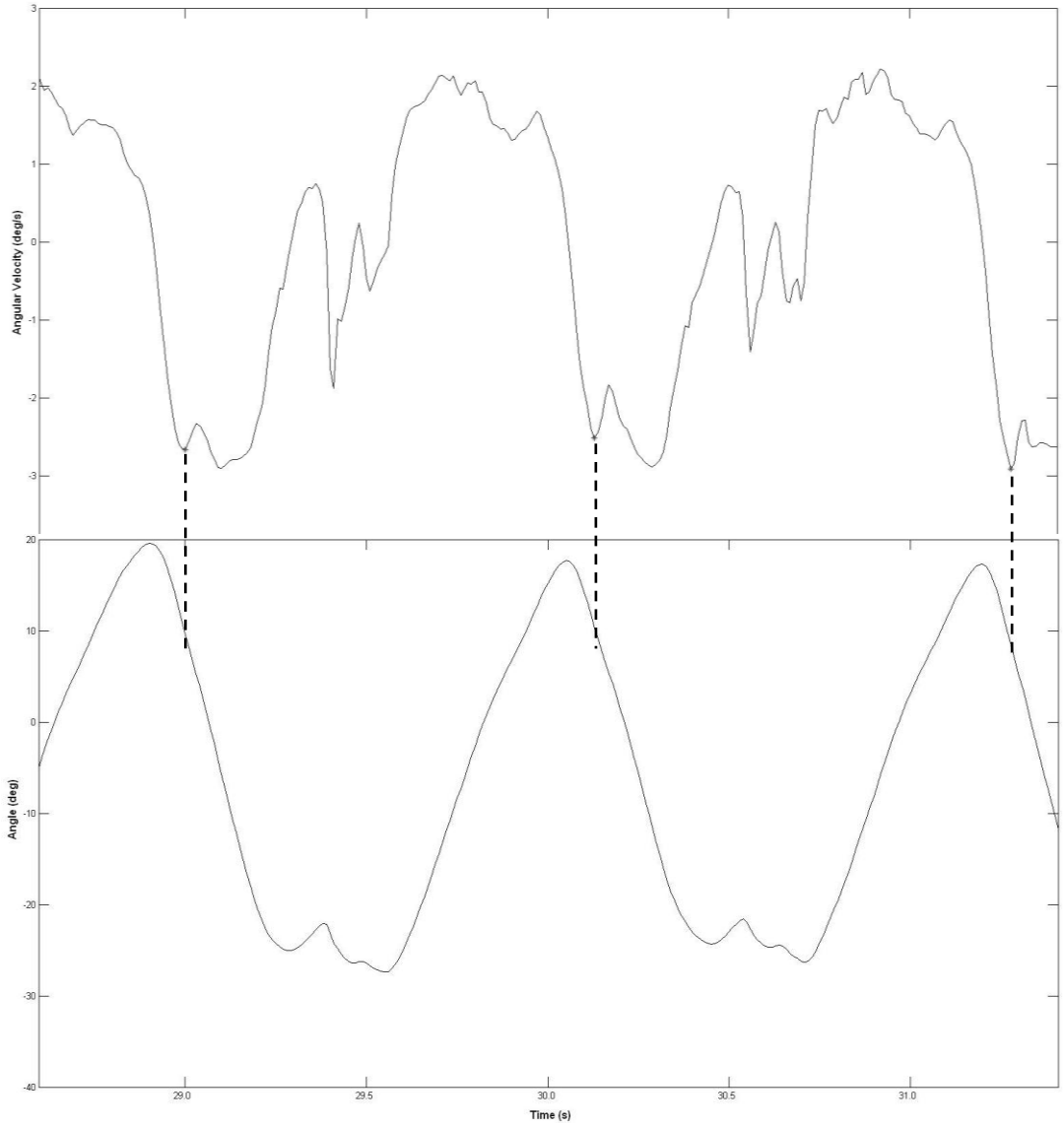


Figure A.3: Top: Anterior-posterior angular velocity (^{o}/s) of the thigh; Bottom: corresponding pitch angle (degrees) of the thigh; ambulation at a comfortable gait speed of a PD patient; visually identified heel strikes (asterix) recorded by the heel tap/step finder algorithm; black dashed lines added for identification of angles corresponding to heel strikes.

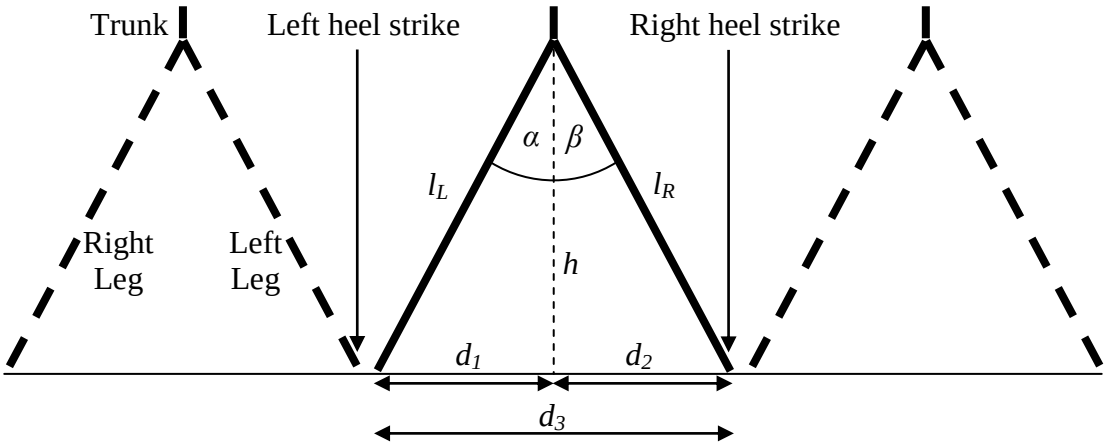


Figure A.4: A three-link (inverted) pendulum model used in calculations of step length and cadence. The central figure depicts the state of the model at the instant of a right heel strike. Dashed lines indicate preceding and consequent steps. Left and right leg lengths (l_L, l_R) are considered constant as measured for each participant. Angles α and β denote anterior-posterior (pitch) angular displacement of the left and right legs respectively, measured at the level of the thighs. Step length (d3) at the instant of a heel strike is calculated as the sum of left (d1) and right (d2) leg distances from the vertical.

Equations used to calculate step lengths at the time of heel strike as the sum of left and right leg distance from vertical.

$$d_1 = l_L \sin \alpha \quad \textbf{Equation A.2}$$

$$d_2 = l_R \sin \beta \quad \textbf{Equation A.3}$$

$$d_3 = d_1 + d_2 \quad \textbf{Equation A.4}$$

Wherein left and right leg lengths (l_L and l_R) denote legs of the pendulum and are considered constant as measured for each participant. Angles α and β denote anterior-posterior (pitch) angular displacement of the left and right legs respectively, measured at the level of the thighs by Xsense orientation sensors at the instant of consecutive heel strikes. For quality control and validation, step lengths were also calculated by the number of steps and distance traversed in each investigated walking segment.

CHAPTER VII

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