# Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait

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Doctoral Dissertation

# Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait

by

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# ABSTRACT

Parkinson's disease (PD) is a neuro-degenerative disorder caused by the loss of neurotransmitter called "dopamine" in substantia nigra (SN), basal ganglia (BG). Most of PD patients manifest gait and balance disturbances in advanced stages which causes problems of falling. Postural instability (PI) is one of the factors leading to falls. Falls do not only cause the problems of fracture, but also the problems of disabilities and hospitalization. It also leads to the long-term caring and increases cost of treatments. The quality of life (QoL) of the patients may be reduced with such a problem. The burdens are also drawn to the family members, caregivers and societies. PD patients experience the problems of sensory, motor and cognitive deficits. Reasons that can bring about the problem of falls are the impairments of the systems. The problems of impaired sensation, reduced postural stability, decreased arm swing, and impaired cognition can be associated together as regards the neural circuits of the BG. Currently, falls sill often occur in the patients with freezing of gait (FOG) and balance disturbances, which present the symptoms, when the disease turns to advanced stages. Poor balance problems and falls can be detected when the patients fell down on the floor or reported fall history to their clinicians or physical therapists (PTs). Recent balance assessments/tools have hardly explained relationships among sensory, motor, and cognitive aspects. It is difficult to understand the 3 systems' impairments involving PI and FOG. It would be splendid to be able to acknowledge the scale of PI and understand the interaction of the systems in terms of center of pressure (CoP) in order to evaluate balance and provide to the patients with appropriate treatments for the ultimate goal of improving postural control, preventing falls and improving QoL.

This dissertation focused on the presence of the influences of sensory, motor and cognitive deficits toward postural control in PD by raising the main research question (MRQ); What is Parkinson's disease (PD) patients' postural control?, and the 2 subsidiary research questions; SRQ 1: What is balance measurement for evaluating balance dysfunction in Parkinson's disease (PD)? SRQ 2: How to evaluate the progression of Parkinson's disease (PD)? This dissertation illustrated 4 sub-studies with the purposes as follows;

**Study I:** To investigate the effects of visual input (VI) as clinical predictors of postural instability (PI) in Parkinson's disease (PD)

**Study II:** To evaluate the arm swing patterns as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

**Study III:** To determine the arm swing patterns with auditory cues as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

**Study IV:** To study the impact of cognitive loading as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

**Method:** 60 patients with PD were recruited to participate in this study under the informed consent approved by the ethical committee board, Faculty of Medicine, Thammasat University, Thailand. General demographic data and clinical scores were recorded. The subjects were instructed to perform in eye, arm swing and cognitive loading sessions of the balance assessment measured by Nintendo Wii balance board (NWBB) in standing position by physical therapist (PT)

researcher. *Study I*: stand naturally with eyes open and eyes closed in the total of 90 s. *Study II*: swing arms alternate and synchronous followed by the instructed program in the total of 170 s. *Study III*: swing arms alternate and synchronous followed by the instructed program with auditory cues in the total of 170 s. *Study IV*: read a material and count dates backward followed by the instructed program in the total of 170 s.

**Conclusions:** Parkinson's disease (PD) patients' postural control is disturbed by the deteriorations of sensory, motor and cognitive aspects. Specific balance measurements for evaluating balance dysfunction in PD were proposed in study I – IV. *Study I*: visual input can be clinical predictors of PI in PD. *Study II*: arm swing patterns; alternation and synchronization can be applied as clinical predictors of PI and FOG in PD. *Study III*: auditory cues effects on the arm swing patterns toward center of pressures. *Study IV*: cognitive loading effects on standing balance and postural stability in PD patients. It is prominent in PD patients with FOG. The progression of PD can be evaluated by the integration of postural control data in sensory, motor and cognitive parts. Degree of postural instability (DPI) was discovered to determine PI in patients with PD.

**Keywords**: Progressive predictors, Parkinson's disease, Postural instability, Freezing of gait, Balance dysfunction

# DEDICATION

To my dear beloved family and country Thailand as well as Japan

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# CHAPTER 1

# INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder caused by the deterioration of basal ganglia (BG). The symptom involves mainly to motor system. The primary clinical manifestation of PD is resting tremor, rigidity, bradykinesia and postural instability (PI). The symptoms are getting worse from time to time as called "*progressive disorder*". The secondary motor symptoms are masked face, stoop posture, and arm swing reduction. These problems can lead to falls and limit activities of daily living (ADL) which finally lower the patients' quality of life (QoL) and increase chances to develop psychological problems. Non-motor symptoms are loss of sense of smell, constipation, rapid eye movement (REM) sleep disorder, mood disorders, orthostatic hypotension and cognitive dysfunction.

Postural instability (PI) and freezing of gait (FOG) are common problems manifesting in Parkinson's disease (PD), however, there is no scale to measure or predict the progression of the disease by analyzing postural control with the underlying; sensory, motor and cognitive impairments. This dissertation focuses on evaluating standing balance toward postural instability (PI) and freezing of gait (FOG) to be a concept of explaining relationships of sensory, motor and cognitive impairments on postural control in Parkinson's disease (PD) in order to be progressive predictors utilized in clinical practice.

## 1.1 Background

### 1.1.1. Parkinson's disease

Parkinson's disease (PD) is a neuro-degenerative disorder caused by the loss of neurotransmitter called "dopamine" in substantia nigra (SN), basal ganglia (BG) (Jankovic, 2008). Most PD patients manifest problems of movement, coordination, physical function or mobility called "motor symptoms". The primary motor symptoms are the cardinal symptoms, which present

in tremor, rigidity, bradykinesia, and postural instability (PI). The secondary motor symptoms are other symptoms, which are involved with motor system such as masked face, stooped posture (Fig. 1.1-A), freezing of gait (FOG), arm swing reduction, micrographia, speech problems, sexual dysfunction, difficulty swallowing, and so on. The other symptoms called "non – motor symptoms" which present in ways that are difficult to recognize; such as loss of sense of smell, constipation, rapid eye movement (REM) sleep disorder, mood disorders, orthostatic hypotension, cognitive dysfunction (memory difficulties, slowed thinking, confusion and dementia), and so on (Jankovic, 2008; Parkinson's disease foundation, 2015). Sensory impairment such as proprioception is also manifested in patients with PD (Pastor et al., 1993; Khudados et al., 1999; De Nunzio et al., 2007).

Severity of Parkinson's disease (PD) can be categorized into three stages; early, moderate and advanced (Jankovic, 2008; Parkinson's disease foundation, 2015). Postural instability (PI) is one of the factors leading to falls (Johnson et al., 2013). There are up to 68% of patients with Parkinson's disease (PD) suffered from the problem (Michalowska et al., 2005; Balash et al., 2005). Falls do not only cause the problems of fracture, but also the problems of disabilities and hospitalization. These also lead to long-term caring and increase cost of treatments (Lachman et al., 1998). The quality of life (QoL) of the patients has been reduced with such a problem (Bloem et al., 2001; Gray & Hildebrand, 2000; Bloem et al., 2001) (Fig. 1.1-B). The burdens have also been drawn to family members, caregivers and societies. The patients experience gait and balance disturbances in advanced stages, which cause problems of falls (Bloem et al., 2004, Johnson et al., 2013) to the patients.

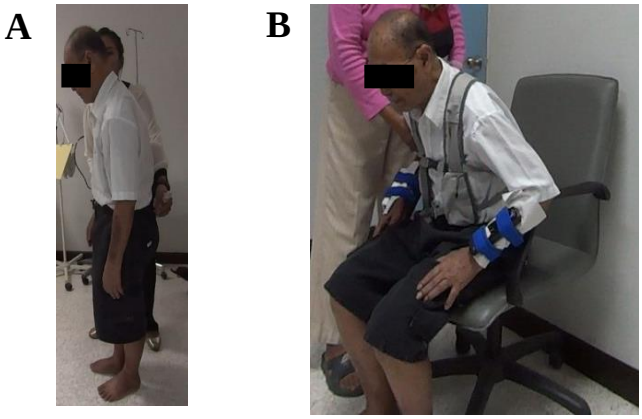



**Fig. 1.1**. Stooped posture manifested in Parkinson's disease patient (A). A difficulty of lifting from a chair caused by motor symptoms of Parkinson's disease (B).

The problems of balance and gait disturbances that PD patients have encountered since they were diagnosed with PD as early stages until the disease progresses to moderate to advanced stages (as illustrated in Fig. 1.2). The severity of disease increases from time to time as it is progressive disorder. Balance disturbances occur in all stages of the disease, however, PD patients in advanced stages experience more problems from loss of balance and have high tendency of falling (Colnat-Coulbois et al., 2011; Bryant et al., 2014). Postural instability (PI) is a well-known terminology for balance disturbances in PD. PI is a main factor in PD leading to the problems of fear of falling, lack of balance confidence and face of falls (Adkin et al., 2003; Swanenburg et al., 2013; Bryant et al., 2014). In advanced stages, the patients manifest the difficulty of stepping forward or turning which is because of a common problem of gait disturbances in PD called "freezing of gait or FOG" (Nieuwboer, A. & Giladi, N., 2011). FOG is considered as a problem related to PI and brings about falls (Schlenstedt et al., 2016). Arm swing reduction (ASR) is one of secondary motor symptoms of PD (Jankovic, 2008; Parkinson's disease foundation, 2015). ASR causes imbalance to human postural control. According to normal human balance control during standing and walking, arm swing plays important role in balancing body (Winter, 1995). To prevent severe injuries occurred by falls, arm movements as fall guarding are a strategy to prevent such terrible situations (Krishnan, 2012). ASR is associated with one of motor symptoms called "rigidity". It affects on abnormal postural control in PD patients, which is a part of bringing about balance disturbances and PI (Kwon et al., 2014). Once, a PD patient fells down on the floor, the capability of ability moving arms to slow down the fall or to grasp objects in front to pull the body up is reduced leading to severe injuries. Cognitive impairment (CI) is apparently related to postural instability and gait disorders (PIGD) with freezing of gait (FOG) (Heremans et al., 2013; Maruyama & Yanagisawa, 2006; Morris et al., 2000). It is reported a factor associated with PI and FOG in PD patients (Amboni et al., 2015). Falls often occur in PD patients with PI and FOG, which have been obviously noticed when the disease turns to advanced stages (Bryant et al., 2014).

Poor balance problems and falls can be detected when the patients fell down on the floor or reported fall history to their clinicians or physical therapists (PTs). Falls result from balance and gait disturbances, which stem from PI, FOG (Allen et al., 2011 & Bryant et al., 2014), visual and proprioceptive deficits (Azulay et al., 1999; Shumway-Cook & Woollacott, M., 2000; Colnat-Coulbois et al., 2011 & Brown et al., 2016), as well as cognitive impairments (Makizako et al., 2013 & Amar et al., 2015). The capability of controlling posture to neutral position originates from

the normal state of sensory, motor and nervous systems. PD patients manifest the deterioration of the three systems because of the degeneration of BG (Pasma et al., 2014), therefore, PD patients have high chance to face problems of balance disturbances and experience falls (Crouse et al., 2016). Clearly, the deterioration of basal ganglia (BG), which results in the impairments of the motor and non-motor systems, and sensory part, finally brings about the problem of falls in patients with PD.

Consequently, PI and FOG are dominant factors to increase fear of falling and lead to physiological and psychological problems; such as fracture, immobilization, and depression and so on. The hospitalization is be in long term, which will increase cost of treatments and family expenses. Finally, these will bring about family burdens and reduction of quality of life (QoL).

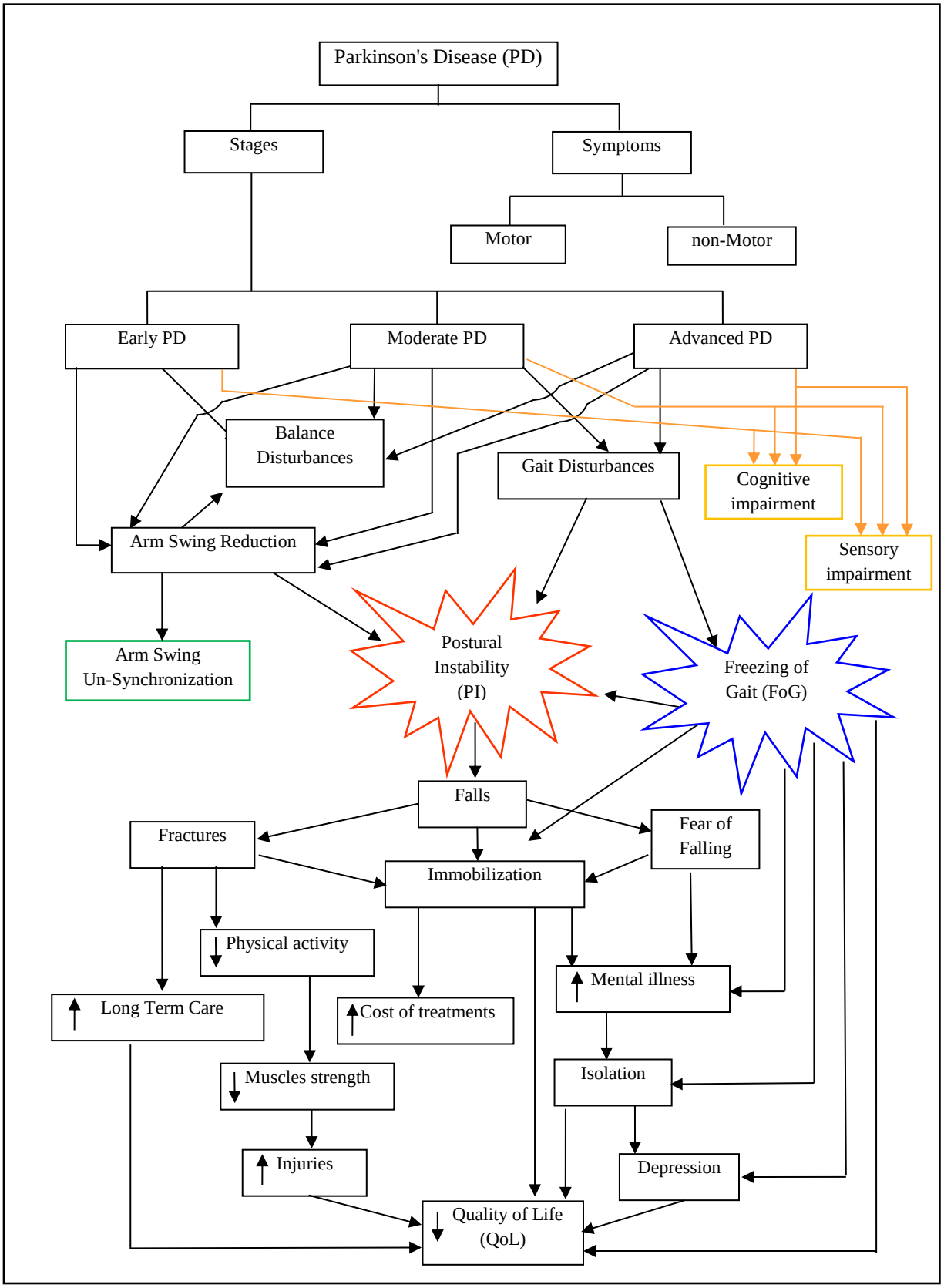



**Fig. 1.2**. Schematic of research background

## Current clinical assessments for Parkinson’s disease

Recently, clinicians, particularly neurologists and movement disorder specialists, diagnose patients with Parkinson’s disease (PD) by taking neurological history and examination. Some imaging modalities such as Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), or Dopamine Transporter (DAT) SPECT will be performed before making a diagnosis of PD (Lingor et al., 2001; Jankovic, 2008).

Progression of the disease is commonly assessed by using Hoehn and Yahr scale (Hoehn & Yahr, 1969) and Unified Parkinson's Disease Rating Scale (UPDRS) (Visser, Marinus & Bloem, 2003). Balance is generally evaluated by Mini-BESTest (Horak et al., 2009), Timed up and Go (Podsiadlo and Richardson, 1991), Tinetti balance test (Tinetti, 1986), Berg balance scale (BBS) (Berg, 1989), Romberg’s test (Rogers, 1980), Functional reach test (Duncan et al., 1990), clinical balance test of sensory interaction and balance (CTSIB) (Shumway-Cook and Horak, 1986), balance error scoring system (BESS) (Finnoff et al., 2009), star excursion balance test (SEBT) (Gribble et al., 2012) and Activities-specific Balance Confidence (ABC) scale (Powell & Myers, 1995). Freezing of gait is assessed by Freezing of Gait questionnaire (FOG-Q) (Nilsson & Hagell, 2009). Cognitive assessment is evaluated by Montreal Cognitive Assessment (MoCA) (Kandiah et al., 2014). Mental state is assessed by MMSE or in Thailand; we apply Thai Mental State Examination (TMSE) (Muangpaisan et al., 2015). Activities of daily living (ADL) is assessed by Schwab & England Activities of Daily Living (SE-ADL) (McRae et al., 2002)

Recent balance assessments/tools are not integrated to classify patients with different levels of postural instability (PI) before they faced a fall. It is difficult to understand the three systems' impairments involving with PI and falls. It would be splendid to be able to acknowledge the scale of postural instability (PI) and understand the interactions of the systems in terms of center of pressure (CoP) in order to evaluate balance and provide appropriate treatments to Parkinson's disease (PD) patients for the ultimate goal of preventing falls and improving quality of life (QoL).

## 1.2 Problem Statement

In this study, we evaluated postural control in patients with Parkinson's disease (PD) through Nintendo Wii balance board (NWBB) during standing. Most of the patients manifest problems of postural instability (PI) which brings about fear of falling, limits activities daily living (ADL), increases risk of falls, causes falls and finally leads to immobilization, long-term hospitalization and depression, which is considered poor quality of life (QoL). The reports of sensory, motor and cognitive impairments on PI have been separately illustrated. Moreover, there are mysterious issues regarding the disease and its pathology. Clinicians, physical therapists (PTs) and researchers have studied about the disease in various aspects to clarify more how to cure patients with Parkinson's disease (PD) in order to help reduce problems from the deterioration and complication. Recently, balance assessments are not integrated to be able to explain the relationships of sensory, motor and cognitive aspects by evaluating postural control to classify subclinical disease of postural instability (PI) and freezing of gait (FOG) in Parkinson's disease (PD).

The problems of this research are as follows:

- *There is no specific scale for evaluating Parkinson's disease (PD) patients' postural control in the 3 dimensions of sensory, motor and cognitive impairments.*

Patients with Parkinson's disease (PD) encounter balance dysfunction resulted in underlying causes. There is no scale for clinicians and physical therapists (PTs) to comprehend degree of postural instability (DPI) regarding the impairments of postural control. In other words, it is difficult for clinicians to acquire balance data of patients or people who do not really show balance impairments based on using current clinical balance assessments.

- *Assessing postural control with current balance assessments for PD patients is time consuming.*

In current clinical situation, evaluating balance for individual is definitely time consuming. It is difficult to manage and complete a set of balance assessment in a short visit. Moreover, PTs are also unable to evaluate postural control and prescribe targeted treatments resulting from no recently specific techniques to identify balance regarding the deterioration of sensory, motor and cognitive impairments. As a result, PD patients and people, who do not show balance impairments,

cannot be evaluated underlying balance dysfunction and receive direct and appropriate interventions for solving the problems simultaneously.

## 1.3 Research Objectives

This research is designed to propose progressive predictors of Parkinson's disease (PD) based on postural instability (PI) and freezing of gait (FOG) through the influences of the impairments of sensory, motor and cognitive on postural control in terms of center of pressure (CoP) displacements. The specific objectives of this research include:

**Study I:** To investigate the effects of visual input (VI) as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

**Study II:** To evaluate the arm swing patterns as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

**Study III:** To determine the arm swing patterns with auditory cues as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

**Study IV:** To study the impact of cognitive loading as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

## 1.4 Research Questions

This dissertation aims to respond with the following reaserch questions;

**Main research question (MRQ)**

What is Parkinson’s disease (PD) patients’ postural control?

**Subsidiary research question (SRQ)**

SRQ 1: What is balance measurement for evaluating balance dysfunction in Parkinson's disease (PD) patients?

SRQ 2: How to evaluate the progression of Parkinson's disease (PD) patients?

## 1.5 Research Hypotheses

This dissertation hypotheses are categorized into 5 main parts for

- Study I: sensory session
- Study II: Motor session I
- Study III: Motor session II
- Study IV: Cognitive session
- The integration of study I - IV

*Study I: sensory session (Visual input)*

We hypothesized if visual input (VI) could be clinical predictors of postural instability (PI) in Parkinson's disease (PD)? The verification processes were in 5 parts. 1) whether visual input (VI) distributes to postural instability (PI) in Parkinson's disease patients with freezing of gait (PD+FOG)? 2) whether visual input (VI) distributes to postural instability (PI) in Parkinson's disease patients without freezing of gait (PD-FOG)? 3) whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients with visual input (VI)? 4) whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients without visual input (VI)? and 5) whether postural control with visual input (VI) and (appropriate) clinical assessent predictors have relationship with freezing of gait (FOG)? 5.1) whether clinical assessments are redundancy? and 5.2) whether postural control with visual input (VI) and clinical assessent predictors have relationship with freezing of gait (FOG)? The details of experiments were described in chapter 4.

*Study II: Motor session I (Arm swing)*

We hypothesized if arm swing could be clinical predictors of postural instability (PI) in Parkinson's disease (PD)? The verification methods were in 8 parts. 1) whether postural control of Parkinson's disease (PD) patients in arm swing alternation (Alt) is different from synchronization (Syn)? 2) whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients in arm swing alternation (Alt). 3) whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients in arm swing synchronization (Syn). 4) whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing alternation (Alt) correlates with clinical assessments? 5) whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing synchronization (Syn) correlates with clinical assessments? 6) whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing synchronization (Syn) correlates with clinical assessments? 7) whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing synchronization (Syn) correlates with clinical assessments? and 8) whether postural control in arm swing synchronization (Syn) and severity of disease can be a fall predictor? The details of experiments were explained in chapter 5.

*Study III: Motor session II (Arm swing with auditory cues)*

We hypothesized if arm swing with auditory cues could be clinical predictors of postural instability (PI) in Parkinson's disease (PD)? The verification processes were in 9 parts. 1) whether postural control of Parkinson's disease (PD) patients in arm swing alternation (Alt) with no cues (NC) is different from auditory cues (AC)? 2) whether postural control of Parkinson's disease (PD) patients in arm swing synchronization (Syn) with no cues (NC) is different from auditory cues (AC)? 3) whether auditory cues (AC) influence on postural control in arm swing alternation (Alt) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG)? 4) whether auditory cues (AC) influence on postural control in arm swing synchronization (Syn) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG)? 5) Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing alternation (Alt) with auditory cues

(AC) correlates with clinical assessments? 6) whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing synchronization (Syn) with auditory cues (AC) correlates with clinical assessments? 7) whether postural control in the arm swing patterns with auditory cues (AC) and clinical assessent predictors have relationship with freezing of gait (FOG)? 8) whether postural control in arm swing alternation (Alt) with auditory cues (AC) and severity of disease can be a fall predictor? and 9) whether postural control in arm swing synchronization (Syn) with auditory cues (AC) and severity of disease can be a fall predictor? The details of experiments were illustrated in chapter 6.

*Study IV: Cognitive session (Cognitive loading)*

We hypothesized if cognitive loading could be clinical predictor of postural instability (PI) in Parkinson's disease (PD)? The verification methods were in 7 parts. 1) whether reading (RE) disturbs postural control in Parkinson's disease (PD) patients? 2) whether counting backward (CB) disturbs postural control in Parkinson's disease (PD) patients? 3) whether cognitive loading aggravates postural control of Parkinson's disease patients with freezing of gait (PD+FOG)? 4) whether cognitive loading aggravates postural control of Parkinson's disease patients without freezing of gait (PD-FOG)? 5) whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in reading (RE) correlates with clinical assessments? 6) Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in counting backward (CB) correlates with clinical assessments? and 7) Whether postural control in the cognitive loading and clinical assessent predictors have relationship with freezing of gait (FOG)? The details of experiments were given in chapter 7.

*The integration of study I - IV*

We hypothesized if postural control in sensory, motor and cognitive elements were significant to be progressive predictors of Parkinson's disease (PD)? The verification processes were in 2 parts. 1) whether postural control in sensory, motor and cognitive elements are significant to be progressive predictors of Parkinson's disease (PD)? and 2) whether the selected elements can

be progressive predictors of Parkinson's disease (PD)? The details of verification processes were exemplified in chapter 8.

The hypotheses' details of each study are as follows;

1. *Whether visual input (VI) can be clinical predictors of postural instability (PI) in Parkinson's disease (PD)?*

1.1 Whether visual input (VI) distributes to postural instability (PI) in Parkinson's disease patients with freezing of gait (PD+FOG)

$H_0$ = Visual input (VI) does not distribute to postural instability (PI) in Parkinson's disease patients with freezing of gait (PD+FOG)

$H_1$ = Visual input (VI) distributes to postural instability (PI) in Parkinson's disease patients with freezing of gait (PD+FOG)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of center of pressure (CoP) parameters of PD+FOG during eyes open

$\mu_2$ = The average of CoP parameters of PD+FOG during eyes closed

1.2 Whether visual input (VI) distributes to postural instability (PI) in Parkinson's disease patients without freezing of gait (PD-FOG)?

$H_0$ = Visual input (VI) does not distribute to postural instability (PI) in Parkinson's disease patients without freezing of gait (PD-FOG)

$H_1$ = Visual input (VI) distributes to postural instability (PI) in Parkinson's disease patients without freezing of gait (PD-FOG)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of CoP parameters of PD-FOG during eyes open

$\mu_2$ = The average of CoP parameters of PD-FOG during eyes closed

1.3 Whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients with visual input (VI)?

$H_0$ = Postural control with visual input (VI) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG) is better than without freezing of gait (PD-FOG)

$H_1$ = Postural control with visual input (VI) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG) is not better than without freezing of gait (PD-FOG)

$$H_0 : \mu_1 > \mu_2$$

$$H_1 : \mu_1 \leq \mu_2$$

$\mu_1$ = The average of CoP parameters during eyes open of PD+FOG

$\mu_2$ = The average of CoP parameters during eyes open of PD-FOG

1.4 Whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients without visual input (VI)?

$H_0$ = Postural control without visual input (VI) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG) is better than without freezing of gait (PD-FOG)

$H_1$ = Postural control without visual input (VI) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG) is not better than without freezing of gait (PD-FOG)

$$H_0 : \mu_1 > \mu_2$$

$$H_1 : \mu_1 \leq \mu_2$$

$\mu_1$ = The average of CoP parameters during eyes closed of PD+FOG

$\mu_2$ = The average of CoP parameters during eyes closed of PD-FOG

1.5 Whether postural control with visual input (VI) and (appropriate) clinical assessent predictors have relationship with freezing of gait (FOG)?

1.5.1. Whether clinical assessments are redundancy?

$H_0$ = Clinical assessments are not inter-correlated variables

$H_1$ = Clinical assessments are inter-correlated variables

$H_0$ : $r = 0$, $r_1$ is not relavant to $r_2, r_3, \ldots. r_n$

$H_1$ : $r \neq 0$, $r_1$ is relavant to $r_2, r_3, \ldots. r_n$

r = Linear correlation coefficient

1.5.2. Whether postural control with visual input (VI) and clinical assessent predictors have relationship with freezing of gait (FOG)?

$H_0$ = Postural control with visual input (VI) and clinical assessent predictors do not have relationship with freezing of gait (FOG)

$H_1$ = Postural control with visual input (VI) and clinical assessent predictors have relationship with freezing of gait (FOG)

| | |
|---|---|
| $H_0$ : | $\mu$ is not relevant to FOG |
| $H_1$ : | $\mu$ is relavant to FOG |

$\mu_1$ = Postural control with visual input (VI) and clinical assessent predictors

FOG = Parkinson's disease patients ($PD_{total}$, PD+FOG and PD-FOG)

2. *Whether arm swing can be clinical predictors of postural instability (PI) in Parkinson's disease (PD)?*

2.1 Whether postural control of Parkinson's disease (PD) patients in arm swing alternation (Alt) is different from synchronization (Syn)?

$H_0$ = The effect of arm swing alternation (Alt) is similar to synchronization (Syn)

$H_1$ = The effect of arm swing alternation (Alt) is different from synchronization (Syn)

| | |
|---|---|
| $H_0$ : | $\mu_1 = \mu_2$ |
| $H_1$ : | $\mu_1 \neq \mu_2$ |

$\mu_1$ = The average of CoP parameters of arm swing alternation (Alt)

$\mu_2$ = The average of CoP parameters of arm swing synchronization (Syn)

2.2 Whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients in arm swing alternation (Alt)?

$H_0$ = Postural control in arm swing alternation (Alt) of PD patients with freezing of gait (PD+FOG) is similar to without freezing of gait (PD-FOG)

$H_1$ = Postural control in arm swing alternation (Alt) of PD patients with freezing of gait (PD+FOG) is different from without freezing of gait (PD-FOG)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of CoP parameters in arm swing alternation (Alt) of PD+FOG

$\mu_2$ = The average of CoP parameters in arm swing alternation (Alt) of PD-FOG

2.3 Whether freezing of gait (FOG) influences on postural control in Parkinson's disease (PD) patients in arm swing synchronization (Syn)?

$H_0$ = Postural control in arm swing synchronization (Syn) of PD patients with freezing of gait (PD+FOG) is similar to without freezing of gait (PD-FOG)

$H_1$ = Postural control in arm swing synchronization (Syn) of PD patients with freezing of gait (PD+FOG) is different from without freezing of gait (PD-FOG)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of CoP parameters in arm swing synchronization (Syn) of PD+FOG

$\mu_2$ = The average of CoP parameters in arm swing synchronization (Syn) of PD-FOG

2.4 Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing alternation (Alt) correlates with clinical assessments?

$H_0$ = CoP in arm swing alternation (Alt) of PD patients with and without freezing of gait (FOG) does not have correlation with clinical assessments

$H_1$ = CoP in arm swing alternation (Alt) of PD with and without freezing of gait (FOG) has correlation with clinical assessments

$H_0$ : r = 0

$H_1$ : r ≠ 0

r = Linear correlation coefficient

2.5 Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing synchronization (Syn) correlates with clinical assessments?

$H_0$ = CoP in arm swing synchronization (Syn) of PD patients with and without freezing of gait (FOG) does not have correlation with clinical assessments

$H_1$ = CoP in arm swing synchronization (Syn) of PD with and without freezing of gait (FOG) has correlation with clinical assessments

$H_0$ : r = 0

$H_1$ : r ≠ 0

r = Linear correlation coefficient

2.6 Whether postural control in the arm swing patterns and clinical assessent predictors have relationship with freezing of gait (FOG)?

$H_0$ = Postural control in the arm swing patterns and clinical assessent predictors do not have relationship with freezing of gait (FOG)

$H_1$ = Postural control in the arm swing patterns and clinical assessent predictors have relationship with freezing of gait (FOG)

$H_0$ : μ is not relevant to FOG

$H_1$ : μ is relavant to FOG

$\mu$ = The average of CoP parameters in the arm swing patterns and clinical assessent predictors

FOG = Parkinson's disease patients with and without freezing of gait

2.7 Whether postural control in arm swing alternation (Alt) and severity of disease can be a fall predictor?

$H_0$ = Postural control in the arm swing alternation (Alt) and severity of disease can not predict falls

$H_1$ = Postural control in the arm swing alternation (Alt) and severity of disease can predict falls

$$H_0 : OR = 1$$

$$H_1 : OR \neq 1$$

OR = Odds ratio of postural control in the arm swing alternation (Alt) regarding severity of disease

2.8 Whether postural control in arm swing synchronization (Syn) and severity of disease can be a fall predictor?

$H_0$ = Postural control in the arm swing synchronization (Syn) and severity of disease can not predict falls

$H_1$ = Postural control in the arm swing synchronization (Syn) and severity of disease can predict falls

$$H_0 : OR = 1$$

$$H_1 : OR \neq 1$$

OR = Odds ratio of postural control in the arm swing synchronization (Syn) regarding severity of disease

*3. Whether arm swing with auditory cues can be clinical predictors of postural instability (PI) in Parkinson's disease (PD)?*

3.1 Whether postural control of Parkinson's disease (PD) patients in arm swing alternation (Alt) with no cues (NC) is different from auditory cues (AC)?

$H_0$ = The effect of arm swing alternation (Alt) with no cues (NC) is similar to auditory cues (AC)

$H_1$ = The effect of arm swing alternation (Alt) with no cues (NC) is different from auditory cues (AC)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of CoP parameters of arm swing alternation (Alt) with no cues (NC)

$\mu_2$ = The average of CoP parameters of arm swing alternation (Alt) with auditory cues (AC)

3.2 Whether postural control of Parkinson's disease (PD) patients in arm swing synchronization (Syn) with no cues (NC) is different from auditory cues (AC)?

$H_0$ = The effect of arm swing synchronization (Syn) with no cues (NC) is similar to auditory cues (AC)

$H_1$ = The effect of arm swing synchronization (Syn) with no cues (NC) is different from auditory cues (AC)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of CoP parameters of arm swing synchronization (Syn) with no cues (NC)

$\mu_2$ = The average of CoP parameters of arm swing synchronization (Syn) with auditory cues (AC)

3.3 Whether auditory cues (AC) influence on postural control in arm swing alternation (Alt) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG)?

$H_0$ = Postural control in arm swing alternation (Alt) with no cues (NC) of PD patients with freezing of gait (PD+FOG) is equal to with auditory cues (AC)

$H_1$ = Postural control in arm swing alternation (Alt) with no cues (NC) of PD patients with freezing of gait (PD+FOG) is not equal to with auditory cues (AC)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of CoP parameters of PD+FOG in arm swing alternation (Alt) with no cues (NC)

$\mu_2$ = The average of CoP parameters of PD+FOG in arm swing alternation (Alt) with auditory cues (AC)

3.4 Whether auditory cues (AC) influence on postural control in arm swing synchronization (Syn) of Parkinson's disease (PD) patients with freezing of gait (PD+FOG)?

$H_0$ = Postural control in arm swing synchronization (Syn) with no cues (NC) of PD patients with freezing of gait (PD+FOG) is equal to with auditory cues (AC)

$H_1$ = Postural control in arm swing synchronization (Syn) with no cues (NC) of PD patients with freezing of gait (PD+FOG) is not equal to with auditory cues (AC)

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

$\mu_1$ = The average of CoP parameters of PD+FOG in arm swing synchronization (Syn) with no cues (NC)

$\mu_2$ = The average of CoP parameters of PD+FOG in arm swing synchronization (Syn) with auditory cues (AC)

3.5 Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing alternation (Alt) with auditory cues (AC) correlates with clinical assessments?

$H_0$ = CoP in arm swing alternation (Alt) with auditory cues (AC) of PD patients with and without freezing of gait (FOG) does not have correlation with clinical assessments

$H_1$ = CoP in arm swing alternation (Alt) with auditory cues (AC) of PD with and without freezing of gait (FOG) has correlation with clinical assessments

$$H_0 : r = 0$$

$$H_1 : r \neq 0$$

r = Linear correlation coefficient

3.6 Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in arm swing synchronization (Syn) with auditory cues (AC) correlates with clinical assessments?

$H_0$ = CoP in arm swing synchronization (Syn) with auditory cues (AC) of PD patients with and without freezing of gait (FOG) does not have correlation with clinical assessments

$H_1$ = CoP in arm swing synchronization (Syn) with auditory cues (AC) of PD with and without freezing of gait (FOG) has correlation with clinical assessments

$$H_0 : r = 0$$

$$H_1 : r \neq 0$$

r = Linear correlation coefficient

3.7 Whether postural control in the arm swing patterns with auditory cues (AC) and clinical assessent predictors have relationship with freezing of gait (FOG)?

$H_0$ = Postural control in the arm swing patterns with auditory cues (AC) and clinical assessent predictors have relationship with freezing of gait (FOG)

$H_1$ = Postural control in the arm swing patterns with auditory cues (AC) and clinical assessent predictors do not have relationship with freezing of gait (FOG)

$$H_0 : \mu \text{ is relevant to FOG}$$

$$H_1 : \mu \text{ is not relavant to FOG}$$

$\mu$ = Postural control in the arm swing patterns with auditory cues (AC) and clinical assessent predictors

FOG = Parkinson's disease patients with and without freezing of gait

3.8 Whether postural control in arm swing alternation (Alt) with auditory cues (AC) and severity of disease can be a fall predictor?

$H_0$ = Postural control in the arm swing alternation (Alt) with auditory cues (AC) and severity of disease can not predict falls

$H_1$ = Postural control in the arm swing alternation (Alt) with auditory cues (AC) and severity of disease can predict falls

$$H_0 : OR = 1$$

$$H_1 : OR \neq 1$$

OR = Odds ratio of postural control in the arm swing alternation (Alt) with auditory cues (AC) regarding severity of disease

3.9 Whether postural control in arm swing synchronization (Syn) with auditory cues (AC) and severity of disease can be a fall predictor?

$H_0$ = Postural control in the arm swing synchronization (Syn) with auditory cues (AC) and severity of disease can not predict falls

$H_1$ = Postural control in the arm swing synchronization (Syn) with auditory cues (AC) and severity of disease can predict falls

$$H_0 : OR = 1$$

$$H_1 : OR \neq 1$$

OR = Odds ratio of postural control in the arm swing synchronization (Syn) with auditory cues (AC) regarding severity of disease

*4 Whether cognitive loading can be clinical predictor of postural instability (PI) in Parkinson's disease (PD)?*

4.1 Whether reading (RE) disturbs postural control in Parkinson's disease (PD) patients?

$H_0$ = Reading (RE) does not disturb postural control in Parkinson's disease (PD) patients

$H_1$ = Reading (RE) disturbs postural control in Parkinson's disease (PD) patients

$$H_0 : \mu_1 - \mu_2 = 0$$

$$H_1 : \mu_1 - \mu_2 \neq 0$$

$\mu_1$ = The average of CoP parameters of PD patients during reading

$\mu_2$ = The average of CoP parameters of PD patients before reading

4.2 Whether counting backward (CB) disturbs postural control in Parkinson's disease (PD) patients?

$H_0$ = Counting backward (CB) does not disturb postural control in Parkinson's disease (PD) patients

$H_1$ = Counting backward (CB) disturbs postural control in Parkinson's disease (PD) patients

$$H_0 : \mu_1 - \mu_2 = 0$$

$$H_1 : \mu_1 - \mu_2 \neq 0$$

$\mu_1$ = The average of CoP parameters of PD patients during Counting backward

$\mu_2$ = The average of CoP parameters of PD patients before Counting backward

4.3 Whether cognitive loading aggravates postural control of Parkinson's disease patients with freezing of gait (PD+FOG)?

$H_0$ = Cognitive loading does not aggravate postural control in Parkinson's disease patients with freezing of gait (PD+FOG)

$H_1$ = Cognitive loading aggravates postural control in Parkinson's disease patients with freezing of gait (PD+FOG)

$$H_0 : \mu_1 - \mu_2 = 0$$

$$H_1 : \mu_1 - \mu_2 \neq 0$$

$\mu_1$ = The average of CoP parameters of PD+FOG during receiving cognitive loading

$\mu_2$ = The average of CoP parameters of PD+FOG before receiving cognitive loading

4.4 Whether cognitive loading aggravates postural control of Parkinson's disease patients without freezing of gait (PD-FOG)?

$H_0$ = Cognitive loading does not aggravate postural control in Parkinson's disease patients without freezing of gait (PD-FOG)

$H_1$ = Cognitive loading aggravates postural control in Parkinson's disease patients without freezing of gait (PD-FOG)

$$H_0 : \mu_1 - \mu_2 = 0$$

$$H_1 : \mu_1 - \mu_2 \neq 0$$

$\mu_1$ = The average of CoP parameters of PD-FOG during receiving cognitive loading

$\mu_2$ = The average of CoP parameters of PD-FOG before receiving cognitive loading

4.5 Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in reading (RE) correlates with clinical assessments?

$H_0$ = CoP in reading (RE) of PD patients with and without freezing of gait (FOG) does not have correlation with clinical assessments

$H_1$ = CoP in reading (RE) of PD with and without freezing of gait (FOG) has correlation with clinical assessments

$$H_0 : r = 0$$

$$H_1 : r \neq 0$$

r = Linear correlation coefficient

4.6 Whether postural control of Parkinson's disease (PD) patients with and without freezing of gait (FOG) in counting backward (CB) correlates with clinical assessments?

$H_0$ = CoP in counting backward (CB) of PD patients with and without freezing of gait (FOG) does not have correlation with clinical assessments

$H_1$ = CoP in counting backward (CB) of PD with and without freezing of gait (FOG) has correlation with clinical assessments

$$H_0 : r = 0$$

$$H_1 : r \neq 0$$

r = Linear correlation coefficient

4.7 Whether postural control with cogntive loading and clinical assessent predictors have relationship with freezing of gait (FOG)?

$H_0$ = Postural control with cogntive loading and clinical assessent predictors have relationship with freezing of gait (FOG)

$H_1$ = Postural control with cogntive loading and clinical assessent predictors do not have relationship with freezing of gait (FOG)

| | | |
|---|---|---|
| $H_0$ | : | $\mu$ is relevant to FOG |
| $H_1$ | : | $\mu$ is not relavant to FOG |

$\mu$ = Postural control with cogntive loading and clinical assessent predictors

FOG = Parkinson's disease patients with and without freezing of gait

*5 Whether postural control in sensory, motor and cognitive elements are significant to be progressive predictors of Parkinson's disease (PD)?*

5.1 Whether postural control in sensory, motor and cognitive elements are significant to be progressive predictors of Parkinson's disease (PD)?

$H_0$ = All elements are selected to be a dominant component

$H_1$ = Some elements are selected to be dominant component (s)

| | | |
|---|---|---|
| $H_0$ | : | FL $\geq$ 0.7 |
| $H_1$ | : | FL $<$ 0.7 |

FL = Factor loading in terms of % of variance

5.2 Whether the selected elements can be progressive predictors of Parkinson's disease (PD)?

$H_0$ = The selected elements can not be progressive predictors of Parkinson's disease (PD)

$H_1$ = The selected elements can be progressive predictors of Parkinson's disease (PD)

$$H_0 : OR = 1$$

$$H_1 : OR \neq 1$$

OR = Odds ratio of postural control in the arm swing alternation (Alt) with auditory cues (AC) regarding severity of disease

## 1.6 Research Design

This study is designed on the basis of *Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait in Parkinson's Disease*. The sub-studies in this dissertation are based on the research questions as shown in Fig. 1.3. We propose the research direction to progressive predictors of Parkinson's disease (PD) based on postural instability (PI) and freezing of gait (FOG) which highlights the influences of the 3 impairments on PD patients' postural control, namely sensory, motor and cognitive. We mainly illustrate the interactions of the three systems deteriorated by the basal ganglia (BG) in terms of center of pressure (CoP) and describe the relationships between postural control and clinical assessments covering the deficits for the ultimate purpose of explaining degree of postural instability (DPI) in Parkinson's disease (PD)

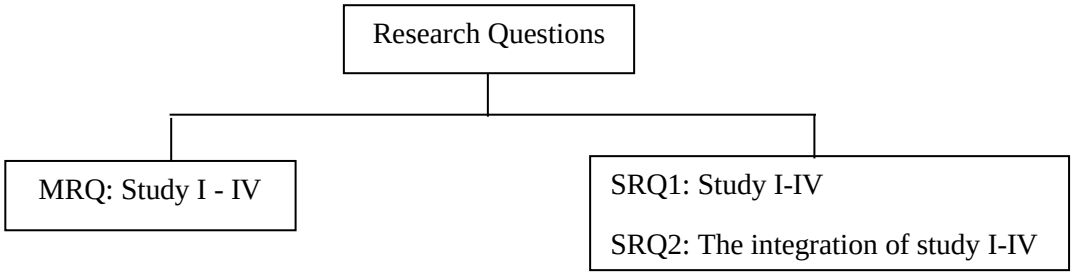



**Fig. 1.3**. The sub-studies design in this dissertation to respond to research questions.

The study constructed in this research is based on the three main impairments. By exploring sensory, motor and cognitive aspects, we designed the study protocol to collect the posturographic data during disturbing sensory, motor and cognitive functions as shown in Fig. 1.4. Clinical assessments were proceeded before evaluating the patients' postural control. The evaluation of Parkinson's disease (PD) patients' balance was performed in 3 sessions; sensory, motor and cognitive. We inserted the interrupted sessions to the balance assessment to verify how the three impairments influence on the patients' postural control by disturbing the three functions in standing balance. First, the sensory session was divided into 2 sub-sessions; eyes open (EO) and eyes closed (EC). We cut off visual inputs and observed how they aggravate the patients' postural control. Second, the motor session was categorized into 2 sub-sessions of arm swing patterns; alternation (ALT) and synchronization (SYN). The participants were instructed to swing arm alternate and synchronous which we observed the effects of the two dynamic standing balance patterns on the patients' postural control. Third, the cognitive session was also grouped into two sub-sessions; reading (RE) and counting backward (CB). Cognitive loading was addressed to verify its effects on the patients' postural stability by guiding them to read a material and count date backward.

The outcome of this research is to study the posturographic data of Parkinson's disease (PD) patients in the three impairments that could enhance the understanding of the interactions of sensory, motor and cognitive functions on postural control in the patients and would be beneficial for future studies.

*Experimental design*

The study procedure in this study was designed in three sections; sensory, motor and cognitive. Participants were asked to perform on Nintendo Wii balance board (NWBB) to be assessed postural control. Clinical assessments in terms of balance confidence, cognition, freezing of gait (FOG), activities of daily living (ADL) were employed to evaluate the patients. The length of the data collection was 30 - 45 minutes depending on patients' symptoms/conditions.

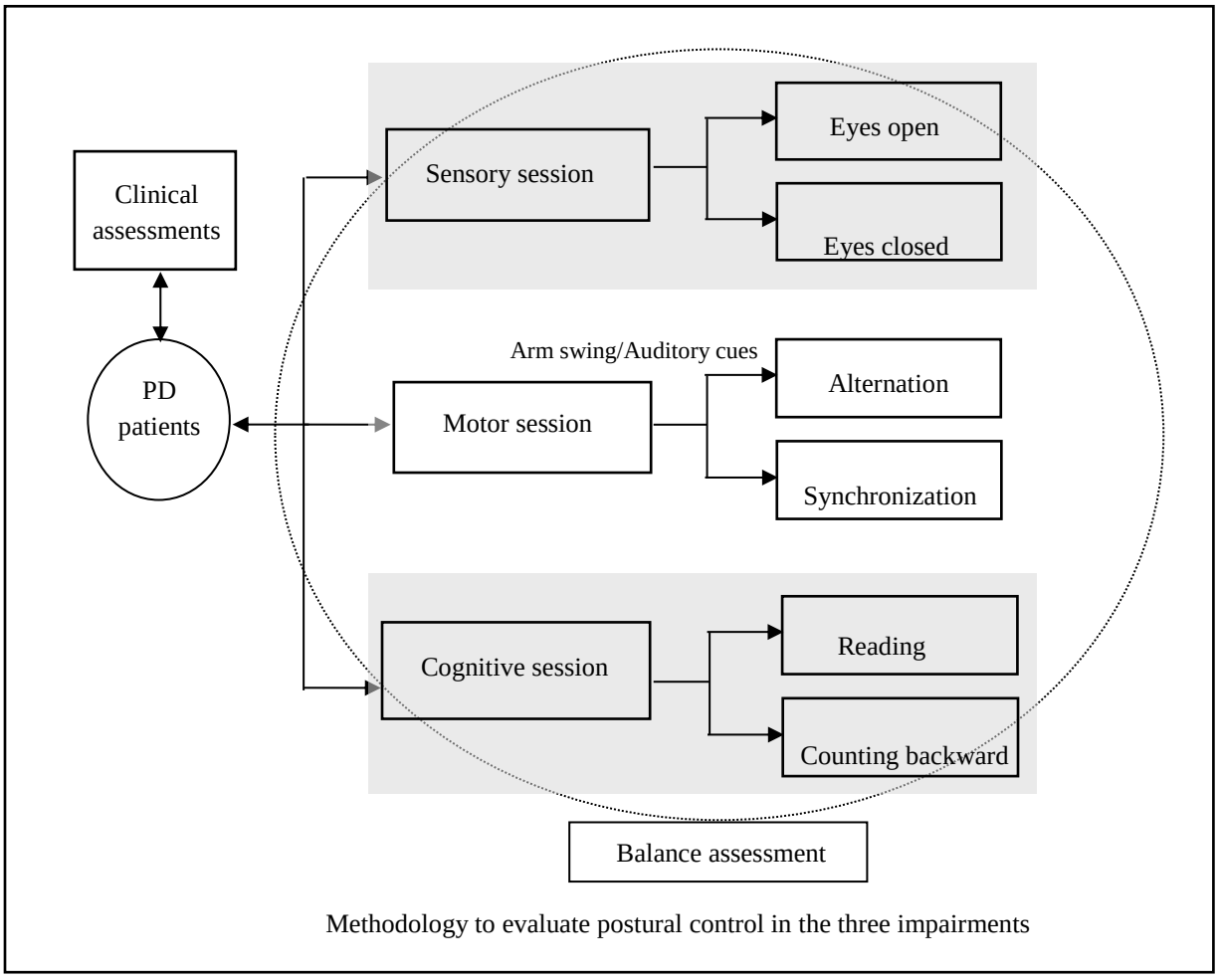



**Fig. 1.4**. Empirical model of the methodology of balance assessment

## 1.7 Conceptual Framework

The conceptual framework of the study is shown in Fig. 1.5. The research focused on the relationship between motor, non-motor symptoms and sensory impairment in Parkinson's disease (PD) patients. By pointing to classifying postural instability (PI) in PD, the study was designed to cover the three main impairments of standing balance. Motor symptoms are manifested related to motor part, which can be divided into two aspects; primary and secondary. Primary symptoms are resting tremor, rigidity, bradykinesia, and postural instability (PI). Secondary symptoms can be expressed in freezing of gait (FOG), marked face, stooped posture, speech problems, and decreased arm swing, and so on. Non-motor symptoms are not involved with motor expression such as

cognitive impairment, sleep disorder, bladder problem, and so on. Impaired sensation involved with postural control is also a reason leading to postural instability (PI) in Parkinson's disease (PD). The impairments of sensory, motor and cognitive were evaluated by this study designed balance assessment. The results of balance assessment showed center of pressure (CoP) which represented the ability of postural control in Parkinson's disease (PD) patients.

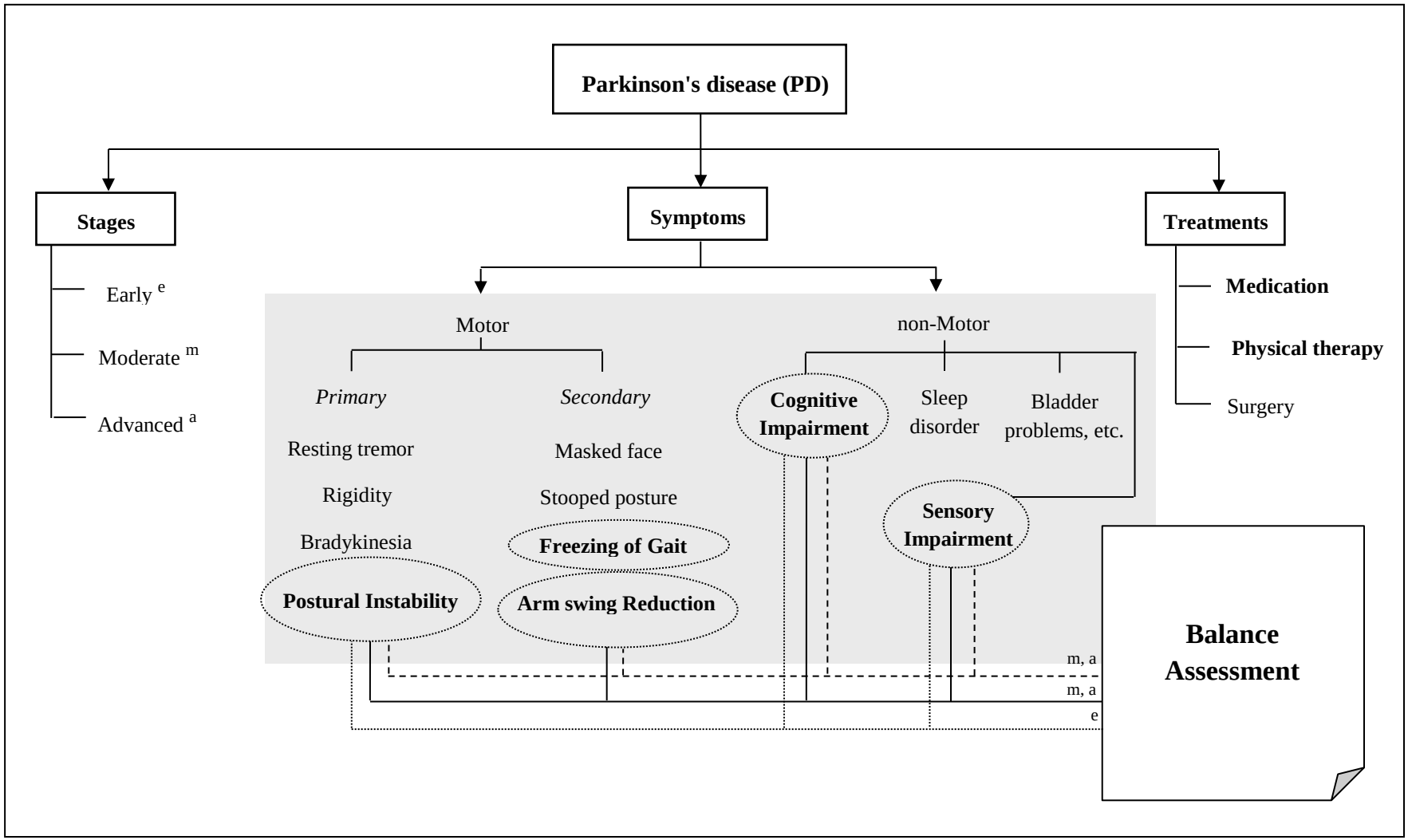



**Fig. 1.5**. Conceptual framework of the study

## 1.8 Operational terminology

1. Center of pressure (CoP):

   The center of body mass on the ground, which is the ground reaction force vector represents the sum of all forces acting between a physical object and its supporting surface.
2. Path length (PL):

   Total length (mm) of the path followed by CoP during controlling posture.
3. Sway area (SA):

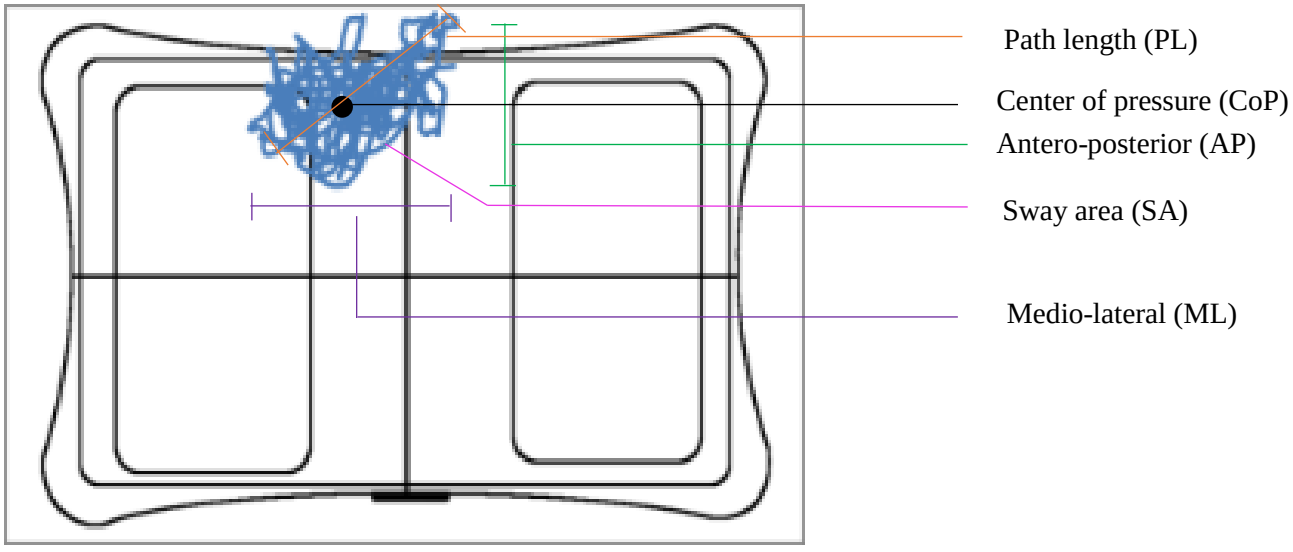
   Area subtended to the path ($cm^2$)
4. Root mean square (RMS):

   RMS is the square root of the arithmetic mean of the squares of the values, or the square of the function that defines the continuous data.
5. Medio-lateral (ML) displacement:

   The movements of CoP along the X-axis (cm)
6. Antero-posterior (AP) displacement:

   The movements of CoP along the Y-axis (cm)

**Fig. 2.8.** An example of center of pressure (CoP) trajectories with operation



## 1.9 Significance and Originality of the Study

Novelty

This study demonstrated the relationship of sensory, motor and cognitive deficits on postural instability (PI) and freezing of gait (FOG) in Parkinson's disease (PD), and proposed degree of postural instability (DPI) as progressive predictors of Parkinson's disease (PD). DPI is a new scale for evaluating postural control in PD patients.

Significance and Originality

This research is unique, important and significant for Parkinson's disease (PD) patients and academics. The significance and originality of this study as shown in Fig. 1.6. Although, there are several studies explaining about postural instability (PI) and freezing of gait (FoG) in PD, there are no protocols to describe the interconnections between sensory, motor and cognitive deficits, which influence on PI and FoG in PD. We conducted the sub-studies to evaluate postural control in PD patients in the 3 terms; sensory, motor and cognitive, in order to create a model of degree of postural instability (DPI) of PD.

First, the sensory part illustrated the correlations between visual dependency (lack of visual input) and severity of disease and falls on PI and FOG. Second, the motor part explained the relationship between the two arm swing patterns and postural control, which demonstrated the motor impairment of PD through the movements of arms and the ability of controlling posture. Moreover, it was an emphasis of auditory cues toward arm swing and PI, which theoretically auditory cues help regulating the rhythm of movements. This study showed the effects of the cues on arm swing toward postural control in PD. Third, the cognitive part described the impact of cognitive loading on postural control, which expressed the interactions between neural circuits in the brain through center of pressure (CoP).

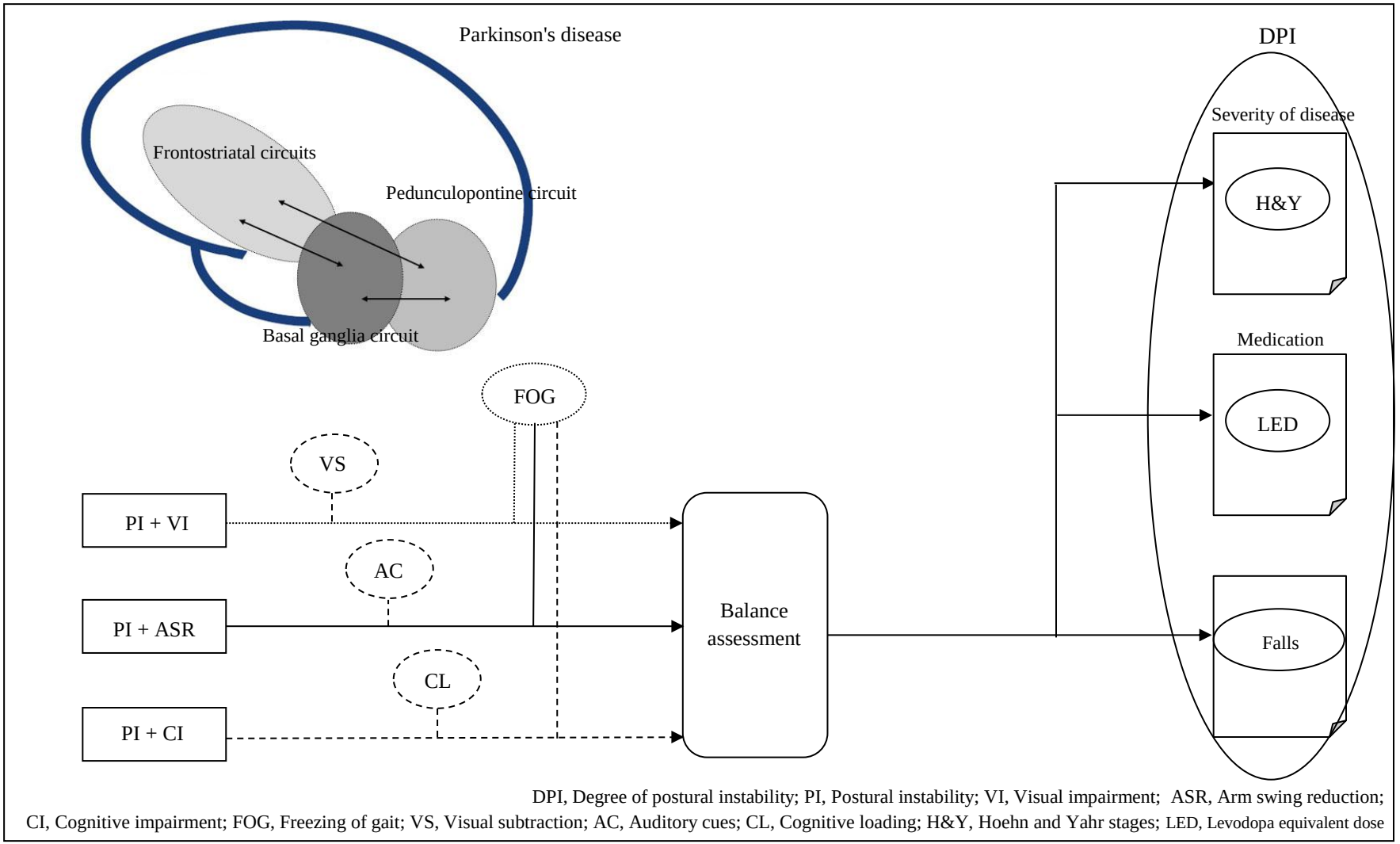



**Fig. 1.6**. Significance and originality of the study

Applicability

The significance and originality of this study as shown in Fig. 1.6. Degree of postural instability (DPI) can be applied to clinical practice for clinicians, PTs, researchers and PD patients. It can be implemented for evaluating postural control and/or developing rehabilitation programs for improving balance, fall prediction, exercise alert as mobile phone applications, and balance training programs on Nintendo Wii balance board (NWBB).

## 1.10 Structure of the Dissertation

This dissertation is organized into ten chapters. The following chapters are structured as follows;

***Chapter 2*** describes the summary of the previous literature on the scope of Parkinson's disease (PD), postural instability (PI) in Parkinson's disease (PD); deteriorations of sensory-motor systems and cognitive function, freezing of gait (FOG) in Parkinson's disease (PD), and Physical therapy in neurorehabilitation for Parkinson's disease (PD). The involved topics bring about the processes of evaluating postural control in Parkinson's disease (PD).

***Chapter 3*** provides the details of research methodology including the criteria of subjects who were recruited to participate in this study, the instrumentation, the experimental procedures and statistical analysis methods of all sub-studies in this dissertation.

***Chapter 4*** illustrates the study of balance assessment in sensory session by providing the details of the background and how sensory impairments effect on postural instability (PI) in Parkinson's disease (PD) patients, the research methodology comparing the tests between normal state and cutting off visual input state, the analyses between eyes open (EO) and eyes closed (EC) were expressed significant values of the results, the discussion and conclusion were comprehended the research.

***Chapter 5*** presents the study of motor session. The dynamic standing balance of arm swing movements was performed to evaluate individual postural control. The analyses and results

described the effects of the aggravation of motor function for the sake of the arm swing patterns; alternation (Alt and synchronization (Syn), toward postural stability. The analyses, results, discussion and conclusion were clarified related issues and summed the experimental processes up.

***Chapter 6*** explains the effect of auditory cues on postural stability in Parkinson's disease (PD) during swing arms alternate and synchronous. The comparisons of no cues (NC) and with auditory cues (AC) conditions were stated to show how auditory cues (AC) play role on the arm swing patterns through the center of pressure (CoP) which is a way to control posture. The discussion and conclusion were addressed for further studies.

***Chapter 7*** investigates cognitive dysfunction toward postural control in patients with Parkinson's disease (PD). It contains the experimental procedure of cognitive testing based on balance. The analyses and results reported the influences of cognitive loading on postural control and the correlations between the patients' center of pressure (CoP) and clinical assessments. The discussion and conclusion were indicated to simplify the contents.

***Chapter 8*** bridges the relationships of sensory, motor and cognitive sessions from the chapter 4 – 7 by demonstrating a model of the interactions of brain circuits to explain how the impairments have effects on postural stability in Parkinson's disease (PD).

***Chapter 9*** summarizes the results of each sub-study, namely sensory, motor and cognitive deficits that influence on postural control in patients with Parkinson's disease (PD). It concludes the significant points of the degree of postural instability (PI) in this research by providing a model of progressive predictors of Parkinson's disease (PD) based on postural instability (PI) and freezing of gait (FOG) through the three systems, and the implementations in clinical practice and academic/research areas.

# CHAPTER 2

# LITERATURE REVIEW

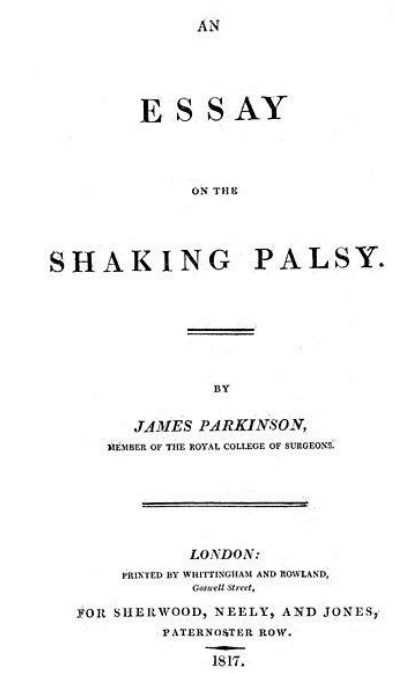
The main content of this chapter is to summary the previous literatures on the postural instability (PI), freezing of gait (FoG), and impairments causing balance problems in Parkinson's disease (PD) patients. The literature reviews are classified into five sections. Section 2.1 summarizes the details of Parkinson's disease (PD) by explaining in definition, epidemiology and etiology, pathophysiology, clinical manifestation, stages of disease. Section 2.2 describes the causes and problems of postural instability (PI) in Parkinson's disease (PD). Section 2.3 reviews the abnormal standing balance in Parkinson's disease (PD) by providing the details of sensory, motor and cognitive impairments. Section 2.4 presents the details of freezing of gait (FOG) in Parkinson's disease (PD) Section 2.5 indicates the details of physical therapy in neurorehabilitation for Parkinson's disease (PD).

## 2.1. Parkinson's Disease (PD)

*Definition*

Parkinson's disease (PD) is a neurodegenerative disorder aggravating both motor and non-motor symptoms. It was first described by James Parkinson in 1817 in "An Essay on the Shaking Palsy" (Parkinson, 1817) as expressed in Fig. 2.1. The main causes of the disease are unknown, however, most researchers, who are interested deeply in its pathophysiology, found the deterioration of substantia nigra; especially on the pars compacta, which functionally produce a neurotransmitter ***"dopamine"*** (Lang and Lozano, 1988). The pathological hallmarks of PD are the depletion of dopaminergic neuron cells and the presence of intracytoplasmic inclusions *"Lewy bodies (LBs)"*. The LBs are combined with protein fibrils called *"α-synuclein"* (Hatano & Hattori, 2011; Cookson et al., 2012). The deterioration of substantia nigra results in the four cardinal manifestations; resting tremor, rigidity, bradykinesia and postural instability (PI) (Jankovic, 2008).

The most commonly used for clinical diagnosis is Unified Parkinson's Disease Rating Scale (UPDRS) as shown in Table 2.1.



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Gaswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

**Fig. 2.1.** An essay on the Shaking Palsy by James Parkinson (Parkinson, 1817)

Parkinson's disease (PD) is also known as a progressive disorder. Patients with PD do not suffer only from its symptoms, but they do also turn from early stage to advanced stage along with their duration of disease (Lang and Lozano, 1988). The disease is divided into 3 main stages; early, moderate and finally advanced stages which causes the problems of encountering side effects of long-term medication (Goudreau, 2006). Severity of the disease is assessed by Hoehn and Yahr scale as shown in Table 2.2 (Michael et al., 2006). The motor symptoms usually occur unilateral side, but gradually spread to the contralateral side. The deterioration of substantia nigra causing PD limits patients' activities daily living (ADL), brings about problems of falls and fractures (Cheng et al., 2014), and finally lowers quality of life (QoL) (Shulman et al., 2008; Tan et al., 2012).

**Table 2.1**

The United Kingdom Parkinson Disease Society Brain Bank's clinical criteria for the diagnosis of Parkinson disease (Gibb & Less, 1988).

| Step | Criteria |
|---|---|
| **1** | Diagnosis of Parkinson's disease<br>- Presence of Bradykinesia<br>At least one of the following criteria<br>- Rigidity<br>- 4 to 6 Hz tremor<br>- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction |
| **2** | Exclusion criteria for Parkinson's disease<br>- History of repeated stroke with stepwise progression of parkinsonian features<br>- History of repeated head injury<br>- History of definite encephalitis<br>- Oculogyric crisis<br>- Neuroleptic treatment at the onset of symptoms<br>- More than one affected relative<br>- Sustained remission<br>- Strictly unilateral features after three years<br>- Supranuclear gaze palsy<br>- Cerebellar signs<br>- Early severe autonomic involvement<br>- Early severe dementia with disturbances of memory, language and praxis<br>- Babinski's sign<br>- Presence of a cerebral tumor or communicating hydrocephalus on computed tomography (CT) scan<br>- Negative response to high dose of levodopa |
| **3** | Presence of at least three of the following supportive prospective criteria<br>- Unilateral onset<br>- Rest tremor present<br>- Progressive disorder<br>- Persistent asymmetry affecting side of onset most<br>- Excellent response (70 to 100%) to levodopa<br>- Severe levodopa induced dyskinesia<br>- Levodopa response for 5 years or more<br>- Clinical course of 10 years or more |

*Epidemiology and Etiology*

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. It is the second most occurred next to Alzheimer's disease (de Lau & Breteler, 2006). PD happens approximately 80% of Parkinsonism. A wide range in age from 20 to 80 with a mean of 55 years of both sexes. The prevalence of PD is approximately 160/100,000, and the incidence is about 20/100,000/year (Rowland, 1995). A study of the world's most populous nations revealed the number of PD increasing from 4.1 to 4.6 million in 2005, which will be rising by double to 8.7 to 9.3 million in 2030 (Dorsey et al., 2007). In Japan, the prevalence and incidence of PD has been studied and found that it had increased, primarily because of the age of population (Yamawaki et al., 2009). Moreover, the projection of PD patients will be highly increasing over the age of 50 in 2005 to 2030 (Dorsey et al., 2007). The incidence rates of PD in Europe were 5/100,000 to 346/100,000 (Campenhausen et al., 2005). The incidence of PD occurring in men was higher than women (Wooten et al., 2004; de Lau & Breteler, 2006). Age has been reported a factor related to increasing the incidence of PD. PD has rapidly developed in the patients after age of 60 (de Lau & Breteler, 2006).

The dominant cause of PD is unknown; however, PD has been reported to be involved with the contribution of multiple genetic and environmental factors (Moore et al., 2005; Hatano, T. and Hattori, N., 2011; Tan, L.C.S., 2013). Mutations of gene encoding *α-synuclein* may be a factor leading to developing of PD. This type of protein has been considered to be relevant to the procedures of dopamine storage (Moore et al., 2005). Regarding the environmental factors, people, who are in risk of developing PD, have been reported the exposure to pesticides, herbicides, farming, iron, and/or live in rural areas or nearby chemical industries (Olanow & Tatton, 1999). Nevertheless, etiological studies have indicated the lower risk of developing PD in caffeine intakes and cigarette smoking (Ross et al., 2000; Hernan et al., 2002; Allam et al., 2004). It was about 60% of non-cigarette smokers to have risk of PD than cigarette smokers, and about 70% of non-caffeine drinkers to have risk of PD than caffeine drinkers in a systematic etiological study (Hernan et al., 2002).

*Pathophysiology*

The pathology of Parkinson's disease (PD) is distinctive. Degeneration of the neuromelanin-containing neurons (a dark pigment) in the brainstem occurs, especially in the substantia nigra pars compacta (SNc); a part of basal ganglia (BG), that gives rise to the nigrostiatal pathway, and in the lucus ceruleus; the surviving neurons contain eosinophilic cytoplasmic inclusions known as *Lewy bodies*, the pathogenic hallmark of the disease (Rowland, 1995; Longstaff, 2005). Basal Ganglia consist of four nuclei; Striatum (caudate nucleus, Putamen), Globus pallidus (Interna; GPi, Externa; GPe), Subthalamic nucleus (STN), Substantia nigra (SN). There are two motor pathways in the basal ganglia; direct and indirect pathways, which both receive the neural circuits from the cerebral cortex from the part of premotor cortex ($M_1$), primary motor area (PMA), supplementary motor area (SMA), and cingulate motor area (CMA) (Lang & Lozano, 1998).

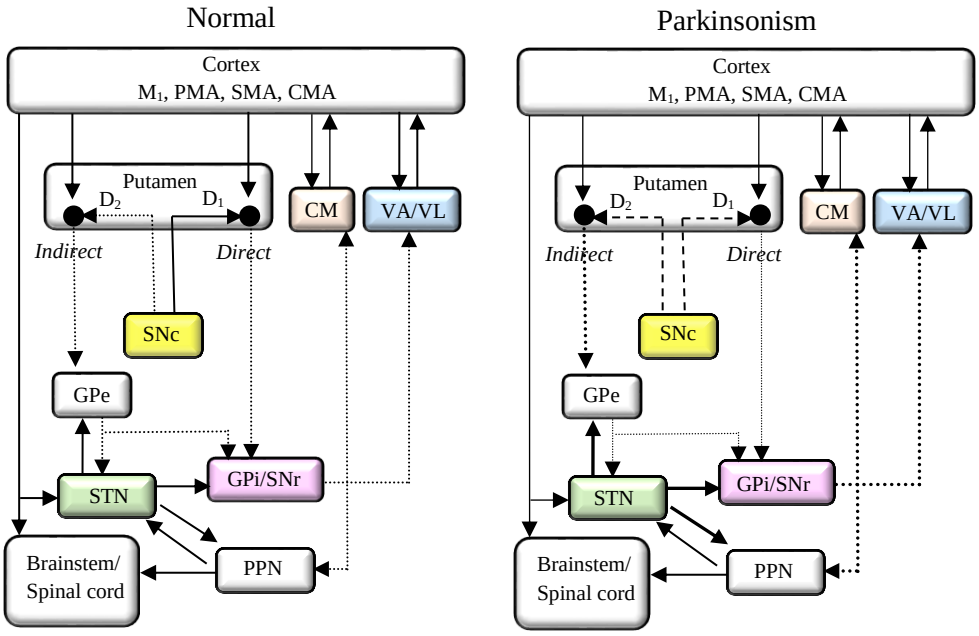



**Fig. 2.2.** Model of basal ganglia comparing between normal persons and patients with Parkinson's disease. Thick lines indicate excitatory pathways, dotted lines indicate inhibitory pathways, and line thickness expresses strength/weakness of stimulation/inhibition. (Lang & Lozano, 1998, modified by the author).

The cerebral cortical input projected to basal ganglia (BG) goes to striatum in the part of putamen. Substantia nigra par compacta (SNc) is the prominent source of dopamine projections. The direct and indirect pathways carry its own dopamine receptors. Dopamine D1 receptors are transmitted in direct pathway, on the other hand, dopamine D2 receptors are transmitted in indirect pathway, which function in stimulating and inhibiting the pathways, respectively (Obeso et al., 2000). In people with normal motor control, in direct pathway, excitatory projection from D1 receptors inhibits functions of GPi/SNr. Interestingly, D2 receptors works oppositely in indirect pathway. Inhibitory projection from D2 receptors inhibits the functions of GPe, which brings about transmitting normal inhibitory output to STN. STN transmits excitatory output to GPi/SNr. At these locations, the inhibitory from direct pathway and the excitatory from indirect pathway are balanced which results in projecting normal inhibitory output from GPi/SNr to inhibit centromedian thalamic nucleus (CM), ventral anterior and ventral lateral thalamic nuclei (VA/VL) and pedunculopontine nucleus (PPN). PPN projects excitatory output to brain stem and spinal cord to control posture and movement normally (Obeso et al., 2000; Visser & Bloem, 2005).

In patients with BG degeneration such as Parkinson's disease (PD), the depletion of dopamine receptors at SNc leads to diminishing both excitatory and inhibitory outputs to putamen in direct and indirect pathways, respectively. In direct pathway, this affects on reducing inhibitory projection to GPi/SNr, which also leads to diminishing inhibitory projection to CM, VA/VL and PPN. In contrast, due to the reduction of D2 receptors in indirect pathway, the inhibitory output projected by putamen to GPe is higher than normal. This output suppresses the function of GPe, so the inhibitory output transmitted by GPe to STN and GPi/Snr is less than normal, which aggravates CM, VA/VL and PPN by increasing the inhibitory projection (Obeso et al., 2000; Visser & Bloem, 2005). The imbalance of neural circuits in the brain occurs causing abnormal motor and non-motor symptoms (Visser & Bloem, 2005; Benitez-Burraco et al., 2016). The degeneration of BG results in problems in various aspects, particularly as regards abnormal movements.

*The relationships of the basal ganglia (BG) to the major components of the motor system.*

The basal ganglia (BG) and the cerebellum maybe viewed as key elements in two parallel reentrant systems that receive input from and return their influences to the cerebral cortex through discrete and separate portions of the ventrolateral thalamus (VA). They also influence the brain stem and, ultimately, spinal mechanisms (Eric et al, 2000). The distinct roles of BG are known in motor and cognitive functions. BG is involved in enabling of training motor performances, voluntary movements, and balance control. It stores motor programs in the motor cortex (Visser & Bloem, 2005; Knierim, 2015). The other function is owing to the association between BG and prefrontal cortex. BG is also involved in enabling and selecting cognitive, executive, motivational/ emotional programs (Leisman et al., 2014; Knierim, 2015). The relationship of the BG, the cerebral cortex and the cerebellum are complex and have not been clear (Fig. 2.3). However, previous studies revealed the inter-connections of BG, motor and cognitive functions regarding the problems occurring on BG (Obeso et al., 2000; Santens et al., 2003; Lewis et al., 2013; Visser & Bloem, 2005; Meireles, 2012; Leisman et al., 2014; Aarsland, 2016).

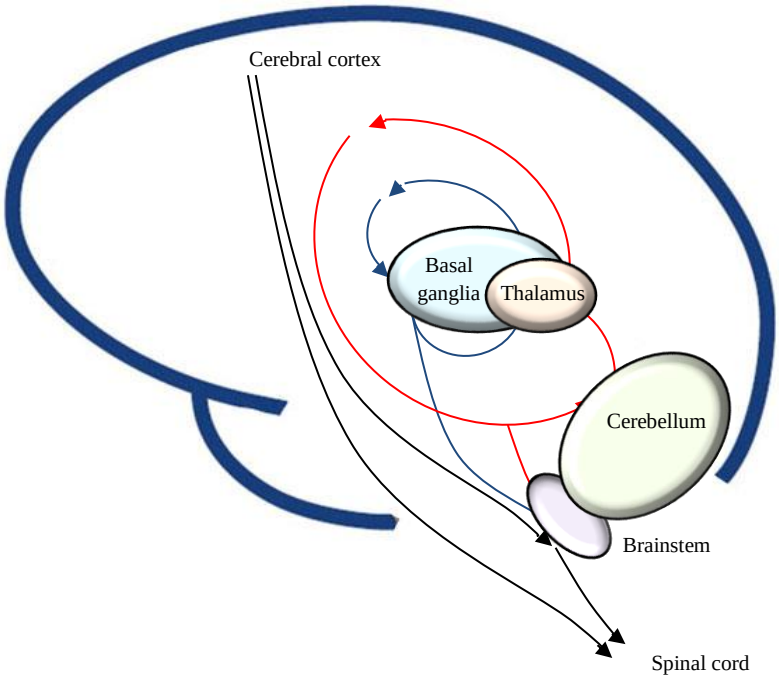



**Fig. 2.3.** The relationship of the basal ganglia to the major components of the motor system. (Eric et al, 2000, modified by the author)

The inter-connection between BG and the related regions; cerebral cortex, thalamus, pons, and cerebellum for cognitive function was described by Leisman et al., 2014. This was considered to substantiate a cortico-striato-thalamo-cortical loop, which functions in cognition rather than motor control. Problems causing degeneration of BG lead mainly to subthalamic nucleus (STN) and striatum. The function of projecting output to pons form STN is reduced disturbing the circuits as exemplified in Fig. 2.4.

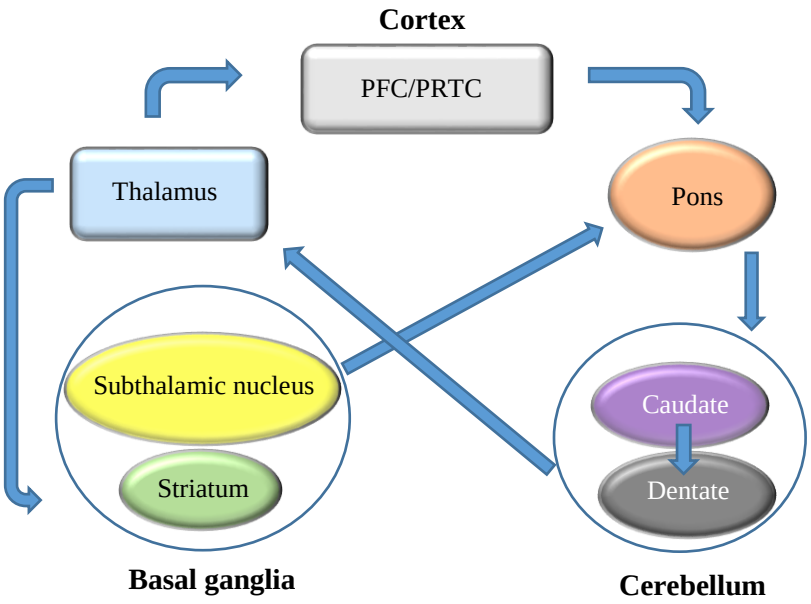



**Fig. 2.4.** Model of cerebellar modulation of cognition. (Leisman et al., 2014, modified by the author)

*Basal ganglia (BG) and postural control*

It has long been regarded to the predominant functions of BG involved with motor control such as controlling posture, correcting movements and working in cognitive function, motivational and emotional behavior. Nevertheless, recently BG are recognized to play an additional role in sensory processing, cognition and behavior. BG functions might be relevant to executive function, motor planning and programming, muscle tone control, motor flexibility, sensory-motor integration, postural response. The damages of BG will aggravate normal postural control causing balance disturbances. (Visser & Bloem, 2005). The common manifestation of patients with BG dysfunction is shown in Table 2.2 (Visser & Bloem, 2005).

**Table 2.2**

Basal ganglia function which might be associated with postural control (Visser & Bloem, 2005)

| Basal ganglia function | Symptoms |
|---|---|
| • Storing and automatic execution of motor plans | • Gait akinesia / freezing |
| • Motor flexibility, adaptive behavior to environmental changes | • Postural inflexibility |
| • Somatosensory integration | • Stooped posture<br>• Contraversive pushing |
| • Muscle tone regulation | • Axial stiffness |
| • Gain control of automatic postural responses | • Exaggerated destabilizing responses<br>• Diminished stabilizing responses<br>• Co-contraction |
| • Cognition, motivation and emotional aspects of behavior | • Impaired scaling of postural responses under conditions of uncertainty<br>• Fear of falling |

*Clinical features of Parkinson's disease (PD)*

**Primary motor symptoms**

There are four cardinal features represented Parkinsonism; tremor, rigidity, bradykinesia, postural instability.

*Tremor:* The tremor observed in PD is present at rest, it usually disappears or decreases with movement. It shows the rhythm about 4-7 Hz.

*Rigidity:* The rigidity of PD may be characterized as either "lead pipe" or "cogwheel." The *cogwheel* type of rigidity is a combination of *lead-pipe rigidity with tremor*. In rigidity, there is an increased resistance to movement throughout the entire range in both directions without the classic clasp-knife reflex characteristic of spasticity.

*Bradykinesia:* Bradykinesia (a decrease in motion) and akinesia (a lack of motion) are characterized by an inability to initiate and perform purposeful movements. They are also associated with a tendency to assume and maintain fixed postures. All aspects of movement

are affected, including initiation, alternation in direction, and the ability to stop a movement once it is began.

*Postural Instability:* Postural instability or loss of postural reflexes occurs later in the disease. The patient has difficulty righting himself after being pulled off balance. It is a serious problem in Parkinsonism that leads to increase episodes of falls.

**Secondary motor symptoms**

*Flexed posture:* As the disease progresses, the patient begin to assume a flexed posture, particularly to the elbows, knees, thorax, and neck. Eventually, the flexion can become extreme. The patient begins to walk with the arms flexed at the elbows and forearms placed in front of the body, and with decreased arm swing. With the knee slightly flexed, the patient tends to shuffle the feet, which stay close to the ground and are not lifted up as high as in normal; with time, there is loss of heel strike, which would normally occur when the foot moving forward is placed onto the ground.

*Gait festination:* This is a gait characterized by a progressive increase in speed and shortening of stride as if the individual is trying to catch up with his or her center of gravity. Forward festination is called "propulsion", backward festination is known as "retropulsion". The festinating gait may be caused by the decreased equilibrium responses.

*Freezing:* The freezing phenomenon usually begins with start hesitation, that is, the feet take short, sticking, shuffling steps before the patient can begin walking. With progression, the feet seem to walk through a crowded space or when trying to move fixed distance in a short period of time (Umphred, 1995; Goetz, 2007).

**Non-motor symptoms**

*Rapid eye movement (REM) sleep disorder:* This is characterized by lack of muscle atonia during REM sleep and enactment of dream content. RBD is relevant to PD and has high incidence in PD patients. PD patient with RBD mainly presents rigid type, has longer disease duration, more

severe motor and non-motor symptoms and poorer activity of daily living (ADL) and life quality (Hu & Zhang, 2015).

*Cognitive dysfunction:* About one quarter to one third of PD patients have mild cognitive impairment (MCI). Dropping in the level of dopamine brings about cognitive change in PD, which is involved in regulating the body's movements. The cognitive changes related to dopamine declines are typically mild. The cognitive impairment in PD has a tendency to be limited to one or two mental domains, and their severity will vary individually. The domains most often affected executive functions, attention difficulties, slowed thinking, word-finding, learning and remembering information, memory sparing, imagery and spatial processes (Parkinson's disease foundation, 2015).

## Stages of the Disease

Parkinson's disease (PD) is a progressive disorder. Usually the initial symptom is a resting tremor or micrography (bradykinesia of the upper extremity) unilaterally. With time rigidity and bradykinesia are seen and postural alterations begin to occur. This commonly starts with an increase in neck, hip, trunk and hip flexion, which accompanied by a decrease righting and equilibrium responses, leads to a decreasing ability to balance. Table 2.3 demonstrates the Hoehn and Yahr staging of PD, we can see the stages of Parkinson's disease (PD) run from the mild stage (stage 1) to the severe stage (stage 5) which illustrates the level of inability or in need of assistance. (Michael et al., 2006)

Table 2.3

Modified Hoehn and Yahr (1967) staging (Michael et al., 2006)

| Stage | Criteria |
|---|---|
| Stage 0 | No sign of disease |
| Stage 1 | Unilateral disease |
| Stage 1.5 | Unilateral plus axial involvement |
| Stage 2.5 | Mild bilateral disease, without recovery on pull test |
| Stage 3 | Mild-to-moderate bilateral disease; some postural instability; Physically independent |
| Stage 4 | Severe disability; still able to walk or stand unassisted |
| Stage 5 | Wheelchair bound or bedridden unless aided |

*Treatments*

*Pharmacological approaches:* There is good evidence for curing PD symptomatic conditions with pharmacological approaches. The principles of pharmacological treatments are to substitute dopaminergic substance diminishing from the deterioration of BG and to relief symptomatic conditions with slow progression of the disease. An evidence-based review of the initial pharmacological management of the classic motor symptoms of PD identified literature between January 1985 and February 2014. The study was revealed levodopa is the most effective medication for treating the motor symptoms of PD (mild symptoms and age < 60 years), such as monoamine oxidase type B inhibitors [MAOBIs], amantadine, anticholinergics, β-blockers, or dopamine agonists, which may be to avoid motor complications related to levodopa therapy Connolly & Lang, 2014).

Medication-related motor complications such as motor fluctuations and dyskinesia, and other medication adverse effects such as nausea, psychosis, and impulse control disorders and related behaviors are the side effects of taking long-term medication (Olanow et al., 2004; Connolly & Lang, 2014). Levodopa therapy has been reported its effects on postural instability (PI) in PD. A study reported that anticipatory postural adjustments is not affected by levodopa, but refining postural adaptation with task experience is accompanied by levodopa (Hall et al., 2013).

The relationship between PI freezing of gait (FOG) was studied along with the effects of medication. It is noted that although the interaction among PI, FOG, axial motor disability remains complex, the cortico-subcortical networks are involved with FOG and dopaminergic networks In addition, PI are correlated with severity of FOG (Nantel & Bronte-Stewart, 2014). Levodopa was also indicated its effects in improving postural control mechanisms in early PD (Beuter et al., 2008). Dopaminergic medication has not only been reported the efficacy toward PI, but it has been also indicated in normalizing sensory-motor performances and inducing deficits in the processing of proprioceptive information (Mongeon et al., 2009). However, in advanced stages, PD patients are less likely to respond to supra-maximal levodopa dose (Fabbri et al., 2016).

*Non-pharmacological approaches:* A number of non-pharmacological approaches have been indicated for improving physical activities, cognitive training and brain stimulation. A study of an evidence-based analysis of physical therapy in PD revealed specific treatments for PD; cueing strategies to improve gait, posture, and the confidence to carry, cognitive movement strategies to improve transfers, exercise to improve balance and training of joint and muscle power to improve physical capacity (Keus et al., 2007; Keus et al., 2009). Currently, pharmacological studies to improve cognitive function have been limited; however, there are techniques proposed to increase cognitive ability in PD patients (Hindle et al., 2013). A technique was proposed to train cognitive function and improve postural control by Makizako et al., 2013. By implementing a cognitive task concomitant with a balance task, attention was demanded to complete both of the tasks, which improved both cognitive function and balance control simultaneously.

Deep brain stimulation (DBS) is a strategy to cope with the motor complications of PD, which mimic the effects of levodopa therapy. Acute and long-term results after a DBS operation show a dramatic and stable improvement of a patient's clinical condition. DBS may involve mechanisms causing abnormal neural projections in PD (Benabid, 2003). Most patients corresponding to DBS are relatively young onset of PD, and are aged less than 70 years at the time of surgery (Pollak, 2013).

## 2.2. Postural instability (PI) in Parkinson's disease (PD)

Postural instability (PI) is one of the most common cardinal features occurring in PD. It is a motor symptom criterion that neurologists and movement disorder specialists observe and evaluate to diagnose the disease. Normal postural control requires the integration of the information stemming from the three main sources; visual, vestibular, and proprioceptive (Watson & Owen, 2014), which will be processing in the central nervous system. According to the deterioration of BG, PD patients manifest postural control abnormality, which leads to disturbing the normal balance mechanism (Jankovic, 2008; Fukunaga et al., 2014).

Generally, the problems of PI are mentioned when PD patient turn to advanced stages of the disease (Horak et al., 1992). PI results in falls, immobilization, disabilities and long-term caring (Pickering et al., 2007; Duncan et al., 2012). Fear of falling and/or lack of balance confidence occur in patients with PD and balance disturbances (Adkin et al., 2003; Lee et al., 2016). Impaired postural control in Parkinson's disease (PD) can be indicated by the abnormalities of weight distribution, the ability to control body sway and the frequency of falls (Fukunaga et al., 2014; Doná et al., 2016).

PI can be induced by dyskinesia; especially in "ON" time dyskinesia causing the increase of COP net displacement in PD which mainly influence on the changes of balance control (Armand et al., 2009; Franchignoni et al., 2005). Consequently, PI will bring about the high incidence of falls and decrease the quality of PD patients' lives (Wood et al., 2002; Mak et al., 2009). Causes of PI are diverse. The impairment of balance, loss of postural reflexes, presenting gait disturbances, or orthostatic hypotension are the factors which lead to PI, and finally bring about falls and long term hospitalization (Pickering et al., 2007; Matinolli et al., 2009).

PI has been related to Hoehn & Yahr scale, duration of disease, and UPDRS motor score (Geurts et al., 2011; Amboni et al., 2015). Amboni reported that Parkinson's disease (PD) patients with freezing of gait (FOG) showed significant relationship of Hoehn & Yahr scale, and UPDRS part II (Amboni et al., 2015).

## 2.3. Abnormal standing balance in Parkinson's disease (PD)

### 2.3.1. Deterioration of sensory system

It has been formerly known that basal ganglia (BG) dysfunction attributes to the impairments of sensory organization (Chong et al., 1999; Abbruzzese & Berardelli, 2002; Jacobs & Horak, 2006; Vaugoyeau & Azulay, 2010). Based on the sensory integration of human balance; visual, vestibular and proprioceptive systems, PD patients experience the problems of balance dysfunction (Pasma et al., 2014; Rinalduzzi et al., 2015). The impairment of visual - postural circuit related to BG plays role in controlling posture. (Bronstein et al., 1990; Pasma et al., 2014; Rinalduzzi et al., 2015). Postural abnormalities in PD are involved with the malfunction of sensorimotor system (Adamovich et al., 2001; Carpenter et al., 2004; Vaugoyeau & Azulay, 2010). Several studies emphasized on the disequilibrium of postural stability induced by the interruption of the sensory inputs (Pastor et al., 1993; Khudados et al.,1999; De Nunzio et al., 2007). To compensate the proprioceptive impairment, PD patients require the other sensory inputs such as visual and vestibular to orientate and stabilize posture (Pastor et al., 1993; Vaugoyeau et al., 2007; Vaugoyeau et al., 2011). The relationships between postural control and FOG have been reported which are also related to the sensory deficits (Nantel et al., 2012; Pelykh et al., 2015; Schlenstedt et al., 2016; Huh et al., 2016).

Since the impairments of postural control in PD are not homogenous and the association between PI and FOG are unclear (Blaszczyk & Orawiec, 2011). Recent clinical assessments have been utilized to evaluate the problems, however, there are multi-components subside. It is obscure to explain relationship between PI, FOG and visual input on multi-clinical assessments to detect subclinical PI.

2.3.2. Deterioration of motor system

One physiological factor causing PI is muscle hypertonicity. To maintain normal posture, muscle tone must remain in its normal state. PD patients experience muscle hypertonicity which is the impaired ability of motor neurons in regulating descending pathways increasing excitability of muscle spindles (Double & Crocker, 1995). Abnormal muscle tone causes the inability of controlling postural muscles for maintaining normal balance. This leads to PI in PD. Due to the main motor symptoms of the disease; tremor, bradykinesia, rigidity, and postural instability (PI), the problems of freezing of gait (FOG) and balance dysfunction are commonly found in advanced stages of the disease. FOG is a parkinsonian gait characterized by small steps, shuffling gait, feeling one's feet are glued to the ground, and/or difficulty of stepping forward which represents muscle hypertonicity (Jankovic, 2008; Rinalduzzi, Trompetto, & Marinelli, 2015).

Patients with PD generally face the problem of arm swing reduction. It can occur in both early and advanced stages of the disease. Researchers have been interested in arm swing asymmetry by conducting studies to discover the effects of arm swing toward various variables in PD. As the effects of the disease, both symmetry of arm swing and coordination are reduced. Huang and the colleagues reported that PD had higher arm swing asymmetry (ASA) significantly different from the controls. They attached accelerometer on subjects' wrist to investigate arm angular acceleration which found that ASA was significantly correlated with the UPDRS score [limbs], on the other hand maximal cross-correlation (MXC) was significantly correlated with the tremor subscore [limbs] (Huang et al., 2012). Roggendorf and the colleagues studied the arm swing asymmetry during walking on treadmill by utilizing ultrasound based motion analysis. They found that PD with Hoehn & Yahr stage I and stage II had the same result of arm swing reduction on more effected side (MAS). The movement of arm in retroversion was highly significant difference between early PD and controls (Roggendorf et al., 2012). Lewek and colleages et al. studied the arm swing magnitude and asymmetry to find out the benefit in the evaluation of early PD. They found that PD patient had significantly different in arm swing asymmetry when compared with control subjects. However, the result of arm swing magnitude had no significant difference between the PD and control (Lewek et al., 2010). Arm swing in PD patients with FOG has a tendency to reduce more than without FOG.

In addition, losing balance and facing falls result in the inability to control center of mass (COM) within center of pressure (COP). Once, COM is shift out of COP, a tendency to fall occurs (Swanenburg et al., 2013 & Horak et al., 2015).

### 2.3.3. Deterioration of cognitive function

Cognitive impairment (CI) is an important problem for Parkinson's disease (PD) patients. It is a common non-motor symptom that could occur in the early stages, and develop progressively in the advanced stages of the disease (Dujardin, Moonen, & Behal, 2015; Mak, Su, & Williams, 2015). The degree of CI in PD ranges from mild cognitive impairment (PD-MCI) to dementia (PDD), resulting in burden to family members and caregivers (Mak et al., 2015). The onset of cognitive decline in PD is often associated with older age, lower level of education, greater disease severity, postural instability (PI) and gait difficulty subtype (PIGD), and a long duration of the disease.

Several studies reported interferences between postural control and cognitive tasks passing the visuospatial pathways. Attentional demands such as auditory cues and cognitive tasks have been applied to distract cognitive function to evaluate stabilizing posture capability (Cook, 2000; Kelly, Johnson, & McGough, 2015; Nantel, McDonald, Tan, & Bronte-Stewart, 2012). To maintain normal human balance, there are three systems required; sensory input (visual, vestibular, proprioceptive), integration (cerebrum, cerebellum, basal ganglia (BG)), and motor output (vestibulo-ocular reflex, motor impulses for eye movements, motor impulses which help adjusting posture) (Peterka, 2002; Watson & Owen, 2014). In normal state, the inputs and motor outputs are in equilibrium. In PD, according to the degeneration of BG, the loss of dopaminergic neurons in PD affects several subcortical pathways, which lowers the capability of distributing motor outputs and brings about the motor symptoms (Santens, Boon, Van Roost, & Caemaert, 2003) causing PI in PD patients. PI is one of the parkinsonian motor symptoms that usually occurs at the later stage of the disease, with increased risk of falling and near falls in PD patients, resulting in poor quality of life (QoL; Balash et al., 2005; Lachman et al., 1998). Cognitive decline has been reported that it is associated with PD patients with PIGD. PD patients with PIGD and CI have a high tendency to develop dementia as well (Meireles & Massano, 2012) as illustrated in Fig. 2.5.

CI is well-known in PIGD patients with FOG (Heremans, Nieuwboer, & Spildooren, 2013; Maruyama & Yanagisawa, 2006; Morris, Iansek, Smithson, & Huxham, 2000). This is because prefrontal cortex and BG play important roles in both cognitive and gait functions. Deterioration of these pathways may affect each other and cause FOG, CI, and PI, as well as the impairments of the frontostriatal neural circuitry leading especially to CI (Kelly et al., 2015; Lewis, Dove, & Robbins, 2003; Mahoney, Holtzer, & Izzetoglu, 2016).

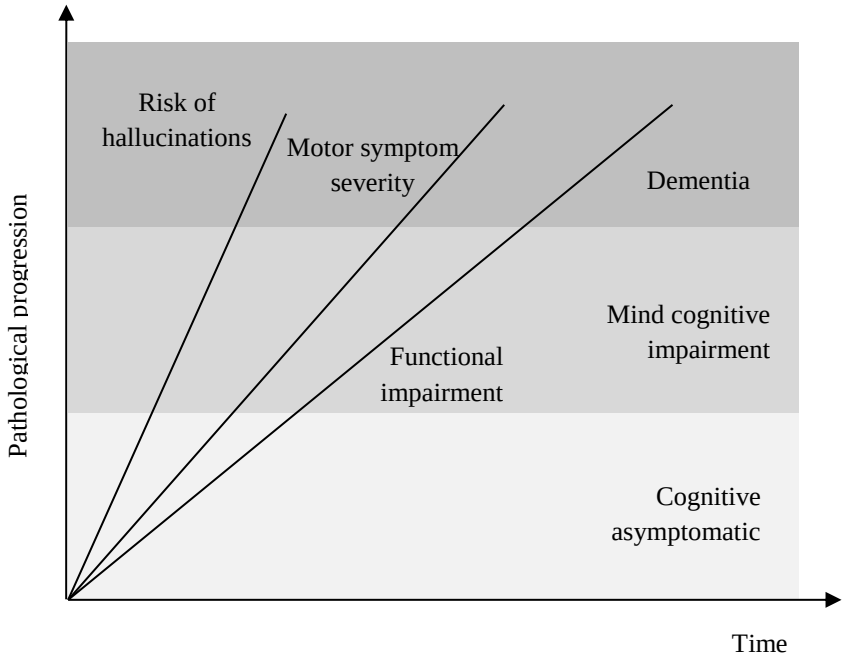



**Fig. 2.5.** The progression of PD with the mild stage of cognitive impairment until the stage of dementia (Meireles & Massano, 2012)

## 2.4. Freezing of gait (FOG) in Parkinson's disease

Definition

Freezing of gait (FOG) is a common and disabling motor symptom in patients with PD. It is defined as *"brief, episode absence or marked reduction of forward progression of the feet despite the intention to walk"* (Nutt JG et al., 2011). This episodic gait pattern can bring about

postural instability (PI), increase fear of fallings and finally lead to falls, fracture and immobility (Bloem et al., 2004; Franchignoni et al., 2005; Genever et al., 2005; Robinson et al., 2005; Voss et al., 2012; Morris et al., 2011). Medications; mainly levodopa, provides less effects to the patients in long term receiving treatment which causes side effects to the patients. There are two phases of medication; "On" and "Off", which the medication provides effects and no response to the patients, respectively (Morris et al., 2001). FOG also generally found in patients with motor fluctuations which are the clinical manifestation mostly experience when the disease progresses (Nutt et al., 2011).

Pathophysiology of Freezing of Gait (FOG)

The main problem of freezing of gait (FOG) results from the abnormality of basal ganglia circuit (Lewis & Barker 2009). The reduction of dopamine at the substantia nigra leads to the over activity of the GPi/SNr output nuclei resulting in the magnificent inhibition on both the thalamus and pedunculopontine nucleus (PPN), causing the decrease of the excitatory nuclei to the cerebrum and the spinal cord (Lewis & Barker 2009).

Characteristics of Freezing of Gait (FOG)

Recently researchers has discovered and identified the characteristics of FOG; however, it is unclear explaining the pathophysiology of the symptom. FOG is a type of gait disturbances expressing when PD patients start walking or turning. Nutt et.al reported that the unique aspects of the gait could be defined into six types; Initiating gait, turning, stopping, avoiding obstacles, adapting locomotion to the person's goals (Nutt et al., 2011). The most recent review about PD symptoms indicated that FOG could be found in both legs and fingers, which mostly discover when the patients are turning, in narrow pathways, or in stressful situations (Nutt et al., 2011). PD patients generally experience FOG by facing with the difficulty of leaving the foot from the ground. The feeling of the feet are being glued to the ground is common reported by the patients. The frequency of legs trembling happens about 3-8 Hz. Step length is decreased, while cadence is increased. However, it is special that various types of cues (Nutt et al., 2011) can solve FOG.

Previous study reported significant difference between PD patients with (PD+FOG) and without FOG (PD-FOG) on FOG-Q score (Vervoort et al., 2013). FOG has been reported the association of duration of disease and duration of levodopa therapy (Giladi et al., 1992; Giladi et al., 2001). Contrarily, no significant differences were found on duration of disease and UPDRS (part III) motor score (Vervoort et al., 2013). Static postural control has been analyzing between PD+FOG and PD-FOG by Nantel and Bronte-Stewart, 2014. They found the correlations between severity of FOG and antero-posterior excursion and medio-lateral velocity.

Although postural instability (PI) is a common cause leading to fall in patients with PD, freezing of gait (FOG) is also found as a confounding factor of falls in Parkinson's disease (PD) (Bloem et al., 2004; Johnson et al., 2013; Huh et al., 2016).

## 2.5 Physical therapy in neurorehabilitation for Parkinson’s disease (PD)

Physical therapy is the most common used form for alleviating physiological dysfunctions or in allied health care for PD (Nijkrake et al., 2006). Physical therapist (PT) is a physical medicine and rehabilitation specialty that remediates impairments and promotes mobility, function, and quality of life through examination, diagnosis, prognosis, and physical (Physical Therapy, 2015). Neurorehabilitation for Parkinson's disease (PD) is a complex medical process for recover functional problems originating from a nervous system deterioration leading to developing PD, and to alleviate problems and improve physical functionality of PD patients (McDowell, 1994; Carter et al., 2011; Nudo, 2014; Krucoff et al., 2016). Physical therapist's functions are diverse; screening, examination, evaluation, diagnosis, prognosis, plan of treatment, intervention and prevention (Nudo, 2014; Dijkers et al., 2012). In the part of intervention, there are various physical modalities in the treatment of neurological dysfunction, which will be optimized in appropriate ways regarding nervous system injury (Galea et al., 2012).

The main goal of physical therapy for PD are to improve physical capability from physical limitations such as gait and balance problems, activities daily living (ADL) dependency. By increasing strength, mobility, endurance and correcting posture as well as training to regain

patterns of normal movements (Mutch et al., 1986; Keus et al., 2004). Physical therapy treatments are diverse depending on specific physiological limitation, goal setting, and treatment plans. Keus et al., 2009, presented the six specific dominant parts for physical therapy. By indicating the treatment goals in three sections according to the limitations and Hoehn and Yahr scale for the specific goals of improving transfers, posture, reaching and grasping, balance and gait, and physical capacity as illustrated in Fig. 2.6.

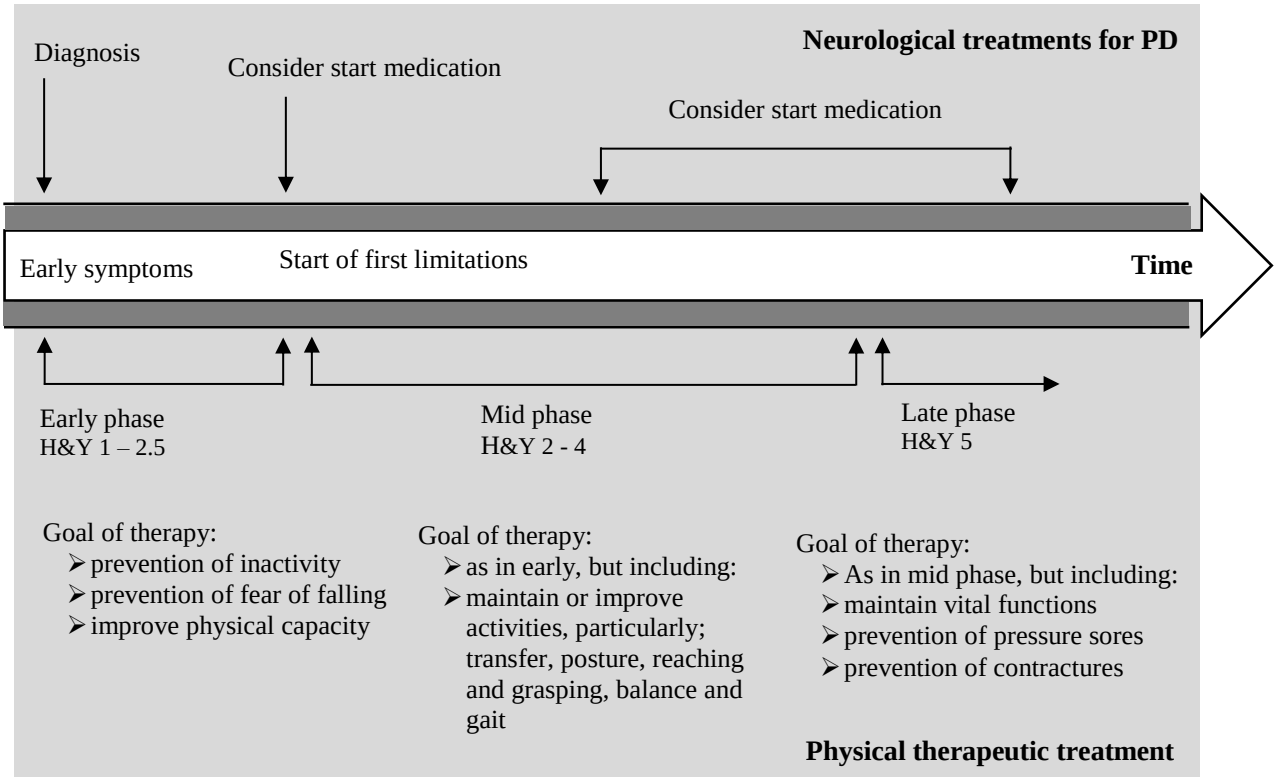


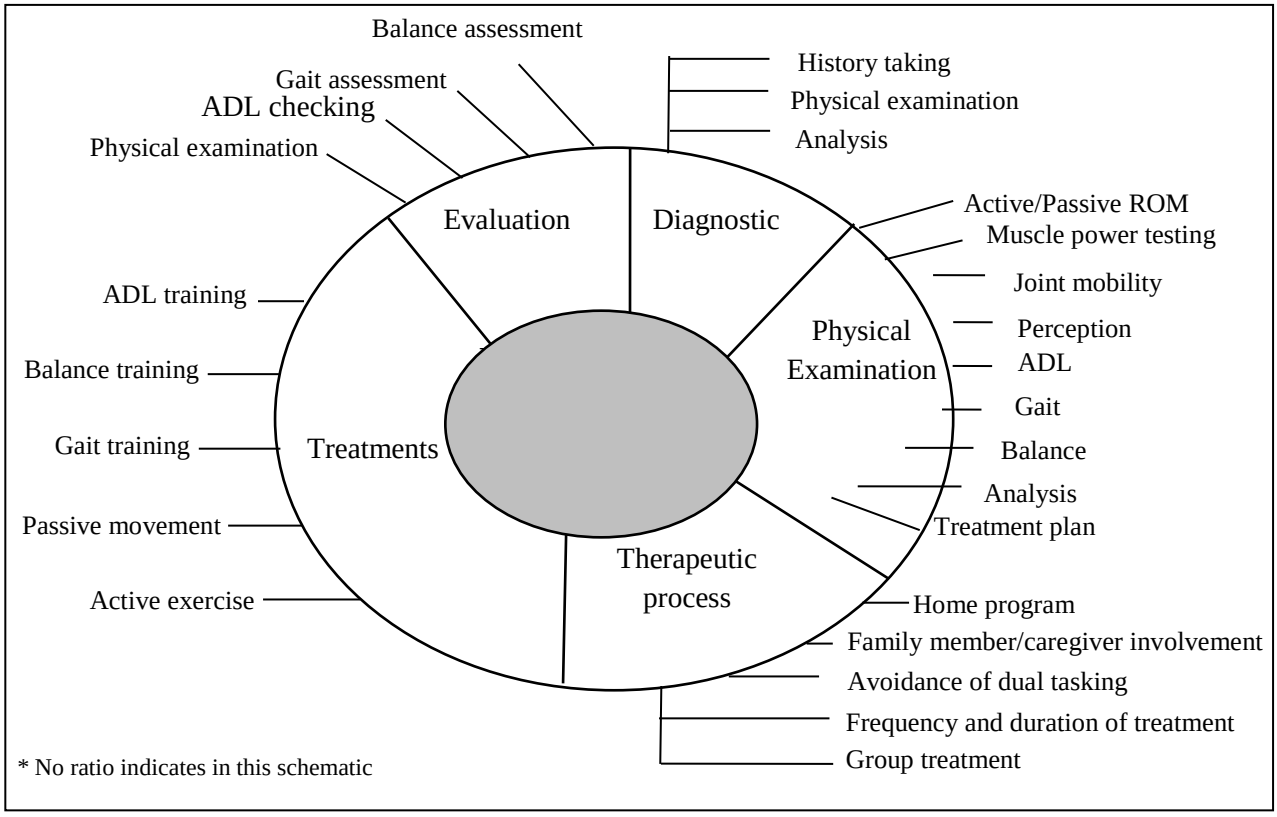

**Fig. 2.6.** Model of specific treatment goals in neurorehabilitation for PD (Keus et al., 2009)

The goals of treatment in physical therapy can be categorized into three phases, early, mid and late. In early phase (H&Y 1 – 2.5), most PD patients visit physical therapists with the problems of low activities comparing in the past, lack of balance confidence as usual and have a feeling of fear of falling, as well as the limit physical capacity. In mid phase (H&Y 2 – 4), treatments can be maintained; however, the patients present more physically inactive such as poor posture, limit ability to transfer independently, poor gait and balance. In late phase (H&Y 5), the patients manifest more physical dysfunction. Most of the patients are in bed ridden. Physical therapy

treatments from mid stage are in need to be maintained. In addition, concerning the vital functions and pressure sores as well as contractures are the main the goals in this phase.

PTs play an important role in allied health care and neurorehabilitation for Parkinson's disease in improving physical functions and quality of life of PD patients. The role can be divided into five main segments; diagnosis, physical examination, therapeutic process, treatments and evaluation. The details of each part are as exemplified in Fig. 2.7.

**Fig. 2.7.** Practical Model for Neurorehabilitation in Parkinson's disease



Treatment strategies

Cueing strategies; visual, auditory, tactile, attention

*Visual Cues:* PD patients have good responses toward visual cues during obstructing with the FOG phenomena. For example, stripes on the floor, laser cues or walking stick by which the patients step forward the cues to solve the problem of FOG. Showing how to lift the leg up and step forward (Lee et al., 2012; Cancela et al., 2014).

*Auditory Cues:* Auditory cue is considered an option for solving the FOG problem and gait related activities in PD (van Wegen et al., 2006; Lee et al., 2012). A study of auditory cue and FOG has been conducted to study the effects of the cuing on gait. It is noted that actionrelevant sensory cues induced greater reductions in temporal variability (Young et al., 2016). Nombela and colleagues reviewed the influence of rhythm on PD. They explained how rhythm facilitate movement and enhance motor performance, which is involved the process of neural circuits related to the neuro-functional circuits of PD. It is known that rhythmical stimulation can facilitate movement and may influence to sequential movements, which are needed for PD (Nombela et al., 2013).

*Tactile Cues:* Applying a manual technique by tapping at hip joints each side reciprocally during walking (Lim et al., 2005). Tactile cue is considered one of cueing strategies in order to solve gait problems in PD patients. However, there is unclear in the results of the effects of the cue and the proprioceptive deficits on gait in PD (Lee et al., 2012; Cancela et al., 2014). Tan and the colleagues studied the proprioceptive deficits in PD with and without FOG. They used vibration to the patellar tendon to be an input for tactile stimuli. They found that the tactile stimuli provided significant response to PD patients with FOG (Tan et al., 2011).

*Attention:* Ask the patients to focus on a task wishing to do. For example, if a patient wants to go to a kitchen, then he needs to emphasize on his goal by focusing on his legs and each step of walking to go to the kitchen successfully (Lim et al., 2005).

# CHAPTER 3

# METHODOLOGY

This chapter describes the outline of research methodology to show all of the processes of conducting research in this dissertation. The step of research activities are summarized in Fig. 3.1. The detail of each chapter is abbreviated to provide in overall view in Table 3.1. In briefly, the research methodology in this dissertation includes (i) the study of sensory session which aims to understand the effects of visual inputs on postural instability (PI) (ii) the study of motor session which determined the effects of arm swing patterns on postural control (iii) a study of auditory cues in the part of motor session which expressed the effects of the cues on PI (iv) cognitive session is performed to understand its impacts on PI.

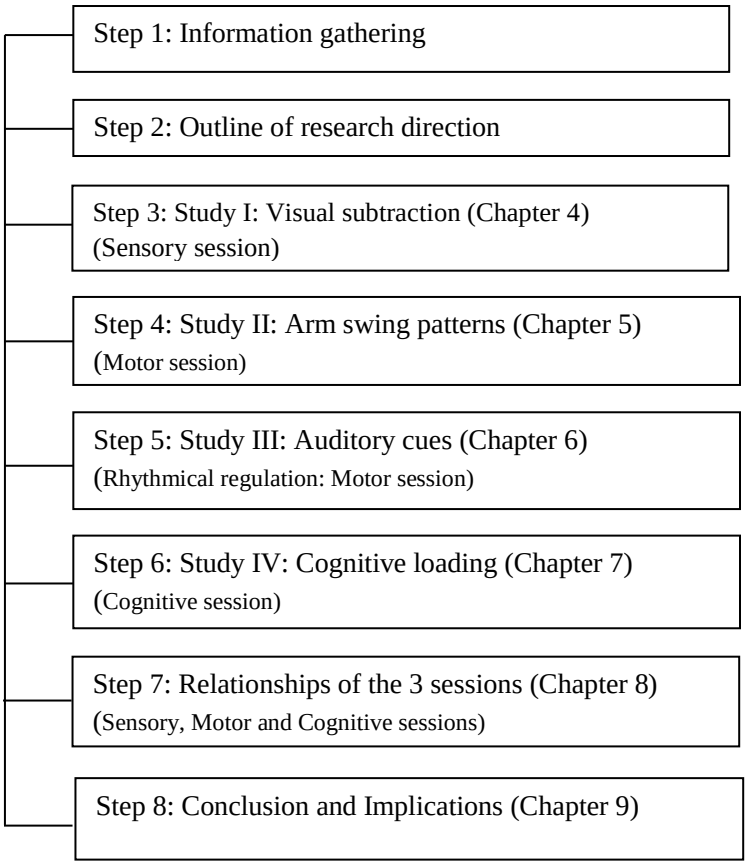



**Fig. 3.1.** Outline of research methodology

**Table 3.1**

Outline of the four experimental and one descriptive studies

| Content | Chapter 4 | Chapter 5 | Chapter 6 | Chapter 7 | Chapter 8 |
|---|---|---|---|---|---|
| Main objectives | To elucidate visual subtraction (VS) distributing to postural instability and freezing of gait (FOG) in patients with Parkinson's disease (PD) to explain relationships of VS, PI and FOG. | To evaluate the relationship between arm swing patterns and clinical assessments in Parkinson's disease (PD) patients with different stages of disease. | To determine the effects of auditory cues on postural instability in patients with Parkinson's disease (PD). | To study the impact of cognitive loading toward postural stability in Parkinson's disease (PD) patients with freezing of gait (FOG). | To propose the relationships of sensory, motor and cognitive deficits toward postural control in Parkinson's disease (PD). |
| Methods | Open eyes - Close eyes during balance test | Arm swing; Alternation - Synchronization during balance test | Arm swing; No cues and Auditory cues during balance test | Cognitive loading; Reading - Counting backward during balance test | Integrate results of the sensory, motor and cognitive sessions |
| Outcome measures | Posturographic parameters | Posturographic parameters | Posturographic parameters | Posturographic parameters | Posturographic parameters |
| Statistical analyses | Kolmogorov-Smirnov, Mann-Whitney U test, Wilcoxon Signed-Rank test, Principal Component Analysis (PCA), Multiple Regression analysis, Odds Ratio analysis. | Kolmogorov-Smirnov, Mann-Whitney U test, Chi-square test, Wilcoxon Signed-Rank test, Spearman's Rho correlation, Multiple Regression analysis, Odds Ratio analysis. | Kolmogorov-Smirnov, Mann-Whitney U test, Chi-square test, Wilcoxon Signed-Rank test, Spearman's Rho correlation. Multiple Regression analysis, Odds Ratio analysis. | Kolmogorov-Smirnov, Mann-Whitney U test, Chi-square test, Wilcoxon Signed-Rank test, Spearman's Rho correlation. Multiple Regression analysis. | Principal Component Analysis (PCA), Odds Ratio analysis. |
| Implementations | A balance assessment, Guidelines for screening and evaluating balance in PD. Applications on mobile phone/NWBB. | A balance assessment, Guidelines for screening and evaluating balance in PD. Applications on mobile phone/NWBB. | A balance assessment, Guidelines for screening and evaluating balance in PD. Applications on mobile phone/NWBB. | A balance assessment, Guidelines for screening and evaluating balance in PD. Applications on mobile phone/NWBB. | A balance assessment, Guidelines for screening and evaluating balance in PD. Applications on mobile phone/NWBB. |

## 3.1 Participants

Sixty patients with PD were recruited from Thammasat University hospital, Thailand to participate in this study. All PD patients were diagnosed by neurologists and provided informed written content before starting the study. This study was approved by the Ethics Board Committee of the Faculty of Medicine, Thammasat University (MTU-EC-IM-1-056/58). General demographic data and clinical scores were recorded. The inclusion and exclusion criteria for recruiting the subjects are as follows;

*Inclusion criteria*

PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria (UKPDSBB) (Hughes et al. 1992). Clinical staging of PD were classified according to the Modified Hoehn and Yahr scale (H&Y) (Hoehn and Yahr 1967). Patients who were age range 30 – 80 years, able to stand independently for at least 3 minutes and regular follow - up were included to this study.

*Exclusion criteria*

Patients who were with other neurological problems, atypical parkinsonism e.g. vascular parkinsonism, parkinsonism plus, drug-induced parkinsonism, motor weakness such as severe sensory neuropathy and cerebellar ataxia, unable to stand still without support, severe dyskinesia, psychological problems, vestibular dysfunction, postural hypotension, and partial or complete blindness or deaf were excluded.

All subjects with PD were tested during the on-time medication, which was received the effects of medication without presenting excessive rigidity, bradykinesia or tremor.

The participants were allocated among different studies as shown in Fig. 3.2.

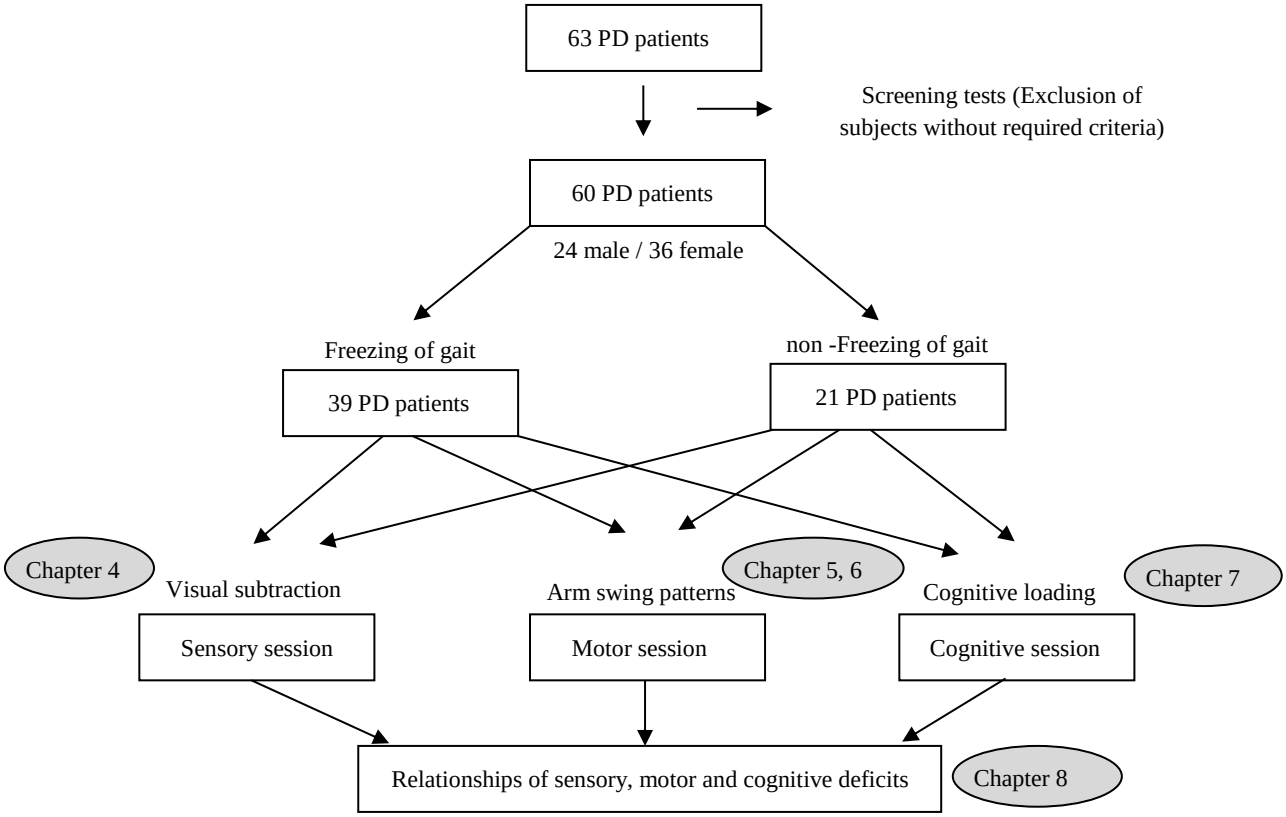



**Fig. 3.2.** Study population for chapters 4 - 8

*Study population*

The preliminary of arm swing showed that the average of Path length of PD patients during arm swinging was 153.09 ± 73.13 and sway area was 30.96 ± 38.83. Therefore, the sample size of this study was calculated by the formula below;

$$n = \left( \frac{Z_{\frac{\alpha}{2}} \sigma}{e} \right)^2$$

σ = standard deviation of the population ($\sigma^2$, variance)

*e* = standard error between the average of X of the population and the average of X of sample of the population

When standard error of the average *(e)* was set less than 26.

Path length

N = ((2.575)(73.13) / 26)*2

= 52.4

Sway area

N = ((2.575)(38.83)/14)*2

= 50.9

Hence, the expected subjects in this study was 55 – 60 cases.

## 3.2 Instrumentation

Standing balance was measured by the posturographic balance platform; Nintendo Wii Fit (Nintendo of America Inc, Redmond, WA) (Clark et al., 2010). It consists of a novel balance board system with a specific written program by one of the authors. The programmed software was developed from the Wiimote library, which receives the data via Bluetooth connection on PC. The library has been tested by many programmers and no issue is known concerning its validity.

The input device is a platform that measures the distribution of weight bearing. The Wii Fit (Fig. 3.3) tracks changes in the Center of Pressure (CoP) by detecting the shifting of subjects' weight, without stepping or moving the feet while standing on the particular platform. Frequently, the platform detects shifts in weight bearing in the antero-posterior and medio-lateral dimensions.

**Fig. 3.3.** Nintendo Wii balance board

Balance assessments in standing position for PI in PD were measured by force platform or as known as posturography system and Nintendo Wii balance board (NWBB) (Blaszczyk et al., 2007; Geurts et al., 2011; Ickenstein et al., 2012; Abujaber et al., 2015; Doná et al., 2016) which are standard measurements besides pull test. NWBB has been proved to detect the quantitative kinematics of center of pressure (CoP) and to be a valid tool for assessing balance (Clark et al., 2010; Koslucher et al., 2012; Abujaber et al., 2015).

## 3.3 Study Protocols

### 3.3.1 Sensory session

- Stand on the balance board. Look at a marker on the wall about 100 seconds. Close eyes for 30 seconds. Open eyes, and look at the marker again for 40 seconds.

### 3.3.2 Motor session I

- Stand on the balance board. Swing arm alternous for 30 seconds. Stop swinging arm and stand still for 30 seconds. Swing arm synchronous for 30 seconds. Stop swinging arm and stand still for 40 seconds.

### 3.3.3 Motor session II

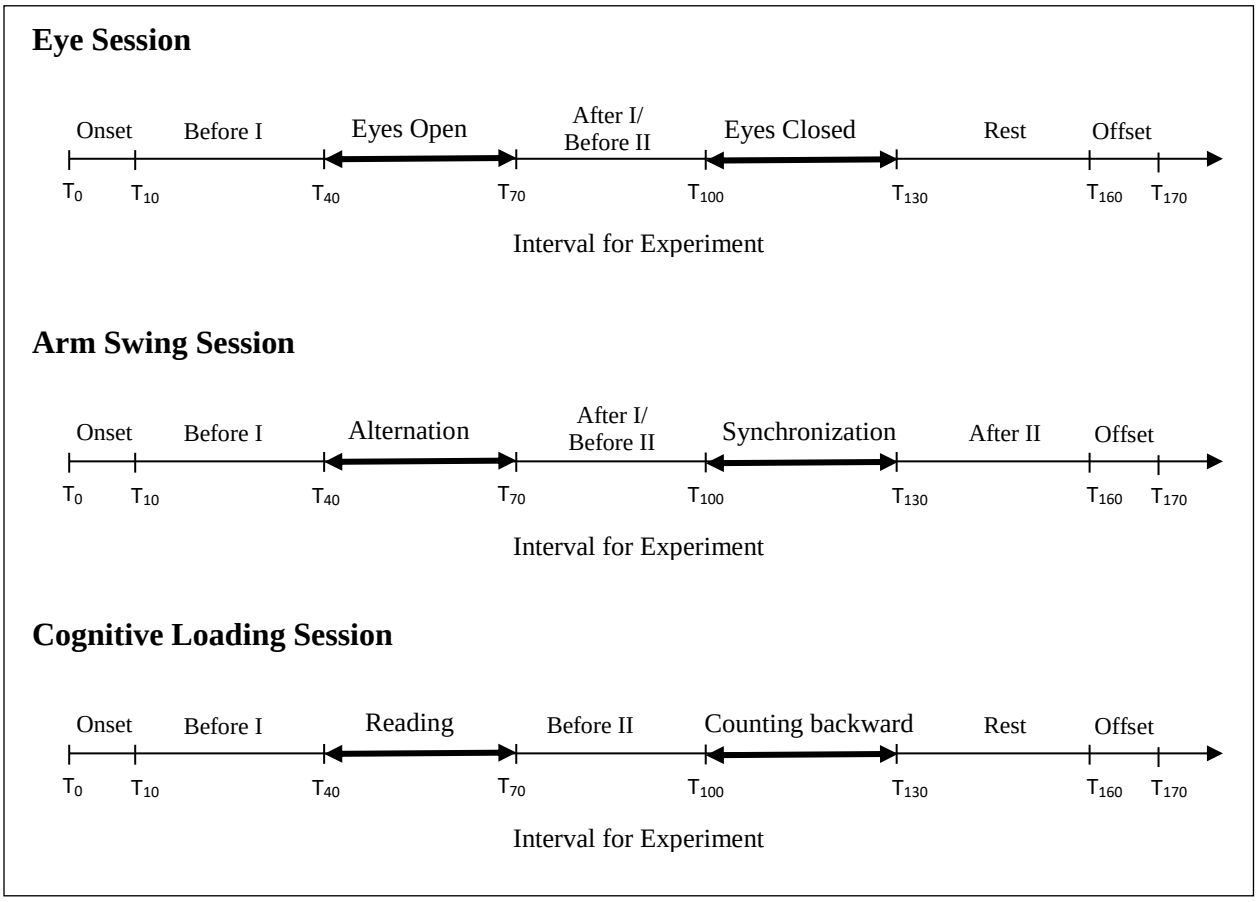
- Stand on the balance board. Swing arm alternous followed by auditory cues (AC) 100% of individual arm swing cycle for 30 seconds. Stop swinging arm and stand still for 30 seconds. Swing arm synchronous for 30 seconds followed by auditory cues (AC) 100% of individual arm swing cycle. Stop swinging arm and stand still for 40 seconds.

### 3.3.4 Cognitive session

- Stand on the balance board. Read a material for 30 seconds. Stop reading and look at a marker on the wall for 30 seconds. Count dates backward for 30 seconds. Stop counting and look at a marker on the wall for 40 seconds.

The details of study protocols are illustrate as in Fig. 3.4.

**Fig. 3.4.** Experimental procedure of all sessions in this study




## 3.4 Experimental Procedures

### 3.4.1. Clinical assessment

- The written informed consent was obtained from patients.

- The vital signs, physical examination and neurological examination were evaluated in both patients and control.

- The following study assessments were evaluated in PD patients as age, duration of the disease, dominant side, concurrent medical history, levodopa equivalent dose (LED), H&Y, UPDRS part II and III, FOG-Q, mini-BESTest, MoCA, TMSE, ABC, Schawab & England ADL and number of falls within 12 months prior to enter the study.

### 3.4.2 Balance assessment

*Questionnaires for evaluating balance and quality of live*

The stage of Hoehn and Yahr (H&Y), the score of the Unified Parkinson's Disease Rating Scale (UPDRS) III, the score of mini-BESTest, the Activities-specific Balance Confidence (ABC) Scale (ABC), the score of Thai Mental State Examination (TMSE), the FOG-Q, concurrent medical history and medications, vital signs as blood pressure (mmHg) and pulse rate (bpm) and weight (kg) and height (cm), body mass index (MBI), other parameters as age (years), gender, dominant side, age onset (years), duration of disease (years), levodopa equivalent dose (LED).

*Balance evaluation on Nintendo Wii balance board*

The participants were instructed to stand naturally on the balance platform (Wii Fit) and look at a marker, which was three meters from the board. The study was performed by the same balance platform, which was calibrated daily before each data collection. The three Wii remote controllers were attached at the patients' forearms and back. The medial borders of each foot were apart about 10 centimeters. The subjects were asked to perform tasks each session for a total of 170 seconds.

The center of pressure (CoP) in terms of path length (PL), sway area (SA), root mean square (RMS), medio-lateral (ML) and anteroposterior (AP) (Visser et al., 2008) were analyzed corresponding with the Unified Parkinson's Disease Rating Scale (UPDRS) motor (item 18-31) subscore (Visser et al., 2003), Levodopa Equivalent Dose (LED) (Alexoudi et al. 2015), Freezing of Gait questionnaire (FOG-Q) (Nilsson & Hagell, 2009) and Montreal Cognitive Assessment (MoCA) (Kandiah et al., 2014), Thai Mental State Examination (TMSE) (Muangpaisan et al., 2015), Activities-specific Balance Confidence (ABC) scale (Powell & Myers, 1995), Schwab & England Activities of Daily Living (SE-ADL) (McRae et al., 2002), Mini-BESTest (Franchignoni et al., 2010).

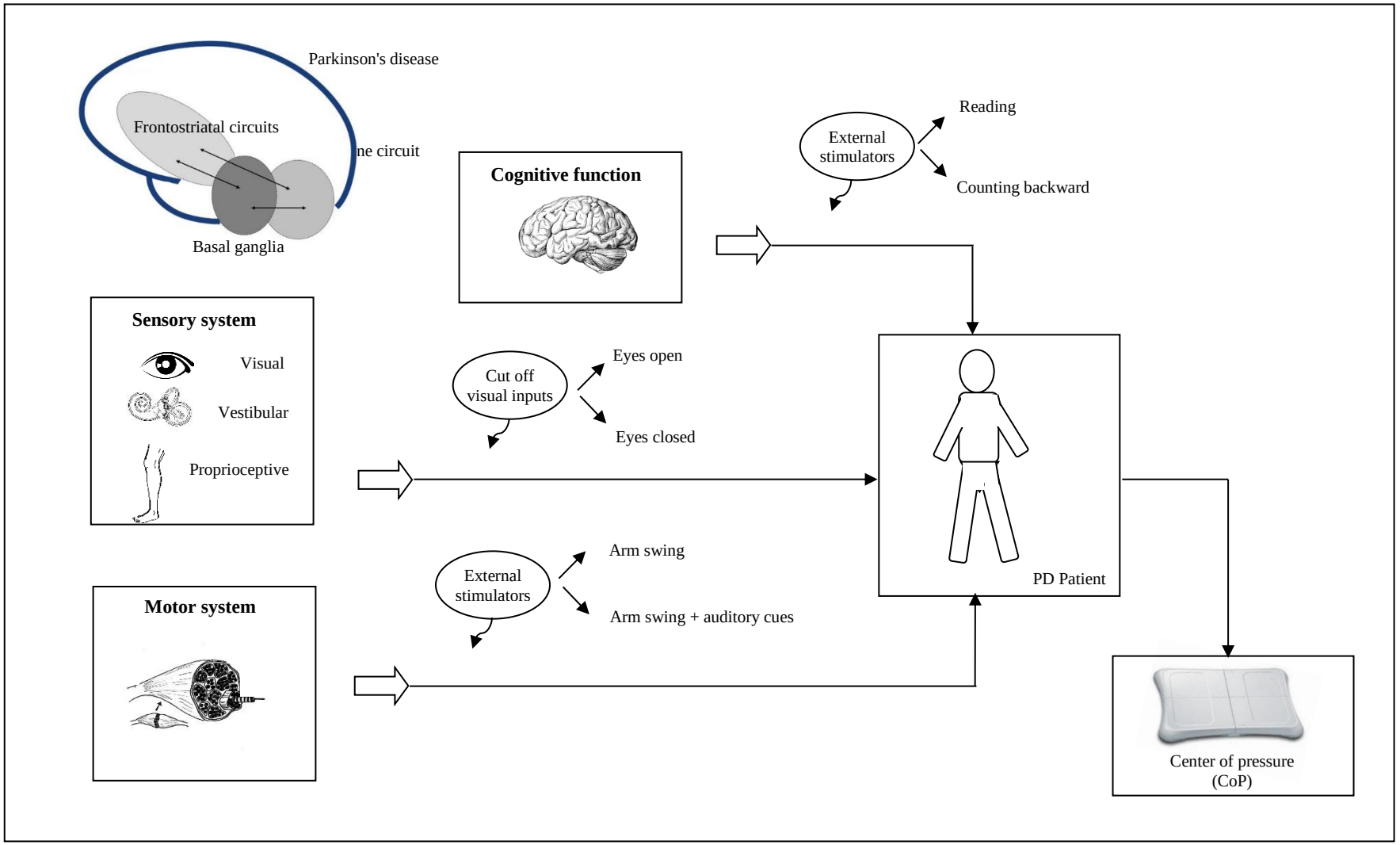



**Fig. 3.5.** Research methodology of this study

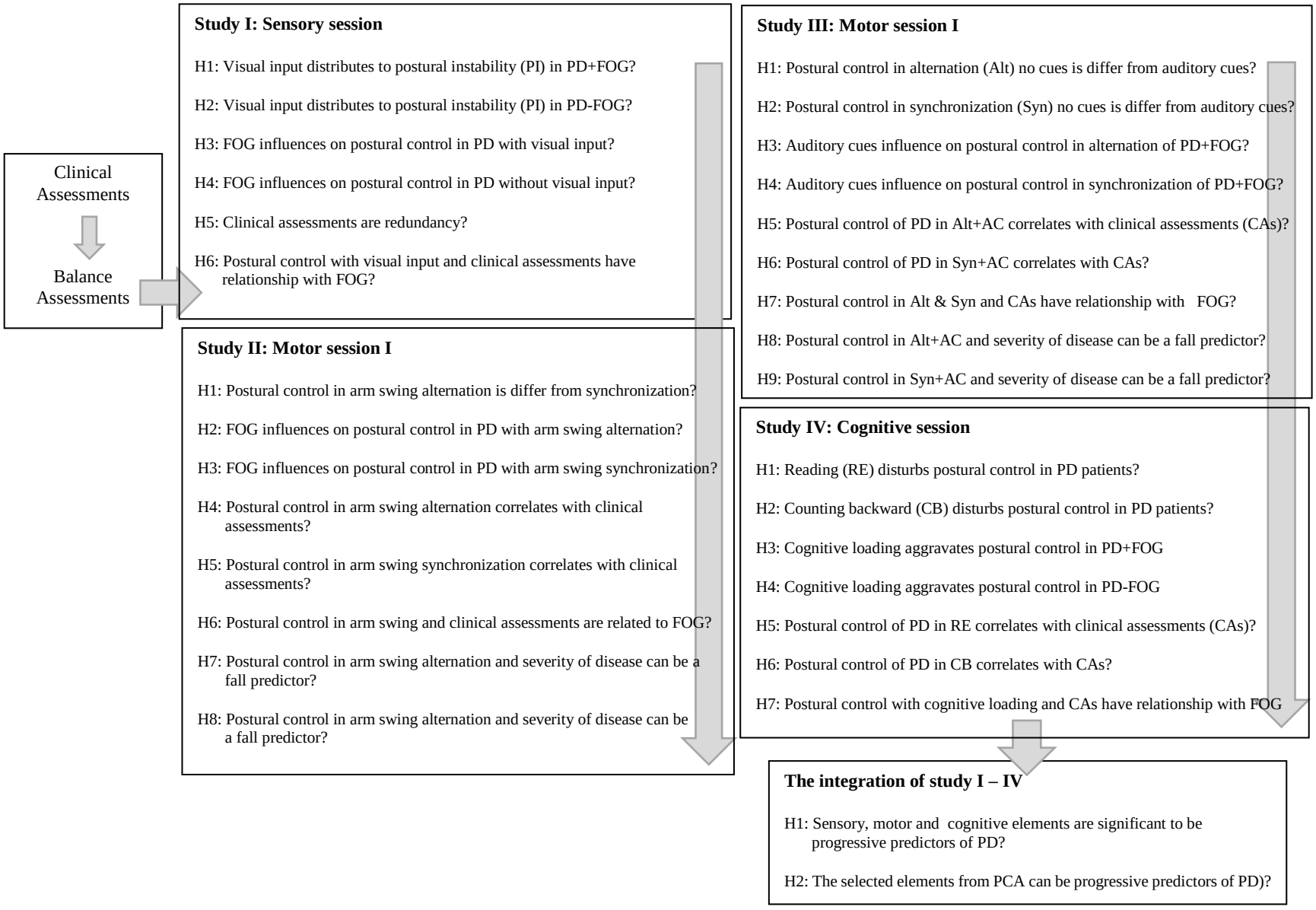



**Fig. 3.6.** Research methodology regarding research hypotheses

# CHAPTER 4

# CLINICAL PREDICTORS OF POSTURAL INSTABILITY IN PARKINSON'S DISEASE BASED ON VISUAL INPUT AND FREEZING OF GAIT

This chapter explores visual input (VI) toward postural control in patients with Parkinson's disease (PD). By evaluating center of pressure (CoP) while the patients were opening and closing eyes. We hypothesized that Parkinson's disease with freezing of gait (PD+FOG) would present more impaired postural control during without visual input (eyes closed, EC), and clinical assessments for PD are redundancy with similar dimensions which can be reduced to shorten time of evaluation postural instability (PI) and freezing of gait (FOG) in PD appropriately in recent clinical circumstances. The purpose of this study is (1) to elucidate visual input (VI) distributing to postural instability (PI) and freezing of gait (FOG) in patients with PD and (2) evaluated clinical symptoms with multi-clinical assessments in various aspects to identify PI and FOG as clinical predictors by utilizing Nintendo Wii balance board (NWBB) in order to explain relationships of visual input, PI and FOG.

## 4.1 Research Methodology

*Participants*

The details of participants were explained in Chapter III.

*Instrumentation*

The details of instrumentation were described in Chapter III.

*Experimental Procedures*

Subjects' disease severities were evaluated using UPDRS (part III), (item 18-31) (Visser et al., 2003). Levodopa Equivalent Dose (LED) (Alexoudi et al. 2015), Freezing of Gait questionnaire (FOG-Q) (Nilsson & Hagell, 2009) and Montreal Cognitive Assessment (MoCA) (Kandiah et al., 2014), Thai Mental State Examination (TMSE) (Muangpaisan et al., 2015), Activities-specific Balance Confidence (ABC) scale (Powell & Myers, 1995), Schwab & England Activities of Daily Living (SE-ADL) (McRae et al., 2002), Mini-BESTest (Franchignoni et al., 2010) were also determined. Data collection is as shown in Fig. 4.1.

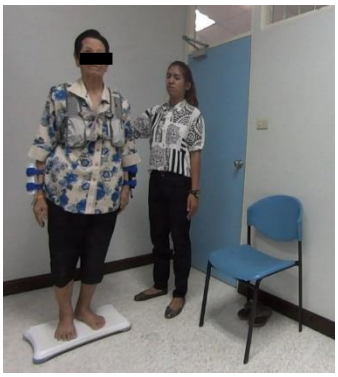


**Fig. 4.1.** Data collection

*Posturographic analysis; center of pressure (CoP) measurements*

Participants were asked to stand on the Nintendo Wii balance board (NWBB) (Nintendo of America Inc, Redmond, WA) (Clark et al., 2010), and look at a marker which was 3 meters apart from the NWBB. All subjects were instructed to stand still with arms align with the body in 90 seconds under the two consecutive tests; eyes open (EO) and eyes closed (EC). Each test was 30 seconds with 10-second rest between the tests. The data were collected automatically by a written program, which was developed, from the Wiimote library. The data were transferred from the balance board to PC via Bluetooth connection. The center of pressure (CoP) in terms of path length (PL), sway area (SA), root mean square (RMS), mediol-ateral (ML) and antero-posterior (AP) were assessed (Visser et al., 2008).

*Statistical analysis*

The time series of CoP trajectories of the total subjects (n=60) were reported by the Wii program. The descriptive analyses of the posturographic parameters were evaluated in average (mean) and standard deviation (SD). SPSS 22.0 (IBM Corp, Armonk, NY) was applied to calculate the data. All variables were tested the normality by Kolmogorov-Smirnov. Age, age of onset, duration of disease, H&Y, UPDRS (motor score), LED, FOG-Q, TMSE and MoCA were analyzed means by the non-parametric Mann-Whitney U test for numerical data and Chi-square test for categorical data. The sub-analysis was employed by categorizing the participants into two groups,

with FOG (PD+FOG) (n=39) and without FOG (PD-FOG) (N=21). PD+FOG were classified by total score of FOG-Q ≥6 score based on the six questions of freezing of gait questionnaire (FOG-Q) (Giladi et al., 2000). The comparison of means' differences of CoP between EO and EC conditions was calculated by Wilcoxon Signed-Rank test. The statistical significance level was set at *p-value* less than 0.05. To reduce the number of independent variables (clinical assessments) and to investigate correlations among clinical variables, principal component analysis (PCA) was applied. Inter-correlations among clinical variables (demographic characteristics, medication, severity of disease, tremor, gait and balance, cognitive function, activities daily living and mental state) were determined by PCA. To examine relationship between Center of pressure (CoP) and clinical variables, multiple regression analyses were performed between path length (PL) and clinical variables (medication, severity of disease, gait and balance because of the calculation of PCA).

## 4.2 Results

*Clinical characteristics*

The characteristics of PD subjects were categorized into two groups; PD with FOG (PD+FOG) (n=39) and PD without FOG (PD-FOG) (n=21). The range of age and duration of disease were 43-89 years old and 0.5-17 years respectively. Hoehn and Yahr scale was 1-3. (UPDRS) motor score range was from 6-58. The mean age of all subjects (60 cases) was 66.48±10.32 (mean±SD) years, duration of disease 5.31±3.42 years, UPDRS motor score 22.87±12.18, LED 627.44±372.95 mg/day. FOG-Q score 8.3±5.54. Significant increases were found in duration of disease, H&Y scale, UPDRS motor score, levodopa, LED, and FOG-Q in PD+FOG as shown in Table 4.1. Significant differences between PD+FOG and PD-FOG were also observed in age of onset, ABC, Mini-BESTest and SE-ADL.

*Visual input (VI) and freezing of gait (FOG)*

PD patients in total (60 cases) were noticed significant differences between eyes open (EO) and eyes closed (EC) in PL ($p < 0.001$), RMS (0.048), ΔML ($p = 0.001$) and ΔAP ($p = 0.005$).

Most of the CoP parameters in EC were higher than EO. In EO, PD+FOG showed significant higher SA (*p = 0.004*), RMS (*p = 0.002*) and ΔAP (*p = 0.006*) than PD-FOG. In EC, PD+FOG presented significant higher SA (*p = 0.060*) and RMS (*p = 0.008*) than PD-FOG. Comparing between EO and EC in PD+FOG, we found the significant increase in PL (*p = 0.002*). Likewise, in PD-FOG, we observed the significant increase in PL (*p = 0.001*) as shown in Table 4.2.

**Table 4.1**
Clinical assessments of Parkinson's disease (PD) patients with FOG (PD+FOG) and without FOG (PD-FOG)

| Variable | PD+FOG (n=39) | PD-FOG (n=21) | *p* |
|---|---|---|---|
| Gender (M/F) | 14/25 | 10/11 | 0.240 [a] |
| Age, yrs (SD) | 65.13 ± 10.32 | 69 ± 10.08 | 1.99 |
| Age of onset, yrs (SD) | 58.99 ± 10.87 | 65.2 ± 10.27 | 0.030* |
| Duration of disease, yrs (SD) | 6.14 ± 3.57 | 3.79 ± 2.42 | 0.002** |
| Hoehn and Yahr, scale (SD) | 2.36 ± 0.69 | 1.86 ± 0.62 | <0.001** |
| UPDRS motor score (SD) | 24.72 ± 13.13 | 19.43 ± 9.59 | 0.034* |
| Levodopa, mg/day (SD) | 577.87 ± 342.94 | 382.14 ± 220.79 | 0.020* |
| LED, mg/day (SD) | 722.41 ± 392.23 | 452.62 ± 247.85 | 0.007** |
| PIGD subtype, n (%) | 97.44 | 71.43 | 0.001[a**] |
| FOG-Q, scores (SD) | 11.72 ± 3.51 | 1.95 ± 1.43 | <0.001** |
| Tremor present, n (%) | 87.18 | 85.71 | 0.630[a] |
| Axial tremor present, n (%) | 87.18 | 76.19 | 0.006[a**] |
| TMSE, scores (SD) | 25.33 ± 3.21 | 26.14 ± 2.65 | 0.110 |
| MoCA | 18.87 ± 5.05 | 19.81 ± 5.5 | 0.394 |
| ABC, scores (SD) | 64.02 ± 22.33 | 84.06 ± 13.32 | <0.001** |
| Mini-BESTest, scores (SD) | 16.23 ± 6.5 | 21.86 ± 4.14 | 0.002** |
| SE ADL, scores (SD) | 77.9 ± 12.18 | 90 ± 8.37 | <0.001** |

UPDRS, Unified Parkinson's Disease Rating Scale; LED, Levodopa Equivalent Dose; PIGD, Postural Instability and Gait Disorder; FOG-Q, Freezing of Gait Questionnaire; TMSE, Thai Mental State Examination; MoCA, Montreal Cognitive Assessment; ABC, Activities of Balance Confident; SE ADL, Schwab & England Activities of Daily Living. [a] Chi-square analysis. All other variables were analyzed by Mann-Whitney U test.
**p < 0.05, **p < 0.01.*

**Table 4.2**
Means and standard deviations of posturographic data in eyes open (EO) and eyes closed (EC) sessions of patients with Parkinson's disease (PD)

| | EO | | | EC | | | EO vs EC | |
|---|---|---|---|---|---|---|---|---|
| | PD+FOG | PD-FOG | $p^a$ | PD+FOG | PD-FOG | $p^a$ | $p^{b,}$ PD+FOG | $p^{b,}$ PD-FOG |
| PL | 90.53 ± 41.25 | 80.72 ± 19.87 | 0.284 | 344.2 ± 148.07 | 90.92 ± 19.61 | 0.926 | 0.002** | 0.001** |
| SA | 9.96 ± 11.56 | 10.24 ± 23.11 | 0.004** | 12.17 ± 27.05 | 11.14 ± 26.82 | 0.060* | 0.481 | 0.159 |
| RMS | 2.83 ± 3.04 | 1.89±2.78 | 0.002** | 3.24 ± 3.81 | 1.93 ± 1.47 | 0.008** | 0.113 | 0.149 |
| ΔML | 2.61 ± 1.84 | 2.45 ± 3.01 | 0.816 | 12.21 ± 59.68 | 2.34 ± 3.25 | 0.069 | 0.553 | 0.728 |
| ΔAP | 3.26 ± 1.24 | 2.71 ± 1.51 | 0.006** | 3.52 ± 1.73 | 3.29 ± 1.44 | 0.124 | 0.222 | 0.112 |

EO = eyes open; EC = eyes closed; PL = path length; SA = sway area; RMS = root mean square; ΔML = maximal medio-later – minimal medio-later displacements; ΔAP = maximal antero-posterior – minimal antero-posterior displacements.
$p^a$ = Mann-Whitney U test, $p^b$ = Wilcoxon Signed-Rank test.
**p < 0.05, **p < 0.01.*

**Table 4.3**

Means, standard deviations, inter-correlations among clinical assessment variables

| Variables | M | SD | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Demographic | | | | | | | | | | | | | | | | | | |
| 1. Gender | - | - | - | | | | | | | | | | | | | | | |
| 2. Age | 66.48 | 10.316 | -.016 | - | | | | | | | | | | | | | | |
| 3. Age of onset | 61.17 | 10.995 | .041 | .950** | - | | | | | | | | | | | | | |
| Medication | | | | | | | | | | | | | | | | | | |
| 4.Levodopa | 509.37 | 318.021 | -.298 | -.352** | -.479** | - | | | | | | | | | | | | |
| 5.LED | 627.98 | 369.797 | -.248 | -.422** | -.585** | .907** | - | | | | | | | | | | | |
| Severity of disease | | | | | | | | | | | | | | | | | | |
| 6.H&Y | 2.183 | 0.701 | .014 | .300** | .174 | .052 | .075 | - | | | | | | | | | | |
| 7.UPDRS III | 22.87 | 12.184 | -.103 | .223 | .150 | .060 | .043 | .750** | - | | | | | | | | | |
| 8. DD | 5.32 | 3.389 | -.178 | -.028 | -.340** | .471** | .599** | .347* | .189 | - | | | | | | | | |
| Tremor | | | | | | | | | | | | | | | | | | |
| 9. Tremor | 4.35 | 3.668 | -.164 | -.334 | .109 | .003 | -.063 | -.093 | .156 | .422* | - | | | | | | | |
| Gait and balance | | | | | | | | | | | | | | | | | | |
| 10. FOG | 8.3 | 5.540 | .067 | -.104 | -.219 | .386** | .363* | .374** | .478** | .331** | -.031** | .509** | .681** | - | | | | |
| 11. Mini-BESTest | 18.20 | 6.353 | -.085 | -.244* | -.131 | -.315** | -.098 | -.098 | -.491** | -.393* | .132* | -.627** | -.641** | -.495** | - | | | |
| 12. ABC | 71.032 | 21.775 | -.162 | -2.38 | -.179 | -.145 | .004 | .016 | -.475** | -.402** | -.073** | -.532** | -.709** | -.649** | .555** | - | | |
| Cognition | | | | | | | | | | | | | | | | | | |
| 13. MoCA | 19.21 | 5.190 | -.132 | -.339* | -.359* | .127 | -.098 | .152 | -.339* | -.451* | -.163* | -.407** | -.308* | -.127 | .246 | .371* | - | |
| Activities daily living | | | | | | | | | | | | | | | | | | |
| 14. SE-ADL | 82.17 | 12.363 | -.059 | -.100 | -.010 | -.266* | -.154 | -.131 | -.544** | -.569** | -.028** | -.551** | -.606** | -.544** | .351* | .441** | .347* | - |
| Mental state | | | | | | | | | | | | | | | | | | |
| 15. TMSE | 25.62 | 3.026 | -.123 | -.334* | -.340* | .085 | .151 | .219 | -.330** | -.420** | -.058** | -.446** | -.402** | -.249* | .396* | .431** | .719** | .482** |

DD, duration of disease; LED, levodopa equivalent dose; H&Y, Hoehn and Yahr scale, UPDRS III, Unified Parkinson's Disease Rating Scale, motor score; FOG-Q, Freezing of gait questionnaire; ABC, Activities of balance confident; MoCA, Montreal cognitive assessment; SE ADL, Schwab & England Activities of Daily Living; TMSE, Thai mental state examination. Data were calculated by principal component analysis (PCA).

*$p < 0.05$, **$p < 0.01$.

*Relationship among clinical variables*

We applied Principal component analysis (PCA) with squared multi-correlations as initial estimates of communalities to reduce redundancy factors of the clinical variables. The correlations between each clinical variable were illustrated. Relationships between each clinical variable were noticed by the inter-correlations among clinical variables as shown in Table 4.3. Levodopa and LED as dopamine therapy for PD were significantly correlated with age, age of onset, and duration of disease. H&Y was significantly correlated with age and duration of disease. As also shown in Table 4.3, gait and balance variables were significantly correlated with duration of disease, severity of disease, medication, cognitive assessment, ADL and mental state tests. Conversely, gait, balance, and ADL assessment variables were not significantly correlated with age and age of onset, except Mini-BESTest that correlated with age.

The clinical predictors can be defined into two components according to the result of scree plot as illustrated in Fig. 4.2 (Wuensch, 2012; Keho, 2012; Jackson et al., 2015). Table 4.4 indicates factor loadings of clinical assessments. For the independent variables (demographic, medication, severity of disease, tremor, gait and balance, cognition, ADL and mental state), the presence of the two high components were indicated from the four components (Wuensch, 2012; Keho, 2012). The eigenvalues in terms of percentage were summarized by showing the 36.573% of total variance in component 1, and 22.1 60% of total variance in component 2. It is obvious that component 1 and 2 present the relative largest amounts of variance whereas subsequent components show only small amounts of variance. The first component included H&Y, UPDRS III, FOG-Q, whereas the second component included LED, levodopa, and duration of disease regarding high positive factor loadings (Factor loadings >0.6 were selected as higher level of clinical assessment) (Keho, 2012).

**Fig. 4.2.** Scree plot of eigenvalues for clinical assessments

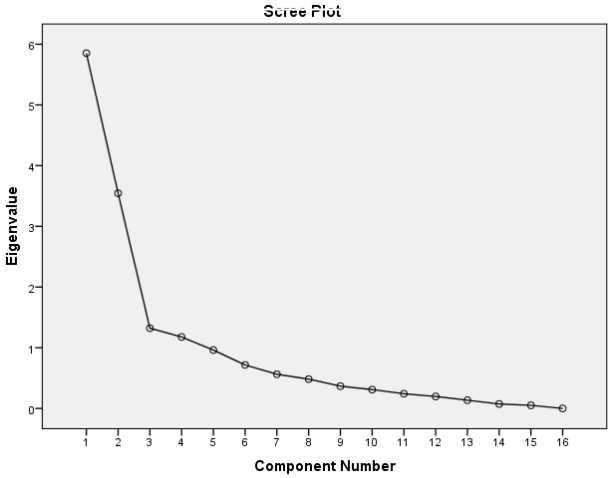


**Table 4.4**
Factor loadings of clinical assessments

| Clinical assessment | Principal component | |
|---|---|---|
| | 1 | 2 |
| *Component 1* | | |
| H&Y | **0.808** | |
| UPDRS III | **0.766** | |
| FOG-Q | **0.666** | |
| Age | 0.383 | |
| Age of onset | 0.252 | |
| *Component 2* | | |
| LED | | **0.884** |
| Levodopa | | **0.808** |
| Duration of disease | | **0.621** |
| FOGQ | | 0.466 |
| MoCA | | 0.379 |
| TMSE | | 0.356 |

Inclusion within a component (determined by highest loading); H&Y, Hoehn and Yahr scale; UPDRS III, Unified Parkinson's Disease Rating Scale, motor

*Relationship between clinical variables and center of pressure (CoP)*

We operated multiple regression analyses to investigate the incremental validity of the posturographic data to describe variance in clinical predictors. The posturographic parameters were verified to be clinical predictors based on the clinical assessments variables. Multiple regression analyses were carried out to relate dependent variable; path length (PL) and high loaded components of clinical variables regarding PCA including H&Y scale, UPDRS motor score (item 18-31), FOG-Q, LED, levodopa and duration of disease as independent variables. All variables were set as numerical variables.

As shown in Table 4.5, associations between path length (PL) variable and clinical variables were observed in $PD_{Total}$-EO; levodopa ($R^2 = 0.217$, $p = 0.021$), LED ($R^2 = 0.190$, $p = 0.043$), H&Y ($R^2 = 0.204$, $p = 0.029$) and duration of disease ($R^2 = 0.340$, $p < 0.001$). In $PD_{Total}$-EC, relationships were found in FOG-Q ($R^2 = 0.300$, $p = 0.002$). Meanwhile, we found relationship only in PD+FOG-EC in FOG-Q ($R^2 = 0.538$, $p < 0.001$). On the other hand, no relationship was found in PD-FOG in both EO and EC conditions.

Ninety-five percent confidence interval (CI) was accounted for the association of FOG-Q score and posturographic data, in terms of path length (PL) in PD+FOG and PD-FOG. Relationship

between PL and FOG-Q between EO and EC was demonstrated. PL in EC was higher than in EO corresponding to FOG-Q score in PD+FOG and PD-FOG. PL showed more fluctuated in PD+FOG than PD-FOG as illustrated in Fig. 4.3. The 95% confidence ellipse of mean ML and AP displacements in eye open (EO) and eye closed (EC) between PD+FOG and PD-FOG were illustrated in Fig. 4.4.

**Fig. 4.3.** Ninety-five percent confidence interval (CI) of path length (PL) and FOG-Q between eyes open (EO) and eyes closed (EC): (A) PD+FOG and (B): PD-FOG.

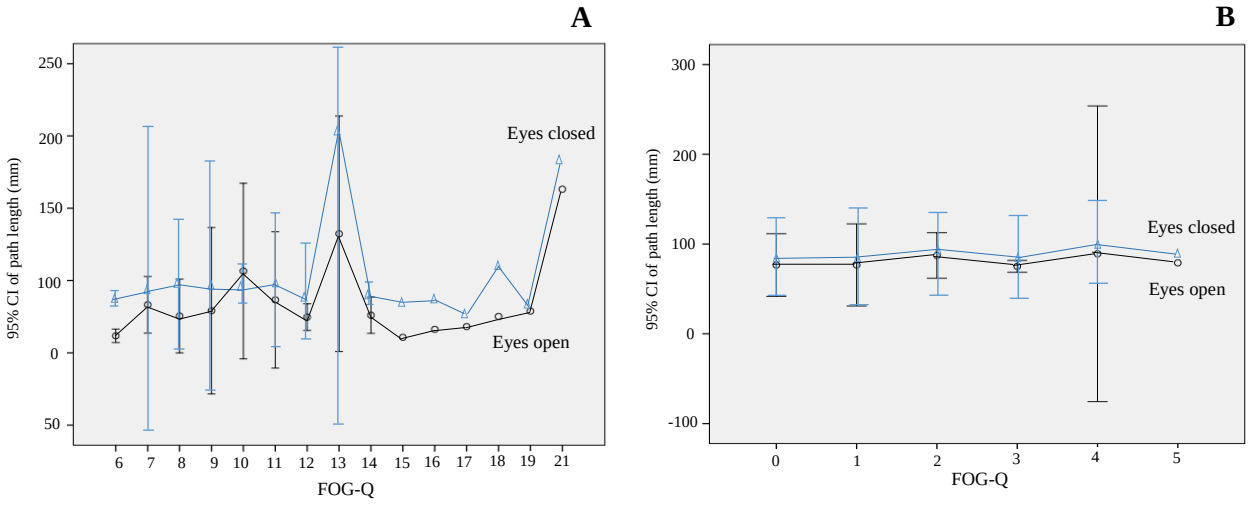



**Fig. 4.4.** Ninety-five percent confidence ellipse of mean ML, and AP displacements between PD patients with freezing of gait and without freezing of gait: (A) eyes open (EO), (B) eye closed (EC).

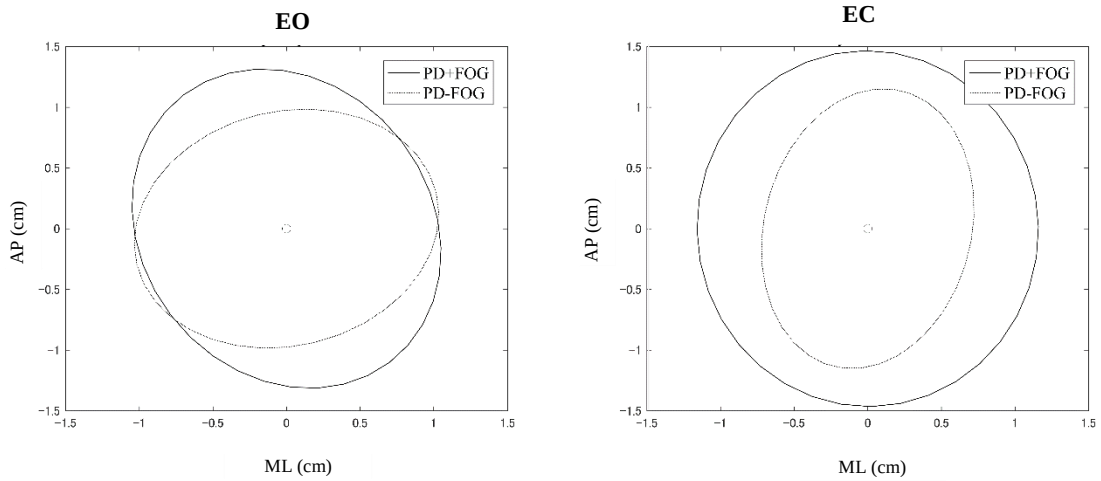


**Table 4.5**
Multiple regression analyses between the 6-selected clinical variables and path length (PL)

| | Clinical variables | Regression statistic | | | | | |
|---|---|---|---|---|---|---|---|
| Group | | $R^2$ | Adj $R^2$ | $\Delta R^2$ | df | f | *p* |
| $PD_{Total}$-EO | Medication | | | | | | |
| | 1.Levodopa | 0.217 | 0.143 | 0.217 | 5, 53 | 2.929 | 0.021* |
| | 2.LED | 0.190 | 0.114 | 0.190 | | 2.489 | 0.043* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.204 | 0.129 | 0.204 | | 2.717 | 0.029* |
| | 4.UPDRS III | 0.074 | -0.013 | 0.074 | | 0.851 | 0.520 |
| | 5. DD | 0.340 | 0.277 | 0.340 | | 5.450 | <0.001** |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.023 | -0.134 | 0.023 | | 0.147 | 0.979 |
| $PD_{Total}$-EC | Medication | | | | 5, 53 | | |
| | 1.Levodopa | 0.132 | 0.050 | 0.132 | | 1.609 | 0.174 |
| | 2.LED | 0.122 | 0.039 | 0.122 | | 1.477 | 0.213 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.138 | 0.056 | 0.138 | | 1.691 | 0.153 |
| | 4.UPDRS III | 0.104 | 0.020 | 0.104 | | 1.235 | 0.306 |
| | 5. DD | 0.017 | 0.023 | 0.107 | | 1.269 | 0.291 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.300 | 0.234 | 0.300 | | 4.544 | 0.002** |
| PD+FOG-EO | Medication | | | | | | |
| | 1.Levodopa | 0.221 | 0.085 | 0.221 | 5, 31 | 1.758 | 0.151 |
| | 2.LED | 0.247 | 0.126 | 0.247 | | 2.037 | 0.101 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.082 | -0.066 | 0.082 | | 0.552 | 0.736 |
| | 4.UPDRS III | 0.058 | -0.094 | 0.058 | | 0.379 | 0.859 |
| | 5. DD | 0.249 | 0.128 | 0.249 | | 2.056 | 0.098 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.177 | 0.044 | 0.177 | | 1.332 | 0.277 |
| PD+FOG-EC | Medication | | | | | | |
| | 1.Levodopa | 0.120 | -0.022 | 0.120 | 5, 31 | 0.847 | 0.527 |
| | 2.LED | 0.107 | -0.037 | 0.107 | | 0.744 | 0.597 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.130 | -0.010 | 0.130 | | 0.926 | 0.478 |
| | 4.UPDRS III | 0.119 | -0.023 | 0.119 | | 0.835 | 0.535 |
| | 5. DD | 0.084 | -0.064 | 0.084 | | 0.566 | 0.725 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.538 | 0.464 | 0.538 | | 7.227 | <0.001** |
| PD-FOG-EO | Medication | | | | | | |
| | 1.Levodopa | 0.154 | -0.128 | 0.154 | 5, 15 | 0.547 | 0.738 |
| | 2.LED | 0.127 | -0.164 | 0.127 | | 0.438 | 0.815 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.436 | 0.246 | 0.436 | | 2.307 | 0.096 |
| | 4.UPDRS III | 0.381 | 0.175 | 0.381 | | 1.848 | 0.164 |
| | 5. DD | 0.252 | 0.002 | 0.252 | | 1.008 | 0.446 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.163 | -0.116 | 0.163 | | 0.584 | 0.712 |
| PD-FOG-EC | Medication | | | | | | |
| | 1.Levodopa | 0.271 | 0.028 | 0.271 | 5, 15 | 1.114 | 0.394 |
| | 2.LED | 0.365 | 0.153 | 0.365 | | 1.724 | 0.190 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.325 | 0.101 | 0.325 | | 1.447 | 0.264 |
| | 4.UPDRS III | 0.300 | 0.067 | 0.300 | | 1.286 | 0.321 |
| | 5. DD | 0.190 | -0.080 | 0.190 | | 0.704 | 0.629 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.087 | -0.217 | 0.087 | | 0.286 | 0.914 |

Adj, adjusted; LED, levodopa equivalent dose; H&Y, Hoehn and Yahr scale, UPDRS III, Unified Parkinson's Disease Rating Scale; DD, duration of disease; PIGD, Postural Instability and gait disorder; FOG-Q, Freezing of gait questionnaire.
**p < 0.05, **p < 0.01.*

## 4.3 Discussion

The main purposes of this study were to reveal relationship of visual input (VI), postural instability (PI) and freezing of gait (FOG), and to present the most essential and significant clinical variables to identify PI and FOG as clinical predictors for Parkinson's disease (PD) patients by using principal component analysis (PCA) and multiple regression analysis techniques. We investigated postural control between PD patients with FOG (PD+FOG) and without FOG (PD-FOG). Multiple clinical assessments were employed to evaluate PI and FOG as standard measurement. Our study pointed the consistency with the previous studies regarding the association between PI and FOG. PD+FOG presented poorer postural control than in PD-FOG (Pelykh et al., 2015; Schlenstedt et al., 2016; Huh et al., 2016). Significant increase of antero-posterior (AP) sway in PD+FOG in this study was concordant with the study conducted by Nantel et al., 2012 showing the significant correlation between FOG and AP excursion. The positive correlation was also found between SA, ΔML (medio-lateral) and ΔAP (antero-posterior) in PD+FOG in this study supported by the study of Schlenstedt et al., 2016. It is noted that a progressive marker for PD can be investigated by analyzing postural sway changed with disease progression according to UPDRS motor scores, which ML sway was more sensitive to measure than AP sway (Martini et al., 2012).

The deterioration of postural control in PD patients has been clearly described the relationship of severity of the disease and PI as an aspect of illustrating stages of the disease. It is a factor to be related to PI and FOG (Geurts et al., 2011; Amboni et al., 2015), however, we found that age-developed the disease was not significant to predict PI and FOG (Visser et al., 2013). FOG-Q score can be a good and appropriate factor to evaluate with balance assessment to identify subclinical PI in PD patients, which was also confirmed by the study of Vervoort et al., 2013. Similarly, UPDRS and MMSE (TMSE in this study) scores had no significant differences. It is controversial to explain the relationship of duration of disease and PI. This study found the relationships of the duration of disease and PI, which is supported by the study of Schlenstedt et al., 2016. Oppositely, no significant differences were found between duration of disease and PI as well in the study of Vervoort et al., 2013.

Moreover, our study showed the dopaminergic therapy affected on postural control in PD patients. To confirm the study of Beuter et al., 2008, our study noticed the correlation

between levodopa equivalent dose (LED) and antero-posterior sway (ΔAP) which was also consistent with the study of Nantel & Bronte-Stewart, 2014 as results of the dopaminergic medication on the PI and FOG in PD. The higher dose of medication was indicated in the studies for the patients with FOG. The results of multiple analyzes showed significant models for predicting PD with FOG (PD+FOG). Although, the R-squared of those models are low which mean they do not explain much of variation of the data, they are significant with low p-value ($p<0.05$). In other words, the models were discovered to predict FOG by the methodology of this study.

Since the neuroanatomical basis of PI and visual deficit is unclear, however, visual input plays role in postural control in basal ganglia (BG) on the part of visual - postural circuit in PD. By showing the significant increases in eyes closed (EC) condition in path length (PL), sway area (SA), medio-lateral (ML) and antero-posterior (AP) sway (Bronstein et al., 1990; Pasma et al., 2014; Rinalduzzi et al., 2015). This study was also along with the studies of Pastor et al., 1993; Khudados et al.,1999; De Nunzio et al., 2007; Blaszczyk et al., 2007, that the interruption of visual inputs affected on postural stability in PD by expressing higher path length (PL) and postural sway. We found that the evaluation of postural control in quiet standing position and visual dependency on Nintendo Wii balance board (NWBB) could be a progressive marker for subclinical assessment for PD according to the correlations between the center of pressure (CoP) trajectories and severity of the disease. The relationships between PL, SA, ΔML, ΔAP and H&Y scale and duration of disease were consistently found with the studies by Geurts et al., 2011; Panyakaew et al., 2015. Meanwhile, a measurement to assess the association of VI, PI and FOG in PD patients is feasible by utilizing Nintendo Wii balance board (NWBB) which is simple and affordable to manipulate with low spaces for most current clinical situations.

The limitations of our study should be addressed. First, the sample size of each group was small and unequal. We recruited the patients based on the patients who visited the outpatient department. It was difficult to equal the number of patients each group with the time constraint. Second, it was a lack of healthy control group to compare with the PD patients, which would help us understand more on the data set and confirm the understanding of postural control of PD in terms of PI and FOG. Third, the FOG group was categorized by using the FOG-Q score only. To confirm that the participants exactly manifested FOG, we classified them

with FOG-Q score. If they had FOG-Q score ≥6 in which their score at least covered all questions of FOG-Q, they were in PD+FOG group. The criteria might not be enough to classify the groups. There might be some patients whom were not shown in each group appropriately with other sub-criteria. Last, the NWBB is a fixed balance board, which we could not distinguish more between visual and proprioceptive impairments individually.

Our findings in this study are benefit for categorizing subclinical symptoms within the framework of balance assessment of VI and FOG. Individual PD patients show unpredictable postural stability with different clinical tests' scores. The more we approach the subclinical symptoms, the more benefits the patients can gain. Future perspective studies would enhance broadly of the understanding of PI and FOG in PD. The further prospective studies are needed to identify the predictive variables of PI and FOG as well as fall risk factors to predict falls and simultaneously evaluate postural stability. As well as, to develop programs for predicting the progression of the disease and for training PD patients to improve balance and/or prevent falls.

## 4.4 Conclusion

The relationship of visual input (VI), postural instability (PI), and freezing of gait (FOG) was discovered which could be an ideal of a new clinical technique for evaluating balance in patients with Parkinson's disease (PD). visual input (VI) distributes to postural instability (PI) in both Parkinson's disease patients with freezing of gait (PD+FOG) without freezing of gait (PD-FOG). Levodopa therapy, freezing of gait questionnaire (FOG-Q), Hoehn and Yahr scale (H&Y) and duration of disease are potentially clinical predictors for CoP analysis. Visual dependency is associated with postural stabilization and freezing of gait (FOG) in PD. This may be considered a measure for clinical predictors of PI and FOG to assist identifying subclinical PI in PD.

# CHAPTER 5

# ARM SWING AS CLINICAL PREDICTORS OF POSTURAL INSTABILITY IN PAKINSON'S DISEASE

This chapter investigates the influences of arm swing (AS) on postural control in terms of center of pressure (CoP). The correlations between clinical assessments and posturographic data were evaluated. We conducted the study of dynamic postural control by examining two types of arm swing patterns; alternation and synchronization. The purpose of this study is to evaluate the arm swing patterns and clinical assessments in patients with Parkinson's disease (PD) with different stages of the disease. We hypothesized that whether the two arm swing patterns can be clinical predictors of postural instability in PD.

## 5.1 Research Methodology

*Participants*

The details of participants were explained in Chapter III.

*Instrumentation*

The details of instrumentation was described in Chapter III.

*Experimental procedures*

The participants were instructed to stand on the balance platform (Wii Fit), arms were along with the body, and look at a marker, which was 3 meters from the board. The study was performed by the same balance platform, which was calibrated daily before each data collection. The medial borders of each foot were apart about 10 centimeters. The subjects were introduced to perform two arm swing patterns; alternation and synchronization within 170 seconds (Fig. 5.1). They were assessed in on medication.


**Fig 5.1.** Data collection.
A – Alternation,
B - Synchronization

The center of pressure (CoP) in terms of path length (PL), sway area (SA), root mean square (RMS), medio-lateral (ML) and antero-posterior (AP) (Visser et al., 2008) were analyzed corresponding with the Unified Parkinson's Disease Rating Scale (UPDRS) motor (item 18-31) subscore (Visser et al., 2003), levodopa equivalent dose (LED) (Alexoudi et al. 2015), freezing of gait questionnaire (FOG-Q) (Nilsson & Hagell, 2009) and Montreal Cognitive Assessment (MoCA) (Kandiah et al., 2014).

*Statistical analysis*

SPSS 22.0 (IBM Corp, Armonk, NY) was applied to calculate the data. All variables were tested the normality by Kolmogorov-Smirnov. Age, age of onset, duration of disease, H&Y, UPDRS (motor score), LED, FOG-Q, TMSE and MoCA were analyzed means by the nonparametric Mann-Whitney U test and Chi-square test, appropriately. The sub-analysis was employed by categorizing the participants into two groups, freezing of gait (FOG) (n=39) and non-freezing of gait (non-FOG) (N=21). PD patients with FOG were classified by total score of FOG-Q ≥6 score based on the six questions of freezing of gait questionnaire (FOG-Q) (Giladi et al., 2000). The comparison of means' differences of Center of Pressure (CoP) between arm swing alternation and synchronization were calculated by Wilcoxon Signed-Rank test. The correlations

between clinical variables and posturographic parameters were analyzed by Spearman's rho correlation. Multiple regression analyses were proceeded whether path length (PL) variables in arm swing alternation (Alt) and arm swing synchronization (Syn) predict PD, PD with FOG (PD+FOG) and PD without FOG (PD-FOG). The statistical significance level was set at *p-value* less than 0.05.

## 5.2 Results

**Table 5.1**
Clinical characteristics of the participants in this study

| Variable | All participants (n=60) |
|---|---|
| Gender (M/F) | 24/36 |
| Age, yrs (SD) | 66.48 (10.32) |
| Age of onset, yrs (SD) | 61.27 (10.96) |
| Duration of disease, yrs (SD) | 5.31 (3.42) |
| Hoehn and Yahr, stages (SD) | 2.18 (0.7) |
| UPDRS motor score (SD) | 22.87 (12.18) |
| UPDRS motor score, Right side (SD) | 7.53 (4.83) |
| UPDRS motor score, Left side (SD) | 7.42 (5.1) |
| Levodopa, mg/day (SD) | 511.22 (320.42) |
| LED, mg/day (SD) | 627.44 (372.95) |
| PIGD subtype, n (%) | 86.67 |
| Dyskinesia present, n (%) | 71.67 |
| Freezing of gait present, n (%) | 93.33 |
| FOG-Q, scores (SD) | 8.3 (5.54) |
| Tremor present (%) | 86.67 |
| Axial tremor, present (%) | 83.33 |
| TMSE, scores (SD) | 25.62 (3.03) |
| MoCA | 19.21 (5.19) |
| ABC, scores (SD) | 71.03 (21.78) |
| Mini-BESTest, scores (SD) | 18.2 (6.35) |
| SE ADL, scores (SD) | 82.2 (12.47) |
| Fall history, n (%) | 35 |
| Recent Falls, n (%) | 13.33 |

UPDRS, Unified Parkinson's Disease Rating Scale; LED, Levodopa equivalent dose; PIGD, Postural Instability and gait disorder; FOG-Q, Freezing of gait questionnaire; TMSE; Thai mental state examination; MoCA; Montreal cognitive assessment; ABC, Activities of balance confident; SE ADL, Schwab & England Activities of Daily

The analyses of arm awing and clinical assessments on postural instability in PD comparing between arm swing alternation (Alt) and synchronization (Syn) in 60 PD cases were performed. Clinical characteristics of the participants in this study were expressed in Table 5.1. Age range was 43 – 89 years old. Age of onset was 37 – 81 years old. Duration of disease was 0.5 -17 years.

Maximum dose of levodopa was 1832.5 mg/day. Maximum dose of levodopa equivalent dose was 1952.5 mg/day. Maximum PIGD sub-score was 16. UPDRS score range was 6 – 58. Maximum FOG-Q score was 21.

The averages and standard deviations of arm swing alternation (Alt) and synchronization (Syn) in 60 PD cases were shown in Table 5.2. We found the two types of arm swing patterns were significantly different in sway area (SA) ($p = 0.029$), maximal ML ($p < 0.001$), minimal ML ($p < 0.001$), minimal AP ($p < 0.001$), ΔML ($p < 0.001$) and ΔAP ($p < 0.001$).

**Table 5.2**
The averages and standard deviations of alternation (Alt) and synchronization (Syn)

| Parameters | Alternation | Synchronization | *p-value* |
|---|---|---|---|
| Path length, mm (SD) | 202.81 (98.93) | 198.6 (105.2) | 0.498 |
| Sway area, $cm^2$ (SD) | 29.99 (27) | 25.75 (24.63) | 0.029* |
| RMS (SD) | 7.6 (7.1) | 6.57 (5.68) | 0.103 |
| Max ML, cm (SD) | 1.78 (2.23) | 0.96 (2.12) | <0.001* |
| Min ML, cm (SD) | -3.27 (2.47) | -2.79 (2.43) | <0.001* |
| Max AP, cm (SD) | 5.67 (1.78) | 5.71 (1.89) | 0.974 |
| Min AP, cm (SD) | 0.49 (1.86) | -2.19 (14.15) | <0.001* |
| ΔML, cm (SD) | 5.04 (2.65) | 3.75 (1.89) | <0.001* |
| ΔAP, cm (SD) | 5.18 (1.75) | 7.89 (14.1) | <0.001* |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement. Wilcoxon Signed Ranks test was calculated.

The sub-analysis of arm swing patterns comparing between the patients who presented freezing of gait (FOG) and without FOG (39:21 cases) revealed no significant differences in alternation. On the other hand, significant differences were observed in synchronization in SA ($p = 0.013$), RMS ($p = 0.010$), Δ ML ($p = 0.013$), and Δ AP ($p = 0.015$) as shown in Table 5.3.

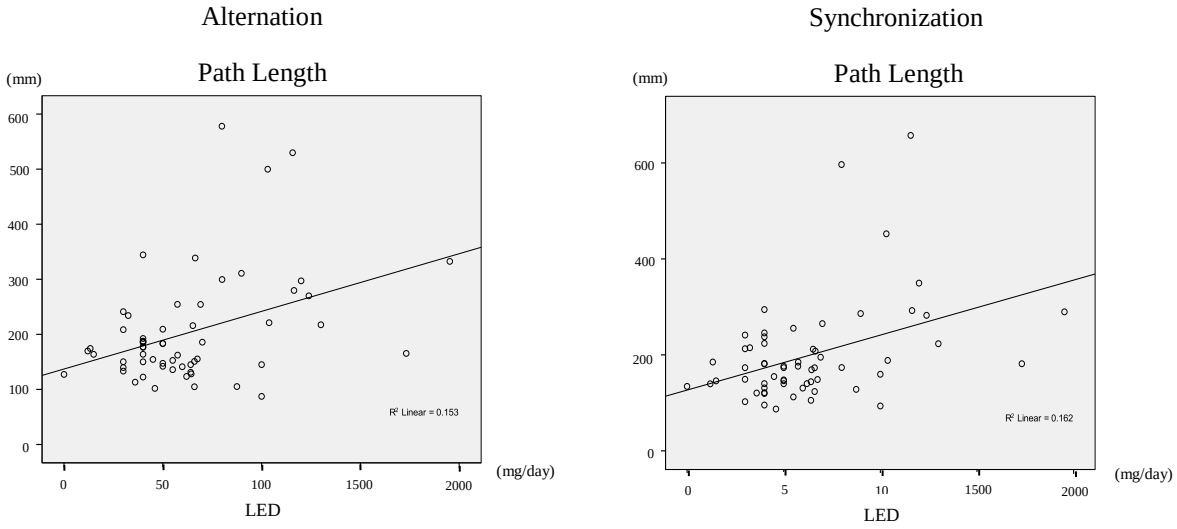
**Table 5.3**
The averages and standard deviations of arm swing alternation (ALT) and synchronization (SYN) comparing between the patients with and without freezing of gait (FOG)

| Parameters | FOG (n=39) | non-FOG (n=21) | *p-value* | FOG (n=39) | non-FOG (n=21) | *p-value* |
|---|---|---|---|---|---|---|
| | Alternation | | | Synchronization | | |
| Path length, mm (SD) | 217.5 (114.6) | 175.6 (52.15) | 0.399 | 215.3 (126.2) | 171.72 (48.82) | 0.334 |
| Sway area, $cm^2$ (SD) | 33.9 (31.1) | 22.79 (15.15) | 0.178 | 31.24 (29.41) | 16.92 (8.94) | 0.013* |
| RMS (SD) | 8.48 (7.74) | 5.98 (5.52) | 0.183 | 7.74 (6.7) | 4.67 (2.68) | 0.010* |
| Max ML, cm (SD) | 1.73 (2.23) | 1.87 (2.86) | 0.744 | 1.05 (2.19) | 0.83 (2.06) | 0.484 |
| Min ML, cm (SD) | -3.55 (2.73) | -2.75 (1.85) | 0.362 | -3.19 (2.63) | -2.15 (1.97) | 0.055 |
| Max AP, cm (SD) | 5.96 (1.64) | 5.13 (1.93) | 0.060 | 6.09 (1.83) | 5.09 (1.86) | 0.078 |
| Min AP, cm (SD) | 0.5 (1.91) | 0.47 (1.79) | 0.784 | -3.34 (17.96) | -0.33 (1.79) | 0.654 |
| Δ ML, cm (SD) | 5.27 (2.88) | 4.62 (2.16) | 0.254 | 4.23 (2.16) | 2.97 (0.99) | 0.013* |
| Δ AP, cm (SD) | 5.46 (1.99) | 4.66 (1.03) | 0.171 | 9.43 (17.85) | 5.43 (1.4) | 0.015* |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio-lateral displacement - Minimal Medio- lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement. Mann-Whitney U test was calculated.

The correlation sub-analyses of FOG and non – FOG. In alternation pattern, positive correlations were noticed between LED and COP parameters (PL, SA, Δ ML and Δ AP) as illustrated in Fig. 5.2, and between DD and PL (*p = 0.046*). The negative correlation was found in age of onset and PL (*p = 0.029*). In non-FOG group, positive correlation was observed between DD and Δ ML (*p = 0.008*) as shown in Table 5.4. In synchronization pattern, positive correlations were also noticed between LED and COP parameters (PL, SA, Δ ML and Δ AP) as illustrated in Fig. 5.4, and between DD and PL (*p = 0.012*), SA were also presented the positive correlations, as well as fall history and SA, Δ ML in the FOG group as shown in Table 5.5.

**Fig. 5.2.** Correlation analysis between LED and path length (PL) in arm swing conditions (Alternation (Alt) and Synchronization (Syn).




Multiple regression analyses were calculated between path length (PL) and clinical variables as shown in Table 5.6. Relationships were observed in PD-Total-ALT; levodopa ($R^2$ = 0.177, *p = 0.001*) and LED ($R^2$ = 0.153, *p = 0.002*). In PD-Total-SYN, relationships were noticed in levodopa ($R^2$ = 0.158, *p = 0.002*) and LED ($R^2$ = 0.162, *p = 0.001*). Meanwhile, we found relationship in PD+FOG-ALT in levodopa ($R^2$ = 0.189, *p = 0.007*) and LED ($R^2$ = 0.171, *p = 0.011*) as well. In PD+FOG-SYN, associations were found in levodopa ($R^2$ = 0.163, *p = 0.013*) and LED ($R^2$ = 0.154, *p = 0.016*) as well. Relationships were also expressed in PD-FOG-ALT in levodopa ($R^2$ = 0.351, *p = 0.005*) and LED ($R^2$ = 0.190, *p = 0.048*).

**Table 5.4**
Correlations of each clinical variablse between PD patients with FOG and non – FOG in arm swing alternation.

| | Posturographic Variable | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | FOG (n=39) | | | | non-FOG (n=21) | | | |
| | Path Length | Sway Area | ΔML | ΔAP | Path Length | Sway Area | ΔML | ΔAP |
| Gender | NS | NS | NS | NS | NS | NS | NS | NS |
| Age | NS | NS | NS | NS | NS | NS | NS | NS |
| Age of onset | -0.358 (0.029)* | NS | NS | NS | NS | NS | NS | NS |
| DD | 0.330 (0.046)* | NS | NS | NS | NS | NS | 0.442 (0.045)* | NS |
| H&Y | NS | NS | NS | NS | NS | NS | NS | NS |
| UPDRS | NS | NS | NS | NS | NS | NS | NS | NS |
| LED | 0.481 (0.003)* | 0.466 (0.004)* | 0.496 (0.002)* | -0.393 (0.016)* | NS | NS | NS | NS |
| PIGD | NS | NS | NS | NS | NS | NS | NS | NS |
| Axial | NS | NS | NS | NS | NS | NS | NS | NS |
| TMSE | NS | NS | NS | NS | NS | NS | NS | NS |
| ABC | NS | NS | NS | NS | NS | NS | NS | NS |
| Mini-BESTest | NS | NS | NS | NS | NS | NS | NS | NS |
| FOG-Q | NS | NS | NS | NS | NS | NS | NS | NS |
| MoCA | NS | NS | NS | NS | NS | NS | NS | NS |
| SE-ADL | NS | NS | NS | NS | NS | NS | NS | NS |

Correlation (p-value); ALT, Alternation; SYN, Synchronization; ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement; DD, Duration of disease; H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; LED, Levodopa equivalent dose; PIGD, Postural Instability and gait disorder; TMSE; Thai mental state examination; ABC, Activities of balance confident; FOG-Q, Freezing of gait questionnaire; MOCA; Montreal cognitive assessment; SE ADL, Schwab & England Activities of Daily Living. Spearman correlation was calculated. NS, Not significant.

**Table 5.5**
Correlations of each clinical variable between PD patiemts with FOG and non – FOG in arm swing synchronization.

| | Posturographic Variable | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | FOG (n=39) | | | | non-FOG (n=21) | | | |
| | Path Length | Sway Area | ΔML | ΔAP | Path Length | Sway Area | ΔML | ΔAP |
| Gender | NS | NS | NS | NS | NS | NS | NS | NS |
| Age | NS | NS | NS | NS | NS | NS | NS | NS |
| Age of onset | -0.395 (0.015)* | -0.323 (0.050)* | -0.037 (0.024)* | -0.369 (0.025)* | NS | NS | NS | NS |
| DD | 0.408 (0.012)* | 0.375 (0.022)* | NS | 0.405 (0.013)* | NS | NS | NS | NS |
| H&Y | NS | NS | NS | NS | NS | NS | NS | NS |
| UPDRS | NS | NS | NS | NS | NS | NS | NS | NS |
| LED | 0.499 (0.002)* | 0.516 (0.001)* | 0.420 (0.010)* | 0.505 (0.001)* | NS | NS | NS | NS |
| PIGD | NS | NS | NS | NS | NS | NS | NS | NS |
| Axial | NS | NS | NS | NS | NS | NS | NS | NS |
| TMSE | NS | NS | NS | NS | NS | NS | NS | NS |
| ABC | NS | NS | NS | NS | NS | NS | NS | NS |
| Mini-BESTest | NS | NS | NS | NS | NS | NS | NS | NS |
| FOG-Q | NS | NS | NS | NS | NS | NS | NS | NS |
| MoCA | NS | NS | NS | NS | NS | NS | NS | NS |
| SE-ADL | NS | NS | NS | NS | NS | NS | NS | NS |

Correlation (p-value); ALT, Alternation; SYN, Synchronization; ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement; DD, Duration of disease; H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; LED, Levodopa equivalent dose; PIGD, Postural Instability and gait disorder; TMSE; Thai mental state examination; ABC, Activities of balance confident; FOG-Q, Freezing of gait questionnaire; MOCA; Montreal cognitive assessment; SE ADL, Schwab & England Activities of Daily Living. Spearman correlation was calculated. NS, Not significant.

**Table 5.6**
Multiple regression analyses between clinical predictors and path length in motor session I

| | Clinical variables | Regression statistic | | | | | |
|---|---|---|---|---|---|---|---|
| Group | | $R^2$ | Adj $R^2$ | $\Delta R^2$ | df | f | *p* |
| $PD_{Total}$-ALT | Medication | | | | | | |
| | 1.Levodopa | 0.177 | 0.163 | 0.177 | 1, 58 | 12.513 | < 0.001** |
| | 2.LED | 0.153 | 0.139 | 0.153 | | 10.491 | 0.002* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.002 | -0.015 | 0.002 | | 0.115 | 0.735 |
| | 4.UPDRS III | 0.025 | 0.008 | 0.025 | | 1.494 | 0.226 |
| | 5. DD | 0.052 | 0.035 | 0.052 | | 0.081 | 0.081 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.032 | 0.015 | 0.032 | | 1.903 | 0.173 |
| $PD_{Total}$-SYN | Medication | | | | | | |
| | 1.Levodopa | 0.158 | 0.143 | 0.158 | 1, 58 | 10.852 | 0.002* |
| | 2.LED | 0.162 | 0.148 | 0.162 | | 11.236 | 0.001* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.000 | -0.017 | 0.000 | | 0.023 | 0.880 |
| | 4.UPDRS III | 0.027 | 0.010 | 0.027 | | 1.595 | 0.212 |
| | 5. DD | 0.037 | 0.020 | 0.037 | | 2.203 | 0.143 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.015 | -0.002 | 0.015 | | 0.872 | 0.354 |
| PD+FOG-ALT | Medication | | | | | | |
| | 1.Levodopa | 0.189 | 0.166 | 0.189 | 1, 35 | 8.141 | 0.007* |
| | 2.LED | 0.171 | 0.147 | 0.171 | | 7.210 | 0.011* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.001 | -0.028 | 0.001 | | 0.030 | 0.864 |
| | 4.UPDRS III | 0.024 | -0.004 | 0.024 | | 0.872 | 0.357 |
| | 5. DD | 0.055 | 0.028 | 0.055 | | 2.031 | 0.163 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.001 | -0.027 | 0.001 | | 0.047 | 0.829 |
| PD+FOG-SYN | Medication | | | | | | |
| | 1.Levodopa | 0.163 | 0.139 | 0.163 | 1, 35 | 6.812 | 0.013* |
| | 2.LED | 0.154 | 0.130 | 0.154 | | 6.368 | 0.016* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.001 | -0.027 | 0.001 | | 0.043 | 0.837 |
| | 4.UPDRS III | 0.057 | 0.030 | 0.057 | | 2.097 | 0.156 |
| | 5. DD | 0.066 | 0.039 | 0.066 | | 2.454 | 0.126 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.002 | -0.027 | 0.002 | | 0.063 | 0.804 |
| PD-FOG-ALT | Medication | | | | | | |
| | 1.Levodopa | 0.351 | 0.317 | 0.351 | 1, 19 | 10.269 | 0.005* |
| | 2.LED | 0.190 | 0.148 | 0.190 | | 4.471 | 0.048* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.005 | -0.048 | 0.005 | | 0.086 | 0.773 |
| | 4.UPDRS III | 0.001 | -0.051 | 0.001 | | 0.024 | 0.879 |
| | 5. DD | 0.063 | 0.014 | 0.063 | | 1.287 | 0.271 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.013 | -0.039 | 0.013 | | 0.250 | 0.623 |
| PD-FOG-ALT | Medication | | | | | | |
| | 1.Levodopa | 0.123 | 0.077 | 0.123 | 1, 19 | 2.666 | 0.119 |
| | 2.LED | 0.054 | 0.004 | 0.054 | | 1.089 | 0.310 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.024 | -0.028 | 0.024 | | 0.464 | 0.504 |
| | 4.UPDRS III | 0.022 | -0.029 | 0.022 | | 0.429 | 0.520 |
| | 5. DD | 0.000 | -0.053 | 0.000 | | 0.002 | 0.962 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.007 | -0.045 | 0.007 | | 0.136 | 0.716 |

Adj, adjusted; $\Delta R^2$, R square change; LED, levodopa equivalent dose; H&Y, Hoehn and Yahr scale, UPDRS III, Unified Parkinson's Disease Rating Scale; DD, duration of disease; FOG-Q, Freezing of gait questionnaire; ALT, alternation; SYN, synchronization.
*$p < 0.05$, **$p < 0.01$.

Table 5.7 shows odds ratio (OR) for postural instability (PI) for falls compared to no falls in arm swing alternation (Alt). The odds in H&Y stage 3 is 0.916 indicating increased odds of PD with falls. The 95% confidence interval of the odds ratio (0.009, 0.779) indicates that odds of PD in H&Y stage 3 is significant higher to face falls compared to no falls (at 0.05 significance level) because the CI does not contain 1.

The odds ratio (0.916) means there is a statistically significant "association" between PI and falls in H&Y stage 3. The 95% confidence interval for the OR does not contain 1; we can conclude that there is a statistically significant "association" between PI and falls in path length (PL) during arm swing alternation in H&Y stage 3. 91.6 % of H&Y stage 3 in arm swing alternation revealed the probability of falls in PD patients with PI.

**Table 5.7**
Odds Ratio in arm swing alternation (Alt)

| H&Y | Odds Ratio | 95% CI | Pearson Chi-Square | Likelihood Ratio |
|---|---|---|---|---|
| 1 | [Δ] | [Δ] | 0.129 | 0.058 |
| 1.5 | 0.474 | 0.031 – 8.867 | 0.651 | 0.658 |
| 2 | [Δ] | [Δ] | 0.064 | 0.068 |
| 2.5 | 0.227 | 0.192 – 3.115 | 0.717 | 0.719 |
| 3 | 0.916 | 0.009 – 0.779 | 0.009* | 0.030* |

[Δ] Cannot be computed odds ratio on account of no patients with no falls

** $p < 0.05$, ** $p < 0.001$*

Accordingly, Table 5.8 represents odds ratio for PI for falls compared to no falls in arm swing synchronization (Syn). The odds in H&Y stage 3 is 0.827 indicating increased odds of PD with falls. The 95% confidence interval of the odds ratio (0.030, 0.987) indicates that odds of PD in H&Y stage 3 is significant higher to face falls compared to no falls (at 0.05 significance level) because the CI does not contain 1.

The odds ratio (0.827) means there is a statistically significant "association" between PI and falls. The 95% confidence interval for the OR does not contain 1; we can conclude that there is a statistically significant "association" between PI and falls in path length (PL) of arm swing synchronization in H&Y stage 3. 82.7 % of H&Y stage 3 in arm swing synchronization expressed the probability of falls in PD patients with PI as shown in Table 5.8.

**Table 5.8**
Odds Ratio in arm swing synchronization

| H&Y | Odds Ratio | 95% CI | Pearson Chi-Square | Likelihood Ratio |
|---|---|---|---|---|
| 1 | [Δ] | [Δ] | 0.129 | 0.058 |
| 1.5 | 0.474 | 0.031 – 8.867 | 0.651 | 0.658 |
| 2 | 0.227 | 0.192 – 3.115 | 0.717 | 0.719 |
| 2.5 | 0.375 | 0.148 – 2.632 | 0.519 | 0.525 |
| 3 | 0.827 | 0.030 – 0.987 | 0.032* | 0.036* |

[Δ] Cannot be computed odds ratio on account of no patients with no falls

** $p < 0.05$, ** $p < 0.001$*

## 5.3 Discussion

This research is mainly to explain relationship between the arm swing patterns and clinical assessments in patients with Parkinson's disease (PD) with different stages of the disease. Although studies of dynamic postural control during arm swinging are rare, it is important to measure dynamic standing balance to gain more understanding of postural control in various aspects in order to be fundamental data before creating a measure for balance assessment. Postural instability (PI) in PD is mysterious. In this study, we found interesting significant results toward postural control in PD. The center of pressure (CoP) during arm swing movements in PD patients were significantly different with healthy elderly control subjects, which is consistent with the study of Huang and collages (Huang et al., 2012). The alterations of CoP as regards the 2 arm swing patterns; alternation (Alt) and synchronization (Syn) are significant differences in patients with PD. However, the comparison between PD with FOG (PD+FOG) and without FOG (PD-FOG) revealed the significant differences in arm swing synchronization (Syn) in sway area (SA), root mean square (RMS), ΔML and ΔAP which might be originated from the effects of the arm swing synchonization (Syn) pattern providing more interferences toward posture, more than the arm swing alternation (Alt). In other word, arm swing synchonization (Syn) influenced on the alteration of center of mass (CoM) more than arm swing alternation (Alt) by showing the significant differences of the posturographic data toward center of pressure (CoP) (Swanenburg et al., 2013 & Horak et al., 2015). Interestingly, These differences were obvious between CoP of PD+FOG and PD-FOG (Pelykh et al., 2015; Schlenstedt et al., 2016).

The relationships between path length (PL) and levodopa equvalent dose (LED) in both arm swing alternation (Alt) and synchronization (Syn) were found in this study which represents association between the alteration of CoP during swing arms and the medication (Beuter et al., 2008). The correlations between various clnical assessments and posturographic variables in arm swing alternation (Alt) and synchronization (Syn) in PD with FOG (PD+FOG) and without FOG (PD-FOG) were expressed in PD+FOG and PD-FOG which showed the relationship between postural instability (PI), FOG and clinical assessments. The distinctive clinical factors were age of onset, duration of disease (DD) and LED which is consistent with the study of (Johnson et al., 2013). This study presented models of predicting PD with PI, PD+FOG and PD-FOG by showing the association between PI and medication (Beuter et al., 2008). Even though, the R – squared of each model is low, those models are significantly exist. The odds ratios illustrated the evidence of PD patients facing falls in H&Y stage 3 in both arm swing alternation (Alt) and synchronization (Syn), which is confirmed the relation between severity of disease and PI in PD (Geurts et al., 2011; Amboni et al., 2015). Prediction models with low R – squared have been found in studies of medicine, public healths and so on with individual aspects. It is noted that PD patients with H&Y stage 3 have high percent of odds in facing falls significantly in both arm swing patterns, which can be interpeted that there is a relationship of PI and falls and severity of disease in PD. However, it is hardly to state that the two arm swing patterns can be clinical predictors of PI in PD. Further studies need to be conducted to access more understanding of PI, FOG and arm swing coordination in patients with PD.

## 5.4 Conclusion

Arm swing alternation and synchronization patterns influence on the alteration of center of pressure (CoP) in patients with Parkinson's disease (PD). Freezing of gait (FOG) influences on postural control of PD patients in arm swing alternation (Alt) and synchronization (Syn) were not clear. Correlations between CoP during both arm swing patterns and clinical assessments were significantly noticed, particularly in PD with FOG (PD+FOG). Models to predict FOG from postural instability (PI), the arm swing patterns, and medication might be possible in the future. The concept of applying arm swinging to predict falls is revealed in moderate PD.

# CHAPTER 6

# EFFICACY OF AUDITORY CUES ON ARM SWING TOWARD POSTURAL CONTROL IN PARKINSON'S DISEASE

This chapter determines the effects of auditory cues on the two arm swing patterns; alternation and synchronization toward the alteration of center of pressure (CoP) in patients with Parkinson's disease (PD). Dynamic postural control during arm swinging with auditory cues (AC) was carried out. The aim of this study is to determine the effects of auditory cues on postural instability (PI) in patients with PD. We hypothesized that whether the arm swing patterns can be clinical predictors of postural instability in PD.

## 6.1 Research Methodology

*Participants*

The details of participants were explained in Chapter III.

*Instrumentation*

The details of instrumentation was described in Chapter III.

*Experimental Procedures*

The participants were instructed to stand naturally on the Nintendo Wii balance platform (NWBB) and look at a marker, which was 3 meters from the board. The study was performed by the same balance platform, which was calibrated daily before each data collection. The medial borders of each foot were apart about 10 centimeters. The subjects were asked to perform two arm swing patterns; alternation (Alt) and synchronization (Syn) with auditory cues (AC). The test was

carried out by inviting subjects to stand on the platform and swing arms followed by given signals and programmed sounds for a total of 170 seconds. Each session was proceeded followed by a written program. The program collected the data automatically.

The center of pressure (CoP) in terms of path length (PL), sway area (SA), root mean square (RMS), medio-lateral (ML) and antero-posterior (AP) (Visser et al., 2008) were analyzed corresponding with the Unified Parkinson's Disease Rating Scale (UPDRS) motor (item 18-31) subscore (Visser et al., 2003), levodopa equivalent dose (LED) (Alexoudi et al. 2015), freezing of gait questionnaire (FOG-Q) (Nilsson & Hagell, 2009) and Montreal Cognitive Assessment (MoCA) (Kandiah et al., 2014).

*Statistical analysis*

The time series of CoP trajectories of the total subjects (n=60) were reported in terms of path length (PL), sway area (SA), root mean square (RMS), antero-posterior (AP) and medio-lateral (ML) displacements by the Wii program. The descriptive analysis of the posturographic parameters was evaluated in average (mean) and standard deviation (SD).

SPSS 22.0 (IBM Corp, Armonk, NY) was applied to calculate the data. All variables were tested the normality by Kolmogorov-Smirnov. Age, age of onset, duration of disease, H&Y, UPDRS (motor score), LED, FOG-Q, TMSE and MoCA were analyzed means by the nonparametric Mann-Whitney U test and Chi-square test, appropriately. The sub-analysis was employed by categorizing the participants into two groups, freezing of gait (FOG) (n=39) and non-freezing of gait (non-FOG) (N=21). PD patients with FOG were classified by total score of FOG-Q ≥6 score based on the six questions of freezing of gait questionnaire (FOG-Q) (Giladi et al., 2000). The comparison of means' differences of Center of Pressure (CoP) between arm swing alternation with no cues (Alt_NC) and with auditory cues (Alt_AC) and synchronization with no cues (Syn_NC) and with auditory cues (Syn_AC) were calculated by Wilcoxon Signed-Rank test. The correlations between clinical variables and posturographic data after Alt_AC and after Syn_AC were analyzed by Spearman’s rho correlation. Multiple regression analyzes were proceeded whether path length (PL) variables in Alt_AC and Syn_AC predict PD, PD with FOG (PD+FOG) and PD without FOG (PD-FOG). The statistical significance level was set at *p-value* less than 0.05.

## 6.2 Results

The study of the effects of arm swing toward postural control comparing between no cues (NC) and auditory cues (AC) in 60 patients with Parkinson's disease (PD). The averages and standard deviations of arm swing alternation (Alt) and synchronization (Syn) were shown in Table 6.1. In arm swing alternation, statistically significant differences in maximal ML ($p = 0.042$), maximal AP ($p = 0.025$) and minimal AP ($p = 0.010$) were noticed. Meanwhile, in arm swing synchronization, statistically significant differences in were observed. RMS ($p = 0.042$), maximal ML ($p = 0.054$), maximal AP ($p = 0.029$), minimal AP ($p = 0.041$) and Δ ML ($p = 0.002$) as shown in Table 6.1 and 6.2, respectively.

**Table 6.1**
The averages and standard deviations of arm swing alternation (Alt) comparing between no cues and auditory cues.

| Parameters | No Cue | Auditory Cues | *p-value* |
|---|---|---|---|
| Alternation | | | |
| Path length, mm (SD) | 202.81 (98.93) | 196.67 (87.7) | 0.740 |
| Sway area, $cm^2$ (SD) | 29.99 (27) | 30.46 (26.11) | 0.763 |
| RMS (SD) | 7.6 (7.1) | 8.15 (7.89) | 0.241 |
| Max ML, cm (SD) | 1.78 (2.23) | 2.91 (6.84) | 0.042* |
| Min ML, cm (SD) | -3.27 (2.47) | -3.08 (2.22) | 0.502 |
| Max AP, cm (SD) | 5.67 (1.78) | 5.83 (1.81) | 0.025* |
| Min AP, cm (SD) | 0.49 (1.86) | 0.88 (1.92) | 0.010* |
| Δ ML, cm (SD) | 5.04 (2.65) | 5.99 (6.65) | 0.321 |
| Δ AP, cm (SD) | 5.18 (1.75) | 4.95 (1.85) | 0.645 |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement. Wilcoxon Signed Ranks test was calculated.

**Table 6.2**
The averages and standard deviations of arm swing synchronization (Syn) comparing between no cues and auditory cues.

| Parameters | No Cues | Auditory Cues | *p-value* |
|---|---|---|---|
| Synchronization | | | |
| Path length, mm (SD) | 198.6 (105.2) | 195.3 (91.87) | 0.435 |
| Sway area, $cm^2$ (SD) | 25.75 (24.63) | 29.3 (28.28) | 0.100 |
| RMS (SD) | 6.57 (5.68) | 7.2 (5.59) | 0.042* |
| Max ML, cm (SD) | 0.96 (2.12) | 1.32 (2.1) | 0.054* |
| Min ML, cm (SD) | -2.79 (2.43) | -2.84 (2.3) | 0.925 |
| Max AP, cm (SD) | 5.71 (1.89) | 6.72 (5.68) | 0.029* |
| Min AP, cm (SD) | -2.19 (14.15) | -0.18 (1.89) | 0.041* |
| Δ ML, cm (SD) | 3.75 (1.89) | 4.16 (2.12) | 0.002* |
| Δ AP, cm (SD) | 7.89 (14.1) | 6.9 (5.87) | 0.972 |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement. Wilcoxon Signed Ranks test was calculated.

The sub-analysis of arm swing patterns comparing between the patients who presented freezing of gait (FOG) and without freezing of gait (non-FOG) (39:21 cases). In arm swing alternation, it was revealed the effects of auditory cues (AC) on the FOG group in minimal AP (*p = 0.022*), and on the non-FOG group in maximal AP (*p = 0.023*) as explained in Table 6.3. In arm swing synchronization, auditory cues indicated its effects on Δ ML significantly (*p = 0.016*) in the FOG group. In other words, no significant differences were found in non-FOG group as expressed in Table 6.4.

**Table 6.3**
The averages and standard deviations of arm swing alternation (Alt) comparing between no cues and auditory cues in Parkinson's disease (PD) patients with and without freezing of gait (FOG).

| Parameters | FOG (n=39) | | | non-FOG (n=21) | | |
|---|---|---|---|---|---|---|
| | No Cues | Auditory Cues | *p-value* | No Cues | Auditory Cues | *p-value* |
| Alternation | | | | | | |
| Path length, mm (SD) | 217.5 (114.6) | 204.1 (96.11) | 0.280 | 175.6 (52.15) | 183.1 (70.11) | 0.322 |
| Sway area, $cm^2$ (SD) | 33.9 (31.1) | 32.4 (27.7) | 0.845 | 22.79 (15.15) | 26.9 (23.25) | 0.414 |
| RMS (SD) | 8.48 (7.74) | 8.44 (6.95) | 0.469 | 5.98 (5.52) | 7.42 (9.12) | 0.305 |
| Max ML, cm (SD) | 1.73 (2.23) | 2.07 (2.58) | 0.192 | 1.87 (2.86) | 4.22 (10.46) | 0.794 |
| Min ML, cm (SD) | -3.55 (2.73) | -3.25 (2.31) | 0.438 | -2.75 (1.85) | -2.73 (1.97) | 0.958 |
| Max AP, cm (SD) | 5.96 (1.64) | 5.93 (1.87) | 0.290 | 5.13 (1.93) | 5.63 (1.67) | 0.023* |
| Min AP, cm (SD) | 0.5 (1.91) | 1 (2.08) | 0.022* | 0.47 (1.79) | 0.7 (1.67) | 0.135 |
| Δ ML, cm (SD) | 5.27 (2.88) | 5.32 (2.45) | 0.577 | 4.62 (2.16) | 6.94 (10.24) | 0.357 |
| Δ AP, cm (SD) | 5.46 (1.99) | 4.95 (2.15) | 0.171 | 4.66 (1.03) | 4.93 (1.17) | 0.274 |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement. Wilcoxon Signed Ranks test was calculated.

**Table 6.4**

The averages and standard deviations of arm swing synchronization (Syn) comparing between no cues and auditory cues in Parkinson's disease (PD) patients with and without freezing of gait (FOG).

| Parameters | FOG (n=39) | | | non-FOG (n=21) | | |
|---|---|---|---|---|---|---|
| | No Cues | Auditory Cues | *p-value* | No Cues | Auditory Cues | *p-value* |
| Synchronization | | | | | | |
| Path length, mm (SD) | 215.3 (126.2) | 210.5 (110.2) | 0.229 | 171.72 (48.82) | 171.43 (44.33) | 0.794 |
| Sway area, $cm^2$ (SD) | 31.24 (29.41) | 35.25 (34.15) | 0.421 | 16.92 (8.94) | 20 (10.26) | 0.114 |
| RMS (SD) | 7.74 (6.7) | 8.53 (6.61) | 0.163 | 4.67 (2.68) | 5.13 (2.38) | 0.149 |
| Max ML, cm (SD) | 1.05 (2.19) | 1.39 (2.39) | 0.139 | 0.83 (2.06) | 1.21 (1.58) | 0.205 |
| Min ML, cm (SD) | -3.19 (2.63) | -3.25 (2.56) | 0.983 | -2.15 (1.97) | -2.21 (1.68) | 0.821 |
| Max AP, cm (SD) | 6.09 (1.83) | 7.46 (7.13) | 0.058 | 5.09 (1.86) | 5.56 (1.43) | 0.192 |
| Min AP, cm (SD) | -3.34 (17.96) | -0.28 (2.04) | 0.109 | -0.33 (1.79) | -0.03 (1.67) | 0.170 |
| Δ ML, cm (SD) | 4.23 (2.16) | 4.64 (2.44) | 0.016* | 2.97 (0.99) | 3.42 (1.18) | 0.067 |
| Δ AP, cm (SD) | 9.43 (17.85) | 7.74 (3.35) | 0.728 | 5.43 (1.4) | 5.59 (1.4) | 0.575 |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement. Wilcoxon Signed Ranks test was calculated.

The correlation sub-analyses of each clinical assessment and path length after swinging arms alternate and synchronous while the PD patients simultaneously received auditory cues (AC) were calculated. We found AC has effects on center of pressure (CoP) of patients with Parkinson's disease (PD) in arm swing alternate. Positive correlations between Hoehn and Yahr (H&Y) and path length (PL) ($p = 0.016$), Levodopa equivalent dose (LED) and sway area (SA) ($p = 0.008$), and fall history and PL ($p = 0.022$). Negative correlation was observed between Thai mental state examination and SA ($p = 0.035$). On the other hand, no significant correlations of after swinging arm synchronous as shown in Table 6.5.

Multiple regression analyses were calculated between path length (PL) and clinical predictor variables. Associations between the variables were observed in PD-Total-ALT; levodopa ($R^2 = 0.169$, $p = 0.001$) and LED ($R^2 = 0.115$, $p = 0.005$). In PD-Total-SYN, relationships were noted in levodopa ($R^2 = 0.236$, $p < 0.001$) and LED ($R^2 = 0.194$, $p < 0.001$) as well. Meanwhile, we found relationship in PD+FOG-ALT in levodopa ($R^2 = 0.230$, $p = 0.003$) and LED ($R^2 = 0.205$, $p = 0.005$) also. In PD+FOG-SYN, relationships were also noticed in levodopa ($R^2 = 0.194$, $p = 0.006$) and LED ($R^2 = 0.168$, $p = 0.012$). On the other hand, the relationship was found merely in PD-FOG-ALT in levodopa ($R^2 = 0.235$, $p = 0.026$), and PD-FOG-ALT in levodopa ($R^2 = 0.219$, $p = 0.033$) as shown in Table 6.6.

**Table 6.5**
Correlations of each clinical assessment and after swinging arms alternation (Alt) and synchronization (Syn) with auditory cues in patients with Parkinson's disease (PD).

| | Posturographic Variable | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | After ALT | | | | After SYN | | | |
| | Path Length | Sway Area | ΔML | ΔAP | Path Length | Sway Area | ΔML | ΔAP |
| Age | NS | NS | NS | NS | NS | NS | NS | NS |
| Age of onset | NS | NS | NS | NS | NS | NS | NS | NS |
| DD | NS | NS | NS | NS | NS | NS | NS | NS |
| H&Y | 0.314 (0.016)* | NS | NS | NS | NS | NS | NS | NS |
| UPDRS | NS | NS | NS | NS | NS | NS | NS | NS |
| LED | NS | 0.166 (0.008)* | NS | NS | NS | NS | NS | NS |
| PIGD | NS | NS | NS | NS | NS | NS | NS | NS |
| Axial | NS | NS | NS | NS | NS | NS | NS | NS |
| TMSE | NS | -0.275 (0.035)* | NS | NS | NS | NS | NS | NS |
| ABC | NS | NS | NS | NS | NS | NS | NS | NS |
| Mini-BESTest | NS | NS | NS | NS | NS | NS | NS | NS |
| FOG-Q | NS | NS | NS | NS | NS | NS | NS | NS |
| MoCA | NS | NS | NS | NS | NS | NS | NS | NS |
| SE-ADL | NS | NS | NS | NS | NS | NS | NS | NS |

Correlation (p-value); ALT, Alternation; SYN, Synchronization; ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement; DD, Duration of disease; H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; LED, Levodopa equivalent dose; PIGD, Postural Instability and gait disorder; TMSE; Thai mental state examination; ABC, Activities of balance confident; FOG-Q, Freezing of gait questionnaire; MOCA; Montreal cognitive assessment; SE ADL, Schwab & England Activities of Daily Living. Spearman correlation was calculated. NS, Not significant.

**Table 6.6**
Multiple regression analyses between clinical predictors and path length in motor session II

| | Clinical variables | Regression statistic | | | | | |
|---|---|---|---|---|---|---|---|
| Group | | $R^2$ | Adj $R^2$ | $\Delta R^2$ | df | f | *p* |
| $PD_{Total}$-ALT | Medication | | | | | | |
| | 1.Levodopa | 0.169 | 0.154 | 0.169 | 1, 58 | 11.585 | 0.001** |
| | 2.LED | 0.115 | 0.131 | 0.115 | | 8.556 | 0.005* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.001 | -0.017 | 0.001 | | 0.031 | 0.860 |
| | 4.UPDRS III | 0.017 | 0.000 | 0.017 | | 0.972 | 0.328 |
| | 5. DD | 0.027 | 0.010 | 0.027 | | 1.606 | 0.210 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.018 | 0.001 | 0.001 | | 1.064 | 0.307 |
| $PD_{Total}$-SYN | Medication | | | | | | |
| | 1.Levodopa | 0.236 | 0.223 | 0.236 | 1, 58 | 17.618 | < 0.001** |
| | 2.LED | 0.194 | 0.179 | 0.194 | | 13.679 | < 0.001* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.005 | -0.013 | 0.005 | | 0.274 | 0.603 |
| | 4.UPDRS III | 0.007 | -0.011 | 0.007 | | 0.390 | 0.535 |
| | 5. DD | 0.050 | 0.034 | 0.050 | | 3.019 | 0.088 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.030 | 0.013 | 0.030 | | 1.784 | 0.187 |
| PD+FOG-ALT | Medication | | | | | | |
| | 1.Levodopa | 0.230 | 0.208 | 0.230 | 1, 35 | 10.482 | 0.003* |
| | 2.LED | 0.205 | 0.183 | 0.205 | | 9.046 | 0.005* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.006 | -0.022 | 0.006 | | 0.217 | 0.644 |
| | 4.UPDRS III | 0.019 | -0.009 | 0.019 | | 0.662 | 0.421 |
| | 5. DD | 0.087 | 0.061 | 0.087 | | 3.319 | 0.077 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.014 | -0.014 | 0.014 | | 0.495 | 0.486 |
| PD+FOG-SYN | Medication | | | | | | |
| | 1.Levodopa | 0.194 | 0.171 | 0.194 | 1, 35 | 8.449 | 0.006* |
| | 2.LED | 0.168 | 0.144 | 0.168 | | 7.075 | 0.012* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.001 | -0.028 | 0.001 | | 0.034 | 0.855 |
| | 4.UPDRS III | 0.057 | 0.030 | 0.057 | | 2.213 | 0.154 |
| | 5. DD | 0.057 | 0.030 | 0.057 | | 2.113 | 0.155 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.001 | -0.027 | 0.001 | | 0.039 | 0.844 |
| PD-FOG-ALT | Medication | | | | | | |
| | 1.Levodopa | 0.235 | 0.195 | 0.235 | 1, 19 | 5.835 | 0.026* |
| | 2.LED | 0.118 | 0.072 | 0.118 | | 2.550 | 0.127 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.088 | -0.044 | 0.008 | | 0.149 | 0.704 |
| | 4.UPDRS III | 0.000 | -0.052 | 0.000 | | 0.009 | 0.923 |
| | 5. DD | 0.114 | 0.067 | 0.114 | | 2.441 | 0.135 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.005 | -0.048 | 0.005 | | 0.086 | 0.773 |
| PD-FOG-SYN | Medication | | | | | | |
| | 1.Levodopa | 0.219 | 0.177 | 0.219 | 1, 19 | 5.314 | 0.033* |
| | 2.LED | 0.114 | 0.067 | 0.114 | | 2.435 | 0.135 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.000 | -0.052 | 0.000 | | 0.008 | 0.931 |
| | 4.UPDRS III | 0.001 | -0.052 | 0.001 | | 0.020 | 0.890 |
| | 5. DD | 0.018 | -0.034 | 0.018 | | 0.345 | 0.564 |
| | Freezing of gait | | | | | | |
| | 6. FOG-Q | 0.003 | -0.050 | 0.003 | | 0.048 | 0.829 |

Adj, adjusted; $\Delta R^2$, R square change; LED, levodopa equivalent dose; H&Y, Hoehn and Yahr scale, UPDRS III, Unified Parkinson's Disease Rating Scale; DD, duration of disease; FOG-Q, Freezing of gait questionnaire; ALT, alternation; SYN, synchronization.
*$p < 0.05$, **$p < 0.01$.

Odds ratio for postural instability (PI) for falls compared to no falls in H&Y with different stages of the disease in arm swing alternation with auditory cues (Alt_AC) is shown in Table 6.7. The odds ratio in H&Y stage 3 cannot be computed because there was no PD patients with no falls (all patients presented falls, so no falls is "0").

**Table 6.7**
Odds Ratio in arm swing alternation (Alt) with auditory cues (AC)

| H&Y | Odds Ratio | 95% CI | Pearson Chi-Square | Likelihood Ratio |
|---|---|---|---|---|
| 1 | Δ | Δ | 0.087 | 0.033* |
| 1.5 | 0.081 | 0.092 – 12.671 | 0.950 | 0.950 |
| 2 | 0.227 | 0.192 – 3.115 | 0.717 | 0.719 |
| 2.5 | 0.313 | 0.302 – 5.712 | 0.717 | 0.714 |
| 3 | Δ | Δ | 0.005* | 0.003* |

Δ Cannot be computed odds ratio on account of no patients with no falls

** $p < 0.05$, ** $p < 0.001$*

Correspondingly, odds ratio for PI for falls compared to no falls in arm swing synchronization with auditory cues (Syn_AC) is presented in Table 6.8. The odds in H&Y stage 3 is 0.827 indicating increased odds of PD in falls in arm swing synchronization. The 95% confidence interval of the odds ratio (0.030, 0.987) indicates that odds of PD in H&Y stage 3 is significant higher to face falls compared to no falls (at 0.05 significance level) because the CI does not contain 1.

The odds ratio (0.827) means there is a statistically significant "association" between PI and falls. The 95% confidence interval for the OR does not contain 1; we can conclude that there is a statistically significant "association" between PI and falls in path length (PL) of Syn_AC in H&Y stage 3. 82.7 % of H&Y stage 3 in Syn_AC expressed the probability of falls in PD patients with PI.

**Table 6.8**
Odds Ratio in arm swing synchronization (Syn) with auditory cues (AC)

| H&Y | Odds Ratio | 95% CI | Pearson Chi-Square | Likelihood Ratio |
|---|---|---|---|---|
| 1 | Δ | Δ | 0.192 | 0.102 |
| 1.5 | 0.081 | 0.092 – 12.671 | 0.950 | 0.950 |
| 2 | 0.375 | 0.148 – 2.632 | 0.519 | 0.525 |
| 2.5 | 0.313 | 0.302 – 5.712 | 0.717 | 0.714 |
| 3 | 0.827 | 0.030 – 0.987 | 0.032* | 0.036* |

Δ Cannot be computed odds ratio on account of no patients with no falls

** $p < 0.05$, ** $p < 0.001$*

## 6.3 Discussion

This research is purposefully to investigate the effects of auditory cues on the two arm swing patterns; alternation (Alt) and synchronization (Syn) toward postural control in patients with Parkinson's disease (PD). The relationship between center of pressure (CoP) during swinging arms and receiving auditory cues (AC) and clinical assessments in Parkinson's disease (PD) was reported. Previous studies on dynamic standing balance evaluation during swinging arms are rare-defined; however, it is splendid to measure dynamic standing balance to gain more understanding of the effects of AC on dynamic postural control in PD patients, which will be fundamental knowledge before producing rehabilitation programs. Human's brain circuities are complex and mysterious. Even the deterioration occurred on basal ganglia (BG) causing PD, external cues such as visual, auditory cues can play roles on neural circuities, which help improve responses of body movements (Lewis et al., 2013; Wegen et al., 2016; van den Heuvel et al., 2016). In this study, significant differences of CoP during swinging arms between no cues and AC in PD patients have been found; nevertheless, the effects of AC toward postural control in PD with FOG (PD+FOG) and PD without FOG (PD-FOG) were not clearly revealed in both arm swing patterns; alternation (Alt) and synchronization (Syn). These might be resulted from the auditory cues set at 100% of arm swing cycle. Interestingly, the CoP after arm swing alternation (Alt) showed positive correlations between path length (PL) and Hoehn and Yahr (H&Y), between sway area (SA) and levodopa equivalent dose (LED) which implied regarding association of postural control, severity of disease and medication (Beuter et al., 2008).

This study presented models of predicting PD with PI, PD+FOG and PD-FOG by showing the association between PI and medication (Beuter et al., 2008). Although, the R – squared of each model is low, those models are significant. Prediction models with low R – squared have been found in health literature. The odds ratio (OR) illustrated the evidence of PD patients facing falls in H&Y stage 3 in arm swing synchronization (Syn) with AC, which is confirmed the relation between severity of disease and PI in PD (Geurts et al., 2011; Amboni et al., 2015). Further studies need to be conducted to access more understanding of PI, FOG and arm swing coordination in patients with PD.

## 6.4 Conclusion

Auditory cues (AC) effect on postural control during both arm swing alternation and synchronization patterns; however, the effects of AC on postural control of PD+FOG and PD-FOG were unclear. The effects of AC during arm swing synchronization in PD+FOG were also ambiguous. Correlations between CoP after arm swing alternation with auditory cues and clinical assessments were found. No significant correlations were observed between CoPs during arm swing synchronization in PD-FoG. Models to predict FOG from postural instability (PI), the arm swing patterns with auditory cues (AC) and medication might be possible in the future. The concept of applying arm swinging with auditory cues (AC) to predict falls is exposed in moderate PD.

# CHAPTER 7

# IMPACT OF COGNITIVE LOADING ON POSTURAL CONTROL IN PARKINSON'S DISEASE WITH FREEZING OF GAIT

This chapter investigates the part of cognitive function on postural stability in Parkinson's disease (PD) patients. We interfered the function by providing two external stimulators; reading (RE) and counting backward (CB) to the patients. Cognitive impairment (CI) is an important problem for patients with PD. It is a common non-motor symptom occurring in early stages and developed progressively to advanced stages of the disease. The purpose of this study is to study the effects of cognitive loading toward postural stability in PD patients particularly with FOG.

## 7.1 Research Methodology

*Participants*

The details of participants were explained in Chapter III.

*Instrumentation*

The details of instrumentation was described in Chapter III.

*Experimental Procedures*

The participants were instructed to stand naturally on the balance platform (Wii Fit) and look at a marker, which was 3 meters from the board. The study was performed by the same balance platform, which was calibrated daily before each data collection. The medial borders of each foot were apart about 10 centimeters. The subjects were asked to perform two tasks in

cognitive loading session, namely reading and counting backward. The test was carried by inviting subjects to stand on the platform and read a material as well as count days backward; starting from Sunday, Saturday, Friday,..... to Monday, for a total of 170 seconds. Each session was proceeded followed by a written program. The program collected the data automatically.

The center of pressure (CoP) in terms of path length (PL), sway area (SA), root mean square (RMS), mediol-ateral (ML) and antero-posterior (AP) (Visser et al., 2008) were analyzed corresponding with the Unified Parkinson's Disease Rating Scale (UPDRS) motor (item 18-31) subscore (Visser et al., 2003), levodopa equivalent dose (LED) (Alexoudi et al. 2015), freezing of gait questionnaire (FOG-Q) (Nilsson & Hagell, 2009), Thai Mental State Examination (TMSE; Muangpaisan et al., 2015) and Montreal Cognitive Assessment (MoCA) (Kandiah et al., 2014).

*Statistical analysis*

The CoP trajectories time series of of the total subjects (n=60) were reported in terms of path length (PL), sway area (SA), root mean square (RMS), antero-posterior (AP) and medio-lateral (ML) displacements by the Wii program. The descriptive analysis of the posturographic parameters was evaluated in average (mean) and standard deviation *(SD)*.

SPSS 22.0 (IBM Corp, Armonk, NY) was applied to calculate the data. All variables were tested the normality by Kolmogorov-Smirnov. Age, age of onset, duration of disease, H&Y, UPDRS (motor score), LED, FOG-Q, TMSE and MoCA were analyzed means by the nonparametric Mann-Whitney U test and Chi-square test, appropriately. A sub-analysis was employed by categorizing the participants into two groups, freezing of gait (FOG) (n=39) and non-freezing of gait (non-FOG) (N=21). PD patients with FOG were classified by a total score of FOG-Q ≥6. The comparison of mean differences of CoP between before I (before reading) and reading, and before II (before counting backward) and counting backward were calculated by Wilcoxon Signed-Rank test. The Spearman's rho correlation was utilized to calculate correlation between H&Y stages and posturographic parameters. The statistical significance level was set at *p-value* less than 0.05.

## 7.2 Results

*Clinical characteristics*

In total, 60 PD patients participated in this study and descriptive statistics were utilized to characterize the participants. Twenty-four (40%) were men, and 36 (60%) were women. The participants were 43 to 89 years old, and the mean age was 66.48 ± 10.32 years (M ± SD). The age of onset was 61.27 ± 10.96 years, duration of disease was 5.31 ± 3.42 years, and UPDRS motor score was 22.87 ± 12.18. The non-parametric statistics were utilized in this study and the participants' demographic and clinical assessments in PD-FOG and PD-non-FOG are summarized in Table 1. Mean ages (65.13 ± 10.32 vs. 69 ± 10.08, $p = 1.99$) and cognitive abilities test scores (18.87 ± 5.05 vs. 19.81 ± 5.5, $p = .394$) as well as TMSE scores (25.33 ± 3.21 vs. 26.14 ± 2.65, $p = .110$) of the participants were not significantly different between groups. The significant differences were found in age of onset ($p = .030$), duration of disease ($p = .002$), H&Y stages ($p < .001$), and UPDRS motor sub-score ($p = .034$). The clinical assessments, LED, and FOG-Q score were significantly increased in the group of FOG ($p = .007$, $p < .001$, respectively).

*Posturographic data*

In the reading sub-session, the posturographic data of 60 PD cases were compared between before I and reading (RE), and before II and counting backward (CB). Significant increases of PL were found in RE ($p < .001$) and CB ($p < .001$). Significant increase was found in ΔML in CB ($p = .012$). None of the other parameters were found to be significantly different as shown in Table 7.2. The CoP trajectories illustrated the characteristics of CoP movements within each condition. The PD-FOG showed higher postural sway than PD-nonFOG in all scenarios. The CoP movements in RE were larger than Before I. Similarly, in CB, they revealed higher sway area and fluctuation than Before II as illustrated in Fig. 7.1.

**Table 7.1**

The summarization of subjects' characteristics and clinical assessments comparing between the PD patients with freezing of gait (FOG) and non-freezing of gait (non-FOG) subgroups.

| Variables | FOG (n=39) | non-FOG (n=21) | $p^a$ |
|---|---|---|---|
| Age, yrs (SD) | 65.13 ± 10.32 | 69 ± 10.08 | 1.99 |
| Age of onset, yrs (SD) | 58.99±10.87 | 65.2 ± 10.27 | 0.030* |
| Duration of disease, yrs (SD) | 6.14 ± 3.57 | 3.79 (2.42) | 0.002** |
| Hoehn and Yahr, stages (SD) | 2.36 ± 0.69 | 1.86 ± 0.62 | <0.001** |
| UPDRS motor score (SD) | 24.72 ± 13.13 | 19.43 ± 9.59 | 0.034* |
| LED, mg/day (SD) | 722.41 ± 392.23 | 452.62 ± 247.85 | 0.007** |
| FOG-Q, scores (SD) | 11.72 ± 3.51 | 1.95 ± 1.43 | <0.001** |
| TMSE, scores (SD) | 25.33 ± 3.21 | 26.14 ± 2.65 | 0.110 |
| MoCA (SD) | 18.87 ± 5.05 | 19.81 ± 5.5 | 0.394 |

UPDRS, Unified Parkinson's Disease Rating Scale; LED, Levodopa equivalent dose; FOG-Q, Freezing of gait questionnaire; TMSE; Thai mental state examination; MOCA; Montreal cognitive assessment.

** $p < 0.05$, ** $p < 0.01$*

[a]Mann – Whitney U test

**Table 7.2**

The average and standard deviation of posturographic data comparing between before I-II and during cognitive loading (reading and counting backward) in the 60 PD patients.

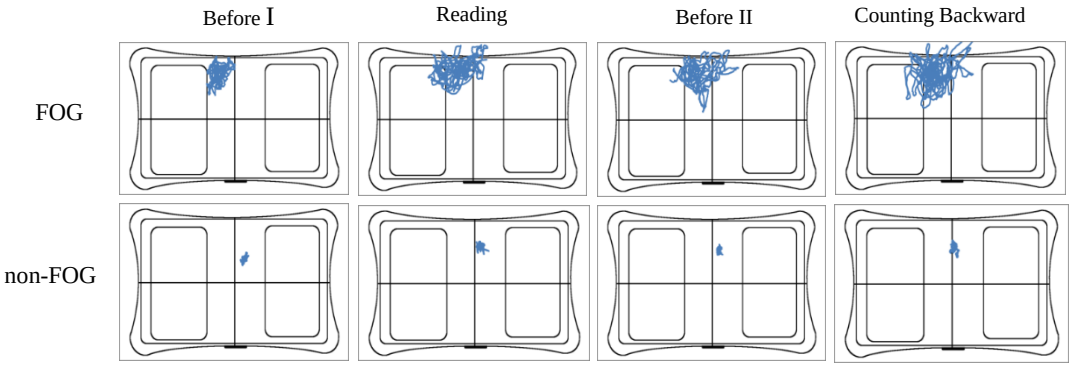
| COP | Before I | Reading | $p^b$ | Before II | Counting Backward | $p^b$ |
|---|---|---|---|---|---|---|
| Path length, mm (SD) | 86.86 ± 37.3 | 101.42 ± 61.96 | <0.001** | 95.37 ± 48.47 | 117.33 ± 84.08 | <0.001** |
| Sway area, $cm^2$ | 10.07 ±11.61 | 13.13 ± 21.12 | 0.361 | 15.06 ± 20.94 | 21.9 ± 37.28 | 0.162 |
| RMS (SD) | 2.74 ± 2.75 | 3.77 ± 5.97 | 0.156 | 3.95 ± 4.98 | 6.59 ± 13.57 | 0.083 |
| Max ML, cm (SD) | 0.49 ± 2 | 0.67 ± 2.39 | 0.943 | 0.82 ± 2.46 | 5.74 ± 35.74 | 0.284 |
| Min ML, cm (SD) | -2.34 ± 2.45 | -2.43 ± 2.49 | 0.462 | -2.37 ± 2.1 | -2.85 ± 2.86 | 0.339 |
| Max AP, cm (SD) | 5.31 ± 1.74 | 5.46 ± 1.98 | 0.256 | 5.36 ± 1.96 | 5.23 ± 1.97 | 0.477 |
| Min AP, cm (SD) | 2.34 ± 1.63 | 2.32 ± 1.61 | 0.415 | 1.9 ± 1.64 | 1.69 ± 1.9 | 0.232 |
| Δ ML, cm (SD) | 2.83 ± 1.14 | 3.1 ± 2.77 | 0.416 | 3.19 ± 2.45 | 8.59 ± 36.46 | 0.012* |
| Δ AP, cm (SD) | 2.97 ± 1.14 | 3.14 ± 1.48 | 0.286 | 3.46 ± 1.75 | 3.54 ± 2.03 | 0.880 |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio- lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement.

** $p < 0.05$, ** $p < 0.01$*

[b]Wilcoxon Signed-Rank test

**Fig. 7.1.** Center of Pressure (CoP) trajectories in the PD patients with and without FOG comparing between before I and reading, and before II and counting backward.




The sub-analysis was calculated by dividing the patients into two groups: FOG (n = 39) and non-FOG (n = 21). In the RE sub-session, significant increases of PL between Before I and RE were found in both PD-FOG ($p < .001$) and PD-non-FOG ($p < .001$). PL in PD-FOG was larger than PD-non-FOG (111.32 ± 74.31 vs. 83.05 ± 16.98). No significant differences were observed in other posturographic parameters.

In the CB sub-session, the sub-analysis illustrated that between Before II and CB, significant increases of PL were noticed in both PD-FOG ($p < .001$) and PD-nonFOG ($p < .001$). The significantly increased difference in ΔML was found only in PD-FOG ($p = .042$). PL in PD-FOG were higher than in PD-non-FOG (131.13 ± 100.4 vs. 91.71 ± 25.3). Meanwhile, ML in FOG were larger than in non-FOG (11.54 ± 43.86 vs. 3.11 ± 2.6) as demonstrated in Fig. 7.2. No statistically significant differences in other parameters were observed as expressed in Table 7.3.

**Table 7.3**
The average and standard deviation of posturographic data comparing the PD patients with FOG and non-FOG between before I and reading, before II and counting backward.

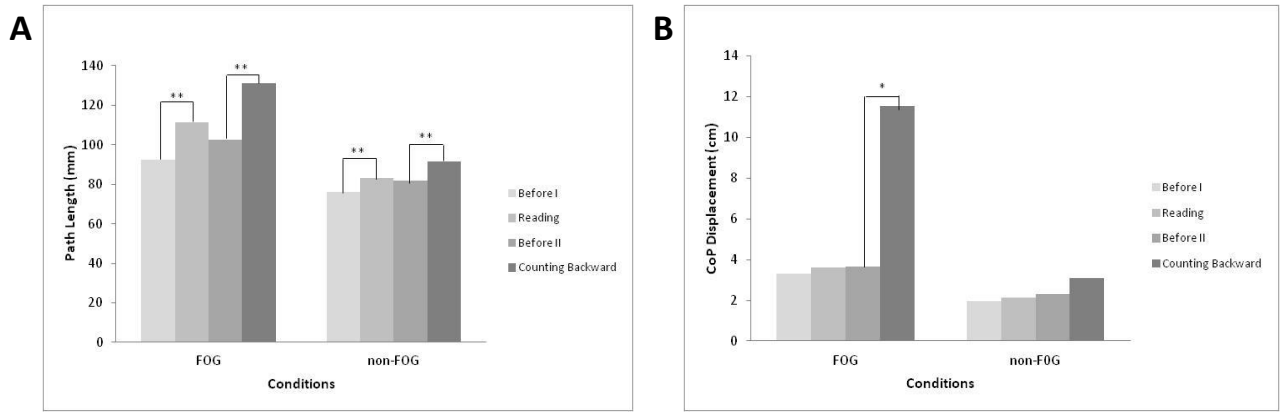
| Parameters | FOG (n=39) | | | non-FOG (n=21) | | |
|---|---|---|---|---|---|---|
| | Before I | Reading | $p^b$ | Before I | Reading | $p^b$ |
| Path length, mm (SD) | 92.62 ± 44.11 | 111.32 ± 74.31 | <0.001** | 76.18 ± 14.93 | 83.05 ± 16.98 | <0.001** |
| Sway area, $cm^2$ (SD) | 12.51 ± 13.27 | 17.4 ± 25.1 | 0.258 | 5.53 ± 5.47 | 5.22 ± 3.81 | 0.455 |
| RMS (SD) | 3.34 ± 3.14 | 4.94 ± 0.75 | 0.081 | 1.62 ± 1.24 | 1.61 ± 1.05 | 0.903 |
| Max ML, cm (SD) | 0.43 ± 2.27 | 0.75 ± 2.75 | 0.662 | 0.59 ± 1.42 | 0.52 ± 1.59 | 0.681 |
| Min ML, cm (SD) | -2.87 ± 2.77 | -2.96 ± 2.13 | 0.357 | -1.37 ± 1.27 | -1.61 ± 1.59 | 0.823 |
| Max AP, cm (SD) | 5.6 ± 1.85 | 5.82 ± 2.19 | 0.283 | 4.76 ± 1.38 | 4.81 ± 1.36 | 0.575 |
| Min AP, cm (SD) | 2.39 ± 1.76 | 2.31 (1.78) | 0.303 | 2.25 ± 1.39 | 2.33 ± 1.27 | 0.862 |
| Δ ML, cm (SD) | 3.3 ± 2.45 | 3.62 (3.2) | 0.422 | 1.96 ± 0.98 | 2.14 ± 1.26 | 0.689 |
| Δ AP, cm (SD) | 3.22 ± 1.17 | 3.5 (1.67) | 0.185 | 2.51 ± 0.94 | 2.48 ± 0.71 | 0.986 |
| | Before II | Counting Backward | | Before II | Counting Backward | |
| Path length, mm (SD) | 102.7 ± 57.58 | 131.13 ± 100.4 | <0.001** | 81.77 ± 18.23 | 91.71 ± 25.3 | <0.001** |
| Sway area, $cm^2$ (SD) | 19.04 ± 24.26 | 27.98 ± 44.36 | 0.241 | 7.67 ± 9.32 | 10.61 ± 12.45 | 0.414 |
| RMS (SD) | 4.5 ± 5.8 | 8.78 ± 16.3 | 0.105 | 1.99 ± 1.77 | 2.51 ± 2.99 | 0.455 |
| Max ML, cm (SD) | 0.95 ± 2.72 | 8.38 ± 44.3 | 0.346 | 0.59 ± 1.9 | 0.84 ± 1.88 | 0.627 |
| Min ML, cm (SD) | -2.72 ± 2.19 | -3.16 ± 2.93 | 0.562 | -1.71 ± 1.77 | -2.26 ± 2.69 | 0.487 |
| Max AP, cm (SD) | 5.68 ± 2.17 | 11.54 ± 43.86 | 0.635 | 4.78 ± 1.36 | 4.67 ± 1.44 | 0.578 |
| Min AP, cm (SD) | 1.82 ± 1.78 | 5.54 ± 2.17 | 0.110 | 2.05 ± 1.38 | 1.96 ± 1.27 | 0.741 |
| Δ ML, cm (SD) | 3.67 ± 2.7 | 11.54 ± 43.86 | 0.042* | 2.3 ± 1.59 | 3.11 ± 2.6 | 0.144 |
| Δ AP, cm (SD) | 3.86 ± 1.9 | 3.99 ± 2.27 | 0.732 | 2.73 ± 1.12 | 2.71 ± 1.15 | 0.768 |

RMS, Root mean square; ML, Medio-lateral displacement; AP, Antero-posterior displacement, ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement.

** $p < 0.05$, ** $p < 0.01$*

[b]Wilcoxon Signed-Rank test

**Fig. 7.2.** The bar charts showing the comparisons of CoP between before I and reading, and before II and counting backward in the PD patients with FOG and non-FOG. A. Path length (PL) B. Medio-lateral (ML).




* $p<0.05$, ** $p<0.01$ * $p<0.05$, ** $p<0.01$

*Correlation analysis*

Spearman correlation was used to perform the correlation between severity of disease according to Hoehn and Yahr (H&Y) stages and posturographic variables in RE and CB tasks. Table 7.4 and Fig. 7.3 illustrates that H&Y stages correlated with PL (*p=0.014*), SA (*p=0.001*), ΔML (*p=0.029*), and ΔAP (*p<0.001*) in RE. No correlations were found among the posturographic variables in CB. The 95% confidence ellipse of mean medio-lateral (ML), and antero-posterior displacements between PD-FOG and PD-non-FOG of RE and CB were demonstrated in Fig. 7. 4.

**Table 7.4**
Correlation between severity of disease (Hoehn and Yahr stages) and posturographic variables

| | Correlation | *p-value* [c] |
|---|---|---|
| Reading | | |
| Path Length | 0.316 | 0.014* |
| Sway Area | 0.404 | 0.001** |
| ΔML | 0.282 | 0.029* |
| ΔAP | 0.473 | <0.001** |
| | | |
| Counting backward | | |
| Path Length | 0.229 | 0.078 |
| Sway Area | 0.135 | 0.304 |
| ΔML | 0.149 | 0.257 |
| ΔAP | 0.220 | 0.092 |

ΔML, Maximal Medio-lateral displacement - Minimal Medio-lateral displacement; ΔAP, Maximal Antero-posterior displacement - Minimal Antero-posterior displacement. * $p < 0.05$, ** $p < 0.01$
[c]Spearman's Rho correlation.

**Fig. 7.3.** Correlation analysis between severity of the disease (Hoehn and Yahr stages) and path length (PL), sway area (SA), medio-lateral (ML), and antero-posterior (AP) displacements in reading (RE) and counting backward (CB) conditions.

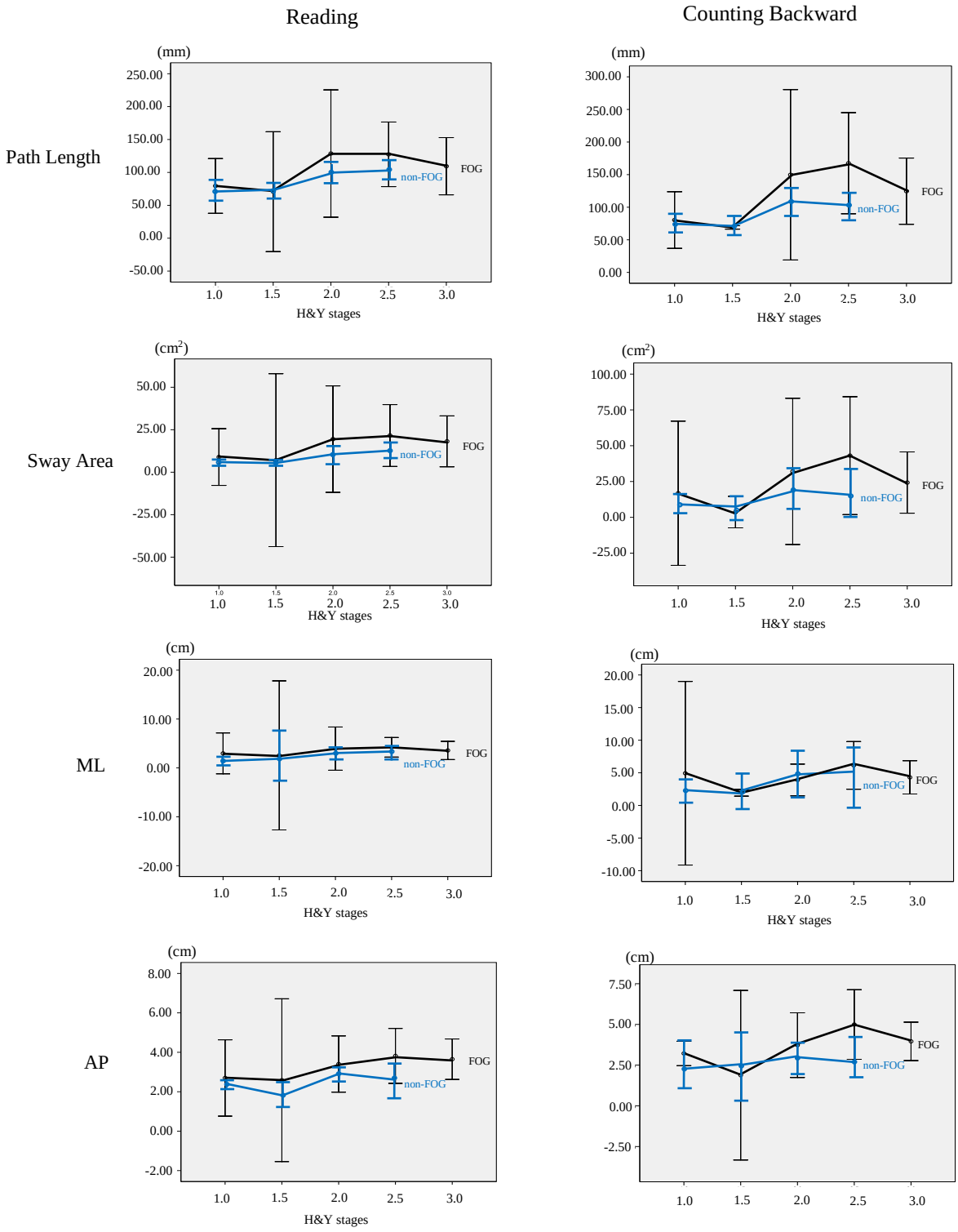
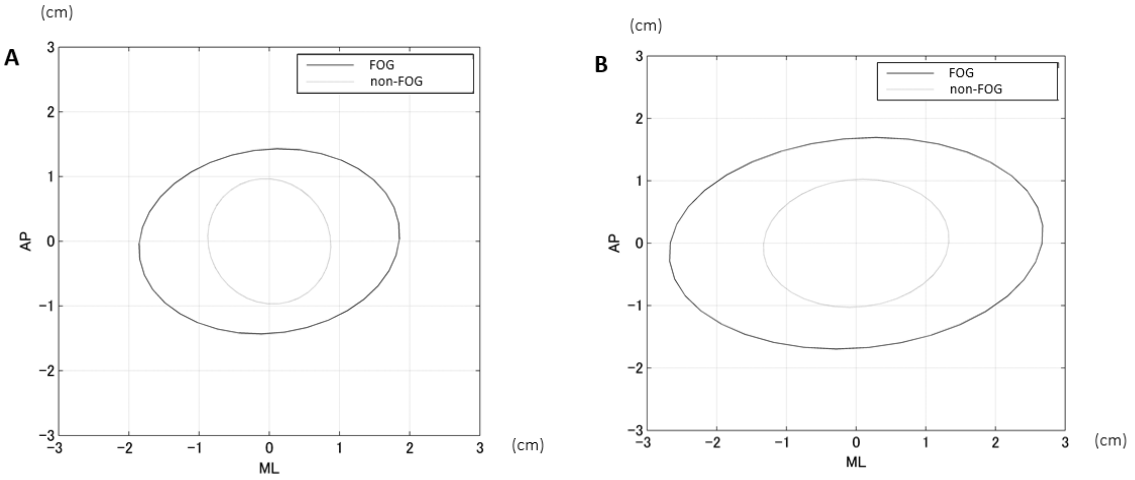


**Fig. 7.4.** 95% confidence ellipse of mean medio-lateral (ML) and antero-posterior displacements between FOG and non-FOG. A. Reading (RE) B. Counting backward (CB).




Multiple regression analyses were calculated between posturographic variables and clinical predictor variables. Associations between the variables were noticed in PD-Total-RE; levodopa ($R^2 = 0.221$, $p < 0.001$), LED ($R^2 = 0.150$, $p = 0.002$), and FOG-Q ($R^2 = 0.110$, $p = 0.010$). In PD-Total-CB, relationships were found in levodopa ($R^2 = 0.232$, $p < 0.001$), LED ($R^2 = 0.162$, $p = 0.001$), DD $R^2 = 0.065$, $p = 0.049$), and FOG-Q ($R^2 = 0.108$, $p = 0.010$) as well. Meanwhile, we found relationship in PD+FOG-RE in only levodopa ($R^2 = 0.194$, $p = 0.006$), LED ($R^2 = 0.127$, $p = 0.031$), as well as in PD+FOG-CB in levodopa ($R^2 = 0.190$, $p = 0.007$), LED ($R^2 = 0.125$, $p = 0.032$). On the other hand, the relationship was found merely in PD-FOG-RE in H&Y ($R^2 = 0.222$, $p = 0.031$) as shown in Table 7.5.

**Table 7.5**
Multiple regression analyses between clinical predictors and path length in cognitive session

| | Clinical variables | Regression statistic | | | | | |
|---|---|---|---|---|---|---|---|
| Group | | $R^2$ | Adj $R^2$ | $\Delta R^2$ | df | f | *p* |
| $PD_{Total}$-RE | Medication | | | | | | |
| | 1.Levodopa | 0.221 | 0.208 | 0.221 | 1, 58 | 16.476 | < 0.001** |
| | 2.LED | 0.150 | 0.135 | 0.150 | | 10.213 | 0.002* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.056 | 0.040 | 0.56 | | 3.461 | 0.068 |
| | 4.UPDRS III | 0.009 | -0.009 | 0.009 | | 0.501 | 0.482 |
| | 5. DD | 0.046 | 0.029 | 0.046 | | 2.775 | 0.101 |
| | Gait and balance | | | | | | |
| | 6. FOG-Q | 0.110 | 0.095 | 0.010 | | 7.192 | 0.010* |
| $PD_{Total}$-CB | Medication | | | | | | |
| | 1.Levodopa | 0.232 | 0.219 | 0.232 | 1, 58 | 17.537 | < 0.001** |
| | 2.LED | 0.162 | 0.147 | 0.162 | | 11.193 | 0.001* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.060 | 0.044 | 0.060 | | 3.685 | 0.060 |
| | 4.UPDRS III | 0.005 | -0.013 | 0.005 | | 0.267 | 0.607 |
| | 5. DD | 0.065 | 0.049 | 0.065 | | 4.033 | 0.049* |
| | Gait and balance | | | | | | |
| | 6. FOG-Q | 0.108 | 0.093 | 0.108 | | 7.033 | 0.010* |
| PD+FOG-RE | Medication | | | | | | |
| | 1.Levodopa | 0.194 | 0.171 | 0.194 | 1, 35 | 8.402 | 0.006* |
| | 2.LED | 0.127 | 0.102 | 0.127 | | 5.081 | 0.031* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.008 | -0.020 | 0.008 | | 0.289 | 0.595 |
| | 4.UPDRS III | 0.006 | -0.022 | 0.006 | | 0.229 | 0.635 |
| | 5. DD | 0.025 | -0.003 | 0.025 | | 0.893 | 0.351 |
| | Gait and balance | | | | | | |
| | 6. FOG-Q | 0.071 | 0.045 | 0.071 | | 2.683 | 0.110 |
| PD+FOG-CB | Medication | | | | | | |
| | 1.Levodopa | 0.190 | 0.166 | 0.190 | 1, 35 | 8.189 | 0.007* |
| | 2.LED | 0.125 | 0.100 | 0.125 | | 4.982 | 0.032* |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.011 | -0.017 | 0.011 | | 0.406 | 0.528 |
| | 4.UPDRS III | 0.018 | -0.010 | 0.018 | | 0.636 | 0.431 |
| | 5. DD | 0.043 | 0.016 | 0.043 | | 1.574 | 0.218 |
| | Gait and balance | | | | | | |
| | 6. FOG-Q | 0.069 | 0.043 | 0.069 | | 2.604 | 0.116 |
| PD-FOG-RE | Medication | | | | | | |
| | 1.Levodopa | 0.028 | -0.023 | 0.028 | 1, 19 | 0.545 | 0.470 |
| | 2.LED | 0.003 | -0.049 | 0.003 | | 0.065 | 0.801 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.222 | 0.181 | 0.222 | | 5.424 | 0.031* |
| | 4.UPDRS III | 0.110 | 0.063 | 0.110 | | 2.340 | 0.143 |
| | 5. DD | 0.017 | -0.035 | 0.017 | | 0.323 | 0.576 |
| | Gait and balance | | | | | | |
| | 6. FOG-Q | 0.129 | 0.083 | 0.129 | | 2.811 | 0.110 |
| PD-FOG-CB | Medication | | | | | | |
| | 1.Levodopa | 0.037 | -0.014 | 0.037 | 1, 19 | 0.730 | 0.403 |
| | 2.LED | 0.004 | -0.049 | 0.004 | | 0.070 | 0.794 |
| | Severity of disease | | | | | | |
| | 3.H&Y | 0.145 | 0.100 | 0.145 | | 3.229 | 0.088 |
| | 4.UPDRS III | 0.079 | 0.031 | 0.079 | | 1.633 | 0.217 |
| | 5. DD | 0.031 | -0.020 | 0.031 | | 0.615 | 0.442 |
| | Gait and balance | | | | | | |
| | 6. FOG-Q | 0.080 | 0.032 | 0.080 | | 1.652 | 0.214 |

Adj, adjusted; $\Delta R^2$, R square change; LED, levodopa equivalent dose; H&Y, Hoehn and Yahr scale, UPDRS III, Unified Parkinson's Disease Rating Scale; DD, duration of disease; FOG-Q, Freezing of gait questionnaire; RE, Reading; CB, Counting backward.
*$p < 0.05$, **$p < 0.01$.

## 7.3 Discussion

The results of this study demonstrated that the cognitive loading influences postural control in patients with PD. The balance platform, Nintendo Wii Fit, utilized in this study with the written program and the cognitive loading sessions, reading (RE) and counting backward (CB), are applicable for identifying PD patients with balance disturbances particularly with FOG. The cognitive loading sessions affected the changes of CoP trajectories while the participants were asked to follow the tasks.

This suggests the ability of controlling posture of PD patients in standing while receiving the cognitive loading tasks is defective. The interferences from the tasks may disturb the brain's circuits resulting in the destabilizing of the postural muscles. The results are accordant with previous studies that PI can be found in patients with abnormal muscle tone, and the patients with the deterioration of BG present poor balance as depicted by Fig. 7.1 and the large diameter of CoP trajectories (Double & Crocker, 1995). The degeneration causes patients to lose the capability of controlling their balance (J. E. Visser & Bloem, 2005), which is similar to the results in this study. A previous study reported the effect of CIs on balance showing the reduction of ML control in PD (Shin, Han, Jung, Kim, & Fregni, 2011). In this study, counting backward required greater postural control than reading, which might be interpreted that the counting backward was more difficult than the reading. It led to recruiting more muscles for controlling posture to maintain balance.

According to the function of BG in correcting postural responses, patients with PD gradually lose the ability of maintaining balance following the progression of the disease. The patients in advanced stages facing the problems of FOG expressed PI. MCIs have been found in the early stages (Lewis et al., 2003) where patients do not exactly manifest FOG. This statement supports our results that the non-FOG group presented the inability of controlling posture while receiving cognitive commands. ML control might be associated with the execution or cognition in PD. We found that the stabilizing in ML movements in PD-FOG was increased during counting backward. We can conclude that PI, CI, and FOG in PD have interaction. Previous studies reported CI and FOG were related. This study identified the connections of CI and FOG in terms of the CoP parameters (Heremans et al., 2013; Maruyama & Yanagisawa, 2006; Morris et al., 2000). Morever, our study supports the studies

of Kelly et al. (2015), Mahoney et al. (2016), and Lewis et al. (2003) that perhaps the deterioration of prefrontal cortex and BG lead to the impairments of postural control in PD. Our study represents the interaction between PI, CI, and FOG, which could be explained by the decoupling of frontoparietal cortical circuits and BG (Shine et al., 2013). The deterioration of pedunculopontine nuclei (PPN) and their network could interrupt neural substrates and result in FOG (Fling et al., 2013; Shine et al., 2013; Youn et al., 2015). These influences were expressed in the postural control of PD-FOG in this study after receiving the cognitive loading tasks.

Several studies over the years (Doná et al., 2016; Frenklach, Louie, Koop, & Bronte-Stewart, 2009; Hiorth, Larsen, Lode, & Pedersen, 2014; Nantel & Bronte-Stewart, 2014) reported the severity of the disease and the stages of the disease followed by the increase of age, age of onset, duration of disease, H&Y, UPDRS, and dopaminergic medication. These have caused changes in postural control and resulted in the increase of risk of falling and fall incidence. These factors are also presented in this study by showing significant differences between PD-FOG and PD-non-FOG. PD patients with high progression of the disease presented large dimensions of PL and SA, and an increase in ΔML and ΔAP displacements. In addition, this study confirms the study by Pelykh, Klein, Bötzel, Kosutzka, and Ilmberger (2015). They documented the large dimensions of radius and sway path of the CoP in PD-FOG. The deficiency of postural control in PD-FOG during quiet standing is also concordant with the study of Schlenstedt et al. (2016). The abnormality of postural control in PD can be distributed to postural sensory impairment and was confirmed by the studies of Frenklach et al., 2009; Huh et al., 2016. PD-FOG presented worse postural control than non-FOG which can be attributed to the impairment of sensory receptors. This is supported by the study of Huh et al., 2016 that postural sensory deficits also correlated with FOG. Moreover, we found that LED was associated with PD-FOG and PD-non-FOG. These results were previously confirmed by a study by Nantel & Bronte-Stewart, 2014, which represented the contribution of dopaminergic therapy to FOG.

PL and postural sway in ML directions were significantly higher in PD-FOG than in PD-non-FOG while receiving cognitive loading. These results state the effects of cognitive declines toward PI in PD. The specific results showed in FOG that the patients have worse postural control compared with PD-non-FOG.

We acknowledge that our present study has design of experiment limitations. Our study has limited sample size. After sub-analyzing the data into two groups, the sample size of the FOG group was double the nonFOG group. This difference in study could definitely affect the results. There was no normal control group. The CoP displacements in before II might receive effects from the reading sub-session. This subsequently might lead to the results comparing the before II and counting backward sub-session. In further studies, we will enlarge the study population and adapt a study protocol to be more precise and include a resting period between each sub-session. The results encourage that specific balance programs could be considered to improve balance and cognitive function to reduce risks of falling and related problems in the future as well as to improve patients' QoL.

## 7.4 Conclusion

Our study proposed that postural control in PD patients was influenced by the cognitive loading tasks: reading and counting backward. The ability of controlling balance was required more in PD patients with FOG during cognitive demands. The changes of CoP trajectories were particularly prominent in ML displacement while performing the task of counting backwards. Postural control during having cognitive loading of PD with FOG have relationship with medication. These findings represent the interactions between cognitive function, postural control, and FOG in PD.

# CHAPTER 8

# RELATIONSHIPS OF SENSORY, MOTOR AND COGNITIVE DEFICITS TOWARD POSTURAL INSTABILITY IN PARKINSON'S DISEASE

This chapter explains the relationships of sensory, motor cognitive deficits toward postural instability (PI) in Parkinson's disease (PD) in terms of center of pressure (CoP); path length (PL), sway area (SA), root mean square (RMS), antero-posterior and medio-lateral displacements. The influences of each part were described the *degree of postural instability (DPI)* by first reducing redundancy variables with Principal component analysis (PCA) method. We summarized all factors in each session to be calculated by PCA in order to discover the most powerful factor to describe PI under the impairments of the three systems. Second, we applied the factor that was shown by PCA to calculate odds ratio to investigate the probability of falls that can be predicted by the posturographic factor found in PCA.

## 8.1. Experimental procedure

### 8.1.1. Principal component analysis (PCA)

"*Principal component analysis (PCA)* is a multivariate technique that analyzes a data table in which observations are described by several inter-correlated quantitative dependent variables" (Abdi & Willams, 2010). In this research, we applied PCA to calculate posturographic graphic data, namely *path length (PL), sway area (SA), RMS, ΔML and ΔAP* as the main parameters of center of pressure (CoP) in the 8 components; eyes open (EO), eyes closed (EC), arm swing alternation - no cues (Alt_NC), arm swing synchronization - no cues (Syn_NC), arm swing alternation - auditory cues (Alt)_AC), arm swing synchronization - auditory cues (Syn_AC), reading (Re) and counting backward (Cb) to analyze the inter-

correlation coefficients of the components. The correlations between each variables were investigated by analyzing correlation matrix of all variables. The dimension reduction was considered to proceed the data to reduce variable redundancy due to the inter-correlation between variables

The underlying factors are inferred from the correlations among the *p* variables. Each factor is estimated as a weighted sum of the *p* variables. The $i^{th}$ factor is thus

$$Fi = W_{i1}X_1 + W_{i2}X_2 + \ldots + W_{ip}X_p$$

One may also express each of the *p* variables as a linear combination of the m factors,

$$Xj = AijF1 + A2j\ F2 + \ldots + Amj + Uj$$

where $U_j$ is the variance that is unique to variable *j*, variance that cannot be explained by any of the common factors. (Wuensch, 2012)

*Matrix Algebra*

The matrix algebra required in PCA is eigenvectors and eigenvalues. The basic knowledge of matrices is as follows;

**Fig. 8.1.** Example of one non-eigenvector and one eigenvector

$$\begin{pmatrix} 4 & 3 \\ 4 & 0 \end{pmatrix} \times \begin{pmatrix} 1 \\ 3 \end{pmatrix} = \begin{pmatrix} 13 \\ 4 \end{pmatrix}$$

$$\begin{pmatrix} 4 & 3 \\ 4 & 0 \end{pmatrix} \times \begin{pmatrix} 3 \\ 2 \end{pmatrix} = \begin{pmatrix} 18 \\ 12 \end{pmatrix} = 6 \times \begin{pmatrix} 3 \\ 2 \end{pmatrix}$$

**Fig. 8.2.** Example of how a scaled eigenvector is still and eigenvector

$$4 \times \begin{pmatrix} 3 \\ 2 \end{pmatrix} = \begin{pmatrix} 12 \\ 8 \end{pmatrix}$$

$$\begin{pmatrix} 4 & 3 \\ 4 & 0 \end{pmatrix} \times \begin{pmatrix} 6 \\ 4 \end{pmatrix} = \begin{pmatrix} 36 \\ 24 \end{pmatrix} = 6 \times \begin{pmatrix} 6 \\ 4 \end{pmatrix}$$

*Eigenvectors*

Eigenvectors are special in showing compatible sizes when we multiply a square matrix with an eigenvector ( vector $\begin{pmatrix} 3 \\ 2 \end{pmatrix}$ ) as shown in Fig. 8.1. The eigenvector in Fig. 8.2 showed 6 times of the original eigenvector $\begin{pmatrix} 6 \\ 4 \end{pmatrix}$ that we began with.

Fig. 8.1, vector $\begin{pmatrix} 1 \\ 3 \end{pmatrix}$ is not an integer multiple of the original vector, whereas vector $\begin{pmatrix} 3 \\ 2 \end{pmatrix}$ is an eigenvector. It is an arrow starting from the original (0, 0) to the point (3, 2). The square matrix $\begin{pmatrix} 4 & 3 \\ 4 & 0 \end{pmatrix}$ is considered as a transformation matrix. If we multiple a square matrix on the left of a vector, the answer is another vector that is transformed from its original position.

*Eigenvalues*

Eigenvalues are closely related to eigenvectors. As expressed on the Fig. 8.1, the amount by which after the original vector was multiplied was the same. If we have an eigenvector, after we multiply it by any square matrices (n×n), the valued we will have is called eigenvalue which the value is always the same. No matter how small or large a square matrix is, the eigenvector is not different. Eigenvectors and eigenvalues always show in pairs which express the similar values (Smith, 2002).

8.1.2. Odds ratio analysis

Odds ratio (OR) is a measure of association between an exposure and an outcome. An odd illustrates an outcome will happen given a specific exposure, compared to odds of outcome happening in non - exposure (Szumilas, 2010). The calculations of odds of an event and odds ratio are as follows;

$$\text{Odds of an event} = \frac{\text{Probability that the event occurs}}{\text{Probability that the event does not occur}}$$

$$\text{Odds ratio} = \frac{\text{Odds of event for group 1}}{\text{Odds of event for group 2}}$$

In this research, OR was considered to calculate association between PD patients with "falls" and "no falls" under the criteria of severity of disease (Hoehn and Yahr stage 1-3), and under the term of freezing of gait (FOG) (PD+FOG and PD-FOG). As illustrated in Table 8.1, OR for "fall" and "no falls" of PD patients and number of the patients who were and were not H&Y stage x (x is from stage 1 - 3) was computed (Szumilas, 2010).

**Table 8.1**
FOG odds ratio for "falls" compared to "no falls"

| H & Y stage x | Falls | No Falls | Total |
|---|---|---|---|
| No | a | b | a+b |
| Yes | c | d | c+d |

Where

a = Number of PD patients who were not H&Y stage x and faced falls
b = Number of PD patients who were not H&Y stage x and did not face falls
c = Number of PD patients who were H&Y stage x and faced falls
d = Number of PD patients who were H&Y stage x and did not face falls

Odds of FOG for falls = $a/(a+b) \div b/(a+b) = a/b$

Odds of FOG for no falls = $c/(c+d) \div d/(c+d) = c/d$

$$OR = a/b \div c/d = ad / bc$$

**Confidence interval for an odds ratio**

Confidence intervals for an odds ratio are calculated by using the following formula;

Upper 95% CI = $e^{[\ln (OR) + 1.96\sqrt{(1/a+ 1/b+ 1/c+ 1/d]}}$

Lower 95% CI = $e^{[\ln (OR) - 1.96\sqrt{(1/a+ 1/b+ 1/c+ 1/d]}}$

Odds ratio was calculated on account of the probability of path length (PL) in predicting fall history in PD patients by SPSS 22.0 (IBM Crop, Armonk, NY). PL was selected to calculate odds ratio because of the results by PCA.

Path length in eye open (EO), eye closed (EC), arm swing alternation with no cues (Alt - NC), arm swing synchronization with no cues (Syn - NC), arm swing alternation with auditory cues (Alt - AC), arm swing synchronization with auditory cues (Syn - AC), reading (RE), and counting backward (CB) were computed odds ratio.

## 8.2. Results

### 8.2.1. Results of Principal component analysis (PCA)

*Preliminary study*

The value of Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy is 0.793, which is closed to 1. It indicates that the patterns of correlations are large relative, which is good and appropriate for analyzing with principal component analysis (PCA).

**KMO and Bartlett's Test**

| | | |
|---|---|---|
| Kaiser-Meyer-Olkin Measure of Sampling Adequacy. | | .793 |
| Bartlett's Test of Sphericity | Approx. Chi-Square | 628.447 |
| | df | 28 |
| | Sig. | .000 |

**Table 8.2** KMO and Bartlett's Test

The Bartlett's Test is for testing the null hypothesis, which shows whether the original correlation matrix is an identity matrix. The test is highly significant with $p<0.001$. Consequently, the principal component analysis (PCA) is appropriate for this analysis as depicted in Table 8.2.

*Factor extraction*

Table 8.3 illustrates the eigenvalues associated with each linear component; before and after extraction. Before extraction, it was identified eight linear components. The eigenvalues associated with each factor represent the data set described the particular linear component. The

eigenvalues in terms of percentage were summarized by showing the 77.922% of total variance in factor 1. It is obvious that factor 1 presents the relative largest amounts of variance whereas subsequent factors show only small amounts of variance. All factors were extracted with eigenvalues greater than one, which lead to only one most important factor of the total variance in eight components.

**Table 8.3** Total variance explained

**Total Variance Explained**

| | Initial Eigenvalues | | | Extraction Sums of Squared Loadings | | |
|---|---|---|---|---|---|---|
| Component | Total | % of Variance | Cumulative % | Total | % of Variance | Cumulative % |
| 1 | 6.234 | 77.922 | 77.922 | 6.234 | 77.922 | 77.922 |
| 2 | .794 | 9.926 | 87.848 | | | |
| 3 | .315 | 3.940 | 91.789 | | | |
| 4 | .285 | 3.563 | 95.352 | | | |
| 5 | .213 | 2.659 | 98.012 | | | |
| 6 | .100 | 1.252 | 99.264 | | | |
| 7 | .035 | .439 | 99.703 | | | |
| 8 | .024 | .297 | 100.000 | | | |

Extraction Method: Principal Component Analysis.

Table 8.4 shows the communalities of before and after extraction. Before the communalities, all initial factors are 1. The column of extraction displays the variances after extraction, which can be interpreted that all of the eight components are very important for the analysis of PL. Each variance accounts for the association of the percentage of the variance and the individual component. It shows that 78.7 % of the variance associated with PL in eyes open (EO), 64.5 % of the variance associated with PL in eyes closed (EC), 78.2 of the variance associated with arm swing alternation in no cues (Alt_NC), and so on. The component matrix contains the loadings of each variable on each factor. By Kaiser's criteria, the factor 1 was extracted which the variances after extraction are greater 0.7, except PL in eyes closed (0.645) and the average communalities are greater than 0.8 (sum of the values in component matrix divided by the number of communalities; 7.126/8 = 0.891).

**Table 8.4** Communalities and component matrix

**Communalities**

| | Initial | Extraction |
|---|---|---|
| PathLength_EO | 1.000 | .787 |
| PathLength_EC | 1.000 | .645 |
| Alt_PathLength_NC | 1.000 | .782 |
| Syn_PathLength_NC | 1.000 | .756 |
| Alt_PathLength_AC | 1.000 | .780 |
| Syn_PathLength_AC | 1.000 | .835 |
| Re_PathLength | 1.000 | .850 |
| Cb_PathLength | 1.000 | .799 |

Extraction Method: Principal Component Analysis.

**Component Matrix[a]**

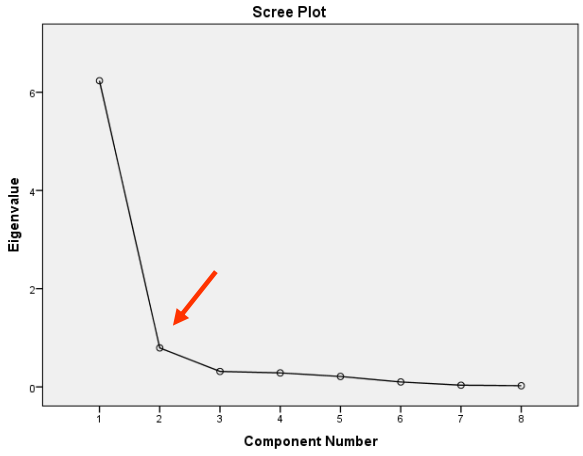
| | Component 1 |
|---|---|
| Re_PathLength | .922 |
| Syn_PathLength_AC | .914 |
| Cb_PathLength | .894 |
| PathLength_EO | .887 |
| Alt_PathLength_NC | .884 |
| Alt_PathLength_AC | .883 |
| Syn_PathLength_NC | .869 |
| PathLength_EC | .803 |

Extraction Method: Principal Component Analysis.

a. 1 components extracted.

The scree plot in Fig. 8.3 expresses the association of eigenvalues in each component. Only 1 component was separated from other components with relatively largest eigenvalue comparing with the other small eigenvalues by the "break point". The component before the break point is assumed that it is meaningful and important for retaining to be rotated. On the other hand, the components after the break point are assumed to be meaningless and unimportant to retain for rotation (Wuensch, 2012; Keho, 2012; Jackson et al., 2015).

**Fig. 8.3.** Scree plot




However, no factor rotation in the analysis of *path length (PL)* was computed, because only 1 component was shown to be the highest loaded component (Wuensch, 2012; Keho, 2012; Jackson et al., 2015). PL in all sessions were selected to summarize and create Table 8.5 to be a model of *degree of postural instability (DPI)* for patients with Parkinson's disease (PD).

### 8.2.2. Results of path length analysis

According to the PCA, we summarized mean and standard deviation (mean ± SD) of *path length (PL)* in Parkinson's disease (PD) patients in sensory, motor and cognitive parts of each session, which can be a model to implement for clinical assessment and/or balance evaluation as demonstrated in Table 8.5.

The values of path length (PL) in each stage of the disease accordance with Hoehn and Yahr (H&Y) scale represent the ability of controlling posture of the PD patients in this study. PL of the three impairments' systems; sensory, motor and cognitive were proposed as a guideline for evaluating postural instability (PI) in PD patients. The table shows the tendency of PL with direct variation. The higher stages of the disease, the larger PL were presented. However, this trend is not consistency to represent PL in mind stages of the disease; we added odds ratio analysis to estimate the risk of falls by considering occurrences of "falls" as dependent variable, and "no falls" as independent variable. With the purpose of gaining confidence to implement the DPI in interpreting PD patients' postural control and risk of falls.

**Table 8.5**
The summarization of mean and standard deviation (mean ± SD) of path length (PL) in Parkinson's disease (PD) patients in sensory, motor and cognitive conditions of each session as degree of postural instability (DPI).

| H&Y | Sensory | | Motor | | | | Cognitive | |
|---|---|---|---|---|---|---|---|---|
| | Visual | | No Cues | | Auditory Cues | | Loading | |
| | EO | EC | ALT | SYN | ALT | SYN | RE | CB |
| 1 | 73.66 ± 21.84 | 73.73 ± 12.41 | 179.39 ± 65.35 | 174.39 ± 65.35 | 191.61 ± 51.53 | 176.3 ± 45.02 | 73.67 ± 15.06 | 81.33 ± 21.83 |
| 1.5 | 75.64 ± 18.65 | 87.83 ± 21.13 | 210.29 ± 64.24 | 197.67 ± 66.95 | 197.02 ± 51.84 | 181.41 ± 44.32 | 79.51 ± 16.07 | 81.3 ± 15.12 |
| 2 | 88.4 ± 46.2 | 103.25 ± 52.04 | 230.2 ± 154.29 | 236.11 ± 172.93 | 203.21 ± 122.12 | 220.6 ± 135.33 | 107.5 ± 75.42 | 124.2 ± 101.93 |
| 2.5 | 92.27±29.93 | 93.33±26.86 | 183.19±61.88 | 184.79±68.78 | 186.52±60.55 | 180.82±78.45 | 107.99±58.94 | 122.07±86.52 |
| 3 | 93.26±40.3 | 122.77±112.55 | 209.73±103.76 | 194.14±86.75 | 203.97±107.92 | 203.46±93.16 | 114.14±76.16 | 140.65±97.58 |

EO, Eyes open; EC, Eyes closed; ALT, Alternation; SYN, Synchronization; RE, Reading; CB, Counting backward

8.2.3. Results of odds ratio analysis

Odds ratios of "fall" and "no falls" were computed in two scenarios; Hoehn and Yahr (H&Y) and freezing of gait (FOG). Table 8.6 shows the cross tabulation between falls – no falls and FOG – no FOG. It reveals the number of PD patients who exposed the cases. 16 PD patients presented falls and FOG. 23 patients showed no falls and experienced FOG. Five patients had falls and were no FOG, and 16 patients revealed no falls and no FOG. The number of PD patients experienced FOG was 39, no FOG was 21. Oppositely, the number of patients faced falls was 21, and no falls was 39.

**Table 8.6** Cross tabulation analysis between falls and freezing of gait (FOG) conditions

**1=FOG, 2=nonFOG * 1=Falls, 2=noFalls**

**Cross tabulation**

Count

| | | 1=Falls, 2=noFalls | | |
|---|---|---|---|---|
| | | 1 | 2 | Total |
| 1=FOG, 2=nonFOG | 1 | 16 | 23 | 39 |
| | 2 | 5 | 16 | 21 |
| Total | | 21 | 39 | 60 |

The Chi-Square tests as shown in Table 8.7 revealed that no significant relation between falls and FOG occurrences with the *p-value = .147* (at 0.05 significance level).

**Table 8.7** Chi-Square analyses between falls and freezing of gait (FOG) conditions

**Chi-Square Tests**

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|---|---|---|---|---|---|
| Pearson Chi-Square | 1.778[a] | 1 | .182 | | |
| Continuity Correction[b] | 1.102 | 1 | .294 | | |
| Likelihood Ratio | 1.839 | 1 | .175 | | |
| Fisher's Exact Test | | | | .258 | .147 |
| Linear-by-Linear Association | 1.749 | 1 | .186 | | |
| N of Valid Cases | 60 | | | | |

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 7.35.

b. Computed only for a 2x2 table

Although the odds ratio of the analysis between falls and FOG is greater than 1 (OR, CI = 2.226, 7.315), but it is not significant. Therefore, this OR cannot be taken to explain the events, which is less likely to happen than not (as illustrated in Table 8.8).

**Table 8.8** Risk estimate for odds ratio analysis

**Risk Estimate**

| | Value | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower | Upper |
| Odds Ratio for 1=Falls, 2=noFalls (1 / 2) | 2.226 | .677 | 7.315 |
| For cohort 1=FOG, 2=nonFOG = 1 | 1.292 | .906 | 1.842 |
| For cohort 1=FOG, 2=nonFOG = 2 | .580 | .247 | 1.361 |
| N of Valid Cases | 60 | | |

Table 8.9 explains odds ratios of *path length (PL)* in all sessions; sensory, motor and cognitive, including eyes open (EO), eyes closed (EC), alternation with no cues (Alt_NC), synchronization with no cues (Syn_NC), alternation with auditory cues (Alt_AC), synchronization with auditory cues (Syn_AC), reading (RE), and counting backward (CB). Odds ratio for falls compared to no falls in EO in H&Y stage 3 is 0.916 indicating increased odds of PD with falls in EO. The 95% confidence interval (CI) of the odds ratio (0.009, 0.779) indicates that odds of PD H&Y stage 3 in EO is significant higher than PD in other stages (at 0.05 significance level) because the CI does not contain 1.

The odds ratio (0.916) means there is a statistically significant "association" between EO, PD H&Y stage 3 and falls. The 95% CI for the OR does not contain 1, we can conclude that there is a statistically significant "association" between EO, PD H&Y stage 3 and falls in PL. 91.6 % of PD H&Y stage 3 in EO revealed the probability of falls.

Odds ratio for falls compared to no falls in EC in PD H&Y stage 3 is 0.888 indicating increased odds of PD H&Y stage three with falls in EC. The 95% CI of the odds ratio (0.012, 1.077) indicates that odds of PD H&Y stage 3 in EC is significant lower than PD in other stages (at 0.05 significance level) because the CI contains 1.

The odds ratio (0.888) means the "association" between EC, PD H&Y stage 3 and falls is not statistically significant. The 95% confidence interval for the OR contains 1, we can conclude

that there is no statistically significant “association” between EC, PD H&Y stage 3 and falls in PL. 88.8 % of PD H&Y stage 3 in EC revealed the probability of falls.

Odds ratio for falls compared to no falls in Alt_NC in PD H&Y stage 3 is 0.916 indicating increased odds of PD H&Y stage 3 with falls in Alt_NC. The 95% CI of the odds ratio (0.009, 1.779) indicates that odds of PD H&Y stage 3 in EC is significant higher than PD in other stages (at 0.05 significance level) because the CI does not contain 1.

The odds ratio (0.916) means the “association” between Alt_NC, PD H&Y stage 3 and falls is statistically significant. The 95% confidence interval for the OR does not contain 1; we can conclude that there is statistically significant “association” between Alt_NC, PD H&Y stage 3 and falls in PL. 91.6 % of PD H&Y stage 3 in Alt_NC revealed the probability of falls.

Odds ratio for falls compared to no falls in Syn_NC in PD H&Y stage 3 is 0.827 indicating increased odds of PD H&Y stage 3 with falls in Syn_NC. The 95% confidence interval of the odds ratio (0.030, 0.987) indicates that odds of PD H&Y stage 3 in EC is significant higher than PD in other stages. (at 0.05 significance level) because the CI does not contain 1.

The odds ratio (0.827) means the “association” between Syn_NC, PD H&Y stage 3 and falls is statistically significant. The 95% confidence interval for the OR does not contain 1; we can conclude that there is statistically significant “association” between Syn_NC, PD H&Y stage 3 and falls in PL. 82.7 % of PD H&Y stage 3 in Syn_NC revealed the probability of falls.

Odds ratio for falls compared to no falls in Alt_AC in PD H&Y stage 3 cannot be computed because there were no patients with no falls recorded in this stage.

Odds ratio for falls compared to no falls in Syn_AC in PD H&Y stage 3 is 0.827 indicating increased odds of PD H&Y stage 3 with falls in Syn_AC. The 95% CI of the odds ratio (0.030, 0.987) indicates that odds of PD H&Y stage 3 in Syn_AC is significant higher than PD in other stages (at 0.05 significance level) because the CI does not contain 1.

The odds ratio (0.827) means the “association” between Syn_AC, PD H&Y stage 3 and falls is statistically significant. The 95% CI for the OR does not contain 1; we can conclude that there is statistically significant “association” between Syn_AC, PD H&Y stage 3 and falls in PL. 82.7 % of PD H&Y stage 3 in Syn_AC revealed the probability of falls.

Odds ratio for falls compared to no falls in RE in PD H&Y stage 3 is 0.888 indicating increased odds of PD H&Y stage 3 with falls in RE. The 95% CI of the odds ratio (0.012, 1.077)

indicates that odds of PD H&Y stage 3 in RE is not significant higher than PD in other stages (at 0.05 significance level) because the CI contains 1.

The odds ratio (0.888) means the "association" between RE, PD H&Y stage 3 and falls is statistically significant. The 95% CI for the OR contains 1, we can conclude that there is no statistically significant "association" between RE, PD H&Y stage 3 and falls in PL. 88.8 % of PD H&Y stage 3 in RE revealed the probability of falls.

Odds ratio for falls compared to no falls in CB in PD H&Y stage 3 cannot be computed because there were no patients with no falls recorded in this stage.

**Table 8.9**
Odds ratio analysis for path length in all sessions of this study.

H&Y = 3

| | Odds Ratio | 95% CI | Pearson Chi-Square | Likelihood Ratio |
|---|---|---|---|---|
| EO | 0.916 | 0.009 – 0.779 | 0.009* | 0.010* |
| EC | 0.888 | 0.012 – 1.077 | 0.028* | 0.031* |
| | | | | |
| Alt – NC | 0.916 | 0.009 – 0.779 | 0.009* | 0.010* |
| Syn – NC | 0.827 | 0.030 – 0.987 | 0.032* | 0.036* |
| | | | | |
| Alt – AC | - $^{\Delta}$ | - | 0.005* | 0.003* |
| Syn – AC | 0.827 | 0.030 – 0.987 | 0.032* | 0.036* |
| | | | | |
| RE | 0.888 | 0.012 – 1.077 | 0.028* | 0.031* |
| CB | - $^{\Delta}$ | - | 0.001* | 0.001* |

EO, Eyes open; EC, Eyes closed; ALT, Alternation; SYN, Synchronization; RE, Reading; CB, Counting backward.

$^{\Delta}$ Cannot be computed odds ratio on account of no patients with no falls

** $p < 0.05$, ** $p < 0.001$*

## 8.4. Discussion

This study proposed a postural control technique to investigate the relationship between motor and non-motor symptoms of Parkinson's disease (PD). Historically, as postural instability (PI) was reported as a motor symptom of PD, several balance measurements were used to evaluate postural control in PD. Additionally, none of the existing measurements explain the relationship between motor and non-motor symptoms of PD. This study conducted balance tests while studying PD symptoms by selecting arm swing reduction (ASR) as a motor symptom, and included non-motor symptoms of visual input (VI), and cognitive impairments (CI). The testing hypothesized a relationship exists between motor and non-motor symptoms, which could be presented in the form of postural control.

The study integrated the postural control data of three elements of sensory, motor, and cognitive across three sessions within the eight elements; eyes open (EO), eyes closed (EC), arm swing alternation (ALT), arm swing synchronization (SYN), arm swing alternation with auditory cues (ALT+AC), arm swing synchronization with auditory cues (SYN+AC), reading (RE) and counting backward (CB). From the results of studies I – IV, we found relationships between postural instability (PI) and (1) visual input (VI) (2) arm swing (3) arm swing and auditory cues (AC), and (4) cognitive loading. The testing hypothesized the postural control data (sensory, motor and cognitive) might be able to be integrated, and the testing profiles of the eight elements might be redundant tests of each other, therefore, applying the principal component analysis (PCA) the redundancy of the eight elements was demonstrated not to exist. The results of KMO and Bartlett's Test demonstrated PCA showed appropriate to analyze the data, hence, the communality matrix revealed only one component with a high factor loading. Therefore, we created *degree of postural instability (DPI)* incorporating all eight elements. The significance of the integration is to explore the relationship of sensory, motor, and cognitive impairments as indicators of balance dysfunction in Parkinson's disease (PD), and propose the elements relationship in terms of postural control.

The DPI is created according to the Hoehn and Yahr (H&Y) scale to infer to the severity of Parkinson's disease (PD). It might be considered to be an index of balance evaluation in PD to describe the relationship of each part of the brain functions involved with visual input, (Bronstein et al., 1990; Chong et al., 1999; Abbruzzese & Berardelli, 2003; Jacobs and Horak, 2006;

Vaugoyeau and Azulay, 2010; Pasma et al., 2014; Rinalduzzi et al., 2015), muscle co-ordination (Double & Crocker, 1995; Debaere et al., 2001; Hdpiuang et al., 2012) and cognition (Cook, 2000; Kelly, Johnson, & McGough, 2015; Nantel, McDonald, Tan, & Bronte-Stewart, 2012; Peterka, 2002; Watson & Owen, 2014; Santens, Boon, Van Roost, & Caemaert, 2003). The DPI with Hoehn and Yahr (H&Y) stage 3 was observed with correlations with patients' fallings. Meanwhile, the visual input, arm swing, arm swing with auditory cues, and cognitive loading were significantly impacted toward postural control in PD.

The findings in this study are useful as a guideline to indicate the relationship of motor and non-motor symptoms of PD in terms of postural control on the basis of sensory, motor, and cognitive deteriorations. It could be utilized to lead further studies by expanding the population size and recruiting participants in different regions and environments. This testing data is based on PD patients in Thailand, but accessing the PD patients' data postural control from other countries with different backgrounds and environments may help to understand the relationships, which external factors contribute to postural instability.

## 8.4. Conclusion

Postural control in sensory, motor and cognitive elements are significant to be progressive predictors of Parkinson's disease (PD). Degree of postural instability (DPI) was calculated and verified by the three techniques; principal component analysis (PCA), categorical analysis of path length (PL), and odds ratio analysis. The selected elements from the finding of PCA can be progressive predictors of Parkinson's disease (PD). Odds ratio revealed that path length of all componenets selected were able to predict falls in Parkinson's disease (PD) patients with Hoehn and Yahr stage 3. Degree of postural instability (DPI) has been produced to respond to balance assessment for Parkinson's disease (PD) patients. It is the combination of sensory, motor cognitive deficits toward postural instability in Parkinson's disease (PD).

# CHAPTER 9

# CONCLUSION AND IMPLICATIONS

In this chapter, we concluded the results of all sub-studies in this dissertation. By following the research questions, *MRQ:* What is Parkinson's disease (PD) patients' postural control? *SRQ 1:* What is balance measurement for evaluating balance dysfunction in Parkinson's disease (PD) patients? SQR 2: How to evaluate the progression of Parkinson's disease (PD) patients? To achieve the objectives of this research, *Study I:* To investigate the effects of visual input (VI) as clinical predictors of postural instability (PI) in Parkinson's disease (PD). *Study II:* To evaluate the arm swing patterns as clinical predictors of postural instability (PI) in Parkinson's disease (PD). *Study III:* To determine the arm swing patterns with auditory cues as clinical predictors of postural instability (PI) in Parkinson's disease (PD). *Study IV:* To study the impact of cognitive loading as clinical predictors of postural instability (PI) in Parkinson's disease (PD). The conclusions of each sub-study were drawn as a model to define degree of postural instability (DPI) which is the knowledge we discovered from this Ph.D. projects.

## 9.1. Conclusion

To achieve the objectives of research, this dissertation was conducted with four experimental and one descriptive studies as presented in chapter 4 - 8. The interesting findings are summary as follows;

*MRQ: Chapter 4 - 8*

Parkinson's disease (PD) postural control is the ability of PD patients to control their center of mass (CoM) within their base of support (BoS), which can be measured by evaluating center of pressure (CoP) which is detected on the ground. The capability of controlling CoP within BoS of PD patients is disturbed by the sensory, motor and cognitive deteriorations. The results of balance assessment form study I – VI revealed

the capability of PD patients in controlling their posture. A model for evaluating postural control of Parkinson's disease patients is shown in Fig. 9.1.

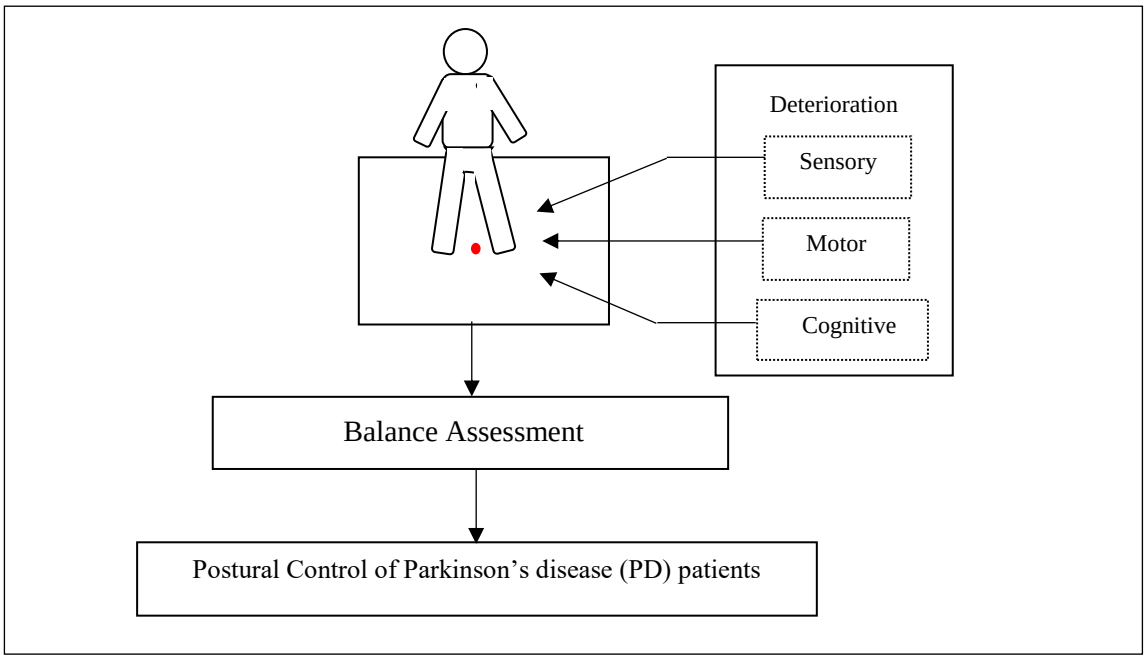



**Fig. 9.1.** Empirical model for evaluating postural control of Parkinson's disease (PD) patients

*SRQ 1: Chapter 4 - 7*

Balance measurement for evaluating balance dysfunction in Parkinson's disease (PD) patients is the assessment in sensory, motor and cognitive impairments toward postural instability (PI) in PD patients. By adding a unique characteristic of gait freezing in PD, the clarification of the ability of controlling posture in PD patients' sub-type is clearer. PI was analyzed by Nintendo Wii balance board (NWBB) in standing position. First, sensory session was carried on in eye open (EO) and eye closed (EC). Second, motor session was combined with motor session I (arm swing) and II (arm swing with auditory cues). These were proceeded in arm swing alternation (Alt) and synchronization (Syn). Last, cognitive session was performed in reading (RE) and counting backward (CB). A model of balance assessment for evaluating balance dysfunction in Parkinson's disease (PD) patients is illustrated in Fig. 9.2.

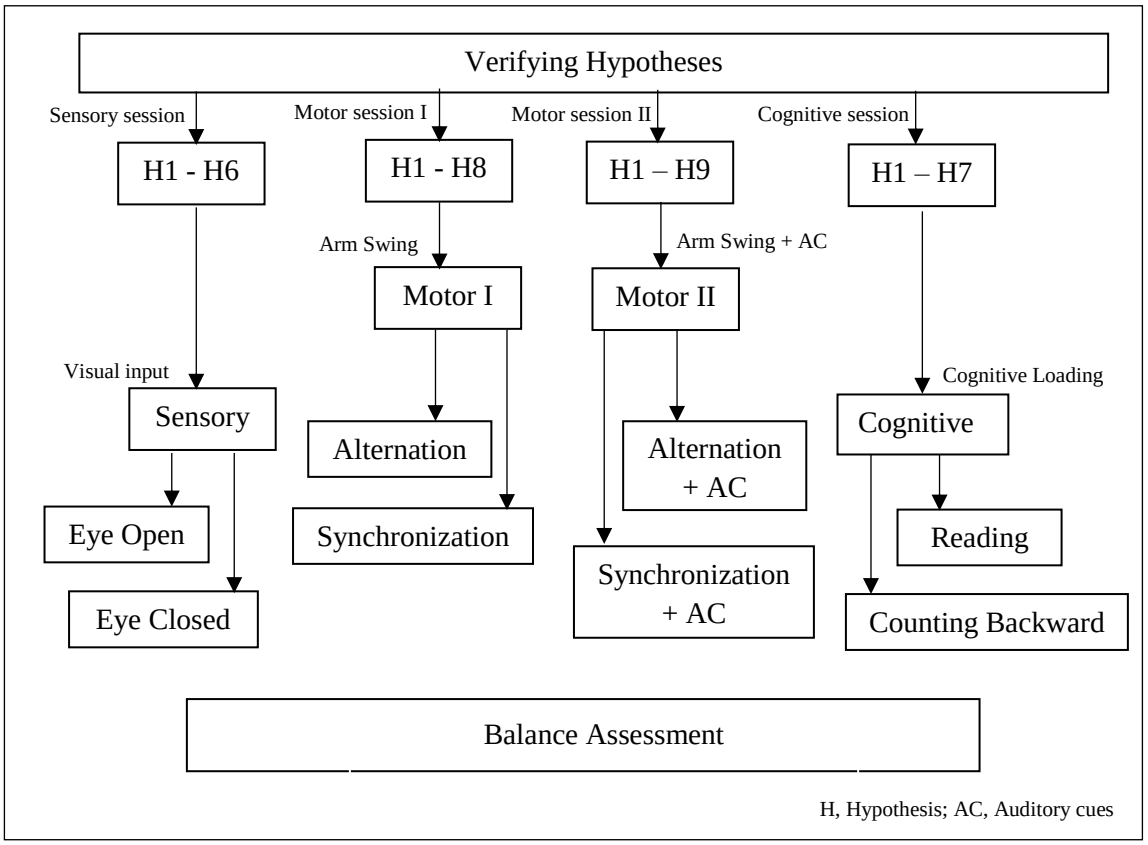



**Fig. 9.2.** Empirical model of balance measurement for evaluating balance dysfunction in Parkinson's disease (PD) patients

*SRQ 2: Chapter 8*

The progression of Parkinson's disease (PD) patients can be evaluated by integrating postural control regarding the sensory, motor and cognitive impairments as parts of motor, non – motor symptoms of PD. The combination of the three elements was proposed in this study as *"Degree of postural instability (DPI)"*. DPI was determined by calculating the distinct posturographic data, *Path length (PL)*, of all sessions; sensory, motor and cognitive with the principal component analysis (PCA) and multiple regression techniques as well as being along with Hoehn and Yahr (H&Y) scale so as to interpret the postural control in terms of progression of the disease. Schematic for creating progressive predictors of Parkinson's disease (PD) is shown in Fig. 9.3.

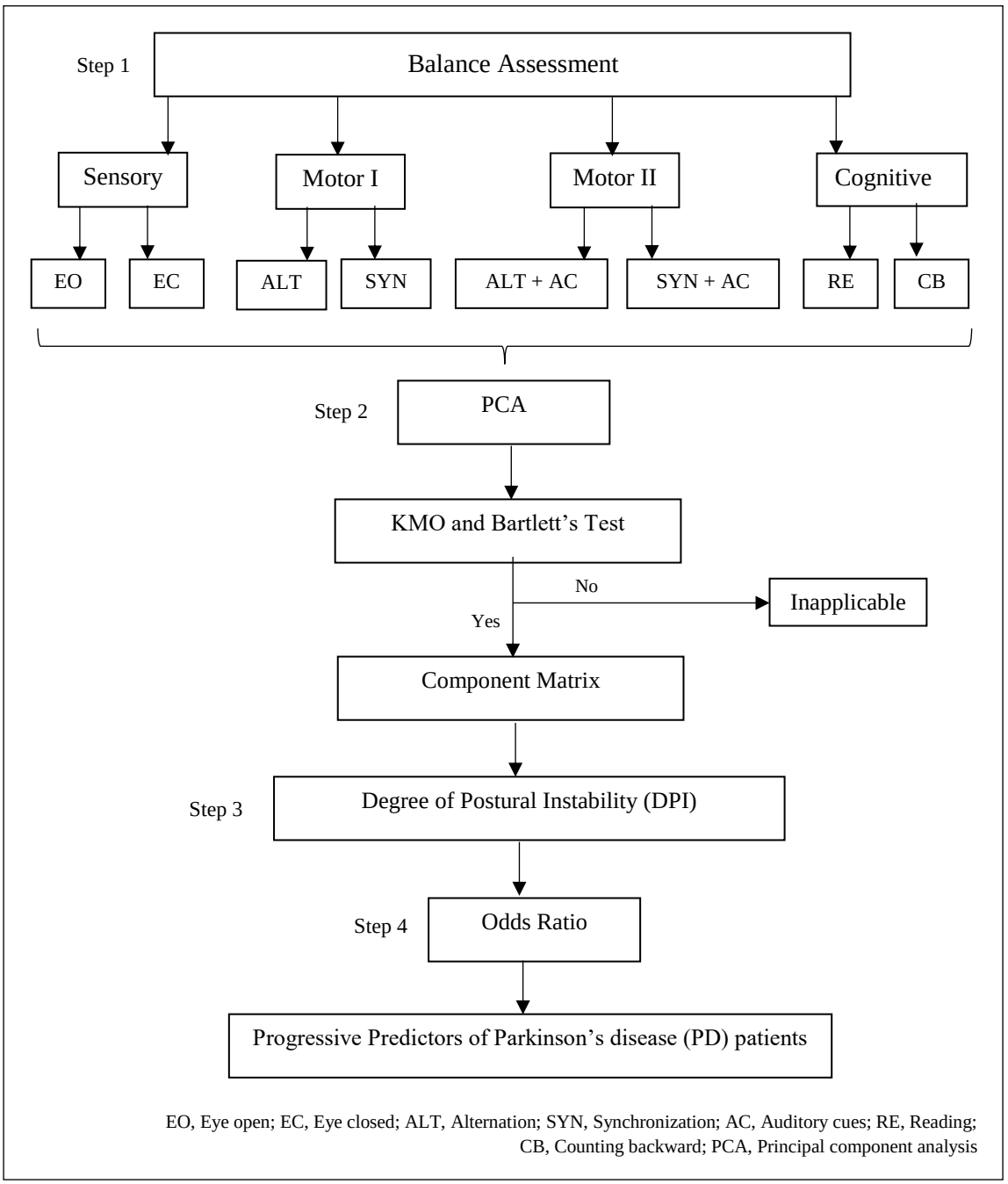



**Fig. 9.3.** Schematic for creating progressive predictors of Parkinson's disease (PD)

Degree of postural instability (DPI) was classified by path length (PL) as a distinctly posturographic parameter to explain changes of center of pressure (COP) in patients with Parkinson's disease (PD). The relationship of motor, non – motor and sensory symptoms regarding balance disturbances can be explained and applied in clinical practice by using DPI to evaluate PD patients' postural control.

## 9.2. Significance of research outputs

### 9.2.1. Contribution to knowledge science

This dissertation stands on *knowledge science* in a way that concerns explicit and bodily tacit knowledge between physical therapist (PT) and Parkinson's disease (PD) patient. The discovered knowledge is *degree of postural instability (DPI)* which originated from the 4 sub-studies and a study of integration of the sub-studies I - IV. *Study I* revealed discovered explicit knowledge of the visual input (VI) as clinical predictors of postural instability (PI) and freezing of gait (FOG) in PD patients. This showed the relationship among postural instability (PI), freezing of gait (FOG) and visual input (VI). *Study II* expressed the discovered explicit knowledge of arm swing as clinical predictors of postural instability (PI) in PD, which showed the relationship between the movements of arms toward the control of body movements passing the detection of center of pressure (COP). *Study III* reported the discovered explicit knowledge of the effects of auditory cues on arm swing as clinical predictors toward postural instability (PI) in PD. This study revealed that auditory cues played role on regulating the arm swing movements. *Study IV* revealed the discovered explicit knowledge of the impact of cognitive loading on postural control, which illustrated the relationship between PI and cognitive impairment and FOG in PD.

*Degree of postural instability or "DPI"* is explicit knowledge, which is the final result of this Ph.D. projects. It is the integration of several explicit knowledge in each significant sub-study. A model of explicit knowledge co-creation of degree of postural instability (DPI) in Parkinson's disease (PD) was drawn to illustrate the processes of knowledge co-creation in neuro - rehabilitation between physical therapist (PT) and Parkinson's disease (PD) patient as shown in Fig. 9.4. Explicit and bodily tacit knowledge of PT and PD patients were gathered and were integrated as an essential idea for conducting the studies. The process of justification was performed to verify the hypotheses on the 3 sessions; sensory, motor and cognitive by the balance assessment. Consequently, the problems of motor and non – motor symptoms were evaluated and were able to interpret parallel with the severity of the disease; Hoehn and Yahr scale (H&Y), medication; levodopa equivalent dose (LED), and falls.

The DPI is the integration of motor and non – motor symptoms, which was discovered to explain the relationship of the 3 systems in the ability of controlling posture. The results after applying the knowledge into clinical practice can be a new idea of further studies in order to create an updated protocol of balance analysis for PD patients. New study designs will be verified again and again to discover more modern and appropriate knowledge/techniques for PD patients in the future.

### 9.2.2. Novelty of the study

- The relationship of visual input, postural instability (PI) and freezing of gait (FOG) (Chapter 4).
- The relationship of arm swing alternation (Alt) and synchronization (Syn), postural instability (PI) and freezing of gait (FOG) (Chapter 5).
- The relationship of arm swing alternation (Alt) and synchronization (Syn) with auditory cues, postural instability (PI) and freezing of gait (FOG) (Chapter 6).
- The relationship of cognitive loading, postural instability (PI) and freezing of gait (FOG) (Chapter 7).
- The integration of sensory, motor and cognitive deficits, postural instability (PI) and freezing of gait (FOG) to propose degree of postural instability (DPI) (Chapter 8)

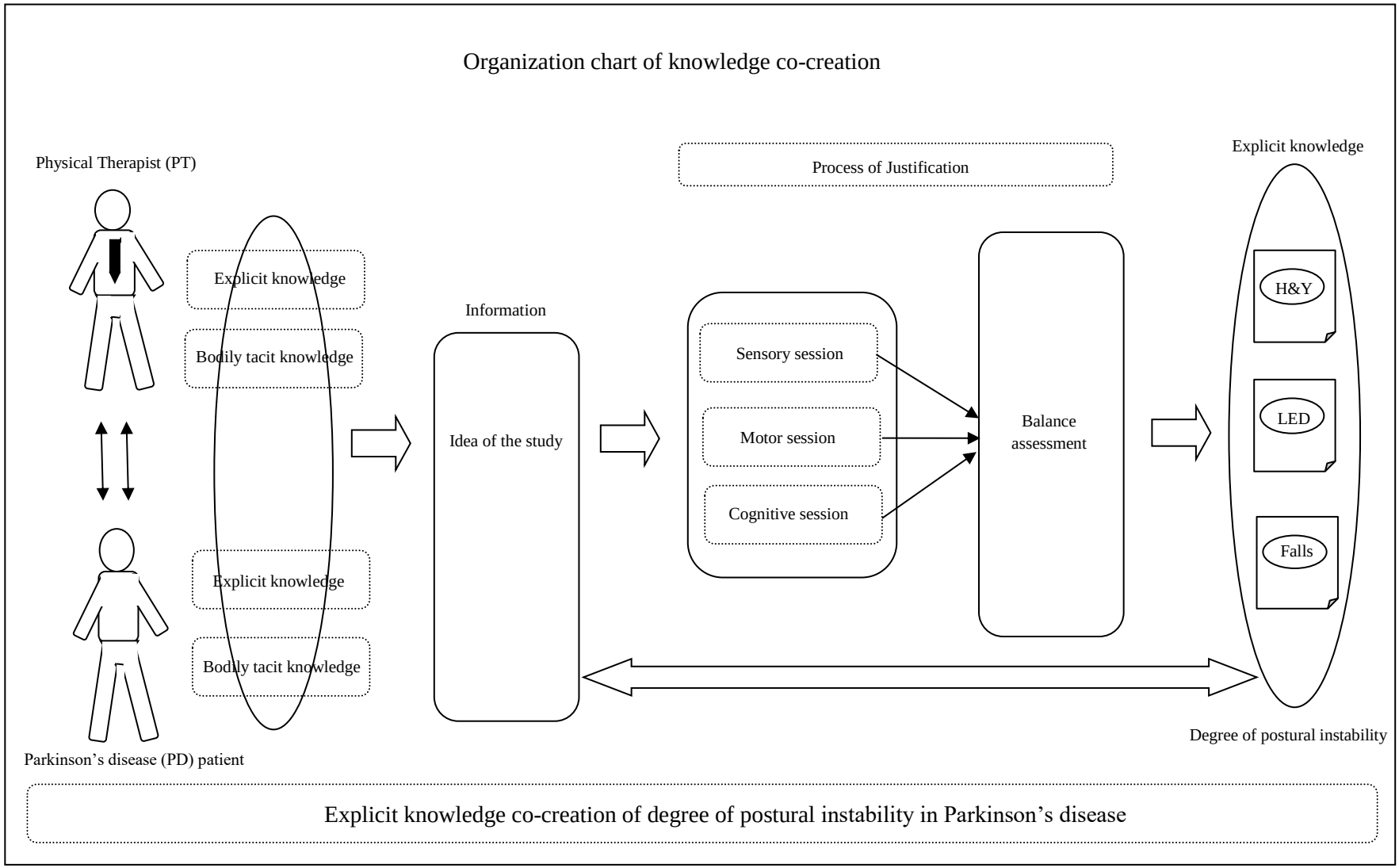



**Fig. 9.4**. Model of explicit knowledge co-creation of degree of postural instability in Parkinson's disease

### 9.2.3. Practical implications

Practical implications can be applied to clinical practice for clinicians/ neurologists/movement disorder specialists, physical therapists (PTs), researchers and patients with Parkinson's disease (PD). It can be implemented for evaluating postural control, and/or developing rehabilitation programs, fall prediction, exercise alert as mobile phone applications, and balance training programs on Nintendo Wii balance board (NWBB).

Degree of postural instability (DPI) can be applied in clinical practice by interpreting results of balance assessment recorded by NWBB. After clinicians/movement disorder specialists, and PTs evaluate clinical symptoms and balance with the experimental procedures as shown in Fig. 9.5. The balance data as known as posturographic parameters will be collected. Path length (PL) was selected as a significantly dominant parameter to calculate and build DPI, as well as to propose in this dissertation. The DPI can be utilized to interpret PD patients' postural control in current clinical practice situations.

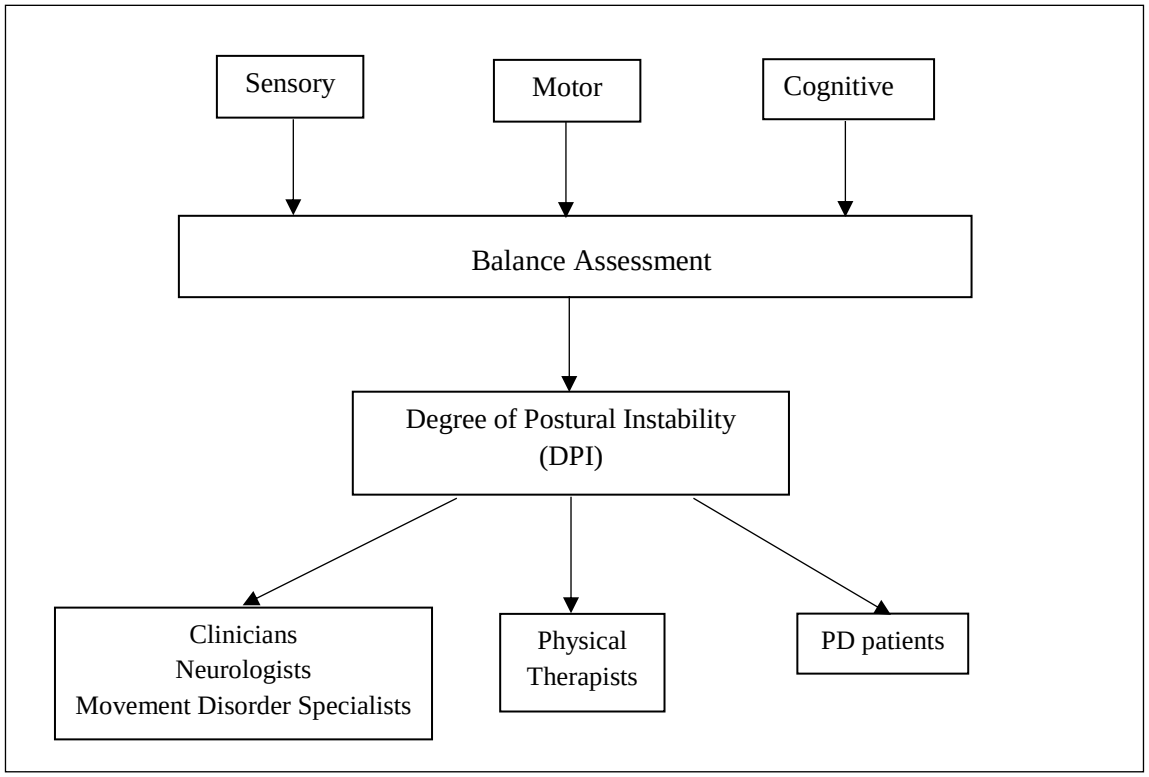



**Fig. 9.5.** Empirical model of a balance assessment for evaluating sensory, motor and cognitive impairments in Parkinson's disease

The benefits of DPI are classified for the 3 groups; clinicians/neurologists/ movement disorder specialists, PTs, and patients with PD. First, clinicians/neurologists/ movement disorder specialists can check the results of balance assessment interpreted by DPI (as shown in Table 9.1) with the traditional assessments. The results can help support the understanding of PD patients' postural control regarding the causes of balance deteriorations; sensory, motor and cognitive, which also present in postural instability (PI) and freezing of gait (FOG). DPI can be considered to correlate with the severity of disease and medication as progressive predictors of PD. DPI is scaled along with Hoehn and Yahr (H&Y) scale, which users can understand the meaning of PD patients' symptoms standardly. Postural control interpreted by DPI can also be beneficial in prescribing medication. By acknowledging the balance disturbances' level, the users can control physical problems according to high level of medication or long-term effect of taking medication.

Second, physical therapists (PTs) can apply DPI for evaluating standing balance before and after training or prescribing treatments/rehabilitation programs. For example, a patient, who was diagnosed with PD 3 years ago, visits a neurologist at a hospital. His severity of disease as assessed by Hoehn and Yahr (H&Y) scale is 2.5. The neurologist consults a physical therapist (PT) for providing rehabilitation programs. At Physical therapy department, the patient will be interviewed and evaluated physical condition, especially gait and balance assessments. As long as PD developed, the main PD patient's problems such as gait, balance and falls can be found in this stage of the disease. Consequently, improving gait-balance and preventing falls will be considered as goal setting for the patient. The balance assessment with NWBB will be performed in all of the 3 systems. After that, the PT can check the path length (PL) of the PD patient with the DPI (Table 9.1). If we assumed that the patient's data matched with the data in H&Y 2.5, then we could report the results of balance assessment as the value mentioned in the Table as *"Pre – treatment"* record. The next step is to prescribe appropriate rehabilitation programs for the patient to improve balance and to prevent falls. Assumedly, the patient have been received the programs for 3 months. The follow – up would be set to record the patient's postural control ability each month. *"Post – treatment"* will be evaluated and compared with *"Pre – treatment"* to check if the standing balance is improved.

DPI is able to apply in 2 ways; (1) each month for adjusting rehabilitation programs, and after 3 months for evaluating balance before and after training. By using

the DPI each month of training, if PTs need to adjust balance-training programs to be most appropriate for patients at each period of follow - up, it will be beneficial for PD patients. Both PT and PD patients can save time of giving and receiving treatments, respectively. Moreover, the patients can obtain the most effective treatments for their conditions to improve the 3 impaired systems and save cost of treatments. (This case is suitable for PD patients who have unstable symptoms), (2) applying DPI after 3 month – training, to compare the effects of (individual) balance training programs, PTs are able to compare results of PL from standard balance assessments between before and after training to DPI. The purpose of this comparison is for creating new rehabilitation programs for PD patients in each level and for developing DPI. (This case is appropriate for PD patients who present stable symptoms).

**Table 9.1**

A progressive predictors' model of degree of postural instability for patients with Parkinson's disease (PD)

| H&Y | Sensory | | Motor | | | | Neural | |
|---|---|---|---|---|---|---|---|---|
| | Visual | | No Cues | | Auditory Cues | | Cognitive | |
| | EO | EC | ALT | SYN | ALT | SYN | RE | CB |
| 1 | 73.66 ± 21.84 | 73.73 ± 12.41 | 179.39 ± 65.35 | 174.39 ± 65.35 | 191.61 ± 51.53 | 176.3 ± 45.02 | 73.67 ± 15.06 | 81.33 ± 21.83 |
| 1.5 | 75.64 ± 18.65 | 87.83 ± 21.13 | 210.29 ± 64.24 | 197.67 ± 66.95 | 197.02 ± 51.84 | 181.41 ± 44.32 | 79.51 ± 16.07 | 81.3 ± 15.12 |
| 2 | 88.4 ± 46.2 | 103.25 ± 52.04 | 230.2 ± 154.29 | 236.11 ± 172.93 | 203.21 ± 122.12 | 220.6 ± 135.33 | 107.5 ± 75.42 | 124.2 ± 101.93 |
| 2.5 | 92.27±29.93 | 93.33±26.86 | 183.19±61.88 | 184.79±68.78 | 186.52±60.55 | 180.82±78.45 | 107.99±58.94 | 122.07±86.52 |
| 3 | 93.26±40.3 | 122.77±112.55 | 209.73±103.76 | 194.14±86.75 | 203.97±107.92 | 203.46±93.16 | 114.14±76.16 | 140.65±97.58 |

EO, Eyes open; EC, Eyes closed; ALT, Alternation; SYN, Synchronization; RE, Reading; CB, Counting backward

The other example of clinical implementation for PTs is for creating a model of rehabilitation for improving arm swing coordination and postural control in PD patients. This is a pilot study for future work. The details of the model creation are described below. *Method:* Dynamic postural control was examined in six patients with Parkinson's disease (PD) by Nintendo Wii balance board (NWBB). They were introduced to perform 2 arm swing patterns; alternation (Alt) and synchronization (Syn) during standing on the board in 3 conditions; before training (no cues), training with auditory cues (100% of arm swing cycle), and after training (no cues) (Fig. 9.6). Postural sway was determined by center of pressure (CoP) in terms of posturographic data. Data analysis included

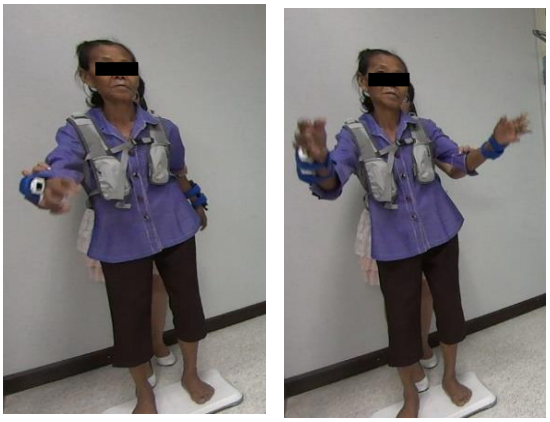
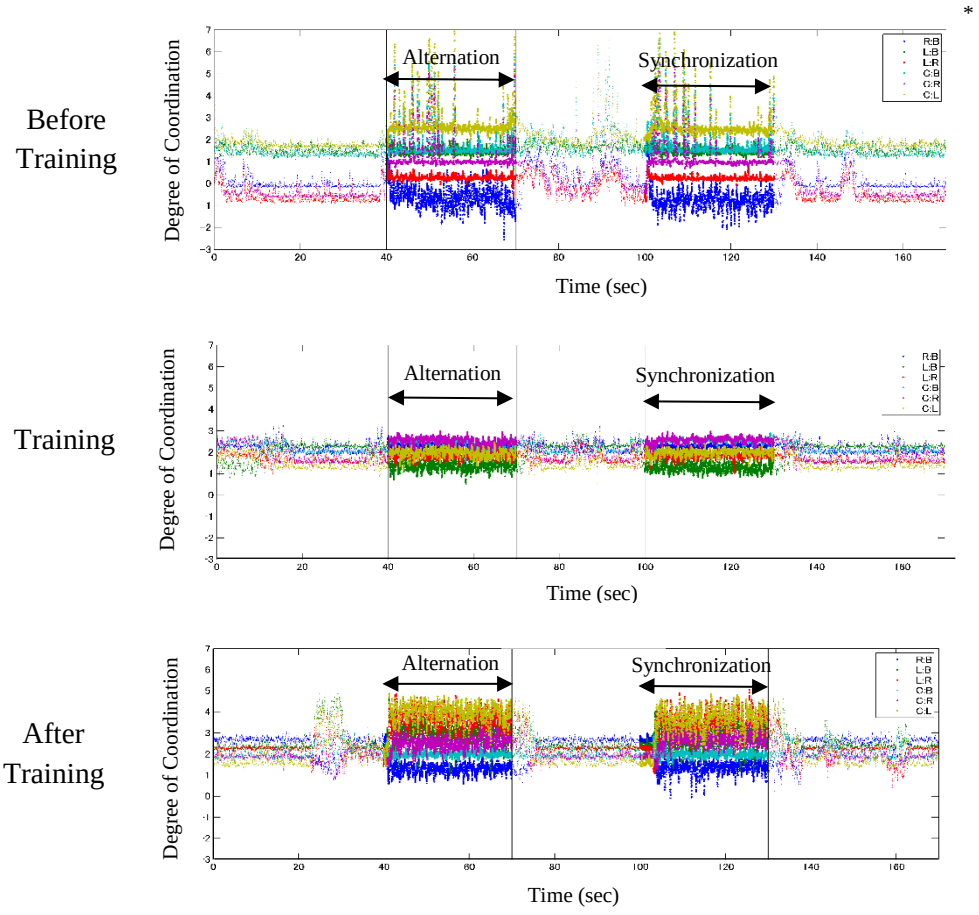


**Fig. 9.6.** Balance training with auditory cues in a patient with Parkinson's disease (PD)

general demographic data, Hoehn and Yahr scale (H&Y), UPDRS III (motor score), levodopa equivalent dose (LED), freezing of gait questionnaire (FOG-Q), PIGD and tremor present and the Montreal cognitive assessment (MoCA). The data were analyzed by using ANOVA, Wilcoxon Signed – Rank test and dimensional clustering method on MATLAB. *Results:* Significant differences among before training, during training with auditory cues (AC), and after training were reveled in PL ($f = 10.582$, $p = 0.001$) and ΔML ($f = 4.468$, $p = 0.03$) in alternation. In synchronization, significant differences were observed in PL, RMS, Min AP and ΔML. Before training showed unsynchronous pattern of degree of coordination comparing with training and after training. The degree of coordination after training was better than before training; however, the unsynchronous pattern was partly remained. Arm swing training with AC expressed better degree of coordination than before training as shown in Fig, 9.7. *Conclusion:* Arm swing training with auditory cues regulated degree of coordination of dynamic postural control in Parkinson's disease.

**Fig. 9.7.** Degree of coordination of arm swing; alternation and synchronization in before training, training and after training with auditory cues.



Last, the benefit of DPI for PD patients is biofeedback. It is simple for the patients to understand graphs of their postural control before, during and after training as shown in Fig. 9.7. Therefore, this will be useful information for PTs to convince the patients to follow rehabilitation programs prescribed regularly which finally the cooperation and attention from the patients would be paid to the training programs. If the patients understand and can learn from changing their balance ability from the biofeedback, they will have high tendency to do exercise and be in discipline. Consequently, the PD patients' postural stability will be improved and risk of falls will be reduced which will promote their health and improve quality of life (QoL). The knowledge implementation of degree of postural instability (DPI) in Parkinson's disease (PD) is illustrated in Fig. 9.8.

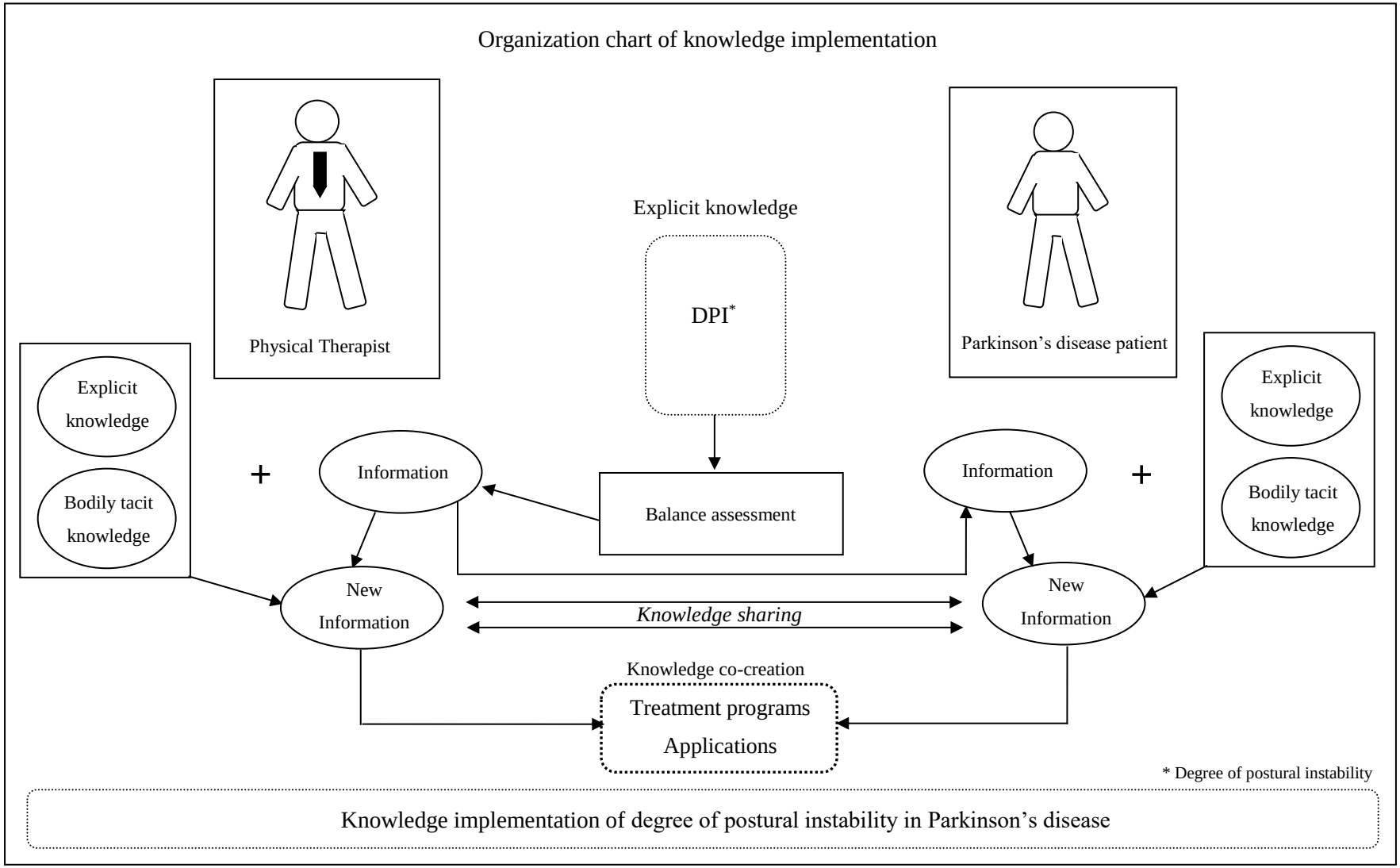
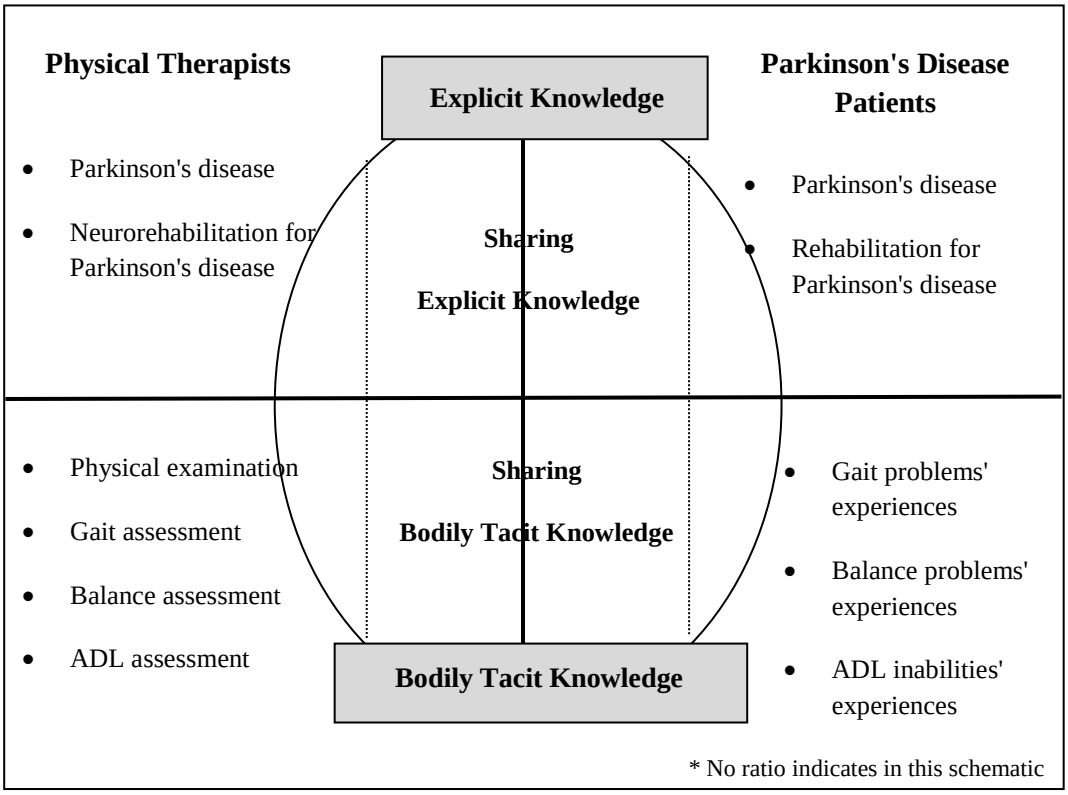



**Fig. 9.8**. Model of knowledge implementation of degree of postural instability in Parkinson's disease

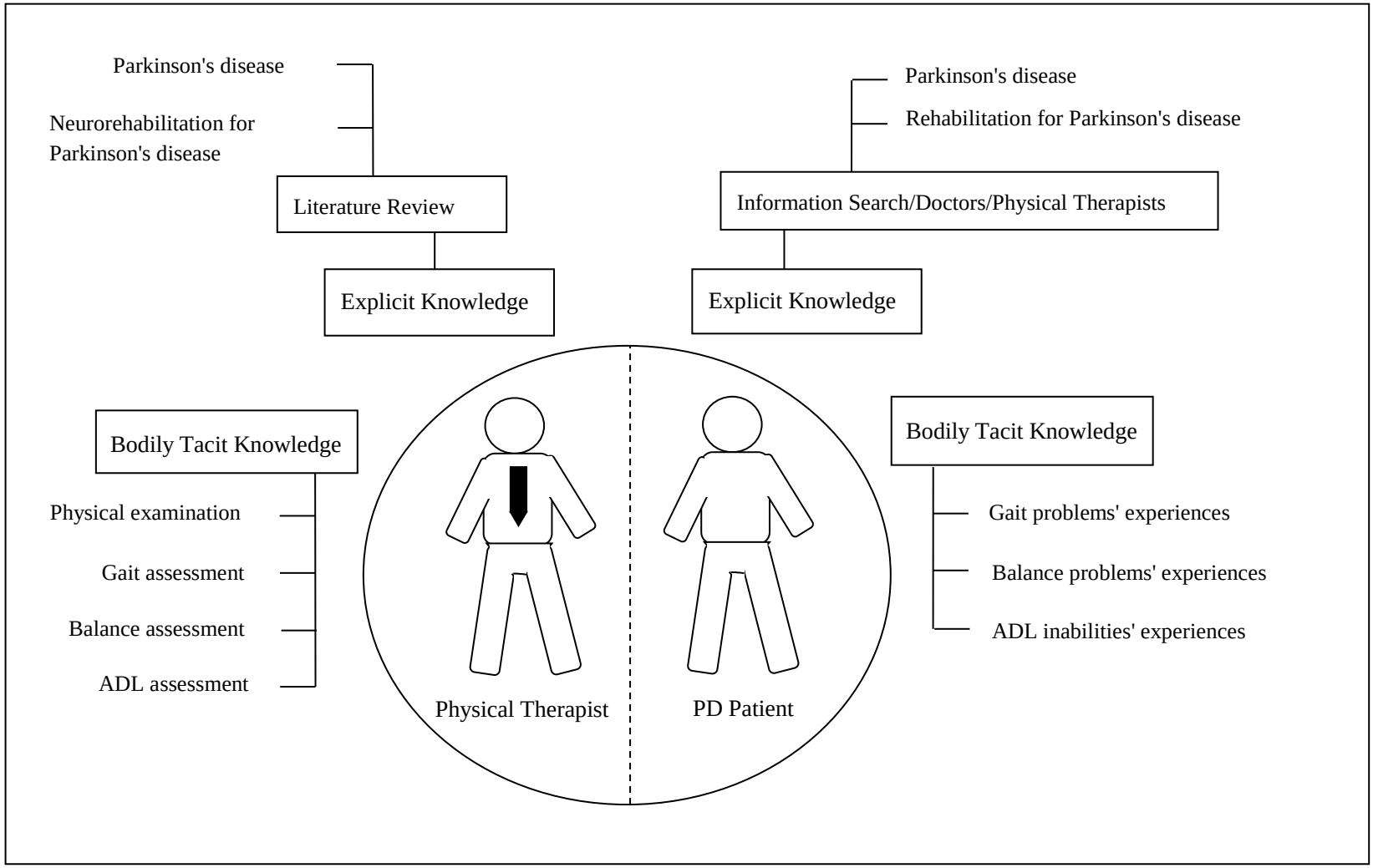
In addition, the knowledge in theories and in practice of PTs and the experiences of the PD patients in terms of explicit and bodily tacit knowledge are significantly groundbreaking knowledge. The theoretical model for co-creating knowledge can be drawn as depicted in Fig. 9.9, which will be able to apply in practice as well as will be a guideline leading to benefits for creating new treatments and improving PTs treatments and PD patients' qualities of life.

**Fig. 9.9.** Theoretical model of knowledge co-creation between physical therapists and Parkinson's disease patients in neurorehabilitation




The theoretical model of knowledge co-creation between PTs and PD patients in neurorehabilitation is the combination between explicit and bodily tacit knowledge of PTs and PD patients as shown on Fig. 9.10.

**Fig. 9.10.** Theoretical model of knowledge co-creation in neurorehabilitation for Parkinson's disease



9.2.4 Social innovation

Degree of postural instability (DPI) proposed in this study is part of social innovation. It was innovated from an inexpensive instrument, which can be implemented in reality and be useful for societies. The Nintendo Wii balance board (NWBB), which was utilized in this research, is easily for local (primary) hospitals especially in developing countries to acquire and use it to evaluate postural control in Parkinson's disease patients and people with balance disturbances. Applying DPI in clinical practice does not only help clinicians/neurologists/movement disorders specialists to assess PD patients' balance, but also support screening neurological problems in advance. By acknowledging the ability of controlling balance individually in advance, people with balance problems will be advised to meet doctors before a neurological disease is developing or the symptoms are getting worse. They will be aware of themselves in taking control calories intake and do exercise to increase muscle strength and prevent fall. This step is a screening process for preventing severe neurological problems and for being part of physical checkup.

The distribution of DPI can be from local (primary) hospital to district hospitals to provincial hospitals, and to international hospitals. It can be part of helping raising level of healthcare development in national level. By starting from the small money, after innovating the knowledge, the value of an inexpensive device is increasing. The more we utilize the device and the methodology, the more idea of knowledge creation and innovation we gain. These will be effective for supporting societies in healthcare development issue. The distribution of this social innovation is as illustrated in Fig. 9.11.

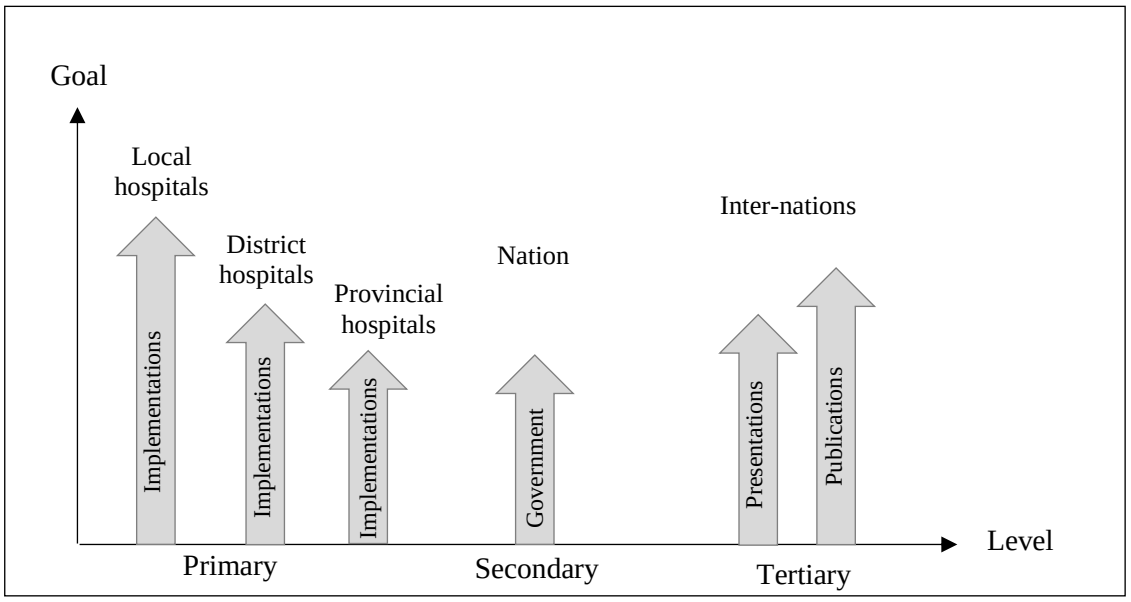



**Fig. 9.11.** Model of knowledge distribution to society

## 9.3. Research limitations

There are limitations to be addressed in this research. First, there was no normal control group to compare with Parkinson's disease patients. Second, the study has limited sample size. After we sub-analyzed the data into 2 groups, the sample size of the FOG group was double of the non-FOG group which might affect on the results. Last, the design of experiment (DOE) had no rest time between sessions, which individual previous data might interfere following data.

## 9.4. Future works

Further studies, we will enlarge the study population and adapt the study protocol to be more precisely, as well as discover new explicit knowledge for balance assessments/rehabilitation programs for Parkinson's disease (PD) patients. The results encourage that (1) specific balance programs would be considered to improve holistic balance function covered sensory, motor and cognitive impairments in order to reduce risks of falling, and complicated problems in the future, to increase balance confidence as well as to improve PD patients' quality of life (QoL), (2) a study for explaining relationship of falls, gait and balance with these deficits to invent a balance checker, (3) a study for examining sensitivity and specificity of degree of postural instability (DPI) would be conducted to develop the measure, (4) a study for examining sensitivity and specificity of degree of postural instability (DPI) would be conducted to develop the measure, (5) a study for finding relationship of cognitive function, gait and balance, (6) a study for exploring relationship of breathing control, gait and balance, and (7) studies for inventing applications for balance assessment and training.

## 9.5. List of publications

Paper published in journals

Buated W., Lolekha P., Hidaka S., Fujinami T. (2016). Impact of Cognitive Loading on Postural Control in Parkinson's Disease with Freezing of Gait, Gerontology and Geriatric Medicine, 2: 1 – 8.

日高　昇平, Wannipat Buated, & 藤波 努. (2016). 重心運動を指標としたパーキンソン病の潜在リスクの推定., SKL-22-05, pp. 26-29.

## 9.6. List of presentations

9.6.1. Domestic conferences

Buated W., Fujinami T., Hidaka S. & Kashyap N. (2014). The Effects of Aging on Balance. The 7th Thailand-Japan International Academic Conference 2014, Tokyo, Japan. (Oral presentation).

Hidaka, S., Kashyap N., Buated W. & Fujinami T. (2014). Dimensional Clustering: Analyzing Cognitive Processes by Fractal Dimensions of Bodily Dynamics. The 31st Annual Meeting of the Japanese Cognitive Science Society, Tokyo, Japan. (Oral presentation).

Hidaka, S., Kashyap. N., Buated, W. & Fujinami, T. (2015). The 29th Annual Conference of the Japan Society of Artificial Intelligence. 1L4-2. (Oral presentation).

日高　昇平, Wannipat Buated, & 藤波 努. (2016). 重心運動を指標としたパーキンソン病の潜在リスクの推定., SKL-22-05, pp. 26-29.

9.6.2. International conferences

Buated W., Fujinami T., Lolekha P., Hidaka. A Rehabilitation Model for Improving Arm Swing Coordination and Dynamic Postural Control in Parkinson's Disease: A Pilot Study. *"The 13th international Conference on Alzheimer's & Parkinson's Diseases", Vienna, Austria. 2017.* (Poster Presentation).

Buated W., Lolekha P., Fujinami T., Hidaka. A Strategy to Classify Parkinson's Disease Patients with Dyskinesia: The Analysis of Center of Pressure with Impact of Cognitive Loading. *"The 20th International Congress of Parkinson's Disease and Movement Disorders",* Berlin, Germany. 2016. (Poster presentation).

Buated W., Katsuhiro U., Lolekha P. Co-Creating Knowledge in NeuroRehabilitation between Physical Therapists and Patients with Parkinson's Disease. *"The 9th World Congress for NeuroRehabilitation",* Philadelphia, USA. 2016. (Poster presentation).

Buated W., Lolekha P., Fujinami T., Hidaka S., Kashyap N. Effects of Cognitive Loading on Standing Balance and Postural Stability in Parkinson's Disease Patients with Freezing of Gait. *"The 21st World Congress on Parkinson's Disease and Related Disorders",* Milan, Italy. 2015. (Oral presentation).

Buated W., Lolekha P., Hidaka S., Kashyap N., Fujinami T. Can Arm Swing be Clinical Predictors of Postural Instability in Parkinson's Disease? *"The 21st World Congress on Parkinson's Disease and Related Disorders",* Milan, Italy. 2015. (Poster presentation).

Buated W., Fujinami T., Hidaka S., Kashyap N. Auditory Cues on Postural Control in Parkinson's Disease: A Pilot Study**.** *"The 19th International Congress of Parkinson's Disease and Movement Disorder*s", San Diego, CA, USA. 2015. (Poster presentation).

Buated W., Fujinami T., Hidaka S., Kashyap N. Balance Assessment for Parkinson. *"The 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders",* Nice, France. 2014. (Poster presentation).

Buated W., Fujinami T. The Effects of External Cues and Arm Swing Co-ordination on

Freezing of Gait in Parkinson's Disease. "*The International School on Knowledge Co-Creation*", Bangsan, Thailand. 2014. (Oral presentation).

Lolekha P., Buated W., Hidaka S., Kashyap N., Fujinami T. Clinical Predictors of Postural Instability in Parkinson's Disease: the Nintendo Wii Balance Board Posturographic Study *"The 21st World Congress on Parkinson's Disease and Related Disorders"*, Milan, Italy. 2015. (Poster presentation).

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# APPENDIX A

## Eligibility Checklist

### Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait

**Inclusion Criteria**

| Criteria | Yes | No |
|---|---|---|
| 1. Diagnosed Parkinson's Disease | | |
| 2. Age 30 - 80 years | | |
| 3. Regular follow up every 3 month | | |
| 4. Hoehn and Yahr scale 1 – 3 | | |
| 5. Able to stand independently at least 3 minutes | | |

**Exclusion Criteria**

| Criteria | Yes | No |
|---|---|---|
| 1. Other neurological conditions; vascular parkinsonism, parkinsonism plus, drug-induced parkinsonism, motor weakness (severe sensory neuropathy, cerebellar ataxia ) | | |
| 2. Unable to stand still without support | | |
| 3. Severe dyskinesia | | |
| 4. Psychological problems | | |
| 5. Vestibular dysfunction | | |
| 6. Postural hypotension | | |
| 7. Partial or complete blindness or deaf | | |

**Summary:** ☐ Include ☐ Exclude (Reasons:.....)

# APPENDIX B

## Case Record Form

## Patient Information Sheet

## Inform Consent

# Case Record Form

**Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait**

---

## 1. General Information

**Subject No** :.....

Eligibility: ☐ yes no ☐

Group: ☐ PD ☐ Healthy elderly ☐Others (Specify .....)

**Name**: ..... **Surname**:.....

Gender : ☐ Male ☐ Female Age:..... years Weight: .....kg.

Height:.....cm. Dominant side:.... Leg length: Rt.....cm. Lt.....cm.

BMI..... Duration of disease:..... years Onset of disease:.....

H&Y stage: .....

**Presenting symptoms**: ☐ Tremor ☐ Rigidity ☐ Bradykinesia
☐ Postural instability ☐ Freezing of Gait ☐ Shuffling gait
☐ En bloc turning ☐ Stoop posture ☐ Speech disorders
☐ Sleep disorders ☐ Behavioral disorder ☐ ANS disorders

**Current symptoms**: ☐ Tremor ☐ Rigidity ☐ Bradykinesia
☐ Postural instability ☐ Freezing of Gait ☐ Shuffling gait
☐ En bloc turning ☐ Stoop posture ☐ Speech disorders
☐ Sleep disorders ☐ Behavioral disorder ☐ ANS disorders

**Medication**

| Medication | Dose (mg/day) | Conversion factor | Levodopa equivalent dose |
|---|---|---|---|
| Levodopa (IR) | | x 1 | |
| Levodopa (HBS) | | x 0.75 | |
| Entacapone/ Stalevo | | LD x 0.33 | |
| Pramipexole | | x 100 | |
| Ropinirole | | x 20 | |
| Rotigotine | | x 30 | |
| Peribidil | | x 1 | |
| Bromocriptine | | x 10 | |
| Rasagiline | | x 100 | |
| Apomorphine | | x 10 | |
| Others | | | |

Antidementia ☐ Donepezil ☐ Rivastigmine ☐ Galantamine ☐ Memantine

Antidepressant ☐ SSRI (Fluoxetine, Sertraline) ☐ SNRI (Venlaflaxine, Duroxetine)

☐ TCA (Amitriptyline, Nortriptyline) ☐ SARI (Trazodone)

☐ NaSSA (Mirtazapine) ☐ Others (Agomelatine, Bupropion)

Antipsychotic ☐ Haloperidol ☐ Risperdal ☐ Quatiapine

☐ Others……

Anxiolytics ☐ Clonazepam ☐ Lorazepam ☐ Alprazolam ☐ Sleep medication

**Motor complication**

☐ Predictable wearing off ☐ Unpredictable On/Off ☐ Dose failure

☐ Peak dose dyskinesia ☐ Biphasic dyskinesia ☐ Off dystonia

**Motor fluctuation**: ☐ no ☐ yes Type: ☐ Wearing-off ☐ Dyskinesia

☐ On-Off fluctuation ☐ Others (Specify .....)

**Fall History**: ☐ No ☐ yes; Number of falls within 12 months..... times

**ON Time**: **UPDRS iii**:.....sub score (total)

**UPDRS iii**:.....sub score (left)

**UPDRS iii**:.....sub score (right)

**Questionnaire Assessments**

**FOG-Q** score: .....

**TMSE** score: .....

**ABC** score: .....

**Mini BESTest** score: .....

**SE ADL** score: .....

**PIGD** subtype: .....

**MoCA** score:.....

## 2. Schwab & England ADL scale

| | |
|---|---|
| Completely independent | □ 100% Normal<br>□ 90% Some slowness<br>□ 80 % Takes twice as long, conscious of difficulty and slow<br>□ 70% 3-4 times as long in some |
| Some dependency | □ 60 % Can do most chores, but slow and much effort. Error |
| More dependent | □ 50% Slower, difficulty in everything |
| Very dependent | □ 40 % Can assist with all chores but few alone<br>□ 30 % Dose a few chores alone or begins alone, need help<br>□ 20 % Nothing alone |
| Totally dependent | □ 10 % |
| Vegetative, Bedridden | □ 0 % |

## 3. Gait and balance

| Tremor | | | PIGD | | |
|---|---|---|---|---|---|
| Part 2.10 tremor (1) | | 4 | Part 2.11 Falling (5) | | 4 |
| Part 3.17 Rest tremor | | 20 | 2.12 Gait and balance (3) | | 4 |
| 3.16 Action tremor | | 8 | 2.13 Freezing of gait (4) | | 4 |
| | | | Part 3.10 Gait | | 4 |
| | | | 3.12 Postural instability | | 4 |
| Total T | | 32 | Total P | | 20 |
| (Tx20)/(Px32) | | | □ tremor dominant > 1.5 | | |
| | | | □ PIGD <1 | | |
| | | | □ Unidentified 1-1.5 | | |

| Axial subscore | | | PIGD subscore | | |
|---|---|---|---|---|---|
| 27: Arising from chair (3.9) | | 4 | 13: Falling (5) | | 4 |
| 28: Posture (3.13) | | 4 | 14: Freezing (2.13,(4)) | | 4 |
| 29: Gait (3.10) | | 4 | 15: Walking (2.12,(3)) | | 4 |
| 30: Postural stability (3.12) | | 4 | 29: Gait 3.10 | | 4 |
| | | | 30: Postural stability 3.12 | | 4 |
| Total | | 16 | | | 20 |

## 4. The Activities-specific Balance Confidence (ABC) Scale

| 0% 10 20 30 40 50 60 70 80 90 100% |
|---|
| no confidence completely confident |
| *"How confident are you that you will not lose your balance or become unsteady when you…* |
| 1. …walk around the house? ____%<br>2. …walk up or down stairs? ____%<br>3. …bend over and pick up a slipper from the front of a closet floor ____%<br>4. …reach for a small can off a shelf at eye level? ____%<br>5. …stand on your tiptoes and reach for something above your head? ____%<br>6. …stand on a chair and reach for something? ____%<br>7. …sweep the floor? ____%<br>8. …walk outside the house to a car parked in the driveway? ____%<br>9. …get into or out of a car? ____%<br>10. …walk across a parking lot to the mall? ____%<br>11. …walk up or down a ramp? ____%<br>12. …walk in a crowded mall where people rapidly walk past you? ____%<br>13. …are bumped into by people as you walk through the mall?____%<br>14. … step onto or off an escalator while you are holding onto a railing?____%<br>15. … step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? ____%<br>16. …walk outside on icy sidewalks? ____% |

## 5. Freezing of Gait Questionnaire (FOG-Q)

| |
|---|
| *1. During your worst state—Do you walk:*<br>0 Normally<br>1 Almost normally—somewhat slow<br>2 Slow but fully independent<br>3 Need assistance or walking aid<br>4 Unable to walk |
| *2. Are your gait difficulties affecting your daily activities and independence?*<br>0 Not at all<br>1 Mildly<br>2 Moderately<br>3 Severely<br>4 Unable to walk |
| *3. Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?*<br>0 Never<br>1 Very rarely—about once a month<br>2 Rarely—about once a week<br>3 Often—about once a day<br>4 Always—whenever walking |
| *4. How long is your longest freezing episode?*<br>0 Never happened<br>1 1–2 s<br>2 3–10 s<br>3 11–30 s<br>4 Unable to walk for more than 30 s |
| *5. How long is your typical start hesitation episode (freezing when initiating the first step)?*<br>0 None<br>1 Takes longer than 1 s to start walking<br>2 Takes longer than 3 s to start walking<br>3 Takes longer than 10 s to start walking<br>4 Takes longer than 30 s to start walking |
| *6. How long is your typical turning hesitation: (freezing when turning)*<br>0 None<br>1 Resume turning in 1–2 s<br>2 Resume turning in 3–10 s<br>3 Resume turning in 11–30 s<br>4 Unable to resume turning for more than 30 s |

**6. Mini-BESTest:** Balance Evaluation Systems Test

| |
|---|
| ***ANTICIPATORY*** |
| **1. SIT TO STAND**<br>*Instruction*: ***"****Cross your arms across your chest. Try not to use your hands unless you must. Do not let your legs lean*<br>*against the back of the chair when you stand. Please stand up now.****"***<br>(2) Normal: Comes to stand without use of hands and stabilizes independently.<br>(1) Moderate: Comes to stand WITH use of hands on first attempt.<br>(0) Severe: Unable to stand up from chair without assistance, OR needs several attempts with use of hands. |
| **2. RISE TO TOES**<br>*Instruction*: *"Place your feet shoulder width apart. Place your hands on your hips. Try to rise as high as you can onto your*<br>*toes. I will count out loud to 3 seconds. Try to hold this pose for at least 3 seconds. Look straight ahead. Rise now."*<br>(2) Normal: Stable for 3 s with maximum height.<br>(1) Moderate: Heels up, but not full range (smaller than when holding hands), OR noticeable instability for 3 s.<br>(0) Severe: < 3 s. |
| **3. STAND ON ONE LEG**<br>*Instruction: "Look straight ahead. Keep your hands on your hips. Lift your leg off of the ground behind you without touching or*<br>*resting your raised leg upon your other standing leg. Stay standing on one leg as long as you can. Look straight ahead. Lift*<br>*now."*<br>***Left:*** *Time in Seconds Trial 1:_____Trial 2:_____*<br>(2) Normal: 20 s.<br>(1) Moderate: < 20 s.<br>(0) Severe: Unable.<br>***Right:*** *Time in Seconds Trial 1:_____Trial 2:_____*<br>(2) Normal: 20 s.<br>(1) Moderate: < 20 s.<br>(0) Severe: Unable |
| ***REACTIVE POSTURAL CONTROL*** |
| **4. COMPENSATORY STEPPING CORRECTION- FORWARD**<br>*Instruction: "Stand with your feet shoulder width apart, arms at your sides. Lean forward against my hands beyond your*<br>*forward limits. When I let go, do whatever is necessary, including taking a step, to avoid a fall."*<br>(2) Normal: Recovers independently with a single, large step (second realignment step is allowed).<br>(1) Moderate: More than one step used to recover equilibrium.<br>(0) Severe: No step, OR would fall if not caught, OR falls spontaneously. |
| **5. COMPENSATORY STEPPING CORRECTION- BACKWARD**<br>*Instruction:* ***"****Stand with your feet shoulder width apart, arms at your sides. Lean backward against my hands beyond your*<br>*backward limits. When I let go, do whatever is necessary, including taking a step, to avoid a fall."*<br>(2) Normal: Recovers independently with a single, large step.<br>(1) Moderate: More than one step used to recover equilibrium.<br>(0) Severe: No step, OR would fall if not caught, OR falls spontaneously. |
| **6. COMPENSATORY STEPPING CORRECTION- LATERAL**<br>*Instruction: "Stand with your feet together, arms down at your sides. Lean into my hand beyond your sideways limit. When I* |

*let go, do whatever is necessary, including taking a step, to avoid a fall."*
*Left*
(2) Normal: Recovers independently with 1 step
(crossover or lateral OK).
(1) Moderate: Several steps to recover equilibrium.
(0) Severe: Falls, or cannot step.
*Right*
(2) Normal: Recovers independently with 1 step
(crossover or lateral OK).
(1) Moderate: Several steps to recover equilibrium.
(0) Severe: Falls, or cannot step.
**Use the side with the lowest score to calculate sub-score and total score.**

***SENSORY ORIENTATION***

**7. STANCE (FEET TOGETHER); EYES OPEN, FIRM SURFACE**
*Instruction: "Place your hands on your hips. Place your feet together until almost touching. Look straight ahead. Be as stable*
*and still as possible, until I say stop."*
*Time in seconds:_____*
(2) Normal: 30 s.
(1) Moderate: < 30 s.

**8. STANCE (FEET TOGETHER); EYES CLOSED, FOAM SURFACE**
*Instruction: "Step onto the foam. Place your hands on your hips. Place your feet together until almost touching. Be as stable*
*and still as possible, until I say stop. I will start timing when you close your eyes."*
*Time in seconds:_____*
(2) Normal: 30 s.
(1) Moderate: < 30 s.
(0) Severe: Unable.
(0) Severe: Unable.

**9. INCLINE- EYES CLOSED**
*Instruction: "Step onto the incline ramp. Please stand on the incline ramp with your toes toward the top. Place your feet*
*shoulder width apart and have your arms down at your sides. I will start timing when you close your eyes."*
*Time in seconds:_____*
(2) Normal: Stands independently 30 s and aligns with gravity.
(1) Moderate: Stands independently <30 s OR aligns with surface.
(0) Severe: Unable.

***DYNAMIC GAIT***

**10. CHANGE IN GAIT SPEED**
*Instruction: "Begin walking at your normal speed, when I tell you 'fast', walk as fast as you can. When I say 'slow', walk very*
*slowly."*
(2) Normal: Significantly changes walking speed without imbalance.
(1) Moderate: Unable to change walking speed or signs of imbalance.
(0) Severe: Unable to achieve significant change in walking speed AND signs of imbalance.

**11. WALK WITH HEAD TURNS – HORIZONTAL**
*Instruction: "Begin walking at your normal speed, when I say "right", turn your head and look to the right. When I say "left"*
*turn your head and look to the left. Try to keep yourself walking in a straight line."*
(2) Normal: performs head turns with no change in gait speed and good balance.
(1) Moderate: performs head turns with reduction in gait speed.
(0) Severe: performs head turns with imbalance.

**12. WALK WITH PIVOT TURNS**
*Instruction: "Begin walking at your normal speed. When I tell you to 'turn and stop', turn as quickly as you can, face the*
*opposite direction, and stop. After the turn, your feet should be close together."*
(2) Normal: Turns with feet close FAST (< 3 steps) with good balance.
(1) Moderate: Turns with feet close SLOW (>4 steps) with good balance.
(0) Severe: Cannot turn with feet close at any speed without imbalance.

**13. STEP OVER OBSTACLES**
*Instruction: "Begin walking at your normal speed. When you get to the box, step over it, not around it and keep walking."*
(2) Normal: Able to step over box with minimal change of gait speed and with good balance.
(1) Moderate: Steps over box but touches box OR displays cautious behavior by slowing gait.
(0) Severe: Unable to step over box OR steps around box.

**14. TIMED UP & GO WITH DUAL TASK *[3 METER WALK]***
*Instruction TUG: "When I say 'Go', stand up from chair, walk at your normal speed across the tape on the floor, turn around,*
*and come back to sit in the chair."*
*Instruction TUG with Dual Task: "Count backwards by threes starting at ___. When I say 'Go', stand up from chair, walk at*
*your normal speed across the tape on the floor, turn around, and come back to sit in the chair. Continue counting backwards*
*the entire time."*
*TUG: _____seconds; Dual Task TUG: _____seconds*
(2) Normal: No noticeable change in sitting, standing or walking while backward counting when compared to TUG without
Dual Task.
(1) Moderate: Dual Task affects either counting OR walking (>10%) when compared to the TUG without Dual Task.
(0) Severe: Stops counting while walking OR stops walking while counting.

**7. Interview**

| | |
|---|---|
| PT: | What problem are you having due to your Parkinson's disease? |
| Pt: | A. I can't stand up when I sat on a chair. I need someone to help me. That really bother me.<br>B. I have problems during walking.<br>C. I am afraid of getting falls. |
| PT: | What problem bring you to therapy? |
| Pt: | A. I can't walk independently.<br>B. I have been fallen so many times this month.<br>C. I am afraid of walking alone outside. |
| PT: | What is the most severe symptom that often bothers you ? |
| Pt: | A. Walking.<br>B. Unable to control my hands/trunk.<br>C. Postural instability. |
| PT: | What do you do to when you have that problem (the problem mentioned above)? |
| Pt: | A. I don't know. Just sitting on a chair.<br>B. Stop moving.<br>C. Do not go out often. Keep staying at home. |
| PT: | Do you need anyone to help you do activities daily living (ADL) at home? |
| Pt: | A. Yes, sometimes.<br>B. I can do many things by myself, but sometimes I need helps.<br>C. I often really need helps. |

# Patient Information Sheet

**Research title:** Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait

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**Dear, All participants**

You are invited to participate in the research titled *"Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait"*. In this case, you are a Parkinson's disease (PD) or a healthy elderly subject. First of all, before you make a decision to participate in this study, please do read and make clear in this following document, in order to acknowledge the reasons and understand in the details of the study. If you have any questions, please do not hesitate to contact us.

Moreover, you are allowed to participate in this study by your family, friends or individual doctor. You have enough time to consider your decision. If you made decision to participate in this study, please sign your name on the inform consent sheet below.

**Background and Rationale:**

Parkinson's disease (PD) is a neurodegenerative disorder caused by the deterioration of basal ganglia (BG). The symptom involves mainly to motor system. The primary clinical manifestation of PD is resting tremor, rigidity, bradykinesia and postural instability (PI). The symptoms are getting worse from time to time as called "*progressive disorder*". The secondary motor symptoms are masked face, stoop posture, and arm swing reduction. These problems can lead to falls and limit activities of daily living (ADL) which finally lower the patients' quality of life (QoL) and increase chances to develop psychological problems. Non-motor symptoms are loss of sense of smell, constipation, rapid eye movement (REM) sleep disorder, mood disorders, orthostatic hypotension and cognitive dysfunction.

Postural instability (PI) and freezing of gait (FOG) are common problems manifesting in Parkinson's disease (PD), however, there is no scale to measure or predict the progression of the disease by analyzing postural control with the underlying; sensory, motor and cognitive impairments. This dissertation focuses on evaluating standing balance toward postural instability (PI) and freezing of gait (FOG) to be a concept of explaining relationships of sensory, motor and cognitive impairments on postural control in Parkinson's disease (PD) in order to be progressive predictors utilized in clinical practice.

**Objectives of this Study:**

I. To investigate the effects of visual input (VI) as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

II. To evaluate the arm swing patterns as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

III. To determine the arm swing patterns with auditory cues as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

IV. To study the impact of cognitive loading as clinical predictors of postural instability (PI) in Parkinson's disease (PD).

**Methods of this Study:**

The clinical assessments were arranged at the outpatient department, Thammasat University Hospital, Thailand. The patients were interviewed by physical Therapists (PTs) and were assessed physical conditions and balance assessment with mini-BESTest, as well as were instructed to complete questionnaires; Unified Parkinson's Disease Rating Scale (UPDRS) III, the Montreal Cognitive Assessment (MoCA), the Activities-specific Balance Confidence (ABC) Scale, the score of Thai Mental State Examination (TMSE), the Schwab & England Activities of Daily Living (SE-ADL) and the Freezing of Gait questionnaire (FOG-Q).

The study procedure in this study was designed in three sections; sensory, motor and cognitive. Participants were asked to perform on Nintendo Wii balance board (NWBB) to be assessed postural control. Clinical assessments in terms of balance confidence, cognition, freezing of gait (FOG), activities of daily living (ADL) were employed to evaluate the patients. The length of the data collection was 30 - 45 minutes depending on patients' symptoms/conditions.

**Participant's Responsibility to this Study:**

To gain success form this study, we would like to urge you for your kindly cooperation. Please do follow our instructions strictly. And please inform us if you have any abnormal symptoms during you are participating in the study.

**Risk Factors:**

Risk factors that can occur from the study protocol is in low level. It is because the researcher will fasten belt patients before running the examination and the researcher will guard the patients from being fallen. The assessment will be conducted safely for all participants and an assistant will aware and be ready to help as far as it has been concerned. Moreover, the screening test would be proceeded before the test starting to separate and consider patients who have high risk of falls. Therefore, the risk factors for this study is low as mentioned.

However, generally Parkinson's disease patients have a tendency to be fallen. It depends on the stages of the disease. The researcher was realized and considered this point as well as designed the study to be appropriate for the type of patients. The patients would be protected and assisted immediately, in case of necessity. In addition, the patients would get enough rest break between each session to prevent fatigue, which could bring about receiving injuries. This procedure can help reduce the risk of falls to the patients.

**Benefits:**

All participants will be physically assessed and will be evaluated balance in 3 sessions. The participants will be informed the results of their balance and how to adapt those to be benefit for their diary living individually.

**Rules and Regulations of Participating in this Study** (Please do follow)

- Please be honest while providing personally medical current and history to the researcher.
- Please inform the researcher whenever participants found something abnormal during the examination.

**Participation and the End of the Study:**

The participation of this study is in an agreement of each participant. If you are unwilling to participate in the study, you can either reject or cancel the participation anytime. The withdrawal of the study will not affect on current or future treatments.

The researcher can withdraw a participant for a reason of safety. Besides, in case of unable to abide by the rules and regulation of the study, and the case of being high risk of falls or injuries, the researcher has right to withdraw such a participant.

**Protection of Participants' Information:**

The information, which will be lead to each participant, will be concealed and will not disclose to public. In case of the study gets published, participant's name and address will also be hide as usual. Only code of individual subjects will be reported.

According to your inform consent, the researcher has a right to access your medical history, although the study will have been done.

**The Declaration of Rights of Participants in this Study:**

1. You will acknowledge the purposes and methods of this study.
2. You will be explained the research methodology and involved medical instruments of this study by the researcher.
3. You will be explained the risks and discomfort which can happen in this study.
4. You will be explained about the benefits of participating in this study.
5. You will acknowledge the options of treatments or medical instruments, which will result in benefits and side effect of each treatment and instrument.
6. You will acknowledge methods of treatments, in case we find other diseases form physical assessment and after being participated in this study.
7. You have a right to ask about this study and methods related to this study.
8. You will acknowledge that the compliance to participate in this study, you have a right to withdraw anytime without getting any affects.
9. You will receive a copy of inform consent with your signature.
10. You will have a right to consider whether you prefer to participate in this study or not without compulsion or deception.

If you do not receive any compensation caused by any injuries or illness, which would occurred from the study, or if you do not obtain in what described on the patient information sheet, please inform the Ethical committee, (Name..... Hospital, (Address.....), Tel (.....).

**Thank you so much for your distribution and cooperation.**

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# Inform Consent

**Research Title:** Progressive Predictors of Parkinson's Disease Based on Postural Instability and Freezing of Gait

Date...../...../.....

My name is (Mr./Mrs./Ms)..... Address ..... who is ..... of (Mr./Mrs./Miss)..... I have already read the patient information sheet attached. I do allow (Mr./Mrs./Miss)..... to participate in this study.

I have received the copy of the inform consent, which I declared my name, and the patient information sheet. Before I signed in this inform consent, the participant and I had been described by the researcher about the objectives of this study, the duration of the study, the methods, and the risk factors or symptoms which might happen from the study, as well as the benefits that would result from the study and other related treatments. The participant and I had had enough time and a chance to ask questions and had clarified all suspicion so as to be well understood in the protocol. The researcher had answered the questions willingly until the participant and I were satisfied.

The participant and I were informed from the researcher that if any accidents happened from the study, the participant would receive a treatment by no charge.

I understood the eligibility that the participant could cancel the study anytime without inform reasons and the cancellation of this study would not affect any rights to receive treatments toward this disease or other rights which the participant should obtain from the hospital in the future.

The researcher confirmed to keep individual documents confidentially, and could be disclosed the information particularly when I consented merely. Other persons, on behalf of the ethical committee, the supporter to this study and the world health organization (WHO) may access the document in order to investigate and compile the participant data. All in all, the process must proceed as regard to the purpose of verifying the data only. With this inform consent, I did agree the verification in medical history of the participant.

The researcher also confirmed that there was no additional collecting data after the participant or I had rejected the participation to the study. Moreover, if we needed the document to be destroyed, the researcher would manage it.

I understood that the participant and I have rights to access and edit personal data appropriately and could cancel the researcher's right in accessing participant's personal data by informing the researcher.

I am realized that the confidential research data as well as the medical history will be passed processes; such as collecting data, recording data to computer, inspecting, analyzing, and reporting the data for the purpose of educations. Including to be the information for medication and medical instrument's research in the future only.

I have already read the sentences above and completely understood in all details. I am willing to allow (Mr./Mrs./Ms)..... participate in this study.

.....

( )
Family member/Relative/Caregiver

...../...../.....

I have already explained the important information to the participant; the purposes, the methods of this study, the risk factors and accidental injuries or symptoms which might occur in this study, including the benefits which participants could receive in details. Moreover the family member/relative/caregiver as the name above was acknowledged and clearly understood, as well as willingly signed to the inform consent.

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( )
Researcher

...../...../.....

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( )
Witness

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