Classification of handwriting kinematics in automated diagnosis and monitoring of Parkinson's disease

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Doctor of Philosophy

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged ; and, ethics procedures and guidelines have been followed. I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

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2. Zham, P., Kumar, D., Viswanthan, R., Wong, K., Nagao, K.J., Arjunan, S.P., Raghav, S., and Kempster, P.: 'Effect of levodopa on handwriting tasks of different complexity in Parkinson's disease: a kinematic study', *Journal of Neurology*, 2019, pp. 1-7

3. Zham, P.Z., Kumar, D.K., Dabnichki, P., Arjunan, S. & Raghav, S. Distinguishing different stages of Parkinson's disease using composite index of speed and pen-pressure of sketching a spiral. *Frontiers in Neurology* **8**, 435 (2017)
   Selected as the featured article with worldwide media coverage.
   - http://www.bbc.com/news/health-41176738
   - http://www.9news.com.au/health/2017/09/07/20/28/new-screening-test-for-parkinsons-disease
   - http://journal.frontiersin.org/article/10.3389/fneur.2017.00435/full

4. Zham, P., Arjunan, S., Raghav, S. & Kumar, D.K. Efficacy of guided spiral drawing in the classification of Parkinson's disease. *IEEE Journal of Biomedical and Health Informatics* (2017)

5. Zham, P, Kumar,D.K., Kempster,P., R., Arjunan, S., Wong, K., Nagao, J. & Raghav, S. Progressive micrographia verses writing speed in Parkinson's disease: Levodopa effect (drafted)

International Conferences

1. Zham, P., Kumar, D.K., Dabnichki, P., Raghav, S. & Keloth, S.M. Dynamic handwriting analysis for assessing movement disorder. in *13th International Conference of Applied computing* 220-224 (IADIS, Manheim, Germany, 2016)

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Preface and Authorship attribution

This research is performed in collaboration with RMIT, Dandenong Neurology and Monash health centre

- Chapter 4 is based on a journal article(Zham et al., 2017a) published in the IEEE Journal of Biomedical and Health Informatics in 2017.
- Chapter 5 is based on a journal article(Zham et al., 2017b) published in Frontiers in Neurology in 2017.
- Chapter 6 is based on a journal article(Zham et al., 2019a) published in the Journal of Neurology in March 2019.
- Chapter 7 is based on a journal article(Zham et al., 2019b) published in Frontiers in Neurology in April 2019.
- Chapter 8 is based on a drafted manuscript which will be submitted soon.

In all the above journal I am the first author and been involved in all stages of publication.

I was involved in designing experiment, data acquisition, data analysis, software design and development for collecting and analysis of data, selection of analytical tools, statistical analysis, and drafting the article.

Abstract

Parkinson's disease is one of the most prevalent neurodegenerative conditions. Currently, there is no standard clinical tool available to diagnose PD. One of the research priorities is to come up with biomarkers which will improve the diagnostic process and can be used for the clinical test. At present, the only way to assess this disease is by visually observing the symptoms of the patient which is performed only by expert neurologists. As of now, there is no treatment to prevent the progression of PD. However, there is an elemental drug 'Levodopa' (L-dopa) available to control the disease by increasing dopamine cells in the brain. It is important to detect PD and start treatment in the early stages as it helps to control the symptoms and significantly delays the development of motor complications.

In this study fine motor symptoms handwriting has been studied. As a first objective I have conducted the experiments on the significant number of patients and age-matched control (112 Participants:56 PD and 56 controls), and thus completed the task of data collection. The system developed extracts the dynamic features of the handwriting/drawing, reports the possible strength of dynamic features providing a basis for automated analysis. The advantage of this approach is that patients are not required to follow complex commands, and the analysis can be fully automized. I anticipate that following appropriate clinical tests already planned, the system will be able to detect early disease symptoms remotely outside hospitals or clinics. It could also be used for self-evaluation by patients with neuromuscular and motor neuron disorders. This device can be used without compromising on the comfort level of Patients who may still prefer writing with an ink pen on plain paper.

This study proposes a new feature 'Composite Index of Speed and Pen-pressure' (CISP) to distinguish between different stages of Parkinson's disease. The experiment also demonstrated a method which can be used with guided spiral drawing to improve classification results to predict Parkinson's disease. Further, I recommend using a panel of writing tasks which might prove to be an effective biomarker for cell loss in the substantia nigra and the associated dopamine deficiency. Thus, models developed can be used in designing an automated application for predicting and monitoring Parkinson's disease.

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Chapter 1   Background

1.1   Medical background

Parkinson's disease (PD) is a progressive neurological condition which is caused by a low level of dopamine in certain parts of the brain. The average age of diagnosis is 65. Parkinson's disease in the remote and regional area is more than the metropolitan city. Currently, it is assessed only by expert neurologists who visually observe the symptoms of a patient. However, due to lack of a standard tool or method, many times disease goes undiagnosed. On an average, the under-diagnosed rate is 29%. The maximum rate in some regions of Australia has gone up to 70%. Nearly 70,000 people in Australia are living with Parkinson's disease. Costs due to PD is increasing at an alarming rate (Economics, 2015). It is imperative to come up with biomarkers that improve the diagnostic process and can be used for the clinical tests. Levodopa is an elemental drug which helps to increase dopamine and as an effect improves Parkinsonian motor dysgraphia (McDowell et al., 1970).

Dopamine is the neurotransmitter in the brain. PD is caused when dopamine production reduces in the mid-brain area called Substantia Nigra (SN). The reason for this reduction is unknown. Figure 1.1 shows the difference between dopamine pathway in a healthy subject and a PD patient. As shown in Figure 1.1 D1, direct pathway helps in an excited movement whereas D2, which is an indirect pathway, helps to suppress the action. A disturbance in the balance between this pathway characterizes the disease. 50-60% of dopamine neurons are lost by the time neurologist are able to detect PD as per current clinical methods (Becker et al., 2002; Ross et al., 2004).
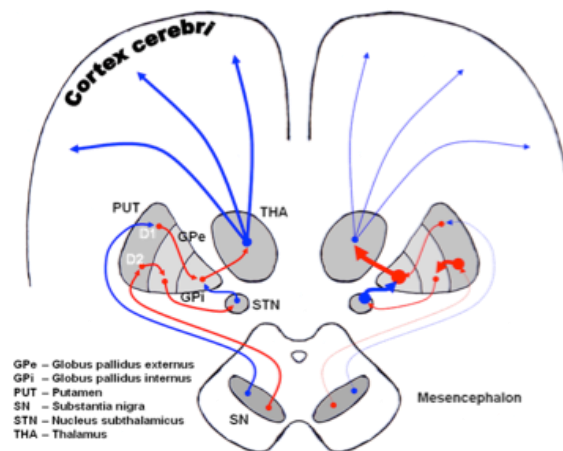
Figure 1.1 The left side shows a normal brain, and the right side shows the PD brain dopamine pathway. Blue colour indicates excitatory pathways whereas red is inhibitory pathways

PD Symptoms can be divided into two types; Motor and Non-motor as shown in Figure 1.2.

1.1.1 Motor Symptoms

Cardinal motor symptoms used to diagnose PD are Tremor, Rigidity, Akinesia (or bradykinesia) and Postural instability (Jankovic, 2008).
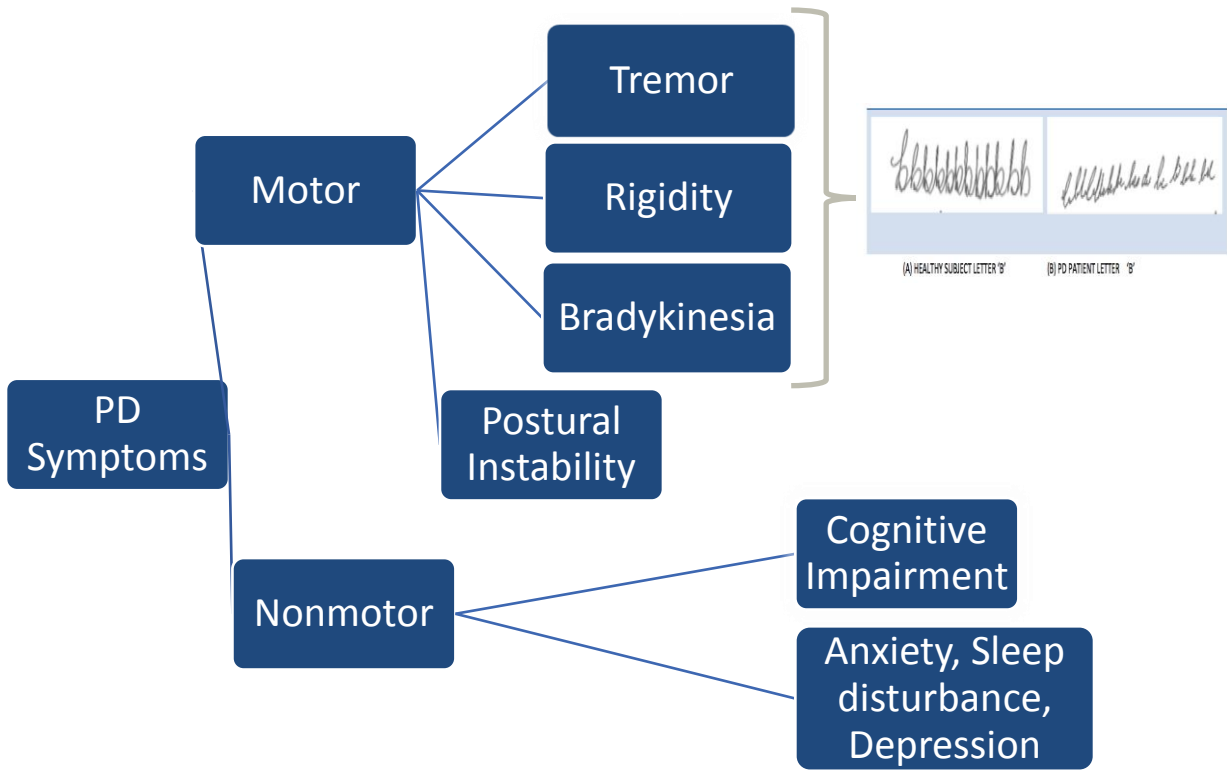
Figure 1.2 PD Symptoms

- *Bradykinesia*: The individual's movements become increasingly slow and over time muscles may randomly "freeze". In the early stage of PD, bradykinesia has been found to be the topmost symptom (Politis et al., 2010).

- *Rigid muscles*: Muscle stiffness or resistance to movement affects most of the people with PD. It may occur in different parts of the body. Generally, in PD patient rigidity is observed in limbs. In

the upper extremities by observing the full range of motion in limbs and it is tested at wrist, elbow, and shoulders (Perlmutter, 2009).

- *Tremor:* Tremor is one of the most important movement abnormalities observed in PD patients. It is observed in 75% of PD patients (Helmich et al., 2012). It usually starts with one hand and then affects one side of the body (Economics, 2015). It may occur at rest, during postural position or voluntary movements; it can be seen in the hands, feet or other body parts; and tremor frequency may vary from low (4–5 Hz) to high (8–10 Hz).

- *Postural Instability*: Impaired balance and postural instability are observed in the later stage of PD. Postural instability can cause PD patient to have a stooped posture (Yao et al., 2013).

1.1.2   Non-motor symptoms

Non-motor symptoms in PD goes untreated as it gets missed most of the times during evaluation. Most common of them include sleep disturbance, cognitive dysfunction, anxiety, depression, and autonomic dysfunction (Jankovic, 2008).

Cognitive dysfunction

It has been found that PD patient suffers from cognitive dysfunction, which can range from mild to severe. Pfeiffer, H.C.V., et al. found that 70% of PD patients show some kind of cognitive impairment in the early stages (Pfeiffer et al., 2014).

A cognitive domain can be classified into five types of functions:
  i.   Attention and working memory i.e.; short-term memory like while driving a car, reading sentence.
  ii.   Executive functions i.e.; planning, conceptualising, organising, evaluating
  iii. Language; while speaking or writing, one's abilities to find words and names by category and comprehend
  iv.   Memory; Memory refers to the brain's ability to store, consolidate and retrieve information and recognize
  v.   Visuospatial function; Ability to calculate the current position in relation to any object while moving, for example drawing shapes.

1.2 Rating Scales

There are different rating scales used to evaluate motor and non-motor disability in PD. In this study, I have used the scale which is most commonly used for clinical purposes and recommend by neurologist. This includes -Unified Parkinson's Disease Rating Scale (UPDRS) MDS-UPDRS, Hoehn&Yahr Stage (H/Y) and the Schwab & England Scale (S/E) (Goetz et al., 2004; Goetz et al., 2008). The cognitive Impairment test was performed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). For more details, see Appendices (A).

1.3 Literature review

Micrographia

Micrographia is the medical term for "small handwriting". Parkinson's disease patients often have handwriting that looks cramped. Individual letters tend to be smaller than normal, and words are spaced closely. In some cases, a person with PD may start writing a letter in their regular handwriting but gradually begins to write in a smaller font. This is termed as 'Progressive Micrographia' (Lewitt, 1983; Shukla et al., 2012; Raudmann et al., 2014). It is said to happen due to bradykinesia. Figure 1.3 shows the comparison between normal handwritten text and that of PD patient with progressive micrographia (Zham et al., 2016). It has been observed that in about 50-63% of PD patients the handwriting starts reducing in size (Shukla et al., 2012).

Chang et al., compared horizontal and vertical handwriting and found PD subjects showing micrographia in horizontal direction did not show in vertical direction (Chang et al., 2016). Kim et al., compared free handwriting versus copying sentence and suggest that copying sentence is more effective than free handwriting task (Kim et al., 2005) and queuing can help in reducing micrographia (Kim et al., 2015) whereas Nackaerts et al., who studied the effect of visual cueing on handwriting samples of 15 PD and 15 healthy subjects indicate that visual target lines of 1.0 cm improved the writing in contrast to lines spaced at 0.6 suggesting that line spacing of different size may not show similar improvement in micrographia (Nackaerts et al., 2017).

(A) HEALTHY SUBJECT LETTER 'B'   (B) PD PATIENT LETTER 'B'
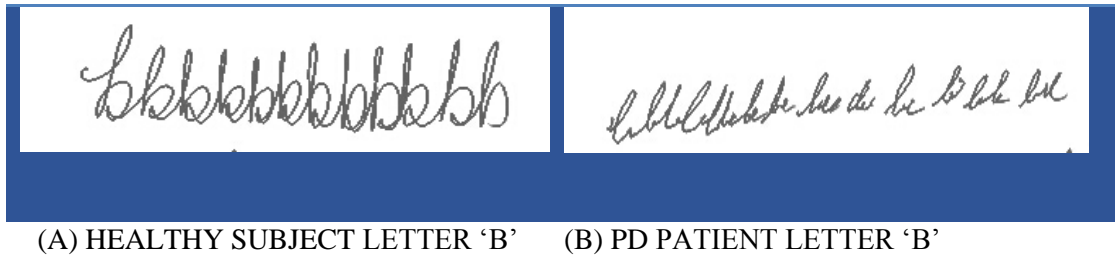
Figure 1.3 Letter b written by (a) healthy subject and (b) PD patient with micrographia(Zham et al., 2016)

Writing letter el:

Smits et al., recorded pen tip trajectories for circle, spiral and line drawing and repeated character 'elelelel' and sentence writing, performed by Parkinson's disease patients and healthy control participants. The width of the 'e' and length of letter 'l' in 'elel' task was significantly smaller in Parkinson disease patients compared to healthy control participants (Drotar et al., 2014; Smits et al., 2014).

Drawing Spiral

Saunders-Pullman, R., et al. identified the use of spiral as a suitable option to identify differences between healthy and PD patients (Pullman, 1998). Spiral drawing has shown promising results even in the early stage of PD (Shukla et al., 2012; Graça and Cevada, 2014). Longstaff and Heath suggest that PD subjects draw the spirals slower and with less pen pressure than controls (Longstaff and Heath, 2006).Spiral can not only help in measuring tremor (Pullman, 1998) in PD but also distinguishing PD from other tremor causing syndromes(Tolonen et al., 2015).

Cognitive Impairment

PD in earlier days was recognized as a movement disorder related disease, but later it was observed that it affects non-motor symptoms too. One of such non-motor symptoms is Cognitive Impairment. Cognitive impairments are common even in newly diagnosed Parkinson disease patients, with deficits being most prominent in the domains of memory and executive functions. Older age at disease onset is likely to be an important determinant of cognitive dysfunction in Parkinson disease. Williams-Gray studied early Stages of PD patients and found that from the onset of PD within +3.5 years, 75% show some kind of cognitive impairment (Williams-Gray et al., 2007). Cognitive impairment is related to the mental processing of

memory, attention, abstract thinking, problem-solving, language, and visual-perceptual abilities. Another study where PD patients were observed for 5 years also says, 75% have shown cognitive impairment and the domain which was affected more were memory and psychomotor (Broeders et al., 2013). Shukla et al., also found a strong correlation between micrographia and cognition (Shukla et al., 2012). Handwriting and handwriting-like movements in drawing scenarios are reducing working memory performance to a similar extent (Longstaff et al., 2003).

As a step toward automating the detection process Pereira et al., used an algorithm such as Support Vector Machine(SVM), Naïve Bayes classifier and was able to achieve about 78.9% of recognition rates with Spiral drawing (Pereira et al., 2015). A study by Unlu et al., suggests that pen-tip pressure shows interesting outcome which may be helpful in differentiating PD handwriting (Ünlü et al., 2006).

1.4   Current challenges

Current challenges of diagnosis of PD includes:
1. Excessive clinician time required for assessment.
2. Assessment outcome is highly dependent on the expertise of the doctor.
3. It depends on the fidelity of the answers provided by the patient.
4. In the early stages, symptoms are not visible, which delays diagnosis that has a vital effect on the treatment outcome.
5. Clinical assessment is conducted by neurologists. This requires access to large urban-based clinics and often the cost may be prohibitive to some people resulting in patients seeking the assessment only after the advanced manifestation of clinical symptoms.

1.5   Motivation to choose Handwriting

Except for postural instability, other cardinal symptoms, i.e. tremor, rigidity and bradykinesia which starts in early stages can be measured using handwriting (Smits et al., 2014). It can also help to understand the impact of nonmotor symptoms which are rarely studied in previous studies (Brown and Marsden, 1991; Broeder et al., 2014)(Figure 1.4).

6
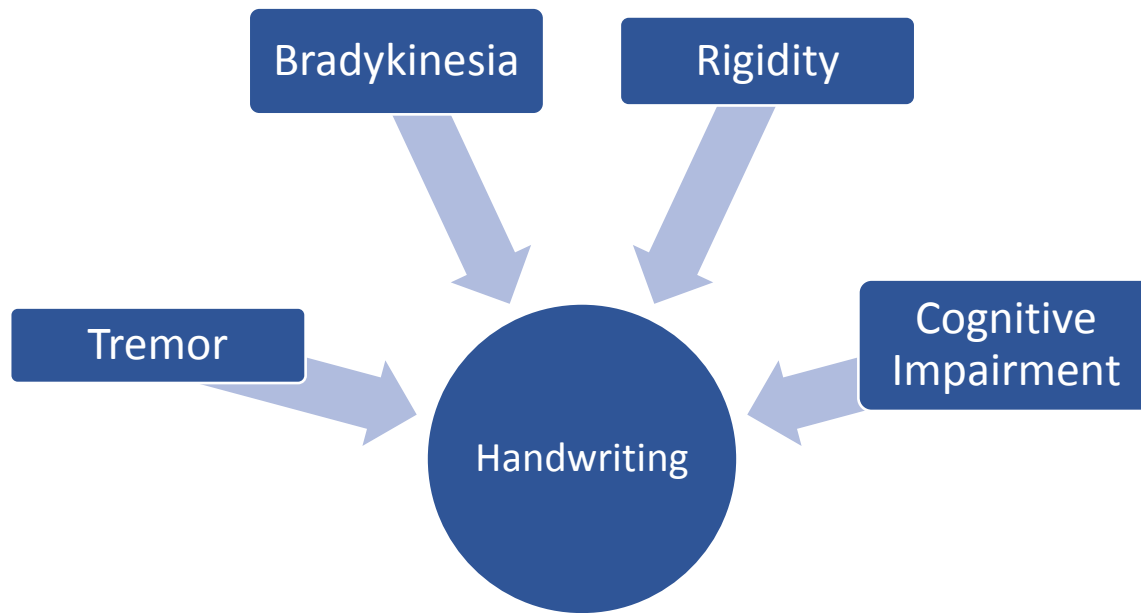
Figure 1.4 Symptoms impacting handwriting

1.6   Problem Statement

This research program provides the tool which can be used in urban clinics to assess PD in preliminary stages. It will also overcome few gaps from the research work done till date. This experiment uses an inexpensive system that digitally records and performs dynamic feature analysis. In this thesis, different writing tasks and their dynamic features have been studied. The work compares the current dynamic features and writing tasks and suggests a method to improve classification accuracy in the diagnosis of Parkinson's disease.

Researchers have found that handwriting can be used to identify Parkinson's disease; however, identifying the level of severity is important for optimal clinical decision. Very few research papers have worked on studying the severity level. This work presents a new feature which shows a significant improvement in distinguishing different stages of Parkinson's disease.

Studies suggest that levodopa is effective in improving motor skills. Handwriting is one such skilled motor activity which is affected due to Parkinson's disease. Researchers have suggested the use of kinematic features of handwriting in distinguishing Parkinson's disease. This paper examines the dopaminergic

influence on handwriting with different memory load and its impact on kinematic features. In this work, different handwriting data related to PD are studied. Total of 112 subjects participated in the study.

This research study identifies biomarkers based on dynamic features of handwriting and provides an easy-to-use application for commercially available inexpensive digital hand-held devices that can be used in urban clinics to assess PD in preliminary stages.

The study demonstrates methods to improve the efficacy of previous research methods in detecting PD.

1.7　Outline of the Thesis

Later in the thesis, Chapters are divided into phases as below:

- *Chapter 2* sets out to drive aim, scope and research questions along with current research challenges that guided the actual research.
- *Chapter 3* justifies the materials, subjects, and methods used for the experiment in detail. Implementation of different components of the application and features are explained.

Following Chapters are derived from research question of Chapter 2

- *Chapter 4* lays out the criteria for the classification of kinematic features to detect Parkinson's disease using different machine learning algorithms.
- *Chapter 5* shows the criteria use for clustering Parkinson's disease based on the severity of disease using a composite index of speed and pen-pressure (CISP) of handwriting.
- *Chapter 6* undertakes the analysis of handwriting of different complexity in Parkinson's disease and the effect of levodopa on it.
- *Chapter 7* studies the relation between progressive micrographia and kinematic features
- *Chapter 8* reveals the effect of levodopa on kinematic features of PD showing progressive micrographia symptoms.
- *Chapter 9* Conclusion and future work, a retrospective of the research is made, and possible future work is proposed.

Chapter 2 Aim and Objective

2.1   Aim

This study aims to analyze the dynamic features of handwriting and identify biomarkers that can be used to

- **To diagnose the disease**

Diagnosing the disease in an early stage is very crucial to control the disease

- **Monitor the progress of the disease**

Parkinson's disease can be categorized into various stages based on the severity of symptoms

- **Measure the effect of treatments**

Levodopa is an elemental drug which is used to control the disease however it is important to understand the effect of medication

2.1.1   Objective

The objective is to
- Come up with an inexpensive system that digitally records and performs dynamic feature analysis which can be used to detect Parkinson's disease.
- Come up with features to distinguish between different stages of PD.
- Improve the classification with new features.
- Investigate the effect of cognitive impairment on handwriting.
- Study relation between micrographia and kinematic features.

2.2   Advantage of a current research experiment

- This test is easy to perform, and the setup is simple.
- Can be performed in a very short time (<15 Minutes).
- No complicated setup.
- The device is not expensive.
- Automates the process of detection and monitoring.

Hence it can be made a preliminary test which can be performed in any metropolitan or remote areas.

2.3　Research questions and objectives

Below are the research questions which will be covered in the coming Chapters

1. **Which dynamic features and writing tasks are effective in the diagnosis of Parkinson's disease in the early stage?**

   Kinematics of handwriting can be used to distinguish between PD and controls (Rosenblum et al., 2013). Drotar et al., has analyzed different writing tasks and showed that for prediction 'Sentence' has outperformed all the other writing tasks whereas, 'Spiral drawing' performed poorly in prediction using classifier (Drotár et al., 2015). However, on the contrary, other researchers have analyzed drawing and suggested kinematics of Spiral is effective (Saunders-Pullman et al., 2008; Stanley et al., 2010). No correlation has been established so far between these different writing experiments and relevant dynamic features. More detail in Chapter 4.

   Objective
   - The objective is to come up with the features and writing task which can be used in the classification of PD.

2. **How to distinguish between various stages of Parkinson's disease using dynamic features of handwriting?**

   Research studying the severity level in Parkinson's disease are seldom. Identifying the level of severity is important for optimal clinical decision. Saunders et al., successfully quantified drawing of the spiral and identified the features that were associated with severity levels of the disease among PD patients. While this is extremely useful to demonstrate the association, the maximum correlation coefficient reported using dynamic features was around 0.4 (Saunders-Pullman et al., 2008). More details in Chapter 5.

Objective:

- The aim of the work is to establish a reliable computer-based assessment of the spiral sketching on a digital tablet for assessment of the severity of the disease.

3. **What is the effect of levodopa on the handwriting of different complexity?**

Medication effects have not always been considered in most of the handwriting research (Pullman, 1998; Rosenblum et al., 2013; Drotár et al., 2016). Responsiveness of Levodopa is important to disease monitoring role for computerized writing. The shortcomings of earlier studies conducted on Levodopa response have been commonly confined to the repetition of a few letters such as 'e' and 'l' (Eichhorn et al., 1996; Cobbah and Fairhurst, 2000).More detail in Chapter 6.

Objective:
- Investigate the difference between the *on* and *off* states for PD patients for different writing activities which range from repeating two letters, 'e' and 'l', to copying a long sentence and written fluency test. Measure the group difference between PD patients in On-state with control subjects to determine which of the activities are significantly different post medication.

4. **What is the relation between progressive micrographia and kinematic features in Parkinson's disease? How levodopa improves size vs kinematic features?**

Van Gemmert et al., suggests as processing demand increases stroke size reduces in PD and stroke duration remains unchanged (Van Gemmert et al., 2001) in contrast to Teulings and Stelmach who did not find any difference in size but saw an increase in stroke duration in PD (Teulings and Stelmach, 1991). Wu, et al., suggest levodopa improved consistent micrographia. However progressive micrographia results are not clear(Wu et al., 2015). From the previous studies, it is unclear how kinematic feature differs in PD showing a progressive decrement in size compared to those who do not show decrement and effect of levodopa in both the group. More detail in Chapter 7 and Chapter 8.

Objective

- This aim of this study is to determine the relationship between kinematic features of the handwriting and the size of handwriting in PD patients and compare it with the controls. A baseline was first established by studying the kinematic features over repetitive writing by age-matched Control participants and comparing it with the PD patients of medium severity.

Chapter 3 Materials and Methods

3.1   Recording Equipment

Wacom Intuos Pro Large, A3 size digital tablet with the sensor ink pen was chosen for the experiments. Pen trajectories were captured using customised software developed in C# programming language running on a tablet with a Windows operating system (Figure 3.1). The gathered data was stored in CSV files.

Pen trajectories recorded are $x - y$ coordinates, pen-tip pressure, tangent pressure, azimuth, altitude and time stamp.

For this research study $x - y$ coordinates, pen-tip pressure and time stamp where used;

- *x*, *y* coordinates are received in pixels and converted into millimetre.
- Pen-tip pressure (*pr*) recorded is unit-less with the range; 0–1,024 units.
- The device had a *s*ampling rate of 133 Hz.

Figure 3.1 Device used for performing handwriting and drawing experiment

3.2   Participants

One hundred twelve subjects participated in this study; 56 PD patients and 56 age-matched Controls. The experimental protocol was approved by RMIT University and Monash Health Human Research Ethics Committee and in accordance with the Helsinki Declaration (revised 2004) refer Appendices (C). All participants were informed and provided their oral and written consent before the start of this experiment. The PD patients were recruited from a neurology clinic - Monash Medical Centre and Dandenong Neurology, Melbourne, Australia, while the Controls were friends, caregivers and volunteers from multiple aged-care facilities. All complied with the Queen Square Brain Bank criteria for idiopathic PD (Hughes et al., 1992). The presence of any advanced disease clinical milestone—visual hallucinations, frequent falling, cognitive disability, need for institutional care (Kempster et al., 2010)—was an exclusion criterion which was performed by a senior neurologist.

31 PD patients recording is taken after a regular dose. Chapter 4 and Chapter 5 results are based on these groups. 25 PD patients recording was taken in *on* and *off* state of levodopa dose (Figure 3.2). *off* state recording is taken after fasting for at least 12 hours without levodopa dose. The *on* state is taken after 60 minutes where maximum improvement is observed (Poluha et al., 1998). Motor function in *off* and *on* states was scored by a neurologist on the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) (Goetz et al., 2008). For detail refer Appendices (A). The cognitive screening was performed using the Montreal Cognitive Assessment (MoCA) test (Nasreddine et al., 2005) (Appendices (B). Levodopa equivalent daily doses were calculated using standard conversion factors.
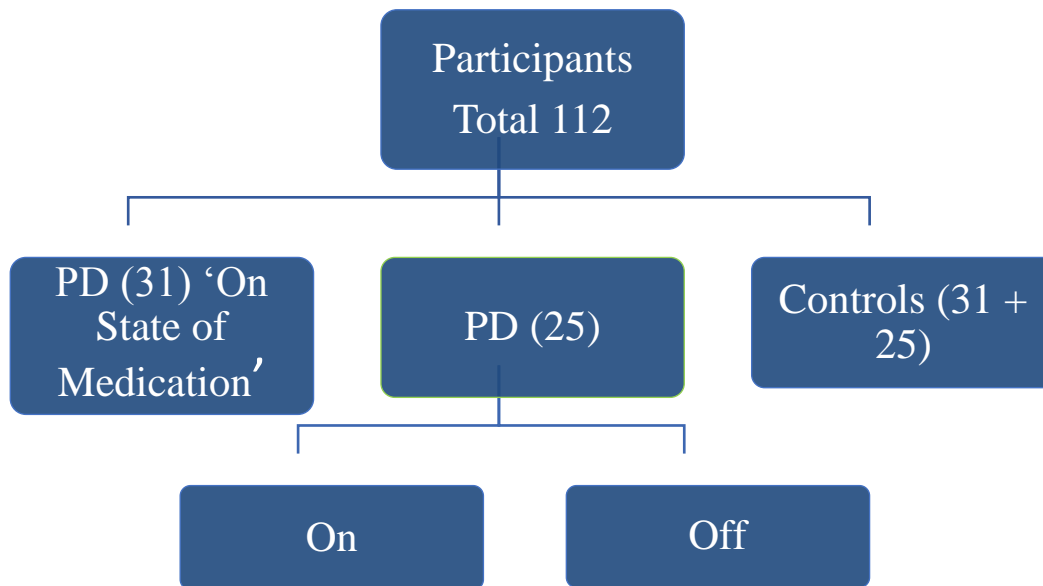
Figure 3.2 Distribution of participants into groups

Participants were sitting in a comfortable position while writing. Figure 3.3 (A) and Figure 3.3 (B). are images captured while the subject was performing the tasks. For more images refer Appendices (D)

A	**B**
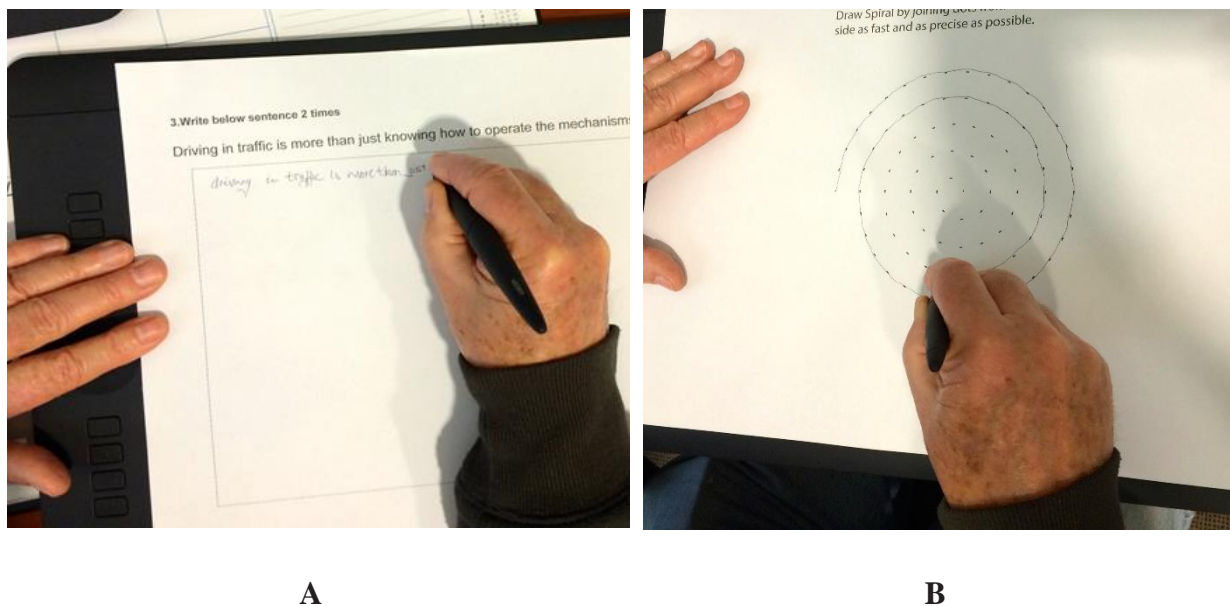
Figure 3.3 A: Subject writing sentence, B: Subject drawing guided spiral (Zham et al., 2017b)

3.3   Handwriting Task

Handwriting specimens are obtained for 7 different tasks.

1. Repeating the letter 'e' (Cobbah and Fairhurst, 2000)
2. Repeating the letter '*b*' then repeating the letter '*d*'
3. Repeated writing of '*bd*'
4. Repeatedly writing the word '*hello'* (Tucha et al., 2006)
5. Copying a sentence (Zham et al., 2017a)
6. Written Animals Category Fluency Test (Pfeiffer et al., 2014)
7. Sketching guided Spiral

The task of repeatedly writing of the letter *e* is the most basic assessment of the fine motor skills of writing. Because writing strokes are differentially affected by PD, the letters '*b*' and '*d*' were chosen for Tasks 2 and 3 (Thomassen and Teulings, 1983; Eichhorn et al., 1996). In Task 3 alternate letters were used to increase memory load. Task 4 was a word which contains the letter '*e*' and '*l*'. The more complex Tasks 5 and 6 have increased levels of cognitive loading. Task 5 required attention and visuospatial memory. Category fluency tasks are widely used in neurology clinics and have been effective for PD (Henry and Crawford, 2004). It is based on working memory and searching for stored information(Pfeiffer et al., 2014). Task 6 was a written version of the Category Fluency Test. Subjects were asked to write names of animals horizontally, to a maximum of 20. Task 7 was drawing a spiral by joining the guided dots in a continuous manner (Wang et al., 2005). Guiding spiral was used to avoid the potential bias of someone who may attempt to manipulate the size (Zham et al., 2016)(more detail in Chapter 5). No time limit was set for any of the tasks. Table 3.1 shows sample images of all writing tasks performed by a PD participant.

Table 3.1 Sample images of writing tasks written by PD patients (Zham et al., 2017a)

Task 1

Task 2

Task 3

Task 4

Task 5

Task 6
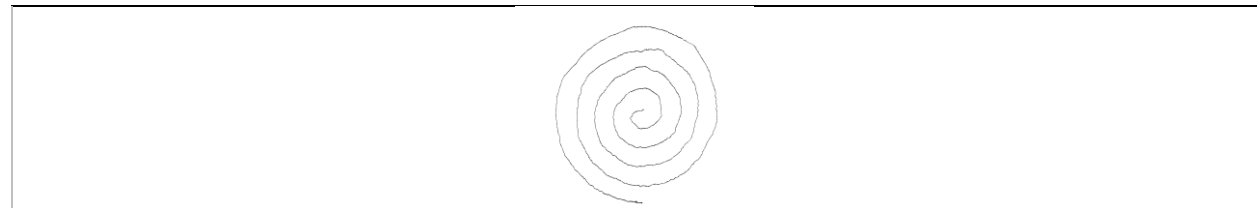
Task 7

3.4   Computation of features

To compute the kinematic features, an application was developed in c# which uses the trajectories obtained from samples(Table 3.1). The data was segmented to identify segments between each pen-down and corresponding pen-up; pen-down is identified based on pen-tip pressure where $p > 0$.

The length of each segment, d_i, was computed (Equation 3.1). The threshold of 0.5 mm was set, and segments that corresponded to less than 0.5 mm of distance travelled were considered as noise and deleted. The remaining N segments and parameters were relabeled, i (1 to N).

The total time duration for each segment is T_i (Equation 3.2). Based on these, dynamic features were calculated as tabulated in Table 3.2. Below are the equations showing the calculation of average speed which is obtained using Equation 3.3. The speed for each segment was weighted with the length of that segment to get the weighted average speed, $\bar{S}_w$ and was computed (Equation 3.4) (Zham et al., 2017b). Weighted segment ensured that small segments associated with pen-up motions did not unduly influence the results. All the features (Table 3.2) are calculated in similar manners. $D \rightarrow (x)$, $D \rightarrow (y)$, $\varphi(t)$ and p_n are also calculated only for guided spiral (refer Chapter 4).

$$d_i = \sum_{n=0}^{m_i} \sqrt{(x_{n+1} - x_n)^2 + (y_{n+1} - y_n)^2} \qquad (3.1)$$

$$T_i = \frac{m_i}{133} \qquad (3.2)$$

$$s_i = \frac{d_i}{T_i} \qquad (3.3)$$

$$\bar{S}_w = \frac{\sum_{i=1}^{N} d_i s_i}{\sum_{i=1}^{N} d_i} \qquad (3.4)$$

Table 3.2 Dynamic Features used for different writing tasks (Zham et al., 2017a)

	Features	Description
1.	s	Distance travel divided by duration while Pen Tip is moving on the surface.
2.	$\bar{v}_x$	The rate at which Pen Tip changes its position in the x direction.
3.	$\bar{v}_y$	The rate at which Pen Tip changes its position in the y direction.
4.	v/v_{max}	The magnitude of the rate at which Pen Tip changes its position in x, y-direction divided by maximum velocity.
5.	SD (v)	Standard Deviation of velocity.
6.	a_x	The rate at which Pen tip velocity changes in the x direction.
7.	a_y	The rate at which Pen Tip velocity changes in the y direction.
8.	a_{maxx}	Maximum acceleration of Pen Tip in the x direction.
9.	a_{maxy}	Maximum acceleration of Pen Tip in the y direction.
10.	pr	Pen -Tip Pressure applied on the surface [Range:0-1023].

Chapter 4 Classification based on kinematic features to detect Parkinson's disease

4.1   Introduction

Handwriting in Parkinson's disease gets affected due to associated motor symptoms; stiffness, bradykinesia, and tremor. As handwriting is non-invasive and symptoms appear in early stages, researchers are looking for a possibility of developing an inexpensive automated tool which can help in the screening of Parkinson's disease. Micrographia (Letanneux et al., 2014) is one of the early stage markers, however, many a times patients visually observe the changes in their handwriting and use that feedback to adjust their handwriting, which can make the results unreliable (Nackaerts et al., 2015).

Several studies showed a reduction in kinematic and Pen-tip Pressure of handwriting is observed in Parkinson's disease (Rosenblum et al., 2013; Drotár et al., 2016). Kinematic feature and Pen-tip Pressure of writing tasks also get influenced by writing styles such as manuscript, cursive and text size (van Drempt et al., 2011). To overcome this, many studies also suggested drawing and sketching tasks. Most of the studies suggest the use of Spiral to detect Parkinson disease (Saunders-Pullman et al., 2008; Stanley et al., 2010). However, there are some shortcomings in the spiral drawing. It can get influenced due to the placement of the centre point of the spiral (Wang et al., 2008). Drotár et al., when compared a different writing task for Parkinson's disease, found Spiral performed poorly (Drotár et al., 2013).

This Chapter reports the development of a system for automated assessment of dynamic handwriting features extracted for guided spiral drawing and addressing the current shortcomings. This study uses a classifier to validate the results by comparing it with different writing tasks. This study also proposes the dynamic features which help to improve the results significantly.

4.2   Materials and Methods

Step 1: Data Acquisition
- Customized software developed for data acquisition
- 31 PD and 31 Control Group participated for this experiment

Step 2: Data Processing
- Customized software was developed for data processing which takes input from step1
- Filter noise
- Extract coordinates x,y,pressure and time stamps

Step 3: Feature Extraction
- Calculate dynamic features for each segment when pen is touching the surface
- New Features:
- ❖Angular features
- ❖Direction Inversion

Step 4: Feature Selection
- Features subset selection technique used for this experiment is Relief F

Step 5: Classification
- Naïve Bayes Random Sampling Algorithm was used

Step 6: Result interpretation
- Area under ROC is obtained

Figure 4.1 Steps performed in this experiment

4.2.1 Experimental device and subjects

Classification on kinematic features were performed using steps as depicted in Figure 4.1.

For step 1 Sixty-two subjects handwriting samples were used in this experiment; 31 PD patients and 31 age-matched Controls. All PD patients were in *on* state of medication. For details on exclusion criteria refer 3.2. The demographic and clinical data are shown in Table 4.1. Step 2 Data processing details is as mentioned in previous chapter (Chapter 3 Section 3.1).

Table 4.1 Demographic and Clinical Information of the participants

Demographics	PD	Control Group
Number of Subjects, n	31	31
Age, years	70.1 ± 9.79	72.87 ± 6.5
Gender male, female	24,7	24,7
Disease duration, years	5.74 ± 4	-
UPDRS-III	17.03 ± 7.13	-

n represents a number of subjects; Values are mean$\pm$ SD.

4.2.2 Handwriting Task

Handwriting specimens used for this experiment were for four different tasks (Chapter 3 Section 3.3).

1. Copying a sentence,
2. Repeating the letter '*b*' then repeating the letter '*d*'
3. Repeated writing of '*bd*'
4. Sketching guided Spiral

4.2.3   Feature Extraction

In Step 3 feature (data points) 1-to-10 (Chapter 3 Section 3.3) are calculated for all the 4 tasks. Further four new features are identified D_x, D_y, Pn and φ which are calculated only for Task 4 (Guided Spiral) as they are based on the angle of drawing and may get influenced by writing styles Table 4.2.

Table 4.2 Features for Guided Spiral

New features introduced in Spiral		
1.	$D \rightarrow (x)$	Number of times a change occurs in the x-direction.
2.	$D \rightarrow (y)$	Number of times a change occurs in the y-direction.
3.	$\varphi(t)$	Arctangent (ATAN2) which is an angle in radians between the positive x-axis of a plane and the point given by the coordinates (x, y) on it.
4.	p_n	Logarithmic value of distance travelled by pen divided by φ

4.2.4   Classification

To perform classification the first step was to select the appropriate features that are essential for dynamic writing analysis (Unnikrishnan et al., 2013). This is performed using Relief-F using Orange 3.3 data mining suite (Figure 4.1 Step 4) (Altalhi et al., 2017). Best five features were selected based on rank. The next step, Step 5 was to perform classification for which the Naïve Bayes Algorithm was chosen (Kotsavasiloglou et al., 2017) Validation strategy used was stratified random sampling (Foster et al., 2014) with 80% data for training and 20% for testing and the procedure was repeated 20 times.

The sensitivity, specificity, and accuracy of classification were computed, and these were used to generate the receiver operating characteristics (ROC). The area under the curve (AUC) for ROC was computed (Figure 4.1 Step 6). The precision, weighted average (F1) and Error rate (ERR) were also computed (Zham et al., 2017a).

Spearman rank-order correlation coefficient analysis was performed for PD and CG for each writing task to understand the strength of association between the features for each task.

4.3   Results

Table 4.3 shows the top five features for all the tasks and Table 4.4 (A) shows results with AUC in the range of 0.74 to 0.78. The results indicate that irrespective of memory load which varies from Task 1; visual inspection and copying sentence to Task 2&3; the reputation of letters or Task 4; Drawing a spiral shows no major difference. However, factors which increase the efficacy of spiral is obtained using $D \rightarrow (x)$ and $\varphi(t)$ features as shown in Table 4.3(4b). Figure 4.2 (A, B) shows the AUC curve obtained from Table 4.4.

Table 4.3 Five highest ranked features (Zham et al., 2017a)

Tasks	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
1	pr	$\bar{v}_y$	a_y	SD (v)	s
2	pr	a_{maxx}	SD (v)	$\bar{v}_x$	s
3	a_y	SD (v)	s	v/v_{max}	a_{maxy}
4a	pr	$\bar{v}_y$	$\bar{v}_x$	v/v_{max}	s
4b	pr	φ	p_n	D_x	a_{maxy}

Table 4.4 Naïve Bayes Classification results (Zham et al., 2017a)

(A) Based on the top 5 ranking Naïve Bayes Random Sampling					
Tasks	AUC	CA	F1	Precision	ERR
1	0.748	0.681	0.648	0.688	0.319
2	0.787	0.738	0.693	0.760	0.263
3	0.671	0.704	0.643	0.731	0.296
4a	0.767	0.677	0.654	0.678	0.323
(B) Task 4 results when $\varphi(t)$ feature is considered for the Spiral drawing					
4b	**0.933**	**0.832**	**0.826**	**0.832**	**0.168**

Where AUC indicates Area under ROC, CA Classification Accuracy, F1 weighted average of the precision and recall, Precision indicate positive predictive value and Recall is Sensitivity
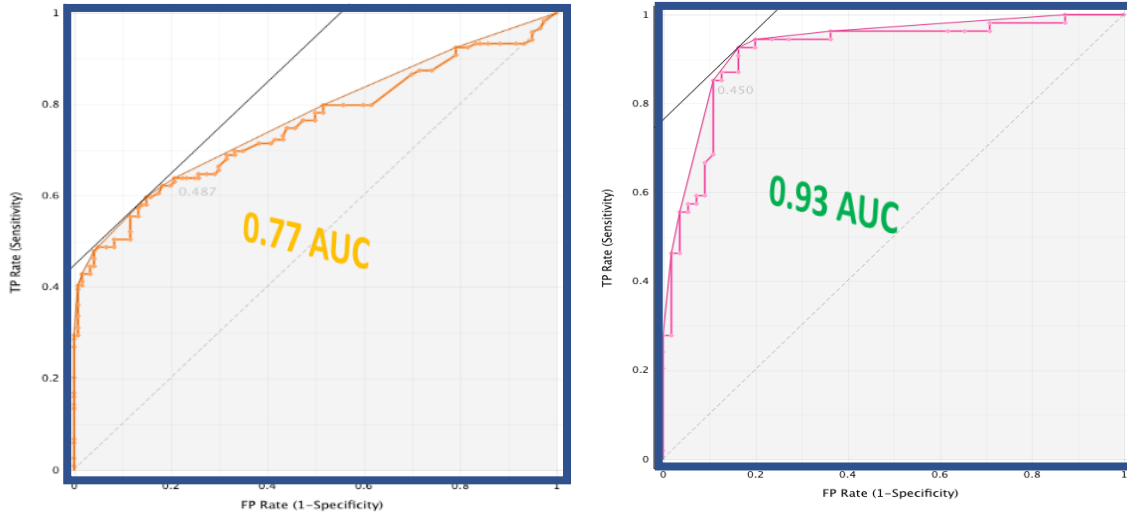
Figure 4.2 AUC Curve obtained for guided spiral for 4(a) and 4(b) in Table 4.4

4.4   Discussion and Conclusion

Drotár et al., has shown that when contribution for different writing tasks are measured Spiral has the lowest prediction with a classification accuracy of 0.65 whereas highest prediction was obtained by writing a sentence with a classification accuracy of 0.78 using SVM (Drotár et al., 2016). Pereira et al., were able to get the accuracy of 0.78 using Naïve Bayes (Pereira et al., 2015). Sadikov et al., showed maximum accuracy which can be obtained using Spiral is 0.89% (Sadikov et al.). The common factor which influences Sadikov et al., and this study is use of feature $\varphi(t)$.

In this study, I used a fixed size spiral which does not get affected by interpersonal variability versus varying size spiral, where results can be biased as patients try to manipulate writing size (Longstaff et al., 2003). Calculations of the features are not dependent on the location of the spiral's starting point(Wang et al., 2008) and thus the analysis can be performed automatically. Further, it helped to increase the efficacy by using $D \rightarrow (x)$ which also showed moderate correlation using Spearman's rank-order correlation coefficient.

This study shows that when the contribution of different handwriting tasks is measured

Spiral efficacy can be improved by using appropriate features ($D \rightarrow (x)$ and $\varphi(t)$). Hence Spiral drawing is very effective in accessing and automated prediction of Parkinson's disease. Further studies are required to identify ways to improve the efficacy of other writing tasks.

Based on Journal Article

Zham, P., Arjunan, S., Raghav, S. & Kumar, D.K. Efficacy of guided spiral drawing in the classification of Parkinson's Disease. *IEEE Journal of Biomedical and Health Informatics* (2017)

Chapter 5 Monitoring severity of PD based on Clustering using Composite index of Speed and Pen-pressure of Handwriting

5.1 Introduction

Bradykinesia and rigidity are symptoms that often start in the initial stage of PD (Politis et al., 2010). The effect is also noticed in the handwriting and sketching of patients as seen in the previous chapter. With the increased availability of digital tablets and smartphones, recording some dynamic features of the handwriting has become fast and reliable. Such features can be obtained automatically allowing for rapid on-line assessment of patients (Surangsrirat and Thanawattano, 2012). Kinematic and pen-pressure features of handwriting and sketching have been analysed and developed for applications such as biometrics (Unnikrishnan et al., 2013) and indicative markers for PD (Drotár et al., 2016). The kinematics of spiral drawing can be used to determine the amplitude of tremor (Kraus and Hoffmann, 2010), bradykinesia (Banaszkiewicz et al., 2008) and dyskinesia (Liu et al., 2005). It has successfully differentiated between distal and proximal tremor (Wang et al., 2005) and identifying early stages of PD disease (Stanley et al., 2010).

The previous chapter showed that Spiral is more robust and is able to diagnose PD more efficiently when compared to other handwriting tasks. However, along with detecting Parkinson's disease, identifying the progression of disease and level of severity is equally important for clinical decisions. Saunders et al., was successful in determining kinematic features of drawing the spiral and differentiating Parkinson's disease into groups based on severity levels of the disease (Saunders‑Pullman et al., 2008). However, the maximum correlation coefficient was moderate (r=0.4).

In this Chapter, dynamic features of the guided spiral are investigated, and a new feature with a stronger association between UPDRS score and dynamic features is proposed, This helps to distinguish between healthy subjects and PD patients with different levels of severity more effectively. The work aims to establish a reliable computer-based assessment of the spiral sketching on a digital tablet which can be automated for assessment and monitoring of severity of a disease.

5.2 Materials and Methods

5.2.1 Subjects

In this study total, 55 Participants (27 PD and 28 Controls) participated. PD patients were on regular levodopa dose. Demographic and clinical data are shown in Table 5.1. Part III of the UPDRS Scale (Q18-31) and overall PD stage assessment was done using the Modified Hoehn and Yahr (H&Y) Scale. Severity Level (SL) 0 indicates the Control group with no PD symptoms. Based on UPDRS III (Fahn and Elton, 1987) and modified H and Y rating scale (Hoehn and Yahr, 1998; Goetz et al., 2004) further groups were labelled as SL: 1-3 (Table 5.2). No patients were in the late-stage of the disease or were bedridden.

Table 5.1 Demographic and Clinical Information of the participants (Zham et al., 2017b)

Demographics	Control Group	PD
Number of Subjects, n	28	27
Age, years	71.32$\pm$7.21	71.41$\pm$9.37
Gender male/ female	21/6	22/6
Clinical Information		
Disease duration, years	-	6.7$\pm$4.44
UPDRS-III	-	17.59$\pm$7.69

Values are represented as; mean$\pm$ SD.

Table 5.2 Groups based on Severity Levels (Zham et al., 2017b)

Severity Level	Number of Subjects	UPDRS Sec III Score (0-56)	UPDRS $Mean \pm SD$	Modified H&Y Stages (Sec V)
0	28	0	-	0
1	12	> 0 & < 15	10.75 ± 2.18	1, 1.5
2	8	≥ 15 & ≤ 23	18.38 ± 2.83	2, 2.5
3	7	> 24	28.43 ± 2.64	≥ 3

5.2.2 Handwriting Task

Guided spiral (ref 3.3 Task 7) was used for this study. Guiding dots were printed on the A3 paper helping patients to sketch the spiral. The spiral shape was obtained using Equation 5.1:

$$r = a + b\theta^{1/c} \tag{5.1}$$

Where a is the starting point offset, b controls the distance between successive turnings and c =1 to obtain Archimedean Spiral. Based on the size of the spiral developed by Saunders-Pullman (Saunders-Pullman et al., 2008) and preliminary study with PD patients, a=7.5 and incremental change 2π b=15 i.e b=2.387 were considered. The resultant spiral had 4.5 revolutions, maximum radius = 75 mm with incremental changes of 15 mm. The starting point was 7.5mm and the distance between two consecutive dots in the Archimedean spiral was 12 mm as shown in Figure 5.1 (A).Figure 5.1(B) shows PD patient drawing Spiral on paper with digital tablet.
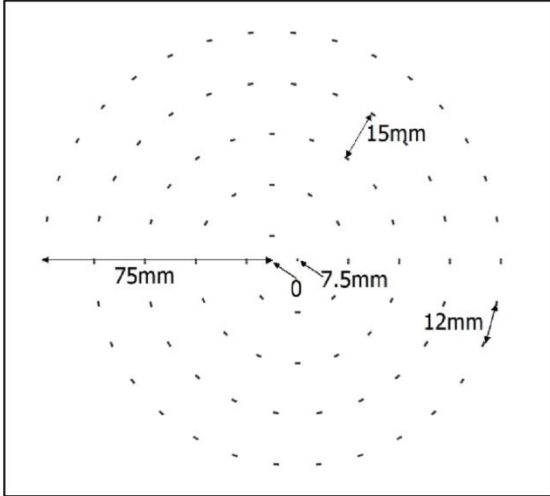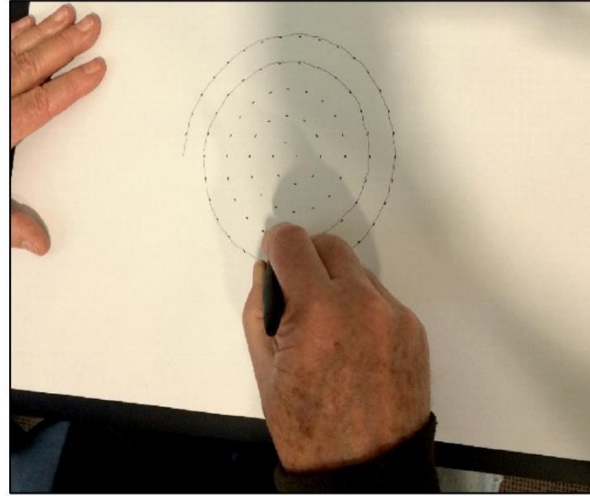
Figure 5.1(A) Dot-guided spiral and (B) Participant drawing the spiral (Zham et al., 2017b)

5.2.3 Features Computation

Computation of Speed $(\overline{S}_w)$ and Pen-pressure $(\overline{pr}_w)$ were performed using weighted average Equation 5.2 and Equation 5.3. Further composite index of speed and pen-tip pressure of the spiral sketching, $\overline{CISP}$ was calculated using Equation 5.4.

$$\overline{S}_w = \frac{\sum_{i=1}^{N} d_i s_i}{\sum_{i=1}^{N} d_i} \tag{5.2}$$

$$\overline{pr}_w = \frac{\sum_{i=1}^{N} d_i \overline{pr_\iota}}{\sum_{i=1}^{N} d_i} \tag{5.3}$$

$$\overline{CISP} = \overline{S}_w * \overline{pr}_w \tag{5.4}$$

5.2.4 Statistical Methods

Based on Shapiro-Wilk test for normality, nonparametric tests Mann-Whitney U test was used to determine the difference between PD and CG and k-sample Kruskal-Wallis test was performed to distinguish between different severity levels among the PD as it contains 3 groups. Sensitivity, specificity, and accuracy of classification were computed using SVM (Support vector machine algorithm). The area under the ROC curve (AUC) was computed to understand the ability to differentiate between PD and CG. Spearman rank-order correlation coefficient analysis was conducted to ascertain the association between the groups based on SL for all the features.

5.3 Results

Normalized value [0-1] of weighted average speed $(\overline{S_w})$, average pen-tip pressure $(\overline{pr_w})$ and average CISP of sketching $(\overline{I_{spr}})$ for PD and Control Groups (CG) showed that for all the features, the values for PD are significantly lower compared to CG (Figure 5.2). Mann-Whitney U test result shows statistically significant difference for each value; Speed $U=233$, $p = 0.0159$; Pen-pressure $U = 139$, $p < 0.001$ and CISP $U= 130$, $p < .001$ indicating a significant group difference between PD and CG.
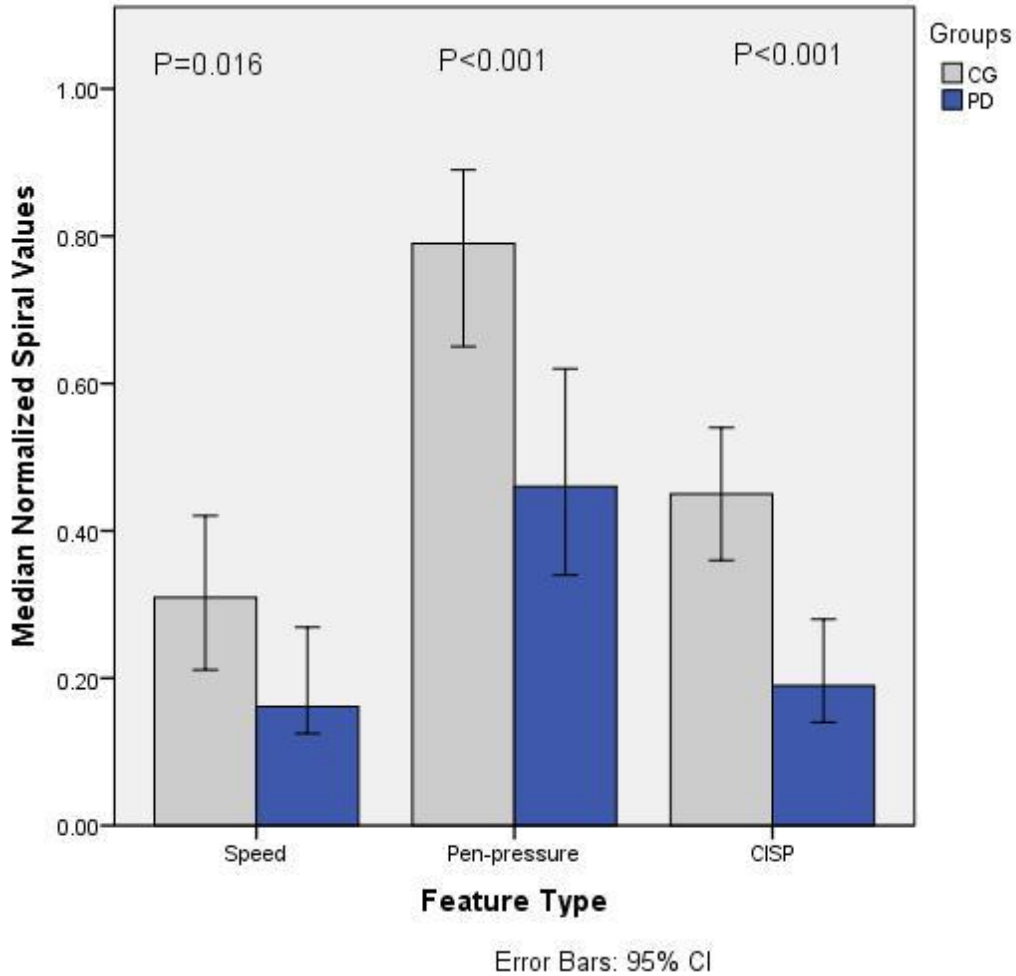
Figure 5.2 Bar chart showing median normalized values [0-1] of Speed, Pen-pressure and CISP for PD and CG (Zham et al., 2017b)

Specificity and Sensitivity showed the classification accuracy of 79.1 % with Area Under ROC curve as 86.2% for CISP whereas when speed and pen-pressure were considered the classification accuracy of 68.2% with Area Under ROC curve as 83.2% was obtained.

When Normalized values [0-1] for all the three features for different groups of PD based on SL are compared, it is observed that the values of all the parameters reduced with severity levels. Non-parametric k-sample Kruskal-Wallis test reveals statistically significant difference between groups for CISP ($\chi^2(3) = 8.753, p = 0.013$) whereas Speed ($\chi^2(3) = 5.907, p = 0.052$) and Pen-Pressure ($\chi^2(3) = 4.064, p = 0.131$) did not show statistically significant difference ($\alpha = 0.05$). The result shows that speed and pen-pressure, independently, may not be as effective as CISP. Bonferroni correction method was used to counteract the problem of inflated type I errors while engaging with the PD sub-groups.

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Pairwise comparison showed a significant difference (p=0.009) for SL-3 and SL-1. However, no significant difference was found for SL-2 /SL-1 (p=0.283) and SL-1/ SL-3 (p=0.709).
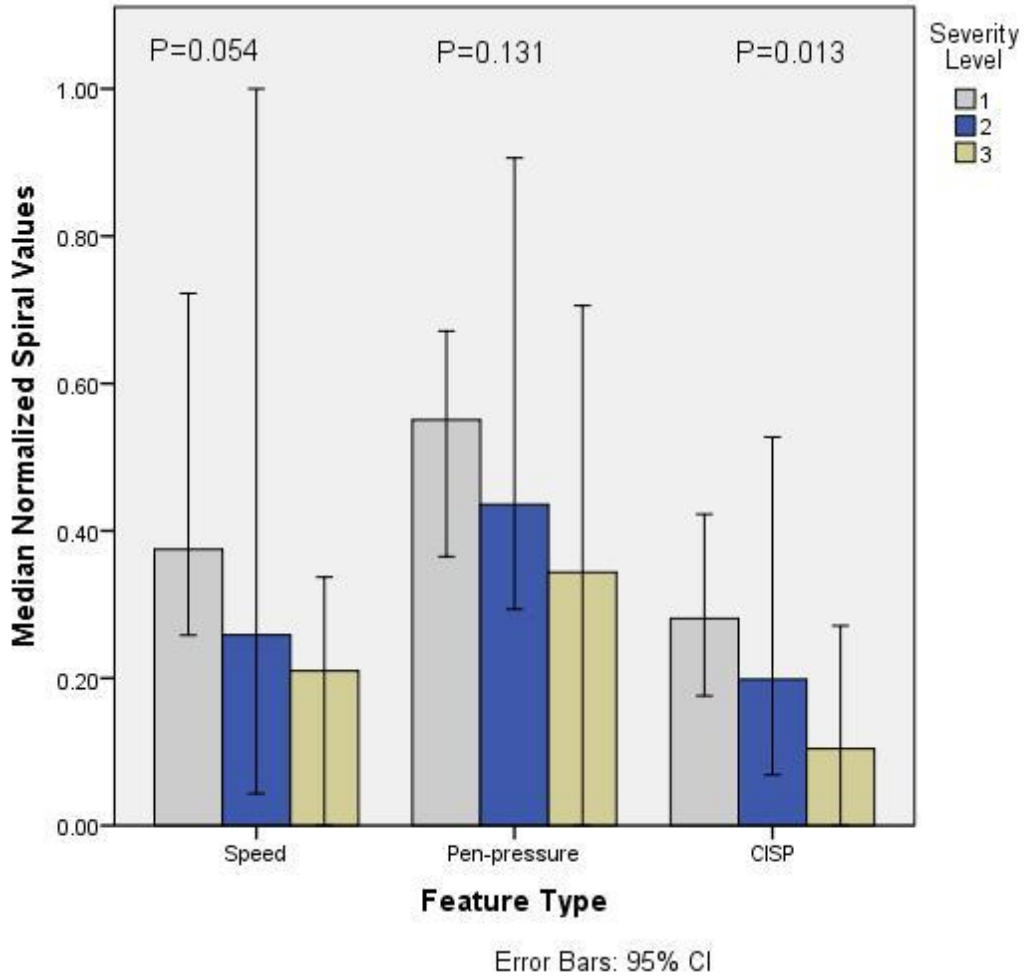
Figure 5.3 Bar chart showing median normalized values [0-1] of Speed, Pen-pressure and CISP Vs. Severity Level [1-3] of PD (Zham et al., 2017b)

Spearman rank-order correlation coefficient analysis results between all groups and the three parameters corresponding to the dynamics of sketching the spiral as shown in Table 5.3(A). Table 5.3(B) shows the analysis outcome when only PD groups are considered. From Table 5.3A, it is observed that r_s = -0.421 for speed and r_s = -0.584 for pen-pressure while for CISP r_s = - 0.641.

The coefficient, r_s, for CISP = -0.568 whereas speed and pen-pressure show r_s = -0.475 and r_s = -.383 respectively when the 3 PD groups without CG were considered. Three levels of severity of PD by CISP

and speed was moderate (in range of 0.4 to 0.59) while it was weak (in range of 0.2 to 0.39) for pen-tip pressure.

Table 5.3 Spearman correlation coefficients of Spiral for dynamic features (Zham et al., 2017b)

(A)   Severity Level 0-3 considered

Spiral	Speed	Pen-Pressure	CISP
SL (group)	-0.421^{**} *(0.001)*	-0.584^{**} *(<0.001)*	-0.641^{**}*(<0.001)*
UPDRS Sec III	-0.415^{**} *(0.002)*	-0.591^{**} *(<0.001)*	-0.650^{**}*(<0.001)*
H &Y Scale(V)	-0.405^{**}*(0.002)*	-0.580^{**} *(<0.001)*	-0.631^{**}*(<0.001)*
S & E scale(VI)	0.455^{*} *(0.017)*	0.466^{*} *(0.014)*	0.631^{**} *(<0.001)*

(B)   Only PD Considered (Severity Level 1-3)

Spiral	Speed	Pen-Pressure	CISP
SL (group)	-0.475^{*}*(0.012)*	-0.383^{*}*(0.49)*	-0.568^{**}*(0.002)*
UPDRS Sec III	-0.412^{*}*(0.033)*	-0.404^{*}*(<0.037)*	-0.573^{**}*(0.002)*
H &Y Scale(V)	-0.394^{*}*(0.042)*	-0.356 *(0.068)*	-0.518^{**}*(0.006)*
S & E scale(VI)	0.455^{*}*(0.017)*	0.466^{*}*(0.014)*	0.631^{**}*(<0.001)*

r_s *(P-values) values of Spearman Correlation coefficients where* n=55 (A) and n=27(B), *Correlation is significant at the* 0.01 *level* $(2-tailed)^{**}$ *and* 0.05 *level* $(2-tailed)^{*}$, *–ve values indicate correlation is negative.*

5.4　Discussion and Conclusion

Bradykinesia is well documented among PD studies. Speed is one of the main features which is highly affected due to bradykinesia(Hallett and Khoshbin, 1980). Statistical analysis result for Speed in this Chapter are in line with earlier findings of Saunder et al., (Saunders-Pullman et al., 2008) who found that PD patients sketched the spiral slower than the healthy subjects. However, values of speed being moderate are unsuitable for diagnosis of the disease.

Furthermore, the outcome suggests that the pen-tip pressure was lower with patients having higher severity of the disease (Figure 5.3). This extends the earlier findings (Rosenblum et al., 2013; Drotár et al., 2016) who found there was a difference in the pen-tip pressure between PD patients and healthy subjects. Main resons for the reduction in the pen-tip pressure; increased complexity(Schomaker and Plamondon, 1990) bradykinesia(Hallett and Khoshbin, 1980) and rigidity(Drotár et al., 2016). Significant numbers of PD patients have a loss of cognitive skills (Pfeiffer et al., 2014) making the task of sketching the guided spiral more complex and challenging with increased severity of the disease. Thus, reduction in the pen-tip pressure may be an indicator of cognitive loss and hence an indicator of the severity of the disease. The hypothesis is that bradykinesia can also lead to a decrease in force capacity. However, some finding does not fully support this hypothesis(Majsak et al., 1998).In this study, correlation analysis shows that there is a moderate correlation between pen-tip pressure and level of severity and thus by itself is unsuitable for diagnosis of the disease.

The composite feature proposed in this chapter is suitable for differentiating between PD and CG, and between SL 1 and SL 3 but not for SL1 and SL2 nor between SL2 and SL 3. The results show that the classification accuracy, sensitivity, specificity and area under ROC curve is higher for CISP than for the speed and pen-tip pressure taken as individual features.

The novelty in this study is that it has identified CISP of sketching as a new feature. This has a strong correlation with the severity of the disease and hence can be considered for diagnosing the level of PD (Table 3.3). CISP of sketching combines the speed and pen-tip pressure features, thereby including the bradykinesia, rigidity and cognitive skills which are the important symptoms of the severity of the disease. This study has shown that measuring the CISP during the spiral drawing task on a digital tablet can be useful for diagnosing and monitoring of PD patients. This study has developed a customized software and methodology to record and automatically analyse the sketching of a spiral. The test requires very simple instructions and takes only 5 minutes (approximately) to complete. This system is suitable to be used by a

generalized clinician and would facilitate in differentiating the severity of disease making the management of the disease more effective.

Based on Journal Article

Zham, P.Z., Kumar, D.K., Dabnichki, P., Arjunan, S. & Raghav, S. Distinguishing different stages of Parkinson's disease using composite index of speed and pen-pressure of sketching a spiral. *Frontiers in Neurology* **8**, 435 (2017)

Chapter 6 Effect of Levodopa on the handwriting of different complexity

6.1 Introduction

Previous Chapter showed that kinematic features of the drawing are effective in diagnosing and monitoring the progression of the disease (Zham et al., 2017b). Kinematic features of handwriting and drawing have also been proposed as a biomarker (Rosenblum et al., 2013) and recommended for the detection of PD (Drotár et al., 2013; Pereira et al., 2015). However, most research studies have only looked at levodopa *on* states.

Parkinson's disease is associated with the loss of dopamine and Levodopa (L-dopa) medication is used to provide dopamine to the patient and overcome the loss. It has been found to be effective for its management (McDowell et al., 1970) and studies have shown that L-dopa improves the motor symptoms (refer Chapter 1). Responsiveness to dopaminergic drugs is important to a disease monitoring role.

Cobbah et al. performed a preliminary study on 6 PD patients to determine the change in handwriting in response to the medication and found improvement in handwriting velocity and acceleration in response to the drugs. However, this is not universally accepted (Cobbah and Fairhurst, 2000) and Eichhorn et al. did not find any correlation between improvement in individual writing due to medication (Eichhorn et al., 1996). Tucha et al have studied kinematics feature and noticed that medication improves the handwriting kinematic features but results in partial restoration of automatic movement execution (Tucha et al., 2006). Poluha et al found that levodopa improved stroke speed but not the size (Poluha et al., 1998). Medication may be less effective when dual task are performed simultaneously as it may add to memory loading and makes a writing task more complex (Broeder et al., 2014).

One major shortcoming in the earlier studies has been that each of these has investigated only one handwriting activity such as the repetition of letter 'e' and 'l'. However, such an approach would not allow investigating whether the improvement was due to improvement in motor skills or in the ability to perform complex tasks such as simultaneously read and write. This study has investigated the difference between the *on* and *off* states for PD patients for six different handwriting activities which range from repeating letter 'e' to copying a long sentence. I have also measured the group difference between PD patients in *on* state with Control subjects to determine if PD patients are able to reach to the level of writing similar to Controls after medication.

6.2 Materials and Methods

6.2.1 Subjects

As tabulated in Table 6.1, handwriting samples of 49 age-matched volunteers (24 PD and 25 Controls) were studied.

Table 6.1 Demographic and clinical information, PD patients and Controls (Zham et al., 2019a)

Demographics	PD	Control Group	P Values
Number of Subjects, n	24	25	
Age, years	71.6 ± 7.14	69.7 ± 5.88	0.25^a
Gender male, female	13,11	14,11	0.9^b
Handedness Right, Left	20,4	23,2	0.42^b
Highest educational level [Secondary, Tertiary]	18,6	13,12	0.14^b
Disease duration, years	5 ± 2.88	-	-
UPDRS-III *ON* [0-132]	19.6 ± 8.62	-	-
UPDRS-III *OFF* [0-132]	26.80 ± 9.50	-	-
Tremor Subscore: UPDRS $3.15 - 3.18$ [0-20]	3.67 ± 4.62	-	-
MoCA [0-30]	27.2 ± 2.63 (range 23-30)	28.0 ± 1.70 (range 24-30)	0.37^a
L-dopa equivalent daily dosage (mg)	473 ± 292	-	-

Values are mean±SD, Comparison between groups is performed using [a]Independent t test and [b]Chi-Square test 2-tailed

All participants were recruited in PD outpatient clinic at Monash Hospital, Melbourne Australia. Control participants were friends, spouses, colleagues of an individual with PD and did not have any known neurological disorder. For cognitive assessment, the suggested cut-off score for the MoCA test is 26 (Nasreddine et al., 2005). Based on MoCA test all participants score were above 26 except 4 of them whose scores were 20,23,24 and 25 whereas in Control Group all of them scored above 26 except 2 subjects whose score were (24 and 25). Mean levodopa equivalent daily dose (LEDD) was 473(SD=292) milligrams (Tomlinson et al., 2010). Patients have discontinued medication for at least 12 hours prior to the *off* state test as stated in Chapter 3. UPDRS motor test and handwriting experiment were performed two times before the medication and after 1 hour of medication (*on* State).

6.2.2 Handwriting Tasks

Handwriting specimens were obtained for six different tasks [refer Chapter 3 Task 1-6], which also has an increased level of complexity and attention for each successive task (Figure 6.1).

Task 1: Repeating letter 'e'

Task 2: Repeating letter 'b' then repeating letter 'd'

Task 3: Repeatedly writing letters 'bd'

Task 4: Repeatedly writing Word 'hello'

Task 5: Copying a 'sentence'

Task 6: Written Animals 'Category fluency test'
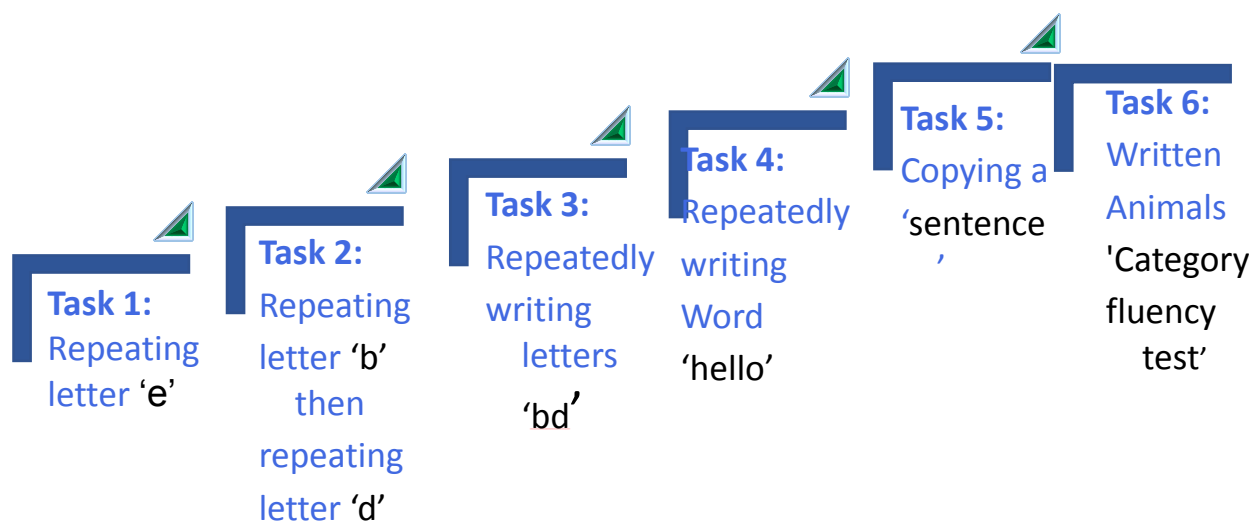
Figure 6.1 Handwriting task of different complexity

Task 1, repeating letter 'e' was selected because it has been noticed as an effective letter in PD (Smits et al., 2014). A single character task was favoured because the kinematic comparisons between first and final letters were better standardised. The letter 'e' has a rounded form with roughly equal height and width, completed with a single pen stroke. Based on the literature, strokes during writing are affected in PD hence letter 'b' and 'd' were chosen (Eichhorn et al., 1996) for Task2. In Task 3, to increase the load, participants were asked to write letter b and d alternatively. For Task 4, the word 'hello' was repeated. Tasks 5 and 6 were more complex with increased levels of cognitive loading. In Task 5, participants copied a sentence which was printed on paper The size of the print was big enough and none of the participants had any visual problem in reading. Task 6, Fluency test involved working memory and searching for stored information (Pfeiffer et al., 2014). For sample images of all writing tasks performed by a PD participant (refer 3.3).

6.2.3 Computation of kinematic features

In this Chapter, the focus is on velocity and acceleration along both vertical & horizontal axes in order to understand the effects in each direction (Ma et al., 2013). The kinematic features studied were: (i) speed of pen tip while moving on the surface S, (ii) velocity in x-direction $\bar{v}_x$ and y direction $\bar{v}_y$ and (iii) rate of change of velocity of the pen tip in x direction a_x and y direction a_y.

6.2.4 Statistical analysis

The aim of the current Chapter is;

a) *To investigate the dopaminergic effect on the different writing task.*
   For this data was grouped into 2 groups PD in *on* state and PD in *off* state. Non-parametric Wilcoxon signed-rank test was chosen as the repeated measure and was performed on the same sets of participants (Corder and Foreman, 2014).

b) *To determine if PD shows any closeness to Controls after taking L-dopa dose for different handwriting task.*
   For this, two groups considered were Controls and PD patients post medication. Mann Whitney U test was chosen as a group contains different sets of Participants (Corder and Foreman, 2014).

6.3 Results

Figure 6.2 shows the mean value of the speed of handwriting for all the tasks. From the graph, it can be observed that for all the writing tasks, PD post medication shows improvement when compared with pre-medication. When PD in *on* state is compared with Controls, a significant difference is observed for all the tasks. When PD in *off* state and *on* state are compared, a significant difference for Task 1 and Task 2 is evident whereas, for Task 3 and Task 4, this difference reduces and for Task 5 and Task 6, no difference is noticed.
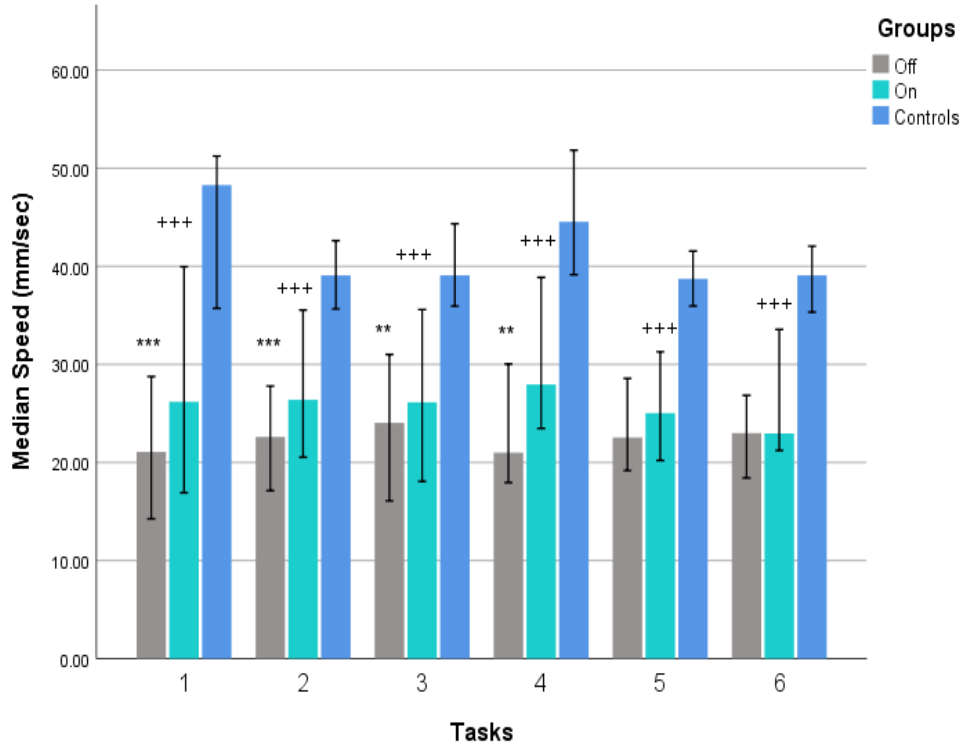
Figure 6.2 Bar chart showing median speed for 6 tasks for 3 groups PD (on and off) and Controls (Zham et al., 2019a)

Table 6.2 shows the median (*M*) and Table 6.3 shows Effect size values of different handwriting tasks for all the 3 groups: PD in *on* state, PD in *off* state and Controls.

Table 6.2 Kinematic features for the 6 writing tasks

	Median					
	Task 1	Task 2	Task 3	Task 4	Task 5	Task 6
Speed, s **(mm/sec)**						
Off	21.16	22.60	24.02	20.99	22.54	22.99
On	26.18***	26.38***	26.13**	27.94**	25.04	22.95
Controls	48.28+++	39.08+++	39.07+++	44.54+++	38.71+++	39.07+++
Horizontal velocity, $\overline{v}_x$ **(mm/sec)**						
Off	16.43	11.05	11.03	12.78	13.18	13.00
On	21.28***	12.88*	12.65*	17.13*	15.58	14.24
Controls	19.29++	18.41++	19.29++	19.94+	22.06+++	24.22+++
Vertical velocity, $\overline{v}_y$ **(mm/sec)**						
Off	9.58	15.03	17.45	15.93	15.47	14.07
On	10.47***	17.48***	18.72*	17.45*	15.92	14.92
Controls	31.45++	27.37+++	31.45+++	30.17+++	26.01+++	25.82+++
Horizontal acceleration, a_x **(mm/sec^2)**						
Off	402.71	377.16	307.03	407.81	456.18	436.15
On	679.60***	413.44	435.43*	528.41	558.38	526.61
Controls	682.4++	643.96+++	682.42+++	686.37++	811.99+++	797.42+++
Vertical acceleration, a_y **(mm/sec^2)**						
Off	237.37	488.00	561.41	563.10	543.76	482.18
On	319.85***	544.31***	572.67*	605.78*	567.00	520.73
Controls	1046+++	959+++	1046+++	1013+++	945+++	946+++

Results appear as median. Significant differences between off and on states: ***=P≤0.001, **=P<0.01 and

*=p<0.05 by 2 tailed using Wilcoxon signed rank test. Comparison of PD patients in on states with Controls:

+++=P≤0.001 ++=P<0.01 +=P<0.05 2-tailed using Mann-Whitney U test for total samples n=4

Table 6.3 Effect size for Off-On state and On-Controls Groups

	Effect Size r					
Kinematic Features	**Task 1**	**Task 2**	**Task 3**	**Task 4**	**Task 5**	**Task 6**
Speed, s (mm/sec)						
Off-On	0.59	0.50	0.35	0.36	0.24	0.25
On-Controls	0.45	0.48	0.49	0.53	0.62	0.60
Horizontal velocity, $\overline{v}_x$ (mm/sec)						
On	0.58	0.33	0.32	0.30	0.26	0.19
Controls	0.42	0.39	0.38	0.34	0.51	0.56
Vertical velocity, $\overline{v}_y$ (mm/sec)						
On	0.50	0.51	0.35	0.42	0.25	0.28
Controls	0.41	0.45	0.51	0.54	0.62	0.55
Horizontal acceleration, a_x (mm/sec^2)						
On	0.55	0.27	0.30	0.24	0.23	0.18
Controls	0.43	0.46	0.41	0.39	0.48	0.55
Vertical acceleration, a_y (mm/sec^2)						
On	0.54	0.47	0.31	0.33	0.24	0.30
Controls	0.45	0.51	0.56	0.56	0.60	0.56

From Wilcoxon signed-rank test, when the 2 groups, PD in *on* state and PD in *off* state are considered, a highly significant difference ($p<0.01$) can be observed for all the features for Task 1 and Task 2. However, for Task 3 and Task 4, highly significant difference ($p<0.01$) is observed for only 1 feature; $Speed(s)$. For Task 5 and Task 6, no significant can be seen. Contrary to this when the comparison is performed between PD in *on* state and Controls, using Mann Whitney test, a highly significant difference ($p<0.01$) for all the tasks is seen.

6.4 Discussion and conclusion

This study has investigated the significant effect of L-dopa on the kinematic features of handwriting for 6 different handwriting activities. It has been found that for all the writing tasks, there is some improvement in the speed (s) of the writing strokes (Figure 6.2). The results also show a non-statistically significant increase in the median values from *off* state of medication to *on* state for all kinematic features as well. These results in this study are in agreement with previous studies where improvement in handwriting has been noticed (Cobbah and Fairhurst, 2000; Tucha et al., 2006) showing a positive response of L-dopa for handwriting. All writing tasks require fine-motor skills and hence this shows that L-dopa significantly improves the fine-motor skills of the patients.

The results show that the effectiveness of L-dopa is not uniform across all the writing task. Wilcoxon signed-rank test result indicates that the dopaminergic effect is highly significant ($p<0.01$) for simple handwriting task like repeating letters for all the kinematic features (Table 6.2) whereas tasks that require simultaneous reading and writing such as copying sentences requiring more coordination and attention and category fluency test where cognitive loading is more do not show the significant difference.

The comparison between PD group in *on* state with Controls using Mann-Whitney U test shows that there is significant difference ($p<0.05$) for almost all the writing tasks which is in agreeement with previous studies where handwriting kinematic feature have been found suitable to distinguish between PD in *on* state from Controls (Drotár et al., 2013; Rosenblum et al., 2013; Zham et al., 2017a).

The results of this study show that L-dopa improves the motor skills of the patient significantly but does not effectively improve the handwriting skills when the patient has to read and write at the same time or when cognitive loading is increased. Majority of subjects in this study had the MOCA score greater than 26, and the PD patients symptoms were mild (UPDRS 21.56 ± 8.43), demonstrating that they did not suffer any cognitive impairment. This suggests that there is a non-dopamine based mechanism due to which these patients are unable to perform the tasks of simultaneously reading and writing. Thus, while L-dopa improves the motor-skills of the PD patients, and the patients do not have a cognitive impairment, they are unable to perform tasks that may involve multiple activities or simultaneous processing of information. Since the effect of the medication is not uniform for all handwriting tasks, this study recommends use for sets of handwriting tasks to study the progression of diseases and the effect of medication.

Based on Journal Article

Zham, P., Kumar, D., Viswanthan, R., Wong, K., Nagao, K.J., Arjunan, S.P., Raghav, S., and Kempster, P.: 'Effect of levodopa on handwriting tasks of different complexity in Parkinson's disease: a kinematic study', *Journal of Neurology*, 2019, pp 1-7

Chapter 7 Study of progressive micrographia versus kinematic features in Parkinson's disease

7.1   Introduction

Parkinson's disease affects the motor function due to the loss of dopaminergic neurons in the substantia nigra. This motor function also affects the control of wrist and finger movement due to which handwriting deteriorates (Teulings et al., 1997). One such visible symptom on handwriting is micrographia. Micrographia is manifested as consistent micrographia in which size is constantly reduced or progressive micrographia (PMG) in which the size of the character starts reducing after a few characters (Letanneux et al., 2014).

Micrographia was proposed for detecting PD in the early stages. Earlier studies of handwriting for PD patients were performed by visual inspection and were depended on the history of the handwriting provided by the patients (Klawans, 1986; Shukla et al., 2012). However, obtaining historical handwriting data of the patients is often not feasible. Wu et al., proposed a method based on the comparison of the median sizes obtained from the handwriting of Control subjects (Wu et al., 2015).

With the availability of graphics tablets, kinematic and size features have now been investigated and studies have shown that kinematic features and pen pressure can identify PD patients and monitor the progression of the disease (Drotár et al., 2016; Zham et al., 2017a). Stroke size, velocity, and acceleration are mostly affected in PD (Van Gemmert et al., 2001; Rosenblum et al., 2013) Raudmann et al., study suggests kinematic features are more effective compared to size for detecting PD patients (Raudmann et al., 2014).

PD_pmg requires the assessment of successive strokes over repetitive writing and are seldom (Kim et al., 2005; Ma et al., 2013; Letanneux et al., 2014). Van Gemmert et al., suggests as processing demand increases stroke size reduces in PD and stroke duration remain unchanged (Van Gemmert et al., 2001) in contrast to Teulings and Stelmach who did not find any difference in size but saw an increase in stroke duration in PD (Teulings and Stelmach, 1991). From the previous studies, it is unclear how kinematic feature differs in PD showing a progressive decrement in size compared to those who do not show decrement. This study aims to understand the behaviour of the kinematic features of handwriting with respect to the variation of the

size of letters in PD by grouping them into group showing a reduction in size; Progressive micrographia (PD_pmg) and other PD subjects (PD_o) group and comparing it with Controls.

7.2   Materials and Methods

7.2.1   Subjects

This study was performed based on handwriting samples collected from 25 PD patients and 25 age-matched from Monash Medical Centre. Demographic details of all participants are as shown in Table 7.1.

Table 7.1 Demographic and clinical information, PD patients and Controls (Zham et al., 2019b)

	PD	Control Group	p-value
Number of subjects	24	24	
Age, years	71.6 ± 7.14	69.3 ± 5.74	0.2^a
Gender (male, female)	13,11	14,10	1.0^b
Hand dominance for writing (right, left)	20,4	22,2	0.7^b
Disease duration, years	5 ± 2.88	-	
UPDRS-III *off* [0-132]	26.80 ± 9.50	-	
UPDRS-III dominant upper limb bradykinesia score [0-12]	3.58 ± 1.64	-	

Values are mean$\pm$SD, Comparison between groups is performed using [a]independent t-test and [b]2-tailed Chi-Square test.

Along with Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) (refer Appendices A) (Goetz et al., 2008), dominant upper limb subscores for finger tapping, hand movements and pronation-supination [UPDRS sections 3.4 to 3.6] to understand the amount of bradykinesia in the writing hand have been considered.

7.2.2 Handwriting Tasks

From all the tasks mentioned in Chapter 3 Task 1, writing the letter *e* repeatedly, with pen-up at the end of each letter (Figure 7.1) was selected for this study. Letters were repeated at least 20 times. As stated in Chapter 1 most of the research studies are performed on letter 'el'. In this study, the focus is to study PD_pmg with simple handwriting. However, alternate letters may increase some complexity and memory load (Chapter 6) hence single letter was used for this study. Smit et al., studied the letter 'el' and also found 'e' being more effective and showing a reduction in width hence letter repetition of 'e' was selected.
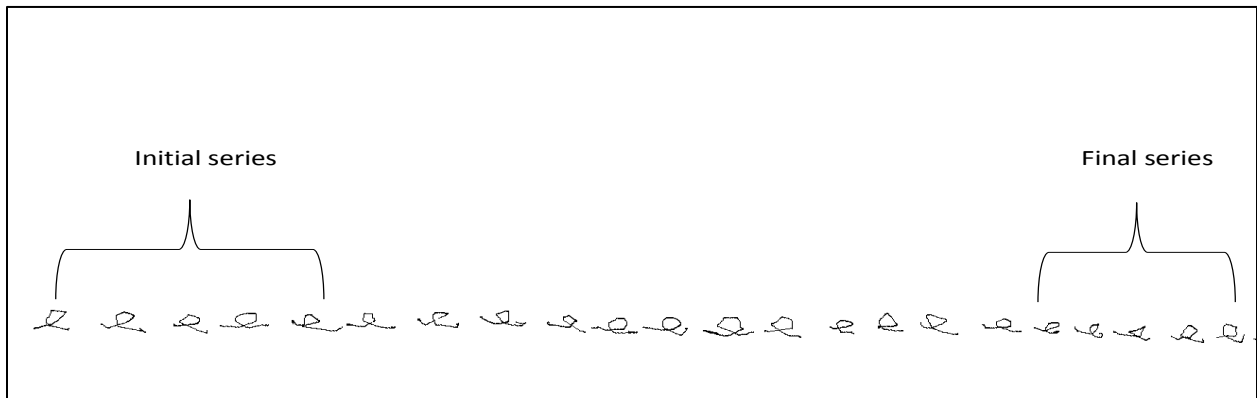
Figure 7.1 Sample of repetition of letter 'e' written by PD patient

7.2.3   Computation of Parameters

As studied previously, the samples were first segmented to identify individual letters based on pen-up and pen-down obtained from the pen-tip pressure data. Segments of length less than 5 mm were found to be noise and were disregarded. The results were eye-balled to confirm the segmentation.

Character size was computed by the stroke length of each character (S_i) (Equation 7.1). Quadrilateral area of the letter was also computed which is used in previous studies of Chinese characters (Ma et al., 2013;

Wu et al., 2015) . Stroke length was based on Euclidean distance where m indicates a number of samples for each letter and i is the total number of characters (Equation 7.1)

$$S_i = \sum_{n=0}^{m} \sqrt{(x_n - x_{n-1})^2 + (y_n - y_{n-1})^2} \qquad (7.1)$$

As shown in Figure 7.1 initial 5 letters and final 5 letters were compared. PD subjects showing greater than 10% reduction in the final series compared to initial series were labelled as PD_pmg, while the others as PD_o. The advantage of this method is that it is not affected due to inter-participant variations in handwriting. Speed, pen-tip pressure and acceleration in x and y directions were computed (Thomassen and Teulings, 1983; Zham et al., 2017a).Table 7.2 shows features considered for this study. For each feature, the mean values of the initial and final sets of 5 e characters were obtained.

Table 7.2 Features calculated for the first and last e series (Zham et al., 2019b)

Feature	Feature Description
Stroke length S	Length of continuous pen stroke to produce letter e
Quadrilateral area	Area of the quadrilateral outlined by the upper, lower, left and right margins of each letter
Horizontal amplitude	Horizontal amplitude defined by margins in x direction
Vertical amplitude	Vertical amplitude defined by margins in y direction
Speed	The speed of the pen tip while moving on the surface
Normalized Pen-tip Pressure	Normalized pen-pressure of the tip $(P_{Avg} - P_{min})/(P_{max} - P_{min})$
Acceleration in x direction	The rate of change of velocity of the pen tip in the x-direction
Acceleration in y direction	The rate of change of velocity of the pen tip in the y-direction

7.2.4 Statistical Analysis

The statistical analysis was performed to first analyse the demographic difference between PD_pmg and PD_o group. Based on the Shapiro-Wilk test, nonparametric Wilcoxon signed rank test was chosen to perform an analysis between the first series and last series pair. To compare PD_pmg, PD_o and controls were compared using distribution-free Kruskal-Wallis with the post-hoc test (du Prel et al., 2010).

7.3 Results

Table 7.3 shows the demographics of the PD_pmg and PD_o groups.

Table 7.3 Demographics of PD_pmg and PD_o groups (Zham et al., 2019b)

	PD_pmg	PD_o	p value
Number of subjects	16	8	
Age, years	70.94$\pm$7.59	73.63$\pm$6.23	$.4^a$
Gender (male, female)	10,6	3,5	$.35^b$
Handedness (right, left)	13,3	7,1	$.83^b$
Disease duration, years	5.1 $\pm$ 2.8	5.3$\pm$3.2	$.84^a$
UPDRS-III *OFF* [0-132]	28.5$\pm$10.33	23.88$\pm$7.86	$.28^a$
UPDRS-III dominant upper limb bradykinesia score [0-12]	3.56$\pm$1.79	3.75$\pm$1.28	$.79^a$

Values are shown as mean$\pm$SD. Comparisons between groups performed using [a]independent t-test and [b]Mann-Whitney U test

16 subjects showed a reduction in size, however statistical analysis related to demographic features shows no significant difference between the groups (PD_pm and PD_o).

Table 7.4 shows effect size r and p values of character size, pen-pressure and kinematic features performed between paired samples (First series; Fs and last series; Ls of characters). Wi lcoxon signed rank test showed when the size of letters reduces significantly with large effect size (r=-0.62) according to Cohen's classification of effect (Cohen, 1988) for PD_pm group, kinematic features of writing (speed and acceleration in x-y direction) except for pen-pressure does not show any major fluctuation. PD_o group showed a significant increment (p<.05) from first to the last series for pen speed and acceleration in x-direction which is similar to Controls with an effect size of moderate to large (Cohen, 1988). However, pen-pressure does not change significantly for these two groups (PD_o and Controls).

Table 7.4 Kinematic and dimensional features of the handwriting of PD and Controls, presented with group median, effect size and p values from exact 2-tailed Wilcoxon signed rank test (Zham et al., 2019b)

Series	PD_pmg			PD_o			Controls		
	Median	Effect Size (r)	P	Median	Effect Size	P	Median	Effect Size (r)	P
Stroke length (mm)									
Initial	18.97	0.62	<.001	16.35	0.53	0.039	19.4	0.22	0.128
Final	14.61			17.63			19.44		
Quadrilateral area(mm^2)									
Initial	30.11	0.63	<.001	28.35	0.35	0.2	30.39	0.14	0.36
Final	18.41			25.41			26.77		
Horizontal amplitude (mm)									
Initial	5.31	0.10	0.6	5.75	0.25	0.38	6.16	0.47	<.001
Final	5.76			6.91			7.39		
Vertical amplitude (mm)									

Initial	4.24	0.62	<.001	5.81	0.53	0.04	4.53	0.33	0.023
Final	3.62			4.34			3.71		
Speed (mm/sec)									
Initial	20.70	0.1	0.98	19.03	0.63	0.008	38.76	0.45	0.001
Final	20.68			26.67			41.23		
Pen-tip Pressure Normalized:0-1(Newton N)									
Initial	0.474 (0.22 N)	0.37	0.034	0.493 (0.23N	0.04	0.945	0.55 (0.25N)	0.04	0.79
Final	0.408			0.472			0.52		
Acceleration in x direction (mm/sec^2)									
Initial	313.453	0.23	0.211	318.26	0.6	0.016	749.2	0.52	0.008
Final	392.885			494.31			999.65		
Acceleration in y direction (mm/sec^2)									
Initial	206.57	0.12	0.562	222.22	0.07	0.844	530.85	0.09	0.55
Final	235.25			260.5			530.11		

(A)

(B)

53
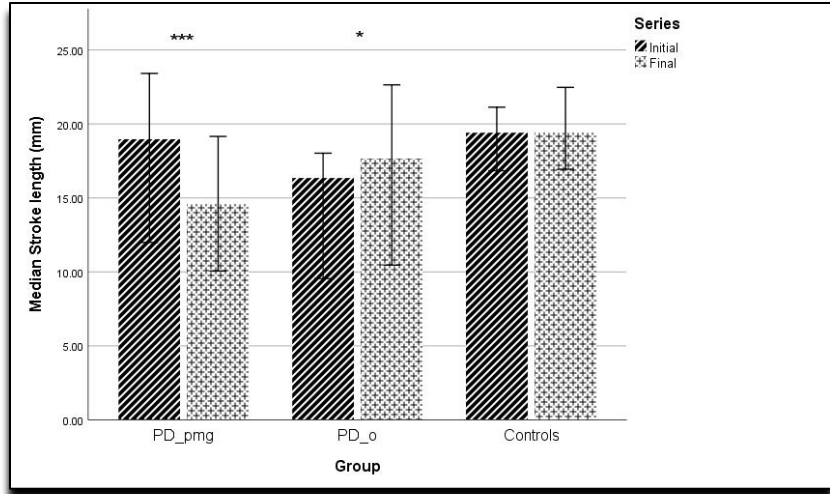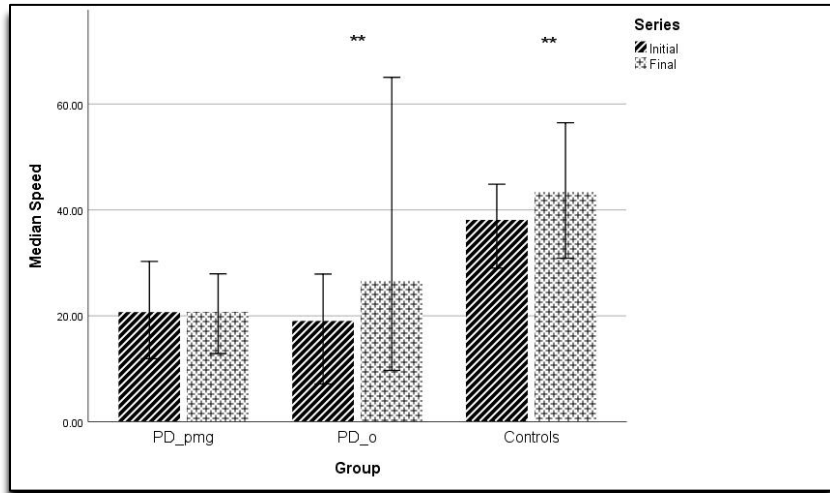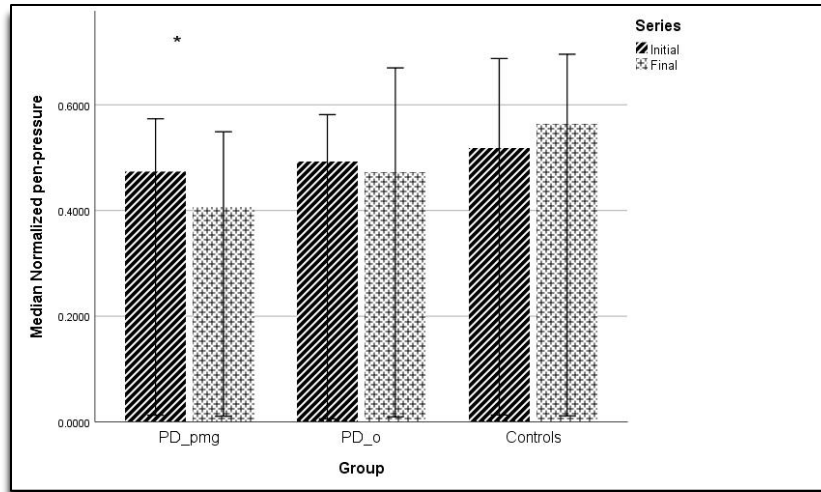
(C)

Figure 7.2 Bar chart showing (a) Stroke length, (b) Speed and (c) Normalized pen-pressure (Zham et al., 2019b)

7.4 Discussion and Conclusion

Writing requires coordination of fingers, wrist, and arm movements. Thumb, index and middle finger play a major role in up-and-down strokes whereas wrist flexions and extension are responsible for small left-and-right movements (Teulings et al., 1997). While writing across the writing surface, wrist and elbow movements are important (Thomassen and Teulings, 1983). The study suggests that fingers get fatigued easily compared to wrist hence the speed of writing increases in the horizontal direction and not vertical(Kushki et al., 2011). This is consistent with findings from this study where no significant changes are observed from start to final series in the vertical direction v_y and a_y for any Groups. Kinematic features in the horizontal al direction a_x increase for elderly Controls and PD_o Group (Teulings and Stelmach, 1991; Van Gemmert et al., 2001) except for PD_pm which suggests PM_pm group is not able to move wrist and elbow like PD_o group.

Micrographia is progressive or consistent depends not only on the decrement in dopamine but also various other factors (Gangadhar et al., 2008; Wu et al., 2015). Our study suggests that subjects showing progressive micrographia versus others, impact differently on kinematic features in handwriting and are not limited to just size. While writing, fluctuation in kinematic features has been noted in the previous studies (Phillips et

al., 1994). However, grouping in PD was rarely done (Kim et al., 2005) and the comparison between the groups (PD_pm and PD_o) was not studied previously.

Kinematic features like acceleration, velocity, and speed are slower in PD (Letanneux et al., 2014; Drotár et al., 2016). Our study is inline with those results. Our studies further segregate the groups which did not show any significant difference in demographics (Table 7.3) though their writing behaviour differs. Kinematic features speed s, velocity, and acceleration in x and y-direction were consistently low in PD_pmg with no significant difference from first to last series($p>0.05$), which means PD_pm group shows slowness throughout the writing.

Teulings et al., who studied strokes in different angle found kinematic features values were lower and vary more in successive strokes in PD compared to Controls (Teulings et al., 1997) and increases from first to the last series (Teulings and Stelmach, 1991). In this experiment speed and acceleration a_x showed significant increment for PD_o and Control Group($p<0.05$). PD_pmg did not show any variation $p >0.05$. Acceleration is dependent on firing frequency of the motor unit which was low in PD_pm group. Pen-pressure also significantly decreased in PD_pmg. One of the possible reasons may be that progressive micrographia along with dopamine depletion, disconnections between the rostral supplementary motor area and rostral cingulate which has been noticed,(Wu et al., 2015) may be responsible.

PD_o group, which is able to maintain pen-pressure ($p >0.05$) while writing shows a significant increase ($p <0.05$) from first to the last series in speed and acceleration a_x; a trend similar to Controls but still fails to achieve kinematic features similar to Controls (based on Kruskal-Wallis with the post-hoc test). This shows irrespective of groups, kinematic features can be considered to distinguish between PD and Controls.

Pen tip pressure can help to assess subtle characteristics and to distinguish between PD and Controls(Drotár et al., 2016). As per Wann John, under normal conditions, while writing the pressure increases steadily (Wann and Nimmo-Smith, 1991). In our experiment, PD_o and Controls did not show any significant difference in pen-pressure however they were able to maintain the Pen-pressure ($p >0.5$) whereas PD_pm group showed a significant reduction ($p <0.05$). In a study of drawing spiral, pen-pressure in PD patients was significantly less compared to Controls. Also with the increase in the severity of disease pen-pressure reduces further (Zham et al., 2017b).This study manifest that PD_pm group and PD_o group shows higher pen-pressure than Controls in the first series. However, PD_pm group was not able to maintain pen-pressure while writing and showed significant reduction $p <0.05$. Overall Pen-pressure between the three group did not show any significant difference. One possible reason may be that in this study, Pen was picked and put

back repeatedly whereas for previous studies most of the tasks involved writing letters jointly or continuously.

Our study shows that PD_pmg is not able to increase speed and acceleration and maintain Pen-pressure while writing (Figure 7.2). As per Wu, T., et al study progressive micrographia is related to a disconnection between the rostral supplementary motor, rostral cingulate and motor area, and cerebellum. Possibly PD_pmg suffers from this disconnection along with basal ganglia dysfunction.

This study shows the strength of kinematic features which is not only able to distinguish between PD and Controls but may be helpful to understand the other neural activities which PD patients may suffer.

This study reports that while writing, PD group showing a reduction in handwriting also shows consistent slowness while writing and is unable to retain Pen-pressure. PD group which does not show any decrement while writing shows kinematic response similar to Controls however overall kinematic features differ significantly from Controls. The subclassification of parkinsonian micrographia into consistent and progressive forms was made almost a century ago but there are problems with a definition of the consistent type, and we have taken the approach that the presence or absence of progressive character is a better way to study this phenomenon. Thus the Kinematic features can play a key role in the diagnosis of both kinds of PD group (PD_pm and PD_o). Segregating PD in groups based on kinematic features and size can further help in better treatment.

This study was conducted in the *off* state of medication. In order to understand how the treatments help in both the group, it is essential to study these features in On state for the same groups.

Based on Journal Article

Zham, P., Kumar, D.K., Kempster, P., Poosapadi Arjunan, S., Wong, K., Nagao, K.J., and Raghav, S.: 'A kinematic study of progressive micrographia in Parkinson's disease', Frontiers in Neurology, 2019, 10, pp. 403

Chapter 8 Effect of medication on Kinematic features of handwriting with Progressive Micrographia in Parkinson's disease

8.1   Introduction

Previous Chapter (Chapter 7) investigated the behaviour of kinematic features differs based on the subcategory of micrographia. Speed of handwriting in PD Patients with progressive micrographia (PD_pmg) were consistently slow whereas other PD and Controls showed an increase in speed as the writing progressed.

Levodopa is the main medicine which improves motor symptoms. Benefits are observed in fine motor symptoms, but it is not clear how much of an improvement is obtained in a group showing micrographia versus others. The aim of this chapter is to determine the effect of levodopa on PD with progressive micrographia group PD_pmg.

8.2   Materials and Methods

Refer Chapter 7 for materials and methods. The outcome of this chapter is based on the experiment conducted for Chapter 7. In this chapter, the analysis were performed on two sets of data which was collected before and post medication.

8.3   Results

Statistical outcome based on Paired Wilcoxon signed rank test
Overall size is improved for both initial and final series from *off* to *on* state. Wilcoxon signed rank test reveals a significant reduction in size from initial to final series in PD_pmg *off* state whereas the reduction in *on* state is not significant (Table 8.1). For PD without progressive micrographia (PD_o) group a significant increase in size is observed in the *off* state whereas in *on* state the increase is not significant. Controls showed a similar size in initial and final series with no significant difference.

The speed of PD_pmg did not show any significant change from initial to final series in *off* and *on* state of medication (Figure 8.1). However, a significant increase in speed is observed from initial to final series for PD_o group in off state, on state and Controls (Table 8.1).

Statistical outcome based on Krushkal walis test

Krushkal walis rank-based test with Bonferroni error correction was studied considering both initial and final series for five categories PD_pmg *on* and PD_pmg *off* state, PD_o *on* and *off* state and Controls. The distribution of size was same for all the categories with *Chi-square* = 8.024 ,*df* = 4 and *p* = 0.91.

Kinematic feature Speed has shown a significant difference within the groups with *Chi-square* = 37.169 *df*=4 and *p*<.001. Pairwise comparision with bonferroni error correction reveals when PD_o group in *off* state is compared with Controls significant diffrence can be observed with *p*=0.001. However, after levodopa dose in *on* state similar distribution with P=0.311 was observed indicating a positive effect of the medication. This effect was not visible in PD_pmg where before and after medication, a significant difference was noticed when compared to Controls with P<.001 and p<0.002 respectively.
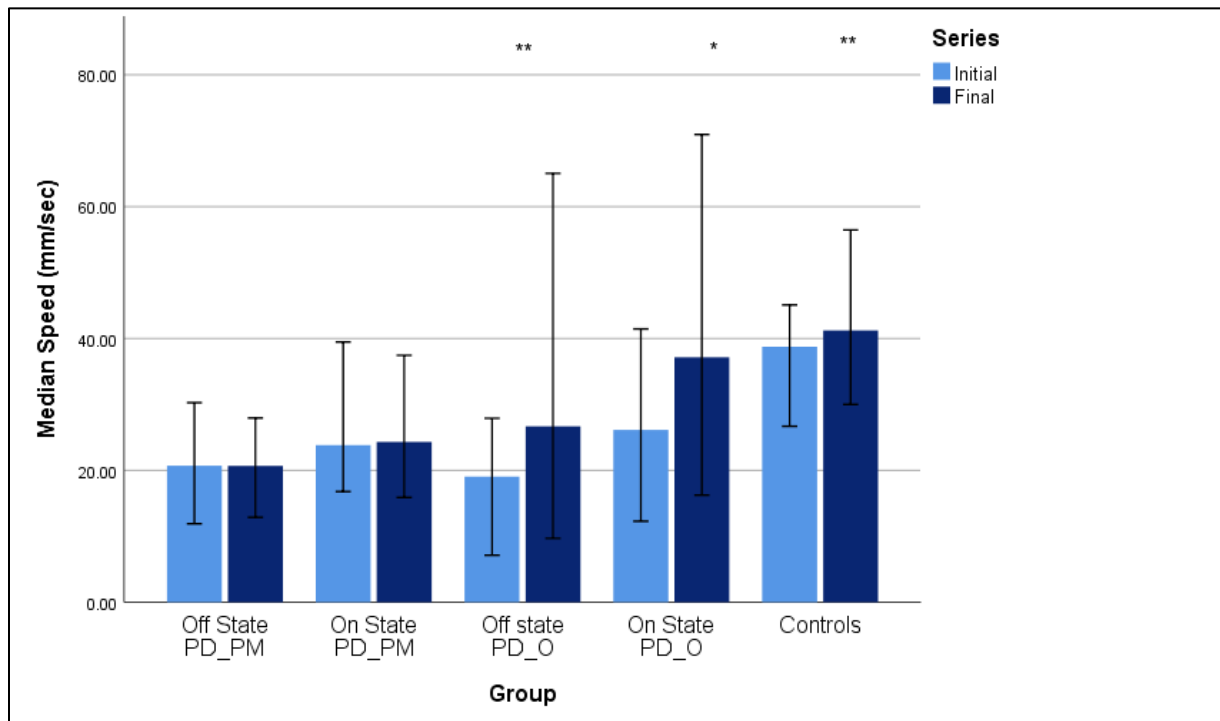
Figure 8.1 Bar-chart (with an error bar of 95% CI) of median writing speeds of PD participants in *off* and *on* states, and Controls. using Wilcoxon signed rank where ** P<.01, *P < 0.05

Table 8.1 Size and Speed of characters for different group of PD and Controls

Medication State	Series	Size		Speed	
		Median[IQR 25th-75th percentile]	P	Median[IQR 25th-75th percentile]	p
Progressive micrographia(PD_PM)					
Off	Initial Series	18.97[12.45-23.10] ↓	<0.001	20.70[11.95-30.17]	0.980
	Last Series	14.61[10.48-19.06]		20.68[13.48-26.70]	
On	Initial Series	17.42[11.40-23.15]	0.083	23.81[17.32-38.29]	0.562
	Last Series	15.47[10.75-21.25]		24.30[16.47-37.24]	
Without progressive micrographia (PD_O)					
Off	Initial Series	16.35[15.00-17.55] ↑	0.039	19.03[10.75-24.47] ↑	0.008
	Last Series	17.63[14.74-20.00]		26.67[14.10-38.56]	
On	Initial Series	18.85[16.3-21.07]	0.313	26.12[14.79-37.26]	0.016
	Last Series	20.44[17.53-21.30]		37.16[16.74-49.90] ↑	
Controls					
Controls	Initial Series	19.40[16.33-21.44]	0.13	38.76[26.51-46.91] ↑	0.001
	Last Series	19.44[16.63-22.47]		41.23[29.25-58.01]	

Results appear as median[]. 2-tailed Wilcoxon signed rank test was performed to compare initial and final series total samples PD=24 and Controls = 24.

59
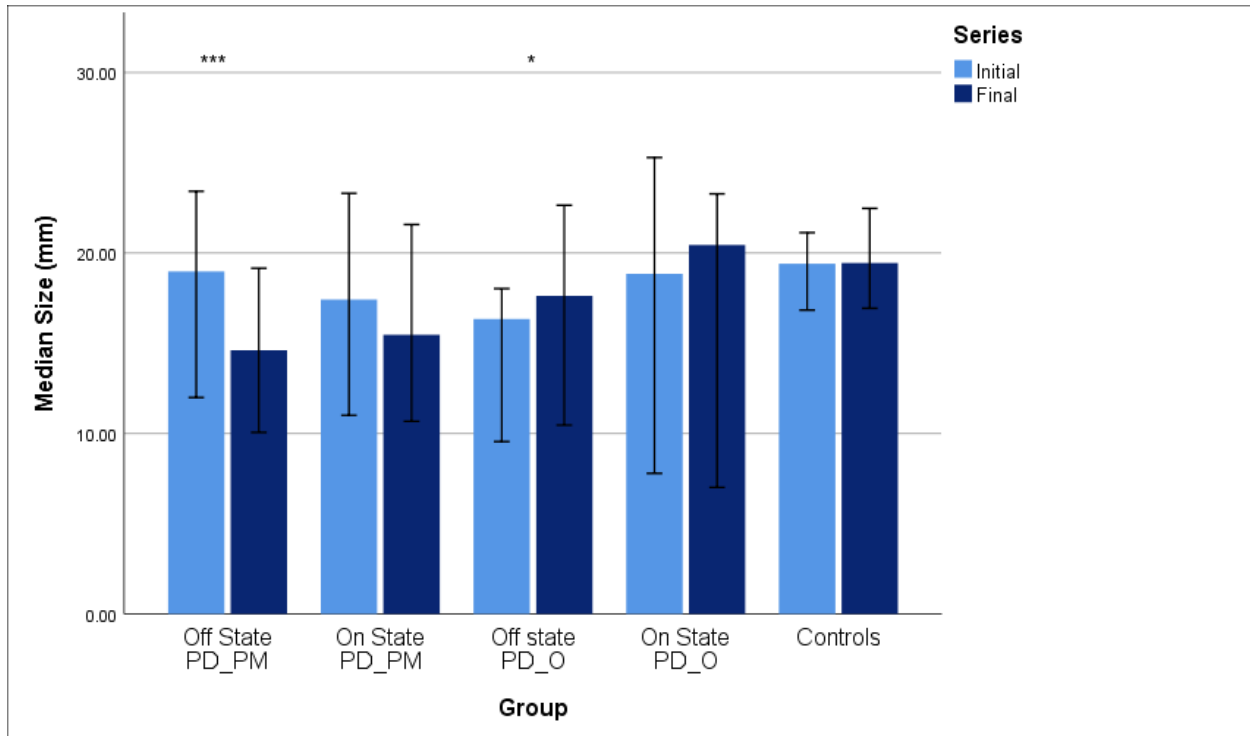
Figure 8.2 Bar-chart (with error bar of 95% CI) of median stroke size of writing in *off* and *on* states, and Controls. using Wilcoxon signed rank where ***p<.001 **, *P < 0.05

8.4   Discussion and Conclusion

Chapter 6 showed that levodopa is less effective as memory load increase while writing. In the current chapter, levodopa effect is studied for the task which was most effective(Thomas et al.) though there is a positive effect of levodopa in both PD group which is inline with a previous study (Cobbah and Fairhurst, 2000) but the impact is not same.

PD_pmg shows improvement in size and progressive micrographia diminish after levodopa dose (Figure 8.2). PD_o group also adjusted the writing size which showed a slight increase in overall size after levodopa dose with no significant difference which shows that handwriting in all the PD group improves after medication. Based on GroupWise comparison (Krushkal walis test) the average size of handwriting was

the same among all groups stating the PD group is able to achieve the size similar to Controls irrespective of micrographia.

Average speed has also shown improvement after levodopa in both the group (Figure 8.1), but it showed a significant difference in *off* and *on* state when compared to Controls stating that PD_pmg group is not able to match the speed of Controls even after levodopa dose and writes consistently slow even after levodopa dose. PD_o group who showed a significant difference before medication did not show the significant difference after medication indicating PD_o group is able to match the speed similar to Controls after medication.

Demographics of PD_o and PD_pmg are similar with no significant difference when UPDRS Section III overall Score and Upper limb bradykinesia score are compared (Table 7.3). However, both the group shows the difference in handwriting before and after medication. Levodopa is more effective in PD_o group and able to improve both size and speed of handwriting and shows output similar to Controls whereas PD_pmg were not able to achieve similar results for kinematic features.

Chapter 9 Summary and Conclusion

9.1 Introduction

Parkinson's disease is a neurological disorder which affects the nervous system, and symptoms worsen over time. Many times, the disease just goes undetected. By the time neurologist detect the Parkinson's disease 60% of neurons responsible for producing dopamine have already degenerated (Becker et al., 2002). There is no cure for PD but synthetic dopamine pharmacological treatments such as Levodopa have been found to be effective when the disease is diagnosed in the early stages. Detecting PD in the early stages is pivotal as starting medication on times helps to delay the complications associated with PD (Lange, 1998). However, the number of researches performed to understand the effect of the medication is seldom. This research outcome can help to improve the overall diagnostic process of Parkinson's disease and understand the effect of medications.

9.2 Main Contributions

This thesis has addressed the current unsolved issues highlighted in Chapter 2

1) **Which dynamic features and writing tasks are effective in the diagnosis of Parkinson's disease in the early stage?**

Classification of different handwriting task was performed with the aim of finding the most effective method and task (Chapter 4). In an initial study of kinematic study, all the handwriting tasks showed a similar outcome which was in line with Drotar et al., study (Drotár et al., 2016).

The main contribution from this chapter is that it has introduced new features, using which the strength of guided Spiral in detecting Parkinson's disease can be improved.

Based on the study it can be concluded that
- Guided spiral is effective in the diagnosis of Parkinson's disease which is independent of languages.
- Use of angular (φ and p_n) and direction change features for archimedean guided spiral were most suitable to distinguish between the PD and Control groups.
- The study has found that the use of appropriate dynamic features is important along with writing the task and plays a significant role to distinguish between Parkinson's disease and Controls.

2) How to distinguish between various stages of Parkinson's disease using dynamic features of handwriting?

Understanding stages of PD is a critical part of the diagnosis process. However, in literature, studies to distinguish between various stages of PD are seldom. The method that I proposed is based on the drawing of figures that are independent of the language of patients which is a substantial advantage over language-based systems that assess changes in the handwriting. This overcomes the potential bias that occurs when patients try to adjust their own drawing (Potgieser et al., 2015). It does not require a strict protocol for the seating posture, as it is independent of the absolute coordinate values. Three parameters were mainly analysed and compared i.e speed, Pen-pressure and CISP. While all the parameters were significantly lower in PD as compared to Controls, and of larger magnitude with increasing PD severity, only CISP was significantly different between the three PD severity groups. CISP also showed discriminatory potential for different severity levels of PD.

Based on Chapter 5 main contribution can be concluded as

- New feature 'CISP' is identified which shows a strong correlation with the severity of PD (>0.6).
- The study has found that the average CISP of sketching a spiral can be used as an assessment method for early-stage diagnosis and also for monitoring the progression of PD.
- The preliminary results of the handwriting experiments are similar to ones reported by clinicians, showing the difference between various stages of PD.
- It provides the patient with a guiding pattern that is self-explanatory, and it does not require the patient to understand commands from the examiner. Hence IQ and cognitive skills of the patient do not affect the results.

3) What is the effect of Levodopa on the handwriting of different complexity?

In literature, different handwriting tasks have been used. Droter et al., have compared different handwriting features and stated that writing a sentence is most effective (Drotár et al., 2016) however so far no one has compared the effect of memory load on PD and impact of medication on a different type of handwriting.

The outcome of Chapter 6 suggests that

- Levodopa is more effective for handwriting tasks which require less cognitive load compared to tasks with more cognitive loading such as copying a sentence and category fluency test.

- Kinematic features showed a significant difference between Control participants and PD patients, for all tasks and in both *on* and *off* states.
- All handwriting tasks which can be used to detect Parkinson's disease may not be applicable to monitor levodopa effect.
- A panel of writing tasks might provide a more stable monitoring system.

4) What is the relation between progressive micrographia and kinematic features in Parkinson's disease? How levodopa improves size vs kinematic features?

Clinically, micrographia is one of the symptoms which is visible in 55-60% of PD patients (Shukla et al., 2012). Ma et al (2013) investigated PD_pmg with Chinese character writing, and focused on the stroke lengths, but did not investigate the associated kinematics (Ma et al., 2013). Chapter 7 demonstrates the relation between stroke length and Kinematics and Chapter 8 shows the effect of Levodopa.

Below are the main conclusions drawn from Chapter 7
- Relationship of Kinematic features vs Size in PD group shows progressive micrographia differs from other PD group.
- Kinematics and Pen-tip pressure profiles suggest that progressive micrographia in PD reflects poorly sustained net force compared to other PD patients not showing progressive micrographia.
- Levodopa improves the size and speed in PD. However, the effect of the medication on kinematic features is more in the PD group who does not show symptoms of progressive micrographia.

9.3   Conclusion

This thesis introduces new kinematic features (CISP, Angular and Direction features) and demonstrates the effectiveness to detect and distinguish PD using Guided Spiral. Kinematic features were further studied across a range of activities and quantified the effect of levodopa during *off* and *on* state. The kinematic analysis has gone beyond previous studies in its exploration of the dynamic basis of progressive micrographia. The study suggests that changes in the horizontal direction are an important aspect of parkinsonian dysgraphia and adds to our understanding of the interplay between 'horizontal micrographia' and progressive change in letter size.

Using machine learning (Naïve Bayes algorithm) on various kinematic features, a substantial ROC AUC

of 0.93 is reached using new angular and direction features which shows the potential of Guided Spiral to detect PD. Further, Spiral was used to detect stages of PD with Spearman correlation as in the results of Chapter 6. Guided spiral drawing is an easy to perform technique. With standard technologies like SmartPen and Digital Tablet, it can be easily used in clinics to capture data for kinematics of arms and other information without compromising on the comfort level of patients, who may still prefer writing with an ink pen on a plain paper. The study shows an overall scientific advancement concerning drawing analysis in the functional assessment of persons with Parkinson's disease. Based on the outcome, this thesis suggests the use of guided spiral as one of the key tasks to be included as part of the preliminary test using dynamic features like angular and direction change features and CISP.

When different handwriting tasks were compared to see the effect of medication, not all have shown uniform outcomes. Levodopa is effective for simple writing activities, denoting improved fine motor control, but the same benefits were not seen for more complex tasks that carry memory and cognitive loads. Significant differences were noticed in kinematic features between Control participants and PD patients. The study suggests that a panel of handwriting tasks with varying memory load will be more helpful to detect and understand the effect of medication in PD.

The work has investigated progressive and consistent micrographia and its relationship with the disease. The results have put in doubt the appropriateness of differentiating between the two types of micrographia and questioned the effectiveness of using micrographia for detecting or monitoring PD. This study's findings will be useful for neurologists investigating movement disorders to develop a deeper understanding of the disease.

This study anticipates performing appropriate handwriting tests as part of a clinical test will ease the diagnosis process. It could also be used remotely for self-evaluation by patients with neuromuscular and movement disorders.

9.4   Limitations and Future work

This study has found that guided spiral has the potential to detect as well as distinguish different stages of Parkinson's disease. Memory load due to task plays an important role and levodopa does not show improvement to the same extent when memory load in the handwriting task increases. There are few limitations and the basis for future work before making it a part of the clinical test. The study to distinguish

between different stages has shown promising results but the sample size was relatively small. Clinical heterogeneity, seen in PD patients like tremor dominance patient's vs akinetic rigidity, early onset versus late onsets and genetic versus sporadic types was not considered in this study. This study has not grouped PD based on tremor. The PD group considered in this study was late onset (above age of 65). There is a need to extend the sample size for each severity level including group showing early onset of PD. The future work should also include a longitudinal study to confirm the suitability of methods for monitoring the progression of the disease.

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Appendices

(A) Rating Scales

The UPDRS (Unified Parkinson's disease rating score), Hoehn & Yahr and Schwab & England scales are the scales in common practice for Parkinson's disease. Their utility is that they objectively rate an individual patient's disability at a particular moment in time. Each scale score is a reflection of disease burden on the individual patient and is useful in describing disease progression and treatment response with time.

The UPDRS is scored from a total of 195 points; higher scores reflect worsening disability.

Hoehn and Yahr scale

Modified Hoehn and Yahr staging

Stage 0	No signs of disease
Stage 1	Unilateral disease
Stage 1.5	Unilateral plus axial involvement
Stage 2	Bilateral disease, without impairment of balance
Stage 2.5	Mild bilateral disease, with 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

Schwab & England Scale

Schwab & England Activities of Daily Living scale

100%	Completely independent. Able to do all chores w/o slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.

90%   Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. May take twice as long. Beginning to be aware of difficulty.

80%   Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowing.

70%   Not completely independent. More difficulty with some chores. X 3-4 as long in some. May spend a large part of the day with chores.

60%   Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors, some impossible.

50%   More dependent. Help with 1/2 of chores. Difficulty with everything.

40%   Very dependant. Can assist with all chores but few alone.

30%   With effort, now and then does a few chores alone or begins alone. Much help needed.

20%   Nothing alone. Can do some slight help with some chores. Severe invalid.

10%   Totally dependant, helpless. Complete invalid.

0%   Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

Unified Parkinson's Disease Rating Scale (UPDRS)

DATE:			TIME	BEFORE MEDICATION	AFTER MEDICATION
Finger taps	Right	0	normal		
		1	mild slowing, and / or reduction in amp		
		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		
	Left	0	normal		
		1	mild slowing, and / or reduction in amp		
		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		
Hand Movements (open and close hands in rapid)	Right	0	normal		
		1	mild slowing, and / or reduction in amp		
		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		
	Left	0	normal		
		1	mild slowing, and / or reduction in amp		
		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		
Rapid alternating movements	Right	0	normal		
		1	mild slowing, and / or reduction in amp		

				BEFORE MEDICATION	AFTER MEDICATION
(pronate and sup)		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		
	Left	0	normal		
		1	mild slowing, and / or reduction in amp		
		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		
Leg Agility (tap heel on ground, amp should be	Right	0	normal		
		1	mild slowing, and / or reduction in amp		
		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		

DATE:			TIME	BEFORE MEDICATION	AFTER MEDICATION
Leg Agility (tap heel on ground, amp should be	Left	0	normal		
		1	mild slowing, and / or reduction in amp		
		2	moderate impaired. Definite and early fatiguing, occasional arrests		
		3	severely impaired. Frequent hesitations and arrests		
		4	can barely perform		
Arising from chair (with arms folded)		0	normal		
		1	slow, may need more than one attempt		
		2	pushes self up from arms or seat		
		3	tends to fall back, may need multiple tries but can with assistance		

		4	unable to arise without help		
Posture		0	normal erect		
		1	slightly stooped, could be normal for older person		
		2	definitely abnormal, mod, stooped, may lean to one side		
		3	severely stooped with kyphosis		
		4	marked flexion with extreme abnormality of posture		
Gait		0	normal		
		1	walks slowly, may shuffle with short steps, no festination or propulsion		
		2	walks with difficulty, little or no assistance, some festination,short steps or propulsion		
		3	severe disturbance, frequent assistance		
		4	cannot walk		
Postural Stability (retropulsion test)		0	normal		
		1	recovers unaided		
		2	would fall if not caught		
		3	falls spontaneously		
		4	unable to stand		
Body Bradykinesia / Hypokinesia)		0	none		
		1	minimal slowness, could be normal, deliberate cha		
		2	mild slowness and poverty of movement, definitely dec. amp of movement		
		3	moderate slowness, poverty, or small amplitude		
		4	marked slowness, poverty, or amplitude		

(B) MOCA Test

NAME :
Education :   **Date of birth :**
Sex :   **DATE :**

VISUOSPATIAL / EXECUTIVE		POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

(E) End
(A)
(5)
(B)   (2)
(1) Begin
(D)   (4)
(3)
(C)

[ ]   [ ]   [ ] Contour   [ ] Numbers   [ ] Hands   __/5

NAMING

[ ]   [ ]   [ ]   __/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

		FACE	VELVET	CHURCH	DAISY	RED	
	1st trial						No points
	2nd trial						

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2   __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B   __/1

Serial 7 subtraction starting at 100   [ ] 93   [ ] 86   [ ] 79   [ ] 72   [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**   __/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]   __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)   __/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler   __/2

DELAYED RECALL

Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	__/5
Optional Category cue							
Multiple choice cue							

ORIENTATION   [ ] Date   [ ] Month   [ ] Year   [ ] Day   [ ] Place   [ ] City   __/6

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Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

(C) Letter of Approval

RMIT UNIVERSITY

21st October 2015

Dear Dinesh

BSEHAPP 22-15 KUMAR Analysis of handwriting and gait in Parkinson's and multiple sclerosis

Thank you for requesting an amendment and extension to your Human Research Ethics project titled: *Analysis of handwriting and gait in Parkinson's and multiple sclerosis* which was originally approved by Science Engineering and Health CHEAN in June 2015 for a period of 2 years.

I am pleased to inform you that the CHEAN has **approved** your request to include the following personal to the project:

Professor Peter Dabnichki from the school of Aerospace, Mechanical and Manufacturing Engineering Students: Ms. Poonam Zham s3570515 and Ms Andrea Silvana Satizabal Orozco s3518807 from the school of Mechanical and Manufacturing Engineering

The CHEAN notes and thanks you for providing all documentation that incorporates these amendments. This documentation will be appended to your file for future reference and your research may now continue.

The committee would like to remind you that:

Please Note: Annual reports are due on the anniversary of the commencement date for all research projects that have been approved by the CHEAN. Ongoing approval is conditional upon the submission of annual reports failure to provide an annual report may result in Ethics approval being withdrawn.

Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at:
www.rmit.edu.au/staff/research/human-research-ethics

Yours faithfully,

Dr Linda Jones
Chair, Science Engineering & Health
College Human Ethics Advisory Network

(D) Sample Images of PD and Controls while performing experiments