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The Feedforward and Feedback Controls on Gait in Adults with Diabetes

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THE FEEDFORWARD AND FEEDBACK CONTROLS ON GAIT IN ADULTS WITH DIABETES

by

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THE FEEDFORWARD AND FEEDBACK CONTROLS ON GAIT IN ADULTS WITH DIABETES

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There are nearly 26 million people with diabetes mellitus (DM) in the US, and half of chronic DMs develop somatosensory deficits due to diabetic polyneuropathy or diabetic peripheral neuropathy (DPN). The absence or impaired somatosensory feedback (e.g. touch sensation or joint proprioception) resulted from the damage of large nerve fiber, and motor deficits such as attenuated muscle strength and abnormal plantar pressure of lower extremity have been identified in DPN, and these sensorimotor impairments lead to an increased number of falls. To reduce the risk of falling, a well-coordinated and adapted limb movement driven by the feedforward (anticipatory) and feedback (reactive) control movement strategies are required to deal with forthcoming and instantaneous perturbations during walking respectively. The top-down feedforward control communicates with the central nervous system (CNS) and forms the basis for computing necessary motor output by simultaneously predicting or correcting errors of event information from the bottom-up feedback control. The altered spatiotemporal gait pattern in DM can either be the compensation of somatosensory feedback deficits or the compromised CNS-driven motor command. Exploring the feedforward and feedback controls not only illustrates the potential cause of the DM's altered gait pattern but also offer the future opportunity to design prospective clinical intervention for DM's safety and wellness.

The overall objective of this study unveiled the impacts of feedforward and feedback control on DM/DPN's dynamic balance during walking. This dissertation adopted a virtual

reality-based obstacle crossing task to examine our central hypothesis of potential altered sensory and CNS-driven motor command of DPN would be manifested through the adjustment of spatiotemporal gait characteristics compared with healthy controls. In addition, we investigated how the visual guidance played a role to the on-line adjustment of these altered gait measures as the compensation. In results, DM demonstrated the compromised feedback control by lowering their maximal toe elevation during crossing and increasing their step width after crossing; while DPN presented the both compromised feedforward and feedback controls by decreasing the toe elevation during crossing and increasing stride/stance time after crossing of obstacle. Besides, the adjustment of the altered spatiotemporal gait characteristics were observed through the visual guidance. With the combination of virtual obstacle crossing task design with the guidance of visual information, the future virtual obstacle crossing training paradigm can be implemented for training diabetes population to reduce the risk of falling.

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CHAPTER I

INTRODUCTION

A. Background

Diabetes mellitus (DM) was firstly documented as a mysterious disease that causes frequent urination along with rapid emaciation back to ancient Egypt in early 1500 B.C.[1] In the first century, the Greek physician describe "diabetes" as a siphon-like condition in which patients were "melting down of flesh and limbs into their urine", and not until late 17th century was the word "mellitus" rendered as "honey" to reflect the finding of sugar in patient's urine[2].

Nowadays, DM has been fundamentally known as the reason of 1) dysfunction of β-cell in pancreas that secrets insulin (insulin dependent or Type 1 DM) or 2) ineffective usage of released insulin with glucose (insulin resistance or Type 2 DM). Clinically, DM can be categorized into four classes as Type 1, Type 2, gestational DM (i.e. DM diagnosed during pregnancy), and other specific types (e.g. genetic deficits in β-cell function, cystic fibrosis, drug- or chemical-induced DM)[3]. As of 2012, 347 million people worldwide have diabetes, and there are approximate 26 million people in the US diagnosed as DM with the estimated prevalence of 12-14%[4, 5]. In addition, DM is ranked as the seventh-place of leading cause of death in this country and gradually increases its socioeconomic burden by costing a hundred billion dollars annually[6].

Approximately 50% of DM over 60 years of age develops sensorimotor deficits due to diabetic peripheral neuropathy (or diabetic polyneuropathy, DPN) which is the most common and widely recognized form of diabetic neuropathy that prominently affects their

activities of daily living[7, 8]. The development and progression of DPN that strongly correlates to glycemic control may affect either sensory (small fiber) or motor (large fiber) nerves, and deteriorates the intact sense of pain, vibration, position, touch and pressure[7]. For example, DPN with delayed afferent nerve sensory inputs or efferent motor outputs[9] not only appears to loss of position, vibration, and tactile sensation of their feet, but also presents a poor postural control during quiet stance when compared to healthy individuals[10, 11].

The risk of falling in diabetic populations is significantly elevated by 78% when compared to healthy elderly[12]. Similarly, a higher falling/tripping accidents in DPN was reported that correlated to the increased spatiotemporal gait variability due to the shortage of sensory feedback information brought from lower limbs toward central nervous system (CNS)[11, 13, 14]. Many studies have summarized that the altered gait pattern of shortened step length, wider step width, increased double support time, and increased step-to-step variability[15-17] in DM due to potential somatosensory deficit during walking were associated with a high risk of falling [11, 12, 14, 16-20].

Overall, walking performance and balance control in DM and healthy controls are studied intensively, but the fundamental mechanism of balance controls, how the controls affect walking performance in more dynamic situations, and how the sensory information (e.g. vision) could be utilized to substitute the somatosensory deficits and assist in performing daily activities successfully (e.g. crossing obstacles) in DM, remains unclear. Therefore, this chapter sought to collate the DM-related literatures in two categories (i.e. the feedforward and feedback controls that impact gait adjustment accordingly and the role of visual information on gait adjustment) and identify several knowledge gaps.

B. Review of the Controls of Gait during Obstacle Crossing Task

The integrated sensory information perceived from visual, vestibular and somatosensory systems is to deal with the variant perturbations of our daily living[21]. To reduce the occurrence of accidents such as tripping and falling, a well-coordinated and adapted limb movement driven by the CNS is required to maintain balance during locomotion. Both feedback and feedforward controls are adopted to deal with unpredictable and foreseen perturbations during walking respectively. The top-down feedforward control that communicates with CNS and rapidly forms the basis for computing necessary motor output by predicting or correcting errors of event information brought by the bottom-up feedback control is needed to execute a more accurate movement for maintaining balance during walking[22, 23]. **Figure 1.1** depicts a general movement such as walking can either be as the result of afferent somatosensory feedback (bottom-up) through perceiving the outward stimuli or an outcome that originates from the CNS-driven efferent motor command (top-down)[24].

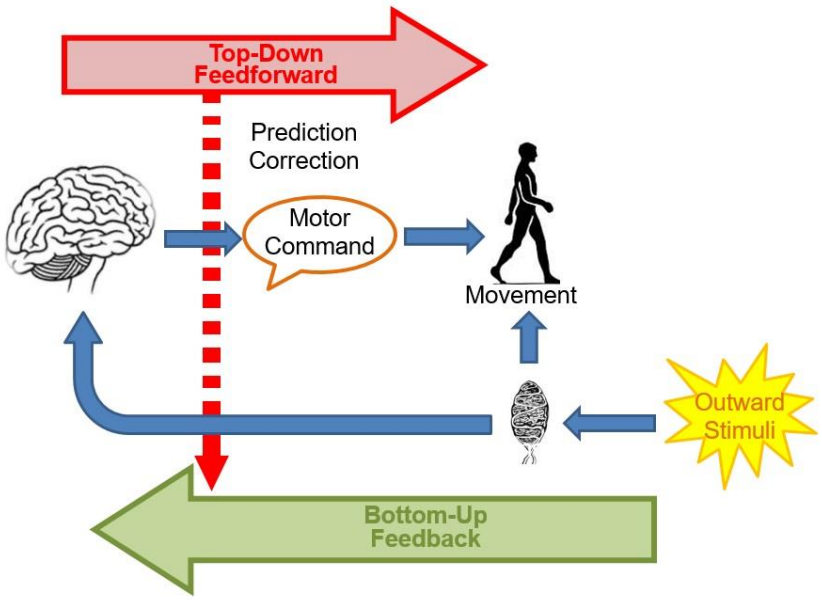


Figure 1.1. The model of bottom-up feedback and top-down feedforward controls on gait.

In human movement analysis, the feedback controls can be examined at the moment when people react on the event instantaneously whereas the feedforward controls can be examined during the period before the event. Therefore, stepping over obstacles or obstacle crossing tasks (OCT) offers different phases such as planning (pre- or approaching the event), crossing (during the event), and recovery (post-event)[25-27] at which the outcomes of feedback and feedforward controls can be examined accordingly.

Hocking et al. contended that both feedforward (i.e. anticipatory) and feedback mechanisms are the key factors that affect adaptive gait diffusely in neural abnormalities population such as DPN populations[26, 28].

However, both feedforward and feedback controls on gait adjustment of DM populations remains obscured. Exploring this underlying mechanism of feedforward and feedback controls not only shed light on the cause of DM's fall incidences during walking, but also offer the future opportunity to better deliver clinical intervention for DM's safety and wellness. Thus, this chapter reviewed and collated the topics of feedforward and feedback controls when performing OCT in healthy, DM and DPN populations, and summarized the related studies in **Table 1.1**.

1. Feedforward Controls of Gait during Obstacle Crossing Task

Obstacle crossing task as a highly cortical command-demanded daily activity (e.g. stepping over the curb on the sidewalk or in/out the bathtub) has been utilized to examine the relationship between cognitive function and lower extremity behavior[27, 29-31]. In feedforward control manner (e.g. when approaching the obstacle), people visually perceive and identify the location of the obstacle when approaching it, the CNS simultaneously "pre-plan" or "pre-judge" the movement strategy in order to complete the task successfully such

as the distance between foot location and obstacle or the height of foot elevation for stepping over the obstacle (i.e. toe clearance)[29, 32-36]. In addition, other optimal spatiotemporal gait characteristics such as gait speed, step length, step duration, step width, were examined during the approaching phase (i.e. planning period) of OCT as the outcomes of how people adjusted proactively[26, 28, 29, 34, 37]. Moreover, the properties of obstacle information such as dimensions, and the distance information of the obstacle relative to subjects are considered in a feedforward manner instead of online (i.e. feedback control) regulation of locomotion[37, 38].

2. Feedback Controls of Gait during Obstacle Crossing Task

In addition to use the top-down feedforward control to accomplish OCT, it is suggested that the spinal reflex pathways or the bottom-up feedback control at the supraspinal level involves in OCT because of the shorter latency of obstacle avoidance than a voluntary movement was observed [39-41]. In feedback control manner, the quick and immediate response to a perturbation that suddenly occurs is of more interest. At the moment of stepping over the obstacle, the outcome measures such as toe clearance, obstacle crossing successful rate, crossing stride/step length, step width and foot distance to the obstacle after OCT, can be categorized as the online reactive response to OCT[25, 26, 29, 31, 42].

Several experimental designs to test the feedback control during OCT were developed including releasing an obstacle based on predicting the heel strike when walking on a treadmill[25, 40, 43], showing up the treadmill-attached obstacles periodically during treadmill walking[44], or projecting a band of light on the walkway at the specific moment of gait cycle during over ground walking[31, 42]. When the obstacles suddenly appeared without knowing when or where they appeared, healthy subjects demonstrated very quick modification of

their swing trajectory in response to the suddenly appeared obstacles[40]. When compared to elders or hemiplegic populations, healthy subjects increased the successful rate as the available response time increased[25, 42]. Healthy subjects also prefer to lengthen their steps as their stepping strategy of crossing obstacles when shorter response time was given[25].

3. Performance Changes in Diabetes during Obstacle Crossing Task

Previous study has observed a higher postural sway in DPN subjects in standing due to the inability to generate proper neuromuscular response[45]. Therefore, a poor feedback control of diabetic population at the moment of OCT could be expected because of the hyperglycemia-induced neuromuscular dysfunction. In pathogenesis study, on the other hand, the hyperglycemia-induced oxidative stress has been indicated of compromising the intact cortical function in DM and caused cognitive disorders such as dementia or depression[46]. Therefore, the feedback and feedforward controls that communicate with neuromuscular controls could be affected by the peripheral nerve changes or the hyperglycemia-induced cortical deterioration.

However, fewer studies examined the performance of OCT in DM. When compared the outcomes of crossing different actual obstacle heights with healthy subjects during over ground walking, DM significantly decreased toe clearance and which increases the risk of tripping or falling[47]. In addition, a virtual obstacle crossing paradigm was introduced by showing the stick figure of individual's self-limb and the height of virtual obstacle to evaluate the outcomes among diabetic populations and healthy controls. As expected, DPN showed significantly lower virtual obstacle crossing rate along with lowered toe clearance due to their illness[48].

Overall, the impact of diabetic's feedforward and feedback controls on spatiotemporal gait characteristics during different settings of OCT remains obscured and need further investigated.

C. Review of the Effect of Visual Information during Obstacle Crossing Tasks

1. The perception-action coupling

Among the aforementioned three major sensory systems that transmit outward information in order to perceive daily, visual perception as the most prominent factor contributes to balance control during walking[21, 49]. The perceived visual information was transmitted from the retina through the optic nerves to the primary visual cortex, and was further processed through the visuomotor dorsal pathway (which is responsible for determining an object's relative location in the environment) to the posterior parietal cortex for producing planned movements[50, 51]. According to the Ecological System Theory: "*We must perceive in order to move, but we must also move in order to perceive*"[52], with respect to the role of visual perception-action coupling to human balance control, the perceived visual information of how posture and movement relates to environment is further analyzed and utilized for movement plan in order to mediate proper foot-placement during locomotion[53], and that during obstacle crossing tasks[36, 54].

2. The use of visual information during obstacle crossing task

Visual information can be used and tested in both feedforward and feedback (on-line) manners separately during obstacle crossing[55]. For instance, the visual information of body relative to the environment (i.e. visual exproprioceptive information) was utilized as an on-line or instantaneous adjustment to fine tune the movement trajectory of lower extremity during OCT (i.e. the feedback control); whereas the visual information of environmental

characteristics (i.e. visual exteroceptive information such as height or color of obstacle) was mainly used for the feedforward control[34, 55-57]. Specifically, human fixed their gaze on the obstacles two steps ahead (visually-guided) during the approaching phase of OCT[38], and the visual information of leading limb along with the stored height information of obstacle make OCT more successfully. Contrary, the action of trailing limb was impaired to a greater extent without viewing the obstacle information at the moment of crossing[58].

Without the intact somatosensory feedback to accurately control the foot placement, DM subjects may utilize other sensory systems, for example, vision, to control their balance when contronted any perturbation that may lead to fall[24]. Our previous studies have found and supported that vision did play an important role among DM subjects to maintain their balance during locomotion. Firstly, the visual information presented through virtual environment regarding subjects' self-perceived motion significantly decreased DM's step length and the variability (i.e. coefficient of variation) of stride time when compared conditions between with and without the visual cue[59]. Secondly, visual perception of self-motion plays a prominent role on reducing stride time variability in DM when compared to the age-matched healthy, and which has been interpreted as decreased the risk of falling during walking[60].

However, how the stepping strategies are adopted and how the visual information plays a role to assist in DM and DPN populations during OCT are the knowledge gaps that depicts why and how DM and DPN trip or fall.

3. The visual information provided through virtual reality technology during obstacle crossing tasks

Virtual reality (VR) technology makes it possible and available offering subjects the real time visual exproprioceptive or exteroceptive information (i.e. characteristics of the object or the limb locations relative to the environment) during stepping activity[61]. One study used the virtual obstacle crossing paradigm and provided individuals with the visual exteroceptive and exproprioceptive information of the upcoming virtual obstacle on a computer monitor[48]. However, how the online gait adjustment through the feedback control with visual information was not examined and the experimental design was not similar to an actual OCT in our daily living.

Studies of a serial stepping over virtual obstacle were conducted in which the virtual obstacle was shown up at varied available response time based on subjects' stride duration by projecting a band of light on the designated walkway[31, 42]. Therefore, both feedback and feedforward controls on OCT can be evaluated by manipulating the timing of viewing event accordingly through the exteroceptive visual information of obstacle's location. Nevertheless, the previous study was limited to the non-accessed visual exproprioceptive information and the plane-like obstacle which subjects does not necessarily raise their feet to step over the obstacle. Thus, based upon the experimental design of stepping over virtual obstacle task by Chen et al[31, 42], we redesigned the virtual OCT by adding the element of visual exproprioceptive information and presented the three-dimensional obstacle task on a cylindrical screen.

4. Knowledge Gaps

Above all, this chapter identified three knowledge gaps below based on the collated literature reviews regarding OCT and DM:

Knowledge Gap 1: OCT has been utilized and examined the proactive and reactive responses due to the feedforward and feedback controls in healthy controls. However, how the adjustment of spatiotemporal gait characters according to the feedforward and feedback controls respectively during OCT, especially in diabetic population, remains obscured.

Knowledge Gap 2: To successfully step over an obstacle, diabetic population, especially in DPN, might use other sensory information, e.g. vision (or visual reliance) to compensate hyperglycemia-induced peripheral nerve impairments. Further study is needed to understand how the visual information could be adopted in DM during OCT.

Knowledge Gap 3: How the changes of spatiotemporal gait characteristics in DM and DPN can be distinguished through the redesigned virtual OCT, and how these changes correlate to the clinical functional balance evaluation, are clinical concerns that need to be answered and further offer clinical suggestions of stepping or fall risk-preventing training exercise.

D. Specific Aims and Hypotheses

Therefore, this dissertation sought to fulfill these knowledge gaps by examining diabetes and healthy age-matched groups while performing a serial virtual obstacle crossing tasks on a treadmill (i.e. the dynamic virtual OCT). The specific aims of the proposed hypotheses of this dissertation were:

SA1: To investigate the impact of feedforward control manner on adjusting spatiotemporal gait characteristics in the three phases (planning, crossing and

recovery) of stepping over the forthcoming virtual obstacles in DM, DPN and age-matched healthy.

H1.1 Comparing to the age-matched healthy and DM, DPN would reduce task successful rate when stepping over the virtual obstacles by decreasing their toe elevation, step length, stride length, step width and by increasing stride time, swing time and stance time;

H1.2 Comparing to the age-matched healthy and DM, DPN would increase the variability of the aforementioned spatiotemporal gait characteristics when stepping over the virtual obstacles.

SA2: To investigate the impact of feedback control manner on adjusting spatiotemporal gait characteristics in the three phases (planning, crossing and recovery) of stepping over the unexpectedly appeared virtual obstacles in DM, DPN and age-matched healthy;

H2.1 Comparing to age-matched healthy, both DM and DPN would reduce task successful rate by decreasing toe elevation, step length, stride length, step width and increase stride time, swing time and stance time while stepping over virtual obstacles;

H2.2 Comparing to age-matched healthy, both DM and DPN would increase variability of the aforementioned spatiotemporal gait characteristics while stepping over virtual obstacles.

SA3: To investigate how the real-time visual exproprioceptive information plays a role in altering the stepping strategy by adjusting the spatiotemporal gait characteristics in DM, DPN and age-matched healthy while stepping over the forthcoming and unexpected appearing virtual obstacles.

H3.1 In the feedforward control condition with the assistance of visual exproprioceptive information, DPN would improve the virtual OCT performance by increasing task successful rate and the aforementioned spatiotemporal gait characteristics and decreasing gait variability;

H3.2 In the feedback control condition with the assistance of visual exproprioceptive information, DM and DPN would improve the virtual OCT performance by increasing task successful rate and the aforementioned spatiotemporal gait characteristics and decreasing gait variability.

E. Chapter Summary and Bridge

Overall, I summarized the potential hazards such as falling and tripping issues that diabetic populations are facing nowadays. In addition, the source of the aforementioned hazards can be due to the compromised feedforward and feedback controls when performing some dynamic tasks. Last but not least, the importance of vision information given through the virtual reality can facilitate the obstacle crossing performance. In the following chapter, I would describe the general methodology of my dissertation specifically to test the hypotheses and to fulfill the knowledge gaps.

Table 1.1. Summary of studies of Obstacle Crossing Task.

Author/Year	Purpose	Subjects	Outcome Measures	Results
Den Otter AR, et al. 2005[25]	Obstacle avoidance strategy in stroke patients was studied under conditions of different time pressure	7 healthy controls; 11 strokes	Individual failure rate, stride velocity, stride length, stride duration	Strokes showed more impaired ability to adequately modify their stepping pattern.
Hocking DR, et al. 2011[26]	To examine the visual control of locomotion during OCT in WS	10 adults with WS; 9 DS; 10 healthy adults	Speed, step duration, step length, distance (of toe) to obstacle	A less flexible and more cautious stepping strategy (reduced speed and step length) was observed in WS group.
Lo OY, et al. 2015[29]	To examine how the VA affects stepping behavior	11 healthy young adults	Toe-obstacle clearances, foot-obstacle horizontal distances, gait velocity, tripping incidence, VA accuracy rate	VA accuracy lowered in hard task; toe-obstacle clearance decreased in trailing leg with increased VA demands.
Chen HC, et al. 1996[31]*	To investigate how dividing attention affects OCT between individuals of any ages	16 young; 16 old adults	Rate of success, obstacle avoidance score, vocal error rate	Dividing attention significantly degraded obstacle avoidance ability in elderly.
Timmis MA & Buckley JG, 2012[34]	To determine when LVF exproprioceptive information is utilized to control/update leading limb trajectory during OCT	12 young adults wore goggles that occluded their LVF unpredictably	Trail foot and lead foot placement distance before and after obstacle; toe clearance	

Muir BC, et al. 2015[35]	To determine if healthy older adults adopt strategies to decreased the likelihood of obstacle contact	19 healthy young adults (< 25); 11 young old (65-79); 18 old adults (80-91)	Step width, step length, gait speed, toe and heel clearances, head angle, obstacle contacts	Step length and gait speed progressively decreased with advancing age; closer foot placement before and after the obstacle.
Rhea CK, et al. 2010[36]	To determine 1. If visually guided action is scaled to visual perception; 2. how task experience influenced action that was scaled to perception	15 healthy young adults	Perceived obstacle height, toe elevation	The motor system is influenced by perception trough pre-perceiving the obstacle height.
Santos LC, et al. 2010[37]	To understand how visual information about an ongoing change in obstacle size is used during OCT for both leading and trailing legs	5 healthy adults	Step speed (before OCT), toe clearance, peak toe elevation, time to clearance, time to peak toe elevation	Acquired visual information of obstacle was used to modulate trail limb trajectory; step was influenced by the time available to acquire visual information.
Chen HC, et al. 1994[42]*	To investigate the ability of individual of any ages to negotiate obstacle under time-critical conditions.	24 young; 24 old adults	Rate of success, available response time	The reduced available response time decreased the obstacle avoidance success rate.
Weerdesteyn V. et al. 2005[43]	To determine the latencies of obstacle	25 young adults; 99 elders	Avoidance success rate, reaction time, toe/heel	Elders showed lower success rate, longer reaction time and longer

	avoidance reaction during treadmill walking		distance (to the obstacle), foot clearance	step strategy, smaller toe and heel distances and larger foot clearance.
Haefeli J, et al 2011[44]	To investigate the interaction between brain and spinal neuronal activity during OCT	12 healthy young adults		
Liu MW, et al. 2010[47]	To compare the trajectory and joint kinematic/kinetic changes of lower extremity in DM and healthy during OCT	14 DM; 14 healthy controls	Walking speed, horizontal foot-obstacle distance, toe clearance, joint angle and moment (of hip, knee and ankle)	DM decreased toe clearance of leading leg, hip abductor moment, increased knee flexor/ ankle plantar flexor moment and dorsiflexion of stance leg
Grewal G, et al. 2012[48]*	To access DPN's lower extremity position perception damage through a virtual obstacle crossing paradigm	13 healthy; 13 DM; 35 DPN	Toe clearance, obstacle crossing successful rate, reaction time	DPN had lowered successful rate of OCT and longer reaction time;
Heijnen MJ, et al. 2014[58]*	To determine whether obstacle height memory that coupled with a visible obstacle position cue could guide the foot	39 healthy young adults for experiment 1; 24 healthy young adults for experiment 2	Foot clearance, toe peak elevation, toe peak position, horizontal distance, stride length, failure rate	Viewing the obstacle online during approach facilitates to guide trail limb obstacle crossing particularly.

	during OCT successfully	

*: virtual obstacle crossing task;
Acronym: DM: diabetes mellitus; DPN: diabetic peripheral neuropathy; DS: Down syndrome; LVF: lower visual field; OCT: obstacle crossing task; VA: visuospatial attention; WS: Williams Syndrome.

CHAPTER II

GENERAL METHODOLOGY

The general experimental protocol was approved and overseen by the Institutional Review Board under the Office of Regulatory Affairs in University of Nebraska Medical Center, UNMC (IRB#: 294-11-FB, **Appendix A**).

A. Subject Eligibility

A total of 32 subjects participated in this study (mean age = 57.19 ± 9.85 years; 16 females); there were eleven participants in the groups of healthy controls (HTY; mean age = 55.18 ± 7.99 years) and Type 2 diabetes (DM; mean age = 55.82 ± 11.7 years) respectively, and ten in diabetic peripheral neuropathy group (DPN; mean age = 60.9 ± 9.42 years). The breakdown by group of subjects' demographic data is listed in **Table 2.1**. The power analysis is included in *Section D* of this chapter to determine the sample size of this study.

Table 2.1. The demographics by group of this study (N = 32).

	HTY (n=11)	DM (n=11)	DPN (n=10)	*p* value
Age (years)	55.18 ± 7.99	55.82 ± 11.7	60.9 ± 9.42	0.44
Height (cm)	170.29 ± 7.97	169.49 ± 11.08	168.66 ± 10.52	0.88
Weight (kg)	76.78 ± 11.38	91.84 ± 19.45	91.23 ± 16.70	0.08
BMI (kg/m^2)	26.43 ± 3.21	31.83 ± 5.20	31.85 ± 3.76	<0.01*
%A1C	--	7.53 ± 1.37	7.68 ± 0.99	0.21
15% Leg Length (mm)	125.86 ± 8.86	123.00 ± 8.19	123.90 ± 8.56	0.51
MMSE (out of 30)	29.11 ± 0.78	29.22 ± 1.39	28.75 ± 1.28	0.52
PWS (m/s)	0.84 ± 0.11	0.81 ± 0.10	0.70 ± 0.23	0.29

*: Kruskal-Wallis test were tested to compare group difference (α=0.05) where DM and DPN show significant higher BMI than healthy group.
Acronym: BMI (Body-Mass Index, where <18.5, 18.5-24.9, 25-29.9 and >30 are defined as underweight, normal, overweight, and obese, respectively); MMSE (Mini Mental Status Examination); PWS (Preferred Walking Speed)

All participants in this study were able to walk on a treadmill independently for at least five minutes, and with normal or adjusted vision acuity with at least of 20/40 in order to well-perceive the visual information during the test. Subjects with Type 2 DM were screened and recruited in Diabetes Center, UNMC and DPN were recruited from the clinics in Department of Neurological Sciences, UNMC; the age-matched healthy participants were recruited through flyers (**Appendix B**) within the metropolitan area. The DPN was diagnosed and examined by neurologists, and which was defined as the presence of either motor or sensory symptoms in the lower extremities or abnormalities seen in quantitative sudomotor axon reflex testing (QSART), quantitative sensory testing (QST) or through the electromyography test. The large fiber peripheral neuropathy in the electrophysiological studies includes abnormal peroneal, tibial or sural nerve conduction and is corresponding to the changes in the needle electromyography; the small fiber neuropathy is defined by abnormalities seen in QSART and/or QST[62].

The exclusion criteria include current pregnancy, recent lower extremity fracture (less than six months), foot deformity, unable to perceive the visual information due to visual impairments and other illness that lead to postural instability such as neurovascular disease and vestibular disorders.

B. Instrumentations

This study was mainly accomplished using the GRAIL system (Motekforce Link, the Netherlands) in the virtual reality laboratory of Biomechanics Research Building, University of Nebraska at Omaha. The GRAIL system consists of a 3D motion capture system, an instrumented treadmill, and virtual reality software that generates virtual scenes. The motion capture system equipped with eight high-resolution Vicon T160 cameras along

with the Vicon Nexus software suite (Vicon, Oxford, UK) acquired and processed the kinematic data of markers from lower extremities at 100 Hz during treadmill walking. A motorized fully instrumented treadmill (Bertec Corp., Columbus, Ohio) which measures all six load components of three-axis forces and moments through the force plate underneath the split belts was used. The D-Flow software (Motek Medical BV, the Netherlands) not only generated virtual scenarios, but also integrated and synchronized each event of motion capture, treadmill triggering and scenario control simultaneously. The virtual scene was projected onto the cylindrical screen ahead by three fore-mounted projectors (**Figure 2.1**). To ensure the safety during treadmill walking, subjects were protected by wearing the harness-like vest with several straps anchored on a ceiling-mounted track system (Solo-Step, Inc., North Sioux City, SD).

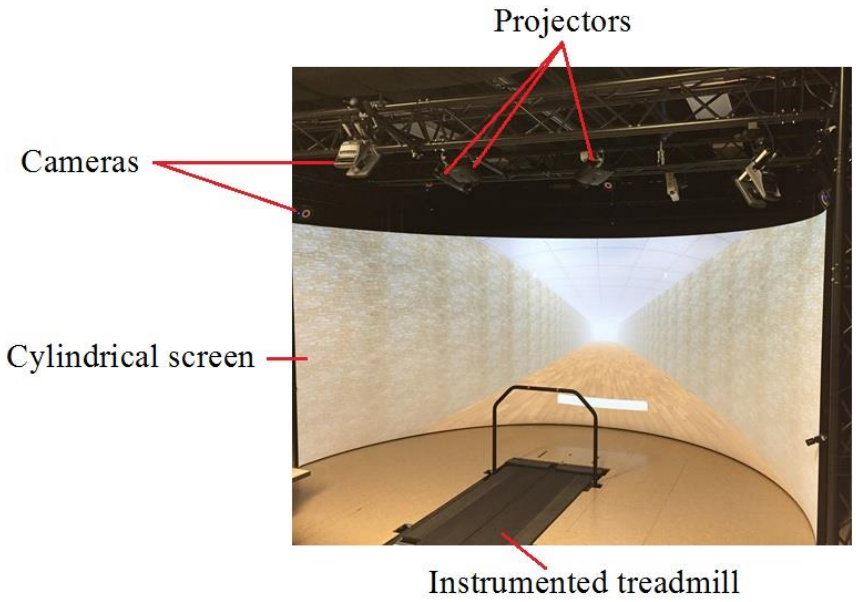


Figure 2.1. The illustration of GRAIL system where the relaive location of cameras, projectors, treamill and cylindrical screen were shown.

C. Experimental Protocol

Upon the completion of consent taken, subjects reported their demographic information such as the date of birth, hand dominance, height, weight, race, most current A1C% (if they were DM/DPN population), years of their illness, and falling history (**Table 2.1**). In order to obtain subjects' general balance performance and mental status, subjects completed two clinical functional balance tests and one clinical cognitive test: Timed up and Go Test (TUG), Berg Balance Scale (BBS) and Mini-Mental Status Examination (MMSE, **Appendix C**). In the TUG, the duration of sit-stand-sit movement within the three-meter distance was timed; in the BBS, the 14 sub-items of functional balance test scored 0~4 each with a total score of 56 was measured; in the MMSE, individual's fundamental cognitive function such as orientation, attention, calculation, recall, language and motor skills were evaluated and quantified (maximum score of 30 points).

Subjects were instructed to wear a wrestling singlet in order to ensure all the reflective markers were well-placed on the bony landmarks; the modified Plug-In-Gait marker set of lower extremity with 17 reflective markers was adopted (the seventh cervical vertebrae, left/right anterosuperior iliac spine, posterosuperior iliac spine, lateral thigh, knee, shank, ankle, toe and heel; **Figure 2.2**). The human model established by the marker set in the Vicon Nexus was further synchronized to the GRAIL system through D-Flow in order to present the real-time virtual toe marker on the cylindrical screen (**Figure 2.3**).

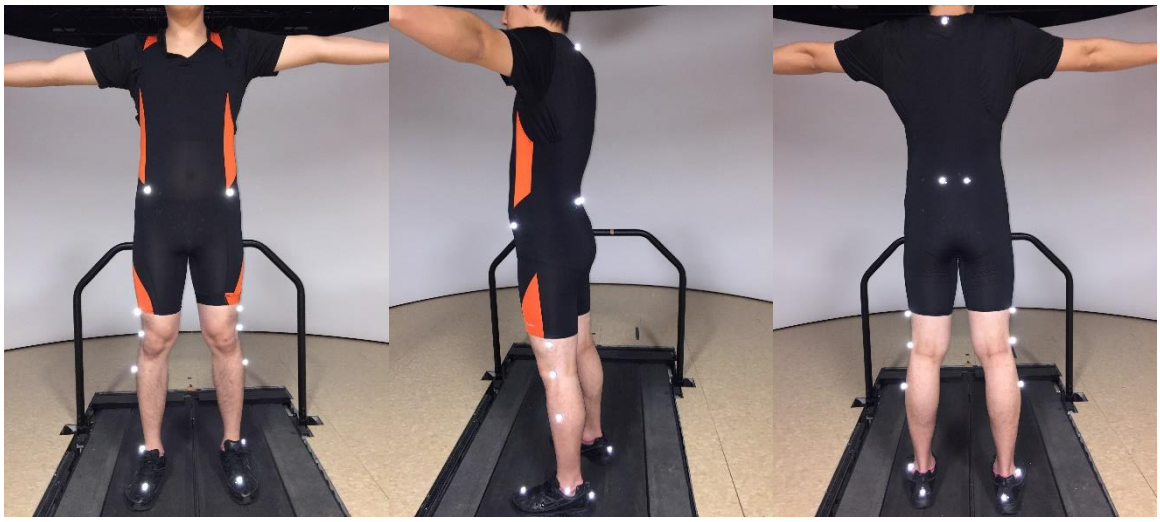


Figure 3.2. The seventeen marker placement according to the modified Plug-In-Gait marker set shown in a) front, b) posterolateral, and c) rear views.

Ensuring all the subjects remember the steps of obstacle crossing task (OCT), the familiarization process was followed the actual-virtual OCT sequence. Subjects firstly stepped over a real object that was of their 15% leg length height (defined as the length between greater trochanter and lateral ankle) 30 times on the ground using the dominant leg as leading leg. The adoption of 15% of leg length as the obstacle height was according to our observation and subjects' feedback in pilot study in which all subjects can easily stepped over the obstacle height with 10% of their leg length along with the higher successful rates. In addition, based on the Americans with Disabilities Acts Accessibilities Guideline[63], a maximal height of the pedestrian curb can be 150 mm (6 inches) where a slope is allowed for this maximal rise. The average 15% of leg length in this study was 124.27 ± 8.35 mm, and was close to the maximal challenging height they may face in their daily livings. After the extra five actual obstacle crossing tasks over ground were recorded, subjects were instructed to walk on the treadmill with their self-selected pace where the

virtual hallway moved toward them accordingly. As soon as subjects familiarized with the speed of treadmill and without any sense of vertigo or uncomfortable, another six-minute virtual OCT was offered for practice.

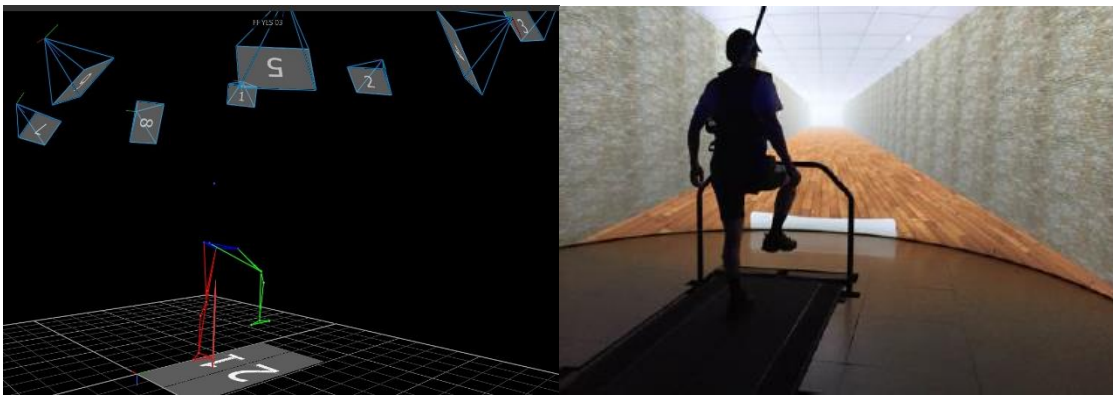


Figure 4.3. The synchronization of performing virtual OCT (right) on the treadmill and in Vicon Nexus environment (left) through D-Flow.

The forthcoming vs. unexpected appearing virtual obstacle

Subjects stepped over the virtual obstacle using their dominant leg as leading leg and were instructed "*To pretend to step over the obstacle as you practiced before, and do not contact it as it is an actual one.*" **(Figure 2.3)** A series of forthcoming virtual obstacles with the dimensions of 45cm (width)* 5cm (depth)* 15% of subject's leg length (height) was created and shown at the end of the hallway and moved toward the subjects with the same self-selected pace on the cylindrical screen.

It has been reported that human's gaze usually focuses on two-step ahead for the feedforward control[64]. Hence, in order to minimize the effect of anjticipation and examine the impact of feedback control during virtual OCT, a virtual obstacle appeared unexpectedly on the cylindrical screen within two-step ahead each subject's step length. Subjects were given the instruction to step over the suddenly appeared virtual obstacle as they previously practiced in the actual one.

Visual exproprioceptive information

To present subject's toes on the screen as the visual exproprioceptive information, a pair of virtual toe marker that pre-synchronized with subjects' right and left toes through D-Flow was shown in real time as subjects' viewing reference. The green dot represented subject's right virtual toe where the red dot represented the left one. This assistance of visual exproprioceptive information was also provided during the period of OCT familiarization (**Figure 2.4**).

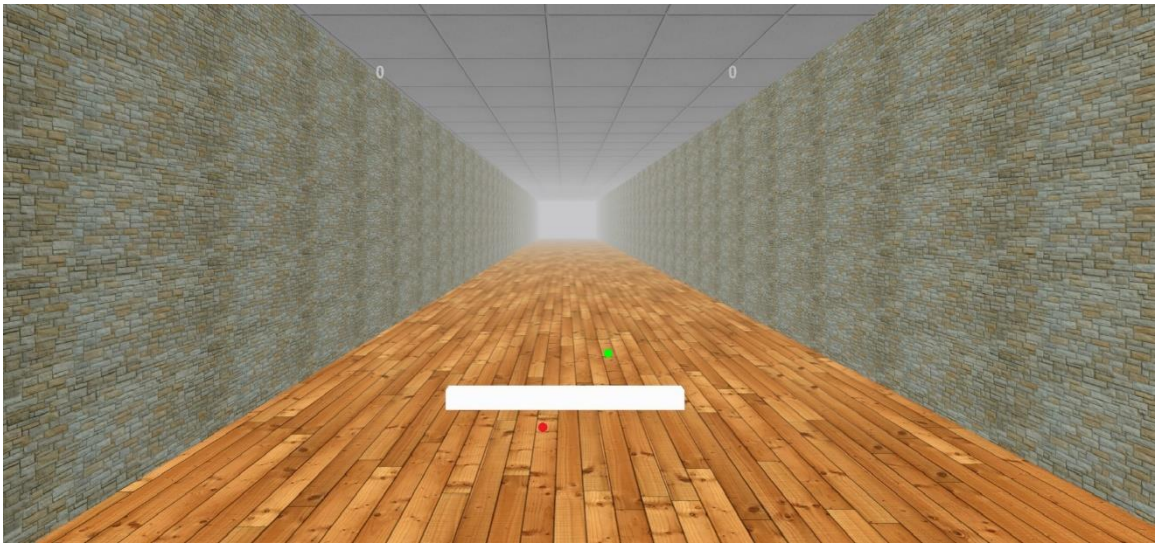


Figure 5.4. A virtual obstacle with the height of 15% subject's leg length shown on the hallway was projected on the cylindrical screen. Noted that a pair of virtual markers was presented in real time as subject's left (red) and right (green) toes.

Collision event

The collision events were defined as any contact occurred between virtual toe marker and virtual obstacle, and were marked as the failures of virtual OCT. Only the outcome variables of successful virtual OCT were analyzed in this study.

The summarized experimental protocol was illustrated in **Figure 2.5**.

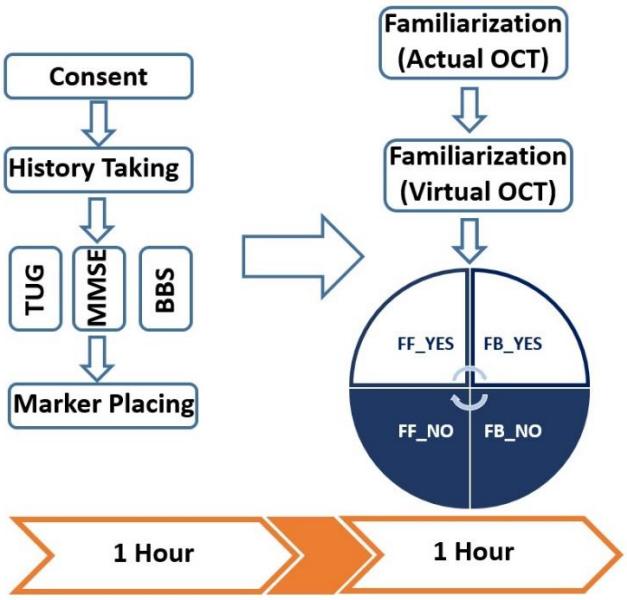


Figure 2.5. The flow of the general experimental protocol of this dissertation.

D. Data Process and Statistical Analysis

Data Process

All data of each single trial were filtered using a 6 Hz zero-lag low-pass Butterworth filter[65] and exported as .csv files for further calculation. The spatiotemporal gait characteristics were calculated using MATLAB program (MathWorks, Inc., Natick, MA), and the definitions of each gait characteristics are described in **Table 2.2**.

Table 2.2. The definition of spatiotemporal gait characteristics of this study.

Gait Characteristics	Acronym	Definition
Maximal Toe Elevation (mm)	*MTE*	The distance between the highest toe position and that of at baseline.*
Step Length (mm)	*SL*	The distance between right and left heel markers in anteroposterior direction.
Stride Length (mm)	*STL*	The distance between two consecutive heel markers of the same foot in anteroposterior direction.
Step Width (mm)	*SW*	The distance between right and left heel markers in mediolateral direction.
Step Time (ms)	*ST*	The duration of right and left heel contact.
Stride Time (ms)	*STT*	The duration of two consecutive heel contacts of the same foot.†
Stance Time (ms)	*STAT*	The duration of heel contact to the following toe-off of the same foot.
Swing Time (ms)	*SWT*	The duration of toe-off to the following heel contact of the same foot.

* The moment of MTE during walking was defined by Khandoker et al[66] and is shown in **Figure 2.6-c**.

† Stride time (STT) consists of stance time (STAT) and swing time (SWT).

The virtual OCT in this study was divided into planning-, crossing- and recovery phases. The planning phase was defined as the period when the last stride length before obstacle crossing. The obstacle crossing phase was the period when either leading or trailing leg stepping over the obstacle (i.e. the stride time during OCT). The recovery phase was defined as the period when first stride length after the crossing phase. **Figure 2.6** illustrates the three phases of OCT and how they were determined through the tracking of toe and heel markers across time respectively.

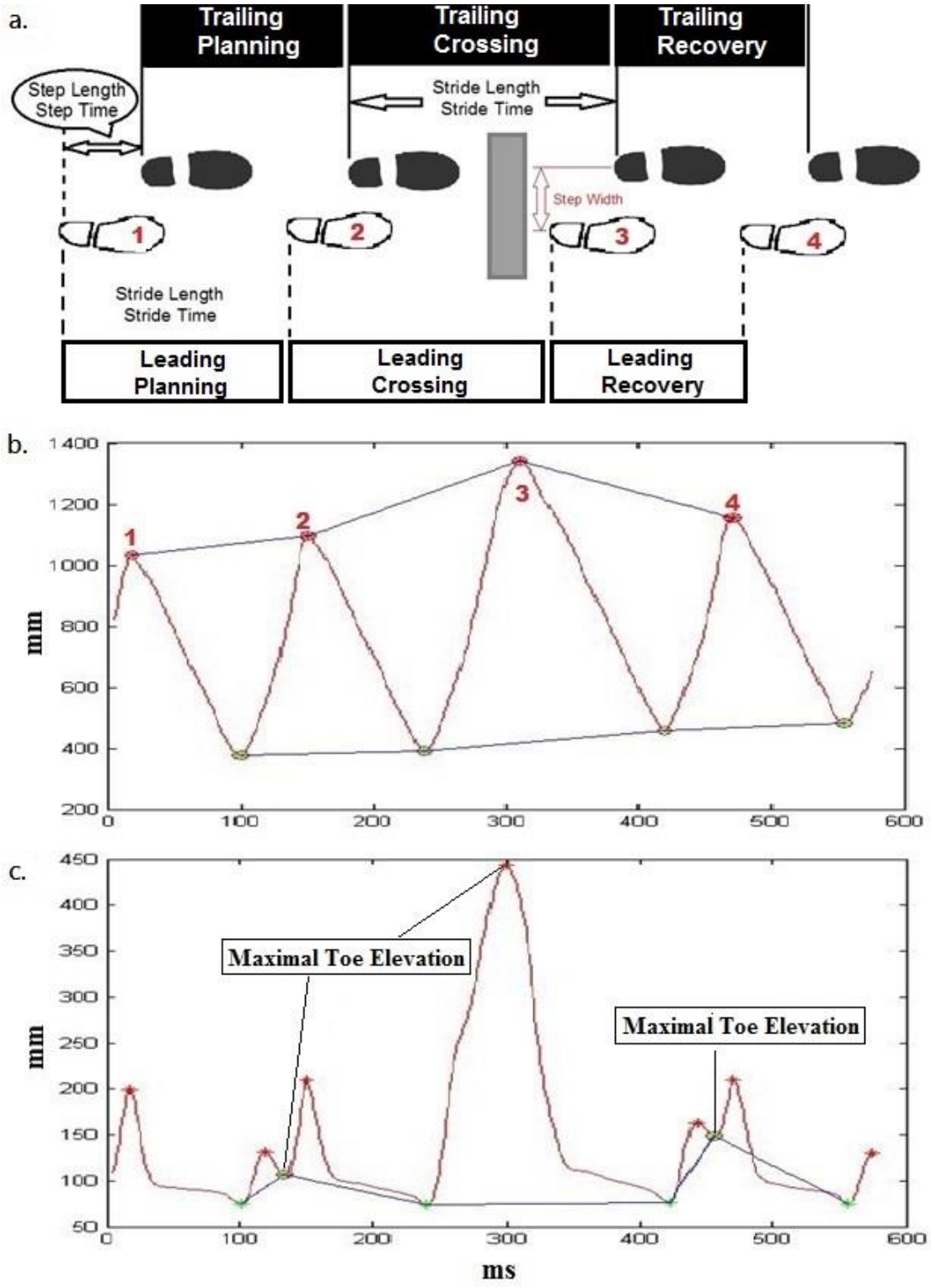
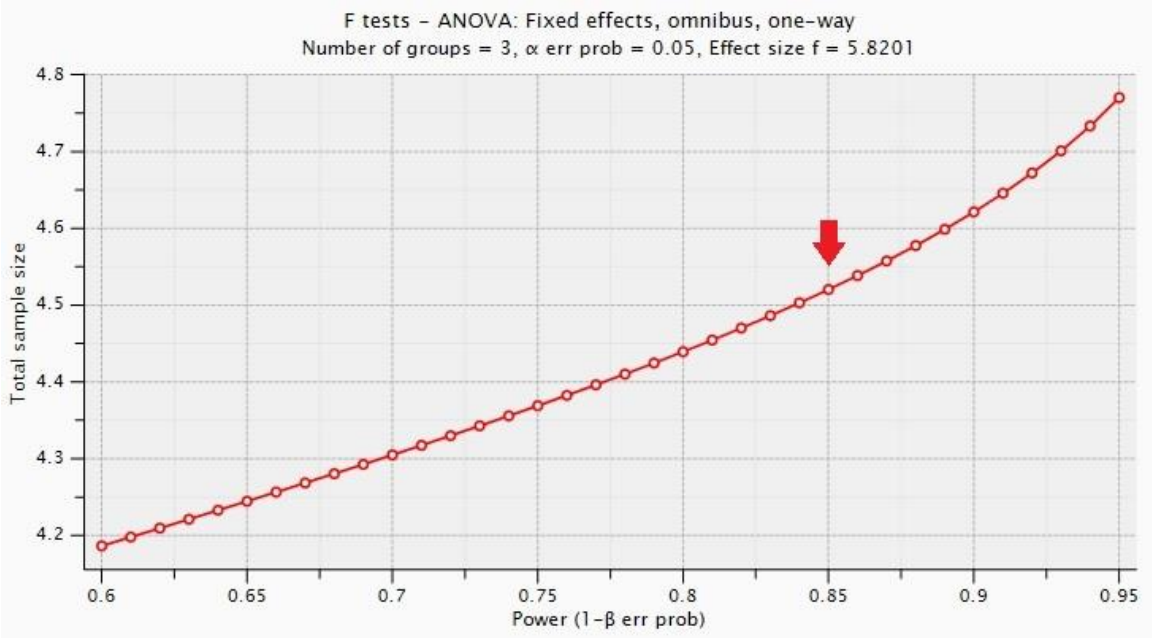


Figure 6.6. a) The planning, crossing, and recovery phases were defined by each stride length before, during and after crossing respectively; b) the plot of displacement over time of the right heel marker in anteroposterior direction where each number represents the moment of heel contact in Figure 2.6-a; c) the plot of displacement over time of the right toe marker in the vertical direction.

Power Analysis

The effect size for estimating sample size in each group was calculated with ANOVA model from the previous published pilot data of HTY, DM and DPN collected under the same experimental protocol (**Appendix D**)[67] using the open-accessed G*Power 3.0 software with the acceptable power rate of 85% and 0.05 alpha-error probability[68, 69]. For examining the between factor difference (i.e. group), the minimal subjects in each group was five persons (**Figure 2.7a**); for examining the within factor (i.e. vision), the estimated minimal subjects in each group was eight (**Figure 2.7b**). Therefore, we proposed ten subjects in each group in this dissertation to ensure the significance of our hypotheses through the sufficient power.

a)



b)

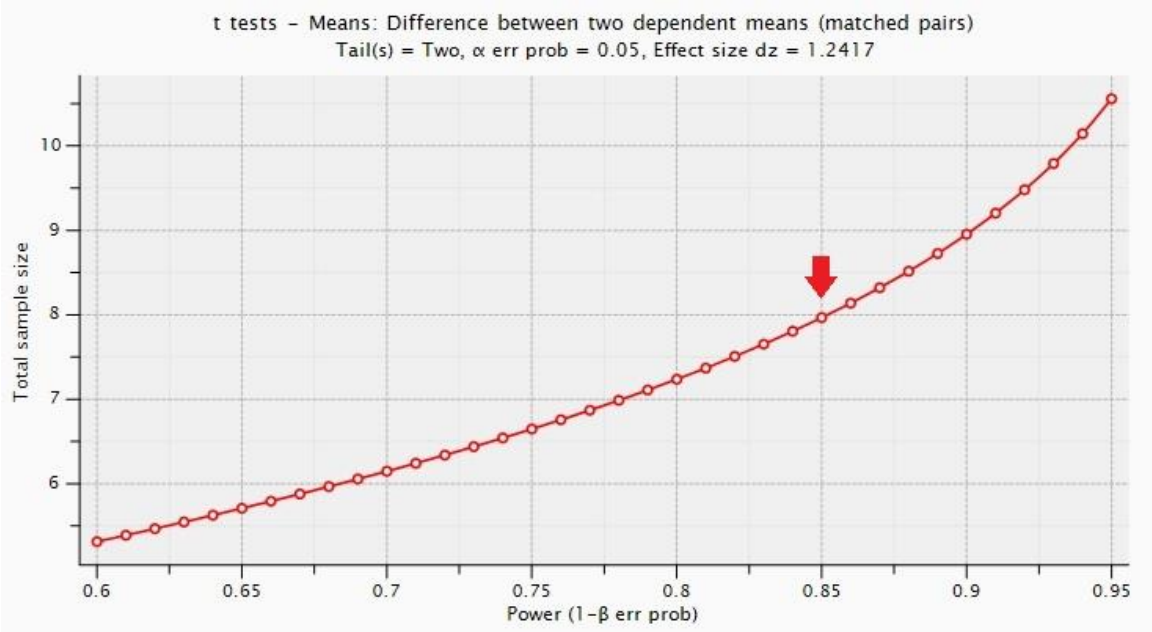


Figure 7.7. The estimated sample sizes in each group across the powers when subjects were stepping over unexpectedly appeared virtual obstacles: a) testing the group effect; b) testing the vision effect within the DPN group.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics software (IBM North America, New York, NY). The Shapiro-Wilk normality test along with the Kurtosis test were adopted to examine the assumption of normally distribution of data. Because of the small sample size (N = 32) acquired and the skewed distribution of data found in this dissertation, the non-parametric analyses were adopted and depicted by aims in each chapter:

In **Specific Aim 1** (*Chapter III*) and **Specific Aim 2** (*Chapter IV*), the Kruskal-Wallis one-way analysis of variance by ranks test was adopted for comparing the between-group difference following by Mann-Whitney U test as multiple comparisons. For testing the within-factor difference (i.e. phase effect), the Friedman analysis of variance by ranks test was adopted following by Wilcoxon signed-ranks test as multiple comparisons. The

adjusted significant level of aforementioned multiple comparisons was applied using Bonferroni correction (i.e. $\alpha = 0.05/3 \approx 0.02$). In addition, the Spearman rank correlation coefficient (ρ) was adopted to depict the relationships among the successful rate of virtual OCT, severity of subject's illness (%A1C of DM/DPN) and spatiotemporal gait characteristics (the significant level was $\alpha = 0.05$).

In **Specific Aim 3** (*Chapter V*), the Wilcoxon signed-ranks test was adopted for testing the effect of visual information on spatiotemporal gait characteristics. To compare the group effect on the dependent variables, similarly, the Kruskal-Wallis one-way analysis of variance by ranks test was adopted following by Mann-Whitney U test as multiple comparisons. The adjusted significant level of aforementioned multiple comparisons was applied using Bonferroni correction (i.e. $\alpha = 0.05/3 \approx 0.02$). The correlation between successful rate of virtual OCT and visual information and that of spatiotemporal gait characteristics were analyzed using Spearman rank correlation coefficient (ρ) with the significant level of $\alpha = 0.05$.

Friedman analysis of variance by ranks test for testing the within factor difference (i.e. phase and vision effect) following by Wilcoxon signed-ranks test as multiple comparisons. For comparing the between group factor difference, the Kruskal-Wallis one-way analysis of variance by ranks test was adopted following by Mann-Whitney U test as multiple comparisons. The significant level of Friedman and Kruskal-Wallis test by ranks were $\alpha = 0.05$. The adjusted significant level of multiple comparisons was applied using Bonferroni correction (i.e. $\alpha = 0.05/3 \approx 0.02$) in order to control for the increased risk of Type I error[70].

CHAPTER III

THE EFFECT OF FEEDFORWARD CONTROL ON ADJUSTING SPATIOTEMPORAL GAIT CHARACTERISTICS DURING VIRTUAL OBSTACLE CROSSING TASKS IN ADULTS WITH DIABETES

A. Introduction

In 2014, there were more than 25.7 million adult populations (age of 20-79 years) who have been diagnosed as diabetes mellitus (DM) in the U.S., and the estimated prevalence rate was nearly 12%[5, 71]. DM was ranked as the seventh-place of leading cause of death which led to approximately 200 thousand DM-related deaths in the U.S.[71] In addition, more than 50% of DM populations develop sensorimotor deficits due to diabetic peripheral neuropathy (DPN) which is the most common form of diabetic neuropathy that prominently affects their activities of daily living[7, 8]. For example, DPN with delayed afferent nerve sensory inputs or efferent motor outputs[9] not only results in poor postural control, but also shows the loss of position, vibration, and tactile sensation of their feet when compared to healthy individuals[10]. DPN also leads to higher spatiotemporal gait variability and increases the incidence of falling/tripping accidents due to the compromised sensory feedback information brought from lower limbs toward central nervous system (CNS)[11, 13, 14]. In addition, more studies pointed out an altered gait pattern in DM which results in a shortened step length, wider step width, increased double support time, and increased step-to-step variability[15-17]. These gait alterations in DM due to potential somatosensory feedback deficit during walking are also associated with a high risk of falling [11, 12, 14, 16-20].

To reduce the occurrence of accidents such as tripping and falling, a well-coordinated and adapted limb movement driven by the CNS is required to maintain balance during locomotion. The top-down feedforward control that communicates with CNS and rapidly forms the basis for computing necessary motor output by predicting or correcting errors of event information brought by the bottom-up feedback control is needed to execute a more accurate movement for maintaining balance during walking[22, 23]. Stepping over obstacles or obstacle crossing tasks (OCT), requires people to adopt the top-down feedforward control to proactively take appropriate anticipatory action such as selecting affordable spatiotemporal gait characteristics in three dimensions before reaching the perturbation[56, 72]. In animal study, the increased discharge of motor cortical cell in cat's motor cortex was observed when stepping over an obstacle on the treadmill, confirming that CNS played a role during OCT[73]. In human locomotion, McFayden et al. firstly rendered a term "anticipatory locomotor adjustments" to depict the preluded voluntary modification by the supraspinal level when confronting an obstacle[41]. This study suggested that OCT could also be controlled at the level below the CNS.

OCT can be divided into three phases as planning (pre-event or approaching the event), crossing (during the event), and recovery (post-event)[25, 26]. The outcomes of spatiotemporal gait characteristics influenced by the aforementioned anticipatory locomotor adjustments or the feedforward control can be examined specifically in the planning and crossing phase between people with neurological illness (e.g. DPN) and healthy control group accordingly. It is speculated that DPN who suffers from compromised sensorimotor deficits would demonstrate the altered gait characteristics during OCT. However, fewer studies examined the performance of OCT in DM or DPN. Even though the different lower extremity

trajectory and joint kinematic/kinetic patterns between DM/DPN and healthy control during OCT was observed[47], evidence regarding how the feedforward control impact the adjustment of DM's gait characteristics during planning and crossing phase of OCT, especially in DPN, remains unknown.

Therefore, the aim of this chapter was to investigate the impact of feedforward control manner on adjusting spatiotemporal gait characteristics in the three phases (planning, crossing and recovery) of stepping over the forthcoming virtual obstacles in DM, DPN and age-matched healthy group. We hypothesized that when comparing to the age-matched healthy control and DM, DPN would show lower task successful rate during OCT along with the altered gait pattern when stepping over the virtual obstacles by decreasing their maximal toe elevation (MTE), step length, stride length, and by increasing step width, stride time, swing time and stance time; in addition, DPN would increase the variability of the spatiotemporal gait characteristics when stepping over the virtual obstacles.

B. Method

Experimental Protocol

Thirty-two subjects (eleven HTY, eleven DM and ten DPN) in this study completed the informed consent approved by the Institutional Review Board in University of Nebraska Medical Center. In order to test our hypotheses, a forthcoming virtual obstacle presented on the screen at least two steps ahead of subjects to ensure each subject has plenty of time to prepare for the upcoming event. More detailed descriptions were included in the *Chapter II*.

Statistical Analysis

For comparing the between-group difference, the Kruskal-Wallis one-way analysis of variance by ranks test was adopted following by Mann-Whitney U test as multiple comparisons. The Friedman analysis of variance by ranks test was adopted for testing the within factor difference (i.e. phase effect) following by Wilcoxon signed-ranks test as multiple comparisons. The adjusted significant level of aforementioned multiple comparisons was applied using Bonferroni correction (i.e. $\alpha = 0.05/3 \approx 0.02$). The Spearman rank correlation coefficient (ρ) was adopted to depict the relationships among the successful rate of virtual OCT, severity of subject's illness (%A1C of DM/DPN) and spatiotemporal gait characteristics (the significant level was $\alpha = 0.05$).

C. Result

Healthy control group (HTY) showed a higher successful rate than DM and DPN on both leading and trailing legs, but the comparison did not reach statistical significance ($p > 0.3$; **Table 3.1**). In addition, a significant moderate correlation between the self-selected walking speed and virtual OCT successful rate in the DPN group was observed ($\rho = 0.67$, $p = 0.03$).

Table 3.1. The successful rate of virtual OCT by group (presented as median and interquartile range, IQR, in parenthesis).

Group / Side	HTY (n=11)	DM (n=11)	DPN (n=10)	*p* value*
Leading	0.92 (0.67-1.00)	0.80 (0.70-0.90)	0.78 (0.53-0.90)	0.35
Trailing	0.58 (0.42-0.67)	0.38 (0.22-0.58)	0.46 (0.17-0.69)	0.32

*: Group differences were compared using Kruskal-Wallis test ($\alpha = 0.05$).

The following results only listed those with significant differences between groups, and were presented in the sequence of spatial, temporal, following by the variability of the gait

characteristics. The gait measurements and their variability were summarized in **Table 3.2 and Table 3.3**.

Spatial gait characteristics

In the crossing phase during OCT, DM showed a significant decreased in the leading MTE (303.03 mm, IQR = 279.34-364.10 mm) when compared to HTY (407.09 mm, IQR = 352.20-469.96 mm; $p = 0.01$). In addition, a negative moderate correlation between the severity (i.e. %A1C) and the leading MTE in DPN during crossing phase was observed ($\rho = -0.41$, $p = .0.28$; **Figure 3.1**).

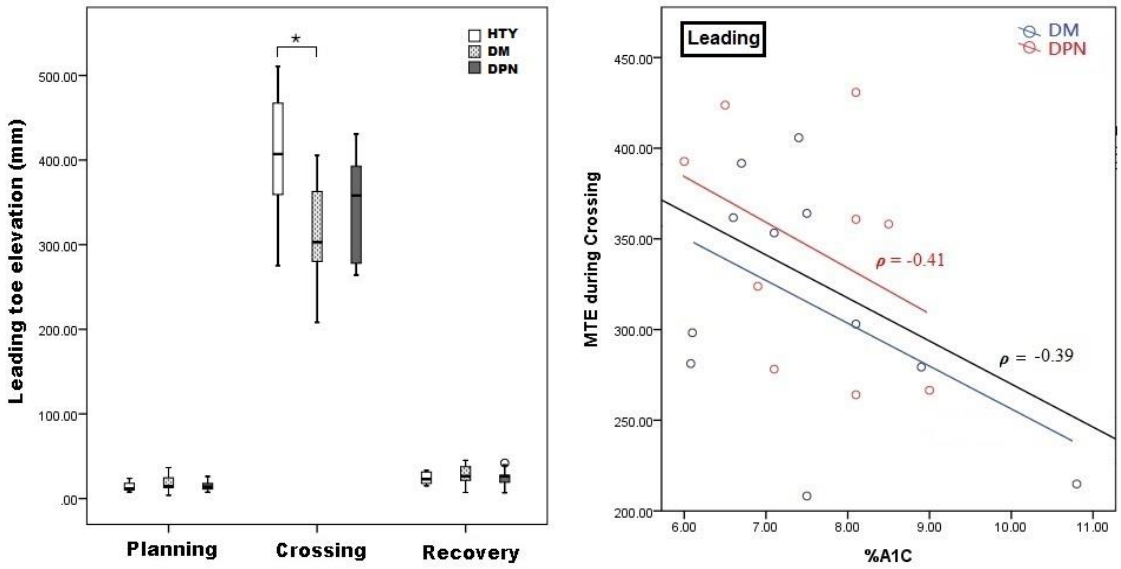


Figure 3.1. The decrease in maximal toe elevation (MTE) observed in DM and DPN's leading leg in which a significant decrease in DM was revealed compared with HTY (left); the negative moderate correlation between %A1C and leading MTE in DPN was shown during the crossing phase of OCT (right).

Temporal characteristics

DPN showed a significant increase in stride time of the leading side in the recovery phase (1565.00 ms; IQR = 1403.41-2150.00 ms; **Figure 3.2a**) and of the trailing side in the crossing phase (1761.25 ms; IQR = 1640.00-2089.72 ms; **Figure 3.2b**) when compared

to HTY (1332.50 ms, IQR = 1303.33-1418.75 ms; p = 0.01 and 1485.71 ms, IQR = 1340.00-1546.00 ms; $p < 0.01$, respectively).

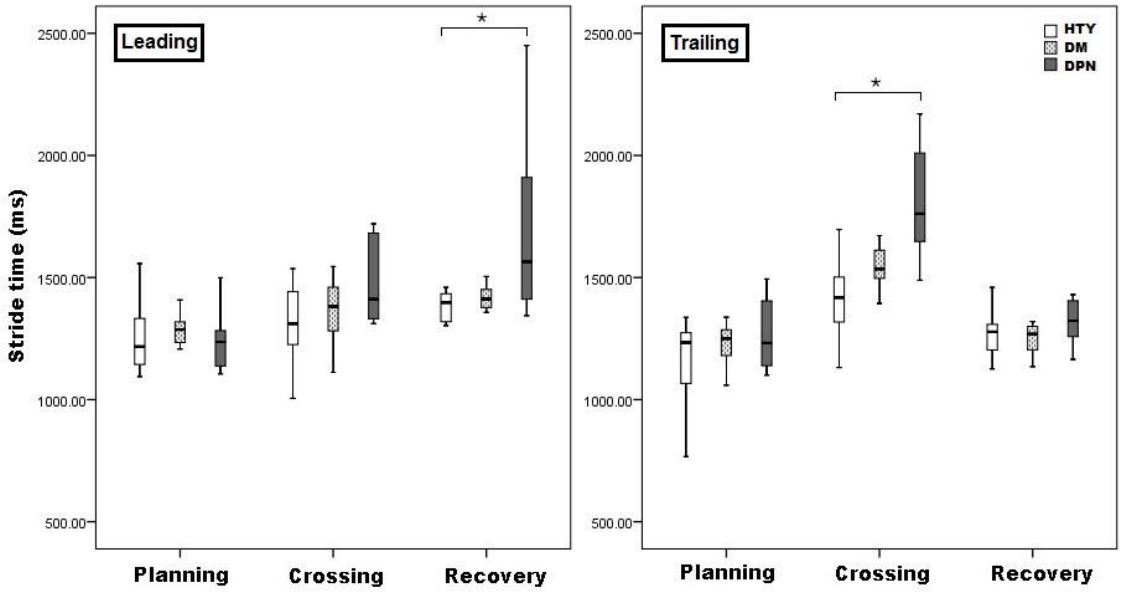


Figure 3.2. The significant increase in stride time observed in DPN versus that in HTY of the leading side during recovery phase (a), and of the trailing leg during crossing phase (b).

DPN showed a significant increase in stance time of the leading side in the recovery phase (1089.00 ms; IQR = 922.22-1493.64 ms) when compared to HTY (858.18 ms, IQR = 844.00-931.67 ms; p = 0.01; **Figure 3.3a**). Similarly, DPN showed a significant increase in stance time of the trailing side in the planning phase (1070.00 ms, IQR = 937.50-1211.67 ms) when compared to HTY (875.00 ms, IQR = 830.00-949.09 ms; $p < 0.01$; **Figure 3.3b**).

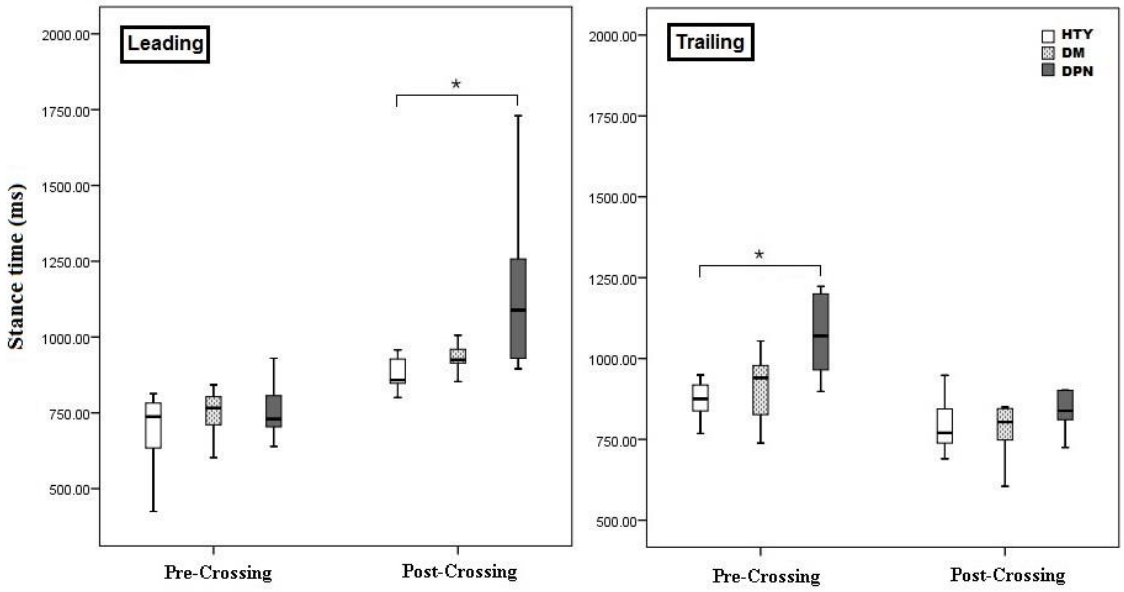


Figure 3.3. The significant increase in stance time observed in DPN versus that in HTY of the leading side in post-crossing (a), and of the trailing leg in pre-crossing phase (b).

In the crossing phase, DPN showed a significant increase in swing time of the trailing side (683.75 ms, IQR = 628.13-734.44 ms) when compared to HTY (606.67 ms, IQR = 558.89-627.27 ms; $p = 0.02$; **Figure 3.4**).

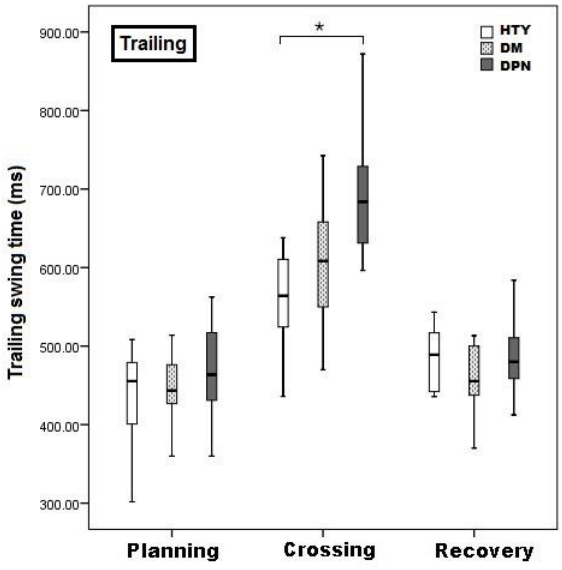


Figure 3.4. The significant increase in swing time of DPN's trailing side versus that in HTY during the crossing phase of OCT was shown.

In the crossing phase, specifically, the trailing stride time showed the moderate negative correlation to virtual OCT successful rate in the HTY group (ρ = -0.53, p = 0.09) while the trailing swing time showed the moderate correlation to virtual OCT successful rate in the DPN group (ρ = 0.61, p = 0.08).

Spatiotemporal gait variability

In the recovery phase, DPN (0.06, IQR = 0.04-0.10) and DM (0.05, IQR = 0.04-0.11) significantly decreased their step length variability when compared to HTY (0.15, IQR = 0.08-0.19, p = 0.006 and p = 0.004, respectively). Conversely, a positive mild correlation between %A1C and step length variability was observed during the recovery phase of OCT (ρ = 0.37, p = 0.15; **Figure 3.5**).

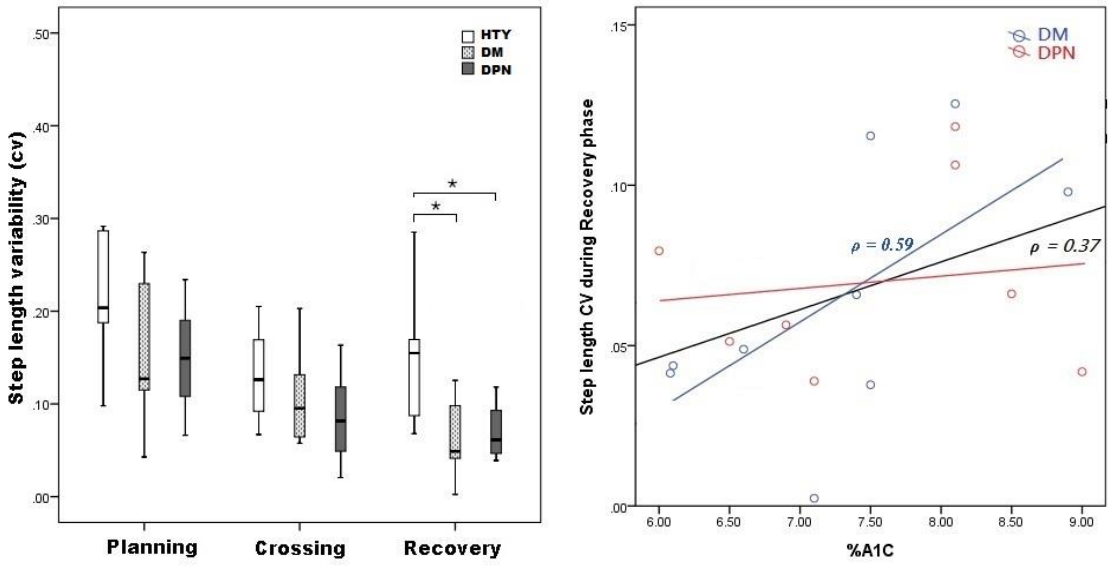


Figure 3.5. The significant decrease in step length variability in DM and DPN versus that in HTY during the recovery phase of OCT was shown (left) while the mild to moderate positive correlation observed between %A1C and step length variability (right).

The following results further described the significant differences found between phases according to the spatiotemporal gait characteristics (**Table 3.2**). Compared with the recovery phase, all three groups significantly increased their trailing stance time in the

planning phase. In addition, compared with the planning and recovery phases, the significant increase in the leading MTE, trailing stride time and swing time of HTY, significant increase in the trailing stride time and swing time of DPN were observed. Lastly, compared with the planning phase, DPN had a significant increase in the leading stride time and stance time in the recovery phase.

D. Discussion

This chapter investigated how the feedforward control impacted the adjustment of spatiotemporal gait characteristics along with the variability during the virtual OCT. We hypothesized that when compared to HTY and DM, DPN groups showed the significant differences of these gait outcome variables and task successful rate. The results supported our hypotheses according to different phases:

Planning phase

The voluntary locomotor modification was planned ahead when confronted with the forthcoming obstacle[41], and the extended stance time of DPN's trailing side in the planning phase suggested that they may have the compromised feedforward control during OCT. The trailing stance time (single leg stance) in the planning phase has been indicated to be important for maintaining stability of leading leg to step over the obstacle[74], therefore, the significant increase in the trailing stance time in DPN versus HTY, not in the leading side, was expected. This result was in accordance with a previous study in which DPN groups showed longer reaction time of lower extremity from lifting the toe to successfully avoid the approaching target[48]; it also supported our hypothesis and indicated that DPN took more time than HTY did at this moment (i.e. the very last step right before the crossing event)

possibly due to the sensorimotor deficits that prolonged the process of judging the upcoming event they perceived[74].

Crossing phase

The severity of DM and DPN (%A1C: 6%~10.8%) was inversely proportional to the successful rate of virtual OCT in both leading and trailing legs (92~38%). This finding supported our hypothesis in which DPN with potentially compromised feedforward control reduced the successful rate of virtual OCT. In addition, MTE is considered as a crucial measure of accomplishing OCT. Previous studies have indicated the reduced MTE during obstacle crossing in healthy adults with distracted attentions[29], elder adults[31] and patients with neurological illness[25, 26, 28, 48], caused the failure of obstacle clearance and sequentially led to trips and falls[74, 75]. The decrease in DM and DPN's leading MTE during the crossing phase was moderately and negatively correlated with their %A1C (**Figure 3.1**), and which provided important evidence that lowered MTE observed in higher %A1C (e.g. DPN) would increase the risk of tripping during OCT[47].

Interestingly, the successful rate of virtual OCT of the trailing leg was lowered than that observed in the leading side in all three groups. This finding was consistent with previous study in which the trailing limb demonstrated more failures than leading limb when stepping over the forthcoming virtual obstacles without any visual cues[58]. From the perspective of limb-independence, the both limb trajectories were controlled independently during OCT, for example, the leading leg is influenced by vision while the trailing leg is guided by a neural representation[32].

In addition, the significant temporal-dependent gait characteristics were apt to explain these findings. In HTY, the moderate negative correlation between successful rate and the

trailing stride time of this study indicated why the lowered successful rate shown in the trailing side. The consistent results from previous study also confirmed that the prolonged stride duration of people with hemiplegia at the moment of obstacle avoidance resulted in the increased failure rates[25].

The significant increase in step length was observed in the crossing phase compared with the other two phases among the three groups. Even though there was no significant group difference, step length in DPN was higher than the other two groups (**Table 3.2**). This finding was consistent with previous research in which a conservative strategy with decreased step length was found that may be detrimental for OCT because the decreased step length increases the likelihood of contacting the obstacle and shorten the duration of reliance on visual information during crossing[25, 35, 75]. It is possible that DPN lengthened their step length in the crossing phase to prevent from the potential contact of the obstacle and increase the successful rate.

Recovery phase

DPN showed the significant increased leading stride time and stance time when compared to HTY. These findings were similar to those data presented from a study of patients with hemiplegia where the slow-walking group showed the higher stride duration when compared to the control group[25]. The longer step duration found during the recovery step in patients with cognitive impairments was indicated as the cortical dysfunction[26], therefore, the higher leading stride time and stance time in DPN after the obstacle crossing event cannot be a well-adapted gait adjustment possibly due to the compromised feedforward control at higher cortical level.

The results of gait variability, however, did not support our hypotheses by showing the significant decreased step length variability in DM and DPN during the recovery phase. This unexpected finding could be explained as DM and DPN tended to select a more rigid status after the event in order to regain their dynamic balance. In addition, the mostly non-significant difference between HTY and DM could be due to the well-controlled glucose level (i.e. %A1C) in DM group which makes them behaved similarly to HTY in this study.

Stepping strategies in DPN

In brief, DPN with sensorimotor deficits adopted different stepping strategies during the virtual OCT as the result of the potential compromised feedforward control (**Table 3.2 and Table 3.3)**.

When preparing for stepping over the forthcoming virtual obstacle, the stance time-lengthening strategy was observed in DPN's trailing side, and this strategy could be a dilemma to DPN. On the one hand, DPN gain more time to process and organize their anticipatory stepping strategy. However, on the other hand, the extended single leg stance time is detrimental to the obstacle crossing behavior in DPN since it challenges their single leg standing balance. The demand of gaining stability in the trailing leg at this moment is important for the leading leg to avoid the obstacle successfully, and the more energy expenditure might be required for DPN while adopting this stepping strategy, especially when most of the DPN in this study had an overweight concern (i.e. with a higher BMI).

At the moment of crossing obstacle, DPN adopted a swing time-lengthening technique in their trailing side as a safer strategy in order to increase the successful rate of OCT.

In the recovery phase (i.e. after obstacle crossing), a stride time and stance time-lengthening strategy was observed in DPN's leading side and caused the same issue earlier

in the planning phase: the trade-off between prolonged processing time and increased energy expenditure.

Interestingly, these significant gait changes observed in DPN were all temporal dependent, which can be inferred to the need of more reaction (processing) time which is due to the compromised sensorimotor deficits in DPN during virtual OCT. As we discussed earlier, the altered temporal gait characteristics could relate to the decrease of virtual OCT successful rate and increased the risk of tripping when DPN attempt to step over an obstacle.

E. Chapter Summary

Taken together, this chapter showed the impact of feedforward control on gait adjustment in DM, DPN and healthy age-matched controls during virtual obstacle crossing task. Specifically, DPN adopted a different stepping strategy that is mostly temporal dependent and the changes of their gait characteristics could potentially due to the compromised feedforward control in both planning and recovery phases of OCT.

Bridging

The significant temporal gait characteristics shown in DPN of this chapter implied that timing plays a critical role affecting the adjustment of gait during OCT. The mostly non-significant difference between HTY and DM may be also due to this timing issue. The scope of following chapter focused on a different bottom-up control on gait during a virtual OCT when time is constrained.

Table 3.2. The changes of spatiotemporal gait characteristic across three different phases of obstacle crossing task (presented as median and interquartile range, IQR, in parenthesis).

Outcomes (Phase / Group)		Planning			Crossing			Recovery		
		HTY	**DM**	**DPN**	**HTY**	**DM**	**DPN**	**HTY**	**DM**	**DPN**
Leading Side	**MTE**	11.87 (10.03)	14.31 (18.80)	13.78 (7.61)	**407.09[a] (117.76)**	**303.03[b] (84.76)**	358.16 (135.90)	22.93 (16.42)	26.44 (16.81)	26.36 (18.97)
	STL	1080.20 (293.79)	1124.66 (320.35)	1063.53 (363.65)	1212.01 (208.49)	1226.98 (211.10)	1223.90 (447.11)	1354.40 (389.69)	1274.35 (455.15)	1339.97 (277.57)
	STT	1217.27 (206.67)	1286.67 (130.36)	1236.67 (178.75)	1310.83 (306.67)	1381.43 (251.25)	1411.11 (371.82)	**1332.5[a] (115.42)**	1412.00 (105.00)	**1565.00[b]** (746.59)
	SWT	445.00 (71.82)	456.67 (64.29)	428.33 (89.77)	616.36 (140.00)	642.00 (112.50)	686.67 (189.18)	478.75 (27.08)	475.00 (66.67)	496.67 (141.51)
	STAT	737. 50 (185.83)	765.83 (114.29)	730.00 (151.58)	--	--	--	**858.18[a] (87.67)**	925.00 (52.68)	**1089.00[b] (571.41)**
Trailing Side	**MTE**	13.17 (13.33)	14.02 (25.15)	13.31 (8.51)	374.78 (225.64)	287.21 (128.79)	288.71 (114.95)	19.18 (26.83)	30.88 (67.73)	88.11 (257.17)
	STL	1022.99 (272.82)	1114.56 (215.06)	1138.14 (267.07)	1525.29 (134.85)	1403.08 (379.04)	1634.99 (333.93)	1243.73 (299.37)	1156.05 (266.05)	1193.98 (270.44)
	STT	1233.64 (252.88)	1250.00 (134.17)	1231.67 (298.92)	**1485.71[a]** (206.00)	1535.00 (156.00)	**1761.25[b]** (449.72)	1290.00 (138.33)	1268.57 (118.28)	1322.92 (175.31)
	SWT	455.45 (93.82)	443.33 (74.94)	463.64 (98.83)	**606.67[a] (68.38)**	608.33 (109.64)	**683.75[b] (106.32)**	489.09 (88.75)	455.50 (72.66)	480.00 (70.90)
	STAT	**875.00[a] (119.09)**	**940.00[a] (166.43)**	**1070.00[b] (274.17)**	--	--	--	770.00 (119.00)	803.33 (110.88)	838.61 (92.81)
SL		563.09 (237.02)	563.58 (109.03)	577.26 (184.32)	863.91 (263.38)	801.42 (118.86)	881.67 (164.66)	630.86 (197.81)	639.25 (90.36)	671.34 (135.97)
SW		118.58 (68.48)	168.16 (81.62)	111.78 (78.69)	129.86 (78.79)	179.01 (47.76)	186.27 (100.21)	147.78 (62.67)	199.16 (38.42)	181.12 (25.85)
ST		254.17 (699.24)	225.00 (571.43)	206.67 (110.92)	275.45 (814.17)	181.25 (425.18)	308.33 (204.68)	320.60 (1126.33)	175.83 (114.46)	158.33 (265.63)

Significant differences of multiple comparison: 1) by group within each phase are in **bold** and shown in different alphabet in upper case; 2) by phase of each group are highlighted when that is different from the other two phases (boxed), between planning and crossing phases (underlined), and between planning and recovery phases(double underlined).

Table 3.3. The changes of spatiotemporal gait variability (coefficient of variation) across three different phases of obstacle task (presented as median and interquartile range, IQR, in parenthesis).

Outcomes \ Phase / Group		Planning			Crossing			Recovery		
		HTY	**DM**	**DPN**	**HTY**	**DM**	**DPN**	**HTY**	**DM**	**DPN**
Lead	**MTE**	0.29 (0.10)	0.26 (0.20)	0.26 (0.24)	0.16 (0.19)	0.12 (0.11)	0.11 (0.05)	0.41 (0.30)	0.41 (0.27)	0.34 (0.29)
	STL	0.11 (0.09)	0.09 (0.06)	0.12 (0.10)	0.13 (0.08)	0.13 (0.09)	0.12 (0.15)	0.08 (0.07)	0.07 (0.04)	0.06 (0.03)
	STT	0.08 (0.07)	0.07 (0.05)	0.11 (0.10)	0.15 (0.07)	0.15 (0.11)	0.14 (0.11)	0.06 (0.06)	0.06 (0.03)	0.06 (0.03)
	SWT	0.14 (0.09)	0.12 (0.11)	0.15 (0.07)	0.15 (0.09)	0.12 (0.09)	0.11 (0.13)	0.07 (0.04)	0.06 (0.03)	0.05 (0.03)
	STAT	0.22 (0.09)	0.17 (0.14)	0.18 (0.09)	--	--	--	0.08 (0.05)	0.09 (0.03)	0.08 (0.06)
Trail	**MTE**	0.35 (0.28)	0.41 (0.42)	0.43 (0.23)	0.15 (0.14)	0.16 (0.21)	0.12 (0.32)	0.29 (0.27)	0.25 (0.19)	0.28 (0.59)
	STL	0.16 (0.14)	0.14 (0.12)	0.14 (0.05)	0.11 (0.09)	0.08 (0.11)	0.08 (0.04)	0.06 (0.04)	0.04 (0.05)	0.05 (0.06)
	STT	0.17 (0.08)	0.14 (0.11)	0.15 (0.11)	0.10 (0.09)	0.07 (0.09)	0.09 (0.04)	0.05 (0.02)	0.04 (0.02)	0.03 (0.10)
	SWT	0.22 (0.13)	0.19 (0.17)	0.16 (0.06)	0.10 (0.05)	0.07 (0.07)	0.08 (0.05)	0.04 (0.03)	0.04 (0.04)	0.03 (0.04)
	STAT	0.15 (0.08)	0.11 (0.06)	0.12 (0.10)	--	--	--	0.07 (0.02)	0.05 (0.01)	0.05 (0.10)
SL		0.20 (0.11)	0.13 (0.12)	0.15 (0.10)	0.13 (0.10)	0.10 (0.08)	0.08 (0.08)	**0.15 (0.10)[a]**	**0.05 (0.07)[b]**	**0.06 (0.06)[b]**
SW		0.29 (0.27)	0.21 (0.21)	0.18 (0.29)	0.29 (0.24)	0.22 (0.20)	0.20 (0.22)	0.17 (0.18)	0.16 (0.32)	0.19 (0.08)
ST		0.90 (1.18)	0.82 (1.42)	1.15 (1.40)	0.60 (0.72)	0.28 (0.89)	0.38 (1.13)	0.48 (0.98)	0.17 (0.15)	0.22 (0.99)

Significant differences of multiple comparison: 1) by group within each phase are in **bold** and shown in different alphabet in upper case; 2) by phase of each group are highlighted when that is different from the other two phases (boxed), between planning and crossing phases (underline), between planning and recovery phases(double underlined), and between crossing and recovery (dashed underline).

CHAPTER IV

THE EFFECT OF FEEDBACK CONTROL ON ADJUSTING SPATIOTEMPORAL GAIT CHARACTERISTICS DURING VIRTUAL OBSTACLE CROSSING TASKS IN ADULTS WITH DIABETES

A. Introduction

The growing rate of diabetes mellitus (DM) is tremendous in the U.S. The estimated prevalence of DM was 12% in adults in 2014[5], and there are approximate 26 million people with the diagnosis of DM in the US[4, 71]. DM population who is over the age of 60 years have more than 50% probability developing diabetic peripheral neuropathy (DPN): a disease which deteriorates the intact sense of pain, vibration, position, touch and pressure, and affects their intact sensorimotor function in their daily livings such as losing the position, vibration, and tactile sensation of their feet, and showing a poor postural control during quiet stance when compared to healthy individuals[7, 9-11]. Eventually, the risk of falling in diabetes is significantly elevated by 78% when compared to healthy elderly[12].

Obstacle crossing task (OCT) is one of the functional components of daily activities such as stepping on the pedestrian curb on the street or stepping into the bathtub at home. The role of feedforward control on adjusting spatiotemporal gait characteristics while confronting with the forthcoming obstacles in DM and DPN has been discussed in the previous chapter, and adults with DPN is likely to have the compromised feedforward control to complete the forthcoming OCT. However, an immediate response or control (i.e. feedback control) on an event that often suddenly occurs (e.g. the instant righting reaction and strategy while being stumbled by the uneven pavement or changing stepping pattern

immediately in order to get rid of undesired area on the walkway) plays a very important role to maintain our balance and reduce the falling or tripping risk[26, 28].

Previous studies have examined the feedback control during OCT such as releasing an obstacle based on predicting the heel strike when walking on a treadmill[25, 40, 43], showing up the treadmill-attached obstacles periodically during treadmill walking[44], or projecting a band of light on the walkway at the specific moment of gait cycle during over ground walking[31, 42], and the outcomes measures of OCT such as toe clearance, obstacle crossing successful rate, crossing stride/step length, step width and foot distance to the obstacle after OCT, have been categorized as the online reactive response to OCT[25, 26, 29, 31, 42]. As obstacles that appeared suddenly without knowing when or where they are at different available response time, healthy subjects modified their swing trajectory very quickly in response to those suddenly appeared obstacles[40] and showed a higher successful rate as the response time increased when compared to elders or hemiplegic populations[25, 42]. Moreover, healthy subjects and patients with stroke preferred to lengthen their steps as a strategy of crossing obstacles[25]. These findings further led to hypothesize that the spinal reflex pathway or even the supraspinal level was involved in controlling feedback control during OCT since the observable latency of obstacle avoidance was shorter than a voluntary movement[39-41].

Taken together, it is of our interest to investigate how the feedback control impacts on adjusting spatiotemporal gait characteristics of DM, DPN and age-matched healthy controls in the three phases (planning, crossing and recovery) of stepping over virtual obstacles that unexpectedly appeared. We hypothesized that comparing to age-matched healthy, DM and DPN would reduce the task successful rate of virtual OCT and decrease

toe elevation, step length, stride length, and increase step width, stride duration, swing duration and stance time. We further hypothesized that comparing to age-matched healthy subjects, DM and DPN would increase the variability of the aforementioned spatiotemporal gait characteristics when stepping over the virtual obstacles.

B. Method

Experimental Protocol

Thirty-two eligible subjects who met the inclusion and exclusion criteria were recruited in this study. Upon the completion of the informed consent process approved by the Institutional Review Board in University of Nebraska Medical Center, subjects went through the process of basic medical history inquiry, examining their mental status (i.e. MMSE), testing their balance function (i.e. TUG and BBS), placing markers for motion capture, and familiarizing the actual and virtual OCT. To test how the feedback control would impact the spatiotemporal gait characteristics during virtual OCT, a virtual obstacle shown up unexpectedly on the cylindrical screen within two steps ahead of subjects. Subjects were instructed to step over the virtual obstacle as similar as they formerly practiced during the actual OCT. In *Chapter II – GENERAL METHODOLOGY*, more detailed description regarding the experimental protocol and the definition of spatiotemporal gait characteristics were included.

Statistical Analysis

The Friedman analysis of variance by ranks test was adopted for testing the within factor difference (i.e. phase effect) following by Wilcoxon signed-ranks test as multiple comparisons. To examine the difference between groups, the Kruskal-Wallis one-way analysis of variance by ranks test was adopted following by Mann-Whitney U test as

multiple comparisons. The significant level of aforementioned multiple comparisons was adjusted using Bonferroni correction (i.e. $\alpha = 0.05/3 \approx 0.02$). The correlations among successful rate of virtual OCT, spatiotemporal gait characteristics, the severity of illness (i.e. %A1C) and the clinical tests (i.e. TUG and BBS) were analyzed using Spearman rank correlation coefficient (ρ) with the significant level of $\alpha = 0.05$.

C. Result

Similar to the results in *Chapter III* (using the feedforward control paradigm), HTY showed higher successful rate during virtual OCT than DM and DPN, and specifically, a significant higher successful rate was demonstrated in healthy subjects' trailing leg versus those in DM and DPN groups ($p < 0.02$). The successful rate in the leading leg of each group was higher than that in the trailing side (**Table 4.1**).

Table 4.1. The successful rate of virtual OCT by group in the feedback control paradigm (presented as median and interquartile range, IQR, in parenthesis).

Group / Side	HTY (n=11)	DM (n=11)	DPN (n=10)	*p* value*
Leading	0.92 (0.92-1.00)	0.83 (0.63-0.92)	0.83 (0.40-1.00)	0.16
Trailing	0.67[a] (0.42-0.83)	0.33[b] (0.11-0.63)	0.37[b] (0.19-0.50)	0.03

*: Group differences were compared using Kruskal-Wallis test (α=0.05); Significant between-group differences were marked with different alphabets in upper case

The following results only listed those with significant difference shown between groups, and were presented in the sequence of spatial, temporal, following by the variability. All the spatiotemporal gait characteristics and the variability can be referred in **Table 4.3 and Table 4.4**.

Spatial gait characteristics

In the crossing phase, DM and DPN showed a significant decrease in the leading MTE (317.53 mm, IQR = 264.37-355.54 mm; 308.01 mm, IQR = 251.70-380.94 mm, respectively) when compared to HTY (411.21 mm, IQR = 359.38-462.19 mm; p = 0.004 and p = 0.02 respectively). In addition, a moderate negative correlation between %A1C and MTE of the leading side was revealed (ρ = -0.40, p = 0.09) in which a moderate negative correlation in DPN was demonstrated (ρ = -0.67, p = 0.04; **Figure 4.1**).

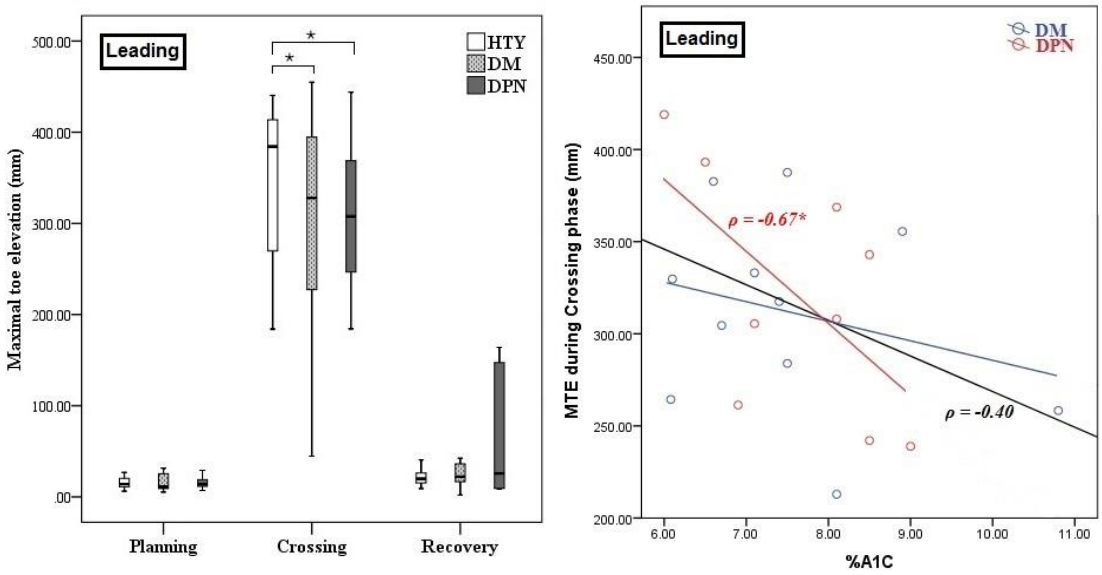


Figure 4.1. The significant reduction in maximal toe elevation (MTE) observed in DM and DPN's leading leg that in HTY (left); the significant moderate negative correlation between %A1C and leading MTE in DPN was shown during the crossing phase of OCT (right).

Both DM and DPN increased their step width in the recovery phase when compared with HTY. Specifically, DM showed a significant increase in step width (219.25 mm, IQR = 162.24-240.79 mm) versus that in HTY (156.06 mm, IQR = 135.54-182.47 mm; p = 0.002; **Figure 4.2**).

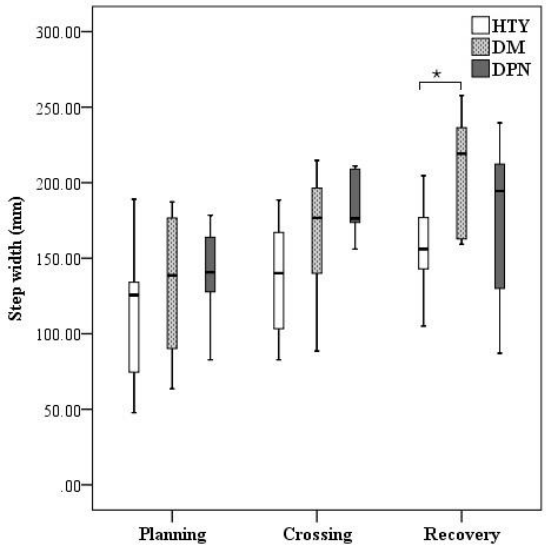


Figure 4.2. The significant increase in DM's step width was revealed when compared with HTY in the recovery phase.

Temporal gait characteristics

DPN showed a significant increase in stride time of leading side in the recovery phase (1529.00 ms; IQR = 1376.25-1685.91 ms) when compared to HTY (1305.45 ms, IQR = 1261.67-1453.75 ms, p = 0.012). In addition, a moderate positive correlation between %A1C and stride time of DPN's leading side was revealed (ρ = -0.40, p = 0.09; **Figure 4.3**).

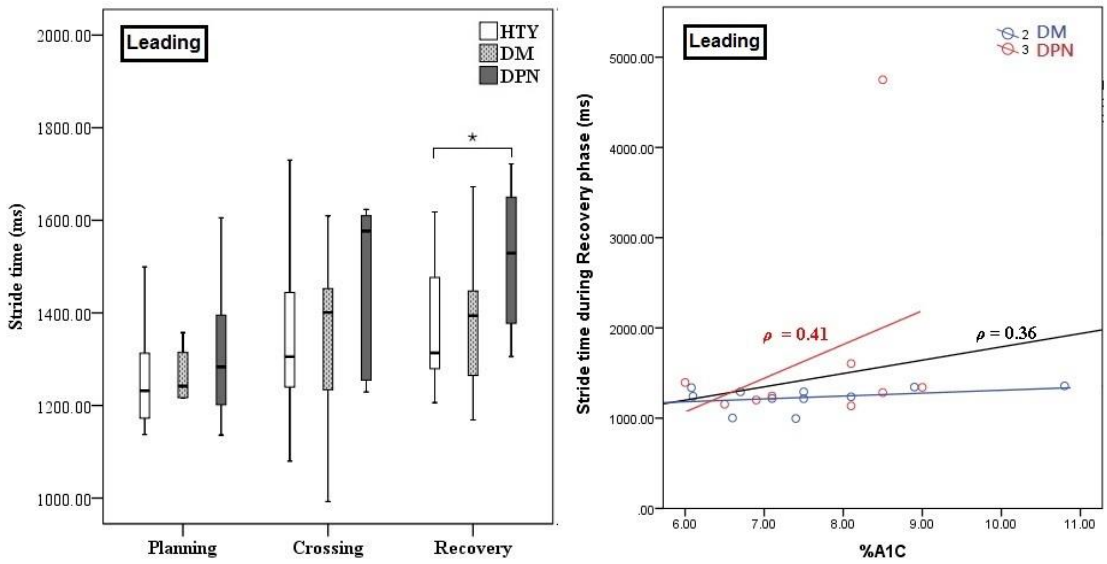


Figure 4.3. The significantly increased stride time was observed in DPN's leading side when compared to that in HTY (left); the moderate positive correlation between %A1C and leading stride time in DPN was shown during the recovery phase of OCT (right).

DPN showed a significant increase in stance time of leading side in the post-crossing moment (1034.00 ms; IQR = 892.50-1123.33 ms) when compared to HTY (835.45 ms, IQR = 802.00-968.75 ms; p = 0.02; **Figure 4.4**).

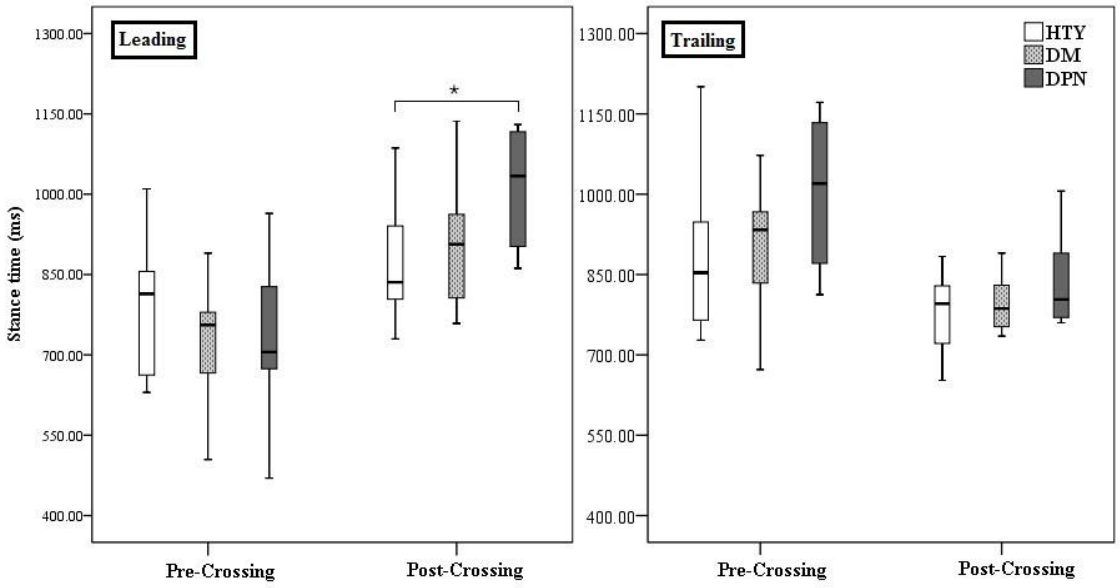


Figure 4.4. The significantly increased leading stance time was shown in DPN when compared to HTY during post-crossing of OCT (left). Noted that the increased stance time observed in DPN's trailing side during pre-crossing phase (right).

Spatiotemporal gait variability

DM showed a significant increase in trailing stance time variability (0.09, IQR = 0.07-0.19) when compared to HTY (0.05, IQR = 0.03-0.08, $p = 0.012$), and a moderate negative correlation between %A1C and stance time variability was observed in which the strong negative correlation was shown ($\rho = -0.73$, $p = 0.04$; **Figure 4.5**).

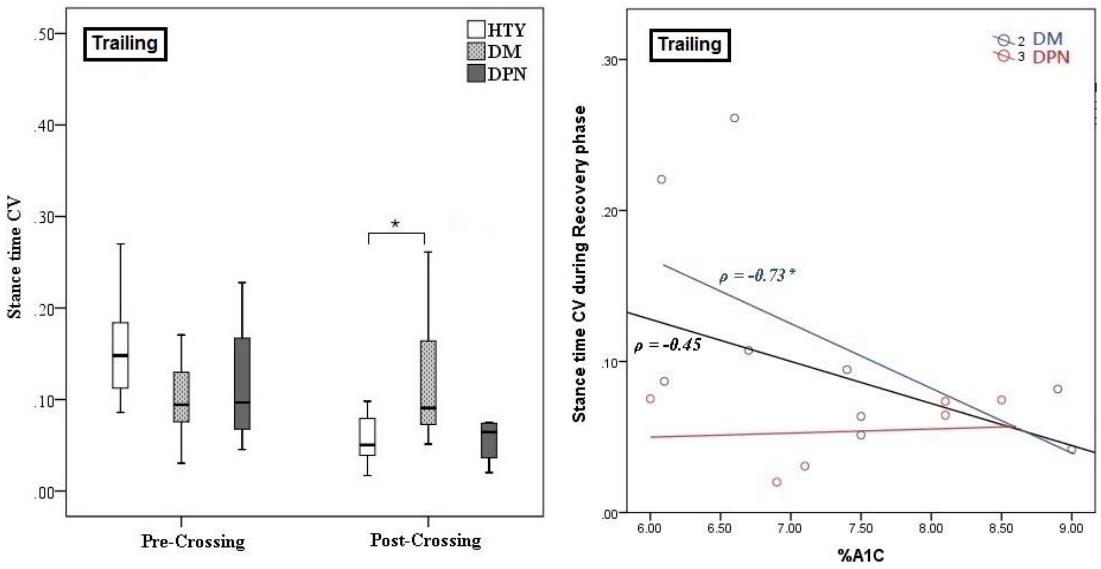


Figure 4.5. The significant increased stance time variability observed in DM's trailing side when compared with HTY during the post-crossing phase of OCT (left). A significantly strong negative correlation between %A1C and stance time variability was revealed at this moment (right).

The following results further described the significant differences found between phases according to the above spatiotemporal gait characteristics (**Table 4.3**). The significant increased leading MTE ($p = 0.012$) and trailing stride time ($p = 0.008$) of the three groups were observed in the crossing phase versus the other two phases. In the recovery phase, DM significantly increased their step width when compared to the other phases ($p < 0.015$). In addition, all three groups significantly increased their leading stride

time (p = 0.008) and stance time (p = 0.013) in the recovery phase when compared with planning phase.

Concerning the relationship between gait characteristics and virtual OCT successful rate, HTY's step width and DM's trailing stance time variability showed a moderate negative correlation to the virtual OCT successful rate in the recovery phase (ρ = -0.63, p = 0.05, and ρ = -0.46, p = 0.26, respectively). In addition, **Table 4.2** depicted the relationship between clinical tests and successful rate of virtual OCT of this study. HTY's trailing leg showed a moderate positive correlation between virtual OCT successful rate and MMSE (ρ = 0.63, p = 0.07); in DM's leading leg, moderate correlations between the successful rate and MMSE (ρ = 0.69, p = 0.04), and between the successful rate and BBS (ρ = 0.72, p = 0.03) were shown; in the DPN's leading leg, a strong negative correlation (ρ = -0.70, p = 0.04) and a strong positive correlation (ρ = 0.83, p = 0.01) were observed between the successful rate and TUG and BBS, respectively.

Table 4.2. The relationship (ρ) between the successful rate of virtual OCT and clinical tests among different groups (N=32).

Successful rate / Tests	HTY (n=11)		DM (n=11)		DPN (n=10)	
	Leading	**Trailing**	**Leading**	**Trailing**	**Leading**	**Trailing**
%A1C	--	--	**-0.75***	-0.46	-0.11	0.13
MMSE	0.22	0.63	**0.69***	0.02	0.04	0.24
TUG	0.21	-0.27	-0.25	0.24	**-0.70***	-0.62
BBS	0.11	<0.01	**0.72***	0.35	**0.83***	0.56

*: significant correlation shown ($\alpha < 0.04$)

D. Discussion

This chapter investigated how the feedback control impacted the spatiotemporal gait adjustment along with the change of gait variability during virtual OCT. We hypothesized that when compared to HTY, DM and DPN groups showed different outcomes in gait variables and their variability. We discussed the gait outcome variables by phases during OCT.

Planning phase

The results of non-significant gait characteristics among groups in the planning phase was contrary to our expectations, and which could be explained by the short response time available for all subjects to react on the virtual obstacle that suddenly appeared within two steps.

Crossing phase

The reduction of successful rate based on the severity of their illness (i.e. %A1C) was a direct evidence showing the speculative compromised feedback control in DM and DPN. While reacting on the unexpectedly appeared virtual obstacle, DM and DPN lowered their virtual OCT successful rates versus that in HTY by 45-51%, and this finding was in accordance with the previous OCT study in patients with neurological disorders. For example, based on the level of severity, Den et al. indicated that stroke patients who walked slower (more severe) showed higher failure rate when stepping over obstacle when compared to those who walk faster (mild severe)[25]. The other study adopted a virtual-game based OCT paradigm and found the similar outcome in which the obstacle crossing successful rate in DPN (more severe with higher %A1C) was lowered by 21~26% versus DM (less severe) and healthy control[48]. The lower successful rate of virtual OCT in DPN

could be explained by the lowered MTE during crossing since the higher MTE was seen as a safety strategy of minimizing the risk of tripping[74]. Hence, the decreased MTE in DM and DPN observed could result in a higher hazard of tripping accidents.

Recovery phase

The increased step width during obstacles crossing has been previously indicated as a compensatory strategy to overcome postural instability[27]. Therefore, DM and DPN might adopt the similar strategy by increasing their step width after crossing the obstacle. They could recover from the previous virtual OCT by taking a lateral step of their trailing leg (i.e. widening their base of support) in order to compensate the possible risk of falling and tripping.

Similar to the results presented in *Chapter III*, DPN showed the significantly increased leading stride time and stance time when compared to HTY after crossing the obstacle. These findings were in accordance with those in stroke patients where the slow-walking group showed the higher stride duration when compared to healthy subjects[25]. In order to recover from stepping over the unexpectedly appeared obstacle on the treadmill, those with sensorimotor deficits, such as in the hemiplegic patients, may take more time (i.e. leading stance time) in their recovery step in order to regain the balance. Similarly, DPN took more stance time in their leading after crossing in order to reach the stability demand before the trailing leg crossed the obstacle[74]. Overall, the increased leading stride time and stance time in DPN after the obstacle crossing event compared to HTY can be seen as the compensation of the compromised sensorimotor controls.

A higher gait variability during walking indicates the poorer stabilization of neuromuscular locomotor which relates to increasing risk of falling[74, 76]. Therefore, the

increased trailing stance time variability in DM and DPN after crossing the obstacle could indicate the poor neuromuscular control in the trailing leg, which could increase the risk of falling[74]. In particular, the significant strong negative correlation between DM's trailing stance time variability and the successful rate confirmed this speculation.

Comparing to the feedforward control paradigm in *Chapter III*, the feedback control paradigm in this chapter demonstrated more significant differences in spatiotemporal gait characteristics in HTY, DM and DPN, and more significant correlations between clinical tests and the successful rate of virtual OCT through MMSE, TUG and BBS. This implied that the experimental design adopting the concept of feedback control could be more sensitive to examine the differences between DM or DPN group versus HTY.

Concerning the relationship between clinical tests and the successful rate of virtual OCT, the BBS revealed significantly strong correlations in DM and DPN. This could be due to the BBS contains sub-tests such as "standing on one leg", "placing alternate foot on step while standing unsupported", "standing unsupported one foot in front", and which are similar to the stepping behavior or could be seen as the requites across the virtual OCT in this study. In addition, a significantly strong negative correlation between the successful rate and TUG was observed. This could be due to TUG examined an individual's immediate response (e.g. acting immediately while hearing of the "Go" instruction) that was also the crucial element for reacting on the unexpectedly appeared virtual obstacle. Taken together, both BBS and TUG could be appropriate to evaluate DM and DPN's capability of reacting on the unexpected and fast events.

Stepping strategies in DM and DPN

When confronted with a time-constrained condition by showing the unexpectedly appeared virtual obstacles, participants with DM and DPN in this study adopted a different stepping strategy as a result of the potential compromised feedback control. These changes of spatiotemporal gait could be revealed by the reduced leading MTE during the crossing phase of OCT in DM and DPN compared with HTY. In addition, the conservative strategy adopted by DM (e.g. increasing the step width) and DPN (e.g. increasing leading stride/stance time) in the recovery phase is the trade-off between prolonged processing time and increased energy expenditure.

When stepping over a suddenly falling obstacle on the treadmill, for instance, Weerdesteyn et al. (2004) found that the mean latency of different obstacle crossing strategies was significantly shorter than that of voluntary stride modification and speculated the subcortical pathway may be involved in OCT[40]. Other research also suggested that the pathway in the supraspinal level could contribute to the phase-dependent modulation during OCT and facilitate a safer crossing performance of obstacle crossing[39, 41]. Those OCT-related literature may explain the gait changes in DM and DPN whose spinal reflex pathways are affected to a certain extent, and those gait differences can be manifested and associated with the poor clinical performance in this study.

E. Chapter Summary

Overall, this chapter demonstrated the influence of feedback control on gait adjustment in DM and DPN during a virtual obstacle-crossing task. Significant differences of spatiotemporal gait characteristics between DM/DPN and HTY can be detected through this feedback control paradigm. DM increased step width whereas DPN increased stance time after crossing; both DM and DPN tended to lower the toe elevation at the moment of crossing and took extra stride time to recover in a time-constrained virtual OCT (i.e. stepping over the unexpectedly appearing virtual obstacle). The significantly strong correlations found in DPN between the successful rate and clinical tests implied that TUG and BBS could be useful to evaluate DPN's capability to overcome future events or perturbations that occur suddenly.

Bridging

This chapter discussed the role of feedback control on gait adjustment when confronting with unexpectedly appeared obstacles, and further showed the feasibility of feedback control paradigm to identify more significant differences in gait of DM and DPN from HTY. The lowered successful rate of this chapter implied more challenges in the feedback control paradigm for subjects to accomplish the task in a shorter period of time. With the compromised sensorimotor control, how patients with DM or DPN can utilize alternative sensory system (e.g. vision) to reduce the fall risk and overcome an unexpected perturbation in their daily livings (e.g. making a bigger step over an uneven pavement). Therefore, I sought to investigate whether the vision can play a role in safely accomplishing the virtual OCT in feedforward and feedback paradigms in the following chapter.

Table 4.3. The changes of spatiotemporal gait characteristic across three different phases of obstacle crossing task (presented as median and interquartile range, IQR in parenthesis).

Outcomes \ Phase / Group		Planning			Crossing			Recovery		
		HTN	DM	DPN	HTN	DM	DPN	HTN	DM	DPN
Lead	MTE	13.37 (12.85)	11.86 (14.35)	8.68 (10.42)	**411.21**[a] (102.82)	**317.53**[b] (91.17)	**308.01**[b] (129.23)	29.29 (18.81)	26.86 (23.90)	26.37 (9.33)
	STL	1167.21 (244.63)	1182.34 (334.76)	1122.13 (198.71)	1310.01 (441.38)	1211.62 (323.61)	1213.77 (298.06)	1338.06 (276.97)	1265.14 (298.80)	1367.83 (162.89)
	STT	1231.67 (200.83)	1241.82 (121.50)	1283.33 (322.31)	1338.00 (219.47)	1400.83 (280.00)	1576.67 (372.65)	**1305.45**[a] (192.08)	1394.00 (250.55)	**1529.00**[b] (309.66)
	SWT	454.17 (49.17)	460.00 (87.50)	479.17 (191.05)	610.00 (126.33)	593.33 (114.33)	630.00 (171.82)	482.50 (34.17)	468.33 (83.33)	492.50 (106.33)
	STAT	708.33 (153.33)	765.83 (202.44)	820.00 (275.42)	--	--	--	**835.45**[a] (166.75)	906.67 (168.64)	**1034.00**[b] (230.83)
Trail	MTE	14.07 (11.56)	10.88 (21.53)	13.95 (9.67)	384.34 (195.13)	327.82 (179.93)	307.55 (166.14)	19.80 (13.67)	22.09 (23.69)	25.77 (144.59)
	STL	1055.65 (317.44)	1059.61 (279.29)	1080.43 (232.27)	1424.78 (162.98)	1435.94 (403.44)	1459.44 (244.31)	1200.34 (247.77)	1299.92 (192.19)	1111.37 (164.21)
	STT	1205.83 (96.06)	1219.00 (150.38)	1293.33 (443.87)	1392.86 (262.08)	1541.67 (285.00)	1700.00 (402.83)	1282.00 (178.33)	1270.00 (60.83)	1271.67 (287.50)
	SWT	439.09 (111.25)	430.00 (93.73)	483.33 (152.50)	612.50 (105.48)	601.67 (110.00)	695.00 (124.83)	460.00 (98.00)	457.50 (56.46)	480.00 (112.67)
	STAT	853.33 (209.58)	933.33 (185.00)	1020.00 (297.23)	--	--	--	795.71 (130.00)	786.67 (84.17)	803.33 (179.00)
SL		599.83 (221.88)	527.49 (172.98)	579.77 (191.68)	880.71 (339.03)	753.69 (132.77)	825.28 (147.21)	654.80 (162.12)	592.23 (165.47)	618.69 (78.33)
SW		125.63 (66.58)	138.66 (91.85)	140.66 (65.89)	140.15 (67.75)	176.65 (77.34)	176.29 (45.18)	**156.06**[a] (46.93)	**219.25**[b] (78.55)	194.54 (103.00)
ST		558.33 (1154.17)	296.67 (462.00)	155.45 (75.00)	545.45 (995.83)	299.17 (462.00)	174.55 (77.25)	322.33 (752.13)	336.25 (954.50)	148.25 (31.58)

Significant differences of multiple comparison: 1) by group within each phase are in **bold** and shown in different alphabet in upper case; 2) by phase of each group are highlighted when that is different from the other two phases (boxed), between planning and crossing phases (underlined), between planning and recovery phases(double underlined), and between crossing and recovery (dashed underline).

Table 4.4. The changes of spatiotemporal gait variability (coefficient of variation) across three different phases of obstacle crossing task (presented as median and interquartile range, IQR in parenthesis).

Outcomes \ Phase / Group		Planning			Crossing			Recovery		
		HTN	**DM**	**DPN**	**HTN**	**DM**	**DPN**	**HTN**	**DM**	**DPN**
Lead	**MTE**	0.32 (0.12)	0.31 (0.33)	0.40 (0.23)	0.20 (0.42)	0.16 (0.10)	0.15 (0.12)	0.38 (0.34)	0.37 (0.21)	0.25 (0.12)
	STL	0.10 (0.11)	0.12 (0.12)	0.09 (0.04)	0.13 (0.08)	0.11 (0.08)	0.11 (0.07)	0.07 (0.07)	0.07 (0.04)	0.06 (0.06)
	STT	0.07 (0.04)	0.08 (0.08)	0.07 (0.06)	0.15 (0.09)	0.13 (0.10)	0.12 (0.08)	0.05 (0.05)	0.07 (0.07)	0.05 (0.04)
	SWT	0.18 (0.11)	0.13 (0.16)	0.12 (0.17)	0.14 (0.12)	0.12 (0.06)	0.10 (0.10)	0.04 (0.08)	0.06 (0.07)	0.05 (0.03)
	STAT	0.18 (0.17)	0.16 (0.20)	0.17 (0.14)	--	--	--	0.07 (0.06)	0.08 (0.09)	0.06 (0.06)
Trail	**MTE**	0.26 (0.16)	0.42 (0.21)	0.40 (0.42)	0.12 (0.12)	0.17 (0.14)	0.25 (0.24)	0.27 (0.49)	0.36 (0.55)	0.40 (0.27)
	STL	0.14 (0.20)	0.15 (0.17)	0.16 (0.11)	0.10 (0.08)	0.06 (0.06)	0.05 (0.01)	0.05 (0.08)	0.08 (0.14)	0.05 (0.10)
	STT	0.09 (0.17)	0.11 (0.12)	0.14 (0.08)	0.09 (0.06)	0.07 (0.06)	0.05 (0.05)	0.04 (0.05)	0.07 (0.07)	0.04 (0.03)
	SWT	0.21 (0.25)	0.15 (0.11)	0.20 (0.10)	0.07 (0.03)	0.08 (0.05)	0.08 (0.09)	0.04 (0.08)	0.05 (0.04)	0.03 (0.06)
	STAT	0.15 (0.09)	0.09 (0.08)	0.10 (0.11)	--	--	--	**0.05[a]** (0.05)	**0.09[b]** (0.12)	0.06 (0.04)
SL		0.23 (0.16)	0.17 (0.15)	0.15 (0.16)	0.11 (0.13)	0.11 (0.05)	0.07 (0.05)	0.08 (0.13)	0.09 (0.09)	0.08 (0.05)
SW		0.27 (0.18)	0.22 (0.16)	0.18 (0.17)	0.32 (0.19)	0.20 (0.12)	0.19 (0.08)	0.17 (0.19)	0.07 (0.19)	0.20 (0.16)
ST		0.37 (0.80)	0.54 (1.30)	0.22 (0.17)	0.38 (0.79)	0.49 (1.04)	0.14 (0.09)	0.32 (1.06)	0.18 (1.02)	0.12 (0.16)

Significant differences of multiple comparison: 1) by group within each phase are in **bold** and shown in different alphabet in upper case; 2) by phase of each group are highlighted when that is different from the other two phases (boxed), between planning and crossing phases (underlined), between planning and recovery phases(double underlined), and between crossing and recovery (dashed underline).

CHAPTER V

THE IMPACT OF EXPROPRIOCEPTIVE VISUAL INFORMATION ON CONTROLLING STEPPING BEHAVIOR DURING VIRTUAL OBSTACLE CROSSING TASK IN ADULTS WITH DIABETES

A. Introduction

The population of diagnosed diabetes mellitus (DM) in the U.S is tremendously increasing, and there is approximately 50% of DM over 60 years of age developing sensorimotor deficits due to diabetic peripheral neuropathy (or diabetic polyneuropathy, DPN). DPN is the most common and widely recognized form of diabetic neuropathy that compellingly affects their activities of daily living[7, 8]. The development and progression of DPN that strongly correlates to poor glycemic control, compromises either sensory (small fiber) or motor (large fiber) nerves, and deteriorates the intact sense of pain, vibration, position, touch and pressure[7]. For example, DPN with delayed afferent nerve sensory inputs or efferent motor outputs[9] not only appears to have the loss of position, vibration, and tactile sensation of their feet when compared to healthy individuals[10], but also presents a poor postural control during quiet stance[11]. In addition, a higher falling/tripping accidents in DPN was reported that correlated to the increased spatiotemporal gait variability due to the lack of sensory feedback information from lower limbs to the central nervous system[11, 13, 14].

Obstacle crossing task (OCT) is one of the common and functional daily activities that highly require cortical command through the top-down control pathway, for instance, stepping upon the pedestrian curb on the street or stepping into the bathtub at home[27, 29-31].

In addition to use the top-down feedforward control pathway to accomplish OCT, it is suggested that the spinal reflex pathways or supraspinal level from the bottom-up feedback control pathway involves in OCT[39-41]. Therefore, it is apt to conceive that DM and DPN might attempt to rely on the other sensory system, such as vision, to compensate their speculative compromised feedback control.

There are two common types of visual information with different specialties: the exteroceptive and exproprioceptive visual information, which involve in the visuomotor transformation in the cortex and plays a very critical role in goal-directed locomotion[77, 78]. In OCT, for instance, the exteroceptive visual information (i.e. information of environmental characteristics such as height or color of obstacle) was mainly utilized for the feedforward control to plan ahead for the crossing event. The exproprioceptive visual information (i.e. information of the body relative to the environment) was utilized for on-line correction or instantaneously fine tune the movement trajectory of lower extremity during the crossing phase of OCT[34, 55-57]. To test the impacts of the aforementioned visual information individually during OCT, many studies manipulate the exteroceptive visual information by altering the dimension or visual structure of the objects[55, 57, 79, 80]. In addition, other studies deprived the exproprioceptive visual information of subjects' lower limb by wearing goggles or carrying loads[55, 80]. However, the approach of depriving expropriocepitve visual information may also sacrifice partial exteroceptive visual information, especially when approaching closely to the obstacles. Hence, one alternative approach is adopting virtual reality technology that renders the advantage of controlling all forms of visual information presented to the subjects (e.g. exteroceptive or

exproprioceptive) and is able to test the effects of visual information on gait adjustment without losing it during locomotion.

Therefore, the aim of this study was to investigate how the visual guidance (i.e. exproprioceptive visual information) played a role in improving the successful rate of virtual OCT, and how it affected the spatiotemporal gait adjustment in feedforward and feedback control paradigms (*in Chapter III and IV*). We hypothesized that with the assistance of visual guidance, the successful rate of virtual OCT would increase in both conditions when compared to those without visual guidance. According to the decreased maximal toe elevation (MTE), increased stride time and swing time in the crossing phase observed in DM/DPN populations in *Chapter III and IV*, we further hypothesized that the visual guidance would compensate the spatiotemporal gait differences in DM/DPN when compared to healthy group (i.e. by increasing the MTE and shortening the aforementioned temporal characteristics in DM/DPN groups) in the crossing phase of OCT.

B. Method

Experimental Protocol

The protocol of this study was approved by the Institutional Review Board under the Office of Regulatory Affairs in University of Nebraska Medical Center, UNMC. The same thirty-two eligible subjects in *Chapter III and IV* (11 HTY, 11 DM and ten DPN) participated in this study and familiarized with both actual and virtual OCT at the height of their 15% leg length prior to the data collection. The feedforward and feedback control paradigms of virtual OCT were given in which subjects stepped over either forthcoming or unexpectedly appeared virtual obstacles respectively presented on a cylindrical screen. The detailed protocol was described in *Chapter II*. In order to examine the effect of visual

guidance on their gait adjustments, a pair of virtual dots that synchronized with subjects' toes was presented on the cylindrical screen as their visual guidance (i.e. exproprioceptive visual information). Subjects were instructed to step over the virtual obstacles on the treadmill with or without the visual guidance as they formerly practiced in an actual OCT. The virtual OCT of this study was composed of three phases (i.e. planning, crossing, and recovery) that was defined by the duration of leading stride length before, during and after the crossing event respectively (**Figure 2.6**). All the spatiotemporal gait characteristics along with the variability (i.e. coefficient of variation, CV) in the three phases of virtual OCT were analyzed.

Statistical Analysis

The Wilcoxon signed-ranks test was adopted for testing the effect of visual information on spatiotemporal gait characteristics (α = 0.05). To compare the group effect on the dependent variables listed in *Chapter II*, the Kruskal-Wallis one-way analysis of variance by ranks test was adopted following by Mann-Whitney U test as multiple comparisons. The adjusted significant level of aforementioned multiple comparisons was applied using Bonferroni correction (i.e. $\alpha = 0.05/3 \approx 0.02$). The correlation between successful rate of virtual OCT and visual information and that of spatiotemporal gait characteristics were analyzed using Spearman rank correlation coefficient (ρ) with the significant level of α = 0.05.

C. Result

The successful rates of virtual OCT in the trailing leg with and without the assistance of visual guidance under the feedforward or feedback control paradigms were illustrated in **Figure 5.1**. HTY showed higher successful rate than those in DM and DPN in both

feedforward and feedback control paradigms. In the feedforward control paradigm, there were more significant differences observed in the trailing leg than leading leg where the successful rates were significantly higher with visual guidance (92% in HTY, 75% in DM and 77% in DPN) than that without visual guidance (58% in HTY, 38% in DM and 46% in DPN; p = 0.01-0.02). The similar findings were shown in the feedback control paradigm which the successful rate increased significantly in DM and DPN under the visual guidance (83% in DM and 88 % in DPN) versus those without visual guidance in the trailing leg (33% in DM and 38% in DPN; p = 0.01-0.02).

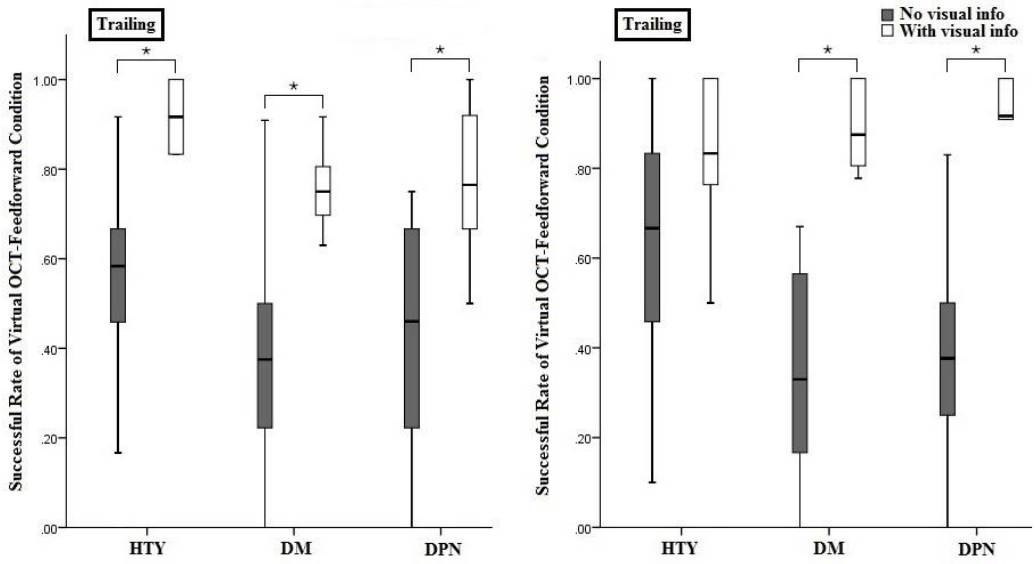


Figure 5.1. The successful rate of virtual OCT in the trailing side was significantly increased with exproprioceptive visual information among the three groups in the feedforward (left) and the feedback control paradigm (right).

Feedforward control paradigm

In spatial gait measures, the visual guidance showed its significant effect on lengthening HTY and DPN's leading stride length in the planning phase when compared with those conditions without visual guidance (1080.20 to 1112.97 mm in HTY, $p = 0.04$ and 1063.53 to 1128.41 mm in DPN, $p = 0.01$ respectively). Specifically, the leading MTE in HTY was significantly increased than that observed in DM and DPN in the crossing phase (451.57 mm versus 297.49 and 342.60 mm, $p < 0.01$; **Table 5.1**).

In temporal gait measures, the visual guidance showed its significant effect on increasing the following outcome variables: HTY's leading stride time ($p < 0.01$), leading and trailing stance time ($p = 0.01$ and $p < 0.05$), trailing swing time ($p = 0.03$) during planning phase, and trailing stance time in recovery phase ($p < 0.05$). The significant effect of visual guidance on decreasing HTY's trailing stance time and DPN's leading swing time were observed ($p < 0.05$ and $p = 0.01$; **Table 5.2**).

Feedback control paradigm

In spatial gait measures, the visual guidance showed its significant effect on decreasing DPN's trailing MTE in the planning phase when compared with those conditions without visual guidance ($p = 0.038$; **Table 5.3**).

The visual guidance did not show any impact on changing the temporal gait characteristics within the group during the three phases of OCT (**Table 5.4**). A significant group effect was found in the recovery phase, DPN's leading stride time and stance time increased significantly more than those in other two groups (both $p < 0.01$).

D. Discussion

The objective of this chapter sought to unveil the role of exproprioceptive visual information in the form of visual guidance in this study during two different virtual OCTs (i.e. feedforward and feedback control paradigms). We hypothesized that the successful rate of virtual OCT would increase with the assistance of visual guidance when compared to those without visual guidance; we also hypothesized that the visual guidance would induce significant differences of spatiotemporal gait characteristics in DM and DPN when compared to the healthy group.

The real-time or on-line exproprioceptive visual information did play a compelling role in increasing the successful rates of virtual OCT in the feedforward or feedback control paradigms. Our findings revealed that both DM and DPN's successful rates of trailing leg were immensely increased in both feedforward (37.5% to 75.0 % in DM, 46.0% to 76.5% in DPN) and feedback control paradigms (33.0% to 83.3% to 37.7% to 87.5% in DPN). The similar outcomes of increased attempts of obstacle avoidance were also observed (i.e. increasing the successful rate of OCT) when stepping over a solid obstacle with the clear visual field versus under the lower-vision obstructed condition in which the exproprioceptive visual information that relates lower limb to the environment was deprived[57].

Feedforward control paradigm

Compared with DM and DPN, HTY altered the gait characteristics more with the exproprioceptive visual information during the planning phase of OCT. The previous research indicated that visual information could be adopted in advance for the OCT in the planning phase in healthy populaiton[49]. Thus, the increased stride length and stride time

(including stance time and swing time) found in HTY with visual guidance in the planning phase was in line with the early indication, and it can be referred to subject gained more time and space in the planning phase when additional visual information is available in order to prepare for the sequential crossing events. Subjects with DPN presented the similar results by increasing their stride length with visual guidance in the planning phase. In addition, the significantly reduced swing time in DPN's leading side can shorten the duration of stance time of the trailing side (**Table 5.2**), which will decrease the instability during walking[74].

In the crossing phase, as we hypothesized, the visual guidance compensated the gait characteristics by reducing the trailing stride time and swing time in DM/DPN. However, the visual guidance did not impact the change in MTE, the differences in MTE between HTY and DM/DPN were still presented in which DM/DPN even further decreased their MTE with visual guidance (303.03 to 297.49 mm in DM and 358.16 to 342.60 mm in DPN). Because of the higher successful rate of virtual OCT with visual guidance, the reduced MTE observed in DM/DPN could be an efficient way for them to step over the obstacle successfully. It was likely that DM/DPN overestimated the height of virtual obstacle when there was no visual guidance as the reference frame, so they exaggerated the crossing behavior by intentionally increased their MTE, and which required more energy [32]. While perceiving the real-time exproprioceptive visual information, in contrast, it allowed DM and DPN controlling their obstacle crossing more efficiently and affordably by reducing their MTE[33], and which may also preserve energy during OCT[32, 41].

In the recovery phase, even though the effect of visual guidance tended to shorten the stride time and stance time on DPN's leading side, DPN still showed the significant

increase in the leading stride time and stance time than HTY and DM. According to the late adjustment to spatiotemporal gait characteristics observed in patients with visuomotor system dysfunction, Hocking et al. speculated that it may be due to the initially affected sensorimotor transformation[26]. The perceived exproprioceptive visual information was transmitted from the retina through the optic nerve to the primary visual cortex, and was further processed through the visuomotor dorsal pathway (which is responsible for determining an object's relative location in the environment) to the posterior parietal cortex for producing planned movements[50, 51]. The speculative prolonged visuomotor processing occurred in DM and DPN's neural pathway may mitigate the impact of visual guidance as we anticipated.

Feedback control paradigm

The role of visual guidance significantly impacted the gait adjustment in DM and DPN, especially during the crossing phase, such as by decreasing the leading MTE in DM/DPN, trailing swing time in DPN, and by increasing the trailing stride time in DPN. Thus, those significant gait differences observed in *Chapter IV* were not detected and revealed in this chapter with the presence of visual guidance. In addition, as discussed earlier, the MTE was readjusted decreasingly close to the obstacle height (i.e. 15% of leg length) in order to accomplish the task successfully with minimal energy consumption[32, 33, 41].

DM was shown with increased step width during level walking when compare to healthy, and the difference was even larger in a challenging environment[17, 81]. However, with the visual guidance, DM in this study decreased the step width after crossing from 219.25 mm to 190.89 mm in the recovery phase and supported our hypothesis. Therefore, the real-time exproprioceptive visual information could enhance subjects' confidence

when confronting the time pressure task (i.e. stepping over unexpected appeared obstacle) by increasing the successful rate of OCT. In addition to this cognitive factor, physiologically, the increased step width has been shown the association with high energy consumption[82]. Therefore, the deceased step width after crossing with visual guidance in DM can be inferred as the efficient adjustment of base of support with minimal energy consumption.

Lastly, the significantly increased leading stride time and stance time in the recovery phase were observed even though the visual guidance was presented. This may be due to the potential compromised visuomotor transformation in DPN which attenuates the impact of visual guidance and take longer time to recover after the crossing event[26].

Stepping strategy in DM and DPN with visual guidance

Stepping over obstacles have been suggested as controlling through spinal reflex pathways or in the supraspinal level that reacts on the event faster than the voluntary movement[39-41]. In this study we sought to answer the question whether the perceived visual information could play a role in modulating the spatiotemporal gait characteristics through visuomotor system when confronting either forthcoming or unexpectedly appeared obstacles. The significant increase in successful rates observed in DM and DPN with the visual guidance (i.e. the real-time visualization of virtual toe markers) in both virtual OCT conditions provide the direct evidence to answer our question.

Specifically in the feedforward control paradigm, the visual guidance significantly impacted HTY's spatiotemporal gait characteristics in the planning phase. The similar effect was also observed in DPN who lengthened their stride length and shortened the swing time of their leading side in order to get ready for obstacle crossing. In the crossing

phase, the visual guidance facilitated in lowering DPN's MTE, which could preserve the energy during obstacle crossing.

In the feedback control paradigm, on the other hand, the impact of visual guidance on gait adjustment was diminished in the planning phase. In contrast, the visual guidance showed its impact on adjusting the MTE, stride time and swing time in the crossing phase, and following adjusting the step width in the recovery phase.

E. Chapter Summary

Altogether, the exproprioceptive visual information that carries information about the position of individual's limb can be specifically generated through the virtual reality for examining the impact of visual guidance on gait adjustment. This chapter presented the evidence of real-time visual guidance can be utilized to adjust the gait performance during obstacle crossing task in DM and DPN.

Table 5.1. The changes of spatial gait characteristic with visual guidance among groups in the feedforward control paradigm (presented as median and interquartile range, IQR in parenthesis).

Phase	Outcomes	Side	Group	HTY		DM		DPN	
			Vision	No	Yes	No	Yes	No	Yes
Planning	MTE	Lead		11.87 (10.03)	13.64 (12.41)	14.31 (18.80)	13.13 (14.30)	13.78 (7.61)	13.91 (9.97)
		Trail		13.17 (13.33)	14.87 (15.85)	14.02 (25.15)	19.31 (15.52)	13.31 (8.51)	12.68 (12.54)
	STL	Lead		**1080.20 (293.79)**	**1112.97 (241.76)***	1124.66 (320.35)	1130.21 (265.89)	**1063.53 (363.65)**	**1128.41 (459.94)***
		Trail		1022.99 (272.82)	1051.57 (278.93)	1114.56 (215.06)	1076.70 (306.68)	1138.14 (267.07)	1081.89 (441.79)
	SL			563.09 (237.02)	568.20 (260.29)	563.59 (109.03)	523.60 (173.66)	577.26 (184.32)	615.69 (214.45)
	SW			118.58 (68.48)	108.72 (67.18)	168.16 (81.62)	144.36 (75.43)	111.78 (78.69)	123.12 (65.65)
Crossing	MTE	Lead		407.09 (117.76)	451.57 (107.26)	303.03 (84.76)	297.49 (120.95)	358.16 (135.90)	342.60 (104.03)
		Trail		374.78 (225.64)	376.13 (162.33)	287.21 (128.79)	313.67 (177.86)	288.71 (114.95)	299.54 (199.36)
	STL	Lead		1212.01 (208.49)	1244.75 (253.18)	1226.98 (211.10)	1181.04 (172.22)	1223.90 (477.11)	1254.23 (448.67)
		Trail		1525.29 (134.85)	1529.16 (405.55)	1403.08 (379.04)	1389.24 (346.89)	1634.99 (333.93)	1505.69 (399.97)
	SL			863.91 (263.38)	802.13 (290.59)	801.42 (118.86)	734.24 (167.27)	881.67 (164.66)	888.92 (291.44)
	SW			129.86 (78.79)	132.53 (68.84)	179.01 (47.76)	169.70 (65.62)	186.27 (100.21)	164.45 (116.35)
Recovery	MTE	Lead		22.93 (16.42)	24.88 (13.76)	26.44 (16.81)	24.47 (20.56)	26.36 (18.97)	20.80 (20.11)
		Trail		19.18 (26.83)	16.70 (14.21)	30.88 (67.73)	18.13 (16.20)	88.11 (257.17)	19.20 (148.81)
	STL	Lead		1354.40 (389.69)	1304.44 (387.08)	1274.35 (455.15)	1297.66 (332.73)	1339.97 (277.57)	1427.29 (283.34)
		Trail		1243.72 (299.37)	1236.61 (335.16)	1156.05 (266.05)	1171.79 (235.02)	1193.98 (270.44)	1172.70 (177.52)
	SL			630.86 (197.81)	664.35 (164.62)	639.25 (90.36)	588.87 (110.05)	671.34 (135.97)	630.96 (104.34)
	SW			147.78 (62.67)	169.30 (61.16)	199.16 (38.42)	206.96 (30.39)	181.12 (25.85)	172.57 (53.75)

*Significant effect of vision among different groups were highlighted in **bold**;
Significant differences of multiple comparison by group within the same visual condition are highlighted when that were different from the other two groups (box) and between HTY and DM (underline).

Table 5.2. The changes of temporal gait characteristics with visual guidance among groups in the feedforward control paradigm (presented as median and interquartile range, IQR in parenthesis).

Phase	Outcomes	Side	Group / Vision	HTY No	HTY Yes	DM No	DM Yes	DPN No	DPN Yes
Planning	STT	Lead		**1217.27 (206.67)**	**1237.50 (295.83)***	1286.67 (130.36)	1298.48 (80.30)	1236.67 (178.75)	1276.36 (200.01)
		Trail		**1233.64 (252.88)**	**1221.67 (352.50)***	1250.00 (134.17)	1237.00 (167.32)	1231.67 (298.92)	1287.08 (208.96)
	STAT	Lead		**737.50 (185.83)**	**819.17 (301.67)***	765.83 (114.29)	767.00 (119.02)	730.00 (151.58)	831.00 (139.50)
		Trail		**875.00 (119.09)**	**986.67 (254.17)***	940.00 (166.43)	914.31 (226.40)	1070.00 (274.17)	1028.29 (368.12)
	SWT	Lead		445.00 (71.82)	463.33 (120.83)	642.00 (112.50)	456.89 (54.41)	**686.67 (189.18)**	**472.02 (99.52)***
		Trail		**455.45 (93.82)**	**485.00 (123.33)***	443.33 (74.94)	438.00 (94.46)	463.64 (98.83)	490.50 (64.65)
	ST			254.17 (699.24)	639.17 (890.00)	225.00 (571.43)	183.06 (668.13)	206.67 (110.92)	177.11 (744.00)
Crossing	STT	Lead		1310.83 (306.67)	1473.00 (464.44)	1381.43 (251.25)	1346.11 (255.67)	1411.11 (371.82)	1506.60 (270.36)
		Trail		1485.71 (206.00)	1595.00 (275.15)	1535.00 (156.00)	1575.14 (270.86)	1761.25 (449.72)	1723.75 (607.08)
	SWT	Lead		616.36 (140.00)	640.00 (109.50)	642.00 (112.50)	590.56 (95.88)	686.67 (189.18)	673.54 (204.46)
		Trail		606.67 (68.38)	625.00 (128.33)	608.33 (109.64)	605.83 (113.56)	683.75 (106.32)	685.34 (252.71)
	ST			275.45 (814.17)	746.67 (751.21)	181.25 (425.18)	236.39 (181.83)	308.33 (204.68)	274.64 (547.70)
Recovery	STT	Lead		1332.50 (115.42)	1393.33 (189.58)	1412.00 (105.00)	1421.58 (195.00)	1565.00 (746.59)	1525.36 (616.44)
		Trail		**1290.00 (138.33)**	**1256.67 (143.64)***	1268.57 (118.25)	1307.43 (185.44)	1322.92 (175.31)	1317.22 (456.75)
	STAT	Lead		858.18 (87.67)	881.11 (169.77)	925.00 (52.68)	923.33 (161.46)	1089.00 (571.41)	1054.82 (470.08)
		Trail		770.00 (119.00)	763.33 (175.00)	803.33 (110.88)	821.88 (147.72)	838.61 (92.81)	876.86 (382.46)
	SWT	Lead		478.75 (27.08)	483.00 (47.88)	475.00 (66.67)	490.00 (102.33)	496.67 (141.51)	500.53 (91.47)
		Trail		489.09 (88.75)	483.33 (91.91)	455.50 (72.66)	481.11 (47.56)	480.00 (70.90)	489.58 (120.74)
	ST			320.60 (1126.33)	797.50 (1018.61)	175.83 (114.46)	249.00 (340.63)	158.33 (265.63)	176.43 (611.46)

*Significant effect of vision among different groups were highlighted in **bold**;

Significant differences of multiple comparison by group within the same visual condition are highlighted when that were different from the other two groups (box), between HTY and DPN (double underline), and between DM and DPN (dashed underline)

Table 5.3. The changes of spatial gait characteristic with visual guidance among groups in the feedback control paradigm (presented as median and interquartile range, IQR in parenthesis).

Phase	Outcomes	Side	Group / Vision	HTY No	HTY Yes	DM No	DM Yes	DPN No	DPN Yes
Planning	MTE	Lead		13.37 (12.85)	13.91 (6.18)	11.86 (14.35)	12.34 (14.40)	8.68 (10.42)	11.63 (7.87)
		Trail		14.07 (11.56)	15.38 (16.05)	10.88 (21.53)	12.88 (23.98)	**13.95 (9.67)**	**10.68 (5.76)***
	STL	Lead		1167.21 (244.63)	1041.32 (270.01)	1182.34 (334.76)	1069.29 (243.45)	1122.13 (198.71)	1102.17 (478.29)
		Trail		1055.65 (317.44)	976.00 (311.95)	1059.61 (279.29)	1080.79 (282.79)	1080.43 (232.27)	1023.85 (347.19)
	SL			599.83 (221.88)	542.79 (238.84)	527.49 (172.98)	499.05 (249.89)	579.77 (191.68)	507.04 (140.89)
	SW			125.63 (66.58)	119.66 (46.46)	138.66 (91.85)	141.32 (94.43)	140.66 (65.89)	121.24 (50.53)
Crossing	MTE	Lead		411.21 (102.82)	378.18 (119.72)	317.53 (91.17)	299.95 (97.12)	308.01 (129.23)	277.98 (124.65)
		Trail		384.34 (195.13)	296.81 (141.87)	327.82 (179.93)	338.60 (174.73)	307.55 (166.14)	266.57 (110.46)
	STL	Lead		1310.01 (441.38)	1276.03 (330.27)	1211.62 (323.61)	1209.34 (218.58)	1213.77 (298.06)	1166.20 (358.96)
		Trail		1424.78 (162.98)	1450.76 (213.02)	1435.94 (403.44)	1381.30 (352.02)	1459.44 (244.31)	1476.65 (260.36)
	SL			880.71 (339.03)	812.59 (298.18)	753.69 (132.77)	752.67 (136.92)	825.28 (147.21)	831.76 (197.35)
	SW			140.15 (67.75)	127.14 (85.18)	176.65 (77.34)	168.17 (57.43)	176.29 (45.18)	166.67 (59.42)
Recovery	MTE	Lead		29.29 (18.81)	19.46 (20.29)	26.86 (23.90)	22.41 (13.50)	26.37 (9.33)	17.66 (18.04)
		Trail		19.80 (13.67)	13.88 (16.73)	22.09 (23.69)	33.53 (89.86)	25.77 (144.59)	18.57 (165.56)
	STL	Lead		1338.06 (276.97)	1351.84 (309.26)	1265.14 (298.80)	1279.11 (271.08)	1367.83 (162.89)	1375.52 (233.38)
		Trail		1200.34 (247.77)	1209.44 (355.00)	1229.92 (192.19)	1169.39 (184.01)	1111.37 (164.21)	1135.95 (156.73)
	SL			654.80 (162.12)	638.95 (131.68)	592.23 (165.47)	599.21 (120.50)	618.69 (78.33)	621.37 (120.88)
	SW			156.06 (46.93)	162.69 (37.26)	219.25 (78.55)	190.89 (85.64)	194.54 (103.00)	164.42 (55.55)

*Significant effect of vision among different groups were highlighted in **bold**;
Significant differences of multiple comparison by group within the same visual condition are highlighted when that were different from the other two groups (box), and between HTY and DM (underline)

Table 5.4. The changes of temporal gait characteristics with visual guidance among groups in the feedback control paradigm (presented as median and interquartile range, IQR in parenthesis).

Phase	Outcomes	Side	Group / Vision	HTY No	HTY Yes	DM No	DM Yes	DPN No	DPN Yes
Planning	STT		Lead	1231.67 (200.83)	1232.73 (308.89)	1241.82 (121.50)	1298.57 (81.67)	1283.33 (322.31)	1291.25 (287.53)
			Trail	1205.83 (96.06)	1200.83 (299.47)	1219.00 (150.38)	1246.00 (107.50)	1293.33 (443.87)	1264.58 (331.88)
	STAT		Lead	708.33 (153.33)	776.36 (193.33)	765.83 (202.44)	724.29 (148.89)	820.00 (275.42)	763.33 (319.98)
			Trail	853.33 (209.58)	950.00 (215.00)	933.33 (185.00)	892.50 (125.28)	1020.00 (297.23)	1116.25 (439.17)
	SWT		Lead	454.17 (49.17)	455.45 (106.59)	460.00 (87.50)	448.57 (52.36)	479.17 (191.05)	471.67 (105.44)
			Trail	439.09 (111.25)	438.18 (96.67)	430.00 (93.73)	432.50 (87.94)	483.33 (152.50)	477.50 (135.85)
		ST		558.33 (1154.17)	355.00 (987.73)	296.67 (585.33)	224.17 (706.67)	155.45 (75.00)	275.56 (639.50)
Crossing	STT		Lead	1338.00 (219.47)	1323.75 (330.45)	1400.83 (280.00)	1322.50 (296.67)	1576.67 (372.65)	1427.74 (566.37)
			Trail	1392.86 (262.08)	1567.50 (242.33)	1541.67 (285.00)	1492.14 (142.88)	1700.00 (402.83)	1748.33 (428.42)
	SWT		Lead	610.00 (126.33)	595.56 (150.76)	593.33 (114.33)	581.11 (68.61)	630.00 (171.82)	679.44 (230.87)
			Trail	612.50 (105.48)	610.83 (94.17)	601.67 (110.00)	593.50 (57.28)	695.00 (124.83)	616.67 (175.25)
		ST		545.45 (995.83)	502.50 (806.44)	299.17 (462.00)	288.75 (638.06)	174.55 (77.25)	397.26 (565.57)
Recovery	STT		Lead	1305.45 (192.08)	1348.89 (182.83)	1394.00 (250.55)	1345.00 (142.29)	1529.00 (309.66)	1574.29 (589.32)
			Trail	1282.00 (178.33)	1221.11 (152.20)	1270.00 (60.83)	1274.29 (98.43)	1271.67 (287.50)	1331.67 (277.00)
	STAT		Lead	835.45 (166.75)	921.25 (158.89)	906.67 (168.64)	895.00 (128.67)	1034.00 (230.83)	1106.43 (464.55)
			Trail	795.71 (130.00)	765.00 (76.67)	786.67 (84.17)	791.51 (97.19)	803.33 (179.00)	845.00 (210.83)
	SWT		Lead	482.50 (34.17)	476.67 (82.92)	468.33 (83.33)	476.67 (49.33)	492.50 (106.33)	487.29 (141.64)
			Trail	460.00 (98.00)	444.17 (79.73)	457.50 (56.46)	467 53 (55.44)	480.00 (112.67)	490.00 (87.17)
		ST		322.33 (752.13)	573.75 (1034.67)	336.25 (954.50)	350.00 (794.46)	148.25 (31.58)	202.73 (857.67)

*Significant effect of vision among different groups were highlighted in **bold**;
Significant differences of multiple comparison by group within the same visual condition are highlighted when that were different from the other two groups (box), between HTY and DPN (double underline), and between DM and DPN (dashed underline).

CHAPTER VI

DISCUSSION

This dissertation was aimed to better understand how subjects with diabetes (DM), diabetic peripheral neuropathy (DPN) and the age-matched healthy controls (HTY) adjust their spatiotemporal gait characteristics using the feedforward and feedback controls during virtual obstacle crossing tasks (OCT) on a treadmill. *Chapters III, IV* and *V* of this dissertation specifically answered the following research questions: "How does the feedforward control impact the stepping behavior in diabetes?", "How does the feedback control impact the stepping behavior in diabetes?" and "How can the visual information impact the adjustment of gait during obstacle crossing?"

In this chapter, I summarized the findings from each chapter and sought to fit these evidence into the model of the feedforward and feedback control on obstacle crossing. I further listed the limitations of this research and stated the future directions as the continuation of this study.

The overall background information of OCT is illustrated in **Figure 6.1**. Upon detecting the forthcoming obstacle through feedforward control, the planning and execution of stepping strategy was originally thought to be occurred in the motor cortex. However, a recent study suggests that the posterior parietal cortex may contribute to this locomotor modulation[78] (*Chapter III*). In addition, crossing an obstacle using feedback control has been speculated as a task which is facilitated through the spinal reflexes or controlled at the suparspinal level[39, 44]. Weerdesteyn et al. performed the obstacle avoidance task in which an actual wooden block fell at different given available response time during treadmill walking and also suggested that a subcortical pathway may be

involved in OCT[40] (*Chapter IV*). Besides the impact of feedforward and feedback controls on OCT, the external exproprioceptive visual information also played a role during OCT[34, 55-57]. The visual information was presented and transmitted from the retina through the optic nerve to the primary visual cortex, and was further processed through the visuomotor dorsal pathway (which is responsible for determining the relative location of an obstacle in the environment) to posterior parietal cortex for making successful stepping strategy[50, 51] (*Chapter V*). As illustrated in **Figure 6.1**, the motor command goes further along the downward pyramidal tract (i.e. corticospinal tract) to modify the voluntary modification of lower leg for the successful OCT[41, 56, 73].

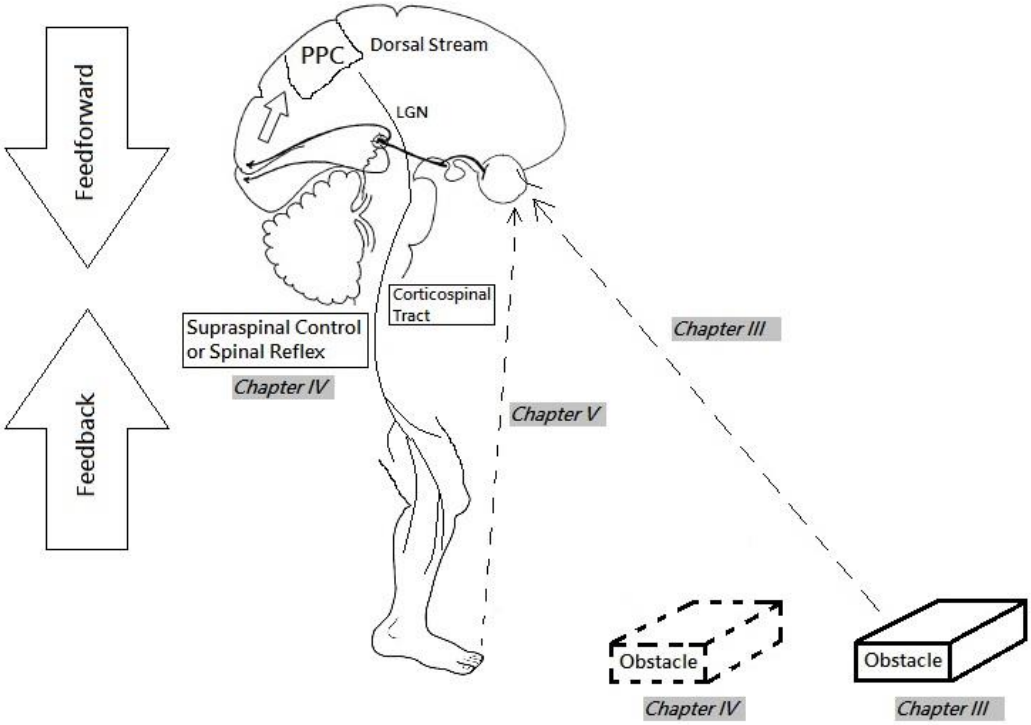


Figure 6.1. A cartoon illustrates how visual information being perceived and transmitted to the locomotor system before stepping over obstalces that appeared differnetly to test the feedforward and feedback control respectivly.

A. Summary of Important Findings

In *Chapter III*, the influence of feedforward control on gait adjustment among different groups was demonstrated. The results suggested that subjects with DPN could have compromised feedforward control during the virtual OCT. DPN tended to lengthen the temporal gait characteristics by adopting the unique stepping strategy in which they 1) extended the trailing stance time in planning phase for preparing the upcoming stepping event; 2) extended trailing stride time (by the increased swing time) in order to mitigate the obstacle contact during crossing phase; 3) extended leading stride time by the increased stance time to recovery from the crossing event. In addition, increased swing time in trailing leg moderately associated with obstacle-crossing successful rate in DPN, in which DPN with compromised sensory system require extended time to process information when stepping over obstacles. Hence, it is likely that tripping or falling incidences will take place in DPN when limited time is available in responding to events that suddenly occur.

Chapter IV presented the evidence of feedback control on gait adjustment among the three groups, especially in DM and DPN, during the virtual OCT. More spatiotemporal gait alterations observed in DM and DPN indicates that the time-constrained feedback control paradigm adopted in this chapter could be more sensitive to detect and elicit the differences between adults with DM and healthy populations. The decreased MTE during crossing phase reflects that DM and DPN might not react on the suddenly appeared obstacles in time due to the sensorimotor deficits. Similar to the findings in the feedforward control paradigm, DPN tended to lengthen the trailing stride time and swing time during the crossing phase, and extended their leading stride time and stance time in the recovery phase in order to gain more time for stepping over the obstacle successfully with both leading

and trailing legs. The significant moderate positive correlation between BBS and the successful rate of virtual OCT in both feedforward and feedback control paradigms indicated that the impaired balance status contributed to the poor successful rate. Based on the results of the correlation, BBS could be an appropriate clinical tool to evaluate DPN's capability of successfully overcome a suddenly appeared events or perturbations in their daily activities.

Lastly, in *Chapter V*, the exproprioceptive visual information about subject limb's position in the virtual environment increased the successful rate of virtual OCT. In the feedforward control paradigm, more significant differences in gait observed in HTY indicated that healthy subjects well-perceived and adapted to the exproprioceptive visual information in planning to prepare for obstacle crossing event; the significant decreased trailing stride time indicated that HTY recovered from the crossing event quickly through the assistance of visual information. Compared with DM, DPN showed more spatiotemporal gait alterations with the presence of the visual guidance. It indicated that DPN relies more on the visual information to compensate their compromised sensorimotor deficits during the planning phase of OCT by increasing leading stride length and decreasing leading swing time. In the crossing phase, DPN increased stride time and decreased swing time in their trailing side when the exproprioceptive visual information was available. The additional visual information also attenuated the group differences in HYT, DM and DPN while obstacle crossing. In the feedback control paradigm, on the other hand, the exproprioceptive visual information impacted DPN's gait adjustment in crossing and recovery phases of OCT when confronting with the suddenly appeared obstacles with limited time of reaction. Unexpectedly, the increased leading stride time and stance time

in the recovery phase of OCT in both feedforward and feedback control paradigms were still observed with the assistance of visual guidance. It may be due to the compromised visuomotor system that prolonged to transmit visual information in DPN.

Overall, these finding reveled the different strategies adopted by DM and DPN when confronted with obstacles. It also provided supportive evidence that perceived real-time visual guidance could be processed and organized in the cortical level to facilitate the control of lower limb during OCT. For example, the reliance of visual exproprioceptive information which facilitates the on-line adjustment of lower limb trajectory in DM or DPN could improve the successful rate of OCT and reduce the risk of falling[55].

In summary, **Table 6.1** included all the major findings in each chapter and simplified with symbols among HTY, DM and DPN.

Table 6.1. The major findings in chapter III~V of this dissertation*.

Outcomes \ Chapter Group	Chapter III (Feedforward)			Chapter IV (Feedback)		
	HTY	***DM***	***DPN***	***HTY***	***DM***	***DPN***
Planning						
Trailing MTE						↓
Leading STL	↑		↑			
Leading STT	↑					
Trailing STT	↓					
Leading STAT	↑					
Trailing STAT	↑	↓	[+]↓			
Leading SWT			↓			
Trailing SWT	↑					
Crossing						
Leading MTE		-- ↓	↓		-- ↓	-- ↓
Trailing STT			+ ↓			[+] ↑
Trailing SWT			+ ↑			[+] ↓
CV_Trailing STL						-- ↑
Recovery						
SW					+ ↓	
Leading STT			+ ↓			+ ↑
Trailing STT	↓		↓			
Leading STAT			+ ↓			+ ↑
CV_SL		--	--			
CV_Trailing STAT					[+] ↓	

*1: The significant group effect on outcome variables compared to HTY in *Chapter III and IV* was marked as +/--; noted that the significant difference between the other two groups was highlighted in boxed.

2. The significant vision effect on outcome variables within the same group in *Chapter V* was symbolized as ↑/↓ in red; the non-significant changes were in black.

3. The impact of visual guidance on gait measures were shaded.

4. The all acronyms and their definitions are listed in **Table 2.2** in *Chapter II*.

Based on the findings of this dissertation, we conceptualize an updated model of feedforward-feedback control on obstacle crossing task in **Figure 6.2a**, and for DPN specific model in **Figure 6.2b**. With the somatosensory deficits in DPN, for example, the compromised feedback control through the spinal reflex or supraspinal control may not contribute to the successful OCT and leads to trip or fall. This speculation was confirmed through the revelation of the obstacle crossing successful rate among HTY, DM and DPN shown in *Chapter III and IV*. Therefore, in order to perform the OCT successfully without falling, this dissertation shows the important evidence that the exproprioceptive visual information presented can compensate for the compromised somatosensory deficits in DPN and increases the successful rate of OCT (**Figure 6.2c**).

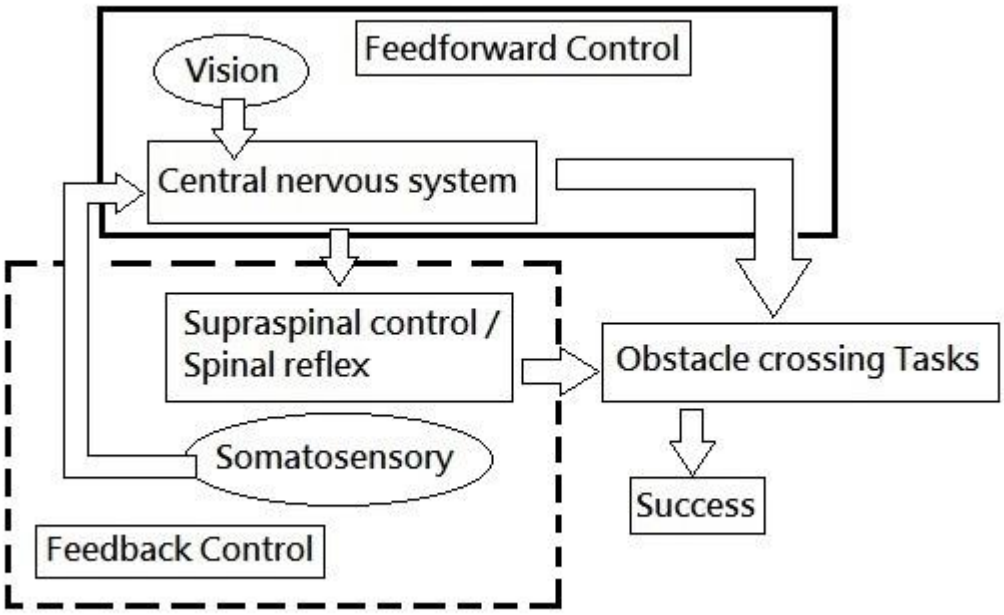


Figure 6.2a. The conceptual model of feedforward (solid square) and feedback (dash square) controls on OCT. Noted that the vision represents the exteroceptive visual information in the feedforward control.

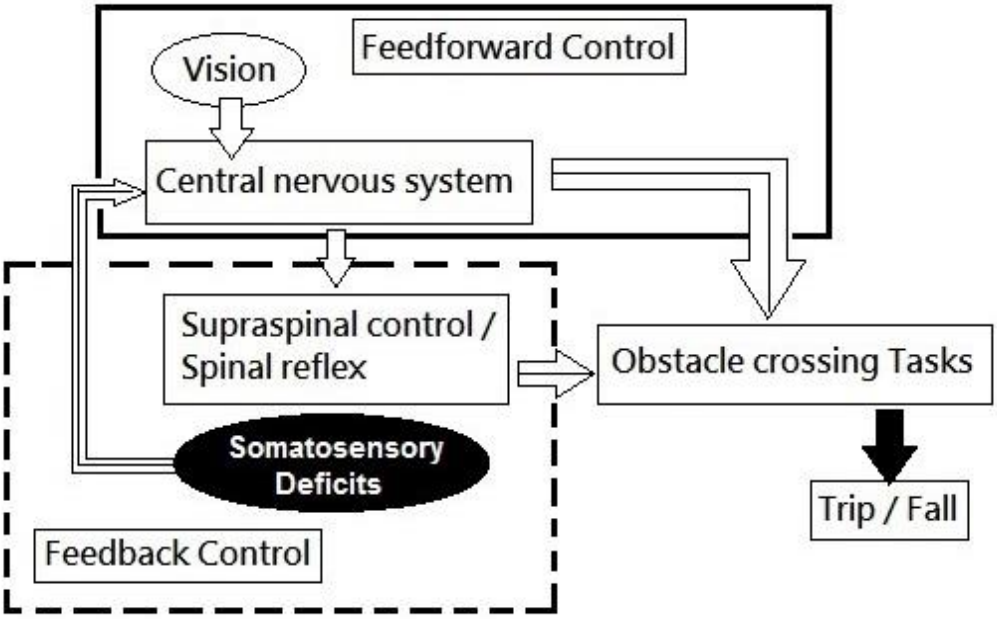


Figure 6.3b. The feedforward and feedback control model when somatosensory deficits appeared in DPN may lead to tripping and falling incidents.

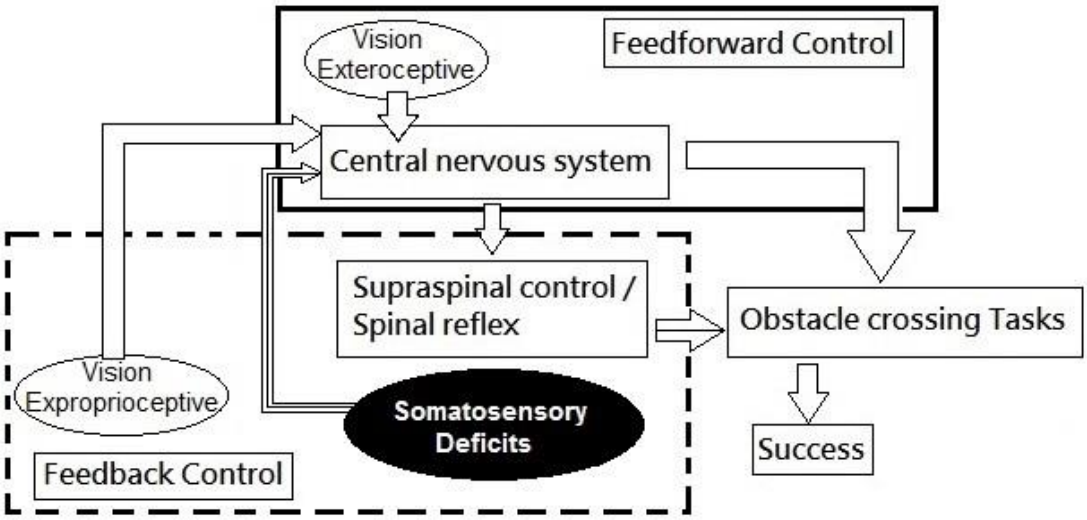


Figure 6.4c. The feedforward and feedback control model when somatosensory deficits appeared. Noted that the impact from somatosensory deficits is attenuated, and the compensation from the visual exproprioceptive information is observed.

B. Limitations of this Dissertation

It has reported that human gaze generally focuses on the environment two-step ahead to plan the navigation or avoid obstacles during walking[64], hence the location of unexpectedly appeared obstacle was mainly designated within two steps ahead of each subject for testing the feedback control in this dissertation. However, according to the findings from recent studies, stepping over obstacles on the treadmill is faster than volitional movement and which is possibly modulated by either the spinal reflex or the supraspinal control level[40, 41, 44]. Several studies manipulated the available response time when an event occurred (i.e. making the actual obstacle fell or the virtual obstacle appeared) at a specific moment of the gait cycle (e.g. mid-stance or early swing)[25, 31, 42, 43, 83]. Therefore, it will be more appropriate and accurate to manipulate the timing of the suddenly appeared virtual obstacle instead of adjusting its distance to the subjects in the future design of virtual OCT.

Besides, this study included DPN with a diagnosis of either sensory or motor dysfunctions through the clinical lab tests. The diverse type of DM and complications of DPN of this study may generate different gait outcome measures that confound the results and wash out the potential group differences. Moreover, there are up to 50% of DM who are asymptomatic, and it has been reported a substantial portion of asymptomatic DM who have peripheral nerve dysfunction through the electrophysiological exams[84]. Since the asymptomatic DM with early nerve dysfunction (e.g. pre-DPN) and the different damages in peripheral nerves of spinal reflexes in DPN (e.g. superficial fibular nerve, tibia nerve, etc.) could influence the crossing behaviors[39], recruiting DM and DPN with a more specific diagnosis based on the neurological tests in the future study is warranted in order to better

conceptualize the proposed feedforward-feedback model on gait adjustment in DM and DPN.

C. Future Directions

In light of the current findings, I listed some domains in which they might be worthy to fulfill the role of feedforward-feedback control on human movement more comprehensively, and benefit the populations who suffer from other similar illness (e.g. sensorimotor deficits) based on the training paradigm which is originated from the concept of this dissertation.

The effect of feedforward and feedback controls on cortical and muscle activity in diabetes

Haefeli et al. utilized electroencephalography (EEG) and electromyography (EMG) to detect the cortical and reflex activity respectively, and investigate the interactions of brain and spinal neuronal activity during obstacle crossing[40, 44]. In addition, the optical topography system with technique of functional near-infrared spectroscopy (fNIRS) makes it possible to detect better cortical activity in terms of hemodynamic response (i.e. oxygenated hemoglobin, OxyHb) in specific cortical locations (e.g. primary sensory and motor cortices and PPC) during treadmill walking[85, 86]. By synchronizing these devices with the current virtual OCT paradigm, a clear picture of DM's neuromuscular control at the cortical level can be illustrated.

Virtual reality-based obstacle training protocols for diabetes

Obstacle crossing as a precision locomotor task involved adaptation, memory, and skill transfer[87, 88]. Besides using the actual OCT as a training paradigm in the elderly[89, 90], recent study also adopted the virtual reality-based obstacle crossing as the intervention for patients

with neurological illness[91]. Setting up a virtual reality-based training paradigm at home might improving DM or DPN's efficient stepping performance (e.g. shortening the duration of recovery phase) with less energy expenditure and more importantly to reduce the incidence of injurious tripping or falling.

D. Conclusions

Patients with diabetes peripheral neuropathy who have the sensorimotor deficits showed a higher chance of contacting the obstacle while stepping over it which increases the probability of tripping or falling. Through the virtual obstacle crossing task paradigm, the impact of feedforward and feedback controls on the stepping performance have examined. In addition, the compromised feedback control in DPN can be compensated by the visual guidance to improve gait performance during obstacle crossing. Lastly, with the combination of virtual obstacle crossing task design with exproprioceptive visual information, the future virtual obstacle crossing training paradigm can be implemented for training diabetes population to reduce the risk of falling.

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APPENDIX A

ADULT INFORMED CONSENT FORM OF THIS DISSERTATOIN

University of Nebraska Omaha

COLLEGE OF EDUCATION
BIOMECHANICS RESEARCH BUILDING

CONSENT FORM

ADULT INFORMED CONSENT FORM

The Impact of Sensory Deficits on Lateral Stability in Adults with Diabetes
The Feedback and Feedforward Controls on Gait in Diabetes

You are invited to take part in this research study. The information in this form is meant to help you decide whether or not to take part. If you have any questions, please ask.

Why are you being asked to be in this research study?

You are eligible to participate because: you are between 19-75 years old and may have either of the following health conditions:

A. Healthy
   You are free of diabetes with no musculoskeletal or pathological problem that may affect your walking.
B. Diabetes mellitus without any symptoms
   You have been diagnosed with Type 2 diabetes. You do not have any symptoms or sensory deficits in your lower extremities.
C. Diabetes mellitus with symptoms
   You have been diagnosed with Type 2 diabetes. In addition, you have been diagnosed with neuropathy (with symptoms such as numbness) in your lower extremities.

However, if you are pregnant you may not participate in this study.

What is the reason for doing this research study?

Walking is a common and important activity of daily living. It requires proper foot placement on the ground to maintain our stability and balance during walking. However, it can be very challenging for some people who have abnormal sensation in their feet such as people with diabetes mellitus. This research study is mainly to figure out how these specific populations control their stability during walking, and eventually to prevent injuries.

What will be done during this research study?

This study requires one visit that will last approximately 2 hours. The following are the procedures you will undergo as a participant in this study. All procedures will be taken place in the Biomechanics Research Building at the University of Nebraska at Omaha. After reading and signing this consent form, your visual acuity and the muscle strength of your lower extremity will be assessed first to ensure your safety during the whole experimental procedures listed below. A visual acuity chart will be shown in front while you are standing; your calf muscle strength will be examined by single leg stance with tip toe and with hand support. In addition, a simple clinical technique will be applied to test your inner ear function. Your head will be fixed to turn 45 degrees either side first, and the researcher will rapidly place your head supported into hanging position

(from sitting position to lying down position). In addition, the 15-minute sensory organization test (SOT) will be adopted if needed by using the NeuroCom balance testing system to verify the presence of vestibular disorders. You will be instructed to put on the vest before they step on the force plate in bare feet. The only instruction to you is "Do your best to keep your balance and stand still." There will be six different conditions (eyes open, eyes closed and moving chamber combined with stable and unstable floor respectively).

General Procedures

As long as you agree to participate in this study, and if you meet the eligibility of this study, you will be asked to complete the walking experiment. To ensure safety while you are walking on the treadmill, you will be secured into a harness attached to a body weight support system. In addition, you will wear comfortable clothing (i.e. athletic shorts). Seventeen reflective markers will be attached on the major bony landmarks of your lower extremity (sacrum, left/right anterosuperior iliac spine, posterosuperior iliac spine, lateral thigh, knee, shank, ankle, toe and heel).

You will practice the actual obstacle crossing task at your 15% leg length high for five minutes, and another five-minute virtual obstacle crossing task on the treadmill with your self-selected pace as familiarization.

Once you get used to the virtual environment, you will be asked to walk three two-minute trials in four different obstacle-crossing conditions in a random order basis. You will be instructed by the experimenter, "P*retend to step over the obstacle as you practice before, and do not contact it as it is an actual one.*" The four conditions are:

1. You will perform the obstacle crossing task by stepping over the sudden appearing obstacle while walking on a treadmill;
2. You will perform the obstacles crossing task by stepping over the forthcoming-perceived virtual obstacle while walking on a treadmill;
3. & 4. You will repeat above procedure but a pair of dots that represent your right and left toes will be shown in front of you to help you complete the crossing task.

You will be asked if you would like to rest or drink water after each trial. Upon completion of data collection, you will receive a questionnaire to evaluate how immersed in the virtual reality (VR) environment you felt.

What are the possible risks of being in this research study?

The potential risks of Sensory Organization Test (SOT) using NeuroCom will be unsteadiness of standing on the force plate. You may be panic and feel dizzy shortly due to the moving chamber and the unstable force plate you step on. The potential risks of walking are similar to those of light physical activity. It includes discomfort, increased respiratory rate, increased heart rate, and dizziness. Possible unsteadiness may occur from walking on the treadmill. In addition, the nauseous or panicked sense due to the imversive in VR may happen. You are free to stop the testing at any time if you feel you are unable to continue. While the researcher performs the technique for checking your inner ear condition, you may have a nystagmus (a kind of involuntary eye movement) or feel a sense of vomiting and fatigue if you have inner ear problem.

What are the possible benefits to you?

There are no potential direct benefits to you in this study. Although you may not directly benefit from this research, future patients with diabetes may benefit from the knowledge that is gained from this study.

What are the possible benefits to other people?

The results of this study will provide better understanding of how diabetic patients with neuropathy control their stability during walking. In addition, society could benefit from this study because it may advance our knowledge how diabetic populations utilize their visual information to maintain balance during walking. Also, the outcomes of the study will contribute to educate diabetic populations and to prevent the risk of falling.

What are the alternatives to being in this research study?

Instead of being in this research study you can choose not to participate.

What will be in this research study cost you?

There is no cost to you to be in this research study.

Will you be paid for being in this research study?

You will receive a $20 Walmart gift card as our appreciation. This gift card will be given to you upon completion of your participation in this study and after signature of receipt, and/or mailed to your physical address.

Who is paying for this research?

The funding resource is the Research and Pilot Grant through School of Allied Health Professions (PI: Dr. Joseph Siu) in University of Nebraska Medical Center.

What should you do if you are injured or have a medical problem during this research study?

If you are injured or have a medical problem as a direct result of being in this study, you should immediately contact one of the people listed at the end of this consent form.

How will information about you be protected?

You have rights regarding the privacy of your medical information collected before and during this research. This medical information, called "Protected Health Information, PHI", typically includes: depending upon the nature of this research, demographic information (like your address and birth date), and your medical history.

By signing this consent form, you are allowing the research team to have access to your PHI. The research team includes the investigators listed on this consent form and other personnel involved in this specific study at the University of Nebraska at Omaha, the University of Nebraska Medical Center, and the Nebraska Medical Center.

Your PHI will be used only for the purpose(s) described in the section "What is the reason for doing this research study?"

Your PHI will be shared, as necessary, with the Institutional Review Board (IRB) and with any person or agency required by law. You are also allowing the research team to share your PHI

IRB Approved
Valid until 05-21-16

with other people or groups listed below. All these persons or groups listed below are obligated to protect your PHI.

You are authorizing us to use and disclose your PHI for as long as the research study is being conducted.

You may cancel your authorization for further collection of PHI for use in this research at any time by contacting the principal investigator in writing. However, the PHI, which is included in the research data obtained to date, may still be used. If you cancel this authorization, you will no longer be able to participate in this research.

The information from this study may be published in scientific journals or presented at scientific meetings but your identity will be kept strictly confidential.

What are your rights as a research subject?

You have rights as a research participant. These rights are explained in this consent form and in *The Rights of Research Participants Subjects* that you have been given. If you have any questions concerning your rights or complaints, talk to the investigator or contact the Institutional Review Board (IRB) by:

- telephone (402) 559-6463.
- Email: IRBORA@unmc.edu
- Mail: UNMC Institutional Review Board, 987830 Nebraska Medical Center, Omaha, NE 68198-783

What will happen if you decide not to be in this research study?

You can decide not to be in this research study. Deciding not to be in this research study will not affect your relationship with the investigator, the University of Nebraska at Omaha or the Nebraska Medical Center.

What will happen if you decide to stop participating once you start?

You can stop being in this research study ("withdraw") at any time before, during, or after the research study begins. Deciding to withdraw will otherwise not affect your care or your relationship with the investigator, the University of Nebraska Medical Center, or the Nebraska Medical Center. You will not lose any benefits to which you are entitled.

You may be taken off the study if you don't follow instructions of the investigator or the research team. If the research team gets any new information during this research study that may affect whether you would want to continue being in the study you will be informed promptly.

DOCUMENTATION OF INFORMED CONSENT

You are freely making a decision whether to be in this research study. Signing this forms means that (1) you have read and understood this consent form, (2) you have had the consent form explained to you, (3) you have had your questions answered and (4) you have decided to be in the research study. If you have any questions during the study, you should talk to one of the investigators listed below. You will be given a copy of this consent to keep.

_____ _____

SIGNATURE OF SUBJECT DATE/TIME

IRB Approved
Valid until 05-21-16

Subject's Initials _____

My signature certifies that all the elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the participant possesses the legal capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

SIGNATURE OF PERSON OBTAINING CONSENT DATE/TIME

Authorized Study Personnel

PRINCIPAL INVESTIGATOR

Chun-Kai Huang, MS	Phone: (402)554-3225

SECONDARY INVESTIGATORS

Ka-Chun Siu, PhD	Phone: (402)554-3773
Nick Stergiou, PhD	Phone: (402)554-3075
Jung-Hung Chien, MS	Phone: (402)554-3225
Jeffrey Kaipust, MS	Phone: (402)553-3228

PARTICIPATING PHYSICIANS/PERSONNEL

Vijay Shivaswamy, MBBS	Phone: (402)559-6205
Pariwat Thaisetthawatkul, MD	Phone: (402)559-4496
Lynn Mack, MD	Phone: (402)559-6205
Amy Neumeister, MD	Phone: (402)559-6205
Ezequiel Piccione, MD	Phone: (402)559-9953

IRB Approved
Valid until 05-21-16

Subject's Initials _____

APPENDIX B

DISTRIBUTED FLIER FOR RECRUITMENT OF THIS DISSERTATION

SUBJECTS NEEDED

to participate in a research project

"The Impact of Sensory Deficits on Lateral Stability in Adults with Diabetes~The Feedback & Feedforward Controls on Gait in Diabetes", IRB#294-11-FB

If You……

- ✓ are 19-75 years old;
- ✓ are healthy or have been diagnosed with Type 2 Diabetes for at least six months;
- ✓ are able to walk independently;
- ✓ wonder how your functional balance performs;
- ✓ want to try the most current virtual technology in Nebraska…

What will you do in this study?

1. Perform actual/virtual obstacle crossing task while walking on a treadmill;
2. Time: a total of up to 2 hours

To make an appointment or for more information, please contact:

Chun-Kai (Kai) Huang
Division of Physical Therapy Education
School of Allied Health Professions/ Diabetes Center-UNMC
Biomechanics Research Building-UNO
(206)734-6406; chunkai.huang@unmc.edu

University of Nebraska Medical Center | BIOMECHANICS RESEARCH BUILDING

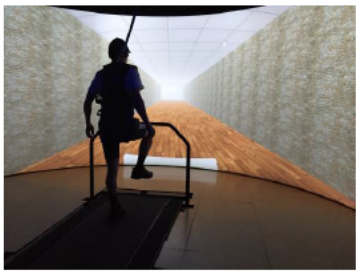
SUBJECTS NEEDED

to participate in a research project

"The Impact of Sensory Deficits on Lateral Stability in Adults with Diabetes~The Feedback & Feedforward Controls on Gait in Diabetes", **IRB#294-11-FB**

If You……

- ✓ are 40-75 years old;
- ✓ are healthy and are able to walk independently;
- ✓ wonder how your functional balance performs;
- ✓ want to try the most current virtual technology in Nebraska…



What will you do in this study?

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University of Nebraska Medical Center

BIOMECHANICS RESEARCH BUILDING

APPENDIX C

QUESTIONNAIRES

MINI MENTAL STATUS EXAMINATION

Orientation to Time	Correct	Incorrect	
What is today's date?	☐	☐	
What is the month?	☐	☐	
What is the year?	☐	☐	
What is the day of the week today?	☐	☐	
What season is it?	☐	☐	
			Total: ____

Orientation to Place			
Whose home is this?	☐	☐	
What room is this?	☐	☐	
What city are we in?	☐	☐	
What county are we in?	☐	☐	
What state are we in?	☐	☐	
			Total:____

Immediate Recall

Ask if you may test his/her memory. Then say "ball", "flag", "tree" clearly and slowly, about 1 second for each. After you have said all 3 words, ask him/her to repeat them – the first repetition determines the score (0-3):

Ball	☐	☐	
Flag	☐	☐	
Tree	☐	☐	
			Total: ____

Attention

A) Ask the individual to begin with 100 and count backwards by 7. Stop after 5 subtractions. Score the correct subtractions.

93	☐	☐
86	☐	☐
79	☐	☐
72	☐	☐
65	☐	☐

Total:_____

B) Ask the individual to spell the word "WORLD" backwards. The score is the number of letters in correct position.

D	☐	☐
L	☐	☐
R	☐	☐
O	☐	☐
W	☐	☐

Total:_____

Delayed Verbal Recall

Ask the individual to recall the 3 words you previously asked him/her to remember.

Ball	☐	☐
Flag	☐	☐
Tree	☐	☐

Total: _____

Naming

Show the individual a wristwatch and ask him/her what it is. Repeat for pencil.

Watch	☐	☐
Pencil	☐	☐

Repetition

Ask the individual to repeat the following:		
"No if, ands, or buts"	☐	☐

3-Stage Command
Give the individual a plain piece of paper and say, "Take the paper in your hand, fold it in half, and put it on the floor."

Takes	☐	☐
Folds	☐	☐
Puts	☐	☐

Reading

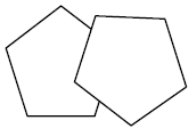
Hold up the card reading: "Close your eyes" so the individual can see it clearly.
Ask him/her to read it and do what it says. Score correctly only if the individual actually closes his/her eyes. ☐ ☐

Writing

Give the individual a piece of paper and ask him/her to write a sentence. It is to be written spontaneously. It must contain a subject and verb and be sensible.
☐ ☐

Copying

Give the individual a piece of paper and ask him/her to copy a design of two intersecting shapes. One point is awarded for correctly copying the shapes. All angles on both figures must be present, and the figures must have one overlapping angle.



☐ ☐

Total Score:_____

Timed Up and Go (TUG) Test

Name:_____ MR: _____ Date:_____

1. Equipment: arm chair, tape measure, tape, stop watch.
2. Begin the test with the subject sitting correctly (hips all of the way to the back of the seat) in a chair with arm rests. The chair should be stable and positioned such that it will not move when the subject moves from sit to stand. The subject is allowed to use the arm rests during the sit – stand and stand – sit movements.
3. Place a piece of tape or other marker on the floor 3 meters away from the chair so that it is easily seen by the subject.
4. Instructions: "On the word GO you will stand up, walk to the line on the floor, turn around and walk back to the chair and sit down. Walk at your regular pace.
5. Start timing on the word "GO" and stop timing when the subject is seated again correctly in the chair with their back resting on the back of the chair.
6. The subject wears their regular footwear, may use any gait aid that they normally use during ambulation, but may not be assisted by another person. There is no time limit. They may stop and rest (but not sit down) if they need to.
7. Normal healthy elderly usually complete the task in ten seconds or less. Very frail or weak elderly with poor mobility may take 2 minutes or more.
8. The subject should be given a practice trial that is not timed before testing.
9. Results correlate with gait speed, balance, functional level, the ability to go out, and can follow change over time.

Normative Reference Values by Age

Age Group	Time in Seconds (95% Confidence Interval)	
60 – 69 years	8.1	(7.1 – 9.0)
70 – 79 years	9.2	(8.2 – 10.2)
80 – 99 years	11.3	(10.0 – 12.7)

Cut-off Values Predictive of Falls by

Group	Time in Seconds
Community Dwelling Frail Older Adults	> 14 associated with high fall risk
Post-op hip fracture patients at time of discharge[3]	> 24 predictive of falls within 6 months after hip fracture
Frail older adults	≥ 30 predictive of requiring assistive device for ambulation and being dependent in ADLs

Date	Time	Date	Time	Date	Time	Date	Time

Subject ID: _____

Berg Balance Scale

Date: _____

SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hand for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or stabilize
( ) 0 needs moderate or maximal assist to stand

STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding on.
( ) 4 able to stand safely for 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unsupported

If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely for 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds

STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assist to sit

TRANSFERS
INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cuing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays safely
( ) 0 needs help to keep from falling

STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding on.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds feet together
( ) 0 needs help to attain position and unable to hold for 15 seconds

Berg Balance Scale continued…

REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)
( ) 4 can reach forward confidently 25 cm (10 inches)
( ) 3 can reach forward 12 cm (5 inches)
( ) 2 can reach forward 5 cm (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper, which is in front of your feet.
( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.)
( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.
( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cuing
( ) 0 needs assistance while turning

PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in > 20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete > 2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)
( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding on.
( ) 4 able to lift leg independently and hold > 10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold ≥ 3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.
( ) 0 unable to try of needs assist to prevent fall

( ) TOTAL SCORE (Maximum = 56)

APPENDIX D

IMPACT OF VISUAL GUIDANCE ON DIABETES' TOE ELEVATION DURING VIRTUAL OBSTACLE CROSSING TASKS

(in the 39th Annual Meeting of the American Society of Biomechanics[67])

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INTRODUCTION

People with more than 15 years of diabetes mellitus (DM) are at a high risk of suffering from diabetic neuropathy (DPN) with abnormal sensation and sensory loss of their feet [1], which increases the incidence of falling or tripping accidents. To maintain stability during locomotion, the reliance of body-based and visual senses (e.g. perception of self-motion) plays a very important role in DPN population to react on all kinds of external perturbations during walking [2].

Obstacle crossing is a common daily activity that might cause tripping accidents in diabetic population due to the insufficient toe elevation [3]. Our previous study indicated that through the perception of self-motion diabetic population decrease their gait variability during walking [4]; it is expected that toe elevation could be adjusted accordingly to cross obstacles successfully through the appropriate visual guidance that orientates body location related to the environment (i.e. exproprioception).

Therefore, this study investigated the effect of visual guidance on toe elevation during virtual obstacle crossing (VOC) tasks among people with Type 2 DM, DPN and age-matched healthy control. We hypothesized that the mean toe elevation in DPN would be significantly higher than other groups, and would be lowered when visual guidance was offered during VOC.

METHODS

Six subjects (two subjects in each Type 2 DM, DPN and age-matched group; one female; mean age: 50.17 years) were recruited to perform the VOC task, which was projected in the front screens and created with the dimensions of 45cm (width) x 20cm (depth) x 15% subject's leg length (height) using D-flow software (Motek Medical BV, the Netherlands). The virtual obstacles either showed up at the end of the corridor and moved towards subjects (Feedforward condition) or suddenly appeared two steps ahead of subject (Feedback condition). Two virtual markers that represented subject's toes were shown on the screen as their visual guidance. Subjects were instructed to elevate their dominant leg (leading leg) to step over the virtual obstacles (Fig 1). The collision event between virtual markers and the virtual obstacle was defined as the failure of obstacle crossing, and only successful trials were analyzed.

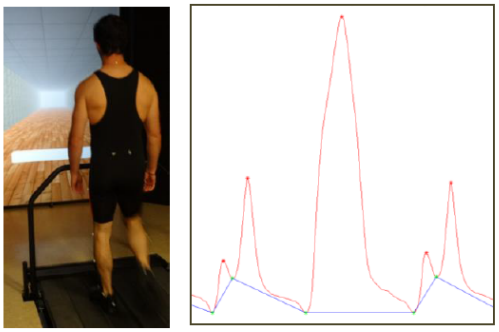

Figure 1: A subject performed a VOC task during treadmill walking (left); the movement of toe marker in sagittal plane during VOC (right).

After the familiarization of six-minute treadmill walking at each individual's self-selected pace, subjects completed four treadmill walking conditions in which consists of Feedforward/ Feedback and

with/without visual guidance conditions (three three-minute trials in each condition).

Three-dimensional spatiotemporal kinematic data were collected using VICON motion capture system at 100 Hz and processed along with Nexus software (Vicon, Oxford, UK). Toe elevation of leading leg during VOC task were calculated using MATLAB program (MathWorks, Inc., Natick, MA) and was defined as the vertical distance between the highest toe marker position and its position during quiet standing (Fig. 1). The mean and variability (coefficient of variance, CV) of toe elevation during VOC task were calculated.

The Kruskal-Wallis one-way ANOVA was conducted to examine the effect of visual guidance on toe elevation among three groups (α=0.05).

RESULTS AND DISCUSSION

The preliminary results shown in Table 1 are in line with our hypothesis even though there was no significant finding ($p > .19$). Both DM and DPN lowered toe elevation during VOC without visual guidance which is expected to cause trip and fall; the visual cue assisted in increasing DM and DPN's toe elevation during VOC when compared to age-matched healthy controls in Feedback condition (Fig. 2). These findings are also in agreement that the leading leg is impacted prominently by the visual cue during obstacle-crossing task from a previous study [5]. The increased toe elevation in DM/DPN due to visual guidance can be inferred as the visual perception reliance that is expected to improve the balance during VOC.

More subjects are warranted to examine if the gait alternations found in the DM group is beneficial to stabilize their gait and reduce fall incidence.

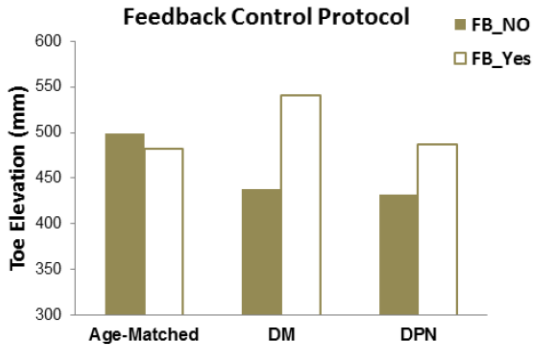

Figure 2: The effect of visual guidance on mean toe elevation (mm) during VOC among age-matched DM and DPN groups. FB: Feedback.

CONCLUSIONS

Overall, compared subjects with Type 2 DM with their age-matched healthy control, this study provides further evidence that visual guidance which offers the real-time location of individual's toe plays a prominent role on facilitating toe elevation and reducing fall risk in diabetic population during walking.

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Table 1.

Condition / Group	Age	BMI	A1C (%)	Toe Elevation (FF)[§]		Toe Elevation (FB)[§]	
				No Guidance	Guidance	No Guidance	Guidance
Healthy	51.0	28.71	--	562.05	582.05	498.30	482.60
DM	46.5	30.44	7.1	451.14	517.05	437.50	541.04
DPN	53.0	34.55	7.8	464.96	452.60	431.71	487.19

[§]FF: Feedforward; FB: Feedback