Neuromodulation of the posterior subthalamic area influences upper limb function in Parkinson’s disease

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Bachelor of Science (Honours)

This thesis is presented for the degree of
Doctor of Philosophy
of The University of Western Australia

School of Sport Science, Exercise & Health, 2014
DECLARATION

I declare this thesis is my own composition, all sources have been acknowledged and my contribution is clearly identified in the thesis. For any work in the thesis that has been co-published with other authors, I have permission of all co-authors to include this work in my thesis.

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STATEMENT OF CONTRIBUTION

This thesis contains work prepared for publication which has been co-authored. The bibliographical details of the work and where it appears in the thesis are outlined below. A statement for each publication that clarifies the contribution of the student to the work is provided.

Chapter Three: The effect of acute posterior subthalamic area micro-lesioning and stimulation on upper limb tremor and activation patterns in Parkinson’s disease

Candidate Contribution

Planning: Contribution to the conception of the ideas, development of the experimental designs and the establishment of laboratory techniques.

Data collection: The candidate was the primary individual involved in data collection at The University of Western Australia. This includes the recruitment of the healthy control participants, and coordination and management of all the testing sessions.

Data analysis: Processing and analysing of the electromyography data, and conduction of statistical analysis (SPSS), organisation of meetings for discussion and data interpretation.

Manuscript: Preparation of manuscript draft, preparations of tables and figures, and revising manuscripts following circulation to co-authors.
Chapter Four: Outcome of elbow rigidity with posterior subthalamic deep brain stimulation in Parkinson’s disease

Candidate Contribution

Planning: Contribution to the conception of the ideas, development of the experimental designs and the establishment of laboratory techniques.

Data collection: The candidate was the primary individual involved in data collection at The University of Western Australia. This includes the recruitment of the healthy control participants, and coordination and management of all the testing sessions.

Data analysis: Processing and analysis of all the data which includes resistive torque and electromyography, and conduction of statistical analysis (SPSS), and organisation of meetings for discussion.

Manuscript: Preparation of manuscript draft, preparations of tables and figures, and revising manuscripts following circulation to co-authors.

Chapter Five: Effects of posterior subthalamic area micro-lesioning and stimulation on upper limb bradykinesia and tremor in Parkinson’s disease

Candidate Contribution

Planning: Contribution to the conception of the ideas, development of the experimental designs and the establishment of laboratory techniques.

Data collection: The candidate was the primary individual involved in data collection at The University of Western Australia. This included the recruitment of the healthy control participants, and coordination and management of all the testing sessions.

Data analysis: Processing and analysis of all the data which included jerk profiles and electromyography, and conduction of statistical analysis (SPSS), and organisation of meetings for discussion.

Manuscript: Preparation of manuscript draft, preparations of tables and figures, and revising manuscripts following circulation to co-authors.
Conference Presentations Resulting from this Research

Oral Communications

ABSTRACT

Parkinson’s disease (PD) is a neuro-degenerative disorder widely believed to be the result of a pathophysiologic loss or degeneration of dopaminergic neurons in the substantia nigra of the basal ganglia system. Tremor, rigidity, and bradykinesia are the three hallmark motor symptoms of PD and are often presented in the upper limb. Whilst a single motor symptom can predominate, it is also common for an individual with PD to display an overlapping of mixed presentation of all these symptoms. As a result, there can be a wide individual differences in the symptomology. The presence of these motor symptoms impairs movement and severely affects the quality of life in individuals with PD.

Deep brain stimulation targeted at specific basal ganglia structures have been utilised to treat the PD motor symptoms with a high level of success. Researchers have reported that a zone in the posterior subthalamic area (PSA) called the zona incerta (ZI), to be a highly effective target for DBS in alleviating the three main symptoms in PD: tremor, rigidity and bradykinesia. Plaha et al. (2006) targeted the caudal division of the ZI (cZI) and found reductions in the motor symptoms of their PD patients. Hamel et al. (2003) on the other hand stimulated the dorsal division of the ZI (dZI) and reported motor improvements in the patients with PD. Previous studies in this area have utilised semi-quantitative assessments and as such, provide a somewhat limited assessment of the alterations in the PD symptoms following intervention. More importantly, there have been no published studies that have compared the outcome between cZI and dZI stimulation within individuals. Therefore, this research aimed to provide insights into these previously unanswered questions to contribute to the existing research on PSA DBS and its efficacy in treating the motor symptoms in PD. This was performed through quantitatively assessing the effect of acute ZI targeted PSA DBS on the three primary upper limb symptoms in
The research problems outlined were addressed through three interrelated studies of the PD symptoms.

Study One investigated the outcomes of ZI targeted PSA DBS on the spectral analysis and electromyography during tremor tasks in PD participants in relation to healthy controls. Trends in the data suggest that increase in the spectral analysis and an altered electromyography activity was present in the PD participants as compared to the controls. The main findings of this study reported proximal and distal segment improvements in tremor, especially for individuals who underwent surgery to have their tremor reduced, in resting and postural tremor with post-operative settings particularly with ZI stimulation.

Study Two quantified the effects of ZI targeted PSA DBS on the rigidity component in PD using a torque, and electromyography based approach during passive movement. Trends in the data suggest that the PD participants generally exhibited higher resistive torque than the healthy controls, indicative of increased rigidity. Overall, the resistive torque and electromyography activity, most notably in the elbow flexors, was reported to be reduced with ZI targeted PSA DBS. Individual data within this study suggest that dZI stimulation may have a greater potential for alleviating the motor symptoms of the tremor-predominant group while the cZI may be a favourable target for the rigid akinetic PD group.

Study Three reported increased values in movement time and jerk profiles (smoothness of the movement), and altered electromyography profile in the PD participants as compared to the healthy controls, indicative of the presence of bradykinesia and action
tremor. Improvements in movement time and jerk profiles were prominent with following DBS to the ZI. Descriptive analysis of the data suggests that there were generally no added benefit on top of micro-lesioning in the PD participants in this acute phase (five days follow-up) of assessment. The findings in this study suggest that the effect of micro-lesioning was enough to produce therapeutic benefits for the PD participants in both sub-groups, at least in the immediate short term.

The outcomes of this ZI targeted PSA DBS research denote its potential benefits in treating the motor symptoms of our PD participants. While the evidence for the benefits of ZI targeted PSA DBS is reported, the mechanism of action of DBS is difficult to expound. It has been suggested that DBS to the areas of and around the ZI may alter the signals to and from structures of the brain that have an influence in the pathophysiology of the motor symptoms in PD, thus, alleviating these symptoms. With this research, there are important considerations that need to be acknowledged such as acute versus longer term assessments (i.e. three, six, and 12 months follow-ups), optimal medication intake of the PD group and its effect on performance, and the relatively small sample size of the sub-groups of PD. Future research quantitatively investigating the longer term outcome of both cZI and dZI stimulation with an adequate sample size of PD participants, specifically in each sub-group, may give clinicians/researchers new information on the identification of the best responders to this novel target site.

Although differences between pre and post-operative assessments were generally non-significant in all three studies, possibly due to the heterogeneity of the whole PD group, individual trends across all three studies suggest potential differences. In addition, the presence of moderate to high effect sizes reported in the studies suggest significant
differences may be observed with a large sample size. This research has outlined evidence into the potential benefits of cZI and dZI stimulation and its effect on the sub-groups of PD. We propose that the ZI is an effective target site for DBS in treating the motor symptoms of PD. Due to the added improvements observed with cZI stimulation in the non tremor-predominant group particularly in reducing rigidity, this division of the ZI may be a favourable site for DBS in this sub-group of PD. As for the tremor-predominant group, we propose the consideration of dZI as a target site for DBS due to the improvements observed in Studies One and Two.
# TABLE OF CONTENTS

Declaration .................................................................................................................. ii
Statement of contribution .......................................................................................... iii
Conference presentations resulting from this research ............................................. v
Abstract ....................................................................................................................... vi
Table of Contents ......................................................................................................... x
List of Figures ............................................................................................................... xvi
List of Tables ................................................................................................................ xx
List of Abbreviations .................................................................................................... xxii
Acknowledgements ....................................................................................................... xxiv

<table>
<thead>
<tr>
<th>Chapter One</th>
<th>Introduction</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Introduction</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>1.2 Statement of the problem</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>1.3 Thesis outline</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>1.3.1 Chapter Three: Study One</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>1.3.2 Chapter Four: Study Two</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>1.3.3 Chapter Five: Study Three</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>1.4 Significance of this research</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>1.5 Limitations</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>1.6 Delimitations</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter Two</th>
<th>Review of the Literature</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 What is Parkinson’s disease?</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>2.2 Pathophysiology of PD</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>2.3 Parkinsonian tremor</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>2.4 Rigidity</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>2.5 Bradykinesia</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>
2.6 History of treatment and interventions ...................... 52
  2.6.1 Ablative surgery ........................................ 53
  2.6.2 Medication ................................................. 53
  2.6.3 Deep brain stimulation .................................... 55
    2.6.3.1 Benefits, indications, contraindications, and side-effects of DBS surgery ................................. 56
    2.6.3.2 Neurophysiology of DBS ............................ 56
    2.6.3.3 Optimal target site for DBS ....................... 58
      2.6.3.3.1 Globus pallidus internus ..................... 59
      2.6.3.3.2 Subthalamic nucleus ............................ 59
  2.7 The posterior subthalamic area ............................. 62
  2.8 The zona incerta ............................................. 63
    2.8.1 Important considerations and future research possibilities ................................................. 65
  2.9 Summary ...................................................... 65
References .................................................................. 67

Chapter Three  Study One: The effect of acute posterior subthalamic area micro-lesioning and stimulation on upper limb tremor and activation patterns in Parkinson’s disease ................. 80
  Foreword ............................................................ 81
  Abstract .............................................................. 82
  3.1 Introduction ..................................................... 83
  3.2 Methods .......................................................... 85
    3.2.1 Participants ................................................ 85
    3.2.2 Study design .............................................. 86
    3.2.3 Experimental tasks ..................................... 87
    3.2.4 Participant preparation ................................ 87
    3.2.5 Data collection and processing ..................... 88
    3.2.6 Statistical analysis ..................................... 90
  3.3 Results .......................................................... 90
Chapter Four

Study Two: Outcome of elbow rigidity with posterior subthalamic deep brain stimulation in Parkinson’s disease.

- Foreword ................................................. 106
- Abstract .................................................. 107
- 4.1 Introduction ......................................... 108
- 4.2 Methods ............................................. 110
  - 4.2.1 Participants ...................................... 110
  - 4.2.2 Study design .................................... 111
  - 4.2.3 Participant preparation ......................... 112
  - 4.2.4 Data collection ................................... 112
  - 4.2.5 Surgical procedure .............................. 114
  - 4.2.6 Pre and post-operative assessments for PD participants .............................................. 115
  - 4.2.7 Data processing .................................... 115
  - 4.2.8 Statistical analysis .............................. 115
- 4.3 Results ............................................... 116
  - 4.3.1 Correlation between the UPDRS and biomechanical assessment ................................. 116
  - 4.3.2 Comparison with healthy controls ............ 118
  - 4.3.3 Trends within the PD sub-groups ................ 118
- 4.4 Discussion ............................................ 123
- 4.5 Conclusion .......................................... 127
- Acknowledgements ....................................... 128
- References ............................................. 129
Chapter Five

Study Three: Effects of posterior subthalamic area micro-lesioning and stimulation on upper limb bradykinesia and action tremor in Parkinson’s disease ........................................ 132

Foreword .............................................................. 133

Abstract .................................................................. 134

5.1 Introduction ....................................................... 135

5.2 Methods ............................................................. 137

5.2.1 Participants ...................................................... 137

5.2.2 Study design ................................................... 138

5.2.3 Experimental tasks ......................................... 139

5.2.4 Participant preparation ..................................... 140

5.2.5 Data collection and processing ......................... 140

5.2.6 Statistical analysis .......................................... 142

5.3 Results ............................................................... 142

5.3.1 Jerk analysis .................................................... 143

5.3.1.1 Comparison between PD and healthy controls ....... 143

5.3.1.2 Comparison within PD group following DBS - Tapping task ...... 146

5.3.1.3 Comparison within PD group following DBS - Pointing task ...... 149

5.3.2 iEMG analysis ............................................... 150

5.3.2.1 iEMG Comparison between PD and healthy controls .......... 150

5.3.2.2 iEMG Comparison within PD group following DBS - Tapping task ...... 150

5.3.2.3 iEMG Comparison within PD group following DBS - Pointing task ...... 152

5.4 Discussion .......................................................... 153

5.5 Conclusion .......................................................... 158

Acknowledgements .................................................. 158

References ............................................................. 159
Chapter Six  General Discussion ........................................... 162

6.1 Summary .............................................................. 163

6.1.1 Chapter Three: The effect of acute posterior subthalamic area micro-lesioning and stimulation on upper limb tremor and activation patterns in Parkinson’s disease ...... 164

6.1.2 Chapter Four: Outcome of elbow rigidity with posterior subthalamic deep brain stimulation in Parkinson’s disease ....................... 166

6.1.3 Chapter Five: Effects of posterior subthalamic area micro-lesioning and stimulation on upper limb bradykinesia and action tremor in Parkinson’s disease ..................... 169

6.2 Synthesis of results .................................................. 171

6.2.1 Tremor-predominant group ......................... 173

6.2.2 Non tremor-predominant group ............... 175

6.2.3 Potential target site for the sub-groups .......... 176

6.2.4 Neurophysiology of ZI targeted PSA DBS ... 176

6.3 Important considerations for this research .......... 177

6.4 Future research ..................................................... 178

6.5 Significance and conclusion ............................... 179

References ............................................................... 180

Appendix ...................................................................... 184

Appendix 1. Sir Charles Gairdner Ethics approval .... 185

Appendix 2. The University of Western Australia Ethics Approval ........................................... 187

Appendix 3. Parkinson’s disease participant information sheet ................................................ 188

Appendix 4. Healthy control participant information sheet ......................................................... 198

Appendix 5. MATLAB code for Study One ............ 203

Appendix 6. MATLAB code for Study Two .......... 206

Appendix 7. MATLAB code for Study Three ........... 208

xiv
Appendix 8. Conference proceeding (oral presentation) for the International Society of Biomechanics 2013, Natal, Brazil ................................. 214

Appendix 9. Conference proceeding (submitted) for the International Society of Biomechanics 2015, Glasgow, Scotland ................................. 216

Appendix 10. Unified Parkinson’s Disease Rating Scale (UPDRS) motor section (III) ......................... 219

Appendix 11. EMG electrode placements ......................... 229
LIST OF FIGURES

CHAPTER TWO – LITERATURE REVIEW

FIGURE 2.1 40
Adapted from de Lau and Breteler, 2006. Illustrates the incidence of PD across different countries.

FIGURE 2.2 44
Adapted from Milanov, 2001. Illustrates the amplitude of tremor EMG in different pathologies.

FIGURE 2.3 51
Adapted from Poizner et al., 1998. Trajectory paths to each of the five target (dark spheres as end points) in a pointing task represented by a healthy control and a PD participant.

FIGURE 2.4 61
Adapted from Yelnik et al., 2007. Subdivisions of the STN.

FIGURE 2.5 63
Axial MRI slice of the Schaltenbrand & Wahren atlas on the locations of the STN (in blue) and ZI (in orange).

FIGURE 2.6 64
Adapted from Mitrofanis, 2005. Location and proposed connections of the ZI in rats.

CHAPTER THREE – STUDY ONE

FIGURE 3.1 94
Individual column chart representation of the mean of the amplitude in frequency (afP) and power (4-7 Hz) at the hand and arm segments for the sub-group of Parkinson’s participants who underwent surgery to reduce the tremor (n = 4) in the resting and postural tasks. Data for micro-lesioning, cZI stimulation and dZI stimulation are presented as a percentage change relative to the participants' pre-operative levels. (A) Hand afP in the resting task, (B) Arm afP in the resting task, (C) Hand afP in the postural task, (D) Arm afP in the postural task, (E) Hand power (4-7 Hz) in the resting task, (F)
Arm power (4-7 Hz) in the resting task, (G) Hand power (4-7 Hz) in the postural task, (H) Arm power (4-7 Hz) in the postural task.

**FIGURE 3.2**

Column chart representation of the mean and standard deviation of the iEMG of all eight muscles (% of SIVC) in the Parkinson’s participants over pre and post-operative assessments and the healthy controls. ST represents the sub group of Parkinson’s participants who underwent surgery to reduce the tremor. (A) Resting task for all Parkinson’s participants (n = 10), (B) Postural tasks for all Parkinson’s participants (n = 10), (C) Resting tasks for the ST group (n = 4), (D) Postural tasks for the group (n = 4).

**CHAPTER FOUR – STUDY TWO**

**FIGURE 4.1**

Static position of the participant.

**FIGURE 4.2**

Line plot representation of the mean and standard deviation bars of the maximum resistive flexor torque, maximum biceps activation (% of SIVC), and maximum triceps activation (% of SIVC) during extension in the tremor predominant Parkinson’s participants (n = 3) over pre and post-operative assessments at (a) 30°/sec, (b) 30°/sec with the contra-lateral cupping task, (c) 90°/sec, (d) 90°/sec with the contra-lateral cupping task. Maximum resistive flexor torque for healthy controls is represented by the black dash line.

**FIGURE 4.3**

Line plot representation of the mean and standard deviation bars of the maximum resistive flexor torque, maximum biceps activation (% of SIVC), and maximum triceps activation (% of SIVC) during extension in the rigid akinetic Parkinson’s participants (n = 4) over pre and post-operative assessments at (a) 30°/sec, (b) 30°/sec with the contra-lateral cupping task, (c) 90°/sec, (d) 90°/sec with the contra-lateral cupping task. Maximum resistive flexor torque for healthy controls is represented by the black dash line.

**FIGURE 4.4**

Individual breakdown of the line plot representation of the mean maximum resistive flexor torque during extension in the 90°/sec with the contra-lateral cupping over pre and post-operative assessments. (a) Tremor-predominant Parkinson’s participants (n = 3), (b) Rigid akinetic Parkinson’s participants (n = 4).
CHAPTER FIVE – STUDY THREE

FIGURE 5.1
The trajectory of a representative pointing trial of a healthy control and a PD participant (PD2) output from the custom LabView program. The blue and red dots represent the nose and target respectively (start and end point of the trajectory).

FIGURE 5.2
Line plot representation of the mean and standard deviation of the movement time, jerk index and normalised jerk in the tremor-predominant Parkinson’s participants (n = 3), represented by black square points and dotted black line, and non tremor-predominant Parkinson’s participants (n = 7), represented by the red circle points and red line, over pre and post-operative assessments in both the tapping and pointing task. The range of healthy control value is represented by the shaded grey area. (A) Movement time in the tapping task, (B) Movement time in the pointing task, (C) Jerk index in the tapping task, (D) Jerk index in the pointing task, (E) Normalised jerk in the tapping task, (F) Normalised jerk in the pointing task.

FIGURE 5.3
Line plot representation of the mean movement time and normalised jerk in the tremor-predominant Parkinson’s participants (n = 3), rigid akinetic Parkinson’s participants (n = 4), and classic Parkinson’s participants (n = 3), over pre and post-operative assessments in the tapping task. (A) Movement time for the tremor-predominant group, (B) Movement time for the rigid akinetic group, (C) Movement time for the “classic” group, (D) Normalised jerk for the tremor-predominant group, (E) Normalised jerk for the rigid akinetic group, (F) Normalised jerk for the “classic” group.

FIGURE 5.4
Line plot representation of the mean movement time and normalised jerk in the tremor-predominant Parkinson’s participants (n = 3), rigid akinetic Parkinson’s participants (n = 4), and classic Parkinson’s participants (n = 3), over pre and post-operative assessments in the pointing task. (A) Movement time for the tremor-predominant group, (B) Movement time for the rigid akinetic group, (C) Movement time for the “classic” group, (D) Normalised jerk for the tremor-predominant group, (E) Normalised jerk for the rigid akinetic group, (F) Normalised jerk for the “classic” group.
Column chart representation of the mean and standard deviation of the iEMG of four muscles (% of SIVC) in the Parkinson’s participants (n = 10) over pre and post-operative assessments and the healthy controls. (A) Tapping task, (B) Pointing task. * denotes significant differences (p = 0.005, p < 0.008).
LIST OF TABLES

CHAPTER THREE – STUDY ONE

TABLE 3.1  86
Parkinson’s disease participant characteristic and medication information.

TABLE 3.2  89
Description of the SIVC collection for all muscles.

TABLE 3.3  91
The spectral analysis for the hand and arm segments of all PD participants for both tasks and all conditions as compared to healthy controls. Data is represented as mean and standard deviation (±1). fP denotes the frequency of the signal.

CHAPTER FOUR – STUDY TWO

TABLE 4.1  111
Parkinson’s disease participant characteristic and medication information.

TABLE 4.2  117
Maximum resistive flexor (FlxT) and extensor torque (ExtT) of the Parkinson’s disease participants (n = 10) and the healthy controls (n = 10) in all settings and conditions. Torque data (N.m) and muscle activation (as a % of SIVC) are represented as mean and standard deviation (±1).

CHAPTER FIVE – STUDY THREE

TABLE 5.1  138
Parkinson’s disease participant information.

TABLE 5.2  141
Description of the SIVC collection for all muscles.
TABLE 5.3

Jerk variables of all participants.
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Amantadine hydrochloride</td>
</tr>
<tr>
<td>afP</td>
<td>Amplitude of frequency</td>
</tr>
<tr>
<td>B</td>
<td>Benserazide</td>
</tr>
<tr>
<td>BG</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td>Bh</td>
<td>Benzhexol Hydrochloride</td>
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<tr>
<td>C</td>
<td>Carbidopa</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetre</td>
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<tr>
<td>COV</td>
<td>Coefficient of variation</td>
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<tr>
<td>cZI</td>
<td>Caudal division of the zona incerta</td>
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<tr>
<td>DBS</td>
<td>Deep brain stimulation</td>
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<tr>
<td>dZI</td>
<td>Dorsal division of the zona incerta</td>
</tr>
<tr>
<td>E</td>
<td>Entacapone</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>ES</td>
<td>Effect size</td>
</tr>
<tr>
<td>ExtT</td>
<td>Maximum resistive extensor torque during flexion</td>
</tr>
<tr>
<td>FlxT</td>
<td>Maximum resistive flexor torque during extension</td>
</tr>
<tr>
<td>fP</td>
<td>Frequency</td>
</tr>
<tr>
<td>GPi</td>
<td>Globus pallidus interna</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>iEMG</td>
<td>Integrated electromyography</td>
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<tr>
<td>JI</td>
<td>Jerk index</td>
</tr>
<tr>
<td>L</td>
<td>Levodopa</td>
</tr>
<tr>
<td>L-Dopa</td>
<td>Levodopa</td>
</tr>
<tr>
<td>Micro</td>
<td>Micro-lesioning</td>
</tr>
<tr>
<td>mm</td>
<td>Millimetre</td>
</tr>
<tr>
<td>N.m</td>
<td>Newton metre</td>
</tr>
</tbody>
</table>
NJ  Normalised jerk
NJ1  Percentage normalised jerk in the primary movement
NJ2  Percentage normalised jerk in the secondary movement
P  Pramipexole
PD  Parkinson’s disease
PD10  Tremor-predominant Parkinson’s disease participant
PD4  Tremor-predominant Parkinson’s disease participant
PD6  Tremor-predominant Parkinson’s disease participant
Pre  Pre-operative levels of the Parkinson’s participants
PreOp  Pre-operative levels of the Parkinson’s participants
PSA  Posterior subthalamic area
R  Rotigotine
S  Second
SCGH  Sir Charles Gairdner Hospital
SIVC  Sub-maximal isometric voluntary contraction
ST  Participants who underwent surgery to control tremor
STN  Subthalamic nucleus
UPDRS  Unified Parkinson's Disease Rating Scale
UWA  The University of Western Australia
V  Volts
ZI  Zona incerta
μs  Microsecond
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CHAPTER ONE

INTRODUCTION
1.1 Introduction

Parkinson’s disease (PD) is a neurological disorder characterised by progressive motor symptoms such as tremor, rigidity, and bradykinesia, the presentation of which may occur in combination or as individual predominant symptoms i.e. tremor-predominant or rigid akinetic [1–4]. The population of individuals with PD is predicted to increase from 10 million worldwide in the year 2000 to 40 million in 2020 and, as a result, the demand for PD healthcare is growing at a tremendous rate [5]. The exact aetiology of PD is still undetermined, evidence has suggested that reduced activity of dopamine-secreting cells within the nuclei of the basal ganglia system to be the prime determinant of PD [6–8]. Dopaminergic medication aimed at restoring the depleted levels of dopamine have been the most successful treatment for PD [9,10], though not without the presence of side-effects [11,12]. Furthermore, a sub-group of PD patients, exhibiting only tremor motor symptoms, have a reduced response rate to these form of medications [13]. In efforts to reduce the negative outcomes of medication and provide a favourable intervention for individuals who do not respond well to medication, deep brain stimulation (DBS) targeted at the globus pallidus interna and the subthalamic nucleus have been advanced to treat the PD motor symptoms with a high level of success [11,14]. However, some studies have reported negative cognitive and emotional side-effects with stimulation particularly to the subthalamic nucleus [15–20].

This has led to an alternative DBS site, the posterior subthalamic area (PSA), to be considered for DBS by some researchers and neurosurgeons [21–27]. These researchers reported that stimulation to the areas of and around the zona incerta (ZI) specifically; the caudal (cZI) and dorsal (dZI) areas, located in the PSA, to be highly effective in alleviating the three main symptoms in PD; tremor, rigidity and bradykinesia, without the
manifestation of severe side-effects [21–27]. Most of these reports in ZI targeted PSA DBS are based on semi-quantitative clinical evaluation of symptoms utilising the Unified Parkinson’s Disease Rating Scale which, although valid and reliable, provides somewhat limited insight into the discrete alterations in the PD motor symptoms following intervention [28,29]. This scale lacks the sensitivity in detecting subtle changes in movement particularly after a surgical intervention; DBS [28,29].

Recently, researchers have begun to apply several biomechanical and signal processing techniques such as spectral analysis; (providing information on the frequency content of the signal), torque-based measurements; (providing information on the rotational force about a joint), kinematic analysis in movement profiles; (providing information on fluency of movement), and integrated electromyography (iEMG) recordings; (providing information on muscular effort during a movement), to quantitatively assess the PD motor symptoms [30–36]. Spectral analysis have been employed in assessing PD tremor to quantify the characteristics of the tremor signal [33,34,36], torque-based measurements are being utilised to detect the degree of resistance in PD rigidity [35,37–40], kinematic analysis such as jerk (smoothness of a movement), which is the rate of change of acceleration, has been used to characterise movement quality related to bradykinesia [30,41,42], and iEMG recordings has been applied to detail the muscular activity during a task [30–36]. The application of these quantitative biomechanical methods to assess alterations in upper limb movement may provide useful insights into the underlying motor impairments of PD and provide further clinical evidence as to the benefits of targeting specific DBS sites.

Little is known about the function(s) of the ZI, with no published quantitative studies
examining its role in upper limb motor control. Therefore, the purpose of this series of studies is to quantify the effect of micro-lesioning and stimulation to the areas of and around the ZI; cZI and dZI on upper limb motor performance of participants with PD. This series of studies is part of an ongoing exploratory research stream at Sir Charles Gairdner Hospital (Perth, Western Australia, Australia) investigating the relationship between the PSA and movement symptoms and functional outcomes in PD participants. This study may provide the first insight into the function of the ZI with regard to the control of upper limb movements.

1.2 Statement of the problem

To date, quantitative studies in assessing the outcomes of stimulation to the PSA, specifically areas of and around the ZI, on upper limb motor function are lacking. In addition, there have been no published quantitative reports examining the acute outcomes of DBS on the three primary symptoms of PD: tremor, rigidity and bradykinesia. This research may have significant implications for improving the execution of various daily activities such as writing, dressing, drinking, etc. Through the use of discrete biomechanical assessment tools: spectral analysis, torque-based measurements, three-dimensional kinematic analysis of jerk, and the assessment of muscle activation via iEMG, we can begin to understand the role of the PSA in modulating movement through DBS, and upper limb symptoms and functions, and thus contribute to the understanding of cortical pathways and potential treatment for individuals with PD.

1.3 Thesis outline

The introduction and literature review provide context for the study and communicate the research problem and approach taken to answer the question. This introduction details a
brief synopsis of each study along with the specific aims and hypotheses. Following the literature review, this thesis is presented as a series of individual papers addressing ZI targeted PSA DBS in treating each of the three main motor symptoms exhibited in PD; tremor, rigidity and bradykinesia. At times the presentation of independent papers may seem repetitive; however it is felt that each paper should stand alone for ease of reading. The thesis is then concluded with a general discussion with an analysis of the research findings, conclusion, and future research.

1.3.1 Chapter Three: Study One

_The effect of acute posterior subthalamic area micro-lesioning and stimulation on upper limb tremor and activation patterns in Parkinson’s disease._

This study utilises a combination of spectral analysis and iEMG in tasks that elucidate resting and postural tremor, to quantify the differences between the PD group and matched healthy controls in the presentation of tremor symptoms. Secondly, the alterations in upper limb tremor following DBS and micro-lesioning to the PSA region where the ZI is located will be quantified using spectral analysis and iEMG.

The aims of this paper are to:

1. Determine the differences in spectral analysis and iEMG in the proximal and distal upper limb segments of PD participants in relation to healthy controls.
2. Investigate the acute effects of micro-lesioning and stimulation to the PSA where the cZI and dZI are located, and its outcome on tremor in the proximal and distal upper limb segments in the PD participants and its sub-groups.
It is hypothesised that:

1. PD participants will exhibit an altered spectral analysis and iEMG levels as compared to the healthy controls in all tasks.

2. Improvements in spectral analysis parameters and iEMG levels more representative of normative values are expected with micro-lesioning and stimulation to the areas of and around the cZI and dZI, in PD participants: specifically for the participants who underwent surgery to treat their tremor, compared to their pre-operative levels, in all segments and tasks.

**1.3.2 Chapter Four: Study Two**

*Outcome of elbow rigidity with posterior subthalamic deep brain stimulation in Parkinson’s disease.*

This study investigates the effect of acute ZI targeted PSA DBS on rigidity utilising a quantitative torque-based approach. Passive resistive torque and electromyography (EMG) data will be assessed at the elbow joint in participants with PD compared to healthy controls at two different passive isokinetic movement conditions and at two different speeds. Secondly, the alterations in upper limb rigidity and EMG activation will be assessed following DBS and micro-lesioning, with particular attention to the outcomes for the rigid-akinetic motor sub-group of PD.

The aims of this paper are to:

1. Determine the differences in rigidity and EMG of the elbow flexors and extensors of PD participants in relation to healthy controls.
2. Investigate the acute effects of micro-lesioning and stimulation to the PSA where the cZI and dZI are located, and its outcome on rigidity and EMG of the elbow flexors and extensors in the PD participants and its sub-groups.

It is hypothesised that:

1. PD participants will exhibit increased resistive torque and altered EMG levels as compared to healthy controls in all tasks and conditions.

2. Improvements: decrease, in resistive torque and EMG levels more representative of normative values are expected with micro-lesioning and stimulation to the areas of and around the cZI and dZI, in the PD sub-groups, particularly with the rigid akinetic participants, compared to their pre-operative levels, in all tasks and conditions.

1.3.3 Chapter Five: Study Three

Effects of posterior subthalamic area micro-lesioning and stimulation on upper limb bradykinesia and action tremor in Parkinson’s disease.

This study utilises three-dimensional kinematic jerk analysis and iEMG in functional tasks, to quantify the differences between the PD group and matched healthy controls in the presentation of bradykinesia and action tremor. Secondly, the alterations in upper limb bradykinesia and action tremor following DBS and micro-lesioning to the PSA region where the ZI is located will be quantified using three-dimensional kinematic jerk analysis and iEMG.
The aims of this paper are to:

1. Determine the differences in bradykinesia, as assessed by jerk measurements and iEMG, of PD participants in the tapping and pointing tasks, in relation to healthy controls.

2. Investigate the acute effects of micro-lesioning and stimulation to the PSA where the cZI and dZI are located, and its outcome on bradykinesia, as assessed by the jerk measurements and iEMG, in the PD participants and its sub-groups in functional upper limb tasks.

It is hypothesised that:

1. PD participants will exhibit increased jerk measurements and altered iEMG levels as compared to the healthy controls in all tasks.

2. Improvements in jerk measurements and iEMG levels more representative of normative values are expected with micro-lesioning and stimulation to the areas of and around the cZI and dZI, in PD participants and its sub-groups compared to their pre-operative levels, in all tasks.

1.4 Significance of this research

As there have been no similar reports on the acute effects of ZI targeted PSA stimulation on tremor control, rigidity and bradykinesia, this research will contribute to our understanding of the role of the PSA in neuromuscular control in PD, and how it may contribute to overall movement execution. In addition, this is the first PSA DBS study to quantitatively determine the acute clinical outcomes of patients following DBS utilising biomechanical tools; spectral analysis, resistive torque, jerk measurements and iEMG. By investigating the outcome of acute ZI targeted PSA DBS through quantitative measures,
this research hopes to uncover mechanisms underlying acute stimulation effects. As PD is characterised by debilitating motor impairments that differentially affect individual patients, this data may assist clinicians and/or specialists to identify individuals who are like to be the best responders to this novel DBS target site for the management of upper limb motor symptoms, improving the efficacy of clinical management, and outcomes for patients with PD.

1.5 Limitations

This study is limited with regards to the sub-groups of PD participants involved. The small number of participants classified within the tremor-predominant and rigid akinetic PD sub-groups decreases the generalisability of the results. Furthermore, the acute outcome of DBS may not necessarily reflect the longer term outcome of a patient as a result of the diminishing effect of micro-lesioning and increased influence of chronic stimulation [43].

1.6 Delimitations

This study will be delimited due to the quantitative nature of the assessment protocols, many of which can only be conducted in laboratory setting and/or require specialised equipment including; three-dimensional analysis, electromyography measurements, and passive isokinetic resistive torque assessments. Additionally, investigating the acute outcome of DBS would ensure reliability and validity of the micro-lesioning effect and reduces the influence of: any possible neuro-plasticity effect due long term adaptation of DBS, altered medication intake, changes in dietary patterns, and lifestyle modification of the PD participants.
References


CHAPTER TWO

REVIEW OF THE LITERATURE
This literature review commences with an initial outline of the definition and epidemiology of Parkinson’s disease, the pathophysiology of the disease along with its three main motor symptoms are discussed. As these symptoms are often exhibited in the upper limb, this review focuses on impairments at the upper limb segments. In this section of the review, the need for quantitative assessments of Parkinson’s disease symptoms is further examined, with particular reference to biomechanical techniques to quantify tremor, rigidity and bradykinesia. This is then followed by a discussion of the history of treatment, the drawbacks of past surgical techniques and medication, and deep brain stimulation as a promising intervention. With the objective of alleviating the negative motor symptoms of this disease, the literature on the benefits, side-effects, neurophysiology, and optimal stimulation sites of deep brain stimulation are reviewed. Subsequently, the posterior subthalamic area, specifically the zona incerta as an alternative target site for stimulation are then appraised. Finally, important considerations and future research possibilities in PSA DBS for Parkinson’s disease, and its implications on the management of PD symptoms, and its influence on the cortical pathways of the brain are addressed.

2.1 What is Parkinson’s disease?

Parkinson’s disease (PD) is a neuro-degenerative disorder which is distinguished by progressively increasing motor and non-motor symptoms [1–4]. It is thought to affect at least one out of 100 individuals over the age of 60, which equates to 0.3 % of the entire industrialised population [4–7]. Early onset of PD is uncommon, although approximately one out of 100,000 individuals diagnosed are under 40 years of age [8]. With an aging population, the demand of PD on healthcare is growing at a tremendous rate, the population of patients with PD worldwide has been predicted to increase from 10 million
in the year 2000 to 40 million in 2020 [9]. Figure 2.1 illustrates the incidence of the PD population across the world [5]. Examining the demographics, the incidence of PD in European countries has been reported to increase dramatically from 60 years of age while China has the lowest reported rate (per 100,000) of PD and incidence appears uniform with age (Figure 2.1). Lau and Breter (2006) highlighted that the evidence to elucidate the difference of incidence of PD in these countries remains inconclusive [5].

![Incidence rate (cases per 100,000 person-years)](image)

Figure 2.1. Adapted from de Lau and Breteler, 2006. Illustrates the incidence of PD across different countries [5].

Individuals with PD experience debilitating motor symptoms such as tremor, rigidity, bradykinesia, postural instability and gait alterations, and also non-motor symptoms such as depression, cognitive declines and visual dysfunctions [6,7,10–17]. Weintraub and colleagues (2008) compiled reports which stated that 70-90% of individuals with PD will exhibit some form of tremor, more than 90% experience rigidity, and 80-90% exhibit bradykinesia [18]. With regards to the non-motor symptoms, depression, altered mood states and cognitive declines are reported to be present in up to 50% of the total PD
population while problems related to vision are reported in more than 70% of the PD population [6,16–18]. Much of the research and assessment in PD has concentrated on the motor symptoms due to its relatively large prevalence, and negative impact on functioning [6,7,10–17].

### 2.2 Pathophysiology of PD

Possible risk factors have been listed to include familial history, and environmental exposure to toxins such as heavy metals and pesticides [5]. That being said, the mechanism(s) of action that are responsible for the negative motor and non-motor outcomes are still unclear. At this point, only assumptions can be made, mostly through extrapolation of the basal ganglia (BG) system from animal models to explain the motor symptoms [19,20]. As such, this literature review will focus on the abnormalities of the BG system and its proposed contribution to the motor symptoms exhibited in PD.

The BG system comprise of the striatum, the global pallidus (external and internal), the subthalamic nucleus (STN), the nucleus accumbens, and the substantia nigra; pars reticula and pars compacta [21–23]. Along with the thalamus and cortex, this system has been proposed to influence the motor, associative and limbic aspects of processing [20]. The manifestation of PD is widely stated to be the result of a greatly reduced activity of dopamine-secreting cells within the substantia nigra and striatum, which then propagates to affect the activity of neurons throughout the BG system [19,23,18]. A review by Bergman and Deuschl (2002), and a study by Burn and colleagues (2006) concluded that due to the complexity of PD and the heterogeneity of its symptomatology, it is possible that several different models may be required to explain the manifestation of the motor symptoms [1,19]. It is imperative to note that an individual’s motor symptoms are not
necessarily generated by the same neural mechanisms [24,25]. In most PD cases, these motor symptoms present as tremor, rigidity and bradykinesia, and are typically displayed in the upper limb [18,26,27]. Furthermore, an individual with PD can present with all of these motor symptoms or as singular predominant symptom i.e. tremor-predominant or rigid akinetic [1–4].

### 2.3 Parkinsonian tremor

A symptom commonly presented in PD is neurological tremor. It is defined as an involuntary-rhythmic movement which is the result of rapid alternating contraction and relaxation of the agonist and antagonist muscles due to disorder(s) of the central nervous system [10,11,28]. This type of tremor, depending on its presentation, is described as (i) rest, (ii) postural, and/or (iii) action tremor [29]. Rest tremor is apparent with the upper limb is at rest, postural tremor is usually exhibited when the limb is maintained against gravity, and action tremor is elucidated during a voluntary movement of the limb [28]. The most prominent form of neurological tremor appearing in PD is resting tremor, although postural and action tremor are also present in some cases [11,27,28,30–33].

Clinically, tremor in PD is quantified through clinical rating scales such as the Unified Parkinson's Disease Rating Scale (UPDRS) [34], although it could be argued that this assessment limits the quantification of tremor due to the complexity of the symptom [35–37]. Grimaldi and Manto (2008) summarises that semi-quantitative clinical scales, such as the UPDRS, can be subjective, present only the short-term information of the condition, and the assessment is not correlated with the mean amplitude of the tremor [35]. As such, researchers have utilised several quantitative biomechanical and signal processing techniques to monitor and analyse tremor [28,33,35,38]. Early work in tremor
assessment focused on kinematic analysis through the use of video recordings [39,40]. This form of analysis has been effective in quantifying tremor in a clinical setting and is usually performed by placing a passive marker on the limb of interest and tracking it frame-by-frame [39,40]. However, this method can be time consuming and less accurate as compared to accelerometers and gyroscopes [28]. Accelerometers and gyroscopes measure the acceleration and angular velocity of a sensor and are commonly used to measure oscillations (i.e. tremor) of a body segment due to its simplicity and cost (inexpensive) [28,33]. Despite the advantages of utilising accelerometers and gyroscopes, the amount of unwanted signals (noise) that may interfere with the original signal (i.e. tremor oscillations) can be quite high [28,33]. The use of optoelectric devices in motion analysis have been widely utilised in the last decade [28,41]. This form of analysis is usually performed through tracking (infra-red cameras) passive (retro-reflective) markers which are affixed to the limb/segment of interest [28]. Although highly accurate, this form of analysis is time consuming, requires highly specialised equipment and is costly [28]. Nevertheless, the advantages of optoelectric devices include; highly accurate measurements of trajectory due to high frequency frame rates for data acquisition; and it allows for multi-segment recordings [28]. Another popular method used to quantify tremor is through surface electromyography (EMG) recordings [28,38,42]. This form of measurement provides information on the activity of the underlying muscle through analysis of the electrical signals which cannot be obtained through the use of the previously mentioned sensors: video recordings, accelerometers, gyroscopes, etc. [28,43]. Surface EMG recordings are highly accurate, although EMG recording devices are costly and requires a degree of knowledge to operate [28]. The data collected through the use of accelerometers, gyroscopes, optoelectric devices, and surface EMG allows for complex analysis of the tremor signal through the use of signal processing methods such as the spectral analysis [28,33,35].
Grimaldi and Manto (2008) outlined that tremor is composed of deterministic (non-random) and stochastic (random) components [35]. The use of surface EMG measurements and signal processing methods such as the spectral analysis and entropy analysis are required to interpret time-series data of nonlinear systems such as PD tremor, in which the frequency content of the signal provides a plethora of information which cannot be obtained through qualitative or semi-quantitative analysis [35,38]. Quantitative reports utilising EMG measurements have found tremor in PD to be of an alternating firing pattern with a high amplitude burst [11,28,33,35,38]. Figure 2.2 illustrates the severity of PD tremor particularly in the resting task (limb supported against gravity) and an action task (when the limb approached a target) compared to other pathologies [38]. The tremor at rest and during an action task (intention) in PD have been shown to have the highest amplitude as compared to the other pathologies, indicative on a higher degree of movement dysfunction during these tasks (Figure 2.2). In terms of postural tremor, PD has the third largest amplitude next to rubral and essential tremor (Figure 2.2).

Figure 2.2. Adapted from Milanov, 2001. Illustrates the amplitude of tremor EMG in different pathologies [38].
With regards to spectral analysis, the mathematical calculation; fast Fourier transformation, gives information about the characteristic of a signal i.e. peak frequency, peak amplitude, and has been a popular method used to quantify biomedical tremor data [33,44,45]. It has been well established that tremor spectra in PD typically range from 3-8 Hz for resting tremor, 4-12 Hz for postural tremor, and 2-7 Hz for action tremor, and is usually of a higher peak amplitude as compared to the healthy population [11,28,33,35,46]. The altered characteristics of EMG activity and of the spectral analysis parameters is suggestive of a BG disorder as investigations in patients with lesioning in areas of the BG, have reported the presence of varying degrees of tremor [28,47].

The cause of tremor (tremorgenesis) is still unclear though it has been proposed to be a result of a disruption in afferent or efferent pathways in the cerebellum, and/or BG [33,35,46,48]. It is understood that they are vital regions in the brain responsible for tremorgenesis. These regions play a crucial role in influencing several neural loops involved in the control of voluntary movement [33]. Examples on these neural loops include the loop between the motor cortex and the BG, and the loop between the cerebellum, the thalamic nuclei and the motor cortex [33]. Manto et al. (2009) stated that tremor is exhibited in patients with lesioning towards the cerebellar region or the BG, indicative of an interruption of the basal ganglia-thalamo-cortical or cerebello-thalamocortical neural loops [33,36]. Hallett (2014) describes tremorgenesis via a background understanding of the neuro-motor system and its role to control the position of the body segments [48]. The author explains that the positioning of a body segment is controlled by a motor command which requires on-going afferent feedback which checks against the original signal, in an ongoing process of movement correction and control. The interaction between the original command and afferent feedback information may
get complicated due to a delay in the time taken to process the feedback, and as such, this process becomes unstable and often oscillatory [48].

In a healthy BG circuit, the networks are known to possess properties which support the control of movement but do not produce tremor oscillations unlike, the BG circuits in PD [46]. This neural activity has been observed through analysing the tremor frequency band correlated with the tremor movement or tremor EMG activity [46,49]. With ongoing research investigating neuronal profiles through spectral analysis and EMG measurements, and interventions that alter these profiles, we will have a clearer understanding on tremor in PD.

2.4 Rigidity

Another symptom widely exhibited in PD is rigidity, defined as the increased resistance of a limb to passive movement [13,50,51]. A distinctive characteristic of rigidity in PD is displayed as a ‘cog-wheel’ type jerk in which the muscle contracts when passively stretched [13,51]. As a result, efforts to move the limb actively or passively, can result in a decrease in movement speed and fluency, and delayed initiation of movement, which combine to make deliberate tasks difficult [51,52]. This presentation of rigidity in PD is often observed more so in the extension phase of a movement and is exacerbated with concurrent contra-lateral limb movement e.g. the resistance of the right limb increases when the left limb is performing a task such as picking up a cup or writing [13,53–56]. Furthermore, individuals who present this symptom may experience pain as well as stiffness due to the hyperactivity of muscular contractions to resist movement [57].
Like tremor, the origin of PD rigidity is still uncertain. Evidence in the literature suggests that the primary influence of PD rigidity is attributed to the neural and non-neural mechanisms operating in parallel [12,51,52,58–61]. The neural components are attributed to the altered muscle activation patterns and/or prolongation of muscle stretch reflexes [12,51,52,58–61]. Studies have reported that the neural mechanism to be the result of an impairment of dopamine dependant structures in the brain [62–66]. This impairment propagates to affect spinal neural activity, altering the function of the agonist and antagonist muscles, which leads to an increased latency in the stretch reflex; whereby muscle continues to provide resistance when stretched, and shortening reaction cycle of a muscle; whereby muscle continues to contract even when passively stretched, thus producing rigidity [62–66].

With regards to the non-neural mechanisms; the change in mechanical properties of the muscle itself, a study by Dietz and colleagues (1981) found greater tibialis anterior EMG activity during the swing phase of a gait as compared to healthy controls, although strength and the EMG patterning of the triceps surae was similar [67]. They postulated that PD rigidity cannot simply be a result of just the neural components as there was limited co-contraction between the tibialis anterior and the triceps surae, concluding rigidity was also a result of changes in the properties of the muscles themselves [67]. This is supported by Watts and colleagues (1986) who reported increased stiffness of the elbow joint in the PD participants during a relaxed state as compared to healthy controls, with no differences in EMG activation [68]. Therefore, it has been suggested that PD rigidity is the result of a combination of both neural and non-neural factors possibly due to an impaired dopaminergic system [12,51,52,58–61]. It is important to note that the main motor symptoms of PD are not necessarily produced by the same neuronal mechanisms;
the manifestation of rigidity is understood to be a dissimilar to tremor as tremor has been found not to dependant on dopaminergic influence [24,25,46,69].

The UPDRS is a widely used clinical tool to assess both upper and lower limb rigidity in PD whereby an assessor perceives the degree of resistance when passively moving the patient’s limb through range of motion and rates the resistance experienced from zero to four [34]. Though widely utilised, the semi-quantitative nature of the UPDRS provides limited assessment of the PD symptoms [70–73]. Consequently some researchers assert that the measurement of rigidity requires a continuous scalar estimates rather than a bounded-ordinal scale such as the UPDRS [74,75]. Thus, contemporary research has placed importance on objectively quantifying PD rigidity through measuring the resistance to externally generated passive movement about the joint of interest [13,53,54,61,75]. Early studies to objectively quantify PD rigidity focused on using only a torque motor to measure the passive resistance of the joint on interest, however, this form of assessment does not provide information on the contribution of the neural mechanisms in rigidity: co-contraction of the muscles [53,54,68]. Recent studies have combined the use of resistive torque (rotational force about a joint) based approaches and EMG measurements during a passive motion in efforts to assess both the neural and non-neural components of rigidity [13,53,54,61,75]. It is reported that an increase in resistive torque; the rotational force about a joint, and altered EMG activity; increased activation of the antagonist muscle(s), are present in individuals with PD compared to healthy controls when the limb of interest is passively moved through joint range of motion, indicative of an enhanced level of rigidity [13,53,54,61,75]. The implementation of a resistive torque-based approach and EMG measurements in quantifying PD rigidity, provides a clearer understanding on the contribution of the neural and non-neural components. The quantitative aspect of these assessments means that potential intra- and
inter-rater variability can be reduced and may help clinicians select an appropriate intervention to treat this symptom in patients with PD [13,53,54,61,75].

2.5 Bradykinesia

While tremor and rigidity are common symptoms of PD, the most disabling motor symptom, as reported by patients, is bradykinesia [18]. It is characterised by the delayed initiation of movement, slowness in the execution of movement, and an impaired ability to perform simultaneous or sequential movement due to insufficient muscle fibre recruitment [14,18,76,77]. Bradykinesia is commonly thought of as a symptom primarily associated with gait, although this is not the case, as it is also highly prevalent in the upper limb [18]. Individuals with bradykinesia find it extremely difficult to perform functional tasks and daily activities that require repetitive or sequenced movements such as pointing, finger tapping, object manipulation, and drinking a glass of water [77,78]. Moreover, it is not uncommon for an individual with PD bradykinesia to have other overlapping PD symptoms, specifically resting and action tremor, further depleting the fluency of movement [14,23]. Movement studies in bradykinesia have found this symptom to be more pronounced when the complexity of the task is increased either by introducing additional tasks or by repeating the movement [14,76].

Traditionally, bradykinesia is clinically appraised through semi-quantitative scales such as the UPDRS [34]. The UPDRS is a very useful assessment in the classification and categorisation of the motor symptoms experienced by patients with PD. However, as the classification is categorical in nature, its use as an outcome measure to quantify change following intervention and characterisation of the symptom itself is somewhat limited. Similar to the assessment of tremor, quantitative assessments such as kinematic analysis
and EMG activity have been utilised by researchers to complement the traditional clinical scales in efforts to explain bradykinesia in greater detail [31,77,79–87]. Dai and Angelo (2013) reviewed studies which have used accelerometers and gyroscopes to quantify bradykinesia in PD and found a high level of success in measuring the movement patterns [37]. However, as reviewed earlier in the tremor section, the amount of unwanted signals (noise) that may interfere with the original signal through the use of accelerometers and gyroscopes can be quite high [28,33]. Performing tasks adopted from the UPDRS such as finger tapping, researchers have employed touch sensitive recording devices in efforts to quantify bradykinesia [88,89]. These touch devices while easy to use, can be costly and the output of which has not been found to be valid when compared to the UPDRS [90]. Poizner et al. (1998) determined the characteristics of PD bradykinesia through the use of three-dimensional motion analysis in functional pointing tasks [81]. Their use of three-dimensional analysis allowed them to investigate important variables in the examination of bradykinesia such as movement time, task accuracy, movement kinematics, and joint coordination patterns with a high level of accuracy [81]. Similar to quantitative assessments in tremor and rigidity, EMG recordings are a widely used tool employed by researchers and clinicians to acquire information on the characteristics of bradykinesia [14,28,31].

Through quantitative assessments, it has been postulated that individuals with bradykinesia exhibit fragmented kinematic profiles (i.e. increased jerk values), increased variability between trials, and increased duration of task completion, due to a disruption of the sequencing between agonist and antagonist muscles [77,79–81,83–86]. A typical kinematic profile of a pointing task between an individual with PD compared to a healthy control is illustrated in Figure 2.3 [81]. Note the smoothness of the trajectories (jerk) degrading and the increased trial-to-trial variability in the PD participant (Figure 2.3).
Jerk, which is the rate of change of acceleration, is a valid profile to quantify bradykinesia as it provides information on the smoothness of the trajectory of movement, which have been found to be affected in individuals with PD [80,91,92]. With regards to the EMG profiles, an altered EMG activity displayed by a fractionated pattern between the agonist and antagonist, reduced amplitude of agonist and antagonist, and shorter burst durations of the agonist muscles are commonly displayed in individuals with bradykinesia [31,82,87]. The alterations in muscular activation such as a reduced amplitude is a clear indication of a reduced force production in the muscles thereby increasing the time it takes to perform voluntary tasks [31,82,87]. The presence of a fractionated pattern between the agonist-antagonist muscles could also indicate the presence of other underlying symptoms such as action tremor, which contributes in reducing the fluency of the movement [31,82,87].

Figure 2.3. Adapted from Poizner et al., 1998. Trajectory paths to each of the five target (dark spheres as end points) in a pointing task represented by a healthy control and a PD participant [81].

The functional and physiological changes associated with the emergence of bradykinesia is not well understood, with some studies arguing a disruption in the BG system to be the
cause [14, 23, 76]. In their review of bradykinesia in PD, Berardelli and colleagues (2001) highlighted that investigations through metabolic imaging studies found a reduced level of activation in areas of the brain, particularly the anterior supplementary motor area, BG and thalamus in individuals with PD as compared to healthy controls [14]. Moroney and colleagues (2008) stated that bradykinesia is a result of inhibition of the thalamus by the globus pallidus interna (GPi) [76]. This inhibition is believed to be a consequence of a degeneration of dopaminergic neurons in the substantia nigra pars compacta which affects the function of critical cortical pathways in the brain [76]. Other studies have proposed bradykinesia to be a result of a synchronisation of voluntary movement pattern with pathological generators such as PD tremor [93, 94]. Carboncini et al. (2001) supported these findings when they reported the presence of action tremor when PD participants performed a movement task [31]. Further research is warranted to shed more light on the pathophysiology of bradykinesia.

2.6 History of treatment and interventions

The amalgamation of these motor symptoms impairs movement and thus can have a significant negative influence on the quality of life of individuals with PD. As PD is a progressive disease, symptoms worsen over time, consequently severely compromising the individual’s ability to perform motor skills, in turn predisposing them to injury and/or abandonment of social/physical activities [7, 80, 95–97]. As a result, the majority of therapeutic, pharmacological and surgical interventions aim to improve the associated motor impairments. The section below reviews the history of PD treatment from the early 1950s as one of the foci of this literature review is to addresses recent investigations in functional neurosurgery. As the PD symptoms: tremor, rigidity and bradykinesia, are
usually presented in the upper limb [18,26,27], the subsequent sections will aim to cover interventions relevant to upper limb therapy.

### 2.6.1 Ablative surgery

In the early 1950s, an accident forced neurosurgeon Irving Cooper (1953) to ligate the anterior choroidal artery of a PD patient, and found a reduction in tremor and rigidity symptoms when the patient awoke [98]. As a result of Cooper’s (1953) findings, the GPi was made the prime target for surgery to alleviate the symptoms in PD. Following this, lesioning, through a process called thermocoagulation; destruction of cell structures, targeted at the GPi and the thalamus with the use of stereotactic apparatus, was the primary surgical intervention to relieve PD symptoms [2,99]. Despite the success in relieving the symptoms in PD, lesioning/ablative surgery was associated with high morbidity and mortality rates [2,100,101]. In addition, the accompanying risks; facial palsy, dysphagia, and cognitive deficits, with this surgery has been reported to be significant [101].

### 2.6.2 Medication

The first well established pharmacological treatment for PD came in the early 19th century and it was in the form of belladonna alkaloids, which are thought to affect the dopaminergic balance in the striatum thereby improving the symptoms in PD [2]. In 1910, Barger and Ewens were the first to synthesise dopamine though its efficacy as a treatment for PD was not established, as at the time it was only known to be a compound for the synthesis of other catecholamines [102]. It was not until the late 1950s, through the discovery of dopamine localisation in the brain, that scientists developed the model of Parkinsonism and how it could be reversed through dopaminergic drug interventions [2].
A widespread use of a dopaminergic drug therapy emerged in the 1960s to supersede ablative surgery due to its associated risks and mortality rates [100,101,103–105]. Levodopa (L-Dopa) has been the most effective form of drug treatment and continues to be the most commonly used medication in PD today [106,107]. The efficacy of L-Dopa have been supported by studies which found improvements in upper limb mobility, rigidity and bradykinesia improvements [55,82,106,108–110]. Powell and colleagues (2011) reported a reduction in resistive torque during a flexion-extension motion at the elbow with L-Dopa use, indicative of a decreased rigidity [55]. Another study investigating the use of L-Dopa found increased movement speeds and improvements in EMG agonist-antagonist firing rate which is suggestive of a decrease in bradykinesia [82]. This improvement in bradykinesia was supported by Pötter-Nerger and colleagues (2009) who reported improvements in tapping scores both in proximal (tasks performed by moving the arm at the elbow and shoulder) and distal (tasks performed by moving only the index finger) segments of the limb [110]. Increased performance in functional tasks was also observed when Tucha et al. (2006) compared the kinematic aspect of handwriting movements in the same PD patients with and without L-Dopa use [109].

Unfortunately, the treatment of PD with L-Dopa is not without side-effects, as patients reported early negative outcomes such as ON-OFF fluctuations, dyskinesia, and subsequently behavioural disorders, cognitive impairments, orthostasis, and lethargy [111,112]. In addition, since PD is a progressive disorder, individuals often develop a tolerance to initial drug administration leading to increases in dosage [103,111,113]. Furthermore, individuals with PD tremor may not respond to medication such as L-Dopa as its pathophysiology is not the result of a decline in dopamine production [114]. In efforts to reduce the negative outcomes of medication, or decreased response to medication, and provide a favourable intervention for people with tremor predominant
PD, a surgical option called deep brain stimulation (DBS) has been advanced to treat the PD motor symptoms [111,115].

2.6.3 Deep brain stimulation

In the early 1990s, the neuro-surgical technique called DBS directed to functional BG targets in humans was observed to replace modern lesioning treatments such as thalamotomy and pallidotomy, and assist in reducing the dependence of medication, ON-OFF fluctuations, and dyskinesia [116]. This became widely available in Australia in the late 1990s, and in the United States of America in 2000s. In addition, individuals with PD tremor who may not respond to medication such as L-Dopa found DBS to be a promising solution to mitigate their tremor symptoms [114]. DBS involves the delivery of electrical signals through chronically implanted electrodes to specific nuclei of the brain [111,116]. These electrodes emit electrical stimulation through an implanted pacemaker/pulse generator which has programmable functions to alter the frequency, amplitude and pulse width of the administered stimulation [7,111,116]. It was Benabid et al. (1991) who first reported the application of long-term DBS through combining the implantable pacemaker technology with chronically implanted electrodes for STN DBS [117]. Subsequently, the work by Benabid et al. (1991) and Sellal et al. (1993) led to the widespread use of long-term DBS (i.e. throughout the patient’s life) to treat the motor symptoms in PD [111]. This surgical technique, through the use of modern stereotactic headframes and sophisticated neuro-imaging computer programs, has given neurosurgeons the ability to plan and target specific brain structures with a high level of accuracy [118,119].
2.6.3.1 Benefits, indications, contraindications, and side-effects of DBS surgery

Reports of the benefits of DBS includes improved motor performances through the suppression of tremor, reduced rigidity, and smooth motor fluctuations in response to medication, all of which contributes to improvements in performing activities of daily living, thus enhancement in the overall quality of life [114,120]. Furthermore, unlike traditional lesioning, DBS is known to be a “reversible” intervention [101,116,121] as the micro-lesioning effect of the surgery has been reported to fade within eight to 12 weeks [122]. Nevertheless, not all individuals with PD are candidates for DBS surgery. The indications for DBS surgery include; (i) individuals with persistent motor fluctuations and dyskinesia: involuntary movement with optimised medical therapy; (ii) individuals exhibiting medication-refractory tremor; and (iii) individuals who are responders to medical therapy though intolerable to its side-effects [114]. The contraindications for DBS surgery include; (i) individuals with significant surgical co-morbidities (i.e. severe heart disease); (ii) individuals with cognitive dysfunction and/or psychiatric disease (overlapping symptoms may complicate the surgical process); (iii) individuals with advanced dementia; and (iv) individuals with a limited life expectancy (as a result of the increased risk of surgery due to decreased metabolic functions) [114]. The most commonly reported side-effects with DBS surgery are due to post-operative wound or hardware infections: up to 2% of cases [120]. An important factor to note with regards to the potential side-effect of DBS, is the residual effect of stimulating surrounding structures. Furthermore, it has also been documented that DBS can induce negative side-effects such as cognitive impairments and mood disorders due to medication reduction after surgery [123–126].
2.6.3.2 Neurophysiology of DBS

Despite considerable research, the neurophysiology and mechanism of action of DBS is still somewhat unclear in terms of motor symptom control. No single mechanism has been identified that accounts for its effect on motor outcomes [111]. Clinical and experimental evidence suggest that the stimulation frequency plays a very important role in the effectiveness of DBS [121,127–131]. A temporary lesion-like effect is exhibited with high-frequency stimulation compared to low-frequency stimulation [121,127–131]. Neuronal oscillations have been reported to influence a range of processes and movement in the body [132]. Hutchison and Dostrovsky (2004) showed that the beta oscillations bands (11 – 30 Hz) are associated with akinesia (disrupted voluntary movement), while gamma bands (> 70 Hz) are considered prokinetic (do not disrupt voluntary movement) [132]. Oscillations in the beta bands are pronounced in PD, and are thought to override voluntary motor gamma band signals, leading to poverty of coordinated movement [21,132–135].

Low-frequency DBS (<10 Hz) has been hypothesised to excite neuronal action potentials, in contrast to the suppression seen with high-frequency DBS [21,128,130]. Brown and colleagues (2003, 2009, 2012) proposed that high frequency DBS (>50 Hz) disrupts and decreases the beta bands while enhancing the gamma bands, leading to improvements in motor performance by alleviating the negative symptoms [21,134,135]. This work is further supported by Bronte-Stewart et al. (2009) which found a prolonged attenuation of the beta bands with STN DBS [133]. However, Carlson et al. (2010) disputed the concept of beta band attenuation and proposed that DBS operates through white matter activation by normalising the pathological activity in the basal ganglia-thalamocortical network.
This beta oscillation theory was also challenged by Gradinaru et al. (2009) who reported that the mechanism of high-frequency DBS may also be attributed to axon tract modulation rather than just the suppression of signals [137]. Other researchers have postulated that high-frequency DBS acts to; (i) jam the neuronal signals by inactivating ion channels [127]; (ii) block information by imposing an efferent stimulus pattern [129,138]; (iii) increase synaptic inhibition to the target of interest [139]; and (iv) synaptic depression by stimulation-induced neurotransmitter depletion [140]. The therapeutic effects of DBS are likely to be due to a combination of the above mechanisms. High-frequency DBS mimics lesioning clinically though it has the advantage of incremental adjustment and reversibility of neurological effects. Currently, the optimal high-frequency stimulation parameters are based on anecdotal evidence and experience of the medical team, as empirical evidence on which to base the selection of these parameters is lacking [141].

2.6.3.3 Optimal target site for DBS

The optimal brain structure of interest for DBS in PD is dependent on the clinical presentation of the patient. Deep brain stimulation of the STN, GPi, and ventral intermediate nucleus have all been reported to be highly effective in alleviating Parkinsonian motor symptoms [111,115]. Benabid et al. (1996) found tremor to be suppressed in the PD patients who underwent ventral intermediate nucleus DBS [142]. The ventral intermediate nucleus has been reported to the primary target site for DBS if the presentation of a pathology is only tremor stimulation [103,116,143,144]. Although highly effective for treating tremor in PD as well as tremor in other pathologies such as essential tremor, it has no effect on dopamine-mediated symptoms such as rigidity, bradykinesia, and dyskinesia. Moreover, it has no effect on individuals presenting ON-
OFF medication fluctuations (patients may switch from severe dyskinesia to immobility in a few minutes), thereby necessitating alternative target stimulation sites [103,116,143,144].

2.6.3.3.1 Globus pallidus internus

There is strong evidence in the literature supporting GPi for DBS surgery to treat the ongoing symptoms in PD, particularly for medication-induced dyskinesias [7,111,145–147]. Burchiel et al. (1999) found improvements in the total UPDRS scores and subscores of tremor, rigidity, and bradykinesia after a 12 month follow-up with GPi DBS in PD [148]. Anderson and colleagues (2005) reported improvements in rigidity and bradykinesia with GPi DBS in PD patients after a one year follow-up [145]. A five year follow-up study by Volkmann and colleagues (2004) revealed a significant reduction of dyskinesia in PD patients who had undergone GPi DBS as compared to their initial preoperative assessments [149]. Brown et al. (1999) stated that participants with GPi stimulation improved significantly on movement initiation and speed of movement execution in upper limb tasks [150]. In addition, they found EMG levels to improve with increasing amplitude during muscular contraction with GPi stimulation [150]. A study by Defebvre and colleagues (2002) on the affect GPi stimulation on the lower limb and trunk kinematics found motor improvements with stimulation compared to no stimulation [151]. Alberts et al. (2008) reported increases in maximum forces in the lower limb and grasping control in the upper limb with GPi DBS [152]. The manifestation of side-effects with GPi DBS are stated to be low with some reports of a decline in verbal fluency [149] and a case study of a patient with recurrent manic episodes [153].
2.6.3.3.2 Subthalamic nucleus

In the past decade, the STN has been the most preferred target site for treating the three principle symptoms of PD; tremor, rigidity and bradykinesia [7,103,111,116]. However, randomised controlled trials by Weaver et al. (2012) and Odekerken et al. (2013), reported that alterations in the primary motor outcomes for STN versus GPi DBS was not statistically different [154,155]. That being said, the majority of STN DBS studies have focused on manual dexterity and movements of the upper limb and unlike the GPi DBS evidence, there are a large number of quantitative studies in STN DBS.

Sturman and colleagues (2004) found that STN DBS reduced the EMG amplitude and increased EMG frequency during resting and postural tasks, reporting that the new EMG profile more closely resembled healthy normative levels [32]. Through the use of EMG measurements and accelerometers, Vaillancourt et al. (2004) reported that PD patients with STN stimulation combined with medication displayed reduced tremor, improved movement speed and muscle activation as compared to medication without stimulation [82]. Shapiro et al. (2007) objectively quantified the effects of STN DBS in PD rigidity through the use of torque-based approach and found improvements in resistive torque values [54]. The data of Rätsep and Asser (2011), further supports the efficacy of STN DBS in reducing PD rigidity through employing semi-quantitative assessments such as the UPDRS and quantitative assessment in the form of myotonometry; an assessment of the mechanical oscillations of the muscle [72]. Dafotakis and colleagues (2008) investigated the effects of STN DBS on proximal and distal upper limb segments in functional upper limb tasks, and found kinematic improvements with stimulation suggesting a reduction in bradykinesia [77]. Similarly, Samer et al. (2008) found a decline
in negative motor symptoms, particularly rigidity and bradykinesia, when they investigated the effects of STN DBS on motor tasks in 52 PD participants [156].

Despite much success in improving motor performance in PD, DBS of the STN has also been reported to produce negative outcomes [124,123,126,125,157,158]. A case study by Diederich, Alesch and Goetz (2000) reported a development of visual hallucinations in a patient when the DBS was turned on [123]. Berney and colleagues (2002) assessed 24 PD patients six months post DBS surgery and found a decline in mood state [124]. Deterioration of speech [158] and an impairment in working memory and cognitive control [126,159] have also found to be associated with STN DBS. A plausible explanation to the manifestation of negative outcomes can be attributed to the structure of the STN being stimulated [160]. Yelnik et al. (2007) explained that the STN is subdivided into three functional portions, namely; (i) limbic (anteriortly); (ii) associative (middle); and (iii) the sensorimotor (posteriorly) as illustrated in Figure 2.4 [160]. Electrode stimulation is intended to affect only the sensorimotor areas of the STN, however the signal spread and/or the inaccurate positioning of the electrodes may inadvertently stimulate the limbic and associative areas, which may contribute to the onset of neuropsychological and possibly psychiatric symptoms [120].

Figure 2.4. Adapted from Yelnik et al., 2007. Subdivisions of the STN [160]
2.7. The posterior subthalamic area

Several researchers have found an alternative target which lies in the posterior subthalamic area (PSA) to be a promising site in the treatment of PD [161–167]. Velasco et al. (2001) found that electrodes placed inferior to the ventral intermediate nucleus, just superior to the STN, resulted in evident tremor and rigidity reductions in 10 PD patients [161]. Hamel and colleagues (2003) implanted electrodes just posterior to the STN and found a marked reduction in tremor symptoms in the PD patients [168]. A 24-month follow-up study in eight PD patients by Kitagawa et al. (2005) found improvements in contralateral tremor (78.3%), contralateral rigidity (92.7%), and contralateral akinesia (65.7%), and handwriting with PSA DBS [163]. Plaha and colleagues (2006) found that electrodes implanted superior to the STN resulted in an improvement in performance; 76% reduction in UPDRS motor scores, in 35 PD patients without eliciting negative symptoms [164]. Following this work, Plaha, Khan and Gill (2008) continued investigating the effect of PSA DBS in PD and found a 94.8% improvement in resting tremor and 88.2% in postural tremor when the stimulator was turned on [165]. Khan et al. (2011) observed significant improvements in the motor symptoms; tremor (84.6%), rigidity (44.6%), and bradykinesia (46.2%) with PSA DBS [166]. The efficacy of PSA DBS in PD is further supported in a study by Blomstedt et al. (2012) who reported improved contralateral tremor (82.2%), rigidity (34.3%) and bradykinesia (26.7%) in several patients [167]. Outside of PD, studies have also found marked reductions in the variation of tremor, dysmetria and ataxia with PSA DBS [162,169,170].
2.8. The zona incerta

The common PSA structure stimulated in those studies was the area called the zona incerta (ZI) [161–167]. The ZI lies in the subthalamic region and is made up of heterogeneous collection of cells [171,172]. The location of the ZI, which is depicted as the orange dot in Figure 2.5, has been suggested by researchers to be a more effective target site for DBS surgery in the treatment of movement disorders such as PD [161–167]. The Kolmac and Mitrofanis (1998) study on rodents employed tracer injections to specific parts of the brain and found that the cells of the ZI distribute throughout the brainstem and may act as a relay to the higher command centres [173]. Since then, researchers have continued exploring possible connectivity pathways and suggestive functions of the ZI in rats [171,172].

Figure 2.5. Axial MRI slice of the Schaltenbrand & Wahren atlas on the locations of the STN (in blue) and ZI (in orange) [174].
Although the exact function(s) of the ZI in humans is still unclear, research on rodents proposed that the connections of the ZI neurons are extensive, with pathways projecting from the cerebral cortex to the spinal cord [171,172] (Figure 2.6). It has been proposed that the rat ZI is separated into four main functions; (i) visceral activity regulation; (ii) influencing sleep and arousal; (iii) orientative motor responses; and (iv) the maintenance of posture and gait [171]. In a study with rodents and primates, Watson et al. (2014) highlighted that the ZI lies in close proximity with major tracts and nuclei known to have an influence in automatic and/or stereotyped movement [172]. Previous studies have also proposed possible functions of the ZI including; Mogenson et al. (1985) who suggested that stimulation of the rat ZI resulted in the generation of locomotor activities and limbic-related movements [175]; Moschovakis (1996) provided evidence that the ZI in primates is involved in instigating head and eye movements [176]; Spencer et al. (1988) reported that arterial pressure and heart rate in rats decreased with ZI stimulation [177]; and Sherman and Guillery (2001) revealed that the ZI plays a role in altering the state of alertness and arousal [178].

Figure 2.6. Adapted from Mitrofanis, 2005. Location and proposed connections of the ZI in rats [171].
2.8.1 Important considerations and future research possibilities

It is important to recognise that the architecture of the ZI in rats differ from humans in regards to size and orientation. Although the architecture maybe different, the support of ZI targeted PSA DBS studies on tremor in humans have demonstrated positive clinical results, inferring that the human ZI may indeed have influences in motor control [161–167]. Note that the ZI alone may not be responsible for changes observed in the studies discussed above. Stimulating the ZI may also stimulate the radiation prelemniscalis area containing the dentato-thalamic fiber bundles, pallido-thalamic fibres and the dorsal and caudal areas of the STN. Depending on the amplitude of the electrical stimulation and accuracy of targeting the ZI, a change seen due to the stimulation to the areas of and around the ZI cannot be attributed only to the site but also to its adjacent structures. Moreover, most of the studies in ZI targeted PSA DBS in humans are based on semi-quantitative clinical evaluation of symptoms such as the UPDRS [161–167]. Although valid and reliable, it provides limited assessment as to the discrete alterations in the PD symptoms following intervention [36,37]. Importantly, there have been no studies that have quantitatively compared the effect of DBS on the different divisions of the ZI; caudal and dorsal. Research utilising quantitative measurements could help shed light on the role(s) of the ZI and the PSA in neuro-motor modulation and upper limb symptoms and functions, but more importantly assess its potential to alleviate specific motor symptoms that may be differentially stimulation-responsive in individuals with PD, so as to assist clinicians to more selectively select candidates for this particular DBS treatment site.

2.9. Summary

Parkinson’s disease is a neurological disorder with progressive motor symptoms, specifically tremor, rigidity and bradykinesia, which are commonly exhibited in the upper
limb, limiting activities of daily living, and impacting upon the quality of life of patients [1–4,18,26,27]. Interventions aiming to alleviate these motor symptoms have found DBS to be an effective treatment modality since its breakthrough in the 1990s [116]. Popular target stimulation sites such as the ventral intermediate nucleus, GPi, and the STN have been used to treat PD individuals with upper limb symptoms [103,116,143,144]. Although improvements are seen in the motor performances of those individuals, side-effects such as cognitive decline, manic disorders and deterioration of speech were also observed [123–126,149,153,157,158].

An alternative target site known as the ZI which is located in the PSA has been proposed by some researchers to be more efficacious with fewer side-effects, however the majority of the evidence supporting this is semi-quantitative [162,164,166,167,179,180]. As important, there have been no comparative investigations into the outcomes of the divisions of the ZI; caudal and dorsal in DBS for the treatment of the PD symptoms. Investigating the properties of the ZI and PSA through DBS may help explain its function and contribution to the neural control of upper limb movement and the neural network. The quantitative study of ZI targeted PSA DBS on the three main motor symptoms in PD may assist clinicians and/or specialists to identify individuals who are the best responders to these target sites; caudal or dorsal division of the ZI, for the management of specific symptoms [162,164,166,167,179,180].
References


CHAPTER THREE

STUDY ONE

The effect of acute posterior subthalamic area micro-lesioning and stimulation on upper limb tremor and activation patterns in Parkinson’s disease
Foreword

The first paper presented in this thesis aimed to investigate the outcome of zona incerta targeted posterior subthalamic area deep brain stimulation on one of the three main motor symptom of PD: tremor. The lack of quantitative assessments in this novel target site limits the information we have on the subtleties of change following surgery. Moreover, the comparative outcome of stimulation to the different divisions of the zona incerta on the sub-groups of Parkinson’s disease, specifically the tremor-predominant sub-group remains unknown. Whether differential stimulation of the divisions of the zona incerta have superiority over another is yet to be determined. It is intended that this paper will be submitted to the journal of ‘Parkinsonism & Related Disorders’.
Abstract

Background: Upper limb tremor is one of the hallmark symptoms in Parkinson’s disease (PD). Qualitative clinical studies report that deep brain stimulation (DBS) of the posterior subthalamic area (PSA), specifically targeting the zona incerta (ZI), is successful in alleviating PD tremor. Our study aimed to investigate the effects of ZI targeted PSA DBS on proximal and distal tremor through use of quantitative assessments.

Methods: Ten PD participants underwent biomechanical assessment then PSA DBS using the MRI-directed implantable guide tube technique. Five days later participants repeated the assessment under three randomised double-blinded conditions: micro-lesioning and high-frequency stimulation of two PSA sub-regions. Thirteen healthy matched controls were each assessed once.

Results: Trends were observed in the spectral analysis and electromyography activity between the pre-operative PD participants and healthy controls. A combination of PSA micro-lesioning and stimulation resulted in a general decrease (non-significant) in spectral analysis parameters and some normalisation of electromyography activity compared to PD baseline levels, particularly for the PD group who underwent surgery specifically to treat tremor.

Conclusion: Our study is the first to quantitatively report proximal and distal segment improvements associated with ZI DBS in resting and postural tremor for participants who underwent surgery for tremor control. This study provides further evidence that the ZI is a good DBS target site for the regulation of tremor and distinguishes its effectiveness on the sub-groups of PD. Future studies utilising additional signal processing methods could help explain the mechanism of action for motor improvements, particularly in patients with tremor predominant PD.

Abstract word count: 250
3.1 Introduction

Tremor is one of the hallmark symptoms in Parkinson’s disease (PD) and can be defined as the rhythmic involuntary shaking of a body part produced by alternating contractions of the agonist and antagonist muscles [1,2]. Upper limb tremor in PD is usually present during rest and occasionally when the limb is unsupported against gravity (postural tremor) [1,3]. To date, the exact pathophysiology of both resting and postural tremor remains to be explained. Hallett (2012) suggested that the pathophysiology of tremor is likely to be a combination of a disorder of both the basal ganglia system and the cerebellar circuits [4].

In most PD cases, the disabling tremor is usually exhibited in the upper limb and as such, can significantly impact upon activities of daily living, meaning that the physical and emotional burden of the disease is increased in these individuals [5,6]. This would include reduced motor performances in daily tasks such as reaching, grasping, and manipulation of objects (i.e. drinking from a cup) [5,6]. Individuals with PD tremor may not respond to medication such as levodopa and often seek surgical intervention to alleviate their symptoms. One option, deep brain stimulation (DBS), is a promising intervention for people with tremor predominant PD [7]. Deep brain stimulation of the posterior subthalamic area (PSA), specifically targeting areas of the zona incerta (ZI), has been a successful option to alleviate tremor in PD [8–15]. In their investigation, Hamel and colleagues (2003) targeted the dorsal division of the ZI (dZI) and found tremor to be reduced in the PD patients [15]. Plaha and colleagues (2006) proposed that the caudal division of the ZI (cZI) to be a more effective target for DBS to alleviate PD tremor [12]. Though much is unknown in the function of the human ZI, animal research has provided evidence that the divisions of the rat ZI receives afferent input from the basal ganglia output nuclei and also motor areas of the cortex, and sends efferent output to the basal
ganglia nuclei and the cortex, suggesting that the ZI has a role in the modulation of movement [16,17]. It has been hypothesised that the therapeutic benefits of ZI targeted PSA DBS [8–15] are a result of the ZI influencing the tremor signals through its vast projection within the brain, particularly with the basal ganglia [12]. However, there have been no comparative studies between the effect of cZI and dZI stimulation on PD tremor.

While the clinical outcome of ZI targeted PSA DBS studies report positive results [8–15], these studies utilised semi-quantitative clinical rating scales, such as the Unified Parkinson’s Disease Rating Scale (UPDRS). Although valid and reliable, it provides categorical assessment of the characteristics of the tremor [18,19], and therefore may not be sensitive to discrete alterations in tremor as a result of intervention. The use of quantitative assessments such as spectral analysis and electromyography activity has been effective in distinguishing pathological from physiological tremor due to the former’s deterministic and stochastic components [3,20–22]. In quantifying tremor data, spectral analysis is generally performed using the fast Fourier transformation in order to provide information about the characteristic of the tremor signal i.e. peak frequency and peak amplitude [3,20]. It has been well established that the spectral analysis of tremor in PD typically range from 3-8 Hz for resting tremor, 4-12 Hz for postural tremor, and is usually of a high amplitude [1,3,22,23]. With regards to the electromyography analysis, the use of integrated electromyography (iEMG); defined as the area under the curve, provides information about the muscular effort required to perform a particular task [24]. An increase in the spectral analysis parameters; peak frequency and peak amplitude, and altered iEMG activity are commonly reported in individuals with PD and is suggestive of a basal ganglia disorder [3,20,21]. Therefore, utilising these forms of quantitative assessments may help characterise PD tremor and uncover the subtleties of movement which may go undetected by semi-qualitative assessments.
We therefore seek to investigate the effects of ZI targeted PSA DBS on proximal and distal tremor in the upper limb during rest and in a postural task, through the use of spectral analysis [3,19,25] and iEMG activity [3,21] in participants with PD and compare this to healthy controls. Through targeting the ZI, the electrode lead will lie in an optimal position allowing the selection of stimulation to two sub-regions of the ZI, specifically the cZI and dZI [12,26]. Pre-operatively, we expect an increase in the spectral analysis and altered iEMG activity in PD participants compared to the healthy controls. We predict the spectral analysis and iEMG activity will move towards normative healthy control values with micro-lesioning. Further improvements are expected with stimulation to the areas of and around the cZI and dZI in PD participants, specifically for the tremor-predominant PD sub-group, compared to their pre-operative assessment levels at the proximal and distal segments and in both tremor inducing tasks.

3.2 Methods

3.2.1 Participants

Ten idiopathic PD participants (7 males, 3 females, age 40-70 years) recruited from the Sir Charles Gairdner Hospital (SCGH) neurosurgical clinic along with 13 healthy aged and gender matched controls participated in this study. Details of the PD participants are presented in Table 3.1. All participants were informed as to the nature of the study and a written consent was obtained (refer to Appendix 3 and 4). Ethical approval was granted by the SCGH ethics committee (2008-065 and 2012-039) and The University of Western Australia (UWA) (RA/4/1/5721) (refer to Appendix 1 and 2).
### Table 3.1: Parkinson’s disease participant characteristic and medication information.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Disease Duration (Years)</th>
<th>Predominant Symptom</th>
<th>Reason For Surgery</th>
<th>UPDRS: Tremor Score</th>
<th>UPDRS: Total Motor Scores</th>
<th>Medication(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD1</td>
<td>20</td>
<td>Rigidity</td>
<td>1, 2</td>
<td>0</td>
<td>21</td>
<td>L/C/E 150/37.5/200 mg (x7); L/B 100/25 mg (x3); A 100 mg (x2)</td>
</tr>
<tr>
<td>PD2</td>
<td>13</td>
<td>Rigidity</td>
<td>1, 2</td>
<td>1</td>
<td>30</td>
<td>L/B 250/50 mg (x5)</td>
</tr>
<tr>
<td>PD3</td>
<td>11</td>
<td>Rigidity</td>
<td>2, 1</td>
<td>0</td>
<td>10</td>
<td>L/C/E 150/37.5/200 mg (x6); P 1.5 mg (x1)</td>
</tr>
<tr>
<td>PD4</td>
<td>12</td>
<td>Tremor</td>
<td>3</td>
<td>9</td>
<td>11</td>
<td>L/C 250/25 mg (x4); P 4.5 mg (x1)</td>
</tr>
<tr>
<td>PD5</td>
<td>17</td>
<td>Classic</td>
<td>1, 2</td>
<td>0</td>
<td>3</td>
<td>R 16mg; E 200 mg (x6); L/C 250/25 mg (x4); L/C 250/25 mg (x0.5); L/C 100/25 mg (x6); L/C 200/50 mg (x1)</td>
</tr>
<tr>
<td>PD6</td>
<td>6</td>
<td>Tremor</td>
<td>3</td>
<td>18</td>
<td>39</td>
<td>No medication</td>
</tr>
<tr>
<td>PD7</td>
<td>12</td>
<td>Rigidity</td>
<td>1, 2</td>
<td>0</td>
<td>6</td>
<td>L/C/E 50/12.5/200 mg (x1); L/B 200/50 mg (x1); A 100 mg (x3); L/C/E 200/50/200 mg (x3); L/C/E 150/37.5/200 mg (x1); L/B 50/12.5 mg (x2)</td>
</tr>
<tr>
<td>PD8</td>
<td>8</td>
<td>Classic</td>
<td>3</td>
<td>8</td>
<td>13</td>
<td>L/B 200/50 mg (x6-7); BH 2 mg (x3)</td>
</tr>
<tr>
<td>PD9</td>
<td>7</td>
<td>Classic</td>
<td>1, 2</td>
<td>0</td>
<td>3</td>
<td>L/C/E 200/50/200 mg (x5); P 0.75 mg (x1); L/B 100/25 mg (x3); L/B 100/25 mg Slow release (x1)</td>
</tr>
<tr>
<td>PD10</td>
<td>4.5</td>
<td>Tremor</td>
<td>3</td>
<td>12</td>
<td>41</td>
<td>No medication</td>
</tr>
</tbody>
</table>

\(^*\) A – Amantadine hydrochloride, B – Benserazide, BH - Benzhexol Hydrochloride, C – Carbidopa, E – Entacapone, L – Levodopa, P – Pramipexole, R – Rotigotine

* Classic symptom refers to the presence of at least two of the following symptoms: tremor, rigidity and bradykinesia

\(^1\) – Motor fluctuations throughout the day with/without medications

\(^2\) – Dyskinesia

\(^3\) – Medication resistance to tremor

UPDRS scores signifies the assessments from the motor section (III) and values are reflective of a medication-ON state

### 3.2.2 Study design

The PD participants underwent two assessment sessions; pre-operative and post-operative at the UWA School of Sport Science, Exercise & Health’s biomechanics laboratory. Following the pre-operative assessment, PD participants underwent bilateral implants to the ZI which was performed at SCGH. Description of the surgery is explained in Thani and colleagues [27]. The participants, accompanied by a member of the SCGH neurosurgical team, returned five days post-surgery for their post-operative assessment which included the addition of three different stimulation settings: i) micro-lesioning/stimulation off, ii) stimulation targeted to the cZI, iii) stimulation targeted to
the dZI. Stimulation administered for all PD participants was set at a frequency of 130 Hz, pulse width of 60 μs, and amplitude of 3.0 V. The order and administration of the stimulation settings were randomised and blinded to both the tester and participants. Food intake, medication, and timing of the PD participants were standardised for at the pre- and post-operative assessments.

3.2.3 Experimental tasks

All participants completed the upper limb tasks whilst seated at a table on a height adjustable chair so that the thigh is horizontal with the ground. Each task commenced with the upper body and limbs in a standardised position; trunk upright, arms close to the body, elbows flexed at approximately 90°, and both hands resting on the table. All participants were given an explanation on how to perform the two upper limb tasks. The resting task consisted of resting in the initial position for a period of 10-seconds. The postural task consisted of starting in the initial position, followed by a 10-second period whereby both arms were elevated horizontally, outstretched with the wrists mildly extended and fingers spread apart. A total of three trials were performed for each task and the presentation order of the tasks was randomised and counterbalanced for each participant/session.

3.2.4 Participant preparation

Prior to data collection, 40 retro-reflective markers were affixed to the participants’ trunk and upper limb using low-allergenic double sided adhesive tape (3M®, St. Paul, MN, USA). Markers were placed on the dominant upper limb of the healthy control participants, and on the most affected limb of the participants with PD. This modified marker placement was adopted from the UWA upper limb model [28]. To assess muscle
activation during the tremor tasks, bipolar Ag/AgCl surface electrodes (ConMed Corporation®, Utica, NY, USA) were placed on the participants’ skin over the eight muscle bellies with 1.5 cm between electrodes after the skin was prepared by shaving, exfoliating and then cleaned with ethanol swabs. The eight muscle bellies used for electromyography recording were as follow: Upper trapezius, latissimus dorsi, pectoralis major, anterior deltoid, biceps brachii, triceps brachii (lateral head), flexor carpi radialis, and extensor carpi radialis. Electrode placement was standardised to allow comparison of electromyography output from pre and post-operative assessments [29].

3.2.5 Data collection and processing

A 12-camera VICON® MX 3D motion analysis system (VICON Peak, Oxford, UK) sampling at 250 Hz was used to determine the trajectory data of the markers, while a NORAXON® Telemyo system (Noraxon, USA, Inc., Scottsdale, AZ, USA) sampling at 2000 Hz synchronised with the motion data was used to collect iEMG data from the surface electrodes. Before the commencement of trials, sub-maximal isometric voluntary contractions (SIVC) were performed for normalisation of iEMG data. As the PD participants fall in the symptomatic population, SIVC is preferred to minimise the fatigability of the process. Details of the SIVC testing procedure for each muscle group is described in Table 3.2. Participants performed a total of three SIVC for each muscle, holding the weight for three second in each trial. The iEMG output during the tremor tasks was then normalised to the average iEMG output from the SIVC trials for each individual muscle.
### TABLE 3.2: Description of the SIVC collection for all muscles.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper trapezius</td>
<td>The participants stood upright with their forearm in a semi-pronated position, elbow extended, arm in a neutral position close to the body, and elevated their shoulders as high as they while holding a five kilogram dumb bell.</td>
</tr>
<tr>
<td>Latissimus dorsi</td>
<td>The participants lay prone with their arm extended, elbow flexed, semi-pronated forearm while holding a four kilogram dumb bell.</td>
</tr>
<tr>
<td>Pectoralis major</td>
<td>The participants lay supine with their arm abducted and elbow flexed at 90°, forearm pronated while holding a four kilogram dumb bell.</td>
</tr>
<tr>
<td>Anterior deltoid</td>
<td>The participants stood upright, arm flexed at 90° with a pronated forearm, elbow extended while holding a two kilogram dumb bell.</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>The participants held a five kilogram dumb bell with an upright trunk, shoulder and arm in a neutral position, elbow flexed at 90°, and with a supinated grip.</td>
</tr>
<tr>
<td>Triceps brachii (lateral head)</td>
<td>The participants lay supine with their arm and elbow flexed at 90°, forearm pronated and with a neutral wrist position while holding a two kilogram dumb bell.</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>The participants sat upright on chair, arm flexed at 90°, forearm horizontally supported on a table in a supinated position, and a neutral wrist (unsupported) position holding a four kilogram dumb bell.</td>
</tr>
<tr>
<td>Extensor carpi radialis</td>
<td>The participants sat upright on chair, arm flexed at 90°, forearm horizontally supported on a table in a pronated position, and a neutral wrist (unsupported) position holding a three kilogram dumb bell.</td>
</tr>
</tbody>
</table>

A total of six and 18 trials were analysed for the pre and post-operative analysis respectively for the PD participants, and a total of six trials were analysed for the healthy control participants. The raw three-dimensional kinematic outputs of the markers were modelled using the UWA upper limb model [28] and the segment origin of each segment was obtained using a customised MATLAB® software (The Mathworks, Natick, MS, USA). The kinematic profiles of interest were the three-dimensional segment origins at the hand and upper arm which is reflective of a distal and proximal segment analysis. Subsequently, the spectral analysis was estimated from the raw three-dimensional kinematic segment origin output using a custom written program (LabView®, National Instruments, Austin, USA). This program first estimates the amplitude spectrum of the vector of the three-dimensional trajectory signals using the available fast Fourier transform routines in LabView. Based on the amplitude spectrum, we evaluated the frequency (fP), amplitude of frequency (afP), power in fP, total power, 1-4 Hz power, and
4-7 Hz power [30]. Processing of the iEMG was performed offline as follows, the raw signal was high passed using a cut-off frequency of 20 Hz, full wave rectified, and again low passed using a cut-off frequency of 6 Hz to create a linear envelope. The iEMG was then calculated using the MATLAB® trapezoidal numerical integration function, and finally normalised to the respective iEMG of the muscle obtained during SIVC (refer to Appendix 5).

3.2.6 Statistical analysis

Due to the variability and non-normalised sample of the PD group, and the dissimilar sample size of the healthy controls, non-parametric statistics were applied. Participant results were also presented as motor sub-group studies and descriptive analysis was applied. The Mann-Whitney U test was used to determine differences between the pre-operative assessments of PD participants relative to the healthy controls while Cohen's $d$ was used to measure the effect size. For within PD group comparisons, a Friedman’s test was used to ascertain significant differences between the pre-operative assessment and the effect of micro-lesioning, and varying stimulation sites on upper limb tremor.

3.3 Results

The discrete values of the groups mean spectral analysis parameters for the hand and upper arm segments during the resting and postural tasks are presented in Table 3.3. As the frequency of pathological tremor fall in the range of 3 – 8 Hz, we have opted to present the data of afP and power in the frequency of 4 – 7 Hz [1]. Nevertheless, it is important to take note that we did observe a similar decreasing trend of total power in the frequency range of 1-10 Hz. There were no reports of negative side effects from the post-operative settings in the PD participants.
TABLE 3.3: The spectral analysis for the hand and arm segments of all PD participants for both tasks and all conditions as compared to healthy controls. Data is represented as mean and standard deviation (±1). fP denotes the frequency of the signal.

<table>
<thead>
<tr>
<th></th>
<th>Hand</th>
<th>Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>PreOp</td>
</tr>
<tr>
<td>Resting</td>
<td>8.588 (0.702)</td>
<td>7.752 (1.822)</td>
</tr>
<tr>
<td>Amplitude in fP</td>
<td>0.001 (0.001)</td>
<td>0.005 (0.004)</td>
</tr>
<tr>
<td>Power in fP</td>
<td>0.001 (0.001)</td>
<td>0.022 (0.045)</td>
</tr>
<tr>
<td>Total Power (1-10 Hz)</td>
<td>0.004 (0.003)</td>
<td>0.072 (0.116)</td>
</tr>
<tr>
<td>Power (1-4 Hz)</td>
<td>0.000 (0.000)</td>
<td>0.001 (0.001)</td>
</tr>
<tr>
<td>Power (4-7 Hz)</td>
<td>0.001 (0.001)</td>
<td>0.046 (0.108)</td>
</tr>
<tr>
<td>Postural</td>
<td>5.127 (3.233)</td>
<td>5.947 (2.592)</td>
</tr>
<tr>
<td>Amplitude in fP</td>
<td>0.005 (0.002)</td>
<td>0.082 (0.126)</td>
</tr>
<tr>
<td>Power in fP</td>
<td>0.020 (0.018)</td>
<td>11.153 (22.468)</td>
</tr>
<tr>
<td>Total Power (1-10 Hz)</td>
<td>0.158 (0.132)</td>
<td>39.069 (76.777)</td>
</tr>
<tr>
<td>Power (1-4 Hz)</td>
<td>0.039 (0.027)</td>
<td>0.839 (1.532)</td>
</tr>
<tr>
<td>Power (4-7 Hz)</td>
<td>0.030 (0.031)</td>
<td>14.185 (23.194)</td>
</tr>
</tbody>
</table>
### 3.3.1 Spectral analysis

Although there were no significant differences between the pre-operative PD participants and healthy controls, there were prominent trends in the mean values for both tasks and segments (Table 3.3). The afP for the pre-operative PD participants (range = 0.005 – 0.096) were elevated as compared to controls (range = 0.001 – 0.005) with a large effect sizes (ES) ranging from 0.83 – 1.47. Power fP in the pre-operative PD participants (range = 0.022 – 18.065) was increased as compared to controls (range = 0.001 – 0.020) with a medium ES (range = 0.63 – 0.76). Similarly, total power for the pre-operative PD participants (range = 0.072 – 41.238) was elevated as compared to controls (range = 0.004 – 0.158). Power (1-4 Hz) displayed analogous increases in the pre-operative PD participants (range = 0.001 – 2.272) as compared to controls (range = 0.000 – 0.039). Lastly, power (4-7 Hz) displayed an increase in the pre-operative PD participants (range = 0.046 – 35.954) as compared to the controls (range = 0.001 – 0.030) with a medium to high ES (range = 0.64 – 0.93).

Post-operatively there was a general decrease (non-significant) in the spectral analysis parameters in both tasks and segments when compared to the pre-operative PD levels (Table 3.3). There was a notable decrease in afP with post-operative settings (range = 0.004 – 0.058) as compared to the pre-operative levels (range = 0.005 – 0.096) with a medium ES displayed at the arm segment (range = 0.57 – 0.71). A decrease in power in fP was displayed with post-operative settings (range = 0.012 – 7.509) as compared to pre-operative levels (range = 0.022 – 18.065). Likewise, power (4-7 Hz) was seen to decrease with post-operative settings (range = 0.044 – 10.925) as compared to pre-operative levels (range = 0.046 – 35.954) with a medium ES exhibited at the arm segment (range = 0.50 – 0.64). There were minimal differences between cZI and dZI stimulation, the data
suggest that micro-lesioning was more pronounced, particularly in the resting task (Table 3.3).

To clinically appraise the results, differences between sub-groups were observed when the participants who underwent surgery to control tremor (ST) were compared to those who underwent surgery to control motor fluctuations and dyskinesia, as such, descriptive analysis was used to present the results (Figure 3.1 and 3.2). Figure 3.1 illustrates the individual percentage change results of afP and power (4-7 Hz) for the ST sub-group. Trends in the spectral analysis were observed in the ST sub-group, with values exhibiting reductions with post-operative settings (Figure 3.1). The afP and power (4-7 Hz) for PD4, PD8 and PD10 show a marked decrease; up to 99-100% in some cases, for both segments in the resting task (Figure 3.1A, 3.1B, 3.1E and 3.1F). The added benefit of cZI and dZI stimulation in these three participants were prominent in the distal (hand) segment (Figure 3.1A and 3.1E). The converse trend was exhibited by PD6 post-operatively. PD6 displayed marked increases in afP and power (1-4 Hz) in both the resting and postural tasks, most notably at the hand segment.

A similar trend was displayed in the postural task at both segments for PD4, PD8 and PD10 with the afP and power (4-7 Hz) decreasing with post-operative settings (Figure 3.1C, 3.1D, 3.1G and 3.1H). The afP for PD6 however, had a decrease at the arm segment with post-operative settings (Figure 3.1D) although the hand segment displayed a slight increase with dZI stimulation (Figure 3.1C). Likewise for the power (4-7 Hz) in the postural task, PD6 exhibited a decrease at the arm in all three post-operative settings (Figure 3.1H) though the converse was observed at the hand with the exception of micro-lesioning (Figure 3.1G). Similar to the resting task, the added benefit of cZI and dZI stimulation were prominent at the distal (hand) segment (Figure 3.1C and 3.1G).
FIGURE 3.1: Individual column chart representation of the mean of the amplitude in frequency (afP) and power (4-7 Hz) at the hand and arm segments for the sub-group of Parkinson’s participants who underwent surgery to reduce the tremor (n = 4) in the resting and postural tasks. Data for micro-lesioning, cZI stimulation and dZI stimulation are presented as a percentage change relative to the participants’ pre-operative levels. (A) Hand afP in the resting task, (B) Arm afP in the resting task, (C) Hand afP in the postural task, (D) Arm afP in the postural task, (E) Hand power (4-7 Hz) in the resting task, (F) Arm power (4-7 Hz) in the resting task, (G) Hand power (4-7 Hz) in the postural task, (H) Arm power (4-7 Hz) in the postural task.
3.3.2 iEMG analysis

There were no significant differences between the pre-operative iEMG of PD participants and that of healthy controls. However, there was a trend of greater iEMG activity in the triceps (ES = 0.81) and anterior deltoid in the resting task for the PD group pre-operatively as compared to controls (Figure 3.2A). Similarly, in the postural task, iEMG values were observed to be greater for the pre-operative PD group in the triceps (ES = 1.05), anterior deltoid (ES = 1.37), and trapezius as compared to controls (Figure 3.2B). A general decrease in iEMG was exhibited at the triceps brachii, anterior deltoid, trapezius, latissimus dorsi, and an increase in iEMG at the flexor carpi radialis was observed with post-operative settings in the whole PD group as compared to their pre-operative levels in both tasks (Figure 3.2A).

In both the resting and postural tasks, a general trend of decrease in iEMG at the triceps brachii, anterior deltoid, trapezius, latissimus dorsi, and an increase in iEMG at the flexor carpi and extensor carpi radialis were exhibited with post-operative settings for the ST group as compared to their pre-operative levels (Figure 3.2C and 3.2D). Due to the large standard deviations, no statistical differences were observed between post-operative settings in the whole PD group and in the ST group (Figure 3.2A and 3.2B).
FIGURE 3.2: Column chart representation of the mean and standard deviation of the iEMG of all eight muscles (% of SIVC) in the Parkinson’s participants over pre and post-operative assessments and the healthy controls. ST represents the sub group of Parkinson’s participants who underwent surgery to reduce the tremor. (A) Resting task for all Parkinson’s participants (n = 10), (B) Postural tasks for all Parkinson’s participants (n = 10), (C) Resting tasks for the ST group (n = 4), (D) Postural tasks for the group (n = 4).
3.4 Discussion

This is the first study to date to quantitatively assess the effects of acute PSA DBS specifically targeting the ZI, on proximal and distal upper limb tremor in resting and postural tasks. Previous semi-quantitative studies investigating the effects of ZI targeted PSA DBS have utilised clinical rating scales, such as the UPDRS [8–15], which can be subjective depending on the experience of the assessor, and provide limited assessment of tremor as this symptom presents itself with a complexity of variations [18,19]. Grimaldi and Manto (2008) outlined that tremor is composed of deterministic (non-random) and stochastic (random) components [22]. The use of electromyography measurements and signal processing methods such as the spectral analysis are required to interpret time-series data of nonlinear signals such as PD tremor, in which the frequency content of the signal provides a plethora of information which cannot be derived through qualitative analysis [21,22].

Although there was no statistical significance, the descriptive data and the medium to large ES reported suggests that there may be support for the hypothesis that, differences potentially exist in afP (ES range = 0.83 – 1.47), power in fP (ES range = 0.63 – 0.76), total power, power (1-4 Hz), power (4-7 Hz) (ES range = 0.64 – 0.93), and iEMG activity (ES range = 0.81 – 1.37) between the pre-operative PD participants and healthy controls [21,30,31]. Increases in spectral analysis parameters and iEMG activity at the triceps, anterior deltoid, and trapezius iEMGs, were observed in the pre-operative PD participants as compared to the healthy controls during the tremor tasks. As expected, post-operatively, the PD participants did exhibit a decrease in the spectral analysis parameters and some iEMG activity (triceps brachii, anterior deltoid and latissimus dorsi) moving towards normative values at both segments and across both tasks with the exception of
the hand in the resting task (Table 3.3). A medium ES was observed for the afP and power (4-7 Hz) ranging from 0.50 – 0.71. These trends concur with previous semi-quantitative studies which found a general decrease in both proximal and distal tremor in PD with PSA DBS [8–14].

The lack of significance in our study may be due to the variability of the tremor parameters, small sample size and heterogeneity in the PD participants which resulted in high standard deviations [32,33]. The altered iEMG at the trapezius and flexor carpi radialis with post-operative settings is however, not in line with our hypothesis. Fradet and colleagues (2009) found that the altered muscle activity in PD is due to the dissimilar adaptation strategy in both activation and planning to complete a movement [34]. We speculate that PSA DBS altered the muscular activity in the timing of agonist-antagonist muscle sequencing when performing the resting and postural tasks by altering both the motor control and sensory systems. Motor unit synchronisation may be responsible for this alteration in muscular activity. Further research in EMG analysis and ZI DBS is warranted to further elucidate the effects of DBS to this target site on muscular activation patterns, this may assist the prescription of post-operative motor rehabilitation plans to optimise patient functioning in the longer term.

Nonetheless, there was a distinct trend of improvements in the ST group through a decrease in the afP and power (4-7 Hz) with post-operative settings, with the exception of one participant (PD6). It has been found that the frequency of pathological tremor lies in the range of 4-7 Hz, therefore a reduction in this range coupled with a reduction in afP is suggestive of diminishing pathological movement characteristic [1]. An important observation is that the decrease in both afP and power (4-7 Hz) in the ST group is seen to
occur at both the hand and arm unlike the results when the PD group was combined together (Table 3.3). As PD tremor is highly prevalent during rest [1,3], our results suggest that the effect of micro-lesioning was enough to elicit tremor reductions in this condition. Moreover, the therapeutic effect is further increased with cZI and dZI stimulation, most prominently at the distal (hand) segment. It is important to note the opposing clinical response of PD6 in comparison to the rest of the ST group. The spectral analysis data suggest that this participant did not experience an initial response to micro-lesioning, and stimulation to the ZI did in fact increase his tremor, predominantly at the hand. Clinical follow-up: three, six and 12 months, with this participant however, suggest good longer term clinical outcomes with improvements noted in both motor and non-motor symptoms. The results of PD6 indicate that assessment in this acute phase of surgery may give a skewed representation of the whole PD group’s clinical outcome, and that DBS is likely to have differential effects in the short, medium and long term as a response to chronic stimulation. Therefore, it is imperative that both acute and longer term assessments be performed to establish new information on identifying the best responders to this novel target site, as well as to optimise rehabilitative programs during recovery of the establishment of optimal stimulation settings for each individual.

The mechanism(s) to explain the improvements in tremor with ZI targeted PSA DBS remains to be elucidated. As there have been no similar studies in ZI targeted PSA DBS and its effect on the sub-groups of PD, it is difficult to make assumptions as to the mechanism behind the efficacy of ZI DBS. Plaha et al. (2008) proposed that the cZI is involved in an important pathway for conduction of tremor oscillations into the cerebello-thalamocortical loop [13]. Hamel and colleagues (2003) proposed that the dZI may act as a vital structure in influencing other brain structures involved in tremor [15]. Our data suggest that both stimulation to the cZI and dZI did in fact reduce the tremor in the ST
group, particularly in the distal (hand) segment. We proposed that micro-lesioning and DBS of the areas of and around the ZI may have a signal modulating effect, leading to a reduction in the severity of tremor. In addition, there are reports from subthalamic nucleus studies that have indicated the role of beta bands in the manifestation of tremor in PD [35–37]. It was hypothesised that subthalamic nucleus DBS decreased the pathological beta bands while increasing the pro-kinetic gamma band thus facilitating movement [35–37]. A similar phenomenon may have occurred with ZI DBS in the current study.

3.5 Conclusion

This novel study reported proximal and distal segment improvements, especially for individuals with tremor-predominant PD in resting and postural tremor with post-operative settings through quantitative measurements. There was however generally no added benefit with cZI and dZI stimulation on top of the micro-lesioning effect in the whole PD group. Previous work has reported the cessation on the micro-lesioning effect within eight to 12 weeks of surgery [38]. Therefore, these findings have positive implications for longer term cZI and dZI DBS, specifically for the tremor-predominant PD group. Our study further supports the work of other ZI targeted PSA DBS research [8–15] supporting its role as being a safe and effective target for DBS surgery to alleviate tremor symptoms. Future research utilising a signal processing method called entropy analysis; which aims to assess the irregularities of a signal, could further illuminate the characteristics of a tremor signal in clearer detail [30]. Moreover, future research with a larger homogeneous sample size of PD participants, could help shed some light on the underlying vicissitudes in the physiological control system which may explain the mechanism of action of DBS in greater detail [30,39,40].

100
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References


CHAPTER FOUR

STUDY TWO

Outcome of elbow rigidity with posterior subthalamic deep brain stimulation in Parkinson’s disease
Foreword

Study One provided evidence on the outcomes of zona incerta targeted stimulation on tremor. The second study presented in this thesis examined the effect of zona incerta targeted posterior subthalamic area deep brain stimulation on the rigidity symptom in Parkinson’s disease. The majority of studies in this area have performed their assessments through semi-quantitative which provides limited information of change following deep brain stimulation. As important, there have been no research investigating the outcome of stimulation to the different divisions of the zona incerta on the sub-groups of Parkinson’s disease, specifically the tremor-predominant and rigid akinetic sub-groups. It is intended that this paper will be submitted to the journal of ‘Parkinsonism & Related Disorders’.
Abstract

Background: Rigidity, a symptom in Parkinson’s disease (PD), is commonly assessed clinically through semi-quantitative scales such as the Unified Parkinson’s Disease Rating Scale (UPDRS). Deep brain simulation (DBS) of the posterior subthalamic area (PSA), specifically targeting the zona incerta has been a successful option to alleviate PD rigidity when medication alone becomes insufficient. Our study investigated the effect of acute PSA DBS on elbow joint rigidity through a quantitative torque-based approach and electromyography measurement in PD and its sub-groups.

Methods: Ten PD participants underwent quantitative biomechanical assessment prior to PSA DBS using the MRI-directed implantable guide tube technique. Five days post-surgery, the assessment was repeated under three randomised double-blinded conditions: (i) micro-lesioning, and high-frequency stimulation of (ii) the caudal ZI (cZI) and (iii) the dorsal ZI (dZI). Ten healthy matched controls were assessed once using the same assessments.

Results: Pre-operative rigidity values were correlated with the UPDRS specifically in the passive 90°/sec cupping task. Trend data suggests that rigidity more closely represented normative values with post-operative settings particularly at the elbow flexors. There were indications that the tremor-predominant group had decreased flexor resistive torque with dZI stimulation, while the rigid akinetic group had decreased flexor resistive torque with cZI stimulation.

Conclusion: The outcome of acute PSA DBS in this study gives researchers/clinicians initial indications of the effectiveness of cZI and dZI stimulation on the sub-groups of PD. Future research should assess the longer term outcome of PSA DBS in order to select the best responders to PSA DBS.
4.1 Introduction

Rigidity, defined as the increased resistance to passive movement of a limb, is one of the prominent debilitating motor symptoms in Parkinson’s disease (PD) [1]. Studies have outlined evidence which points to both neural and non-neural components operating in parallel being responsible for PD rigidity [2–5]. Neural components are attributed to the altered muscle activation while non-neural components may reflect altered architecture of the muscular itself [2–5]. Individuals who present with this symptom may experience pain as well as stiffness as a result of the muscles being tense and contracted. Furthermore, efforts to move the limb, be it active or passive, may lead to short and jerky movements, resulting in a delayed initiation of movement and overall decrease in movement speed, which combine to make deliberate tasks difficult [3,5].

Clinically, rigidity is rated through semi-quantitative scales such as the Unified Parkinson’s Disease Rating Scale (UPDRS) by an assessor who perceives the degree of resistance when passively moving the patient’s limb through range of motion [6]. It has been suggested that the measurement of rigidity requires continuous scalar estimates rather than a bounded-ordinal scale such as the UPDRS [7,8]. Consequently, several studies have developed biomechanical methods to quantitatively assess rigidity using torque (rotational force about a joint) based approaches and electromyography (EMG) measurements [1,4,8–10]. These studies report that resistive torque and EMG activity is increased in PD compared to healthy controls during passive motion, indicative of an increase in rigidity [1,4,8–10]. Combining this resistive torque-based approach and EMG measurements during passive movement, provides a clearer understanding on the contribution of the neural and non-neural components in rigidity. Additionally, the quantitative aspect of these assessments means that potential intra- and inter-rater
variability can be reduced. Utilising quantitative assessments, such as the ones mentioned, may provide more in-depth information to treating clinicians, and potentially assist them to select appropriate intervention(s) for the individual patient [1,4,8–10].

Treatment for rigidity symptoms in PD often included dopaminergic medications, which can significantly decrease the severity of rigidity [5,9,11]. However, PD is a progressive disease whereby the efficacy of medication decreases with continued use in many cases, and the manifestation of other motor side effects becomes more apparent [9]. Deep brain stimulation (DBS) of the posterior subthalamic area (PSA) has been a successful option to alleviate the negative motor symptoms of PD, including rigidity, when medication alone becomes insufficient, thereby improving the quality of life of PD patients [12–17]. Many of these studies have focused their attention on targeting a structure called the zona incerta (ZI), although much still remains unknown with regards to the function of the ZI in humans and its different sub-divisions [18]. Previous research provided evidence that improvements in rigidity scores in PD patients were seen with caudal ZI (cZI) DBS without eliciting negative motor or non-motor symptoms [12–17]. A study by Hamel et al. (2003) investigating the effects of dorsal ZI (dZI) stimulation found significant improvements in the UPDRS scores [19]. The aforementioned studies in cZI and dZI targeted DBS have all utilised semi-quantitative outcome assessments.

There has been no known quantitative DBS research investigating the effects of acute PSA stimulation on rigidity in PD and how it relates to muscular activation. In addition, there have been no studies that have compared the effects of both cZI and dZI stimulation on rigidity profiles. Therefore, there are two aims to this study: Firstly, we seek to examine the differences in rigidity through a torque-based approach and EMG activity at
the elbow joint in patients with PD and a matched healthy control group. Secondly, to determine the acute effects of micro-lesioning [20] and stimulation to the PSA where the cZI and dZI are located, and the outcome on the rigidity and activation of the elbow flexors and extensors in PD and its sub-groups. We expect that pre-operatively, PD participants will display an increase in elbow flexor and extensor resistance torque during passive isokinetic movement, and altered muscular activation patterns as compared to healthy controls. It is predicted that a decrease in elbow flexor and extensor resistance torque, and reduction of muscle activation levels of the PD participants; in all sub-groups, particularly the rigid akinetic participants, will be displayed with micro-lesioning and stimulation to the areas of and around the cZI and dZI following DBS.

4.2 Methods

4.2.1 Participants

Ten participants with idiopathic PD (7 males, 3 females, age 40-70 years) were recruited from the Sir Charles Gairdner Hospital (SCGH) neurosurgical clinic, and 10 healthy aged and gender matched participants were recruited as controls. All PD participants underwent DBS surgery as part of their clinical management. Out of the ten PD participants, three were classified as tremor-predominant and four as rigid akinetic. Details of the PD participants are presented in Table 4.1. All participants were informed as to the nature of the research study and a written consent was obtained (refer to Appendix 3 and 4). Ethical approval for the study was granted by the SCGH ethics committee (2008-065 and 2012-039) and The University of Western Australia (UWA), (RA/4/1/5721) (refer to Appendix 1 and 2).
TABLE 4.1: Parkinson’s disease participant characteristics and medication information.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Disease duration (years)</th>
<th>UPDRS (Total)</th>
<th>UPDRS: Rigidity Score</th>
<th>UPDRS: Tremor Score</th>
<th>Subtype</th>
<th>Medication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD1</td>
<td>20</td>
<td>21</td>
<td>11</td>
<td>0</td>
<td>Rigid</td>
<td>L/C/E 150/37.5/200 mg (x7); L/B 100/25 mg (x3); L/C 200/50 mg (x1); A 100 mg (x2)</td>
</tr>
<tr>
<td>PD2</td>
<td>13</td>
<td>30</td>
<td>9</td>
<td>1</td>
<td>Rigid</td>
<td>L/B 250/50 mg (x5)</td>
</tr>
<tr>
<td>PD3</td>
<td>11</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>Rigid</td>
<td>L/C/E 150/37.5/200 mg (x6), P 1.5 mg (x1)</td>
</tr>
<tr>
<td>PD4</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>9</td>
<td>Tremor</td>
<td>L/C 250/25 mg (x4), P 4.5 mg (x1)</td>
</tr>
<tr>
<td>PD5</td>
<td>17</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>Classic</td>
<td>L/C 250/25 mg (x0.5); L/C 100/25 mg (x6); L/C 200/50 mg (x1)</td>
</tr>
<tr>
<td>PD6</td>
<td>6</td>
<td>39</td>
<td>7</td>
<td>18</td>
<td>Tremor</td>
<td>No medication</td>
</tr>
<tr>
<td>PD7</td>
<td>12</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>Rigid</td>
<td>L/C/E 50/12.5/200 mg (x1); L/B 200/50 mg (x1); A 100 mg (x3); L/C/E 200/50/200 mg (x3); L/C/E 150/37.5/200 mg (x1); L/B 50/12.5 mg (x2)</td>
</tr>
<tr>
<td>PD8</td>
<td>8</td>
<td>13</td>
<td>4</td>
<td>8</td>
<td>Classic</td>
<td>L/B 200/50 mg (x6-7); BH 2 mg (x3)</td>
</tr>
<tr>
<td>PD9</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>Classic</td>
<td>L/C/E 200/50/200 mg (x5), P 0.75 mg (x1); L/B 100/25 mg (x3); L/B 100/25 mg Slow release (x1)</td>
</tr>
<tr>
<td>PD10</td>
<td>4.5</td>
<td>41</td>
<td>0</td>
<td>12</td>
<td>Tremor</td>
<td>No medication</td>
</tr>
</tbody>
</table>

* A – Amantadine hydrochloride, B – Benserazide, BH - Benhexol Hydrochloride, C – Carbidopa, E – Entacapone, L – Levodopa, P – Pramipexole, R – Rotigotine

UPDRS scores signifies the assessments from the motor section (III) and values are reflective of a medication-ON state.

4.2.2 Study design

All PD participants underwent two assessment sessions; pre-operative and post-operatively at the UWA School of Sport Science, Exercise & Health’s biomechanics laboratory. Two days after the pre-operative assessment, they underwent bilateral implants to the ZI at the SCGH. Details of the surgical procedure can be found in Thani et al. 2012 [21]. The participants, accompanied by a member of the SCGH neurosurgical team, returned for the post-operative assessment five days post-surgery. Daily food intake and medication delivery were standardised at the pre- and post-operative assessments as an external control measure. Healthy control participants completed the assessment in a single session.
4.2.3 Participant preparation

Prior to collection, ConMed Corporation® bipolar Ag/AgCl surface electrodes (ConMed, Utica, NY, USA) were placed on the participants’ skin over the muscle belly of the biceps brachii and triceps brachii (lateral head) with 1.5 cm between electrodes after the skin was prepared by shaving, exfoliating and then cleaned with ethanol swabs. Electrode placement was standardised to allow comparison of EMG output from pre and post-operative assessments [22].

4.2.4 Data collection

A Biodex® isokinetic dynamometer (Biodex, M3, Shirley, NY, USA) sampled at 2000 Hz was used to determine the net resistive torque through flexion/extension range of motion at the participant’s dominant elbow. Resistive torque was defined as the passive resistance of the muscle group throughout the imposed range of motion. A NORAXON® Telemyo system (NORAXON, Scottsdale, AZ, USA) sampled at 2000 Hz synchronised with the resistive torque data was used to collect EMG activity from the surface electrodes. Before the commencement of the passive isokinetic trials, sub-maximal isometric voluntary contraction (SIVC) at the biceps and triceps were performed for normalisation of EMG data. As the PD participants fall in the symptomatic population, SIVC is preferred to minimise the fatigability of the process. Participants were asked to hold a five kilogram dumb bell for a period of three seconds with the trunk upright, shoulder in a neutral position, elbow flexed at 90°, and with a supinated grip for their biceps SIVC. Triceps SIVC was performed with the participant lying supine, shoulder and elbow flexed at 90°, forearm pronated and with a neutral wrist position while holding a two kilogram dumb bell for three seconds. Participants performed a total of three SIVC
for each muscle whereby the peak EMG output were then averaged across the three trials for normalisation.

Participants performed passive upper limb isokinetic movements at two different velocities: 30°/sec and 90°/sec on the dynamometer with their dominant arm (healthy controls) or most affected arm (PD participants). The participants sat upright on the Biodex chair, shoulder abducted at 90° and the forearm supinated to align with the dynamometer arm. Axis of rotation at the elbow was aligned with the axis of rotation of the dynamometer as illustrated in Figure 4.1. Their arm and hand were then strapped in place for the passive trials.

A familiarisation trial at both velocities was given to the participants before commencing data collection. In the first condition, participants were asked to relax and not resist or assist the movement while the dynamometer induced a complete cycle of

FIGURE 4.1. Static position of the participant.
flexion/extension motion at the elbow. The second condition repeated the passive flexion/extension at the elbow, with the addition of performing a repeated cupping action (thumb in contact with all four fingers) task with the contra-lateral hand. This task has been incorporated to elicit any underlying tremor present in PD thereby potentially impacting upon rigidity [23]. All participants performed five cycles at each velocity in both conditions whereby the presentation order was randomised and counterbalanced. A 60 second rest was given in between conditions and velocities to minimise elastic dissipative effects. Participants with PD completed the rigidity protocol prior to and following DBS surgery.

4.2.5 Surgical procedure

All DBS leads were surgically implanted and anatomically placed based on MRI-directed implantable guide tube technique under general anaesthesia with no deviations from their pre-planned positions [21] in the context of a pilot non-randomised phase I/II clinical trial (2008-065) and randomised controlled crossover phase II clinical trial (2012-039; ClinicalTrials.gov unique identifier NCT01945567). Leads were placed into the PSA to deliver electrodes to each of the cZI and dZI targets. The planned target is on the border between each ZI sub-region and the subthalamic nucleus. Electrode positions were directly determined from the NeuroGuide™ stylette (Renishaw plc, Wootton-under-Edge, UK) position in relation to the directly visualised subthalamic nucleus borders on T2-weighted axial images for each research participant (for MRI sequence details refer to the study by Thani and colleagues, 2011 [24]). Australian Government Therapeutic Goods Administration regulatory approval for research use of the Renishaw NeuroGuide™ was granted via the Clinical Trials Notification scheme (under clinical trial identifiers: 2008-065 and 2012-039).
4.2.6 Pre and post-operative assessments for PD participants

The post-operative protocol repeated the pre-operative assessment with the addition of three different stimulation settings: i) micro-lesioning/stimulation off, ii) stimulation to the cZI, and iii) stimulation to the dZI. All stimulation administered was set at a frequency of 130 Hz, pulse width of 60 μs, and amplitude of 3.0 V and the stimulation settings presentation order was randomised and blinded to both the tester and participants.

4.2.7 Data processing

Averaged data for five cycles of each condition at each speed and stimulation setting were analysed. Processing and output of both the net resistive elbow flexor (during extension) and extensor (during flexion) torques and EMG data were performed using customised MATLAB® software (The Mathworks, Natick, MS, USA) (refer to Appendix 6). Processing of the EMG data were as follows: high passed filtered using a cut-off frequency of 20 Hz, full wave rectified, and again low passed using a cut-off frequency of 6 Hz in order to obtain a linear envelope, and normalised to the respective muscle SIVC. Torque and joint position data was filtered using a 4\textsuperscript{th} order Butterworth filter with a cut-off frequency of 6 Hz.

4.2.8 Statistical analysis

A two-tailed Spearman’s rank correlation coefficient was used to assess the relationship between the pre-operative UPDRS assessments and maximum resistive torques. An independent sample T-test was used to determine differences between the pre-operative assessments of PD participants and the healthy controls while Cohen's $d$ was used to measure the effect size. Descriptive analysis was used to compare the results between
pre-operative and post-operative conditions in participants with PD (micro-lesioning, cZI and dZI stimulation). All analyses were performed using IBM® SPSS® Statistics 21 (IBM Corporation, Armonk, NY, USA). Due to the spectrum of symptoms in PD being large and variable, differences may be expected between sub-groups of tremor-predominant and rigid akinetic PD groups, as such, descriptive analysis is used to present the results.

4.3 Results

The discrete values of the group mean maximum resistive torque outputs during the passive isokinetic flexion-extension trials are represented in Table 4.2.

4.3.1 Correlation between the UPDRS and biomechanical assessment

In the passive 30°/sec isokinetic task, a significant relationship existed between the maximum resistive extensor torque during flexion (ExtT) and the total score on the UPDRS (r = .675, p = .032), and the maximum resistive flexor torque during extension (FlxT) with both the total score on the UPDRS (r = .644, p = .044) and rigidity sub-score on the UPDRS (r = .640, p = .046) (Table 4.2). Maximum resistive extensor torque during flexion (ExtT) performed in the passive 90°/sec isokinetic task combined with contralateral hand cupping displayed a significant relationship to both the total score on the UPDRS (r = .638, p = .047), and the tremor sub-score on the UPDRS (r = .679, p = .031).
TABLE 4.2: Maximum resistive flexor (FlxT) and extensor torque (ExtT) of the Parkinson’s disease participants (n = 10) and the healthy controls (n = 10) in all settings and conditions. Torque data (N.m) and muscle activation (as a % of SIVC) are represented as mean and standard deviation (±1).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PreOp</th>
<th>Micro</th>
<th>cZI</th>
<th>dZI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Max Extensor Torque During Flexion (N.m)</strong></td>
<td>2.95 (1.14)</td>
<td>1.59 (2.38)*</td>
<td>2.06 (3.31)</td>
<td>2.34 (2.30)</td>
<td>2.57 (3.26)</td>
</tr>
<tr>
<td><strong>Max Flexor Torque During Extension (N.m)</strong></td>
<td>2.51 (1.66)</td>
<td>3.54 (2.54)^</td>
<td>3.63 (2.72)</td>
<td>3.16 (2.03)</td>
<td>2.47 (1.62)</td>
</tr>
<tr>
<td><strong>Maximum Biceps Activation During Flexion (% SIVC)</strong></td>
<td>0.09 (0.05)</td>
<td>0.15 (0.08)</td>
<td>0.17 (0.13)</td>
<td>0.13 (0.10)</td>
<td>0.13 (0.08)</td>
</tr>
<tr>
<td><strong>Maximum Triceps Activation During Flexion (% SIVC)</strong></td>
<td>0.12 (0.12)</td>
<td>0.14 (0.06)</td>
<td>0.16 (0.11)</td>
<td>0.15 (0.11)</td>
<td>0.25 (0.31)</td>
</tr>
<tr>
<td><strong>Max Extensor Torque During Flexion (N.m)</strong></td>
<td>2.13 (1.25)</td>
<td>2.73 (2.96)</td>
<td>2.18 (3.32)</td>
<td>2.20 (2.04)</td>
<td>2.42 (2.24)</td>
</tr>
<tr>
<td><strong>Max Flexor Torque During Extension (N.m)</strong></td>
<td>2.64 (1.74)</td>
<td>4.57 (3.30)^</td>
<td>2.87 (2.99)</td>
<td>2.46 (3.47)</td>
<td>2.22 (1.57)</td>
</tr>
<tr>
<td><strong>Maximum Biceps Activation During Flexion (% SIVC)</strong></td>
<td>0.12 (0.05)</td>
<td>0.20 (0.10)</td>
<td>0.17 (0.12)</td>
<td>0.15 (0.10)</td>
<td>0.18 (0.12)</td>
</tr>
<tr>
<td><strong>Maximum Triceps Activation During Flexion (% SIVC)</strong></td>
<td>0.18 (0.17)</td>
<td>0.22 (0.13)</td>
<td>0.22 (0.18)</td>
<td>0.30 (0.24)</td>
<td>0.28 (0.21)</td>
</tr>
<tr>
<td><strong>Max Extensor Torque During Flexion (N.m)</strong></td>
<td>3.03 (1.61)</td>
<td>2.41 (3.45)</td>
<td>3.15 (2.72)</td>
<td>3.81 (3.66)</td>
<td>3.78 (3.26)</td>
</tr>
<tr>
<td><strong>Max Flexor Torque During Extension (N.m)</strong></td>
<td>2.47 (1.61)</td>
<td>4.47 (3.83)</td>
<td>3.63 (3.11)</td>
<td>3.18 (2.79)</td>
<td>3.51 (2.38)</td>
</tr>
<tr>
<td><strong>Maximum Biceps Activation During Flexion (% SIVC)</strong></td>
<td>0.18 (0.14)</td>
<td>0.23 (0.16)</td>
<td>0.23 (0.19)</td>
<td>0.20 (0.17)</td>
<td>0.21 (0.15)</td>
</tr>
<tr>
<td><strong>Maximum Triceps Activation During Flexion (% SIVC)</strong></td>
<td>0.17 (0.20)</td>
<td>0.24 (0.24)</td>
<td>0.22 (0.13)</td>
<td>0.27 (0.12)</td>
<td>0.28 (0.16)</td>
</tr>
<tr>
<td><strong>Max Extensor Torque During Flexion (N.m)</strong></td>
<td>2.55 (1.11)</td>
<td>4.60 (4.17)^</td>
<td>3.79 (3.44)</td>
<td>5.14 (6.13)</td>
<td>4.22 (3.79)</td>
</tr>
<tr>
<td><strong>Max Flexor Torque During Extension (N.m)</strong></td>
<td>2.52 (1.50)</td>
<td>5.14 (3.65)^</td>
<td>3.90 (3.34)</td>
<td>3.22 (3.05)</td>
<td>3.28 (2.56)</td>
</tr>
<tr>
<td><strong>Maximum Biceps Activation During Flexion (% SIVC)</strong></td>
<td>0.20 (0.10)</td>
<td>0.29 (0.22)</td>
<td>0.25 (0.12)</td>
<td>0.22 (0.13)</td>
<td>0.21 (0.13)</td>
</tr>
<tr>
<td><strong>Maximum Triceps Activation During Flexion (% SIVC)</strong></td>
<td>0.20 (0.18)</td>
<td>0.33 (0.27)</td>
<td>0.38 (0.26)</td>
<td>0.43 (0.36)</td>
<td>0.37 (0.25)</td>
</tr>
<tr>
<td><strong>Max Extensor Torque During Flexion (N.m)</strong></td>
<td>0.12 (0.07)</td>
<td>0.27 (0.20)</td>
<td>0.20 (0.14)</td>
<td>0.18 (0.13)</td>
<td>0.19 (0.14)</td>
</tr>
<tr>
<td><strong>Max Flexor Torque During Extension (N.m)</strong></td>
<td>0.24 (0.24)</td>
<td>0.42 (0.32)</td>
<td>0.42 (0.28)</td>
<td>0.51 (0.39)</td>
<td>0.46 (0.33)</td>
</tr>
</tbody>
</table>

* Significantly different from controls
^ Effects size compared with controls (d = 0.73)
^ Significantly different from controls (d = 0.73)
° Significant relationship with UPDRS Rigidity sub-score (r = 0.640, p = 0.046)
°° Significant relationship with UPDRS Total score (r = 0.679, p = 0.031)
°°° Significant relationship with UPDRS Total score (r = 0.679, p = 0.031)
4.3.2 Comparison with healthy controls

Pre-operatively, there was a trend for PD participants to display increased FlxT and EMG activation of both flexors and extensors in all conditions compared to the healthy controls; this was particularly evident when the passive motion was combined with the contra-lateral cupping task. A significant difference ($p = .049$) and a large effect size ($d = 0.97$) was observed in the passive 90°/sec task with contra-lateral hand cupping. A large effect size was also observed in the passive 30°/sec task with contra-lateral hand cupping ($d = 0.73$) as seen in Table 4.2.

4.3.3 Trends within the PD sub-groups

Given that the most noticeable trends occurred in FlxT, it was deemed appropriate to investigate the alterations in this variable within the PD sub-groups. As the sample sizes for the PD sub-groups are small, descriptive analysis was used to interpret the results. A decrease in FlxT was observed in the tremor-predominant PD group in all passive isokinetic conditions with post-operative settings (Figure 4.2A, 4.2B, 4.2C and 4.2D). Interestingly, stimulation to the dZI exhibited the greatest decrease in all four passive isokinetic conditions (Figure 4.2A, 4.2B, 4.2C and 4.2D). Similarly, maximum biceps and triceps activation (as a % of SIVC) during the extension phase also decreased in all post-operative conditions, particularly dZI stimulation, during the passive isokinetic tasks as compared to pre-operative levels (Figure 4.2A, 4.2B, 4.2C and 4.2D). During this extension motion, the biceps acts as the resistive force while the triceps takes the role in assisting the motion. Altered activation was most evident in the 90°/sec task with contra-lateral hand cupping for tremor predominant participants, where activation of the biceps appeared to replicate the healthy controls (Figure 4.2D).
FIGURE 4.2: Line plot representation of the mean and standard deviation bars of the maximum resistive flexor torque, maximum biceps activation (% of SIVC), and maximum triceps activation (% of SIVC) during extension in the tremor predominant Parkinson’s participants (n = 3) over pre and post-operative assessments at (a) 30°/sec, (b) 30°/sec with the contra-lateral cupping task, (c) 90°/sec, (d) 90°/sec with the contra-lateral cupping task. Maximum resistive flexor torque for healthy controls is represented by the black dash line.
Post-operatively, a similar trend for the FlxT was observed in the rigid akinetic PD group with cZI stimulation displaying the greatest reduction in resistive torque relative to pre-operative levels (Figure 4.3A, 4.3B, 4.3C and 4.3D). However, unlike the tremor-predominant group, maximum triceps activation (as a % of SIVC) during extension appears to increase in the rigid akinetic PD group with post-operative assessments as compared to pre-operative levels (Figure 4.3A, 4.3B, 4.3C and 4.3D). Note that the role of the triceps during this extension motion is to assist the movement. There were minimal differences in muscular activation of the biceps between post-operative settings (Figure 4.3A, 4.3B, 4.3C and 4.3D).

Due to the large within group standard deviation bands, it seems appropriate to investigate individual results of both the tremor-predominant and rigid akinetic sub-groups to investigate the effects of post-operative settings in greater detail. Figure 4.4 illustrates the individual results of the FlxT in both sub-groups in the 90°/sec task with contra-lateral hand cupping. The large standard deviation seen in Figure 4.2 and 4.3 can be explained by the individual variations present for each stimulation setting as seen in Figure 4.4. Note that even though there are large differences in the mean FlxT between participants, there is a trend of decreased resistive torque with post-operative settings in these two sub-groups (Figure 4.4). Stimulation to the dZI seems to have the greatest affect in reducing FlxT in the tremor-predominant sub-group (Figure 4.4A) while cZI stimulation had seemingly the best effect for the rigid akinetic sub-group (Figure 4.4B).
FIGURE 4.3: Line plot representation of the mean and standard deviation bars of the maximum resistive flexor torque, maximum biceps activation (% of SIVC), and maximum triceps activation (% of SIVC) during extension in the rigid akinetic Parkinson's participants (n = 4) over pre and post-operative assessments at (a) 30°/sec, (b) 30°/sec with the contra-lateral cupping task, (c) 90°/sec, (d) 90°/sec with the contra-lateral cupping task. Maximum resistive flexor torque for healthy controls is represented by the black dash line.
FIGURE 4.4: Individual breakdown of the line plot representation of the mean maximum resistive flexor torque during extension in the 90°/sec with the contra-lateral cupping over pre and post-operative assessments. (a) Tremor-predominant Parkinson’s participants (n = 3), (b) Rigid akinetic Parkinson’s participants (n = 4).
4.4 Discussion

To our knowledge, this is the first study to quantify the effects of acute ZI targeted PSA DBS on the rigidity component in PD using a resistive torque and EMG based approach during passive movement. Previous PSA DBS, specifically the ZI targeted studies [13–17,19] investigating rigidity in PD, have utilised semi-quantitative clinical rating scales such as the UPDRS [8,11,25]. Moreover, this is the first known study to investigate the effects of cZI and dZI stimulation on the sub-groups of PD and their individual response to stimulation.

Our results partially confirm our hypothesis, demonstrating a significant relationship between the UPDRS total score for the passive 30°/sec task in both ExtT and FlxT. Only the FlxT displayed a significant correlation with the UPDRS rigidity sub-score at this velocity. A significant correlation was also displayed between the ExtT for the passive 90°/sec task with contra-lateral hand cupping and the UPDRS total and tremor sub-scores. Our data suggest that measuring discrete resistive torque using this approach at higher velocity may elicit the tremor motor component of the PD symptom [11]. Power and colleagues (2011) also reported that the rigidity and/or tremor components of PD may be elicited with contra-lateral limb activation [26]. Therefore, we speculate that the coupled action of a contra-lateral task at higher velocities may increase the severity of proximal and/or distal tremor which then propagates an increased resistive torque due to the increased involuntary action measured by the dynamometer.

The trends in our data suggest that the pre-operative mean ExtT and FlxT of the PD group were generally higher than the healthy controls (Table 4.2). A significant difference was only seen for the FlxT during the passive 90°/sec task with contra-lateral hand cupping.
(p = .049) while a medium effects size was observed in the passive 30°/sec task with contra-lateral hand cupping ($d = 0.73$). As mentioned earlier, this is not surprising as it has been reported that PD rigidity and/or tremor is more pronounced with contra-lateral limb activation and at higher velocities [11,26]. The lack of significance in resistive torque data in the tasks without contra-lateral hand cupping may be attributed to a small sample size of PD sub-groups. Moreover, six out of 10 of the PD participants did not display a high rigidity score as assessed by the UPDRS (Table 4.1), and the PD participants were assessed during their optimal medication-ON state, thereby potentially minimising any difference in upper limb rigidity between the PD patients and the healthy controls [3].

The resistive torque variable that exhibited the most prominent change post-operatively was the FlxT (Table 4.2). The FlxT was seen to move towards healthy control values with post-operative settings in all tasks, most notably in the tremor-predominant group, particularly with dZI stimulation (Figure 4.2). Similarly, the rigid akinetic PD group appeared to have a decrease in FlxT and biceps activation with post-operative settings, particularly with cZI stimulation (Figure 4.3B, 4.3C, and 4.3D). However, the triceps activation appeared to increase in the rigid akinetic PD group, which is indicative of its contribution to assisting the movement (Figure 4.3). It is not surprising to observe a more prominent change in flexor resistive torque during the extension phase of movement, as studies have shown that it is in this phase that the severity of rigidity is more pronounced [1,5,10,27]. These data suggest that rigidity; for the rigid akinetic group and the tremor component; for the tremor-predominant PD group, appears to decrease with PSA micro-lesioning and stimulation which is in line with our hypothesis, although due to the heterogeneity of the sample, this did not achieve statistical significance.
The optimal target size for DBS to alleviate the symptoms of rigidity is still debatable. Early qualitative studies [13–16] demonstrated that rigidity decreased with cZI targeted PSA stimulation. However, a study by Blomstedt and colleagues (2012) presented less improvement in rigidity when the cZI target was stimulated [17]. Hamel et al. (2003) found a decrease in the UPDRS rigidity scores when the areas of and around the dZI were stimulated [19]. Our results indicate that even though rigidity as a whole was seen to decrease, the effect of PSA DBS on the PD sub-groups appears to have varying effects. We observed the largest decrease in FlxT and muscle activation in the tremor-predominant group with dZI stimulation while cZI stimulation displayed the greatest FlxT decrease for the rigid akinetic group. It is important to note that the sample size for this study is small, for this reason the results need to be interpreted with caution. Nevertheless, no studies to date have objectively quantified the differential improvements in rigidity following PSA DBS to the division of the ZI between the different PD sub-groups, therefore it is difficult to speculate upon the mechanism of action of targeted PSA DBS.

A possible explanation for the improvements noted in our study can be attributed to the reduction of autogenic inhibition. Using the theory proposed by Shapiro and colleagues (2007) and Delwaide and colleagues (2000) on their work with subthalamic nucleus DBS, they suggested that a reduction of autogenic inhibition via the spinal Ib interneurons via the basal ganglia is a key mechanism for Parkinsonian rigidity [9,28]. Micro-lesioning and stimulation of and around the PSA where the cZI and dZI are located may have altered the autogenic inhibition: function of the agonist and antagonist muscles, thus reducing the rigidity. For example, stimulation to the areas of and around the cZI of the rigid akinetic group may have led to an increase in triceps activation (agonist) and a decrease in biceps activation (antagonist) during an extension phase of the movement, thus leading to a decrease in FlxT.
Another potential explanation can be credited to the disruption of beta bands with DBS. Studies have provided some evidence, through local field potential recordings of the basal ganglia, indicating that the beta bands, which correlates to the PD symptoms, were seen to be suppressed with DBS [8,29,30]. The majority of research investigated in the ZI though, has been focused on the cZI and its proposed role in modulating Parkinsonian symptoms, specifically tremor [12–17]. The results of this study however suggest that the dZI seems to be favourable for tremor-predominant PD. It is unclear why the dZI had an improved affect than the cZI for the tremor-predominant group. Hamel et al. (2003) hypothesised that the dZI is a prime zone for termination of ascending axons from brain stem nuclei and is the origin for reciprocal innervation [19]. This zone may act as a critical node before transmitting information to the crucial areas of the brain such as the thalamus and cortex which have been found to have an influence on the pathophysiology of PD symptoms, particularly tremor [2,5]. It has also been suggested that the pathophysiology of the motor symptoms in PD do not necessarily share similar mechanisms [31]. DBS of the dZI and areas around it may have modulated the tremor signal leading to an improvement in the resistive torque as reported in our results.

The outcome of this study builds upon the work of other ZI targeted PSA studies [13–17] in its continued effectiveness to treat the negative motor symptoms in PD. Most importantly, this study gives rise to possible hypothesis with regards to the effects of DBS to the two divisions of the ZI on the different motor sub-groups in PD; whether the cZI or the dZI is a more effective DBS target for treating the predominant PD motor symptoms. While the tremor-predominant group had a decrease in triceps activation along with decreased flexor resistive torque, the rigid akinetic group had an increase in triceps activation to assist in reducing flexor resistive torque (Figure 4.2 and 4.3). The different muscular recruitment strategies observed between these two PD groups with post-
operative stimulation raise an interesting question as to whether the cZI or the dZI produce better clinical outcomes in one PD motor sub-group more than the other? Although the standard deviations were large between each sub-groups, individual trends observed indicate that the pattern is analogous as to the therapeutic benefits of ZI stimulation (Figure 4.4).

4.5 Conclusion

Overall, we found resistive torque, most notably in the elbow flexors, was reduced following ZI targeted PSA DBS. An important outcome of this study found no reports of any negative motor or non-motor symptoms with acute ZI targeted PSA DBS which is in agreement with previous research [13–17]. This research supports the ZI as being a target for DBS surgery to safely alleviate rigidity, a negative motor symptoms in PD. Importantly, this research contributes to the existing literature on the possible role of the cZI and dZI DBS on improving the PD symptoms in the motor sub-groups of PD. While the tremor-predominant participants exhibited the most therapeutic benefits with dZI stimulation, cZI stimulation seemed to be a more effective target for the rigid akinetic PD sub-group. Future research should assess the longer term outcome of cZI and dZI stimulation, with the aim of determining if patients with a particular PD motor predominance are the best responders to the different divisions of ZI targeted PSA DBS. Furthermore, as our data suggests that measuring resistive torque may elicit the tremor motor component of PD, we propose that torque-based assessments may be an effective tool to quantify the force of tremor, particularly in tremor-predominant PD.
Acknowledgements

This work was supported by scholarships from the University of Western Australia and Parkinson’s Western Australia Foundation. Thanks to Miss Meg Thorburn, Clinical Nurse Consultant, Sir Charles Gairdner Hospital for providing clinical support to enable inpatient biomechanical assessments, Mr Fausto Panizzolo from UWA for providing assistance with the MATLAB programming component, and Ms Stacy Foo from UWA for providing assistance with data collection.
References


CHAPTER FIVE

STUDY THREE

Effects of posterior subthalamic area micro-lesioning and stimulation on upper limb bradykinesia and action tremor in Parkinson’s disease
Foreword

Study One and Two reported generally positive outcomes with zona incerta targeted stimulation on tremor and rigidity through quantitative assessments. This final study concludes the effect of deep brain stimulation to this novel target site on bradykinesia and action tremor. Current literature lacks the quantitative comparison of stimulation to the different divisions of the zona incerta. Moreover, the outcome of deep brain stimulation for the treatment of bradykinesia and action tremor within the sub-groups of Parkinson’s disease remains unknown. It is intended that this paper will be submitted to the journal of ‘Parkinsonism & Related Disorders’.
Abstract

**Background:** Bradykinesia coupled with action tremor is often observed in Parkinson’s disease (PD) which negatively affects the execution of functional tasks. Semi-quantitative results suggest that deep brain stimulation (DBS) of the posterior subthalamic area (PSA) targeting the zona incerta (ZI) is effective in alleviating these symptoms.

**Methods:** We investigated the effect of ZI targeted PSA DBS on bradykinesia and action tremor through the use of quantitative assessments in the form of jerk measurements and integrated electromyography (iEMG) activity, in 10 idiopathic PD, along with 13 healthy age matched control participants.

**Results:** A significant increase in normalised jerk (NJ) in the secondary movement and a decrease in pectoralis iEMG were found in the pre-operative PD participants compared to the healthy control participants. Post-operative stimulation settings resulted in a significant decrease in movement time, NJ in the primary movement, and pectoralis iEMG in the PD group. Trends within the data suggest that jerk index, NJ, and trial to trial variability, all generally decreased with PSA DBS. Improvements with ZI stimulation on top of micro-lesioning were generally minimal.

**Conclusion:** Improvements in bradykinesia and action tremor specifically in the jerk variables were observed with ZI targeted PSA DBS, particularly with micro-lesioning, although its effect on iEMG warrants further investigation. Through DBS, the projections of the ZI may have an influence in altering signals via structures involved in movement planning. This novel experimental study supports the ZI as an effective target for DBS to reduce bradykinesia and tremor, although long term follow-up is recommended.

Abstract word count: 249
5.1 Introduction

Bradykinesia is one of the main motor symptoms in Parkinson’s disease (PD) and can be defined as the slowness of an active movement [1,2]. A decline in upper limb dexterity, subsequent to bradykinesia, coupled with action tremor is commonly exhibited in individuals with PD, resulting in increased difficulty in the initiation and-executing of functional tasks and daily activities [2,3]. It is important to acknowledge that the presence of resting tremor and dyskinesia, as observed in many PD cases, can also contribute to the decline in the fluency of movement [4]. The exact pathophysiology of bradykinesia is still unclear, although it has been suggested that insufficient muscle fibre recruitment during movement initiation is responsible [5]. Studies from transcranial stimulation and metabolic imaging, report that individuals with PD bradykinesia exhibit basal ganglia deficits and therefore compensatory alterations in the activation of cortical circuits [5–7]. The manifestation of negative motor symptoms, such as bradykinesia, are believed to be associated with these basal ganglia deficits [8,9].

Due to the progressive nature of PD, interventions seek to ameliorate these negative motor symptoms. Initial reports indicate that deep brain stimulation (DBS) of the posterior subthalamic area (PSA), specifically targeting the zona incerta (ZI), to be an effective DBS target site for treating bradykinesia and action tremor in PD [10–14]. Hamel et al. (2003) reported improvements in bradykinesia with stimulation to the dorsal division of the ZI (dZI), while Plaha and colleagues (2006) reported reductions in bradykinesia and tremor with caudal ZI (cZI) stimulation [13,14]. The cZI and dZI divisions have been proposed to influence movement, making it a suitable target site for DBS [15]. However, there have been no direct comparisons between the outcomes of cZI and dZI stimulation on bradykinesia and/or action tremor. While the initial outcomes of ZI targeted PSA DBS
in these studies appears good, they have largely utilised only semi-quantitative clinical rating scales such as the Unified Parkinson’s Disease Rating Scale (UPDRS) to assess the improvements during functional tasks. This assessment is categorical in nature, therefore its use as an outcome measure to assess change following intervention may be somewhat limited.

In efforts to characterise bradykinesia and action tremor in greater detail, and reduce potential intra- and inter-rater variability with qualitative and semi-quantitative assessments, researchers have successfully quantified these symptoms through utilising biomechanical methods such as movement time, jerk profiles, and electromyography [2,16–23]. As bradykinesia is termed the slowness of a voluntary movement [1,2], quantifying it through the use of movement time (analysis of time and displacement) is ideal. Jerk, the rate of change of acceleration, provides a good measure to quantify the smoothness of a motion, which have been found to be affected in individuals with PD [17,24,25]. The quantitative studies which have investigated bradykinesia and tremor profile in PD participants found increases in task movement time along with altered kinematic profiles; increased jerk values, increased variability between trials, and altered electromyography activity, most of which cannot be characterised through using qualitative clinical scales [2,16–23].

Therefore, we seek to investigate the effects of cZI and dZI targeted PSA DBS, on bradykinesia and action tremor in participants with PD, compared to healthy controls. Alterations in motor symptoms will be assessed with the use of quantitative assessments in the form of jerk measurements [17,20,26] and integrated electromyography (iEMG) activity in functional upper limb tasks adopted from the UPDRS. We expect increased
jerk variable values and an altered iEMG activity in PD participants at baseline compared to the controls in all functional assessment tasks. Improvements in jerk variables and iEMG activity are expected with micro-lesioning and stimulation to the areas of and around the cZI and dZI, in PD participants compared with their pre-operative levels, in all functional tasks following ZI targeted DBS surgery.

5.2 Methods

5.2.1 Participants

Ten idiopathic PD (7 males, 3 females, age 40-70 years) patients recruited from the Sir Charles Gairdner Hospital (SCGH) neurosurgical clinic, and 13 aged and gender matched healthy controls participated in this study after giving informed consent (refer to Appendix 3 and 4). The PD participants (detailed in Table 5.1) underwent DBS surgery as part of their clinical management. Out of the ten PD participants, three were tremor-predominant and seven were non tremor-predominant. Out of these seven non tremor-predominant group, four were rigid akinetic while the remaining three (classic group) exhibited at least two main PD motor symptoms; tremor, rigidity and/or bradykinesia. Ethical approval was granted by the SCGH ethics committee (2008-065 and 2012-039) and The University of Western Australia (UWA) (RA/4/1/5721) (refer to Appendix 1 and 2).
TABLE 5.1: Parkinson’s disease participant information.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Disease duration (Years)</th>
<th>Tremor Predominant</th>
<th>UPDRS: Tremor Score</th>
<th>UPDRS (Total)</th>
<th>Medication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD1</td>
<td>20</td>
<td>No</td>
<td>0</td>
<td>21</td>
<td>L/C/E 150/37.5/200 mg (x7); L/B 100/25 mg (x3); L/C 200/50 mg (x1); A 100 mg (x2)</td>
</tr>
<tr>
<td>PD2</td>
<td>13</td>
<td>No</td>
<td>1</td>
<td>30</td>
<td>L/B 250/50 mg (x5)</td>
</tr>
<tr>
<td>PD3</td>
<td>11</td>
<td>No</td>
<td>0</td>
<td>10</td>
<td>L/C/E 150/37.5/200 mg (x6); P 1.5 mg (x1)</td>
</tr>
<tr>
<td>PD4</td>
<td>12</td>
<td>Yes</td>
<td>9</td>
<td>11</td>
<td>R 16mg; E 200 mg (x6); L/C 250/25 mg (x4); L/C 250/25 mg (x0.5); L/C 100/25 mg (x6); L/C 200/50 mg (x1)</td>
</tr>
<tr>
<td>PD5</td>
<td>17</td>
<td>No</td>
<td>0</td>
<td>3</td>
<td>L/C 250/25 mg (x4); P 4.5 mg (x1)</td>
</tr>
<tr>
<td>PD6</td>
<td>6</td>
<td>Yes</td>
<td>18</td>
<td>39</td>
<td>No medication</td>
</tr>
<tr>
<td>PD7</td>
<td>12</td>
<td>No</td>
<td>0</td>
<td>6</td>
<td>L/C/E 50/12.5/200 mg (x1); L/B 200/50 mg (x1); A 100 mg (x3); L/C/E 200/50/200 mg (x3); L/C/E 150/37.5/200 mg (x1); L/B 50/12.5 mg (x2)</td>
</tr>
<tr>
<td>PD8</td>
<td>8</td>
<td>No</td>
<td>8</td>
<td>13</td>
<td>L/B 200/50 mg (x6-7); BH 2 mg (x3)</td>
</tr>
<tr>
<td>PD9</td>
<td>7</td>
<td>No</td>
<td>0</td>
<td>3</td>
<td>L/C/E 200/50/200 mg (x5); P 0.75 mg (x1); L/B 100/25 mg (x3); L/B 100/25 mg Slow release (x1)</td>
</tr>
<tr>
<td>PD10</td>
<td>4.5</td>
<td>Yes</td>
<td>12</td>
<td>41</td>
<td>No medication</td>
</tr>
</tbody>
</table>

* A – Amantadine hydrochloride, B – Benserazide, BH - Benzhexol Hydrochloride, C – Carbidopa, E – Entacapone, L – Levodopa, P – Pramipexole, R – Rotigotine

UPDRS scores signifies the assessments from the motor section (III) and values are reflective of an “ON” medication state.

5.2.2 Study design

The PD participants underwent two assessment sessions; pre-operative and post-operative at the UWA School of Sport Science, Exercise & Health’s biomechanics laboratory. After the pre-operative assessment, they underwent bilateral implants to the ZI which was performed at the SCGH. Detailed description of the surgical procedure can be found in Thani et al. (2012) [27]. The participants, accompanied by a member of the SCGH neurosurgical team, returned five days post-surgery for the post-operative assessment. The post-operative protocol repeated the pre-operative assessment with the addition of three different stimulation settings: i) micro-lesioning/stimulation off, ii) stimulation targeted to the cZI, and iii) stimulation targeted to the dZI. All stimulation administered was set at a frequency of 130 Hz, pulse width of 60 μs, and amplitude of 3.0 V and the stimulation settings presentation order was randomised and blinded to both the tester and participants. Daily food intake and medication delivery of the PD participants were standardised for at the pre- and post-operative assessments as an external control measure.
5.2.3 Experimental tasks

All participants were seated, on a height adjustable chair, at a table in a standardised position with their trunk upright, thighs horizontal to the ground, arms close to the body, elbows flexed at approximately 90° and both hands placed on the table. The participants performed two upper limb tasks, adapted in accordance with the UPDRS, representing functions affected by bradykinesia and action tremor. Assessments were performed only on the most affected limb for the PD participant, and the dominant limb for the healthy control participants. Adequate rest was given between trials to reduce the effects of fatigue. All participants were given a familiarisation trial before the start of data collection, and performed a total of three trials for each task. The two upper limb tasks were as follows:

i) Dot-to-dot tapping task: Participants performed a repetitive pointing movement with the index finger between two circular points in the middle of the table spread 30 cm horizontally apart. They were instructed to point to the targets as accurately and as quickly as possible. Participants completed six consecutive dot-to-dot taps, constituting one trial. Static calibration trials were collected from the index finger on each of the circles separately. These static trials were used as reference points to determine the accuracy of each individual trial.

ii) Finger-to-target pointing task: Participants performed a repetitive pointing movement with the index finger from nose to the target as accurately and as fast as they can. The target was a single retro-reflective marker placed in front of the participant in a standardised position approximately in the middle of the table. Six consecutive pointing actions from the target to the nose signify one successful trial. Static calibration trials were collected at the index finger to
target position. Similar to the dot-to-dot tapping task, these static trials were used to determine the task accuracy for the target.

5.2.4 Participant preparation

Prior to data collection, one retro-reflective marker was affixed to the participants’ most affected (or dominant limb) distal phalanx of the index finger using low-allergenic double sided adhesive tape (3M®, St. Paul, MN, USA). In addition, bipolar Ag/AgCl surface electrodes (ConMed Corporation®, Utica, NY, USA) were placed on the participants’ skin over the four different muscle bellies with 1.5 cm between electrodes after the skin was prepared by shaving, exfoliating and then cleaned with ethanol swabs. The four muscle bellies used for electromyography recording were as follow: latissimus dorsi, pectoralis major, biceps brachii, and flexor carpi radialis. Electrode placement was standardised to allow comparison of electromyography output from pre and post-operative assessments.

5.2.5 Data collection and processing

A 12-camera VICON® MX 3D motion analysis system (VICON Peak, Oxford, UK) with a sample rate of 250 Hz was used to determine the trajectory data of the marker, while a NORAXON® Telemyo system (Noraxon, USA, Inc., Scottsdale, AZ, USA) sampled at 2000 Hz synchronised with the motion data was used to collect electromyography data from the surface electrodes. Before the commencement of trials, sub-maximal isometric voluntary contractions (SIVC) were performed for normalisation of iEMG data. As the PD participants fall in the symptomatic population, SIVC is preferred to minimise the fatigability of the process. Details of the SIVC process is described in Table 5.2.
Participants performed a total of three SIVC for each muscle, holding the weight for three second in each trial, whereby the iEMG output were then averaged for normalisation.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latissimus dorsi</td>
<td>The participants lay prone with their arm extended, elbow flexed, semi-pronated forearm while holding a four kilogram dumb bell.</td>
</tr>
<tr>
<td>Pectoralis major</td>
<td>The participants lay supine with their arm abducted and elbow flexed at 90°, forearm pronated while holding a four kilogram dumb bell.</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>The participants held a five kilogram dumb bell with an upright trunk, shoulder and arm in a neutral position, elbow flexed at 90°, and with a supinated grip.</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>The participants sat upright on chair, arm flexed at 90°, forearm horizontally supported on a table in a supinated position, and a neutral wrist (unsupported) position holding a four kilogram dumb bell.</td>
</tr>
</tbody>
</table>

A total of six and 18 movement trials were analysed for the pre and post-operative analysis respectively for the PD participants, and a total of six movement trials were analysed for the healthy control participants. The start and end movement of the each tap and point was determined by a minimally set tangential velocity and visual inspection of the spatial trajectory reversal as outlined by Poizner and colleagues [18]. The three-dimensional trajectory data of these six taps/points were output, analysed and processed individually, and then averaged for statistical comparison. Three-dimensional trajectory outputs of the index finger were obtained using customised MATLAB® software (The Mathworks, Natick, MS, USA) (refer to Appendix 7). Three-dimensional movement substructures (jerk variables) of the index finger were calculated from the three-dimensional trajectory output using a custom written ‘jerk analysis’ program (LabView®, National Instruments, Austin, USA). The jerk variables analysed were the movement time, total task displacement, directness index, jerk index (JI), normalised jerk (NJ), and percentage normalised jerk in the primary (NJ1) and secondary movement (NJ2), as explained by Elliott et al (2011) [26]. Movement time was used to quantify bradykinesia while the rest of the jerk variables were used to quantify action tremor. The iEMG, which
is represented by the area under the curve, was processed as follows, the raw signal was high passed using a cut-off frequency of 20 Hz, full wave rectified, and again low passed using a cut-off frequency of 6 Hz to create a linear envelope. The iEMG was then calculated using the MATLAB® trapezoidal numerical integration function, and finally normalised to the respective iEMG of the muscle obtained during SIVC (refer to Appendix 7).

5.2.6 Statistical analysis

Due to the variability and the dissimilar sample size of the healthy controls and PD sub-groups, non-parametric statistics were applied. The Mann-Whitney U test was used to determine differences between the pre-operative assessments of PD participants and the healthy controls while Cohen's $d$ was used to measure the effect size. For within PD group comparisons, a Friedman’s test was used to ascertain significant differences between pre-operative levels and the effect of micro-lesioning, and varying stimulation settings. Bonferroni post-hoc correction with the significance level set at $p < 0.008$ was then applied for the comparison between pre and post-operative assessments to determine the nature of significant differences and control for multiple comparisons. All analyses were performed using IBM® SPSS® Statistics 21 (IBM Corporation, Armonk, NY, USA). Descriptive analysis were used to present the results of the PD sub-groups when, due to sample size, statistical analysis were not viable.

5.3 Results

There were no reports of negative motor and non-motor symptoms manifesting from post-operative settings in any PD participant. The outcome of pre and post-operative PD assessments, along with the data of the healthy control participants are presented as
discrete group mean jerk variables. As the spectrum of symptoms in PD is large and variable, differences between sub-groups were observed when separating the tremor-predominant patients from the non tremor-predominant PD group, as such, descriptive analysis was utilised to describe these data. Further breakdown of the results were performed to observe the progress of each individual PD participant with post-operative settings, and differentiate the rigid akinetic group from the classic group. The iEMG outputs are presented as a percentage of the respective muscle SIVC.

5.3.1 Jerk analysis

5.3.1.1 Comparison between PD and healthy controls

No significant differences in accuracy between the two groups were found in any task (Table 5.3). Although non-significant, pre-operatively, there was a general trend of increased movement time in both the whole PD group and non-tremor predominant PD group as compared to the healthy controls in both tasks (Table 5.3). Figure 5.1 illustrates the trajectory of a representative healthy control and a PD participant (PD2) in a pointing task trial. Notice the difference in the initiation of the movement and the additional corrective movement performed by the PD participant as the trajectory moves between the target and the nose (Figure 5.1). The differences in the initiation of the movement would result in an increase in NJ1 for this PD participant. Similarly, differences exhibited in the PD participant during the final sequencing of the task where there is obvious movement correction toward the target, would result in an increase in NJ2. Combined these deviations in movement pathway would result in higher JI and NJ, as these variables are utilised to measure the smoothness of a motion/trajectory.
FIGURE 5.1: The trajectory of a representative pointing trial of a healthy control and a PD participant (PD2) output from the custom LabView program. The blue and red dots represent the nose and target respectively (start and end point of the trajectory).

Normalised jerk in the secondary movement was significantly increased in the whole PD group pre-operatively (48.89) as compared to controls (32.21), $U = 32, p = 0.041$ in the pointing task, as displayed in Table 5.3. Normalised jerk and NJ1 in the tapping task were also elevated in the non tremor-predominant PD group pre-operatively (NJ = 602.50, NJ1 = 460.19) as compared to controls (NJ = 326.11, NJ1 = 235.77) (Table 5.3). Further investigation of these differences found a large effect size for both NJ and NJ1 ($d = 0.79$ for both variables) (Table 5.3). Similarly, in the pointing task, whilst there were no significant differences, large effect sizes was observed for JI ($d = 0.86$) and NJ ($d = 0.97$), these variables were seen to be elevated in the non tremor-predominant PD group prior to surgery (JI = 0.78, NJ = 212.35) as compared to controls (JI = 0.17, NJ = 110.87) (Table 5.3). In this task, there was also a significant difference in NJ2 in the non tremor-predominant PD group prior to surgery (52.95) when compared to controls (32.21), $U = 17, p = 0.024$ (Table 5.3).
TABLE 5.3: Jerk variables of all participants.

<table>
<thead>
<tr>
<th>Condition &amp; COV</th>
<th>Accuracy (mm)</th>
<th>Movement Time (s)</th>
<th>Direct Index</th>
<th>Jerk Index (10^3)</th>
<th>Normalised Jerk</th>
<th>Normalise jerk in 1st Movement</th>
<th>Normalise jerk in 2nd Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tapping</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls Cov</td>
<td>2.98 (1.45)</td>
<td>0.50 (0.10)</td>
<td>1.12 (0.07)</td>
<td>1.45 (1.39)</td>
<td>326.11</td>
<td>194.81</td>
<td>235.77 (148.21)</td>
</tr>
<tr>
<td>Cov</td>
<td>49</td>
<td>20</td>
<td>6</td>
<td>96</td>
<td>46</td>
<td>63</td>
<td>40</td>
</tr>
<tr>
<td><strong>All PD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreOp Cov</td>
<td>4.35 (1.99)</td>
<td>0.56 (0.21)</td>
<td>1.17 (0.16)</td>
<td>4.61 (7.70)</td>
<td>513.15 (471.1)</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>Cov Micro</td>
<td>4.88 (1.39)</td>
<td>0.43 (0.11)</td>
<td>1.14 (0.10)</td>
<td>1.23 (1.29)</td>
<td>287.19</td>
<td>171.75</td>
<td>220.36 (163.41)</td>
</tr>
<tr>
<td>Cov cZ1</td>
<td>4.76 (1.16)</td>
<td>0.45 (0.13)</td>
<td>1.14 (0.09)</td>
<td>1.85 (2.35)</td>
<td>345.44</td>
<td>232.95</td>
<td>239.13 (217.86)</td>
</tr>
<tr>
<td>Cov dZ1</td>
<td>4.79 (1.55)</td>
<td>0.47 (0.13)</td>
<td>1.14 (0.09)</td>
<td>2.44 (3.74)</td>
<td>368.82</td>
<td>301.82</td>
<td>259.02 (239.87)</td>
</tr>
<tr>
<td>Cov</td>
<td>32</td>
<td>28</td>
<td>8</td>
<td>32</td>
<td>50</td>
<td>56</td>
<td>61</td>
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<tr>
<td><strong>Non Tremor</strong></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PreOp Cov</td>
<td>3.84 (1.92)</td>
<td>0.64 (0.21)</td>
<td>1.18 (0.19)</td>
<td>6.11 (8.93)</td>
<td>602.50</td>
<td>473.29</td>
<td>460.19 (371.07)</td>
</tr>
<tr>
<td>Cov Micro</td>
<td>5.78 (1.33)</td>
<td>0.40 (0.07)^*</td>
<td>1.15 (0.12)</td>
<td>0.87 (0.73)^*</td>
<td>244.62 (137.35)^*</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>Cov cZ1</td>
<td>4.72 (1.26)</td>
<td>0.43 (0.09)^*</td>
<td>1.14 (0.11)</td>
<td>1.19 (1.08)^*</td>
<td>285.86 (174.79)^*</td>
<td>81.70 (141.24)^*</td>
<td>104.16 (94.72)</td>
</tr>
<tr>
<td>Cov dZ1</td>
<td>5.00 (1.52)</td>
<td>0.46 (0.07)</td>
<td>1.12 (0.09)</td>
<td>1.70 (1.98)</td>
<td>331.56</td>
<td>214.48</td>
<td>221.95 (144.03)</td>
</tr>
<tr>
<td>Cov</td>
<td>30</td>
<td>15</td>
<td>8</td>
<td>116</td>
<td>65</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td><strong>Pointing</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls Cov</td>
<td>4.54 (3.49)</td>
<td>0.37 (0.09)</td>
<td>1.04 (0.01)</td>
<td>0.17 (0.19)</td>
<td>110.87 (54.33)</td>
<td>78.66 (45.76)</td>
<td>32.21 (15.96)</td>
</tr>
<tr>
<td>Cov</td>
<td>77</td>
<td>24</td>
<td>1</td>
<td>110</td>
<td>49</td>
<td>58</td>
<td>50</td>
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<td><strong>All PD</strong></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>PreOp Cov</td>
<td>7.62 (4.98)</td>
<td>0.41 (0.10)</td>
<td>1.03 (0.01)</td>
<td>0.64 (0.87)</td>
<td>185.76 (126.94)</td>
<td>136.87 (110.06)</td>
<td>48.89 (22.12)^2</td>
</tr>
<tr>
<td>Cov Micro</td>
<td>6.34 (2.63)</td>
<td>0.30 (0.05)^*</td>
<td>1.03 (0.01)</td>
<td>0.10 (0.06)^*</td>
<td>86.55 (26.35)^*</td>
<td>52.33 (21.09)^*</td>
<td>34.23 (13.82)</td>
</tr>
<tr>
<td>Cov cZ1</td>
<td>6.97 (5.20)</td>
<td>0.34 (0.17)^*</td>
<td>1.04 (0.02)</td>
<td>0.70 (0.18)</td>
<td>108.83 (49.85)</td>
<td>73.15 (26.53)</td>
<td>35.70 (17.92)</td>
</tr>
<tr>
<td>Cov dZ1</td>
<td>7.12 (4.28)</td>
<td>0.34 (0.08)^*</td>
<td>1.04 (0.02)</td>
<td>0.16 (0.12)</td>
<td>108.72 (45.02)</td>
<td>73.50 (40.18)^*</td>
<td>35.22 (13.00)</td>
</tr>
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<td>Cov</td>
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<td>1</td>
<td>77</td>
<td>41</td>
<td>55</td>
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<tr>
<td><strong>Non Tremor</strong></td>
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<tr>
<td>Predominant PD</td>
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<td></td>
</tr>
<tr>
<td>PreOp Cov</td>
<td>6.77 (3.47)</td>
<td>0.44 (0.11)</td>
<td>1.03 (0.01)</td>
<td>0.78 (1.01)</td>
<td>212.35 (140.73)</td>
<td>159.41 (124.06)</td>
<td>52.95 (21.88)^2</td>
</tr>
<tr>
<td>Cov Micro</td>
<td>6.33 (2.89)</td>
<td>0.30 (0.04)^*</td>
<td>1.03 (0.01)</td>
<td>0.60 (0.93)^*</td>
<td>79.92 (28.05)^*</td>
<td>51.43 (15.55)^*</td>
<td>28.50 (10.63)</td>
</tr>
<tr>
<td>Cov cZ1</td>
<td>6.57 (3.89)</td>
<td>0.33 (0.04)^*</td>
<td>1.04 (0.01)</td>
<td>0.12 (0.10)^*</td>
<td>96.55 (40.94)^*</td>
<td>65.14 (30.14)</td>
<td>31.41 (13.98)</td>
</tr>
<tr>
<td>Cov dZ1</td>
<td>8.17 (4.62)</td>
<td>0.33 (0.08)^*</td>
<td>1.04 (0.01)</td>
<td>0.17 (0.14)</td>
<td>111.54 (52.16)</td>
<td>78.44 (45.24)</td>
<td>33.09 (15.32)</td>
</tr>
<tr>
<td>Cov</td>
<td>57</td>
<td>24</td>
<td>1</td>
<td>84</td>
<td>47</td>
<td>58</td>
<td>46</td>
</tr>
</tbody>
</table>

The mean (±SD) jerk variables of all Parkinson participants in all settings and conditions along with their respective healthy controls. COV represents the coefficient of variation for the respective variable and participant groups. *Tremor denotes discrete jerk variables for all PD participants (n = 10) while –Tremor denotes all PD participants with the exception of the tremor-predominant PD sub-type (n = 7).

- Significantly different from controls $p < 0.05$
- Significantly different from pre-operative assessment after Bonferroni corrections $p < 0.005$
- Approaching significance from pre-operative assessment after Bonferroni correction $p < 0.008$
5.3.1.2 Comparison within PD group following DBS - Tapping task

In the tapping task, the jerk variables which displayed the most prominent changes with post-operative settings were movement time, JI and NJ. A decrease in movement time, JI, NJ, NJ1 and NJ2 with post-operative settings was observed in the whole PD group as well as the non-tremor predominant group compared to their baseline levels, though these differences did not reach statistical significance when the Bonferroni correction was applied (Table 5.3). Coefficient of variation (COV) for movement time, JI, NJ and NJ2 were seen to decrease in the whole PD group as well as the non-tremor predominant group with post-operative settings, particularly with micro-lesioning though these differences did not reach statistical significance (Table 5.3).

As illustrated in Figure 5.2A, 5.2C, and 5.2E, for the tapping task there was a trend in the tremor-predominant PD group, whereby an increase in all three jerk variables was observed across the post-operative conditions. Interestingly, when results are separated to present each tremor predominant participant’s individual progress, there were no deterioration in movement time and NJ for two tremor-predominant participants particularly with dZI stimulation (PD4 and PD10) (Figure 5.3A and 5.3B). We observe that the results of PD6 skewed of the overall data for the tremor-predominant group towards a deteriorating movement pattern with post-operative settings (Figure 5.2A, 5.2C, and 5.2E). Conversely, during the tapping task, these three jerk variables were seen to decrease with post-operative settings in the non tremor-predominant sub-groups; rigid akinetic and classic group, particularly with micro-lesioning (Figure 5.2A, 5.2C, and 5.2E). This is confirmed upon descriptive analysis of their individual data (Figure 5.3B, 5.3C, 5.3E and 5.3F).
FIGURE 5.2: Line plot representation of the mean and standard deviation of the movement time, jerk index and normalised jerk in the tremor-predominant Parkinson’s participants (n = 3), represented by black square points and dotted black line, and non tremor-predominant Parkinson’s participants (n = 7), represented by the red circle points and red line, over pre and post-operative assessments in both the tapping and pointing task. The range of healthy control value is represented by the shaded grey area. (A) Movement time in the tapping task, (B) Movement time in the pointing task, (C) Jerk index in the tapping task, (D) Jerk index in the pointing task, (E) Normalised jerk in the tapping task, (F) Normalised jerk in the pointing task.
FIGURE 5.3: Line plot representation of the mean movement time and normalised jerk in the tremor-predominant Parkinson’s participants (n = 3), rigid akinetic Parkinson’s participants (n = 4), and classic Parkinson’s participants (n = 3), over pre and post-operative assessments in the tapping task. (A) Movement time for the tremor-predominant group, (B) Movement time for the rigid akinetic group, (C) Movement time for the “classic” group, (D) Normalised jerk for the tremor-predominant group, (E) Normalised jerk for the rigid akinetic group, (F) Normalised jerk for the “classic” group.
5.3.1.3 Comparison within PD group following DBS - Pointing task

In the pointing task, a significant reduction in movement time was found with post-operative settings as compared to pre-operative levels in the whole PD group, $\chi^2(3) = 17.760, p < .000$ (Table 5.3). Post-hoc analysis revealed that this reduction was significant in the micro-lesioning condition ($Z = -2.803, p = 0.005$) and dZI stimulation ($Z = -2.701, p = 0.007$) (Table 5.3). Likewise, a significant difference was observed with post-operative setting for NJ1, $\chi^2(3) = 12.720, p = 0.005$ (Table 5.3). This reduction is attributed to the significant difference observed with micro-lesioning only ($Z = -2.803, p = 0.005$) (Table 5.3). A significant group difference was observed for both JI and NJ with post-operative settings ($\chi^2(3) = 8.760, p = 0.033$) though this difference was not upheld under the Bonferroni corrections (Table 5.3). Nonetheless, large effects sizes were observed for JI ($d = 0.89$) and NJ ($d = 1.08$) with the micro-lesioning setting in this whole PD group as compared to pre-operative levels (Table 5.3). We found a decrease in the movement time, JI, NJ and NJ1 for the non tremor-predominant sub-group with post-operative settings compared to baseline levels, although no significant difference was observed when the Bonferroni correction was applied (Table 5.3). The COV for JI, NJ, NJ1 and NJ2 were seen to decrease with post-operative settings particularly with micro-lesioning, although no significant differences were detected (Table 5.3).

As illustrated in Figure 5.2B, 5.2D, and 5.2F, a general trend of decreased movement time, JI and NJ in the pointing task was observed with post-operative settings, specifically for the non tremor-predominant sub-group. Individual data for the PD participants in the pointing task confirms that micro-lesioning generally had the best response for the rigid akinetic and classic PD groups (Figure 5.4B, 5.4C, 5.4E and 5.4F) while micro-lesioning
and dZI stimulation may have a slightly better effect for the tremor-predominant group in reducing the jerk variables (Figure 5.4A and 5.4D).

5.3.2 iEMG analysis

5.3.2.1 iEMG Comparison between PD and healthy controls

The pre-operative PD group displayed a significant decrease in pectoralis iEMG in the tapping task compared to the controls, U = 33, p = 0.047, with a mean activation of 23% for the PD group and 36% for controls (Figure 5.5A). Similarly, in the pointing task, pectoralis iEMG was decreased for the PD group (15%) in comparison to the controls (22%) with values approaching significance, p = 0.051, as illustrated in Figure 5.5B.

5.3.2.2 iEMG Comparison within PD group following DBS - Tapping task

In the tapping task, there was a statistically significant decrease in pectoralis iEMG in the PD group, ($\chi^2(3) = 12.771, p = 0.005$), with post-operative settings as compared to pre-operative levels (Figure 5.5 A). Post-hoc comparisons found significant differences between the pre-operative activation levels (23% SIVC) and cZI stimulation (13.4% SIVC), ($Z = -2.803, p = 0.005$), and between pre-operative activation levels (23% SIVC) and dZI stimulation (12.1% SIVC), ($Z = -2.701, p = 0.007$). Although there was no significant differences, a decreased in biceps and latissimus dorsi iEMG was observed with all three post-operative settings compared to baseline levels (Figure 5.5A). In general, there were minimal differences between the three post-operative settings during the tapping task (Figure 5.5A).
FIGURE 5.4: Line plot representation of the mean movement time and normalised jerk in the tremor-predominant Parkinson’s participants (n = 3), rigid akinetic Parkinson’s participants (n = 4), and classic Parkinson’s participants (n = 3), over pre and post-operative assessments in the pointing task. (A) Movement time for the tremor-predominant group, (B) Movement time for the rigid akinetic group, (C) Movement time for the “classic” group, (D) Normalised jerk for the tremor-predominant group, (E) Normalised jerk for the rigid akinetic group, (F) Normalised jerk for the “classic” group.
FIGURE 5.5: Column chart representation of the mean and standard deviation of the iEMG of four muscles (% of SIVC) in the Parkinson’s participants (n = 10) over pre and post-operative assessments and the healthy controls. (A) Tapping task, (B) Pointing task. * denotes significant differences (p = 0.005, p < 0.008).

5.3.2.3 iEMG Comparison within PD group following DBS - Pointing task

In the pointing task, pectoralis iEMG was seen to decrease significantly, ($\chi^2(3) = 13.439$, $p = 0.004$), with post-operative settings as compared to pre-operative levels (Figure 5.5B). Post-hoc analysis found a significant decrease in pectoralis iEMG between pre-operative activation levels (15.4% SIVC) and dZI stimulation (7.5% SIVC) as illustrated in Figure
5.5 B, \((Z = -2.666, p = 0.008)\). Biceps iEMG \((\chi^2(3) = 11.878, p = 0.008)\) and latissimus dorsi iEMG \((\chi^2(3) = 10.697, p = 0.013)\) were seen to decrease with post-operative settings as compared to pre-operative levels, although this did not reach statistical significance with Bonferroni correction (Figure 5.5B).

5.4 Discussion

This is the first study, to our knowledge, to quantitatively investigate the role of ZI targeted PSA DBS on PD bradykinesia and action tremor through specific functional movements. Previous studies in this area that have found improvements in bradykinesia and tremor have largely utilised semi-quantitative clinical rating scales such as the UPDRS [10–13]. Importantly, this study examined the differences between cZI and dZI DBS on bradykinesia in PD utilising jerk and iEMG analysis, particularly with respect to the different PD motor sub-groups, tremor-predominant and non tremor-predominant.

A trend of increased movement time was exhibited in the PD group as compared to healthy controls. Although there was no statistical difference in accuracy, a significant increase in NJ2 during the pointing task was present in the whole PD group pre-operatively as compared to controls. In addition, NJ and NJ1 in the tapping task were also elevated in the non tremor-predominant PD group as compared to healthy controls. In the pointing task, the non tremor-predominant PD group displayed a significant increase in NJ2 prior to surgery when compared to controls. Furthermore, a large effect size was observed for JI and NJ in the pointing task as these variables were seen to be elevated in the non tremor-predominant PD group prior to surgery as compared to controls. It has been proposed that there are two components of a movement; the primary submovement responsible for the gross movement and the secondary submovement, performed to
improve the accuracy of the primary submovement [23,28]. The use of jerk measurements such as JI, NJ, NJ1 and NJ2 provides a valid profile to quantify both these components of movement, which have been found to be affected in individuals with PD [17,24,25]. The increase in movement time and jerk measurements observed in the pre-operative PD participants compared to the healthy controls, is indicative of increased bradykinesia and/or action tremor, and is in line with our hypothesis. These findings support the use of movement time and jerk measurements to quantify the severity of bradykinesia and action tremor [2,16–18,20–23]. Moustafa and Poletti (2013) proposed that the motor symptoms in PD are more severe in the non-tremor predominant sub-group as compared to the tremor-predominant sub-group [29]. Therefore it is not an unexpected outcome to observed higher values in movement time and jerk in the non-tremor predominant PD group compared to healthy controls as opposed to the whole PD group compared to the healthy controls.

A significant reduction in pectoralis iEMG activation in the tapping task was observed in the pre-operative PD participants as compared to healthy controls (Figure 5.5A and Table 5.3). This result concurs with that of Fradet et al. (2009) who reported alterations in muscular activation in PD, suggesting that it was due to the dissimilar adaptation strategy to complete a movement task [22]. We did, however expect alterations in iEMG in all four muscles for the PD participants as compared to their healthy controls. These results partially support our hypotheses and are also in partial agreement with previous quantitative studies which report increased electromyography differences between PD and healthy controls [16,17,19,21,30]. The lack of iEMG differences between PD and controls in our study may be due to the PD participants being assessed during their optimal medication state thereby possibly masking the more severe motor symptoms, and adaptations in muscle activation [31].
The whole PD group displayed significant decreases in movement time and NJ1 in the pointing task as a result of DBS (Table 5.3). This demonstrated that PSA DBS specifically with micro-lesioning and dZI stimulation reduced the NJ1 (i.e. jerk during the primary submovement) which propagated to a resultant decreased in movement time (Table 5.3). This reduction is reflective of an improvement in bradykinesia and action tremor, which is in support of previous studies reporting the reduction of PD symptoms with ZI targeted PSA DBS [10–14]. Interestingly, the large effect sizes of JI and NJ suggest that the trend for decreased jerk variables as a result of micro-lesioning is likely to reflect a real difference following surgery for the pointing task. Therefore, future research with an increased sample size may be warranted to develop statistical significance.

With regards to iEMG following DBS in the whole PD group, each muscle group displayed a general trend of decrease in activation (Figure 5.5). Significant reduction of activation was observed following stimulation to the dZI compared to pre-operative levels in both pointing and tapping tasks. Furthermore, cZI stimulation also produced a significant decreased in iEMG in the tapping task compared to pre-operative levels. These levels of activation are well below that of the healthy controls for these tasks. This change in iEMG activity may be due to some form of motor unit de-synchronization as a result of DBS coupled with an optimal medication-ON state, suggestive of a strategy for neuromuscular activation i.e. performing the tapping or pointing tasks [32].

Results from the sub-group analysis clearly presents that the non-tremor-predominant PD participants, rigid akinetic and classic group, demonstrate a positive effect through a decrease in movement time and jerk values, particularly with micro-lesioning. This was true in both tapping and pointing tasks. Nevertheless, the results only reflect the trends of
a data due to a limited sample size, therefore future research assessing a larger sample of
PD sub-groups could shed more light on the outcome of ZI targeted PSA DBS. It should
be noted that we did expect some form of dyskinesia to be present post-operatively,
particularly in the rigid akinetic group, which may have confounded our measurements,
although the clear improvements in the jerk variables with post-operative settings suggest
otherwise.

Despite the clear outcome in the non tremor-predominant group, post-operative data from
the tremor-predominant sub-group was more variable with PD4 and PD10 displaying
slight improvements in the pointing task while PD6 displayed a distinct increase in
movement time and NJ in the tapping task. It may seem that PD6 did not have an initial
positive response with acute PSA DBS. Nevertheless, personal communications with one
of the authors (C.L) suggest good clinical outcomes both with the participant’s motor and
non-motor symptoms after three, six and 12 months follow-up. The results of PD6
indicate that assessment in this acute phase of surgery may give a skewed representation
of the group’s data. On the contrary, acute assessment does provide information on the
effects of DBS in the short term. Therefore, it is important that researchers/clinicians
perform follow-up assessments to establish new information on identifying the best
responders to this novel target site. Assessing initial outcome and ongoing outcomes may
have distinct advantages for the prescription of rehabilitation programs for the optimal
recovery of individuals.

Plaha and colleagues (2006) reported a decline in bradykinesia and tremor when the cZI
was stimulated in patients with PD [13] while Hamel and colleagues (2003) found the
dZI to be an effective target in the treatment of PD symptoms [14]. Neither of these two
studies directly compared the outcome between cZI and dZI stimulations. In addition, there are no studies to have investigated the outcome of ZI DBS in the different sub-groups of PD. Interestingly, a prime observation in this study saw the greatest reduction in bradykinesia and action tremor with the micro-lesioning effect in the non tremor-predominant group, while both micro-lesioning and dZI stimulation appeared to have the best effect for the tremor-predominant group specifically in the pointing tasks (exception of PD6). To avoid skewness and misinterpretation of results, we recommend that assessments in bradykinesia and action tremor be performed with the PD participants grouped according to their predominant motor symptoms. We also noted a general decrease in COV for all jerk variables in all PD groups and in both tasks with post-operative settings, suggestive of a decrease in trial-to-trial variability. This finding is in support of a study by Brown and colleagues (1999), who reported that DBS of the subthalamic nucleus and global pallidus internus resulted in faster movement executions with less variability [33]. Similarly, Potter-Nerger and colleagues (2009) reported improvements in finger tapping scores with subthalamic nucleus DBS [34]. Our results suggest that the ZI may be as effective as the subthalamic nucleus and the global pallidus internus DBS targets for the treatment of bradykinesia and action tremor.

As there is currently limited research in this novel target, forming absolute deductions as to the mechanistic physiology of micro-lesioning and DBS to the ZI can be erroneous. We speculate that the vast projections of the ZI [15] may have an influence in altering signals to and from structures like the cerebellum which have been found to have an influence on movement fluency.
5.5 Conclusion

This is the first study in our knowledge to report improvements in bradykinesia and action tremor with stimulation to the two divisions of the ZI through quantitative measurements. The findings of this study supports the use of kinematic (movement time and jerk) and iEMG analysis to quantify the severity of bradykinesia and action tremor as it provides information which is unattainable through semi-quantitative assessments. Our research supports the role of the ZI being a good and safe candidate target for DBS surgery to improve bradykinesia and action tremor, and builds upon evidence from other ZI targeted PSA DBS studies [10–14]. Moreover, our research also provides initial evidence as to the effectiveness of PSA DBS in the sub-groups of PD which have not been reported in this detail before. These findings suggest that micro-lesioning for the non-tremor predominant group, and micro-lesioning and dZI stimulation for the tremor-predominant group may be efficacious stimulation sites for alleviating PD bradykinesia and action tremor. With future research assessing the longer term outcome of both cZI and dZI stimulation in a larger sample size of PD sub-groups, it may be possible to identify which PD sub-groups are the best responders to ZI targeted PSA DBS.

Acknowledgements

This work was supported by the scholarship from the University of Western Australia and Parkinson’s Western Australia foundation. Thanks to Miss Meg Thorburn, Clinical Nurse Consultant from the Sir Charles Gairdner Hospital for providing clinical support to enable inpatient biomechanical assessments, Mr Neville Pires from UWA for providing assistance with the MATLAB programming component, and Ms Stacy Foo from UWA for providing assistance with data collection.
References


CHAPTER SIX

GENERAL DISCUSSION
6.1 Summary

Parkinson’s disease (PD) is a degenerative disorder of the central nervous system widely believed to be the result of a pathophysiologic loss or degeneration of dopaminergic neurons in the substantia nigra of the basal ganglia (BG) system within the brain [1–4]. Its definitive genesis however, is relatively unknown. This disease is characterised by the manifestation of three main motor symptoms; tremor, rigidity, and bradykinesia, that are often present in the upper limb [5–7]. These symptoms can present as a single predominant symptom or in combination. The manifestation of these motor symptoms impairs movement, compromising an individual’s ability to perform motor skills, in turn predisposing them to injury and/or abandonment of social/physical activities, thus affecting their quality of life [8–12].

Deep brain stimulation (DBS) targeted at specific BG targets has been applied to treat the PD motor symptoms with a high level of success [13,14]. Recently, researchers have targeted an area in the posterior subthalamic area (PSA) called the zona incerta (ZI), suggesting that it is a highly effective site for alleviating the three main symptoms in PD; tremor, rigidity and bradykinesia, without the manifestation of severe side-effects [15–22]. Plaha and colleagues (2006) targeted the caudal division of the ZI (cZI) and found reductions in the motor symptoms of their PD patients [18]. Hamel et al. (2003), on the other hand, provided stimulation to the dorsal division of the ZI (dZI) and also reported motor improvements in patients with PD [22]. There have been no published studies to have compared the outcomes between cZI and dZI stimulation within individuals. Equally as important, there have been no comparative studies between the outcomes of ZI stimulation on the sub-groups of PD. Given that PD is such a heterogeneous condition, it may be more relevant to examine individual or changes occurring within symptoms,
rather than the global change of the whole spectrum of patients with PD. Moreover, most
of the original reports are based on semi-quantitative clinical evaluation of symptoms
such as the Unified Parkinson’s Disease Rating Scale (UPDRS) which, although valid
and reliable, provides only limited categorical assessment of the alterations in the PD
symptoms following intervention [23,24].

Therefore, this research aimed to explore these previously un-resolved questions to
contribute to the existing level of evidence for ZI targeted PSA DBS and its success in
treating upper limb motor symptoms in PD. The research problems outlined were
addressed through three interrelated studies of the alterations in the predominant PD
motor symptoms as a result of ZI DBS. This chapter will summarise the findings of each
of these studies with respect to the hypotheses developed in Chapter One, derive
conclusions based on the results of these studies, and finally provide recommendations
for future research.

6.1.1 Chapter Three: The effect of acute posterior subthalamic area micro-lesioning
and stimulation on upper limb tremor and activation patterns in Parkinson’s disease

No known quantitative studies on PD exist regarding alterations in tremor following acute
PSA micro-lesioning or stimulation specifically targeting the areas of and around the cZI
and dZI. Therefore the aim of this study were to firstly, determine the differences in
tremor through the use of spectral analysis and integrated electromyography (iEMG) in
the proximal and distal upper limb segments of PD participants in relation to healthy
controls. Secondly, investigate the acute effects of micro-lesioning and stimulation to the
PSA where the cZI and dZI are located, and its outcome on tremor in the proximal and
distal upper limb segments in the PD participants and its sub-groups.
The hypothesis that:

“PD participants will exhibit altered spectral analysis and iEMG levels as compared to the healthy controls in all tasks.”

was partially supported. Although there were no statistically significant differences, the descriptive data indicated that spectral analysis parameters were indeed increased both proximally and distally, and altered iEMG activity were exhibited in the pre-operative PD participants as compared to the healthy controls during the tremor tasks.

The secondary hypothesis that:

“Improvements in spectral analysis parameters and iEMG levels more representative of normative values are expected with micro-lesioning and stimulation to the areas of and around the cZI and dZI, in PD participants: specifically for the participants who underwent surgery to treat their tremor, compared to their pre-operative levels, in all segments and tasks.”

was partially supported. A decrease (non-significant) in the spectral analysis parameters at both segments and iEMG activity (triceps brachii, anterior deltoid and latissimus dorsi) moving towards normative values across both tasks (with the exception of the hand in the resting task) were observed with post-operative settings in the whole PD group. There was a distinct trend of tremor improvements with a decrease in the spectral analysis in the PD participants who underwent surgery specifically to relieve their tremor, with the exception of one participant (PD6). In this group, apart from one participant, ZI targeted PSA DBS was particularly effective in reducing tremor through a decrease in the amplitude of frequency and power in the range of 4-7 Hz. There also appeared to be an added benefit of cZI and dZI stimulation for the tremor predominant participants.
specifically in the distal (hand) segment. The decrease in trapezius iEMG and an increase in flexor carpi radialis iEMG with post-operative settings is not in line with our hypothesis. This may be partially explained by an altered adaptation strategy in both activation and planning to complete a movement as a result of PSA DBS, and the potential influence of medication during the assessments.

The descriptive data provides a level of support to the hypothesis that dissimilarities would exist in the spectral analysis and iEMG parameters between pre-operative PD and healthy control participants. Importantly, this novel research reports improvements in resting and postural tremor, at both proximal and distal upper limb segments, following DBS, particularly with stimulation to the ZI. This outcome was particularly apparent for individuals who underwent surgery primarily for tremor reduction. Follow-up clinical assessments of PD6 (not conducted as part of this research), report good clinical outcome for this participant following three, six and 12 months PSA DBS. These data build upon previous work in ZI DBS as to its effectiveness in alleviating the tremor symptoms in PD [16–22,25].

6.1.2 Chapter Four: Outcome of elbow rigidity with posterior subthalamic deep brain stimulation in Parkinson’s disease

Rigidity is one of the prominent symptoms of PD with movement patterns exhibiting a ‘cog-wheel’ type jerk in which the muscles respond when passively stretched. There is evidence pointing to both the neural (altered muscle activation) and non-neural components (altered architecture of the muscle) operating in parallel, being responsible for PD rigidity [26–29]. The success of DBS targeted to the two divisions of the ZI; cZI and dZI in reducing the degree of rigidity has been reported in several studies [17–22],
although no direct comparisons have been made between stimulating the two sites within individuals. In addition, the ZI targeted PSA DBS studies have largely utilised semi-quantitative analysis to assess outcomes of intervention, which potentially limits the assessment of rigidity. Therefore, the aims of this study were to firstly examine the differences in rigidity through a resistive torque-based approach (measures the rotational force of a movement) and electromyography (EMG) activity at the elbow joint in PD and a matched healthy control group. Secondly, to determine the acute effects of micro-lesioning and stimulation to the PSA, where the cZI and dZI are located, on the resistive torque and EMG of the elbow flexors and extensors in PD and its sub-groups.

The hypothesis that:

“PD participants will exhibit increased resistive torque and altered peak EMG levels as compared to healthy controls in all tasks and conditions.”

was partially confirmed. Trends in the data suggest that the PD participants generally exhibited higher resistive torques than the healthy controls, indicative of increased rigidity. A significant difference was only seen for the flexor muscle group during extension during (FlxT) in the passive 90°/sec task with contra-lateral hand cupping (p = .049) while a medium effects size was observed in the passive 30°/sec task with contra-lateral hand cupping (d = 0.73).

The secondary hypothesis that:

“A decrease in resistive torque and peak EMG levels more representative of normative values are expected with micro-lesioning and stimulation to the areas
of and around the cZI and dZI, in PD participants and sub-groups compared to their pre-operative levels, in all tasks and conditions.”

was partially supported. Although there were no statistically significant differences, trends in the data indicate prominent changes for the FlxT with post-operative settings in all tasks. Observational data suggests that FlxT and EMG values at the biceps and triceps decreased post-operatively in all tasks for the tremor-predominant group, most notably with dZI stimulation. It should be noted that the tremor component of the PD symptom can be elicited while performing a contra-lateral limb task and/or if the limb is moved at high velocities (i.e. 90°/sec). Our data reports that dZI stimulation appeared to have the greatest effect for the tremor-predominant sub-group in reducing the resistive torque (possibly the tremor component) and muscular activation at the biceps and triceps. Similarly, the rigid akinetic group also displayed decreases in FlxT and biceps activation post-operatively, particularly with cZI stimulation. However, triceps activation appeared to increase in this group post-operatively.

Overall, we found resistive torque, most notably in the elbow flexors, to be reduced with ZI targeted PSA DBS. This data supports the ZI as being a target for DBS surgery to safely alleviate rigidity, and builds upon the previous work in this area which found similar improvements through semi-quantitative assessments [17–22]. Importantly, this research contributes to the existing literature on the effectiveness of cZI and dZI DBS on improving the PD symptoms in the sub-groups of PD. The outcome of this study suggest that dZI stimulation may have a greater potential for alleviating the symptoms of the tremor-predominant group while the cZI may be a favourable target for the rigid akinetic PD group.
6.1.3 Chapter Five: Effects of posterior subthalamic area micro-lesioning and stimulation on upper limb bradykinesia and action tremor in Parkinson’s disease

A decline in upper limb movement fluency as a result of bradykinesia and action tremor is commonly exhibited in individuals with PD, resulting in an increased difficulty in executing daily functional tasks [10,30]. In efforts to characterise bradykinesia and action tremor in greater detail, researchers have successfully quantified these symptoms utilising biomechanical methods such as movement time, jerk profiles (providing information on the smoothness of the trajectory of movement) and EMG measurements [8,30–37]. Previous studies on ZI targeted PSA DBS do not provide comparison as to the outcomes of stimulation to the different divisions of the ZI on the sub-groups of PD. Therefore, the aims of this study were to firstly investigate the differences in bradykinesia and action tremor, as assessed by jerk measurements and iEMG, of PD participants in the tapping and pointing tasks, in relation to healthy controls. Secondly, to determine the outcome of the acute effects of micro-lesioning and stimulation to the PSA where the cZI and dZI are located, and its outcome on bradykinesia and action tremor, as assessed by the jerk measurements and iEMG, in the PD participants and its sub-groups.

The hypothesis that:

“PD participants will exhibit increased jerk measurements and altered iEMG levels as compared to the healthy controls in all tasks.”

was partially supported. There was a significant increase in normalised jerk in the secondary movement (NJ2) during the pointing task in the whole PD group pre-operatively as compared to the healthy controls. NJ2 was significantly increased in the non tremor-predominant PD group prior to surgery when compared to controls in the pointing task. Furthermore, a large effect size was observed for the jerk index (JI) and
normalised jerk (NJ) in the pointing task for the non tremor-predominant PD group prior to surgery, as these variables were elevated as compared to controls. With regards to iEMG, there was a significant reduction in the pectoralis iEMG in the tapping task for the pre-operative PD participants as compared to healthy controls, indicative of a reduction in muscle fibre recruitment, thereby suggestive of an increase in bradykinesia.

The secondary hypothesis that:

“Improvements in jerk measurements and iEMG levels more representative of normative values are expected with micro-lesioning and stimulation to the areas of and around the cZI and dZI, in PD participants and its sub-groups compared to their pre-operative levels, in all tasks.”

was partially supported. A significant reduction in movement time and normalised jerk in the primary movement (NJ1) were observed with post-operative settings in the whole PD group, specifically in the pointing task. Although non-significant, reductions in JI and NJ with micro-lesioning in this task presented a large effect size, suggestive of a real difference following DBS. There were no added effects of cZI and dZI stimulation on top of micro-lesioning for the non tremor-predominant group. Post-operatively in the tapping task, jerk variables appear to fluctuate within the healthy control range for the tremor-predominant group with the exception of one participant (PD6). In the pointing task however, micro-lesioning and dZI stimulation had a positive effect in reducing the jerk profiles in the tremor-predominant group with the exception of one participant (PD6). Nevertheless, this participant (PD6) as stated earlier, had good long term clinical outcomes post DBS. We also noted a general decrease (non-significant) in the coefficient of variation for all jerk variables in both tasks with post-operative settings, particularly with micro-lesioning, indicative of a decrease in trial-to-trial variability. With regards to
iEMG, dZI stimulation resulted in a significant decrease in iEMG activity of the pectoralis muscle with similar trends (although non-significant), across biceps and latissimus dorsi in the whole PD group as compared to pre-operative levels. This change in iEMG activity is the converse of what we would expect from PSA DBS. Similar to Study One, we speculate that there may be an altered adaptation strategy in both activation pattern as a result of ZI targeted PSA DBS.

The novel comparison of acute cZI and dZI stimulation appeared to result in improvements in bradykinesia and action tremor with stimulation to both of the divisions of the ZI through quantitative measurements. Visual inspection of individual participants’ data suggests that there were generally no added benefit to micro-lesioning in the PD participants in this acute phase of assessment. The therapeutic benefits of ZI DBS may occur over the longer term with chronic stimulation, specifically when the effects of micro-lesioning dissipates [38]. This research supports the role of the ZI being a good and safe target for DBS surgery to improve bradykinesia and action tremor, and adds to the body of evidence from previous ZI targeted PSA DBS studies [18–22,25]. Moreover, the findings in this study suggest that effect of micro-lesioning was enough to produce therapeutic benefits for the PD participants in both sub-groups, at least in the immediate short term.

6.2 Synthesis of results

This is the first series of studies to have quantitatively evaluated the outcomes of ZI targeted PSA DBS in the sub-groups of PD. Importantly, these findings are the first to report comparative data between cZI and dZI stimulation and its outcome on treating the three main upper limb motor symptoms; tremor, rigidity and bradykinesia, in PD. Taken
together, the findings of these studies have clinical relevance for benefits of ZI targeted DBS in the treatment of movement disorders such as PD.

The quantitative assessments such as kinematic analysis, EMG and torque-based measurements between the pre-operative PD and healthy control participants found some significant differences between groups, although it is important to note that many variables of interest were not statistically significantly different between the two groups. It is possible that the lack of significant differences between the two groups was due to the PD participants being assessed during their optimal medication-ON state, thereby possibly negating more severe motor symptoms [27]. Nevertheless, the trends observed in all three studies, particularly when presented as individual case studies, suggest that small but quantifiable differences may actually exist between the PD group and healthy controls. Results from all three studies report increases in spectral analysis, resistive torque, and jerk profiles in the PD group as compared to the healthy controls, indicative of an increase in tremor, rigidity and bradykinesia respectively. These findings suggest that the use of these quantitative biomechanical methods can be a valuable tool in differentiating pathological from non-pathological movement.

The clinical and surgical risks of ZI targeted PSA DBS are the same for all PD participants. Therefore, even small advantages in stimulating one target site over another (i.e. cZI over dZI) in terms of clinical outcome, are very important distinctions for patients and their treating neurosurgical team. Whilst the sample size of the PD sub-groups (i.e. tremor-predominant sub-group) were too small to perform statistical analysis, there were some trends apparent in the data. Specifically, there appeared to be differential results in
terms of outcome of ZI targeted PSA DBS for the tremor-predominant and non tremor-predominant participants (i.e. rigid akinetic and classic group).

6.2.1 Tremor-predominant group

A distinct trend of improvements in tremor was observed with a reduction in the spectral analysis, specifically the amplitude of frequency and the power in the range of (4-7 Hz). There also appeared to be an added benefit of cZI and dZI stimulation, specifically in resting tremor, though no differences in tremor improvements were observed between the two stimulation sites. This finding is in line with previous cZI DBS work by Plaha et al. (2006, 2008), Khan et al. (2011), and Blomstedt et al. (2012) who found significant tremor reductions in their PD participants when assessed with the UPDRS [18–21]. Moreover, our findings support the work by Hamel et al. (2003) who reported reductions in UPDRS tremor scores with dZI stimulation [22]. The novel outcome of altered iEMG profiles observed with post-operative settings in Study One may be explained by an altered adaptation strategy in response to DBS, although further investigations is warranted to shed more light on the effects of PSA DBS and iEMG profiles.

Similarly, post-operative stimulation settings appeared to improve the resistive torque output in this group. This is in support with previously referenced studies which reported improvements in UPDRS total scores with ZI targeted PSA DBS [17–21]. More importantly, the greatest improvements were displayed with dZI stimulation as it resulted in the greatest decrease in both resistive torque and EMG at the elbow. Furthermore, the magnitude of these improvements, suggest that torque-based assessments may be a valuable tool in quantifying the severity of tremor through the assessment of force profiles.
Improvements in movement time and reduction in jerk profiles, were also detected for the tremor predominant group, reflecting a reduction in bradykinesia and action tremor following DBS, with the exception of one participant (PD6). Likewise, the findings of this study were in support of previous research where improvements in UPDRS scores relating to bradykinesia and tremor following ZI targeted PSA DBS have been reported [17–21]. The added benefit of dZI stimulation on top of micro-lesioning was observed in the pointing task in this sub-groups of PD participants. With regards to iEMG, the effect of PSA DBS saw a trend of altered iEMG profile, similar to Study One.

As highlighted earlier, improvements with post-operative stimulation settings were not observed for one PD tremor-predominant participant (PD6). The data from Studies One and Three suggest that this participant did not experience an initial response to ZI targeted PSA DBS, and stimulation actually worsened his motor symptoms acutely. It is interesting that this participant has experienced good longer term clinical outcomes with both motor and non-motor symptoms at three, six and 12 months medical follow-ups (personal communications with Prof Christopher Lind). Acute assessments for this participant did not reflect his eventual outcomes with chronic DBS thereby raising some concern that the use of early biomechanical assessments may not predict longer term outcomes. Therefore, we propose that future investigations, assessing both acute and longer term outcomes, could provide valuable information on the identification of the best responders to DBS.
6.2.2 Non tremor-predominant group

The acute effect of ZI targeted PSA DBS in the non tremor-predominant sub-group of PD participants appears to provide therapeutic benefits through reductions in their motor symptoms. In Study Two, this sub-group was further sub-divided to reflect only the rigid akinetic participants. The data suggests that cZI stimulation appears to be more effective than micro-lesioning and dZI stimulation in improving their rigidity through a reduction in resistive torque and biceps activation during passive elbow extension movement. This finding is in support of previous work which reported improvements in global UPDRS rigidity scores following ZI targeted PSA DBS [17–21]. Despite this decrease in resistive torque and a reduction in biceps activation during passive elbow extension, EMG activation at the triceps were increased in the rigid akinetic group with post-operative settings. This is suggestive of the triceps contribution in assisting the extension movement. This assistive triceps profile was not replicated in any other PD sub group, suggestive of an altered pattern of recruitment for rigid akinetic patients during this task [29,39–41].

Similarly, post-operative settings appeared to improve the bradykinesia and action tremor/dyskinesia, through reductions in movement time and jerk profiles, in the non tremor-predominant group: rigid akinetic and classic. Our findings are in support of Hamel et al. (2003), Plaha et al. (2006, 2008), Khan et al. (2011), and Blomstedt et al. (2012) who reported UPDRS improvements relating to bradykinesia with ZI targeted PSA DBS. There was generally no added benefit with either cZI or dZI stimulation on top of the micro-lesioning for this non tremor-predominant group with regards to movement time or jerk profiles. Despite improved movement scores, the unexpected decrease in pectoralis iEMG with dZI stimulation warrants further investigation. We
hypothesise that DBS may have led to some form of motor unit de-synchronisation in the muscles which altered the iEMG profiles, suggestive of a strategy for neuromuscular activation i.e. performing the tapping or pointing tasks [42]. It should be noted that we may have expected some contamination from dyskinesia being unmasked as a result of DBS, particularly in this group of participants, interestingly though, our results did not observe interferences in movement quality with micro-lesioning and DBS.

6.2.3 Potential target site for the sub-groups

The outcome of DBS for the two sub-groups was similar for all three studies with the exception of one (PD6). As the outcomes presented in this research are based on preliminary data, interpretation of the results must be performed with some caution. From the improvements displayed in tremor, rigidity and bradykinesia, we suggest the consideration of dZI as a target stimulation site for chronic DBS, in treating the tremor-predominant PD sub-group. From the therapeutic outcomes observed with rigidity and bradykinesia, we suggest cZI to be considered a potential target for chronic DBS, in treating PD patients presenting with non tremor-predominant motor symptoms.

6.2.4 Neurophysiology of ZI targeted PSA DBS

While non-randomised phase I/II data supporting ZI targeted PSA DBS has been reported [16–22,25], the mechanism of action of DBS with regards to the ZI as a target is difficult to explain. It may be that the extensive ZI connections to structures including the globus pallidus internus, substantia nigra, pedunculopontine nucleus, interpositus nucleus of the cerebellum, and motor areas of the cerebral cortex indicate a motor regulatory role for the ZI [19,43–45]. This speculative hypothesis could be further addressed using microelectrode or local field potential recordings, and differential stimulation of the ZI
together with correlated quantitative biomechanical assessments in a wider range of pathological conditions including non-PD tremor conditions.

6.3 Important considerations for this research

The outcomes of this ZI targeted PSA DBS research display its potential benefits in treating the motor symptoms of our PD participants, though there are important considerations and limitations to this research that need to be acknowledged. Eight of the 10 PD participants in all three studies were assessed during their optimal medication-ON state thereby reducing their severity of motor symptoms. This is a possible explanation as to the lack of significant differences observed between the PD and healthy control participants at baseline. The relative benefit of ZI targeted PSA DBS would be significantly enhanced should the PD participants be assessed in their medication-OFF state. As this research is part of an ongoing exploratory research stream at Sir Charles Gairdner Hospital (Perth, Western Australia, Australia), assessments were performed in this manner to ensure the participants safety, to enhance patient comfort, and reduce fatigue.

The relatively small sample size, particularly within the PD sub-groups within this research makes statistical comparison difficult. Given the small number of patients who undergo DBS, it is not uncommon for studies to have a limited sample of participants [46–51]. Nevertheless, statistically significant differences were reported, specifically for certain variables of interest in Study Two (resistive torque) and Three (movement time, jerk profiles, and iEMG measurements). The recruitment of a larger population, particularly within the motor-predominant sub-groups is warranted to ensure that these preliminary results are reflective of real change.
6.4 Future research

As addressed in the previous section, although differences displayed in this research between pre and post-operative assessments were generally statistically non-significant, possibly due to the heterogeneity of the whole PD group [52,53], the trends in all three studies suggested real effects of treatment. In addition, the presence of moderate to large effect sizes reported in the studies suggest significant differences may be observed with a larger sample size. The findings in all three studies indicate that ZI targeted PSA DBS exerts a differential outcome dependent of the motor symptoms present. Therefore, the need to recruit an adequate sample size in each of the PD motor sub-groups is required to elucidate statistically significant change from intervention.

Another prospect of future work could be the utilisation of torque-based assessments for evaluating pathological tremor. The findings in Study Two suggest that the dynamometer used to measure resistive torque, can also successfully measure the tremor component of PD. Future research could investigate the force and kinematic profile of tremor through the analysis of resistive torque and its outcome following DBS.

Finally, the initial therapeutic effects of micro-lesioning and ZI targeted PSA DBS may not be fully reflected with acute assessment, as demonstrated from the outcomes of one tremor-predominant participant (PD6). In most cases, DBS involves long-term chronic treatment, therefore there is the potential for brain plasticity changes over time in response to stimulation, and there is also the stimulation-medication relationship that fluctuates until a period of stability is reached. All of these effects are yet to be explored with ZI stimulation. For this reason, future research, assessing the longer term outcome of both
cZI and dZI stimulation, may give clinicians/researchers new information on the identification of the best responders to this novel target site.

6.5 Significance and conclusion

This series of three studies found therapeutic improvements with ZI targeted PSA DBS and adds to the body of evidence in this area [16–22,25]. The quantitative assessments of PD motor symptoms in this investigation have provided insights into the degree of severity and improvements of said motor symptoms that is normally unattainable through qualitative and semi-quantitative analysis. More importantly, this research has outlined preliminary evidence for the potential benefits of cZI and dZI stimulation and its effect on the motor predominant sub-groups of PD. Our investigations suggest that the effect of micro-lesioning targeted to the ZI is enough to provide a potentially therapeutic effect in reducing the three main motor symptoms in our PD participants. It is important to note that this may be due to the temporary lesioning of cZI and dZI and this effect could be recaptured with chronic stimulation. Previous work have reported the cessation on the micro-lesioning effect within eight to 12 weeks or surgery [38]. Therefore, the outcomes of this study have good longer term implications for dZI DBS for the tremor-predominant group and cZI DBS for the non-tremor predominant group. The reduction in tremor, rigidity and bradykinesia with ZI targeted PSA DBS reported in this research is indicative of an improved movement fluency, which we anticipate to have a good transference to improved quality of life for the participants with PD.
References


[29] R. Xia, Physiological and biomechanical analyses of rigidity in Parkinson’s Disease, INTECH Open Access Publisher, 2011.


APPENDIX

1. Sir Charles Gairdner ethics approval 185

2. The University of Western Australia ethics approval 187

3. Parkinson’s disease participant information sheet 188

4. Healthy control participant information sheet 198

5. MATLAB code for Study One 203

6. MATLAB code for Study Two 206

7. MATLAB code for Study Three 208

8. Conference proceeding (oral presentation) for the International Society of Biomechanics 2013, Natal, Brazil 214

9. Conference proceeding (submitted) for the International Society of Biomechanics 2015, Glasgow, Scotland 216

10. Unified Parkinson’s Disease Rating Scale (UPDRS) motor section (III) 219

11. EMG electrode placements 229
APPENDIX 1

Sir Charles Gairdner Hospital

Department of Health

Ethics Ref: 2008-065
Ext. 2999

23 December 2008

Mr Christopher Lind
Neurosurgery
1st Floor G Block
Sir Charles Gairdner Hospital
Hospital Ave
NEDLANDS WA 6009

Dear Mr Christopher Lind

APPLICATION TO CONDUCT HUMAN RESEARCH AT SCGH:
TRIAL 2008-065 The Function of the Human Zona Incerta and its Potential as a Target
for Deep Brain Stimulation Surgery

On behalf of the Sir Charles Gairdner Group Executive I give approval to conduct your research
project at SCGH based on the favourable reviews provided to me by the Research Governance
Unit and the Sir Charles Gairdner Hospital Human Research Ethics Committee. This approval
is granted until 31 December 2011, and on the basis of compliance with all requirements laid
out in your application and with the provision of reports as required by the RGU and approving
HREC in giving their favourable opinion (attached).

The responsibility for the conduct of this study remains with you as the Principle Investigator.
You must notify the Research Governance Unit of any relevant issues arising during the conduct
of the study that may affect continued favourable opinions by the hospital or by an HREC.

Please quote Study number 2008-065 on all correspondence associated with this study.

Yours sincerely


SUE DAVIS
Acting Executive Director of Nursing Services
Sir Charles Gairdner Group
North Metropolitan Health Service
23 August 2012

Professor Christopher Lind
Neurosurgery Clinic
1st Floor G Block
Sir Charles Gairdner Hospital
Hospital Ave
NEDLANDS WA 6009

Dear Professor Lind

APPLICATION TO CONDUCT HUMAN RESEARCH AT SCGH:
TRIAL No: 2012-039
TRIAL TITLE: Randomised crossover trial of deep brain stimulation of
differential posterior subthalamic area regions in Parkinson's disease and tremor

On behalf of the Sir Charles Gairdner and Osborne Park Health Care Group Executive I
give approval to conduct your research project at Sir Charles Gairdner Hospital based on
the favourable reviews provided to me by Research Governance and the Sir Charles
Gairdner Group Human Research Ethics Committee. This approval is granted until 23
August 2015, and on the basis of compliance with all requirements laid out in your
application and with the provision of reports as required by the Research Governance and
the approving HREC in giving their favourable opinion (attached).

The responsibility for the conduct of this study remains with you as the Principal Site
Investigator. You must notify the HREC Office of any relevant issues arising during the
conduct of the study that may affect continued favourable opinions by the hospital or by
an HREC.

Please quote Study number 2012-039 on all correspondence associated with this study.

Yours sincerely

Dr Robyn Lawrence
EXECUTIVE DIRECTOR
SIR CHARLES GAIRDNER AND
OSBORNE PARK HEALTH CARE GROUP

cc: HoD
APPENDIX 2

Our Ref: RA/4/1/5721

Dr. Siobhan Reid
Sport Science, Exercise & Health (School of)
MBDF, M468

Dear Doctor Reid

HUMAN RESEARCH ETHICS APPROVAL - THE UNIVERSITY OF WESTERN AUSTRALIA
Understanding Parkinson’s through objective movement analysis and characterisation

Student(s): Muhammad Aziz - PhD - 20213104, Mohammed Abdul Aziz

Ethics approval for the above project has been granted in accordance with the requirements of the National Statement on Ethical Conduct in Human Research (National Statement) and the policies and procedures of The University of Western Australia. Please note that the period of ethics approval for this project is five (5) years from the date of this notification. However, ethics approval is conditional upon the submission of satisfactory progress reports by the designated renewal date. Therefore, initial approval has been granted from 21 December 2012 to 01 December 2017.

You are reminded of the following requirements:

1. The application and all supporting documentation form the basis of the ethics approval and you must not depart from the research protocol that has been approved.
2. The Human Research Ethics Office must be approached for approval in advance for any requested amendments to the approved research protocol.
3. The Chief Investigator is required to report immediately to the Human Research Ethics Office any adverse or unexpected event or any other event that may impact on the ethics approval for the project.
4. The Chief Investigator must inform the Human Research Ethics Office as soon as practicable if a research project is discontinued before the expected date of completion, providing reasons.

Any conditions of ethics approval that have been imposed are listed below:

Special Conditions
None specified

The University of Western Australia is bound by the National Statement to monitor the progress of all approved projects until completion to ensure continued compliance with ethical standards and requirements.

The Human Research Ethics Office will forward a request for a Progress Report approximately 60 days before the due date. A further reminder will be forwarded approximately 30 days before the due date.

If your progress report is not received by the due date for renewal of ethics approval, your ethics approval will expire, requiring that all research activities involving human participants cease immediately.

If you have any queries please contact the HREO at hreo-research@uwa.edu.au.

Please ensure that you quote the file reference – RA/4/1/5721 – and the associated project title in all future correspondence.

Yours sincerely

[Signature]

Peter Johnstone
Manager, Human Research Ethics
APPENDIX 3

Sir Charles Gairdner Hospital

PARTICIPANT INFORMATION SHEET – PSA DBS PARTICIPANT

Deep brain stimulation for movement disorders – a clinical trial and physiological studies

Chief Investigator: Professor Christopher Lind, Consultant Neurosurgeon

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign the consent form.

Who is funding this study?
This study is funded from public health research grants.

Contact persons:
Should you have questions about the study you may contact:

Professor Christopher Lind, Consultant Neurosurgeon Phone No. 9346 3333
Miss Megan Thorburn, Clinical Nurse Consultant Phone No. 9346 3333

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:

- Why this study might be suitable for you
- The possible risks (side-effects) of the study
- The type, frequency and risks of any medical tests required by the trial
- The nature of your participation including how many visits you will make to the hospital and the university
- Your rights and responsibilities
- Alternative treatments available to you
What is the purpose of the study?
(1) To see which sub-region of the posterior subthalamic area (PSA) of the brain provides the best control of Parkinson’s disease and/or tremor symptoms. To measure and compare any side effects on thinking, mood, and speech with different reversible deep brain stimulation (DBS) settings. To compare prescribed stimulation settings based on detailed imaging against an individualized programming approach for your DBS.
(2) To see which parts of the brain are active during DBS treatment and how deep brain stimulation of the PSA works to improve the negative motor symptoms. By examining electrical activity in the brain we can find out how neurological disorders cause motor disability and how DBS improves motor functions. This will allow us to better understand why different patients benefit in different ways from DBS, and how we can improve programming of the brain stimulators to achieve better results.
(3) To make a detailed analysis of how your walking, tremor and arm function changes with different reversible DBS settings

Why is this study suitable for me?
You have been selected as a suitable candidate for this study because you either have Parkinson’s disease or tremor and your doctors believe you will most likely benefit from DBS of the PSA area of the brain.

How long will I be in this study?
You will be in this study for 14 months.

What will happen if I decide to be in this study?
- Before the day of neurosurgical admission there are 3 separate assessments, the first two of which will influence the decision for surgery:
  1. You will be asked to attend on a Thursday within 4 weeks prior to admission to hospital for surgery.

    **Morning:** You will need to undergo a baseline assessment of the severity and nature of your Parkinson’s disease or tremor and your current quality of life and if you have Parkinson’s disease then we will measure your responsiveness to medications and the assessment will take up to 2 hours. If you do not have Parkinson’s disease but you do have tremor then it will take about 1 hour. This is an important routine part of the final decision to go ahead with surgery, quite apart from research. If you have medications for your movement disorder then you will be asked to withhold them the night prior to this assessment. Depending on your likely disability the morning after withholding medications, your assessment will either be performed in the Functional Neurosurgery Research Clinic as an outpatient visit, or following an overnight stay on ward G66 at Sir Charles Gairdner Hospital if you require more nursing assistance during the assessment. The assessment will be performed by a highly trained and experienced nurse who will be able to help you at every stage. The assessment will be video-recorded to enable later grading of movements by specialists. If you have Parkinson’s disease, you will be given standard doses of medications at a certain point during the assessment to measure your responsiveness to L-dopa-like drugs.

    **Afternoon:** After a break for lunch, you will be asked to undergo a study of the electrical activity of your brain. You will be asked to continue your usual medications at this point and attend the Australian Neuromuscular
Research Institute clinic for up to 2 hours of **measurements of your brain waves and limb movements** using painless stick-on electrodes on your face and head. The researcher will ask you follow some simple instructions including moving your arms or legs or relaxing. This will be well explained at the time so that you don’t get much of a surprise when this happens. A magnetic wand (transcranial magnetic stimulation; TMS) is held near your head for painless and gentle activation of your muscles while recordings are made from the stick-on skin electrodes. After the assessment you will be able to go back to your place of residence.

2. You will be asked to attend a clinic at the University of Western Australia (UWA) Neuropsychiatry Unit in Fremantle for a 2-3 hour baseline **measurement of your thinking, speech fluency, and mood**. Again, this assessment provides clinically important information that sometimes needs to be communicated directly to your neurosurgeon before surgery can proceed. You will be asked questions and will need to solve simple mental puzzles. You should continue your usual medications before, during and after this session as required.

3. You will be asked to attend on a Tuesday within 4 weeks prior to admission to hospital for surgery.

**Morning:** You will be asked to undergo another study of electrical activity of your brain which is held in the Neurology Outpatients Department at Sir Charles Gairdner Hospital. You will be asked to continue your usual medications and the session lasts up to 2 hours for **measurements of your brain waves, head and eye movements** using painless stick-on electrodes on your face and head. The researcher will ask you follow some simple instructions including moving your hands and looking at lights in a darkened room, experiencing gentle touch on your skin to measure your head and eye movement reactions to touch. This will be well explained at the time so that you don’t get much of a surprise when things happen.

**Afternoon:** After a break for lunch, we will take you to the UWA Sports Science motion analysis laboratory in Crawley for an assessment lasting up to 2 hours in which we place sticky dots on your bare arms, legs and trunk and measure the quality of your walking movements using technology initially developed for analysis of athletes. Leading up to this you should take your usual movement disorder medications. You will not be required to do prolonged or strenuous exercise. At the end of this session we will take you back to Sir Charles Gairdner Hospital so you can proceed home.

- On the day of admission to Sir Charles Gairdner Hospital, on a Monday (DAY 1), there are two assessments:

  **Morning:** You will be asked to attend the UWA Sports Science motion analysis laboratory in Crawley for an assessment lasting up to 2 hours in the morning in which we place sticky dots on your arms and measure your tremor and the quality of your arm movements using technology initially developed for analysis of athletes. Leading up to this you should take your usual movement disorder medications. You will not be required to do prolonged or strenuous exercise. At the end of this session we will take you back to Sir Charles Gairdner Hospital for your lunch break.
Afternoon: You will be asked to undergo a positron emission tomography (PET) scan which shows how much glucose is used by each part of your brain at rest. An intravenous line (drip) is placed in your hand or arm to give you the small dose of minimally radioactive glucose that the scanner detects as it moves around your body. You then lie still in the scanner for some minutes before the test is complete. After this you will go to ward G66 as per the instructions of the admissions staff. Later in the afternoon you will meet one of the anaesthetists and prepare for the first procedure for placing your DBS: the MRI scan under anaesthesia the next morning.

- For the next 10 days (DAYS 1 to 11) you will be an inpatient at Sir Charles Gairdner Hospital for surgery (MRI scan with headframe and general anaesthesia on Tuesday (DAY 2) and brain electrode placement on Wednesday (DAY 3) and test stimulation to see what effect DBS has on your symptoms before committing to a long term implanted pulse generator. To facilitate this testing you will have wires hanging out of your scalp for 7 days. This is the case whether you are participating in this study or not. There are no research assessments for this project from Tuesday to Sunday night (DAYS 2 to 7).

1. On the Monday (DAY 8) the final motion analysis will be repeated at UWA in Crawley looking at arm movements in the morning and walking movements in the afternoon, with a break for lunch in between. This will be as before except that this time the brain stimulator will be turned on and off with you and the assessor unaware of the settings changed by the neurosurgical staff member. This is to look at the effects of PSA DBS on the movements.

2. On Tuesday morning (DAY 9) the second of three measurements of your brain waves, head and eye movements will occur and will last up to 3 hours including recording from your brain electrodes and at other times turning the stimulator on. The second and final PET scan will be performed after a lunch break in the afternoon, with your stimulator turned on.

3. On Wednesday (DAY 10) you will have surgery to either remove electrodes (if inadequate improvement has been achieved) or internalise the DBS system with implantation of a pulse generator in your chest. This occurs whether you are part of the study or not. On DAY 11 you are discharged back to your place of residence with the DBS stimulator not switched on.

- Outpatient post-operative follow-up, stimulator programming and assessments

  1. 11 days after discharge from hospital: You will be asked to attend Prof Lind’s neurosurgical outpatient clinic at Sir Charles Gairdner Hospital for checking of surgical wounds and removal of skin staples. After this follow-up, you will be randomly allocated to one of two stimulation programmes and not be told which group you are in. This is important so that we can assess each of the two settings without unduly biasing ourselves. We do not know which of these two settings is best although we know from our previous experience that either setting can give excellent clinical results. Over the course of 6 months you will receive 3 months of each stimulation setting. This study is primarily designed to answer the question: which is the best setting of the two?

  2. At the end of 3 months and 6 months after initial DBS programming, we will ask you to attend the UWA Neuropsychiatry Unit Research Clinic for
measurement of your thinking, speech fluency, and mood (up to 3 hours) and on a subsequent day, our Functional Neurosurgery Research Clinic for assessment of the severity and nature of your Parkinson’s disease or tremor and your current quality of life (up to 3 hours). These are the important assessments that will help us answer the practical question: what is the best setting for PSA DBS? At the end of each assessment, the next setting will be programmed in to your DBS device. After the 6-month assessment, our Neurologist will turn different electrode contacts on or off and to different stimulation patterns and energy levels to try and optimise your tremor or Parkinsonian symptom control. Repeat appointments will be made as per the expertise of the Neurologist to make further changes as required.

3. On two occasions on the same day as your routine clinic visits to see your treating/programming Neurologist we will ask you to undergo repeat measurements of your brain waves and limb movements assessments involving the use of the TMS magnetic wand. The stimulator will be intermittently turned off or on (at a slow rate) for about 1-2 hours while we perform the study.

4. At 12 months after surgery, we will ask you to return for one final measurement of your thinking, speech fluency, and mood in Fremantle (up to 3 hours) and on a subsequent day, our Functional Neurosurgery Research Clinic for assessment of the severity and nature of your Parkinson’s disease or tremor and your current quality of life (up to 3 hours). The results of this assessment will enable us to compare customised settings against the earlier anatomically predetermined settings (the initial two 3-month periods) and will influence our approach to programming in the future.

Are there any reasons I should not be in this study?
Study staff will discuss with you in detail any issues you are concerned about or may pertain to your particular situation.

What are the costs to me?
There are no direct costs to you for the involvement in this study apart from the time taken to perform assessments. The length of admission is the same whether you are involved in the study or not. The assessments will be performed during routine visits for pre-operative assessment and follow-up. We will provide meals and reimbursement of parking costs for your visits.

What are the possible benefits of taking part?
Little is known about the function of the PSA region. The current study is a significant contribution to the world of neuroscience, neurosurgery and neurology. This study offers significant potential benefits including access to highly systematic DBS programming with objective monitoring of what works best for you. This will take a significant amount of your time, but will also take a significant amount of specialist assessment time all focused on measuring the effects of different DBS settings on your symptoms. This should translate into an optimized long-term outcome for you.
How will my safety be ensured?
During the study, you will be accompanied and observed for any potential side effects of deep brain stimulation. Your stimulator settings may be changed should there be any side effects. Do not hesitate to contact the study coordinator or your doctor/clinician in relation to any side effects you think you are experiencing. If the side effects are severe enough, the team may change or even temporarily stop the stimulation to reverse your side effects within seconds.

What alternatives do I have to going on this study?
You may undergo deep brain stimulation surgery without being enrolled in the study. You will undergo routine clinical assessments including assessment of the severity and nature of your Parkinson’s disease or tremor and your current quality of life and, at the discretion of the treating team, measurement of your thinking, speech fluency, and mood which may be necessary to determine your suitability for surgery and the effectiveness and safety of surgery post-operatively at 6 months and 12 months at least. You will undergo programming by standard trial and error technique rather than systematically trialling unbiased (‘blinded’) anatomical settings. There will be no PET scans, no detailed movement analysis at UWA and no measurements of your brain waves.

What are the possible side effects, risks and discomforts of taking part?
Any changes to your stimulator may cause symptoms you dislike. If this is the case, our staff member will be able to reverse this by changing the stimulator settings.

This research study involves exposure to a small amount of radiation from two PET-CT scans. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 6.8mSv. At this dose level, although harmful effects cannot be proven, there is evidence to indicate that such a dose may give a very small risk of developing cancer. This risk is approximately 1 in 2700 which is equivalent to approximately one third the estimated risk of dying on Western Australian roads in the next 10 years. If the radiation dose is unacceptable to you, we would request that you continue to participate in the rest of this study even if you do not wish to undergo PET scanning.

Transcranial magnetic stimulation is a safe, painless method of stimulating small areas of the brain by passing magnetic pulses. It has been in use since the 1980s to study electrical activity of the brain in normal subjects and patients with brain disorders and is used for clinical testing of the integrity of brain pathways. It is now also used for treatment of conditions such as depression and is being trialed for the treatment of stroke and epilepsy. Other electrophysiological measurements involve EEG and EMG measurements using skin or scalp patch electrodes, which are painless.

There is negligible risk associated with the biomechanics studies at UWA looking at arm and walking movements, however the tape used to attach the retro-reflective markers may cause slight temporary skin irritation. For participants with substantial amount of body hair, removal of the tape and markers may also cause a temporary and brief sensation of pain. The tape used for this study is medical grade and unlikely to cause allergic reactions. Any discomfort felt (such as itching) should be short term.
The rest of the study will not pose any risks to you but may cause some inconvenience. This includes having the similar breakfast and lunch meals and medications on DAY 1 and DAY 9 to optimize PET scan results. The timing and frequency of assessments during your hospital admission may reduce the time you have available to spend with your visitors.

There may be side effects that the researchers do not expect and that may be serious. Tell your doctor immediately about any new or unusual symptoms that you get.

What if new information comes along during the study?
Sometimes new information about a treatment becomes available as a study progresses. You will be told about any information that could be important to your decision to continue in the study. If you want to continue in the study, you may be asked to sign a revised consent form.

Stopping the study treatment early:
Participation in this research is voluntary and you are free to withdraw from the study at any time without prejudice. You can withdraw for any reason and you do not need to justify your decision. If you do withdraw we would like to retain the data that we have recorded from you.

What happens at the end of the study?
You will continue to have deep brain stimulation at the end of the study as long as it is providing you with symptom relief. Your follow-up assessments will continue with the ANRI movement disorders clinic and the neurosurgical clinic as needed. Data collected will be analysed and submitted for publication in international peer-reviewed journals so that other doctors and scientists can learn more about the PSA part of the brain and this form of DBS treatment.

What if something goes wrong?
You will receive the best medical care available during and after the study. Medical treatment will be provided at no cost to you for research-related harm. The term “research-related harm” means both physical and mental injury caused by the procedures required by the study. Your participation in this study does not prejudice any right to compensation which you may have under statute or common law.

Will my taking part in this study be kept confidential?
Any personal or health information will be kept private and confidential. It will be stored securely and only authorised personnel will have access to it. Study records with your identity attached will be kept in secure locations in Sir Charles Gairdner Hospital, ANRI and UWA. No names or identifying features will be presented in any reported or published results. Records will be kept for at least 15 years from the time the study is closed, and may be destroyed at any time thereafter.

The investigating doctor, the hospital human research ethics committee, and/or research governance bodies may require access to your study records to verify study procedures and/or data. Some of your information may be sent to authorised individuals in other countries for these purposes. In all cases, these individuals are required to comply with privacy laws that protect you. The result of the research will be made available to other
doctors through medical journals or meetings, though you will not be identifiable in these communications without your permission. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

**Will I find out the results of the study?**
Upon request, the findings of the study will be provided after the analysis is complete.

**Who has reviewed the study?**
The Sir Charles Gairdner Group Human Research Ethics Committee has reviewed this study and has given its approval for the conduct of this research trial. In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

**In the case of a medical emergency you should contact:**
The Neurosurgical Registrar on-call - 08 9346 3333
CONSENT FORM

Deep brain stimulation for movement disorders – a clinical trial and physiological studies

Chief Investigator: Professor Christopher Lind, Consultant Neurosurgeon

Participant Name: _____________________________________________

Date of Birth: ________________

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.

3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.

4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.

5. I agree to take part in this research study and for the data obtained to be published. Publication of information including my name or any other identifying information will only occur if I later provide explicit permission for this to occur.

I do not agree to: ________________________________

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your doctor before signing this Consent Form.

Name of Participant  Signature of Participant  Date

Name of Investigator  Signature of Investigator  Date
The Sir Charles Gairdner Group Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the secretary of the Sir Charles Gairdner Group Human Research Ethics Committee on telephone no. (08) 9346 2999

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.
APPENDIX 4

Sir Charles Gairdner Hospital

PARTICIPANT INFORMATION SHEET  HEALTHY PARTICIPANT

Deep brain stimulation for movement disorders – a clinical trial and physiological studies

Chief Investigator: Professor Christopher Lind, Consultant Neurosurgeon

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign the consent form.

Who is funding this study?
This study is funded from public health research grants.

Contact persons:
Should you have questions about the study you may contact:

Professor Christopher Lind, Consultant Neurosurgeon  Phone No.  9346 3333
Dr Siobhan Reid, Clinical Biomechanist  Phone No.  6488 8781
Muhammad Luqman Bin Abdul Aziz, PhD Candidate  Phone No.  0423 402 748

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

The following information sheet will explain the study and will include details such as:
- Why this trial might be suitable for you
- The possible risks (side-effects) of the study
- The type, frequency and risks of any procedures required by the study
- The nature of your participation including how many visits you will make to the university
- Your rights and responsibilities
What is the purpose of the study?
To study a specific part of the brain called the posterior subthalamic area (PSA) and the globus pallidus (GP) in people undergoing deep brain stimulation surgery. We are establishing a database of the upper limb (arm) movement characteristics in healthy people to provide a comparison group for patients with Parkinson’s disease, tremor or dystonia undergoing surgery.

Why is this study suitable for me?
You have been selected as a suitable candidate for this study because you are the right age (50 – 75 years) and do not have a movement disorder.

How long will I be in this study?
You will be in this study for one testing session (approximately 2 hours).

What will happen if I decide to be in this study?
- You will be asked to attend only one testing session approximately 2 hours long. There will be eight different upper limb tasks. Three-dimensional motion, as well as muscular activity and force analysis will be performed.
- An example of an upper limb task would be to hold both your arm out in front of you for a period of 10 seconds. Other tasks include simple day to day activities such as pointing and drinking.
- All the techniques will be in accordance to the International Society of Biomechanics convention.

Study time-line
- Participants will attend only one testing session as mentioned above.

Are there any reasons I should not be in this study?
This trial is both safe and appropriate for you. Any form of neurological or muscle or bone diseases may exclude you from this study so please discuss with the researcher if you think this applies to you.

What are the costs to me?
There are no direct costs to you for the involvement in this study.

What are the possible benefits of taking part?
There are no personal benefits to you for participating in this study.

How will my safety be ensured?
At all times attention to detail in the performance of tests will help prevent accidents.

What are the possible side effects, risks and discomforts of taking part?
The tape used to attach the retro-reflective markers may cause slight temporary skin irritation. For participants with substantial amount of body hair, removal of the tape and markers may also cause a temporary and brief sensation of pain. The tape used for this study is medical grade and unlikely to cause allergic reactions. Any discomfort felt (such as itching) should be short term.
Stopping the study early:
Participation in this research is voluntary and you are free to withdraw from the study at any time. You can withdraw for any reason and you do not need to justify your decision. If you do withdraw we would like to retain the data that we have recorded from you.

What happens at the end of the study?
Data collected will be analysed and submitted for publication in international scientific journals so that other doctors and scientists can learn more about the brain and movement.

Will my taking part in this study be kept confidential?
Any personal or health information will be kept private and confidential. It will be stored securely and only authorised personnel will have access to it. The study records will be kept in a secure location in the Sir Charles Gairdner Hospital and University of Western Australia. No names or identifying features will be presented in any reported or published results without your permission. Records will be kept for at least 15 years from the time the study is closed, and may be destroyed at any time after that.

The investigating doctor, the human research ethics committees, and/or research governance bodies may require access to your study records to verify study procedures and/or data. Some of your information may be sent to authorised individuals in other countries for these purposes. In all cases, these individuals are required to comply with privacy laws that protect you. Your rights under any applicable data protection laws are not affected by your agreement to participate in this study.

Will I find out the results of the study?
Upon request, the findings of the study will be provided after the analysis is complete.

Who has reviewed the study?
The Sir Charles Gairdner Group Human Research Ethics Committee has reviewed this study and has given its approval for the conduct of this research trial. In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

In the case of any problems you should contact:
Luqman Aziz  +61 423 402 748
CONSENT FORM

Deep brain stimulation for movement disorders – a clinical trial and physiological studies
Chief Investigator: Professor Christopher Lind, Consultant Neurosurgeon

Participant Name: _______________________________________
Date of Birth: _______________

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.

3. I have been able to ask questions and all questions have been answered satisfactorily.

4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.

5. I agree to take part in this research study and for the data obtained to be published. Publication of information including my name or any other identifying information will only occur if I later provide explicit permission for this to occur.

I do not agree to: ________________________________________________

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your doctor before signing this Consent Form.

_________________________________________________________________
Name of ParticipantSignature of ParticipantDate

_________________________________________________________________
Name of InvestigatorSignature of InvestigatorDate
The Sir Charles Gairdner Group Human Research Ethics Committee and The Human Research Ethics Committee of University of Western Australia have given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the secretary of the Sir Charles Gairdner Group Human Research Ethics Committee on telephone no. (08) 9346 2999.

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.
APPENDIX 5

%% Processing of integrated electromyography data for Study One

clc

%% Import the .c3d Files
folder = cd;
[fileName, filePath] = uigetfile('.c3d', 'Select File', folder, 'MultiSelect', 'on');
fullFileName = strcat(filePath, fileName);
BackSlash = strfind(folder, '\');
SubjectName = folder(BackSlash(end)+1:end);
clc

%% Import Data
trialType = ('EMG');
varNames3d = ['RFIN'];
varNamesAnalog = {'Biceps', 'Triceps', 'Pec Major', 'Ant Deltoid', 'Trapezius', 'Lat Dorsi', 'Flexor Carpi Rad', 'Extensor Carpi R'};

for i = 1:length(fileName)
    TrialName{:,i} = fileName{:,i}(1:strfind(fileName{:,i}, '.')-1);
    [MarkerStruct.(TrialName{:,i}), AnalogStruct.(TrialName{:,i}), VideoFrameRate,
     AnalogFrameRate,...
     EventTimes.(TrialName{:,i}), EventTypes.(TrialName{:,i}),
     EventLabels.(TrialName{:,i}), EventSides.(TrialName{:,i})... = readc3duwaStruct_Nexus(fullFileName{i}, trialType, 'default',...
     varNames3d, varNamesAnalog, 'y');
    clc
end

%% Create Event Frames
for i = 1:length(fileName)
    EventFrames.(TrialName{:,i}) = sort(round(EventTimes.(TrialName{:,i}) .* VideoFrameRate));
    EventFramesAnalog.(TrialName{:,i}) = sort(round(EventTimes.(TrialName{:,i}) .* AnalogFrameRate));
end

%% High pass
Wn=1/(AnalogFrameRate/20);
[B,A]=butter(2,Wn,'high');

for i = 1:length(fileName)
    VariableNames = fieldnames(AnalogStruct.(TrialName{:,i}));
    for j = 1:length(VariableNames)
        EMG_filt.(TrialName{:,i}).(VariableNames{j}) = filtfilt(B,A,AnalogStruct.(TrialName{:,i}).(VariableNames{j}));
    end
end

%% Remove DC Offset
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        EMG_Mean.(TrialName{:,i}).(VariableNames{j}) = mean(EMG_filt.(TrialName{:,i}).(VariableNames{j}));
        EMG_Offset.(TrialName{:,i}).(VariableNames{j}) = EMG_filt.(TrialName{:,i}).(VariableNames{j}) - EMG_Mean.(TrialName{:,i}).(VariableNames{j});
    end
end

%% Rectify
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        EMG_rect.(TrialName{:,i}).(VariableNames{j}) = abs(EMG_Offset.(TrialName{:,i}).(VariableNames{j}));
    end
end

%% Low pass
Wn=1/(AnalogFrameRate/6);
[B,A]=butter(4,Wn);
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        EMG_process.(TrialName{:,i}).(VariableNames{j}) = filtfilt(B,A,EMG_rect.(TrialName{:,i}).(VariableNames{j}));
    end
end

%% Create MVC and Trial Structure
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        index = strfind(TrialName,'Trial');
        if index{i} > 0
            Trial.(TrialName{:,i}).(VariableNames{j}) = EMG_process.(TrialName{:,i}).(VariableNames{j});
        end
        if isempty(index{i}) == 1;
            MVC.(TrialName{:,i}).(VariableNames{j}) = EMG_process.(TrialName{:,i}).(VariableNames{j});
        end
    end
end

%% Create True MVC Structure
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        index = strfind(TrialName,'AntDelt');
        index2 = strfind(VariableNames,'Ant_Deltoid');
        if index{i} > 0 & index2{j};
            MVC.New.AntDeltoid(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
        index = strfind(TrialName,'Biceps');
        index2 = strfind(VariableNames,'Biceps');
        if index{i} > 0 & index2{j};
            MVC.New.Biceps(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
        index = strfind(TrialName,'ExtCarpi');
        index2 = strfind(VariableNames,'Extensor_Carpi');
        if index{i} > 0 & index2{j};
            MVC.New.ExtCarpi(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
        index = strfind(TrialName,'FlxCarpi');
        index2 = strfind(VariableNames,'Flexor_Carpi');
        if index{i} > 0 & index2{j};
            MVC.New.FlxCarpi(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
        index = strfind(TrialName,'Lats');
        index2 = strfind(VariableNames,'Lat');
        if index{i} > 0 & index2{j};
            MVC.New.Lats(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
        index = strfind(TrialName,'Pecs');
        index2 = strfind(VariableNames,'Pec');
        if index{i} > 0 & index2{j};
            MVC.New.Pecs(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
        index = strfind(TrialName,'Traps');
        index2 = strfind(VariableNames,'Trap');
        if index{i} > 0 & index2{j};
            MVC.New.Trapezius(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
        index = strfind(TrialName,'Triceps');
        index2 = strfind(VariableNames,'Triceps');
        if index{i} > 0 & index2{j};
            MVC.New.Triceps(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
    end
end

%% Calculate MVC Average and MVC Peaks
VariableNamesNew = fieldnames(MVC_New);
for j = 1:length(VariableNamesNew)
    MVC_New.(VariableNamesNew{:,j}) = nonzeros(MVC_New.(VariableNamesNew{:,j}));
    MVC_Mean.(VariableNamesNew{:,j}) = mean(MVC_New.(VariableNamesNew{:,j}));
end
%% Normalize Trial Data to MVC Mean
TrialName2 = fieldnames(Trial);
for i = 1:length(TrialName2)
    for j = 1:length(VariableNames)
        Trial_Norm.(TrialName2{i}).(VariableNamesNew{j}) = Trial.(TrialName2{i}).(VariableNames{j})./MVC_Mean.(VariableNamesNew{j});
    end
end

%% Crop Trial
for i = 1:length(TrialName2)
    for j = 1:length(VariableNames)
        Trial_Norm.(TrialName2{i}).(VariableNamesNew{j}) = Trial_Norm.(TrialName2{i}).(VariableNamesNew{j})(EventFramesAnalog.(TrialName(:,i))(1):EventFramesAnalog.(TrialName(:,i))(2));
    end
end

%% Find Integrated EMG
for i = 1:length(TrialName2)
    for j = 1:length(VariableNames)
        Int_EMG(j,i) = trapz(Trial_Norm.(TrialName2{i}).(VariableNamesNew{j}))/AnalogFrameRate;
    end
end

%% Export to Excel
xlswrite(strcat(SubjectName, '_EMG.xlsx'), Int_EMG, 'Int_EMG', 'B2')
xlswrite(strcat(SubjectName, '_EMG.xlsx'), VariableNames, 'Int_EMG', 'A2')
xlswrite(strcat(SubjectName, '_EMG.xlsx'), TrialName2', 'Int_EMG', 'B1')
APPENDIX 6

%% Processing of electromyography data for Study Two
function [EMG_proces] = EMG_analysis(EMG)

%% High pass
Wn=1/(2000/20);
[B,A]=butter(2,Wn,'high');
EMG_filt = filtfilt(B,A,EMG);

%% Remove DC Offset
for i=1:size(EMG_filt,2)
    EMG_Offset(:,i) = EMG_filt(:,i) - mean(EMG_filt(:,i));
end

%% Rectify
EMG_rect = abs(EMG_Offset);

%% Low pass
Wn=1/(2000/6);
[B,A]=butter(4,Wn);
EMG_proces = filtfilt(B,A,EMG_rect);

%% Processing of Resistive Torque data for Study Two
clear all
	close all

%% Import the data in the equation that predicts the moment of the rig
[filename2,dir2] = uigetfile('*.csv','Select the .csv file with the trial');
filename2 = strcat(dir2,filename2);
importfile(filename2);
name=data;

%% Import the MVC Biceps
MVC_t = input('How many Biceps MVC trials do you have? ')
for i=1:MVC_t
    [filename1,dir1] = uigetfile('*.csv','Select the .csv file with the MVC trial (Biceps)');
    filename1 = strcat(dir1,filename1);
    importfile(filename1);
    BicepsMVC{i,1}=data;
end

%% Import the MVC Triceps
MVC_t = input('How many Triceps MVC trials do you have? ')
for i=1:MVC_t
    [filename1,dir1] = uigetfile('*.csv','Select the .csv file with the MVC trial (Triceps)');
    filename1 = strcat(dir1,filename1);
    importfile(filename1);
    TricepsMVC{i,1}=data;
end

%% Filter EMG signals
EMG_proces = EMG_analysis(name(:,3:4));
for i=1:MVC_t
    Biceps_process{i,1} = EMG_analysis(BicepsMVC{i,1}(:,3));
    Triceps_process{i,1} = EMG_analysis(TricepsMVC{i,1}(:,3));
end

for i=1:MVC_t
    Bic_max(i)=max(Biceps_process{i,1});
    Tri_max(i)=max(Triceps_process{i,1});
end

Value_to_normBic= mean(Bic_max);
Value_to_normTri= mean(Tri_max);

%% Filter Position and Moment Data
Wn=1/(2000/2);
[B,A]=butter(4,Wn);
Position_filt=filtfilt(B,A,name(:,5));
Session added to remove peaks in Biodex torque

CC = matfiltfilt2(1/2000, 6, 4, 'lp', name(:, 6));
plot(CC)
hold on
plot(Position_filt, 'r')
title('Cut the peak values')
[cutx, cuty] = ginput
F = CC;
i = 1;
while i < length(cutx)
    F(cutx(i): cutx(i + 1)) = NaN;
i = i + 2;
end
LL = spline (1:1:length(F), F, 1:1:length(F));
Moment_filt = filtfilt(B, A, LL);

% Convert position and moment in Newton
Position_ok = 9.544 * Position_filt - 0.529;
Moment_ok = 9.544 * Moment_filt - 0.529;

% Cut the cycles based on the position of the rig
N_cycle = input ('How many cycles do you want to analyse? ')
plot(name(:, 5))
[x, y] = ginput(N_cycle + 1)

% Calculate cycles
for i = 1:length(y) - 1
    Position_cycle{i, 1} = Position_filt(x(i): x(i + 1));
    Moment_cycle{i, 1} = Moment_filt(x(i): x(i + 1));
    Biceps_cycle{i, 1} = EMG_proces(x(i): x(i + 1), 1);
    Triceps_cycle{i, 1} = EMG_proces(x(i): x(i + 1), 2);
end

% Normalize signals to 100 data points
for j = 1:length(Moment_cycle)
    oldtime = 1:length(Moment_cycle{j, 1});
    newtime = 1:length(Moment_cycle{j, 1})/100:length(Moment_cycle{j, 1});
    Biceps_normalized{j, 1} = spline(oldtime, Biceps_cycle{j, 1}, newtime);
    Triceps_normalized{j, 1} = spline(oldtime, Triceps_cycle{j, 1}, newtime);
    Moment_normalized{j, 1} = spline(oldtime, Moment_cycle{j, 1}, newtime);
    Position_normalized{j, 1} = spline(oldtime, Position_cycle{j, 1}, newtime);
end

% Calculate average and standard deviation
Biceps = cat(3, Biceps_normalized(:, 1));
Triceps = cat(3, Triceps_normalized(:, 1));
Moment = cat(3, Moment_normalized(:, 1));
Position = cat(3, Position_normalized(:, 1));
Bic_mean = mean(Biceps, 3);
Bic_std = std(Biceps, 0, 3);
Tri_mean = mean(Triceps, 3);
Tri_std = std(Triceps, 0, 3);
Mom_mean = mean(Moment, 3);
Mom_std = std(Moment, 0, 3);
Pos_mean = mean(Position, 3);
Pos_std = std(Position, 0, 3);

% Print the output
fid = fopen(strrep(filename2, '.csv', 'Results.xls'), 'w');
fprintf(fid, 'Biceps_mean	 std	 Triceps_mean	 std	 Position_mean	 std	 Moment_mean	 std\n');
for i = 1:size(Bic_mean, 2)
    fprintf(fid, 'Biceps_mean(1, i)/Value_to_normBic, Bic_std(1, i)/Value_to_normBic,
    Tri mean(1, i)/Value_to_normTri, Tri_std(1, i)/Value_to_normTri, Pos mean(1, i), Pos_std(1, i), Mom mean(1, i), Mom_std(1, i));
end
plot(Pos_mean)
% Trajectory output for Study Three
clc

clear

%% Import the .c3d Files
folder = cd;
[fileName, filePath] = uigetfile('*.c3d', 'Select File', folder, 'MultiSelect', 'off');
fullFileName = strcat(filePath, fileName);
BackSlash = strfind(folder, '\');
SubjectName = folder(BackSlash(end-1)+1:BackSlash(end)-1);
ConditionName = folder(BackSlash(end)+1:end);
c1c

%% Enter Trial Type
prompt = {'Enter Trial Type'};
dlg_title = 'Trial Type';
um_lines = 1;
def = {''};
options.Resize = 'on';
options.WindowStyle = 'normal';
options.Interpreter = 'tex';
answer = inputdlg(prompt,dlg_title,num_lines,def,options);
[TrialType] = answer{1};

%% Import Data
trialType = ('Luqman');
varNames3d = {'RFIN'};
varNamesAnalog = {'Biceps', 'Triceps', 'Pec Major', 'Ant Deltoid', 'Trapezius', 'Lat Dorsi', 'Flexor Carpi Rad', 'Extensor Carpi R'};
TrialName = fileName(1:strfind(fileName,'.')-1);
[MarkerStruct, AnalogStruct, VideoFrameRate, AnalogFrameRate,...
EventTimes, EventTypes, EventLabels, EventSides]...
= readc3duwaStruct_Nexus(fullFileName, trialType, 'default',...
varNames3d, varNamesAnalog, 'y');
c1c

%% Create Event Frames
EventFrames = sort(round(EventTimes .* VideoFrameRate));
EventFramesAnalog = sort(round(EventTimes .* AnalogFrameRate));

%% Create Column Data
for i = 1:length(EventFrames)-1
    PhaseName(i) = strcat('Phase ', num2str(i));
    Data.(PhaseName(i)) = {{1:length(MarkerStruct.RFIN(EventFrames(i):EventFrames(i+1)-1,:))},...
    {1:length(MarkerStruct.RFIN(EventFrames(i):EventFrames(i+1)-1,:))}/VideoFrameRate,...
    MarkerStruct.RFIN(EventFrames(i):EventFrames(i+1)-1,:)};
end

%% Create Graphs
for i = 1:length(EventFrames)-1
    GraphName(i) = strcat(SubjectName, '_',ConditionName,'_',TrialType,'_',TrialName,'_',
    PhaseName(i),'.jpg');
    subplot(3,1,1)
    plot(Data.(PhaseName(i))(:,3),'linewidth',3)
    title('x')
    subplot(3,1,2)
    plot(Data.(PhaseName(i))(:,4),'linewidth',3)
    title('y')
    subplot(3,1,3)
    plot(Data.(PhaseName(i))(:,5),'linewidth',3)
    title('z')
    saveas(gcf,GraphName(i))
close
end
%% Write Data to csv File
for i = 1:length(EventFrames)-1
    OutPutName{i} = strcat(SubjectName,'_',ConditionName,'_',TrialType,'_',TrialName,'_',
                          PhaseName{i},'_.csv');
    csvwrite_with_headers(OutPutName{i}, Data.(PhaseName{i}), {'Frame', 'Time', 'x',
                       'y', 'z'})
end

%% Processing of accuracy data for Study Three
clear clc

%% Import the .c3D file names
folder = cd;
fileName = uigetfile('*.c3d', 'MultiSelect', 'On');
BackSlash = strfind(folder,'\');
SubjectName = folder(BackSlash(end-1)+1:BackSlash(end)-1);
ConditionName = folder(BackSlash(end)+1:end);

%% Enter Trial Type
prompt = {'Enter Trial Type'};
dlg_title = 'Trial Type';
num_lines = 1;
def = {''};
options.Resize = 'on';
options.WindowStyle = 'normal';
options.Interpreter = 'tex';
answer = inputdlg(prompt,dlg_title,num_lines,def,options);
[TrialType] = answer{1};

%% Enter Left Accuracy Number
prompt = {'Enter Left Accuracy Number'};
dlg_title = 'Left';
num_lines = 1;
def = {''};
options.Resize = 'on';
options.WindowStyle = 'normal';
options.Interpreter = 'tex';
answer = inputdlg(prompt,dlg_title,num_lines,def,options);
[Left] = str2double(answer{1});

%% Enter Right Accuracy Number
prompt = {'Enter Right Accuracy Number'};
dlg_title = 'Right';
num_lines = 1;
def = {''};
options.Resize = 'on';
options.WindowStyle = 'normal';
options.Interpreter = 'tex';
answer = inputdlg(prompt,dlg_title,num_lines,def,options);
[Right] = str2double(answer{1});

%% Import Data
trialType = ('Luqman');
varNames3d = {'RFIN'};
varNamesAnalog = {'Biceps'};
for i = 1:length(fileName)
    TrialName{i} = fileName{i}(1:strfind(fileName{i},'.')-1);
    [MarkerStruct.(TrialName{i}), AnalogStruct.(TrialName{i}), VideoFrameRate,
     AnalogFrameRate,...
     EventTimes.(TrialName{i}), EventTypes.(TrialName{i}), EventLabels.(TrialName{i}),
     EventSides.(TrialName{i})]... = readc3duwaStruct_Nexus(fileName{i}, trialType, 'default',...)
    varNames3d, varNamesAnalog, 'y'};
end clc
%% Create Event Frames
for i = 1:length(fileName)
    EventFrames.(TrialName{i}) = sort(round(EventTimes.(TrialName{i}) .* VideoFrameRate));
    EventFramesAnalog.(TrialName{i}) = sort(round(EventTimes.(TrialName{i}) .* AnalogFrameRate));
end

%% Create Column Data
for i = 1:length(fileName)
    for j = 1:length(EventFrames.(TrialName{i}))
        Data.(TrialName{i}){j} = MarkerStruct.(TrialName{i}).RFIN(EventFrames.(TrialName{i})(j),:);
    end
end

%% Create Vector
for i = 1:length(fileName)
    for j = 1:length(EventFrames.(TrialName{i}))
        Vector.(TrialName{i})(j) = sqrt(Data.(TrialName{i}){j}(1)^2 + Data.(TrialName{i}){j}(2)^2 + Data.(TrialName{i}){j}(3)^2);
    end
end

%% Crop Vector to last 6 taps/points
for i = 1:length(fileName)
    for j = 1:length(EventFrames.(TrialName{i}))
        Vector2.(TrialName{i}) = Vector.(TrialName{i})(end-5:end);
    end
end

%% Subtract Accuracy Points
for i = 1:length(fileName)
    for j = 1:length(EventFrames.(TrialName{i}))
        Vector_Left(i,:) = Vector2.(TrialName{i}) - Left;
        Vector_Right(i,:) = Vector2.(TrialName{i}) - Right;
    end
end

%% xlsx Write
xlswrite(strcat(TrialType,'.xlsx'),Vector_Left,'Vector_Left','B1')
xlswrite(strcat(TrialType,'.xlsx'),TrialName','Vector_Left','A1')
xlswrite(strcat(TrialType,'.xlsx'),Vector_Right,'Vector_Right','B1')
xlswrite(strcat(TrialType,'.xlsx'),TrialName','Vector_Right','A1')

%% Processing of electromyography data for Study Three
clear
cclc

%% Import the .c3d Files
folder = cd;
[fileName, filePath] = uigetfile('*.c3d', 'Select File', folder, 'MultiSelect', 'on');
fullFileName = strcat(filePath, fileName);
BackSlash = strfind(folder, '\');
SubjectName = folder(BackSlash(end)+1:end);
cclc

%% Import Data
trialType = ('EMG');
varNames3d = {'LFIN'};
varNamesAnalog = {'Biceps', 'Triceps', 'Pec Major', 'Ant Deltoid', 'Trapezius', 'Lat Dorsi', 'Flexor Carpi Rad', 'Extensor Carpi R'};

for i = 1:length(fileName)
    TrialName{:,i} = fileName{:,i}(1:strlen(fileName{:,i})-1);
    [MarkerStruct.(TrialName{:,i}), AnalogStruct.(TrialName{:,i}), VideoFrameRate, AnalogFrameRate,...
    EventTimes.(TrialName{:,i}), EventTypes.(TrialName{:,i}),...,
    EventLabels.(TrialName{:,i}), EventSides.(TrialName{:,i})]...
    = readc3duwaStruct_Nexus(fullFileName{i}, trialType, 'default',...
varNames3d, varNamesAnalog, 'y');
clc
end

%% Create Event Frames
for i = 1:length(fileName)
    EventFrames.(TrialName{:,i}) = sort(round(EventTimes.(TrialName{:,i}). * VideoFrameRate));
end

%% Create Event Frames Analog
for i = 1:length(fileName)
    EventFramesAnalog.(TrialName{:,i}) = sort(round(EventTimes.(TrialName{:,i}). * AnalogFrameRate));
end

%% High pass
Wn = 1/(AnalogFrameRate/20);
[B,A]=butter(2,Wn,'high');

for i = 1:length(fileName)
    VariableNames = fieldnames(AnalogStruct.(TrialName{:,i}));
    for j = 1:length(VariableNames)
        EMG_filt.(TrialName{:,i}).(VariableNames{j}) = filtfilt(B,A,AnalogStruct.(TrialName{:,i}).(VariableNames{j}));
    end
end

%% Remove DC Offset
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        EMG_Mean.(TrialName{:,i}).(VariableNames{j}) = mean(EMGfilt.(TrialName{:,i}).(VariableNames{j}));
        EMG_Offset.(TrialName{:,i}).(VariableNames{j}) = EMG_filt.(TrialName{:,i}).(VariableNames{j}) - EMG_Mean.(TrialName{:,i}).(VariableNames{j});
    end
end

%% Rectify
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        EMG_rect.(TrialName{:,i}).(VariableNames{j}) = abs(EMG_filt.(TrialName{:,i}).(VariableNames{j}));
    end
end

%% Low pass
Wn = 1/(AnalogFrameRate/6);
[B,A]=butter(4,Wn);

for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        EMG_process.(TrialName{:,i}).(VariableNames{j}) = filtfilt(B,A,EMG_rect.(TrialName{:,i}).(VariableNames{j}));
    end
end

%% Create MVC and Trial Structure
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        index = strfind(TrialName,'Trial');
        if index{i} > 0
            Trial.(TrialName{:,i}).(VariableNames{j}) = EMG_process.(TrialName{:,i}).(VariableNames{j});
        end
    end
end

%% Create True MVC Structure
for i = 1:length(fileName)
    for j = 1:length(VariableNames)
        index = strfind(TrialName,'Biceps');
        if index{i} > 0 & index2{j}
            MVC_New.Biceps(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
        end
    end
end
```matlab
end
index = strfind(TrialName,'FlxCarpi');
index2 = strfind(VariableNames,'Flexor_Carpi');
if index{i} > 0 & index2{j};
    MVC_New.FlxCarpi(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
end
index = strfind(TrialName,'Lats');
index2 = strfind(VariableNames,'Lat');
if index{i} > 0 & index2{j};
    MVC_New.Lats(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
end
index = strfind(TrialName,'Pecs');
index2 = strfind(VariableNames,'Pec');
if index{i} > 0 & index2{j};
    MVC_New.Pecs(:,i) = max(MVC.(TrialName{:,i}).(VariableNames{j}));
end
end
end

%% Calculate MVC Average and MVC Peaks
VariableNamesNew = fieldnames(MVC_New);
for j = 1:length(VariableNamesNew)
    MVC_New.(VariableNamesNew{j}) = nonzeros(MVC_New.(VariableNamesNew{j}));
    MVC_Mean.(VariableNamesNew{j}) = mean(MVC_New.(VariableNamesNew{j}));
end

%% Normalize Trial Data to MVC Mean
TrialName2 = fieldnames(Trial);
for i = 1:length(TrialName2)
    Trial_Name2.(VariableNamesNew{j}) = Trial.(VariableNamesNew{j});/
    MVC_Mean.(VariableNamesNew{j});
end
end

%% Separate Trial Event Frames
for i = 1:length(TrialName)
    index = strfind(TrialName, 'Trial');
    if index{i} > 0
        Events.(TrialName2{i}) = EventFramesAnalog.(TrialName{i});
    end
end

for i = 1:length(TrialName2)
    for j = 1:length(VariableNames)
        Phase{j} = strcat('Phase_', num2str(j));
        Start.(TrialName2{i}).(Phase{j}) = Events.(TrialName2{i})(:,j);
        End.(TrialName2{i}).(Phase{j}) = Events.(TrialName2{i})(:,j+1);
    end
end

%% Split Normalized Trial Data into Phases
for i = 1:length(TrialName2)
    for j = 1:length(VariableNames)
        for k = 1:length(Phase)
            Trial_Integrated.(TrialName2{i})(j,k) = trapz((1:length(Trial_Norm2.(TrialName2{i}).(VariableNamesNew{j}))), Trial_Norm2.(TrialName2{i}).(VariableNamesNew{j}))./(AnalogFrameRate,Trial_Norm2.(TrialName2{i}).(VariableNamesNew{j})).(Phase{k});
        end
    end
end

%% Calculate Integrated EMG
for i = 1:length(TrialName2)
    for j = 1:length(VariableNames)
        for k = 1:length(Phase)
            Trial_Integrated.(TrialName2{i})(j,k) = trapz((1:length(Trial_Norm2.(TrialName2{i}).(VariableNamesNew{j}))), Trial_Norm2.(TrialName2{i}).(VariableNamesNew{j})).(Phase{k});
        end
    end
end
```
%% Export To Excel
for i = 1:length(TrialName2)
    xlswrite(strcat(SubjectName, '_EMG.xlsx'), Trial_Integrated.(TrialName2{i}), strcat('Integrated_\', TrialName2(i)), 'B2')
    xlswrite(strcat(SubjectName, '_EMG.xlsx'), VariableNamesNew, strcat('Integrated_\', TrialName2(i)), 'A2')
    xlswrite(strcat(SubjectName, '_EMG.xlsx'), Phase, strcat('Integrated_\', TrialName2(i)), 'B1')
end
APPENDIX 8

Deep brain stimulation can influence gait in individuals with essential tremor: Two case studies

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SUMMARY
This is the first pilot study of its kind to assess the effect of acute posterior subthalamic area (PSA) deep brain stimulation on gait, in patients with essential tremor (ET). Two participants with ET underwent 3D biomechanical gait analysis pre and post PSA deep brain stimulation. Peak ankle joint power exhibited increases with micro-lesioning and high-frequency stimulation in both participants. We postulate that the dorsal PSA may have a regulatory role in gait, with deep brain stimulation holding therapeutic potential for gait disorders.

INTRODUCTION
There is evidence to suggest that deep brain stimulation of the PSA may have a role in improving the gait of patients with ET. Animal studies have shown that the Zone lacerta (Zl), located in the PSA, is involved in locomotor control [1]. However, the hypothesis that the Zl, and thus the PSA surgical target, is involved in the control of gait has not been tested in humans. Therefore, the aim of this pilot study was to perform a 3D kinematic and kinetic gait analysis in two ET patients undergoing PSA deep brain stimulation.

METHODS
Two male clinical participants (ET1 and ET2), aged 60 and 63 (Parkinson's Rating Score of 67 and 85 respectively) underwent a non-randomised phase II clinical trial of PSA deep brain stimulation for ET. Surgeries were performed at the Sir Charles Gardiner Hospital using the MRI-directed implantable guide tube technique [2].

Both participants underwent gait analysis using standard 3D gait analysis techniques [3] on two occasions under their preferred walking speed; pre-operatively and post-operatively. Two days following the pre-operative baseline gait assessment, participant ET1 underwent a unilateral brain implant while ET2 underwent bilateral brain implants. The post-operative gait analysis protocol comprised of three stimulation settings: 1) micro-lesioning, 2) stimulation to the dorsal Zl (dZl), and 3) stimulation to the caudal Zl (cZl).

The stimulation settings were standardized for both regions at a pulse width of 60 μs, frequency of 130 Hz, and amplitude of 3.0 V and were randomized and double blinded to both the assessors and participants to reduce bias.

A synchronized 12-camera VICON MX 3D motion analysis system (100 Hz) and a Kistler force plate (2000 Hz) were used to collect raw 3D trajectories and ground reaction force data. Following a residual analysis [4] all marker trajectories and ground reaction force data were filtered using a fourth-order, 8 Hz zero-lag low-pass Butterworth filter. Lower limb joint angle kinematic and kinetic data were calculated using a customized model [5] in the VICON Nexus pipeline, while discrete values and waveform data were outputted using a custom MATLAB program. Data were time-normalized to 101 data points as a percentage of the gait cycle. Joint moment and power were normalized by bodyweight (Nm/kg and W/kg respectively). Spatiotemporal parameters and sagittal plane kinematic and kinetic variables were analyzed. Preliminary data (pre-operative analysis) did not produce a high effect size between groups and no statistical scores were obtained due to the limited sample and the research being treated as an initial pilot study.

RESULTS AND DISCUSSION
Participant ET1
Spatiotemporal parameters
Gait velocity did not differ between post-operative conditions, except in the case of dZl stimulation where velocity increased from 1.1 ± 0.05 m/s at baseline to 1.32 ± 0.05 m/s for dZl stimulation. This slight increase in velocity can be attributed to an increase in cadence from 103 ± 1 steps/min at baseline, to 117 ± 0 steps/min for dZl stimulation. Double support times in all three post-operative conditions were also seen to decrease by 9.15 %, when compared with the baseline level with dZl stimulation having the most change from 1.33 ± 0.01 s to 1.13 ± 0.03 s.
Kinematics
The most prominent kinematic changes were observed at the ankle joint. Ankle range of motion (ROM) showed a marked increase of 57% from 29 ± 0.8° at baseline to 37 ± 2.0° as a result of micro-lesioning and stimulation. The increase in ankle ROM can be largely attributed to the increase in the peak ankle plantar-flexion angle achieved at toe-off.

Kinetics
Mean peak flexion-extension ankle power generation increased following micro-lesioning when compared with baseline levels, with even greater improvements observed with dZI stimulation (Figure 1). Baseline ankle power increased from 3.12 ± 0.08 W/kg to 4.44 ± 0.56 W/kg with micro-lesioning, and subsequently, mean ankle power increased from the 83rd percentile to well above the 90th percentile of normal population values [4] (Figure 1). Furthermore, mean ankle power further increased to 5.52 ± 0.16 W/kg with dZI stimulation.

CONCLUSIONS
A combination of micro-lesioning of the PSA and acute dZI stimulation resulted in an increase in peak ankle power in two ET patients. Interestingly, neither participant complained of problems with gait and nor exhibited gross abnormalities of gait on clinical examination, and both expressed a sense of improvement in gait during at least one stimulation experimental condition. The increase in ankle power generation was the Most striking effect of micro-lesioning of the PSA and stimulation of dZI on the gait patterns of the two participants. The dZI region of the PSA may play a role in gait control. Electrical stimulation experiments of the PSA and other brain sites in ET and other movement disorders including Parkinson’s disease will reveal more about the role of the PSA in gait control.

REFERENCES
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The effect of acute posterior subthalamic area micro-lesioning and stimulation on upper limb tremor and activation patterns in Parkinson’s disease

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INTRODUCTION & OBJECTIVES

Tremor is one of the hallmark motor symptoms of Parkinson’s disease (PD) and can be present at rest or when the limb is unsupported against gravity (postural tremor) [1]. Some individuals with PD tremor have limited response to medication and require surgical intervention to alleviate their symptoms [2]. There is qualitative data to suggest that Deep brain stimulation (DBS) of the posterior subthalamic area, specifically targeting the Zona Incerta (ZI), has been successful in alleviating tremor [3-4], however, they provide limited information on the discrete alterations in tremor following intervention [5]. Our study aimed to investigate the effects of ZI targeted posterior subthalamic area DBS on upper limb tremor through use of quantitative assessments, specifically spectral analysis and integrated electromyography (iEMG). We expect the PD participants to exhibit altered spectral analysis and iEMG levels as compared to the healthy controls all of which will display improvements with post-operative settings.

METHODS

Ten PD participants and 13 healthy matched controls participated in this study. The PD participants underwent two assessment sessions: pre-operative and post-operative. Following the pre-operative assessment, PD participants underwent bilateral implants aimed at the caudal division of the ZI [6]. The PD participants then returned for their post-operative assessment with the addition of three different stimulation settings: i) micro-lesioning, ii) stimulation targeted to the caudal ZI, iii) stimulation targeted to the dorsal ZI. All participants completed two different upper limb tasks aimed at elucidating both resting and postural tremor. A synchronized 12-camera VICON MX 3D motion analysis system (250 Hz) and a Noraxon Telereview System (2000 Hz) were used to collect raw 3D trajectories and electromyography data. The raw 3D kinematic outputs were modelled using the UWA upper limb model [7] and the spectral analysis of the segment origins at the upper arm and hand were estimated using a custom written LabView program [8]. Processing of the integrated iEMG was performed offline using a high pass cut-off frequency of 20 Hz, signal rectification, low pass at 450 Hz, integrated using the MATLAB® trapezoidal numerical integration function, and normalised to submaximal voluntary contraction. Due to the variability and non-normalised sample of the PD group, descriptive analysis was applied.
RESULTS

Spectral analysis

There were prominent trends in the mean values for both tasks and segments between the pre-operative PD participants and healthy controls. Both amplitude of the frequency (aFP) and power (4-7 Hz) were elevated in the pre-operative PD participants (aFP = 0.003 – 0.096, power = 0.046 – 35.954) compared to controls (aFP = 0.001 – 0.005, power = 0.001 – 0.030) and were seen to decrease with post-operative settings (aFP = 0.004 – 0.055, power = 0.044 – 10.925).

Clear trends in the spectral analysis, specifically the aFP were observed in the participants who underwent surgery to control the tremor (TremPD), with observed values moving towards that of healthy controls across the post-operative settings. Figure 1 illustrates the example data of the resting task at the arm segment in the TremPD group. Likewise, there was a resultant decrease in power (4-7 Hz) for the TremPD with micro-lesioning and Z1 DBS in both segments in the resting task. The converse trend was exhibited in one participant in the TremPD group post-operatively.

![Graph showing spectral analysis](image)

*iEMG analysis*

No significant differences in iEMG were found between the pre-operative PD participants and controls. However, there was a trend of greater iEMG activity in the triceps and anterior deltoid in both tasks for the PD group pre-operatively (triceps = 0.89 – 2.96, anterior deltoid = 1.01 – 5.73) compared to controls (triceps = 0.25 – 0.82, anterior deltoid = 0.75 – 3.41). A general decrease (non-significant) in triceps, anterior deltoid and trapezius iEMG was exhibited with post-operative settings (triceps = 0.34 – 1.69, anterior deltoid = 0.29 – 5.26, trapezius = 0.61 – 2.65) in the whole PD group compared to their pre-operative (triceps = 0.89 – 2.96, anterior deltoid = 1.01 – 5.73, trapezius = 1.79 – 5.71) levels in both resting and postural tasks.

CONCLUSION

This novel study quantified improvements in resting and postural tremor, particularly for the TremPD group following Z1 targeted DBS. This research builds upon previous work of others supporting Z1 targeted DBS as being safe and effective in alleviating tremor symptoms. The mechanism leading to tremor reduction with Z1 targeted DBS remains to be elucidated. The vast projections of the Z1 [9] and stimulation may influence the basal ganglia and cerebello-thalamocortical pathways which have been speculated to have an influence on tremor [5]. Future work utilising a combination of signal processing methods together with a larger sample size, could help explain the mechanism of action of DBS in greater detail.
REFERENCES


**APPENDIX 10**

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**Part III: Motor Examination**

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS, the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

- **ON** is the typical functional state when patients are receiving medication and have a good response.
- **OFF** is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "UR" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether those movements interfered with the motor examination.

---

**3a** Is the patient on medication for treating the symptoms of Parkinson's Disease?  ☐ No  ☐ Yes

---

**3b** If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

- ☐ ON: On is the typical functional state when patients are receiving medication and have a good response.
- ☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

---

**3c** Is the patient on Levodopa?  ☐ No  ☐ Yes

- **3.C1** If yes, minutes since last levodopa dose: __________
3.1 SPEECH

Instructions to examiner: Listen to the patient’s free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient’s work, hobbies, exercise, or how he got to the doctor’s office. Evaluate volume, modulation (prosody) and clarity, including slurring, pallilage (repetition of syllables) and tachyphemia (rapid speech, running syllables together).

0: Normal: No speech problems.
1: Slight: Loss of modulation, diction or volume, but still all words easy to understand.
2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow.
3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood.
4: Severe: Most speech is difficult to understand or unintelligible.

3.2 FACIAL EXPRESSION

Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips.

0: Normal: Normal facial expression.
1: Slight: Minimal masked facies manifested only by decreased frequency of blinking.
2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.
3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest.
4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.
3.3 RIGIDITY

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.
1: Slight: Rigidity only detected with activation maneuver.
2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.
3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.
4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.
2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.
3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.
### 3.5 HAND MOVEMENTS

**Instructions to examiner:** Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully and as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal:</td>
<td>No problem.</td>
</tr>
<tr>
<td>1: Slight:</td>
<td>Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.</td>
</tr>
<tr>
<td>2: Mild:</td>
<td>Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.</td>
</tr>
<tr>
<td>3: Moderate:</td>
<td>Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.</td>
</tr>
<tr>
<td>4: Severe:</td>
<td>Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>

### 3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

**Instructions to examiner:** Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal:</td>
<td>No problems.</td>
</tr>
<tr>
<td>1: Slight:</td>
<td>Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.</td>
</tr>
<tr>
<td>2: Mild:</td>
<td>Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.</td>
</tr>
<tr>
<td>3: Moderate:</td>
<td>Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence.</td>
</tr>
<tr>
<td>4: Severe:</td>
<td>Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>
### 3.7 TOE TAPPING

**Instructions to examiner:** Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problem.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>

### 3.8 LEG AGILITY

**Instructions to examiner:** Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>
3.9 ARISING FROM CHAIR

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13.

0: Normal: No problems. Able to arise quickly without hesitation.
1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.
2: Mild: Pushes self up from arms of chair without difficulty.
3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.
4: Severe: Unable to arise without help.

3.10 GAIT

Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for “freezing of gait” (next item 3.11) while patient is walking. Observe posture for item 3.13.

0: Normal: No problems.
1: Slight: Independent walking with minor gait impairment.
2: Mild: Independent walking but with substantial gait impairment.
3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person.
4: Severe: Cannot walk at all or only with another person’s assistance.
### 3.11 FREEZING OF GAIT

**Instructions to Examiner:** While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No freezing.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Freezes once during straight walking.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Freezes multiple times during straight walking.</td>
</tr>
</tbody>
</table>

### 3.12 POSTURAL STABILITY

**Instructions to Examiner:** The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test repetition. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for Item 3.13.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problems: Recovers with one or two steps.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>3-5 steps, but subject recovers unaided.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>More than 5 steps, but subject recovers unaided.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Stands safely, but with absence of postural response; falls if not caught by examiner.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.</td>
</tr>
</tbody>
</table>
### 3.13 POSTURE

Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Not quite erect, but posture could be normal for older person.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected voluntarily to a normal posture by the patient.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.</td>
</tr>
</tbody>
</table>

### 3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA)

Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner’s global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Slight global slowness and poverty of spontaneous movements.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Mild global slowness and poverty of spontaneous movements.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Moderate global slowness and poverty of spontaneous movements.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Severe global slowness and poverty of spontaneous movements.</td>
</tr>
</tbody>
</table>

### 3.15 POSTURAL TREMOR OF THE HANDS

Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No tremor.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Tremor is present but less than 1 cm in amplitude.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Tremor is at least 1 but less than 3 cm in amplitude.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Tremor is at least 3 but less than 10 cm in amplitude.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Tremor is at least 10 cm in amplitude.</td>
</tr>
</tbody>
</table>
### 3.16 KINETIC TREMOR OF THE HANDS

**Instructions to examiner:** This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Tremor is present but less than 1 cm in amplitude.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Tremor is at least 1 but less than 3 cm in amplitude.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Tremor is at least 3 but less than 10 cm in amplitude.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Tremor is at least 10 cm in amplitude.</td>
</tr>
</tbody>
</table>

### 3.17 REST TREMOR AMPLITUDE

**Instructions to examiner:** This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.

As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

#### Extremity ratings

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Slight: &lt; 1 cm in maximal amplitude.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: &gt; 1 cm but &lt; 3 cm in maximal amplitude.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: 3 - 10 cm in maximal amplitude.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: &gt; 10 cm in maximal amplitude.</td>
</tr>
</tbody>
</table>

#### Lip/Jaw ratings

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Slight: &lt; 1 cm in maximal amplitude.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: &gt; 1 cm but &lt; 2 cm in maximal amplitude.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: &gt; 2 cm but &lt; 3 cm in maximal amplitude.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: &gt; 3 cm in maximal amplitude.</td>
</tr>
</tbody>
</table>
### 3.18 Constancy of Rest Tremor

**Instructions to examinee:** This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variably at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:</td>
<td>Normal; No tremor.</td>
</tr>
<tr>
<td>1:</td>
<td>Slight; Tremor at rest is present &lt; 25% of the entire examination period.</td>
</tr>
<tr>
<td>2:</td>
<td>Mild; Tremor at rest is present 26-50% of the entire examination period.</td>
</tr>
<tr>
<td>3:</td>
<td>Moderate; Tremor at rest is present 51-75% of the entire examination period.</td>
</tr>
<tr>
<td>4:</td>
<td>Severe; Tremor at rest is present &gt; 75% of the entire examination period.</td>
</tr>
</tbody>
</table>

### Dyskinesia Impact on Part III Ratings

**A.** Were dyskinesias (chorea or dystonia) present during examination?  
☐ No  ☐ Yes

**B.** If yes, did these movements interfere with your ratings?  
☐ No  ☐ Yes

### Hoehn and Yahr Stage

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:</td>
<td>Asymptomatic.</td>
</tr>
<tr>
<td>1:</td>
<td>Unilateral involvement only.</td>
</tr>
<tr>
<td>2:</td>
<td>Bilateral involvement without impairment of balance.</td>
</tr>
<tr>
<td>3:</td>
<td>Milder to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.</td>
</tr>
<tr>
<td>4:</td>
<td>Severe disability; still able to walk or stand unassisted.</td>
</tr>
<tr>
<td>5:</td>
<td>Wheelchair bound or bedridden unless aided.</td>
</tr>
</tbody>
</table>
## APPENDIX 11

<table>
<thead>
<tr>
<th>Segment</th>
<th>Surface electrodes</th>
<th>Location</th>
<th>Submaximal MVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Trapezius</td>
<td>The electrodes need to be placed at 50% on the line from the acromion to the spine on vertebra C7. In the direction of the line between the acromion and the spine on vertebra C7.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latissimus Dorsi</td>
<td>Palpate scapula. Two electrodes (spaced 2 cm apart) are placed approximately 4 cm below the inferior tip of the scapula, half the distance between the spine and the lateral edge of the torso. Oriented in a slightly oblique angle of approximately 25 degrees.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Pectoralis Major | **Sternal:** - Place the electrodes just medial to the anterior axillary fold over the bulk of the muscle (Left pec)  
**Clavicular:** - Between sternoclavicular joint and the caracoidus process, 2 cm below the clavicle on an angle down and laterally (Right pec) |
<p>| Anterior Deltoid | The electrodes need to be placed at one finger width distal and anterior to the acromion. In the direction of the line between the acromion and the thumb. |</p>
<table>
<thead>
<tr>
<th>Segment</th>
<th>Surface electrodes</th>
<th>Location</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Biceps Brachii</td>
<td>Electrodes need to be placed on the line between the medial acromion and the fossa cubit at 1/3 from the fossa cubit. In the direction of the line between the acromion and the fossa cubit.</td>
<td><img src="image1.jpg" alt="Image" /></td>
<td><img src="image2.jpg" alt="Image" /></td>
</tr>
<tr>
<td>Triceps (Lateral Head)</td>
<td>Electrodes need to be placed at 50 % on the line between the posterior crista of the acromion and the olecranon at 2 finger widths lateral to the line. In the direction of the line between the posterior crista of the acromion and the olecranon process.</td>
<td><img src="image3.jpg" alt="Image" /></td>
<td><img src="image4.jpg" alt="Image" /></td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>Electrodes are placed on the palmar side (volar surface) of the forearm approximately 7-9 cm distal to the medial epicondyle along a line directed toward the muscle tendon of the wrist.</td>
<td><img src="image5.jpg" alt="Image" /></td>
<td><img src="image6.jpg" alt="Image" /></td>
</tr>
<tr>
<td>Extensor Carpi Radialis</td>
<td>Place the electrodes in the upper forearm approximately 5-7 cm distal to the lateral epicondyle along a line connecting the epicondyle and the second metacarpal bone.</td>
<td><img src="image7.jpg" alt="Image" /></td>
<td><img src="image8.jpg" alt="Image" /></td>
</tr>
</tbody>
</table>