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Investigation of Sensorimotor Integration and Control in Parkinson's Disease using Haptics-enabled Robotics and Machine Learning

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Abstract

Non-motor symptoms such as perceptual deficits and cognitive impairments, i.e., deficits in executive functions, presented at an early stage of Parkinson's Disease (PD) substantially affect a PD patient's quality of life and may contribute to motor impairments. Studies have emphasized the need to better understand these impairments and the abnormalities contributing to them as it provides a means to efficiently manage the disease. Further, due to the early onset of these deficits, the contributing abnormalities may be considered a potential biomarker for early diagnosis of PD. However, the impairments and the contributing abnormalities are not yet fully understood, leading to inadequate options to efficiently manage the disease. The Basal Ganglia, the region affected by PD, plays a vital role in Sensorimotor Integration (SMI) and Sensorimotor Control (SMC) functions – two fundamental processes involved in sensory perception and movement planning. The hypothesis is that the impairments in SMI and SMC contribute to deficits in perception and executive functions, leading to motor deficits and these impairments may be altered due to medication. The primary contribution of the thesis is the development of robotic tools for characterizing the SMI and SMC impairments in PD patients. The study's results showed that PD patients suffer from an impaired SMI and SMC circuit that adversely affects multi-sensory integration, movement planning, online error correction, and execution of voluntary movements. Additionally, the findings have shown that dopaminergic medication significantly worsens SMI and SMC impairments. The secondary contribution is the development of a musculoskeletal model that can accurately estimate in-depth SMC features. The developed model may be used to guide and enhance the efficacy of PD-related therapies. The novel findings of the study contribute to advancing our knowledge about the disease and the effect of medication by characterizing the SMI and SMC impairments and demonstrating their contribution to deficits in perception, executive functions, and motor performance. The study's results enable us to better target these deficits through efficient treatment optimization. Further, the thesis describes the development and validation of tools to effectively diagnose, monitor, and individualize the assessment of SMI, SMC, and, consequently, the corresponding non-motor impairments in PD.

Keywords

Parkinson’s Disease, Rehabilitation Robot, Sensorimotor Integration, Sensorimotor Control, Musculoskeletal Model, Cognitive Impairments, Perceptual Impairments, Neural Network Models, Machine learning, Virtual Reality, Subject-Specific Assessment, Dopaminergic Medication.

Summary for Lay Audience

Parkinson's Disease (PD) is one of the most common neurodegenerative disorders, known for its cardinal motor symptoms such as tremor, slowness of movement (bradykinesia), and rigidity. However, non-motor symptoms, such as impairments in perception and cognitive abilities, may be presented earlier than motor symptoms and can significantly affect the patient's quality of life. Further, studies have reported that non-motor symptoms may contribute to the motor symptoms appearing later in the disease, making non-motor symptoms a promising biomarker for an early diagnosis. However, the nature of these non-motor symptoms and their contributors are not fully known, leading to inadequate options for managing these complex symptoms. Consequently, there is a need to better understand them to efficiently manage the disease. Sensorimotor Integration (SMI), which is responsible for accurately perceiving the world around us, and Sensorimotor Control (SMC), which is responsible for planning and execution of movements, have been hypothesized to be impaired in PD, leading to perceptual and cognitive abnormalities. Therefore, in this work, robotic tools were developed to explore the factors contributing to perceptual and cognitive abnormalities and the effect of medication. Multiple robot-based tasks were designed to examine the SMI and SMC performance in PD patients. It was found that the various aspects of SMI and SMC have been impaired in PD patients, leading to abnormalities in perception, and cognitive abilities, thereby affecting the patient's ability to perform day-to-day tasks. Further, the dopaminergic medication has been found to worsen SMI and SMC impairments in PD patients, emphasizing the need to better optimize the treatment. A muscle model that can analyze in-depth SMC parameters was also developed as a potential tool to enhance the efficiency of PD therapies. The findings from the study provide valuable insights into factors contributing to specific non-motor impairments and the effect of medication, allowing us to target these impairments better. Additionally, owing to the lack of existing techniques to monitor non-motor impairments, robotic and simulation tools have been developed and validated. This may be considered a first step to using objective metrics in conjunction with existing clinical tools to better diagnose, monitor, and manage the disease.

Co-Authorship Statement

Chapters 2, 3, 4, and 5 in the thesis include text, figures, and tables from manuscripts that have been published or are under review for publication or are to be submitted for publication. This thesis is in the "Integrated Article" format and contains three publications published in peer-reviewed journals. Yokhesh Krishnasamy Tamilselvam (Y.K.T) is the first author of all three publications. Jacky Ganguly (J.G) is a co-author of one of these publications. Mandar S. Jog (M.S.J) and Rajni V. Patel (R.V.P) are co-authors of all three publications. Chapter-3, entitled: "Sensorimotor Integration in Parkinson's Disease", has been published in IEEE Transactions on Neural Systems and Rehabilitation Engineering (*vol. 31, pp. 3201–3211, 2023*). The content of Chapter-4 ("Sensorimotor Control in Parkinson's Disease: Abnormalities in Movement Planning and Online Error Correction") has been published in the *Nature Scientific Reports (vol. 13, Issue. 1, 2023)*. The content of Chapter-5 ("Subject-Specific Musculoskeletal Model to Analyze Muscle Recruitment Strategies") has been published in the *IEEE Access (vol. 9, pp. 111472-111485, 2021)*. Chapter-2 discusses the methodology used to investigate Sensorimotor Integration and Control in the three manuscripts.

Y.K.T. conducted the research, designed the experiments, developed the robotic tasks and simulations models, collected the data from PD and control participants, performed data processing, data analysis, and wrote the papers. J.G. was a clinical fellow and contributed to the data collection and preparation for one of the papers. M.S.J. was the clinical lead for the project. M.S.J. contributed to developing the research plan, patient recruitment and helped in preparing the papers. R.V.P. was the engineering lead for the project. R.V.P. proposed the research problem, contributed to developing the research plan, led the development of the robotic and haptic environment for the project, and helped in preparing the papers. All research activities of this paper were supervised by R.V.P. and M.S.J., who are joint supervisors of the thesis research of Y.K.T. All funding and resources for this work were provided by R.V.P. and M.S.J.

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List of Abbreviations

ANN - Artificial Neural Networks

ASC - Assistive Sensory Cues

BG – Basal Ganglia

CC - Contractile Component

CN - Caudate Nucleus

CNS – Central Nervous System

COMT - Catechol-O-Methyl Transferase

DBS - Deep Brain Stimulation

DOF - Degrees of Freedom

ECR – Extensor Carpi Radialis

ECU – Extensor Carpi Ulnaris

FCU – Flexor Carpi Ulnaris

FCR – Flexor Carpi Radialis

GABA - Gamma-Aminobutyric Acid

GPe - Globus Pallidus external

GPi - Globus Pallidus internal

ID - Index of Difficulty

KINARM - Kinesiological Instruments for Normal and Altered Reaching Movement

K-NNR - K-Nearest Neighbor

L-1 – Level-1

L-2 – Level-2

L-3 – Level-3

L-4 – Level-4

M1 - Motor Cortex

MAO-B - Monoamine Oxidase B

MDE - Mean Deviation Error

MLE - Maximum Likelihood Estimator

MoCA - Montreal Cognitive Assessment scale

MVC - Maximum Voluntary Contraction

MVE - Minimum Variance Estimate

NN - Neural Networks

PCSA - Physiological Cross-Sectional Area

PD – Parkinson's Disease

PD-OFF – PD patients in the OFF medication state

PD-ON – PD patients in the ON medication state

PEC - Parallel Elastic Component

PET - Positron Emission Tomography

PQ - Pronator Quadratus

PT - Pronator Teres

Put – Putamen

ReLU - Rectified Linear Unit

RMSE - Root Mean Squared Error

SEC - Serial Elastic Component

sEMG - Surface Electromyography

SMA - Supplementary Motor Area

SMC – Sensorimotor Control

SMI – Sensorimotor Integration

SNc - Substantia Nigra pars compacta

SNr - Substantia Nigra pars reticulata

STN - Subthalamic nucleus

UPDRS - Unified Parkinson's Disease Rating Scale

VR – Virtual Reality

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Chapter 1

1 Introduction

This chapter provides a brief overview of the symptoms presented due to Parkinson's Disease (PD). Specifically, the chapter discusses non-motor abnormalities, such as perceptual and cognitive dysfunctions, which may lead to motor abnormalities. With regard to the factors that may contribute to perceptual and motor abnormalities, the current findings about Sensorimotor Integration (SMI), Sensorimotor Control (SMC), and how PD may alter these functions are reviewed in this chapter. The chapter also outlines the treatments available for PD patients and the need for a more patient-specific treatment and monitoring approach. Finally, the hypothesis and the objectives of the thesis are stated.

1.1 Background

Parkinson's Disease is one of the fastest growing neurodegenerative disorders, with age being the most significant risk factor for PD, resulting in the epidemiological burden of Parkinsonism increasing with age. The World Health Organization (WHO) [1] reported that the prevalence of PD has risen globally in the last 25 years, with over 8.5 million individuals diagnosed with PD around the world. PD also places a significant economic burden on the health care system, with costs varying from one country to another. A study in 2010 indicated that the financial burden due to PD exceeds $14.4 billion in the US, which is equivalent to $22,800 per patient [2]. As the aging population increases globally, the number of PD cases is projected to be over 12 million globally by 2040. The lack of a cure, preventive methods, and long-term management strategies for PD highlight the importance of better understanding the disease to equip the healthcare system with newer, innovative techniques to manage the disease efficiently, thereby reducing the burden on the healthcare system and the global population.

PD is caused by the degeneration of dopaminergic neurons in the Basal Ganglia (BG) and is usually characterized by cardinal motor symptoms such as bradykinesia, rigidity, tremor, and postural instability. As the disease progresses, the symptoms may get worse, and the medication or treatments need to be adjusted accordingly. However, the

experience of one PD patient may differ extensively from that of another due to the heterogeneous nature of PD [3]. Consequently, the symptoms and the rate of progression will change from one person to another, necessitating a more individualized treatment approach. Recent studies have focused on exploring non-motor symptoms of PD, such as sensory and cognitive dysfunction, that severely affect the patient's quality of life. Findings indicate that the non-motor symptoms have a more significant impact on the health-related quality of life than the motor symptoms [4]. Furthermore, there is considerable evidence that non-motor impairments, such as perceptual deficits, may be presented much earlier in the disease and contribute to the motor abnormalities presented at a later stage. This makes the non-motor symptoms a potential target for early disease diagnosis. Despite the substantial burden of the non-motor symptoms, little is known about the factors contributing to non-motor symptoms, such as perceptual deficits or impairments in executive functions, and how to manage these symptoms. Moreover, there is a lack of assessment or diagnostic techniques to detect these symptoms early, which may assist in better managing the disease. The objective of the thesis is to unveil and examine the contributors of perceptual deficits and executive functions that lead to motor dysfunctions by developing objective robotic, machine learning and simulation tools to assess specific aspects of non-motor impairments and the impact of dopaminergic medication on these impairments. Further, the thesis also aims to propose technology-driven tools that can be improved to complement the existing subjective scales for an early diagnosis and to individualize the monitoring and management strategies for PD.

1.2 What is Parkinson's Disease?

1.2.1 Epidemiology of Parkinson's Disease

Parkinson's Disease (PD) is recognized as the second most common neurodegenerative disorder – a synucleinopathy, after Alzheimer's disease and is an increasing challenge to public health. A crude prevalence range of 100 to 200 people diagnosed with PD per 100,000 of the population at any time is generally accepted [5] [6]. Globally, the prevalence of PD increased from 2.5 million in 1990 to 6.1 million in 2016 [7]. PD is primarily an illness of later life, as indicated by the prevalence of PD increasing significantly after the age of 70 [8]. As such, the global prevalence of PD is expected to double in the next few

decades due to the increase in population age [9]. With an aging population leading to an increasing trend in the prevalence of PD worldwide, enabling appropriate medical responses to manage PD is likely to prove a more challenging task for neurologists and general physicians.

1.2.2 Etiology of Parkinson's Disease

New evidence regarding PD indicates that it is a multifactorial disorder influenced by age, genetic and environmental factors. Professional exposure to pesticides such as organochlorine [10] and herbicides such as paraquat [11] has been associated with the onset of PD, and its relation grows stronger in the late onset of PD. Further, occupational exposure to heavy metals, such as iron, manganese, aluminum, etc., could also increase the risk for PD [12][13]. Genetics is also a risk factor for PD, as approximately 15% of patients diagnosed with PD have a family history [14] [15], and researchers have linked 23 PARK genes to the cause of PD [14].

1.2.3 Pathology of Parkinson's Disease

The crucial pathological feature of PD is the neuronal loss in the substantia nigra followed by dopaminergic denervation of the striatum [16]. Morphometric studies show a strong correlation between the percentage loss of dopaminergic neurons with the severity of the motor symptoms and disease duration [17]. A lack of dopaminergic signaling is considered responsible for the observed motor symptoms.

Konstantin Tretiakoff described the presence of Lewy bodies in the substantia nigra for PD patients, which is another pathological hallmark of idiopathic PD [18]. Lewy bodies are inclusions of aggregates of abnormally folded protein identified as alpha-synuclein within the cell body, and a mutant form of alpha-synuclein can cause familial PD [19] [20]. However, studies have argued that while non-motor symptoms may be associated with Lewy bodies, patients may experience motor symptoms without the presence of Lewy bodies [21]. Neuroinflammation, an inflammatory response mediated in the brain by astrocytes and microglia, is another pathological PD feature [22] [23].

In 2003, the staging system of PD pathology was proposed by Braak et al. [24] who argued that the progression of PD occurs in six stages. In stages 1 and 2, the peripheral nervous system is affected, and an onset of premotor symptoms is seen in this early stage. In stage 3, along with Lewy body pathology, neuronal loss in substantia nigra pars compacta occurs, leading to the onset of motor symptoms. Regions such as locus coeruleus and the amygdala are affected, followed by the temporal limbic cortex in stage 4. Finally, during stages 5 and 6, the neocortex, prefrontal cortex, and other primary motor and sensory areas get affected [17]. Severe gait impairments and cognitive impairments may present during this later stage. However, the staging system has been a topic of debate as some studies have shown that a proportion of brains affected by PD does not precisely correlate with the Braak staging system [15]. It could be that PD is a very diverse disease in that no two patients experience the disorder the same way.

1.2.4 Models of Basal Ganglia Function in Parkinson's Disease

For a significant part of the 20th century, BG was regarded as the dark basement of the human brain, as very little was known about BG despite its crucial role in motor and cognitive domains [25]. However, recent studies have shed light on the anatomy and functions of BG (one of the largest subcortical structures in the deep forebrain) [26]. The components of BG include striatum (caudate nucleus (CN), putamen (Put)), globus pallidus internal (GPi), globus pallidus external (GPe), subthalamic nucleus (STN), substantia nigra pars reticulata (SNr) and substantia nigra pars compacta (SNc) [27] [28]. Primarily, two neurotransmitters (gamma-aminobutyric acid (GABA) and glutamate) are used to communicate between the structures of BG [29]. Dopamine is a critical neuromodulator of striatal activity, and appropriate functioning of BG requires dopamine to be released by SNc to the input nuclei [27].

While multiple models were proposed to explain the BG circuits, the classical model captures much of the intrinsic connectivity of BG [30]. In the classical model, the BG regulates motor behavior through two pathways: a direct pathway that facilitates movements and an indirect pathway that inhibits movements. Recent evidence also indicates a hyperdirect pathway that can transmit information much more quickly than the direct and indirect pathways [31]. Figure 1.1(a) shows the connectivity of basal ganglia-

thalamo-cortical circuits in a healthy state. As shown in Figure 1.1(a), the dopamine receptor exerts a dual effect on striatal neurons, with the excitatory D1 receptor in the direct pathway and the inhibitory D2 receptor in the indirect pathway [32] [33]. The dopamine-D1 receptors in the direct pathway and dopamine-D2 receptors in the indirect pathway modulate the activity of the thalamus and motor cortex. Therefore, any deficiency in dopaminergic neurons could disrupt the pathway and lead to impairments in motor control, learning, and cognition [34].

The core pathology of PD is the death of dopaminergic neurons in SNc, leading to a depletion of dopamine that is required to modulate the direct and indirect pathways. The depletion of dopaminergic neurons leads to increased neuronal activity in GPi/SNr and increased inhibition of the motor cortex leading to Parkinsonian motor features such as bradykinesia, akinesia, and impairments in motor control [33][35]. Figure 1.1(b) shows the connectivity of basal ganglia-thalamo-cortical circuits in PD subjects. While the classical model of BG provides a clear organization of the BG circuitry, the model struggles to explain complex BG functions. Contrary to the classical model, recent studies have postulated that coordinated activation of direct and indirect pathways is necessary for appropriate timing and synchrony of BG circuits [32][36]. Another BG model proposed was the Rate model, which explained the onset of hypokinetic movements and the dyskinesias observed after medication [34] [37]. Considering the multiple motor, sensory and cognitive impairments in PD being linked to a disrupted BG circuit, studies have hypothesized that PD patients might be better off with no input from BG rather than a distorted input from BG due to abnormal signaling patterns [33].

Medications such as Levodopa or dopamine agonists have been used to restore dopamine levels in BG and thereby restoring normal functionalities of BG. However, growing studies have suggested that these medications can produce an oscillation between deficient and excessively high dopaminergic activity. This erratic oscillation could force an already abnormal and disrupted BG circuit to an even more stressful situation whereby they need to adapt to highly varying levels of dopamine [33]. As such, the dopaminergic medication has been found to negatively affect sensory and cognitive functions. It is evident from the multitude of clinical and experimental studies that BG circuitry is far more

interconnected, and its functions are far more complex and extensive. More work is needed to understand the exact functionalities of BG and to identify the altered physiology of BG due to disorders.

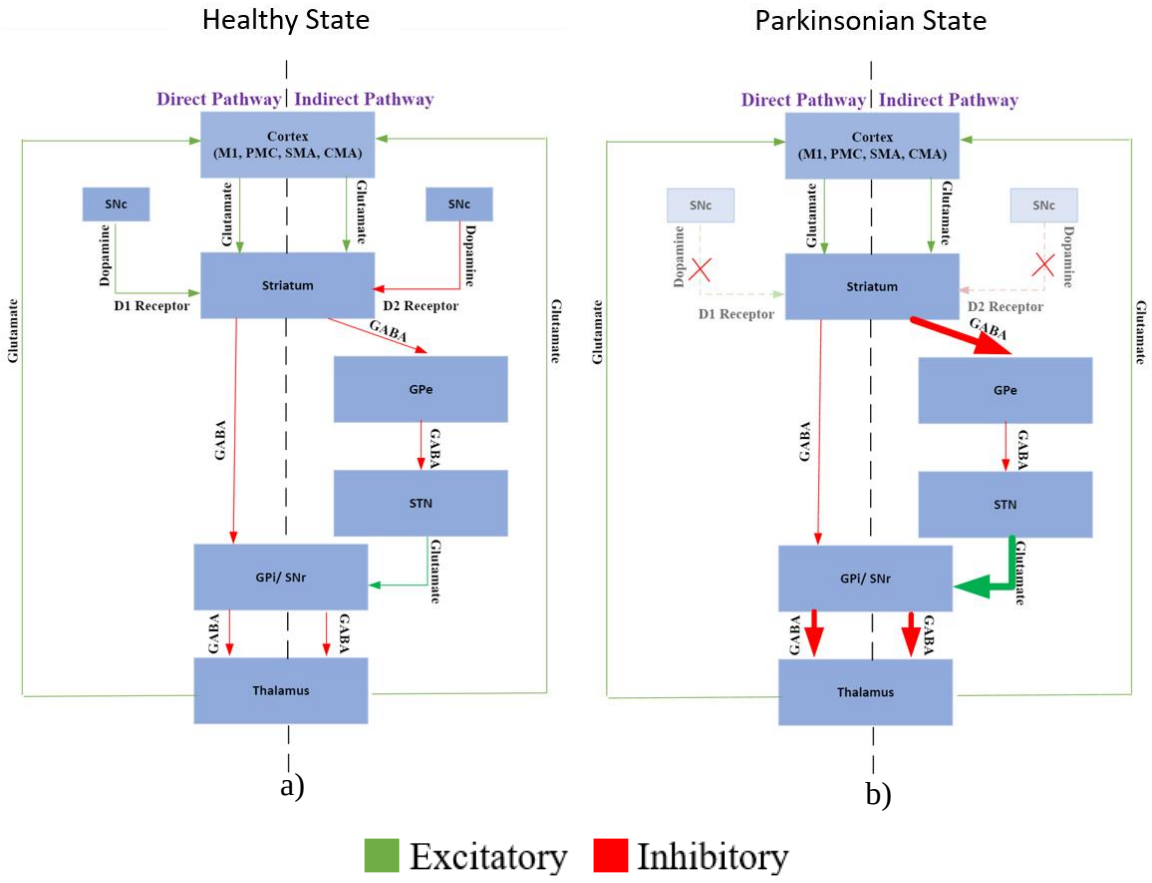


Figure 1.1: BG circuitry in healthy and PD states

Note: The change in thickness of the arrows in the Parkinsonian state represents the increase or decrease in the firing rate of specific connections. Figure 1.1) a) represents the functionality of BG in healthy states, and Figure 1.1) b) represents the functionality of BG in Parkinsonian states. In the Parkinsonian state, the loss of SNc dopamine causes hypoactivity of the direct pathway and hyperactivity of the indirect pathway, leading to excessive GPi output and over inhibition of the thalamus and cortex, thereby suppressing the movement. M1 - primary motor cortex; PMC - pre-motor cortex; SMA, supplementary motor area; CMA - cingulate motor area.

1.3 Symptoms of Parkinson's Disease

Traditionally, PD has been recognized as a disease that primarily affects motor performance, as only the cardinal motor symptoms were associated with PD when it was first described in 1817. However, in the past 10-20 years, PD has been recognized to

present a broad spectrum of non-motor symptoms, including but not limited to cognitive and sensory impairments. Motor and non-motor symptoms become progressively worse as the disease advances, and the rate of progression varies extensively between patients [3]. These symptoms are assessed through various clinical scales such as Unified Parkinson's Disease Rating Scale (UPDRS) and Montreal Cognitive Assessment scale (MoCA), each assessing a specific sub-group of symptoms in PD [38] [39] [40][41]. Recently, with the emergence of biosensors and robotic technologies, numerous objective assessments have also been researched [40][41]. However, not many of these objective assessment tools have been used in clinical practice as of now.

1.3.1 Motor Symptoms

PD is primarily a movement disorder, and thus it is clinically manifested by a triad of motor symptoms caused by dopamine depletion in BG. Cardinal features of this disorder include primary motor symptoms such as rest tremor, bradykinesia, akinesia, rigidity, postural and gait impairments, and also secondary symptoms such as impairment in speech [42], handwriting, saccadic eye movements, hand movements, and precision grip [43]. Since PD is a heterogeneous disease, the symptoms vary extensively from one patient to another. Based on the motor symptoms, PD patients are divided into two major sub-types: akinetic rigid and tremor dominant [44] [45]. Performing complex motor actions requires optimal functioning of elemental processes such as action selection, movement modulation, movement planning, sequencing, coordination, and execution. Furthermore, appropriate sensing of the environment also dramatically influences motor performance. Since motor performance heavily relies on proper functioning and integration of numerous elemental processes, one hypothesis is that motor deficits in PD [43] might arise from abnormalities in the elemental sensory and cognitive processes. However, more work is needed to understand the abnormalities in sensory or cognitive functions and their relation to motor deficits.

1.3.2 Non-Motor Symptoms

Contrary to James Parkinson's description of 'the senses and intellect being uninjured' [46], PD does present a broad spectrum of non-motor symptoms that are found to precede

the onset of motor symptoms. These findings have evolved our understanding of PD from a paradigmatic movement disorder to a more multi-systemic disorder that affects several brain regions, including those that are not directly involved in motor control and only present non-motor symptoms, which are critical determinants of health-related quality of life [47].

1.3.2.1 Cognitive Impairments

Cognitive impairments are a common non-motor symptom presented by PD; an average of 30% of PD patients experience some form of cognitive impairment, which could then progress to dementia in about 80% of the patients [48]. Recent studies have suggested that the cognitive deficit in PD typically affects a plethora of domains, such as executive functions, attention, memory, visuospatial skills, processing speed, and language [49][50].

Visuospatial deficits in PD are considered one of the most common cognitive impairments, as studies have indicated that anywhere between 78% to 93% of PD patients suffer from visuospatial deficits [51][52] [53][54]. It has been reported that visuospatial dysfunctions could adversely affect various paradigms, such as pattern recognition, spatial analysis, constructional ability, forward planning, set-shifting, solving problems, and mental flexibility, leading to a deterioration of motor performance [55] [56]. Another central cognitive domain that is affected due to PD is the frontal-executive function resulting from the close anatomical association of cortico-striatal circuitry with the prefrontal cortex. This deficit in executive function is usually presented at a much earlier stage of PD and can be detected even in newly diagnosed patients [57][58] [59]. The frontal-executive function includes cognitive processes needed to adapt to a new challenging environmental situation by processing relevant information and generating and learning new mental concepts [56]. A few other vital cognitive functions that might be affected due to this deficit are decision-making, planning, and multitasking. Studies [60] have shown that PD patients lack the ability to self-generate a plan and organize a task, a vital function needed to perform a goal-directed task-specific motor movement. A few other studies have also suggested a relationship between executive dysfunction and motor deficits that it might lead to at a later stage [61]. Executive dysfunction was also an important factor in impairments of motor features such as gait and postural stability [57].

Thus, cognitive dysfunction, specifically poorer executive function, is related to worsening motor processes resulting in several motor deficits. However, the full extent of deficits in executive functions, their contributing factors, and their relation to motor deficits are yet to be fully understood. Similar to the slowing of motor movements (bradykinesia), cognitive slowing (bradyphrenia) is also experienced in patients with PD [62] [63]. It has also been found that when the speed of the mental operation task increased, thereby demanding faster cognitive processing and increasing the cognitive load, the cognitive slowing also worsened significantly compared to healthy controls. Therefore, this deficit in processing speed may be due to the inability of PD patients to handle excessive cognitive load resulting in slowing down the cognitive processes. Adams et al. [64] have also indicated that increased cognitive load could adversely affect intelligibility in activities such as speech and even postural stability [65]. More work is needed to understand the relationship between cognitive slowing and the cognitive load associated with a task.

1.3.2.2 Sensory Impairments

In recent times, a growing body of literature has demonstrated that PD may present an array of perceptual deficits in a large proportion of patients at any time during the disease and can be present even before the diagnosis. Common sensory abnormalities include pain, reduced sense of smell, touch, and deficits affecting the perception of other modalities such as proprioception, vision, haptics, and auditory. James Parkinson wrote that the sensation of pain could be the first sign of the impairments [66]. As such, pain is a universal symptom experienced by more than 40% of PD patients [67].

Another prevalent sensory impairment in PD is olfactory dysfunction which is considered an early pre-clinical sign of PD as the dysfunction typically presents 4 to 8 years before diagnosis [68] [69] [70]. Recent evidence suggests that olfactory dysfunction may be a direct consequence of abnormalities associated with the central nervous system [71], as perceptual deficits associated with other modalities have also been reported. Studies also indicate an impairment in taste appreciation among PD patients [72]. Another PD-related sensory deficit was reported in proprioception, i.e., the ability to sense self-movement, joint position, and muscle force. As proprioception plays a vital role in performing various motor movements, a deficit in proprioception could gravely compromise multiple motor tasks,

including goal-directed voluntary movements [73] [74], reflex action, and maintaining postural stability. It has also been suggested that impaired proprioception may lead to increased dependence on visual guidance when performing voluntary movements [75].

A few visual deficits include impairment in visual acuity, color discrimination, contrast sensitivity, and pupil reactivity [76]. PD patients also suffer from an inability to discriminate between irrelevant and relevant visual information, which could explain the phenomenon of freezing of gait in crowded surroundings [77]. PD patients also encounter deficits in object perception, motion perception, and interpreting facial expressions [78][79]. Other oculomotor dysfunctions involve abnormalities in eye movements [80], reduced blink frequency causing dry eyes, and abnormal saccadic and smooth pursuit eye movements [76]. Further, delayed initiation and slowness in eye movements have been reported in PD patients as ocular bradykinesia, which correlates with the bradykinesia experienced in hand movements [81]. The visual perception of displacement and time has also been found to be abnormal in recent studies [82][83][84]. Finally, visual hallucinations commonly associated with high mortality rates have also been reported in 74% of PD patients after 20 years of disease [85]. With dopamine being an important neurotransmitter in the retina, reduced dopamine concentration in the retina is speculated to be a factor in these visual deficits [86] [87][88]. However, optimal visual perception requires the proper functioning of highly interconnected brain regions that extend beyond the functions of the retina. An impairment in central processing or higher-order neural regions is also speculated to play a much bigger role in sensory deficits, including impaired visual perception [81] [89]. This hypothesis has been gaining a lot of attention in recent years as deficits associated with other modalities have been reported indicating a more centralized impairment affecting the perception and interpretation of multiple sensory modalities.

A decline in haptic sensitivity is observed in PD patients as the haptic threshold to detect object curvatures have been elevated when actively or passively exploring the workspace [90]. Haptic perception relies on integrating proprioceptive, tactile, and pressure cues in conjunction with the output from the internal model, which is predicted sensory feedback derived from the efferent motor commands [91] [92]. Therefore, studying the haptic sensitivity and acuity in PD is vital as it would also shed light on how mechanisms

of sensory integration may be affected in PD and its contribution to the sensory and motor deficits experienced by PD patients. Existing evidence also points to several dysfunctions in the auditory system. Dysfunctions in hearing are often hypothesized to be due to impaired neural processing of auditory stimuli [93] and may also arise from impaired integration of multi-modal sensory inputs, which affects the perception of auditory information [94]. Managing sensory impairments in PD is particularly complex as the deficits can arise at any level starting from an impaired peripheral sensory organ to an impairment in sensory pathways that transmits the received sensory information to the brain or the impaired neural regions that process and integrates sensory information to ensure accurate interpretation of the world around us. It is, therefore, necessary to determine the basis for the sensory deficit so that the treatment can be targeted specifically to tackle the impairment that leads to the deficit. With studies hypothesizing that an abnormality in the sensory integration process may be responsible for deficits in perception, it may be beneficial to explore impairments in multi-sensory integration and how they lead to perceptual deficits.

1.3.2.3 Other Non-Motor Impairments

Very few non-motor symptoms that relate to the work described in this thesis have been discussed here. However, several non-motor symptoms are presented during PD, severely affecting the quality of life in about 50% to 60 % of PD patients [95]. In recent times, it has been understood that non-motor symptoms present a greater impact on health-related quality of life than motor symptoms. Certain symptoms, including hallucinations, could be a strong predictor of nursing home placements [96]. Figure 1.2 indicates the predominant non-motor symptoms in PD.

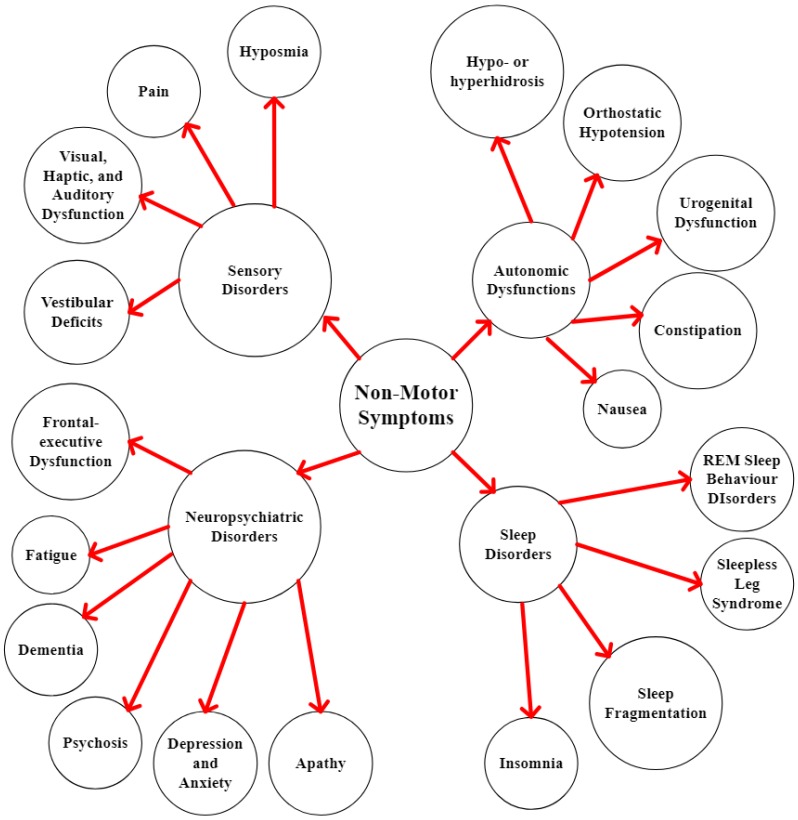


Figure 1.2: Non-motor symptoms in PD

1.4 Treatments for Parkinson's Disease

With the number of people diagnosed with PD expected to double in the next decade, managing PD remains a challenging and complicated task for the global healthcare system. Several treatment options are available to manage the motor and non-motor symptoms experienced by PD patients. A major limitation of the current treatment approach is that due to the diverse nature of the disease, a treatment that may improve one patient's condition may have no effect or even worsen the quality of life in another patient, necessitating a patient-specific approach.

1.4.1 Pharmacological Treatments

Several pharmacological approaches have been available to provide symptomatic relief for the motor symptoms experienced by PD patients. However, they provide little to no benefit

in non-motor symptoms, and more work is needed to understand the effects of these medications on non-motor symptoms.

Dopaminergic medications are the mainstay of the current PD treatment to restore dopamine levels within the depleted dorsal striatum. Developed in the 1960s, levodopa is one of the most common dopaminergic medications prescribed by clinicians and is considered the most successful medication in mitigating the motor symptoms of PD [97] [98] [99]. Although effective in managing motor symptoms, levodopa presents side effects such as dyskinesias, on-off motor fluctuations, nausea, hallucinations, and sleep disturbances, which severely affect the patient's quality of life [100]. Another therapeutic option often introduced as an initial treatment for PD is the dopamine agonists that came on the market in 1978 [98] [101]. Although levodopa is much better at controlling motor symptoms, dopamine agonists are usually considered an initial treatment in patients younger than 60 to avoid the adverse effects of levodopa. While dopamine agonists can reduce the risk factor of dyskinesia, they also include side effects such as compulsive and impulsive behavioral problems, nausea, vomiting, insomnia, constipation, and fainting [98]. Other PD medications, such as monoamine oxidase B (MAO-B) and Catechol-methyl transferase (COMT), work by inhibiting enzymes responsible for the breakdown of dopamine. Out of all the medications, levodopa is considered the gold standard for the treatment of PD despite its side effects. However, recently, there has been a lot of interest in understanding the effect of dopaminergic medications such as levodopa on sensory and cognitive functions.

Medications seem to have a paradoxical effect on sensory abnormalities, such as olfactory dysfunction, which was uninfluenced by the anti-Parkinsonian medication. Dopamine agonists and levodopa are also reported to have acute depressant effects on proprioception [102]. The adverse effects of levodopa, such as visual hallucination, are recognized to worsen with the dose and duration of the levodopa treatment. Dopaminergic medication has had a mixed effect on cognitive deficits, with certain impairments worsening and others improving or unaltered. Studies have indicated an adverse effect of dopaminergic medication on reversal learning, reward processing, and error correction, which can negatively affect motor performance. Results from a few other studies have also

correlated with this finding; dopaminergic medication was found to have decreased cognitive learning, worsened bradyphrenia, and induced attentional instability [103] [104] [105]. Studies exploring detrimental effects of medication on cognition suggest that the impact of medication varies from patient to patient, depending on the affected brain regions [104] [105]. This points to the need for a more patient-specific assessment tool to determine the impairment and the right course of action specific to that patient. A dopamine overdose hypothesis [57] was also put forth to explain these mixed results, which indicated that the effect of medication depends on the affected brain region and stage of illness in PD. According to the dopamine overdose hypothesis, the medication increases dopamine across all regions. While the medication increases the pathologically low dopamine levels in the putamen and dorsal striatum, it overstimulates the ventral striatum, which is not severely dopamine depleted, thereby impairing the functioning of the ventral striatum, leading to several cognitive deficits. This hypothesis explains the differential effect of medication between the motor, sensory and cognitive symptoms and the change in the effect of medication based on the stage of illness.

Therefore, the paradoxical effect of dopaminergic medication on cognitive domains such as executive functions and how it affects motor performance is yet to be understood clearly. This will help in understanding if prescribing dopaminergic medicines at a very early stage of PD to alleviate the motor symptoms could, in turn, increase the rate at which the cognitive deficits worsen in PD, thereby increasing the risk factor of more severe cognitive dysfunctions.

1.4.2 Surgical Treatments

Surgical treatments for PD have been studied since the 1930s and are usually considered for patients in the advanced stages of PD for whom the dopaminergic medication may not be effective in managing motor symptoms. Primary categories in surgical interventions for PD are (1) ablative surgeries and (2) Deep Brain Stimulation (DBS). Based on the lesioned brain regions, ablative techniques can be further sub-categorized into pallidotomy, thalamotomy, and subthalamotomy.

Thalamotomy involves lesioning a part of the thalamus. Hassler et al. [106] were among the first to choose the ventral nucleus of the thalamus as the target region for relief from tremors [107] [108]. Despite the benefits of thalamotomy, it is not recommended due to its detrimental effects, such as increasing the rate of cognitive decline in PD patients [109]. The procedure involving lesioning of globus pallidus or pallidotomy is another surgical technique used to mitigate cardinal motor symptoms in PD [110]. Pallidotomy has been found to mitigate levodopa-induced dyskinesia by about 82% [111] [110]. The final category in the ablative procedure is the subthalamotomy which includes subthalamic lesions. This procedure has emerged only recently, and limited research shows that subthalamotomy has more benefits than many other surgical procedures [109]. In conclusion, ablative surgeries are usually not recommended due to their irreversible nature and high incidence of side effects [112]. In recent times, DBS has replaced ablative surgeries and is a widely used surgical procedure due to its reversibility and adaptability. In 1987, it was discovered that high-frequency stimulation of the thalamus mimics the effects of lesioning done in ablative procedures and suppresses tremors. [113][110]. Several subcortical nuclei, including the ventral intermediate nucleus of the thalamus, GPi, and STN, are targeted for stimulation depending on the desired effects [114][115][107]. The ideal brain target for stimulation is still debated.

While surgical procedures such as DBS effectively control motor symptoms, significant risks such as intracranial or intracerebral hemorrhage, ischemic stroke, and implantation site infection must be considered [116][115][117][118]. Additionally, several domains of cognition were also found to be adversely affected after DBS [119], and its effect on sensory perception is still a topic of debate. Finally, DBS surgery is also highly invasive, which could lead to several other intraoperative and postoperative complications [120]. While non-invasive stimulation techniques [121] have emerged as promising adjunct treatments for PD, more work is needed to understand their efficacy in managing motor and non-motor symptoms and any associated side effects.

1.4.3 Non-Pharmacological Treatments

Non-pharmacological interventions include physical therapies, cognitive rehabilitation programs, video-assisted swallowing therapy, and speech therapies. Rehabilitation

programs can be considered to manage a broad spectrum of symptoms spanning across motor, sensory and cognitive domains. Several symptoms that remain unimproved by medication and surgical treatment may improve with rehabilitation therapies. Furthermore, unlike medication or surgical treatment, these therapies do not pose any risks or side effects that may adversely affect the patient's quality of life.

Rehabilitative therapies have improved motor symptoms such as postural instability, difficulties in upper-limb movement, balance disturbance, and gait. Statistically significant improvements in mobility, such as walking, standing from sitting, and sitting from lying, were observed in patients doing physiotherapeutic exercises. This improvement was seen irrespective of the duration of the disease [122][123][124][125]. Recent innovations in robotics, virtual reality (VR), and wearable technologies have paved the way for an efficient, individualized, and task-specific rehabilitation program that can potentially add more value than traditional approaches [126] [127]. Studies comparing traditional and advanced rehabilitation techniques using VR found that VR rehabilitation has been more effective in improving gait, upper-limb function, and overall quality of life than traditional approaches [128]. In addition to the increased efficacy of the advanced rehabilitation techniques, they require the participants to use visuospatial functions, motor sequencing, higher-order motor control, and other cognitive functions to complete the objectives. Numerous therapies aimed at improving cognitive abilities have been shown to be quite useful in enhancing motor performance in PD patients, as cognitive domains such as executive functions, visuospatial skills, logic memory, and motor learning play a vital role in any task-specific motor action [129] [130]. Reviewing the outcomes of several rehabilitation strategies show that while dopaminergic medication can only briefly improve specific aspects of cognitive functions, non-pharmacological interventions are more effective in improving cognitive abilities (executive functions, movement planning, error correction) that are vulnerable to PD and yet very critical to performing any day-to-day activity without the triad of side effects presented by dopaminergic medications [131][132][133]. The limitation of non-pharmacological intervention stems from an inadequate understanding of the cognitive impairments resulting in an inability to target specific cognitive domains that may be impaired and the lack of patient-specific therapies. Quantification of the cognitive impairments is necessary to address the broad spectrum of

deficits presented by PD. Finally, a patient-specific analysis would help structure the rehabilitation program specific to each patient [134].

Another important aspect that needs to be discussed is sensory cueing, as motor performance improves substantially in rehabilitation programs when provided with multi-modal sensory cueing [135][136], i.e., providing external temporal or spatial stimuli to compensate for the defective generation of internal signals in PD. External sensory cueing was found to reduce gait variability and improve the timing and coordination of upper-limb movements in patients with freezing of gait, suggesting that internal motor control may benefit from the sensory cueing [137] [138] [139]. These findings suggest that cues can be used as an efficient tool for motor learning in PD patients [140]. However, with PD also presenting deficits in the sensory domain, it is vital to quantify the sensory deficits and determine their contributing factors to understand the type and nature of sensory cues that could be most effective. Therefore, a patient-specific approach taking into account their individualized sensory deficits might be necessary to determine the optimal sensory environment for rehabilitation programs.

Rehabilitation therapies have been a promising alternative or adjunct treatment for PD, as advanced rehabilitation techniques present numerous benefits with little to no side effects. The next step should be to provide a more patient-specific rehabilitation program [134] combined with adaptive multi-modal sensory cueing to increase the efficacy of the therapies. To this end, there is a need to quantify and understand the mechanism that contributes to the deficits in sensory and cognitive domains in PD patients. Any deficit related to the motor or cognitive learning should also be explored, as the efficacy of the rehabilitation therapies hinges on the patient's ability to learn, retain and transfer the performance improvements to day-to-day motor or cognitive activities [141][140] [142].

1.4.4 Current Pitfalls and Strategies for Future Treatment

While there is currently no permanent cure for PD, multiple treatments are available to manage the symptoms of PD and slow down the progression of the disease. Dopaminergic medications are very effective in mitigating cardinal motor symptoms; however, recent evidence [143][103] suggests that the effect of medication on sensory or cognitive deficits

is paradoxical. Few studies have reported adverse effects of medication on proprioception [102] and have also shown worsening of cognitive deficits [103] [143]. Therefore, the effect of dopaminergic medication on sensory and cognitive deficits is not fully understood. There is a need to better understand the impact of medication on these deficits, as these multi-modal effects of medication need to be taken into account during treatment optimization. Discussing the need to better optimize the treatments, there is a growing number of studies [144][145][146] that indicate the necessity for a patient-specific approach in analyzing and treating the patient's condition. This need for a patient-specific and targeted treatment applies not only to dopaminergic medication but also to other treatments, such as botulinum toxin or lidocaine, used to treat PD symptoms.

Another promising field of treatment for PD is rehabilitation therapies, which fall under the category of non-pharmacological treatment. As discussed earlier, rehabilitation therapies have been very effective in improving both motor and cognitive abilities with no substantial side effects. However, many unanswered questions must be explored to efficiently employ or optimize these therapies. Therapies targeted to mitigate specific deficits may be more effective than a generic physical therapy. Understanding and characterizing the impairments caused due to PD and the factors contributing to these deficits is essential to better target the deficits through therapies. This is specifically critical in therapies aimed at improving cognitive abilities, as any deficits affecting cognitive function will invariably impair motor functions. With no standard metrics to evaluate cognitive abilities such as executive functions and no in-depth understanding of the sensory and cognitive impairments in PD, any treatment aimed at improving motor function may not be effective. Additionally, there may also be potential benefits to the patients in tailoring a patient-specific rehabilitation system based on an individualized analysis. Another aspect that needs to be considered is that the efficacy of rehabilitation therapies heavily depends on how effectively patients can use the tools provided during the therapies. Numerous studies [135] have emphasized the role of sensory cues in effectively mitigating the symptoms through therapies. Therefore, the type of sensory cues that may be optimal for the therapy and whether the PD patients can use the multi-modal sensory cues needs to be explored to determine the optimal rehabilitation environment that might yield the best

results. Characterizing the deficits in perception, executive functions, and their contributing factors may be essential to structuring and designing rehabilitation systems.

This section discussed the limitations of the current treatment and the strategies that might help improve the efficacy of the existing treatment protocols. The existing treatment protocols, such as dopaminergic medications, have been proven to be very effective in managing motor symptoms. However, the high prevalence of non-motor symptoms [147], such as cognitive or perceptual impairments, has changed how we conceptualize PD. While there have been substantial advances in treating the motor symptoms of PD, current treatment options for perceptual or cognitive impairments are limited. It is necessary to first understand these deficits and the contributing factors before structuring a treatment plan to mitigate the perceptual or cognitive impairments. Recent studies report that non-motor symptoms predate motor symptoms, which makes it vital to understand these deficits and to better manage them [147]. Expanding our knowledge about the sensory and cognitive impairments in PD may assist in determining an efficient and targeted treatment approach.

1.5 Sensorimotor Integration (SMI) and Sensorimotor Control (SMC)

The primary focus of the thesis is to investigate the deficits in Sensorimotor Integration (SMI) and Sensorimotor Control (SMC) in PD patients. This section discusses the neural and mathematical bases associated with the functioning of SMI and SMC in healthy subjects and the current knowledge about the effect of PD on SMI and SMC.

The motor system, which is responsible for driving any voluntary movements, requires information about the environment to appropriately plan and execute the movements. The sensory system collects information about oneself and the world around us through multiple sensory organs and organizes the gathered information. The motor system uses this sensory information to modulate the motor commands based on the demands of the environment. Therefore, the two systems must work together to process and use the sensory information to complete a desired motion. This interaction between the sensory and motor system is called SMI [148][149]. Multi-sensory integration, one of the

components of SMI, is the ability to integrate inputs from multiple modalities to obtain an unambiguous interpretation of the world [150][151]. The perceptual estimate formed through multi-sensory integration aids us in understanding the state of oneself and the environment, which is used to modulate or generate the motor commands to achieve the desired outcome [152][153]. Therefore, the SMI has two distinct facets: (i) multi-sensory integration and (ii) the ability to use the perceptual estimates to appropriately modulate the motor output.

While integrating the multi-modal inputs and using them to modulate motor output is important, how the humans interpret the perceptual estimate and accordingly plan, update, and generate motor commands is also vital to the success of a task-specific voluntary movement. It is this ability to interpret the acquired multi-modal inputs and appropriately plan or correct a planned strategy and execute the planned movement to achieve the outcome(s), which is called the SMC [154]. Apart from the motor and sensory systems, the SMC has an additional contributor, which is the cognitive system that has a role to play in the interpretation of perceptual estimates and aids in a series of decision-making processes to plan and correct motor control strategies [134][155]. While the execution of voluntary movements may require other elemental processes than just movement planning (ability to plan a movement) and online error correction (ability to correct a planned strategy), the thesis focuses primarily on these two aspects when investigating the SMC. Characterizing the deficits related to these aspects of SMC might help us understand the difference in vital SMC functionalities between PD patients and healthy subjects, which may enable us to target these deficits during rehabilitation therapies.

Owing to the high interconnectivity of the brain, it must be noted that the functionalities of SMI and SMC are heavily intertwined and dependent on each other. In other words, SMI and SMC put together are cyclical processes, with one process representing the multi-sensory integration and sensory-motor coupling (integration of sensory and motor system) and the other process focusing on how the multi-modal inputs are being used to plan, update, and execute movements to suit the demands of the environment. Therefore, these two processes need to be studied together as both processes

are interconnected. The exact functioning of SMI and SMC are largely unknown. However, researchers have expended considerable effort in recent years to understand the neural regions involved in the process (Neural Bases) and the mathematic criterion used by the CNS (Computational Models). The thesis does not discuss all the proposed neural and computational hypotheses but focuses on a few that relate to this study or have been used in this study during analysis.

1.5.1 Neural Bases for Sensorimotor Integration

The human brain, with its high interconnectivity, is a very complex network; therefore, the exact regions and their involvement in SMI are still a topic of debate. However, several anatomical models have been hypothesized to explain the brain regions involved in the process of SMI. Riemann et al. [156] have discussed that multi-sensory integration may be initiated in the spinal cord, where the multi-modal sensory inputs from the periphery are filtered before sending them to higher brain regions.

Another school of thought was a hierarchical approach hypothesized by Machado et al. [157] that includes three levels of SMI processing (medullary, subcortical, and cortical level). Other brain regions, such as the bilateral insula and vestibulo-cerebellum [158] [159], were also hypothesized to participate in the SMI functions. In contrast to the hierarchical model proposed by Machado et al. [157], another hypothesis by Monfils et al. [160] proposed a more parallel approach where SMI is carried out in multiple regions of the brain. Aligning with the approach of Monfils et al. [160], another experimental study by Sakai et al. [161] proposed a parallel and concurrent architecture for the sensorimotor processing involved in motor control. Recent evidence also suggests a significant role for BG in SMI. Almeida et al. [162] discussed that the functions of the BG involve the integration of visual and proprioceptive sensory inputs. Another study by Nagy et al. [163] indicated that the caudate nucleus and substantia nigra may play a role in multisensory integration and complex sensory processing functionalities. Jabri et al. [164] have also proposed the BG model to explain its role in sensorimotor integration and processing. These newer studies have indicated a larger role for BG in SMI. However, more work is needed to fully understand BG’s contribution to sensory processing and integration.

Although previous studies have attributed certain functionalities to various brain regions, due to the high interconnectivity, it is challenging to determine the functional contributions of each brain region. This section shows that the SMI may not be a centralized process involving few brain regions but a highly distributed procedure that includes multiple neural regions. Therefore, a neural disorder that affects a specific brain region could potentially disrupt this highly interconnected and distributed process. Specifically, understanding the role of BG in SMI may assist in predicting the deficits that may be presented by disorders such as PD affecting this neural region.

1.5.2 Computational Models for Sensorimotor Integration

It has long been debated that CNS integrates inputs from multiple modalities based on some rationale criterion. Numerous mathematical models have been proposed to explain the criterion used in multi-sensory integration. Ernst et al. [165][166] proposed a Maximum Likelihood Estimator (MLE) model as a criterion for multi-sensory integration. The MLE model assigns a weight to each modality depending on the noise associated with that modality to minimize its effect on the integrated sensory estimate (perceptual estimate). Equation (1.01) shows the mathematical model proposed in MLE.

$$\hat{S} = \sum_{i} W_i S_i \tag{1.01}$$

where W_i is the weight assigned for the modality S_i. The weight for each modality would be determined based on its variance, which is considered a representation of the noise in the sensory signal. Therefore, equation (1.02) was used to determine the weight of each modality to obtain a Minimum Variance Estimate (MVE), i.e., an integrated sensory estimate with lesser variance than the variance present in individual modalities.

$$W_i = \frac{\frac{1}{\sigma_i^2}}{\sum_i \frac{1}{\sigma_j^2}} \tag{1.02}$$

$$\widehat{\sigma^2} = \frac{1}{\sum_{i=1}^{n} \frac{1}{\sigma_i^2}} \tag{1.03}$$

where σ_i is the variance associated to the i^{th} modality. Equation (1.03) shows the variance of the integrated sensory estimate. Biologically, the variance of sensory stimuli may be determined through experience or in real-time using perceptual judgments [150]. Apart from the MLE model, another criterion proposed to explain multi-sensory integration was the competitive integration model [167], which theorizes that the modality with the least variance would be used to drive motor actions, and the remaining modalities would be discarded. Equation (1.04) shows the competitive integration model.

$$\hat{S} = S_i \text{ if } \sigma_i^2 \leq \sigma_j^2 \tag{1.04}$$

A stochastic integration model was also proposed, which is an extension of the earlier model. Equation (1.05) shows the stochastic integration model.

$$\hat{S} = \max P(S|S_v\ S_h\ S_a \ldots) \tag{1.05}$$

where S_v, S_h, S_a represents the visual, haptic, and auditory estimates, respectively. Deneve et al. [167] have discussed a context-dependent Bayesian model for SMI. Another criterion [168][169] proposed for SMI was a causal inference, in which the sensory modalities are combined depending on each modality's causality. For instance, if the stimuli gathered by modalities have a common cause, they are integrated to improve their resulting overall estimate. The Bayes rule mentioned in equation (1.06) was proposed to determine the cause of the sensory stimuli.

$$P(C|S_v, S_h, S_{a,..}) = \frac{P(S_v, S_h, S_{a,..}|C)\ P(C)}{P(S_v, S_h, S_{a,..})} \tag{1.06}$$

where C is the causal structure for the sensory stimuli. An extension of this criterion was the hypothesis [170] [171] that the multi-sensory integration might depend on the spatial and temporal factors of the stimuli in the environment. The modality appropriateness hypothesis proposed by Welch et al. [172][173] discusses that the modality appropriate for a given task at hand is given higher importance and will dominate other modalities. Depending on these hypotheses, the sensory stimuli could undergo various processing, such as complete integration, partial integration, or segregation of the stimuli.

To summarize, there are currently several schools of thought about how SMI may occur in humans, although none of the above-mentioned criteria has been clinically verified or accepted. It is highly challenging to determine the exact SMI criteria as it is currently

not possible to measure the perceptual estimates for a given event from a subject. However, understanding the SMI criteria may be useful in determining how SMI occurs in healthy subjects, which can help explore how it may be affected in PD patients.

1.5.3 Sensorimotor Integration and Parkinson's Disease

The traditional view was that BG dysfunction in PD may disrupt the direct and indirect pathways, thereby affecting the motor ability in the patients. However, several studies that examine the sensory perception and the involvement of BG in sensory processing, integration, and SMI have challenged this traditional view.

Multiple studies have reported perceptual abnormalities in PD patients and how they may affect their quality of life. Maschke et al. [174] reported impairments in kinesthesia among PD patients due to dysfunction in BG. Proprioceptive deficits in PD patients have also been discussed in other literature [175][176][73][75][177][178]. Patients diagnosed with PD exhibit visual dysfunctions, such as impairments in visuospatial construction, depth perception [179], motion, object perception [180][89], and contrast sensitivity [181]. Adams et al. [182][94] reported impairments in loudness perception and speech intensity among PD patients and how intelligibility in speech may vary under dynamic conditions [64]. Findings by Bernardinis et al. [83][84] also point to deficits in visual displacement and temporal perception in PD patients. Deficits in other modalities, such as haptic [90][91] [178] and auditory perception [93] have also been reported among PD patients in multiple studies.

Therefore, there is an extensive number of studies that explored various aspects of sensory deficits in PD, although the factor that contributes to these deficits are still unclear. Certain studies [86] [87][88] have indicated the peripheral sensor organ in PD patients may be impaired. However, the deficits spanning multiple modalities that consequently affect motor movements cannot be explained as a consequence of just the peripheral impairment without considering a central deficit in SMI [94]. Other studies [184][81] have also indicated that the sensory and motor abnormalities in PD may not be due to peripheral impairment but may be related to an abnormality in the central processing of sensory inputs. The involvement of BG in SMI has also been discussed in the earlier section, which

further indicates that the BG dysfunction caused due to PD may lead to an impairment in SMI. It is yet unclear if the sensory and motor deficits observed in PD can be traced back to the abnormal central processing (impaired SMI) resulting from a physiological disturbance in BG function due to PD.

A few studies have explored SMI in PD patients. Dubbioso et al. [185] indicated that a change in the cortical structures where the sensory inputs are integrated might lead to altered SMI. Another study [91] reported an altered SMI in PD patients. However, only haptic perception was evaluated during the study, and multi-modal evaluation was not done to examine the multi-sensory integration. Muller et al. [186] discussed the relationship between cholinergic terminal loss and dopaminergic denervation with postural sensory integration in PD patients. Studies [187][188] have argued that the increased visual dependence observed in PD patients may indicate SMI deficits. The increased visual dependence may imply an inability to organize sensory hierarchy and prioritize sensory information depending on its accuracy and importance to the task at hand. Lewis et al. [189] suggested a defective integrative unit followed by inappropriate motor response may give rise to sensor and motor abnormalities observed in PD patients.

While earlier studies have explored SMI in PD patients, several unanswered questions regarding the functionalities of SMI in PD patients still exist. Experimental studies evaluating SMI only assess the patients on a single modality and do not examine their performance when provided with multi-modal inputs. With multi-sensory integration being one of the vital facets of SMI, evaluating the performance of PD patients when provided with multi-modal inputs is necessary to understand the nature of the SMI impairment. Moreover, considering that humans interact in dynamic environments in their day-to-day life, there is also a need to understand the performance of SMI in dynamic and unpredictable testing conditions. Studies also suggest sensory deficits may be presented earlier than motor impairments and may contribute to motor deficits [190][84][83][191]. Therefore, there is a need to objectively investigate SMI in PD patients and how it relates to sensory and motor abnormalities. Additionally, the effect of medication on SMI is still unknown and needs to be explored. The significance for investigating SMI functionalities in PD patients are several and are as follows:

- Understanding the effect of PD on SMI may inform us more about the disease. It would help understand the factors contributing to the sensory and motor abnormalities, which is necessary to provide a more targeted treatment.
- Studies [135][192][134] have shown that sensory cues may improve the efficacy of rehabilitation therapies if provided appropriately. Characterizing SMI deficits would shed light on the nature of sensory cues that would be beneficial in enhancing the effectiveness of the treatment.
- Evaluating the SMI performance in the OFF and ON states would inform us how medication has altered the SMI, indicating when it is most beneficial for the patients to undergo rehabilitation. Evaluating the effect of the medication is also useful in determining the general treatment plan for the patients.
- While the BG has been linked to SMI functionalities, there is still no clear understanding of the role of BG in SMI. Investigating the SMI performance in a disease such as PD that affects BG may shed some light on the role of BG in SMI.
- Although motor or cognitive evaluations are done as part of clinical practice, the SMI is not evaluated in the patients due to the lack of assessment techniques. An objective tool developed to assess the SMI may be extended to be used in clinics to assess the SMI impairments and provide a more targeted treatment. With studies indicating that non-motor symptoms may present earlier than motor symptoms, it may also be used to diagnose PD early and manage the disease better.

1.5.4 Neural Bases for Sensorimotor Control

Sensorimotor control is a complex process focused on planning and updating a motor plan, requiring the involvement of several brain regions. Although the exact neural bases involved in SMC is still being debated, studies have hypothesized the involvement of specific neural region through clinical and behavioral studies.

Studies [193] have discussed the role of cortical and subcortical regions in optimal decision-making processes as a technique similar to reinforcement learning. Yeom et al. [194] indicated that regions such as the primary motor cortex (M1) and supplementary motor area (SMA) were also active during the movement planning phase. Earlier studies

have shown [195] [196] [197] that SMA may be involved in the planning and preparation of movements, while the pre-SMA shows greater activity during complex and self-initiated movements. Kakei et al. [198] have shown that the neurons in the M1 may be divided to represent either the movement parameters (direction, position, and orientation) or muscle parameters (muscle force and activity). The involvement of M1 in motor unit recruitment and its related strategies has also been studied extensively [199]. Owing to the high interconnectivity between the M1 and BG, which is the affected region in PD, studying the effect of PD on motor unit recruitment may also prove to be useful.

With the effect of PD on SMC being one of the primary foci of this thesis, it may also be beneficial to discuss the role of BG (affected region in PD) in SMC. Numerous studies have indicated that BG's role is vital in movement planning, selection, sequencing, correction, and execution [200] [201] [202]. Calabresi et al. [32] proposed a complex model of the direct/indirect pathways that could account for the concurrent activation of the pathways. This implies that besides movement regulation, BG may also be involved in more complex SMC functionalities. Studies [203][204] have indicated that BG could be involved in memory-guided movements, suggesting that BG may use reinforcement learning to regulate the desired movement. Turner et al. [205] have hypothesized that BG may have a far more vital role in motor learning, modulating the motor outputs, predicting the reward for reinforcement learning, and movement selection or switching [206][207] [208]. Additionally, it has also been inferred that the BG may be responsible for determining the criterion that the CNS had to use in deciding the optimal course of action to complete the desired motion [209]. To add to the mounting evidence of BG's involvement in crucial SMC functionalities, Gurney et al. [210] theorized that the BG has two separate pathways: selection and control pathway. While the selection pathway may be involved in action selection, the control pathway modulates the selection process to accomplish the desired task. Finally, the relationship between the motor unit or muscle recruitment (an important SMC function) with BG has also been discussed [211].

This section discusses the findings from earlier studies pinpointing the neural regions involved in various SMC functions. Based on evidence from earlier literature, it may be understood that BG plays a vital role in movement planning, error correction,

retrieving past experiences to guide the movement process, and determining the SMC criterion. This is on top of its already established role of movement regulation through the direct and indirect pathways. However, more work is needed to fully understand the extent of BG's role in SMC functions.

1.5.5 Computational Models for Sensorimotor Control

Similar to the CNS's criterion for the SMI process, there is numerous evidence that the CNS may also abide by a single or adaptive criterion for action selection, motor learning, movement planning, and online error correction. Although the exact criterion used by CNS is still unknown, researchers have spent considerable time and effort explaining this criterion through computational models. Understanding how the process of SMC may occur in healthy subjects could help pinpoint the deficits in PD patients. Computational models proposed to explain SMC usually tend to contain a cost function that needs to be minimized to obtain the optimal solutions for the SMC problem. Anderson et al. [212] proposed a model that minimizes the metabolic energy spent to perform a motor action. Equation (1.07) shows the cost function for the minimum energy model.

$$C = \frac{\int_0^{t_f} E_{total}^M}{X(t_f) - X(0)}\, dt_f \tag{1.07}$$

where E_{total}^M is total metabolic energy consumed and $X(0)$, $X(t_f)$ represent the position of the center of mass at the initial and final state. Flash et al. [213] and Hogan et al. [214] proposed a minimum jerk model, with the objective of the model being minimizing the jerk in the movement, which would maximize the smoothness of the movement. Equation (1.08) shows the cost function for the minimum jerk model.

$$\mathrm{C} = \frac{1}{2}\int_0^t \left(\left(\frac{d^3x}{dt^3}\right)^2 + \left(\frac{d^3y}{dt^3}\right)^2\right) dt \tag{1.08}$$

where x and y are the coordinates of the fingertip. An extension to the minimum jerk model was the minimum commanded torque model [215], which aims to reduce the torques commanded in the joints. The computational models till now are open-loop optimization models that place minimal emphasis on the importance of sensory feedback in guiding a movement or adapting oneself to a dynamic environment. However, newer models suggest that guiding and correcting motor outputs may occur via a combination of

feedforward and feedback loops. Harris et al. [216] discussed a computational model to minimize the fingertip variance and improve movement accuracy. Harwood et al. [217] have also discussed a similar model to account for the saccade movement in humans. The relationship between speed and accuracy has also been discussed. Earlier studies [216][218][219] have described the speed-to-accuracy trade-off in which the authors have inferred that there may be a tradeoff to increasing the movement speed, i.e., an increase in movement speed may reduce the accuracy. Studies [216] have indicated that the underlying phenomenon related to the speed-to-accuracy tradeoff may be the signal-dependent noise which is the noise present in the neural control signal. Task-specific computational models have also been theorized; Hamilton et al. [220] discussed how humans might approach an obstacle avoidance problem.

Todorov et al. [221][222] proposed an optimal feedback control scheme that abides by the minimum intervention principle as a criterion to correct any movement errors. According to the minimum intervention principle, the SMC model receives the sensory feedback and corrects only the task-relevant error, i.e., only the error that affects the task performance and not task-irrelevant errors. Studies have also attempted to validate this principle [223]. The feedback model discussed here could use sensory feedback and abide by the minimum intervention principle to correct errors. However, the feedback models come with their limitation: the time delay caused due to the feedback loops. The feedforward model does not use a feedback loop and, therefore, may solve the problem of time delay. Desmurget et al. [224], Wolpert et al. [225], and Haruno et al. [226] examined the application of the forward models in SMC. These models could predict motor movement depending on the motor command through a process of continuous learning, and this prediction is then used for motor control. The drawback with the feedforward models would be that online error correction would not be possible without a sensory feedback loop. To overcome this limitation, studies have proposed the internal model, a combination of feedforward and feedback models for movement planning and online error correction. Wolpert et al. [227] discussed the working of the internal model and conducted a study to validate the internal model dictating motor actions. Figure 1.3 shows the internal model hypothesized for SMC. Few studies have also discussed how humans interact with physical objects [228] [229] [230], wherein the impedance of the muscles was controlled

depending on the force required to be exerted on the object of interest. Finally, studies [231][232][199][233] have also explored the CNS's criteria in muscle recruitment, another essential component of SMC.

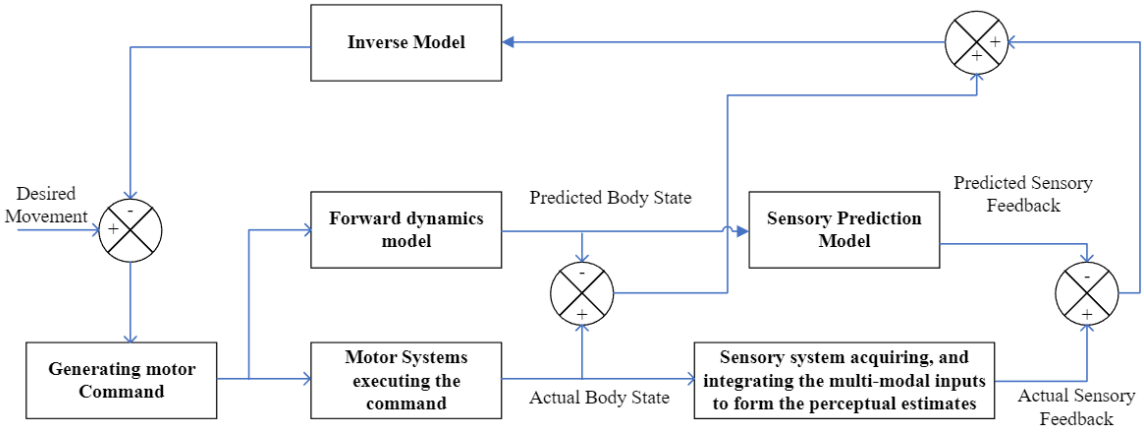


Figure 1.3: Internal model of SMC

As indicated earlier, the computational models discussed in this section shed light on the criterion that may be used in SMC functionalities. Apart from using these models to understand the working of SMC in healthy subjects, they could also be used to pinpoint the SMC deficits in PD patients. As such, in this thesis, specific computational models discussed in this section were used to analyze PD patients to understand how they might differ from healthy subjects in abiding by the computational models. However, it must be noted that the models discussed here are just various schools of thought; no model has been officially recognized as an accurate description of brain functionality.

1.5.6 Sensorimotor Control and Parkinson's Disease

The optimal execution of any motor action relies heavily on properly functioning SMC circuits. While the cardinal motor symptoms have been widely studied, it is only recently that the focus has turned towards studying how PD may affect the fundamental SMC processes, which are the building blocks for any goal-directed motor action.

Studies [61] [57] [234] [235] have discussed the relationship between motor symptoms in PD and dysfunctions in executive functions. Lu et al. [236] tested PD patients with an obstacle avoidance task presented, which implied a deterioration in movement

execution or even planning. Gentilucci et al. [237] theorized that the PD patients may have a deficit in storing and retrieving a planned motor action, leading to regenerating or reprogramming an already generated motor plan. Leis et al. [238] also studied this deficit in retrieving motor plans, and the study's result indicated that PD patients exhibited higher reaction time, movement time, and jerk. It may be that the repetitive reprogramming due to BG's inability to store a motor plan led to slowness and increased difficulty in movement execution and control. Fama et al. [61] tested the sequencing ability in PD patients through motor and cognitive tasks; the PD patients exhibited impairments in higher cortical functioning and motor planning. This deficit in constructing a temporal sequence during movement execution among PD patients has also been widely discussed in other studies [239][240]. Movement switching in PD patients was also studied and found to be impaired [239][240]. Movement switching can be associated with online error correction if asked to do it unexpectedly. However, the switching of movement direction in this study was not unexpected.

Although the earlier studies explored certain aspects of SMC in PD patients, several limitations must be addressed. Most studies discussed earlier use metrics representing motor features such as speed and time taken. However, they neither test the patient's SMC ability specifically nor explore metrics specific to assess motor planning. Additionally, the SMC functions in dynamic environments have not been explored. Testing in dynamic environments may better represent the real world and provide valuable insights into how well the patients may plan or correct movement while performing day-to-day activities. Not much is also known about medication's effect on movement planning and error correction. As indicated earlier, SMC requires the proper functioning of sensory, motor, and cognitive systems. There is still a lack of understanding if the SMC deficits in PD originate from an impairment in motor, sensory, or cognitive domains or a combination of impairments from multiple domains. Finally, comparing the performance of PD patients based on computational models would help determine the aspects or metrics of movement planning or error correction that need to be targeted during treatment. Currently, no study has assessed deficits in PD from the perspective of computational models. Hence, it is safe to conclude that an objective and quantitative characterization of SMC deficits in PD patients is needed to understand the multi-modal effects of PD and consequently optimize

the treatments. There are several reasons to study deficits in SMC functions, especially in the context of movement planning and error correction in PD patients:

- Understanding the SMC deficits would inform us about their relationship with motor deficits and executive dysfunctions, which would help optimize the treatment plan [241].
- Characterizing the SMC deficits in PD would help determine the aspects of SMC that are affected and need to be targeted. Developing metrics to analyze individual domains of SMC may allow us to target each domain separately.
- Exploring the SMC deficits from the perspective of computational models is vital to know how the criterion used in PD may be altered compared to healthy subjects. The cost function equation in these models also informs us of the metrics that must be targeted during treatments.
- Examining the patients under changing or unpredictable testing conditions may help determine how efficiently they can handle simple daily tasks.
- Understanding the impact of medication on SMC deficits is vital, as these complex effects must be considered when determining the treatment plan.
- Clinical scales do not assess SMC functions in PD patients. Moreover, these subjective scales have their limitations. Complementing the existing subjective assessments with quantitative and objective patient-specific analysis of SMC may help better quantify the deficits, thereby improving the quality of care [242].

1.6 Rationale

PD is a highly heterogeneous disease that presents itself differently in different patients, leading to a myriad of motor and non-motor symptoms that must be managed through targeted treatments. It is necessary, therefore, to characterize the symptoms, their contributing factors, and the underlying mechanisms to better target the impairments and manage the disease efficiently. However, the full extent of these non-motor symptoms, specifically deficits in perception and executive functions and their contributors, is not yet fully understood, thereby increasing the difficulty in managing the symptoms. The perceptual deficits and executive dysfunctions greatly impact the patient's quality of life, leading to workplace challenges such as affecting the patient’s ability to drive, write, and

operate heavy machinery. Moreover, studies [190][191] have also indicated that the non-motor symptoms may arise much earlier in the disease and may contribute to the motor deficits that arise later. Finally, how perceptual and cognitive deficits respond to the main treatments of PD, such as dopaminergic medication is also a topic of debate. Therefore, there is a need to better understand the nature of these deficits, the factors that contribute to them, and how the current treatment protocols alter them. Treating a symptom requires understanding the underlying problem that gives rise to the symptoms. Examining and characterizing the factors that contribute to perceptual and executive deficits, and later to motor abnormalities, allows us to understand the underlying mechanism involved in these deficits. This may open new doors to manage these symptoms through a more efficient, individualized, and targeted treatment. Moreover, understanding how the dopaminergic medication, the preferred therapy for PD, alters PD-related impairments may provide valuable insights into treatment optimization.

The SMI functionalities involving the central processing of sensory inputs and the SMC functionalities involving the appropriate planning and correction of voluntary movements are the fundamental building blocks for accurate perception of the world around us and execution of the desired movement. Therefore, impairment in SMI and SMC may lead to deficits in perception, and executive functions, adversely affecting the ability to perform daily activities. Additionally, research has indicated that BG, which is the affected region in PD, may play a critical role in SMI and SMC processes. This implies that a dysfunction in BG may alter the SMI and SMC circuits. Therefore, how PD affects SMI and SMC functions may be the missing piece that needs to be investigated to understand the framework involved in deficits of perception, executive functions, and, consequently, motor abnormalities. This may be vital to effectively treat the disease. Taking this into account and the earlier literature review detailing the symptoms of PD and the neural and computational bases involved in SMI and SMC, this thesis focuses on investigating SMI and SMC functions in PD patients.

Early diagnosis and treatment of PD may prove to be effective and beneficial to the patient's quality of life while also reducing the economic burden on the patient. With non-motor symptoms such as perceptual deficits manifesting much earlier in the disease, these

symptoms and the impairments that give rise to them may be considered promising biomarkers for an early diagnosis [243]. With the accessibility and cost-effectiveness of the technology increasing, a technology-driven tool that can assess and detect these biomarkers may be valuable as an early diagnostic technique that can enhance the quality of care and reduce the economic burden on the patients. Apart from these technologies being looked upon as diagnostic tools, they may also serve as an efficient analysis and monitoring tool that could assist clinicians in optimizing the existing therapies, thereby enhancing the efficacy of the treatments. For the last few decades, considering the diverse nature of PD, there have been growing calls for a more individualized and targeted treatment approach using a patient-specific analysis tool [134]. Therefore, an objective tool to individually analyze domain-specific bio-makers may be useful in providing a patient-specific treatment. Taking these together, the thesis focuses on designing, developing, and utilizing robotic tools and simulation models to investigate and extract biomarkers that provide crucial information about SMI and SMC, which may be useful for an early diagnosis and efficient management of the disease. These objective tools and metrics lay a foundation for our research goal of using innovative, technology-driven tools for diagnosis and treatment.

1.7 Hypothesis

- The hypothesis is that the abnormalities in perception and executive functions observed in PD patients that may lead to motor deficits arise from central impairments associated with SMI and SMC.

- The use of dopaminergic medication for treating PD further alters the functioning of SMI and SMC.

- Impairments in SMI and SMC may be seen more commonly across PD patients, and therefore may be considered a potential biomarker for early diagnosis of PD.

1.8 Objectives

1.8.1 Objective 1: Characterization of SMI impairments in PD Patients

As discussed earlier in this chapter, perceptual abnormalities in PD patients are observed across multiple stages of PD, which may then contribute to motor deficits. Studies [81][244] hypothesize that an impairment in the central processing of sensory inputs such as SMI may lead to sensory deficits, contributing to motor deficits. Dysfunctions in SMI would adversely affect the patient's ability to perceive the environment and adapt their motor output to suit the demands of the environment. Currently, very little is known about the effects of PD on SMI. Understanding and characterizing any SMI deficits would inform us more about the contributors to perceptual and motor abnormalities. This enables us to provide a treatment targeted to mitigate the SMI deficits that would, in turn, mitigate other perceptual and motor deficits. One of the objectives of the work is to investigate and characterize SMI deficits in PD patients under varying sensory conditions. The methodology and results pertaining to the investigation of SMI are provided in Chapter 2 and Chapter 3, respectively.

1.8.2 Objective 2: Effect of Medication on SMI in PD Patients

Dopaminergic medication is effective in mitigating cardinal motor symptoms. However, the effect of medication on perceptual and cognitive dysfunctions has been mixed, inconsistent, and not fully understood. No study has yet analyzed the effect of medication on SMI, which is hypothesized to contribute to perceptual and motor abnormalities in PD. However, understanding the impact of medication on these deficits and the impairments that give rise to these deficits is essential to better optimize the treatment. A treatment that mitigates the cardinal motor symptoms but fails to improve or worsens the overall motor performance due to its adverse effect on the central processing of sensory inputs may negatively impact the patient's quality of life. Therefore, in addition to testing the patients in their OFF state, the patients were also tested in the ON state (one hour after medication). This objective is an extension of the earlier one as the methodology and metrics used to assess the patients in their ON state are the same as the ones described in the earlier objective.

1.8.3 Objective 3: Characterization of SMC impairments in PD Patients

The building blocks for executing voluntary movements are the optimal functioning of SMC components such as movement planning and online error correction. While the cardinal motor symptoms have traditionally grabbed a lot of attention, PD patients also experience difficulties in accurately and efficiently performing even simple day-to-day motor tasks. Factors contributing to motor difficulties are still a topic of debate; it has been hypothesized that a deficit in SMC functions may lead to a cascade of motor deficits affecting the patient's ability to perform motor tasks. However, the nature and extent of the SMC deficits in PD and how they may affect voluntary movements are not fully understood. Moreover, with SMC functions involving multiple domains (sensory, cognitive, and motor), no study has attempted to individually analyze each domain as to how they contribute to SMC and how it may be affected due to PD. This work aims to objectively investigate the SMC functions in PD patients and determine how they differ from healthy subjects. Participants performed an upper-limb obstacle avoidance task under varying testing conditions to evaluate movement planning and online error correction in PD patients. Kinematic data acquired from the task was used to extract features or metrics for individually evaluating sensory, motor, and cognitive domains associated with SMC functions. This work extracted features to investigate these domains based on their involvement in SMC functions and does not evaluate other aspects of the domains. For instance, the cognitive domain is responsible for multiple functions, but in this work, only the cognitive functions related to movement planning and online error correction were assessed. Finally, the SMC performance of all PD and healthy subjects were compared with the existing computational model to understand how PD dysfunction may affect the CNS's criterion to complete the desired task. This would further provide valuable insights about the aspects that needed to be targeted during the rehabilitation therapies. Currently, no study has analyzed the performance of PD patients from the perspective of computational models. The methodology and outcomes related to the evaluation of SMC in PD patients are provided in Chapter 2 and Chapter 4, respectively.

1.8.4 Objective 4: Effect of Medication on SMC in PD Patients

As indicated in section 1.8.2 and earlier sections, the effects of dopaminergic medication on brain functions and computations have been complex and mixed. How medication may affect the SMC functions such as movement planning and error correction is still unknown and need to be understood. It is necessary to not just take into account the effects of medication on cardinal motor symptoms but also its effect on SMC functions which are fundamental to any motor action, to determine the optimal treatment strategy that provides an effective quality of care. Therefore, as an extension of the objective mentioned in 1.8.3, the patients were tested one hour after medication to analyze the effects of medication on SMC functions.

1.8.5 Objective 5: Development of a Robot-based Objective Tool and Metrics to Analyze the SMI and SMC Functions in PD Patients

As previously noted, there is a lack of objective diagnostic and assessment methods to monitor the motor and non-motor symptoms presented by PD, especially the impairments in SMI and SMC functions. Studies [242] have shown that the objective assessment may provide a more accurate representation of the patient's condition than a subjective one and that complementing the existing subjective clinical scales with objective methods helps better monitor PD patients. With PD being a heterogeneous disease, an objective assessment is vital to providing a patient-specific treatment. Further, with the deficit in perception being presented much earlier in the disease than the motor symptoms, there is a need to diagnose the perceptual deficits and the impairments in SMI/SMC that may lead to these deficits as soon as possible. However, clinical scales such as UPDRS or MoCA are not targeted to evaluate the SMI or SMC functions. An objective tool to assess the SMI or SMC functions may assist in diagnosing the disease at an early stage and managing the disease better. In the current work, multiple robot-based tasks were designed and developed to objectively evaluate SMI and SMC using the KINARM endpoint robot. A detailed explanation of the robot-based tasks and the methodology involved in designing them is provided in Chapter-2.

1.8.6 Objective 6: Development of a Subject-specific Musculoskeletal Model to Extract In-depth Features Related to Motor Recruitment

As discussed in this chapter, several studies [245][246][134] have suggested the need to individualize the treatment of PD to improve the efficacy of the treatment plan. While the tool described earlier provides patient-specific objective evaluation of the SMI and SMC performance, evaluating the muscle recruitment behavior may also be useful in optimizing PD-related therapies. Studies have discussed the abnormalities in muscle recruitment behavior due to PD, and a tool to assess the muscle recruitment strategies might be of clinical significance, especially to improve the efficacy of targeted treatments such as injections of lidocaine and botulinum toxin type A. While the sEMG is currently the gold standard to measure muscle parameters used during targeted therapies, this technique has numerous limitations, which are explained in Chapter 2. Therefore, a patient-specific musculoskeletal model has been designed to take the joint kinematic data as an input, and output the individual muscle forces, activity, and the contribution required to complete the desired motion. The model's performance and accuracy were validated using healthy subjects and the model's potential to be used as a guiding tool for targeted therapies has been explored. The methodology and developments pertaining to the musculoskeletal model are provided in Chapters 2 and 5.

1.9 Brief Outline of the Thesis

The thesis includes six Chapters, and a brief overview of each chapter is as follows:

- Chapter 1 – Provides the background information on the symptoms, treatment for PD, and existing knowledge about SMI and SMC in PD.

- Chapter 2 – Gives an overview of the methods used to investigate SMI and SMC impairments in PD. The chapter discusses the robotic tools and metrics for objectively analyzing impairments and provides information about the development of the musculoskeletal model.

- Chapter 3 – Discusses the study's findings related to SMI impairments and the effect of medication.

- Chapter 4 – Discusses the study's findings related to SMC impairments and the effect of medication.

- Chapter 5 - Provides validation of the muscle model and discusses its potential application in targeted therapies.

- Chapter 6 – Provides a detailed overview of all findings and their clinical significance. It also suggests directions for future work, followed by concluding remarks on the research described in the thesis.

1.10 References

[1] Launch of WHO's Parkinson disease technical brief: World Health Organization, "https://www.who.int/news/item/14-06-2022-launch-of-who-s-parkinson-disease-technical-brief," 2022.

[2] S. L. Kowal, T. M. Dall, R. Chakrabarti, M. v. Storm, and A. Jain, "The current and projected economic burden of Parkinson's disease in the United States," *Movement Disorders*, vol. 28, no. 3, pp. 311–318, Mar. 2013, doi: 10.1002/mds.25292.

[3] R. Xia and Z.-H. Mao, "Progression of motor symptoms in Parkinson's disease," *Neurosci Bull*, vol. 28, no. 1, pp. 39–48, Feb. 2012, doi: 10.1007/s12264-012-1050-z.

[4] W. Poewe, "Non-motor symptoms in Parkinson's disease," *Eur J Neurol*, vol. 15, no. s1, pp. 14–20, Apr. 2008, doi: 10.1111/j.1468-1331.2008.02056.x.

[5] O.-B. Tysnes and A. Storstein, "Epidemiology of Parkinson's disease," *J Neural Transm*, vol. 124, no. 8, pp. 901–905, Aug. 2017, doi: 10.1007/s00702-017-1686-y.

[6] Z. Ou *et al.*, "Global Trends in the Incidence, Prevalence, and Years Lived With Disability of Parkinson's Disease in 204 Countries/Territories From 1990 to 2019," *Front Public Health*, vol. 9, Dec. 2021, doi: 10.3389/fpubh.2021.776847.

[7] E. R. Dorsey *et al.*, "Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016," *Lancet Neurol*, vol. 17, no. 11, pp. 939–953, Nov. 2018, doi: 10.1016/S1474-4422(18)30295-3.

[8] T. Pringsheim, N. Jette, A. Frolkis, and T. D. L. Steeves, "The prevalence of Parkinson's disease: A systematic review and meta-analysis," *Movement Disorders*, vol. 29, no. 13, pp. 1583–1590, Nov. 2014, doi: 10.1002/mds.25945.

[9] D. K. Simon, C. M. Tanner, and P. Brundin, "Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology," *Clin Geriatr Med*, vol. 36, no. 1, pp. 1–12, Feb. 2020, doi: 10.1016/j.cger.2019.08.002.

[10] A. Elbaz *et al.*, "Professional exposure to pesticides and Parkinson disease," *Ann Neurol*, vol. 66, no. 4, pp. 494–504, Oct. 2009, doi: 10.1002/ana.21717.

[11] R. J. Dinis-Oliveira *et al.*, "Paraquat exposure as an etiological factor of Parkinson's disease," *Neurotoxicology*, vol. 27, no. 6, pp. 1110–1122, Dec. 2006, doi: 10.1016/j.neuro.2006.05.012.

[12] J. Zayed *et al.*, "Facteurs environnementaux dans l'étiologie de la maladie de Parkinson," *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*, vol. 17, no. 3, pp. 286–291, Aug. 1990, doi: 10.1017/S0317167100030584.

[13] D. A. di Monte, M. Lavasani, and A. B. Manning-Bog, "Environmental Factors in Parkinson's Disease," *Neurotoxicology*, vol. 23, no. 4–5, pp. 487–502, Oct. 2002, doi: 10.1016/S0161-813X(02)00099-2.

[14] H. Deng, P. Wang, and J. Jankovic, "The genetics of Parkinson disease," *Ageing Res Rev*, vol. 42, pp. 72–85, Mar. 2018, doi: 10.1016/j.arr.2017.12.007.

[15] A. Kouli, K. M. Torsney, and W.-L. Kuan, "Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis," in *Parkinson's Disease: Pathogenesis and Clinical Aspects*, Codon Publications, 2018, pp. 3–26. doi: 10.15586/codonpublications.parkinsonsdisease.2018.ch1.

[16] D. W. Dickson, "Neuropathology of Parkinson disease," *Parkinsonism Relat Disord*, vol. 46, pp. S30–S33, Jan. 2018, doi: 10.1016/j.parkreldis.2017.07.033.

[17] A. Kouli, K. M. Torsney, and W.-L. Kuan, "Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis," in *Parkinson's Disease: Pathogenesis and Clinical*

Aspects, Codon Publications, 2018, pp. 3–26. doi: 10.15586/codonpublications.parkinsonsdisease.2018.ch1.

[18] B. Holdorff, "Centenary of Tretiakoff's thesis on the morphology of Parkinson's disease, evolved on the grounds of encephalitis lethargica pathology," *J Hist Neurosci*, vol. 28, no. 4, pp. 387–398, Oct. 2019, doi: 10.1080/0964704X.2019.1622361.

[19] A. N. MacMahon Copas, S. F. McComish, J. M. Fletcher, and M. A. Caldwell, "The Pathogenesis of Parkinson's Disease: A Complex Interplay Between Astrocytes, Microglia, and T Lymphocytes?," *Front Neurol*, vol. 12, May 2021, doi: 10.3389/fneur.2021.666737.

[20] L. v Kalia and A. E. Lang, "Parkinson's disease," *The Lancet*, vol. 386, no. 9996, pp. 896–912, Aug. 2015, doi: 10.1016/S0140-6736(14)61393-3.

[21] L. v. Kalia *et al.*, "Clinical Correlations With Lewy Body Pathology in *LRRK2* -Related Parkinson Disease," *JAMA Neurol*, vol. 72, no. 1, p. 100, Jan. 2015, doi: 10.1001/jamaneurol.2014.2704.

[22] E. C. Hirsch, S. Vyas, and S. Hunot, "Neuroinflammation in Parkinson's disease," *Parkinsonism Relat Disord*, vol. 18, pp. S210–S212, Jan. 2012, doi: 10.1016/S1353-8020(11)70065-7.

[23] J.-K. Lee, T. Tran, and M. G. Tansey, "Neuroinflammation in Parkinson's Disease," *Journal of Neuroimmune Pharmacology*, vol. 4, no. 4, pp. 419–429, Dec. 2009, doi: 10.1007/s11481-009-9176-0.

[24] H. Braak, K. del Tredici, U. Rüb, R. A. I. de Vos, E. N. H. Jansen Steur, and E. Braak, "Staging of brain pathology related to sporadic Parkinson's disease," *Neurobiol Aging*, vol. 24, no. 2, pp. 197–211, Mar. 2003, doi: 10.1016/S0197-4580(02)00065-9.

[25] A. M. Graybiel, "The basal ganglia," *Current Biology*, vol. 10, no. 14, pp. R509–R511, Jul. 2000, doi: 10.1016/S0960-9822(00)00593-5.

[26] J. E. Rubin, C. C. McIntyre, R. S. Turner, and T. Wichmann, "Basal ganglia activity patterns in parkinsonism and computational modeling of their downstream effects," *European Journal of Neuroscience*, vol. 36, no. 2, pp. 2213–2228, Jul. 2012, doi: 10.1111/j.1460-9568.2012.08108.x.

[27] A. Galvan, A. Devergnas, and T. Wichmann, "Alterations in neuronal activity in basal ganglia-thalamocortical circuits in the parkinsonian state," *Front Neuroanat*, vol. 9, Feb. 2015, doi: 10.3389/fnana.2015.00005.

[28] J. L. Lanciego, N. Luquin, and J. A. Obeso, "Functional Neuroanatomy of the Basal Ganglia," *Cold Spring Harb Perspect Med*, vol. 2, no. 12, pp. a009621–a009621, Dec. 2012, doi: 10.1101/cshperspect.a009621.

[29] A. M. Graybiel, "Neurotransmitters and neuromodulators in the basal ganglia," *Trends Neurosci*, vol. 13, no. 7, pp. 244–254, Jul. 1990, doi: 10.1016/0166-2236(90)90104-I.

[30] J. A. Obeso and J. L. Lanciego, "Past, Present, and Future of the Pathophysiological Model of the Basal Ganglia," *Front Neuroanat*, vol. 5, 2011, doi: 10.3389/fnana.2011.00039.

[31] A. Nambu, H. Tokuno, and M. Takada, "Functional significance of the cortico–subthalamo–pallidal 'hyperdirect' pathway," *Neurosci Res*, vol. 43, no. 2, pp. 111–117, Jun. 2002, doi: 10.1016/S0168-0102(02)00027-5.

[32] P. Calabresi, B. Picconi, A. Tozzi, V. Ghiglieri, and M. di Filippo, "Direct and indirect pathways of basal ganglia: a critical reappraisal," *Nat Neurosci*, vol. 17, no. 8, pp. 1022–1030, Aug. 2014, doi: 10.1038/nn.3743.

[33] J. A. Obeso *et al.*, “Pathophysiology of the basal ganglia in Parkinson’s disease,” *Trends Neurosci*, vol. 23, pp. S8–S19, Oct. 2000, doi: 10.1016/S1471-1931(00)00028-8.

[34] A. B. Nelson and A. C. Kreitzer, “Reassessing Models of Basal Ganglia Function and Dysfunction,” *Annu Rev Neurosci*, vol. 37, no. 1, pp. 117–135, Jul. 2014, doi: 10.1146/annurev-neuro-071013-013916.

[35] C. D. Marsden, “Dopamine and basal ganglia disorders in humans,” *Seminars in Neuroscience*, vol. 4, no. 2, pp. 171–178, Apr. 1992, doi: 10.1016/1044-5765(92)90015-T.

[36] K. S. Wang, J. P. McClure, S. K. Alselehdar, and V. Kanta, “Direct and indirect pathways of the basal ganglia: opponents or collaborators?,” *Front Neuroanat*, vol. 9, Mar. 2015, doi: 10.3389/fnana.2015.00020.

[37] M. DeLong and T. Wichmann, “Update on models of basal ganglia function and dysfunction,” *Parkinsonism Relat Disord*, vol. 15, pp. S237–S240, Dec. 2009, doi: 10.1016/S1353-8020(09)70822-3.

[38] J. Opara, A. Małecki, E. Małecka, and T. Socha, “Motor assessment in Parkinson`s disease,” *Annals of Agricultural and Environmental Medicine*, vol. 24, no. 3, pp. 411–415, Sep. 2017, doi: 10.5604/12321966.1232774.

[39] M. Skorvanek *et al.*, “Global scales for cognitive screening in Parkinson’s disease: Critique and recommendations,” *Movement Disorders*, vol. 33, no. 2, pp. 208–218, Feb. 2018, doi: 10.1002/mds.27233.

[40] J. Klucken *et al.*, “Unbiased and Mobile Gait Analysis Detects Motor Impairment in Parkinson’s Disease,” *PLoS One*, vol. 8, no. 2, p. e56956, Feb. 2013, doi: 10.1371/journal.pone.0056956.

[41] P. Gaprielian, S. H. Scott, C. Lowrey, S. Reid, G. Pari, and R. Levy, “Integrated robotics platform with haptic control differentiates subjects with Parkinson’s disease from controls and quantifies the motor effects of levodopa,” *J Neuroeng Rehabil*, vol. 16, no. 1, p. 124, Dec. 2019, doi: 10.1186/s12984-019-0598-5.

[42] S. G. Adams, J. Winnell, and M. Jog, “Effects of interlocutor distance, multi-talker background noise, and a concurrent manual task on speech intensity in Parkinson’s disease,” *Journal of Medical Speech - Language Pathology*, vol. 18, p. 1+, 2010, [Online]. Available: https://link.gale.com/apps/doc/A244280890/AONE?u=googlescholar&sid=bookmark-AONE&xid=ccf43daa

[43] A. A. Moustafa *et al.*, “Motor symptoms in Parkinson’s disease: A unified framework,” *Neurosci Biobehav Rev*, vol. 68, pp. 727–740, Sep. 2016, doi: 10.1016/j.neubiorev.2016.07.010.

[44] E. Qian and Y. Huang, “Subtyping of Parkinson’s Disease - Where Are We Up To?,” *Aging Dis*, vol. 10, no. 5, p. 1130, 2019, doi: 10.14336/AD.2019.0112.

[45] J. Zhang *et al.*, “Akinetic-rigid and tremor-dominant Parkinson’s disease patients show different patterns of intrinsic brain activity,” *Parkinsonism Relat Disord*, vol. 21, no. 1, pp. 23–30, Jan. 2015, doi: 10.1016/j.parkreldis.2014.10.017.

[46] A. L. Bartels and K. L. Leenders, “Parkinson’s disease: The syndrome, the pathogenesis and pathophysiology,” *Cortex*, vol. 45, no. 8, pp. 915–921, Sep. 2009, doi: 10.1016/j.cortex.2008.11.010.

[47] Y. Osaki, Y. Morita, Y. Miyamoto, T. Furushima, K. Furuta, and H. Furuya, “Disease progression and phenotypes of non-motor symptoms in Parkinson’s disease,” *Neurol Clin Neurosci*, vol. 9, no. 1, pp. 83–90, Jan. 2021, doi: 10.1111/ncn3.12468.

[48] M. Lubomski, R. L. Davis, and C. M. Sue, “Cognitive Influences in Parkinson’s Disease Patients and Their Caregivers: Perspectives From an Australian Cohort,” *Front Neurol*, vol. 12, Nov. 2021, doi: 10.3389/fneur.2021.673816.

[49] J. G. Goldman *et al.*, “Cognitive impairment in Parkinson’s disease: a report from a multidisciplinary symposium on unmet needs and future directions to maintain cognitive health,” *NPJ Parkinsons Dis*, vol. 4, no. 1, p. 19, Dec. 2018, doi: 10.1038/s41531-018-0055-3.

[50] D. Aarsland *et al.*, “Parkinson disease-associated cognitive impairment,” *Nat Rev Dis Primers*, vol. 7, no. 1, p. 47, Dec. 2021, doi: 10.1038/s41572-021-00280-3.

[51] F. Boller, “Visuospatial Impairment in Parkinson’s Disease,” *Arch Neurol*, vol. 41, no. 5, p. 485, May 1984, doi: 10.1001/archneur.1984.04050170031011.

[52] S. Davidsdottir, A. Cronin-Golomb, and A. Lee, “Visual and spatial symptoms in Parkinson’s disease,” *Vision Res*, vol. 45, no. 10, pp. 1285–1296, May 2005, doi: 10.1016/j.visres.2004.11.006.

[53] M. Potegal, “Role of the caudate nucleus in spatial orientation of rats.,” *J Comp Physiol Psychol*, vol. 69, no. 4, Pt.1, pp. 756–764, 1969, doi: 10.1037/h0028168.

[54] D. Sukumar, M. Rengaswamy, and V. S. Chakravarthy, “Modeling the Contributions of Basal Ganglia and Hippocampus to Spatial Navigation Using Reinforcement Learning,” *PLoS One*, vol. 7, no. 10, p. e47467, Oct. 2012, doi: 10.1371/journal.pone.0047467.

[55] G. S. Watson and J. B. Leverenz, “Profile of Cognitive Impairment in Parkinson’s Disease,” *Brain Pathology*, vol. 20, no. 3, pp. 640–645, May 2010, doi: 10.1111/j.1750-3639.2010.00373.x.

[56] B. Dubois and B. Pillon, “Cognitive deficits in Parkinson’s disease,” *J Neurol*, vol. 244, no. 1, pp. 2–8, Nov. 1996, doi: 10.1007/PL00007725.

[57] G. Dirnberger and M. Jahanshahi, “Executive dysfunction in Parkinson’s disease: A review,” *J Neuropsychol*, vol. 7, no. 2, pp. 193–224, Sep. 2013, doi: 10.1111/jnp.12028.

[58] L. Ghazi-Saidi, “Visuospatial and Executive Deficits in Parkinson’s Disease: A Review,” *Acta Sci Neurol*, vol. 3, no. 4, pp. 08–26, Mar. 2020, doi: 10.31080/ASNE.2020.03.0172.

[59] J. Koerts, M. van Beilen, O. Tucha, K. L. Leenders, and W. H. Brouwer, “Executive Functioning in Daily Life in Parkinson’s Disease: Initiative, Planning and Multi-Task Performance,” *PLoS One*, vol. 6, no. 12, p. e29254, Dec. 2011, doi: 10.1371/journal.pone.0029254.

[60] R. G. Brown and C. D. Marsden, “An investigation of the phenomenon of ‘set’ in Parkinson’s disease,” *Movement Disorders*, vol. 3, no. 2, pp. 152–161, 1988, doi: 10.1002/mds.870030207.

[61] R. Fama and E. v. Sullivan, “Motor Sequencing in Parkinson’s Disease: Relationship to Executive Function and Motor Rigidity,” *Cortex*, vol. 38, no. 5, pp. 753–767, Jan. 2002, doi: 10.1016/S0010-9452(08)70042-X.

[62] N. Sawamoto, M. Honda, T. Hanakawa, H. Fukuyama, and H. Shibasaki, “Cognitive Slowing in Parkinson’s Disease: A Behavioral Evaluation Independent of Motor Slowing,” *The Journal of Neuroscience*, vol. 22, no. 12, pp. 5198–5203, Jun. 2002, doi: 10.1523/JNEUROSCI.22-12-05198.2002.

[63] D Rogers, A J Lees, E Smith, M Trimble, and G M Stern, “Bradyphrenia in Parkinson’s disease and psychomotor retardation in depressive illness. An experimental study,” *Brain*, vol. 110, no. 3, pp. 761–776, 1987, doi: 10.1093/brain/110.3.761.

[64] S. G. Adams, A. Dykstra, M. Jenkins, and M. Jog, “Speech-to-noise levels and conversational intelligibility in hypophonia and Parkinson’s disease,” *Journal of Medical Speech - Language Pathology*, vol. 16, p. 165+, 2008, [Online]. Available: https://link.gale.com/apps/doc/A191480538/AONE?u=anon~547019d&sid=googleScholar&xid=4995aec4

[65] J. D. Holmes, M. E. Jenkins, A. M. Johnson, S. G. Adams, and S. J. Spaulding, “Dual-Task Interference: The Effects of Verbal Cognitive Tasks on Upright Postural Stability in Parkinson’s Disease,” *Parkinsons Dis*, vol. 2010, pp. 1–5, 2010, doi: 10.4061/2010/696492.

[66] B. Ford, “Pain in Parkinson’s disease,” *Movement Disorders*, vol. 25, no. S1, pp. S98–S103, 2010, doi: 10.1002/mds.22716.

[67] A. Fil, R. Cano-de-la-Cuerda, E. Muñoz-Hellín, L. Vela, M. Ramiro-González, and C. Fernández-de-las-Peñas, “Pain in Parkinson disease: A review of the literature,” *Parkinsonism Relat Disord*, vol. 19, no. 3, pp. 285–294, Mar. 2013, doi: 10.1016/j.parkreldis.2012.11.009.

[68] R. L. Doty, “Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate?,” *Lancet Neurol*, vol. 16, no. 6, pp. 478–488, Jun. 2017, doi: 10.1016/S1474-4422(17)30123-0.

[69] A. Haehner *et al.*, “Prevalence of smell loss in Parkinson’s disease – A multicenter study,” *Parkinsonism Relat Disord*, vol. 15, no. 7, pp. 490–494, Aug. 2009, doi: 10.1016/j.parkreldis.2008.12.005.

[70] J. Wang, H. You, J.-F. Liu, D.-F. Ni, Z.-X. Zhang, and J. Guan, “Association of Olfactory Bulb Volume and Olfactory Sulcus Depth with Olfactory Function in Patients with Parkinson Disease,” *American Journal of Neuroradiology*, vol. 32, no. 4, pp. 677–681, Apr. 2011, doi: 10.3174/ajnr.A2350.

[71] M. Witt *et al.*, “Biopsies of olfactory epithelium in patients with Parkinson’s disease,” *Movement Disorders*, vol. 24, no. 6, pp. 906–914, Apr. 2009, doi: 10.1002/mds.22464.

[72] M. Shah *et al.*, “Abnormality of taste and smell in Parkinson’s disease,” *Parkinsonism Relat Disord*, vol. 15, no. 3, pp. 232–237, Mar. 2009, doi: 10.1016/j.parkreldis.2008.05.008.

[73] T. Klockgether and J. Dichgans, “Visual control of arm movement in Parkinson’s disease,” *Movement Disorders*, 1994, doi: 10.1002/mds.870090108.

[74] T. Klockgether, M. Borutta, H. Rapp, S. Spieker, and J. Dichgans, “A defect of kinesthesia in Parkinson’s disease,” *Movement Disorders*, vol. 10, no. 4, pp. 460–465, Jul. 1995, doi: 10.1002/mds.870100410.

[75] J. Konczak *et al.*, “Proprioception and Motor Control in Parkinson’s Disease,” *J Mot Behav*, vol. 41, no. 6, pp. 543–552, Nov. 2009, doi: 10.3200/35-09-002.

[76] R. A. Armstrong, “Visual Symptoms in Parkinson’s Disease,” *Parkinsons Dis*, vol. 2011, pp. 1–9, 2011, doi: 10.4061/2011/908306.

[77] S.-A. Mcdowell and J. Harris, “Irrelevant peripheral visual stimuli impair manual reaction times in Parkinson’s disease,” *Vision Res*, vol. 37, no. 24, pp. 3549–3558, Dec. 1997, doi: 10.1016/S0042-6989(97)00188-0.

[78] S. Laatu, A. Revonsuo, L. Pihko, R. Portin, and J. O. Rinne, “Visual object recognition deficits in early Parkinson’s disease,” *Parkinsonism Relat Disord*, vol. 10, no. 4, pp. 227–233, Jun. 2004, doi: 10.1016/j.parkreldis.2004.02.001.

[79] J. Waldthaler, C. Krüger-Zechlin, L. Stock, Z. Deeb, and L. Timmermann, “New insights into facial emotion recognition in Parkinson’s disease with and without mild cognitive impairment from visual scanning patterns,” *Clin Park Relat Disord*, vol. 1, pp. 102–108, 2019, doi: 10.1016/j.prdoa.2019.11.003.

[80] M. S. Corin, T. S. Elizan, and M. B. Bender, “Oculomotor function in patients with Parkinson’s disease,” *J Neurol Sci*, vol. 15, no. 3, pp. 251–265, Mar. 1972, doi: 10.1016/0022-510X(72)90068-8.

[81] H. Shibasaki, S. Tsuji, and Y. Kuroiwa, “Oculomotor Abnormalities in Parkinson’s Disease,” *Arch Neurol*, vol. 36, no. 6, pp. 360–364, Jun. 1979, doi: 10.1001/archneur.1979.00500420070009.

[82] M. Bernardinis, S. F. Atashzar, R. V. Patel, and M. S. Jog, “Abnormal Vision-Based Displacement Perception in Parkinson’s Disease,” *Front Neurosci*, vol. 15, Jul. 2021, doi: 10.3389/fnins.2021.676469.

[83] M. Bernardinis, S. F. Atashzar, M. Jog, and R. V. Patel, “Visual Displacement Perception in Parkinson’s Disease Analyzed Using a Computer-Generated Graphical Tool,” in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, 2018. doi: 10.1109/EMBC.2018.8512754.

[84] M. Bernardinis, S. F. Atashzar, M. S. Jog, and R. V. Patel, “Differential Temporal Perception Abilities in Parkinson’s Disease Patients Based on Timing Magnitude,” *Sci Rep*, vol. 9, no. 1, p. 19638, Dec. 2019, doi: 10.1038/s41598-019-55827-y.

[85] M. A. Hely, W. G. J. Reid, M. A. Adena, G. M. Halliday, and J. G. L. Morris, “The Sydney multicenter study of Parkinson’s disease: The inevitability of dementia at 20 years,” *Movement Disorders*, vol. 23, no. 6, pp. 837–844, Apr. 2008, doi: 10.1002/mds.21956.

[86] C. Harnois and T. di Paolo, “Decreased dopamine in the retinas of patients with Parkinson’s disease.,” *Invest Ophthalmol Vis Sci*, vol. 31, no. 11, pp. 2473–5, Nov. 1990.

[87] I. Bodis-Wollner, P. B. Kozlowski, S. Glazman, and S. Miri, “α-synuclein in the inner retina in parkinson disease,” *Ann Neurol*, vol. 75, no. 6, pp. 964–966, Jun. 2014, doi: 10.1002/ana.24182.

[88] T. G. Beach *et al.*, “Phosphorylated α-synuclein-immunoreactive retinal neuronal elements in Parkinson’s disease subjects,” *Neurosci Lett*, vol. 571, pp. 34–38, Jun. 2014, doi: 10.1016/j.neulet.2014.04.027.

[89] R. S. Weil, A. E. Schrag, J. D. Warren, S. J. Crutch, A. J. Lees, and H. R. Morris, “Visual dysfunction in Parkinson’s disease,” *Brain*, vol. 139, no. 11, pp. 2827–2843, Nov. 2016, doi: 10.1093/brain/aww175.

[90] J. Konczak, K. Y. Li, P. J. Tuite, and H. Poizner, “Haptic perception of object curvature in Parkinson’s disease,” *PLoS One*, 2008, doi: 10.1371/journal.pone.0002625.

[91] J. Konczak *et al.*, “Parkinson’s disease accelerates age-related decline in haptic perception by altering somatosensory integration,” *Brain*, vol. 135, no. 11, pp. 3371–3379, Nov. 2012, doi: 10.1093/brain/aws265.

[92] L. Mori *et al.*, “Haptic perception of verticality correlates with postural and balance deficits in patients with Parkinson’s disease,” *Parkinsonism Relat Disord*, vol. 66, pp. 45–50, Sep. 2019, doi: 10.1016/j.parkreldis.2019.06.026.

[93] R. L. Folmer, J. J. Vachhani, S. M. Theodoroff, R. Ellinger, and A. Riggins, “Auditory Processing Abilities of Parkinson’s Disease Patients,” *Biomed Res Int*, vol. 2017, pp. 1–10, 2017, doi: 10.1155/2017/2618587.

[94] J. P. Clark, S. G. Adams, A. D. Dykstra, S. Moodie, and M. Jog, “Loudness perception and speech intensity control in Parkinson’s disease,” *J Commun Disord*, vol. 51, pp. 1–12, Sep. 2014, doi: 10.1016/j.jcomdis.2014.08.001.

[95] N. Solari, A. Bonito-Oliva, G. Fisone, and R. Brambilla, “Understanding cognitive deficits in Parkinson’s disease: lessons from preclinical animal models,” *Learning & Memory*, vol. 20, no. 10, pp. 592–600, Oct. 2013, doi: 10.1101/lm.032029.113.

[96] R. F. Pfeiffer, “Non-motor symptoms in Parkinson’s disease,” *Parkinsonism Relat Disord*, vol. 22, pp. S119–S122, Jan. 2016, doi: 10.1016/j.parkreldis.2015.09.004.

[97] P. Rizek, N. Kumar, and M. S. Jog, “An update on the diagnosis and treatment of Parkinson disease,” *Can Med Assoc J*, vol. 188, no. 16, pp. 1157–1165, Nov. 2016, doi: 10.1503/cmaj.151179.

[98] I. Zahoor, A. Shafi, and E. Haq, “Pharmacological Treatment of Parkinson’s Disease,” in *Parkinson’s Disease: Pathogenesis and Clinical Aspects*, Codon Publications, 2018, pp. 129–144. doi: 10.15586/codonpublications.parkinsonsdisease.2018.ch7.

[99] B. S. Connolly and A. E. Lang, “Pharmacological Treatment of Parkinson Disease,” *JAMA*, vol. 311, no. 16, p. 1670, Apr. 2014, doi: 10.1001/jama.2014.3654.

[100] A. Ramirez-Zamora and E. Molho, “Treatment of motor fluctuations in Parkinson’s disease: recent developments and future directions,” *Expert Rev Neurother*, vol. 14, no. 1, pp. 93–103, Jan. 2014, doi: 10.1586/14737175.2014.868306.

[101] D. J. Brooks, “Dopamine agonists: their role in the treatment of Parkinson’s disease,” *J Neurol Neurosurg Psychiatry*, vol. 68, no. 6, pp. 685–689, Jun. 2000, doi: 10.1136/jnnp.68.6.685.

[102] P. O’Suilleabhain, J. Bullard, and R. B. Dewey, “Proprioception in Parkinson’s disease is acutely depressed by dopaminergic medications,” *J Neurol Neurosurg Psychiatry*, 2001, doi: 10.1136/jnnp.71.5.607.

[103] A. Steinke, F. Lange, C. Seer, M. K. Hendel, and B. Kopp, “Computational Modeling for Neuropsychological Assessment of Bradyphrenia in Parkinson’s Disease,” *J Clin Med*, vol. 9, no. 4, p. 1158, Apr. 2020, doi: 10.3390/jcm9041158.

[104] M. Poletti and U. Bonuccelli, “Acute and chronic cognitive effects of levodopa and dopamine agonists on patients with Parkinson’s disease: a review,” *Ther Adv Psychopharmacol*, vol. 3, no. 2, pp. 101–113, Apr. 2013, doi: 10.1177/2045125312470130.

[105] B. Hanna-Pladdy, R. Pahwa, and K. E. Lyons, “Paradoxical Effect of Dopamine Medication on Cognition in Parkinson’s Disease: Relationship to Side of Motor Onset,” *Journal of the International Neuropsychological Society*, vol. 21, no. 4, pp. 259–270, Apr. 2015, doi: 10.1017/S1355617715000181.

[106] W. C. Koller, R. Pahwa, K. E. Lyons, and A. Albanese, “Surgical treatment of Parkinson’s disease,” *J Neurol Sci*, vol. 167, no. 1, pp. 1–10, Aug. 1999, doi: 10.1016/S0022-510X(99)00139-2.

[107] K. T. Mitchell and J. L. Ostrem, “Surgical Treatment of Parkinson Disease,” *Neurol Clin*, vol. 38, no. 2, pp. 293–307, May 2020, doi: 10.1016/j.ncl.2020.01.001.

[108] P. J. Kelly and F. J. Gillingham, “The long-term results of stereotaxic surgery and L-dopa therapy in patients with Parkinson’s disease,” *J Neurosurg*, vol. 53, no. 3, pp. 332–337, Sep. 1980, doi: 10.3171/jns.1980.53.3.0332.

[109] B. L. Walter and J. L. Vitek, “Surgical treatment for Parkinson’s disease,” *Lancet Neurol*, vol. 3, no. 12, pp. 719–728, Dec. 2004, doi: 10.1016/S1474-4422(04)00934-2.

[110] J. Jankovic, M. Hallett, M. S. Okun, C. Comella, S. Fahn, and J. Goldman, “Surgical treatment of Parkinson disease and other movement disorders,” in *Principles and Practice of Movement Disorders*, Elsevier, 2021, pp. 204-233.e18. doi: 10.1016/B978-0-323-31071-0.00007-X.

[111] A. E. Lang, A. M. Lozano, E. Montgomery, J. Duff, R. Tasker, and W. Hutchinson, “Posteroventral Medial Pallidotomy in Advanced Parkinson’s Disease,” *New England Journal of Medicine*, vol. 337, no. 15, pp. 1036–1043, Oct. 1997, doi: 10.1056/NEJM199710093371503.

[112] J. M. Bronstein *et al.*, “Deep Brain Stimulation for Parkinson Disease,” *Arch Neurol*, vol. 68, no. 2, Feb. 2011, doi: 10.1001/archneurol.2010.260.

[113] A. L. Benabid, P. Pollak, A. Louveau, S. Henry, and J. de Rougemont, “Combined (Thalamotomy and Stimulation) Stereotactic Surgery of the VIM Thalamic Nucleus for Bilateral Parkinson Disease,” *Stereotact Funct Neurosurg*, vol. 50, no. 1–6, pp. 344–346, 1987, doi: 10.1159/000100803.

[114] W. Koller *et al.*, “High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor,” *Ann Neurol*, vol. 42, no. 3, pp. 292–299, Sep. 1997, doi: 10.1002/ana.410420304.

[115] K. A. Follett *et al.*, “Pallidal versus Subthalamic Deep-Brain Stimulation for Parkinson’s Disease,” *New England Journal of Medicine*, vol. 362, no. 22, pp. 2077–2091, Jun. 2010, doi: 10.1056/NEJMoa0907083.

[116] A. Williams *et al.*, “Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson’s disease (PD SURG trial): a randomised, open-label trial,” *Lancet Neurol*, vol. 9, no. 6, pp. 581–591, Jun. 2010, doi: 10.1016/S1474-4422(10)70093-4.

[117] V. J. Odekerken *et al.*, “Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson’s disease (NSTAPS study): a randomised controlled trial,” *Lancet Neurol*, vol. 12, no. 1, pp. 37–44, Jan. 2013, doi: 10.1016/S1474-4422(12)70264-8.

[118] A. P. Duker and A. J. Espay, “Surgical Treatment of Parkinson Disease: Past, present, and future,” *Neurol Clin*, vol. 31, no. 3, pp. 799–808, Aug. 2013, doi: 10.1016/j.ncl.2013.03.007.

[119] V. Rački *et al.*, “Cognitive Impact of Deep Brain Stimulation in Parkinson’s Disease Patients: A Systematic Review,” *Front Hum Neurosci*, vol. 16, May 2022, doi: 10.3389/fnhum.2022.867055.

[120] A. J. Fenoy and R. K. Simpson, “Risks of common complications in deep brain stimulation surgery: management and avoidance,” *J Neurosurg*, vol. 120, no. 1, pp. 132–139, Jan. 2014, doi: 10.3171/2013.10.JNS131225.

[121] K. S. Chen and R. Chen, “Invasive and Noninvasive Brain Stimulation in Parkinson’s Disease: Clinical Effects and Future Perspectives,” *Clin Pharmacol Ther*, vol. 106, no. 4, pp. 763–775, Oct. 2019, doi: 10.1002/cpt.1542.

[122] M. A. Banks and F. Caird, “Physiotherapy benefits patients with Parkinson’s disease,” *Clin Rehabil*, vol. 3, no. 1, pp. 11–16, Feb. 1989, doi: 10.1177/026921558900300102.
[123] A Nieuwboer, W De Weerdt, R Dom, M Truyen, L Janssens, and Y Kamsma, “The effect of a home physiotherapy program for persons with Parkinson’s disease,” *J Rehabil Med*, vol. 33, no. 6, pp. 266–272, Nov. 2001, doi: 10.1080/165019701753236455.
[124] T. A. Scandalis, A. Bosak, J. C. Berliner, L. L. Helman, and M. R. Wells, “Resistance Training and Gait Function in Patients with Parkinson’s Disease,” *Am J Phys Med Rehabil*, vol. 80, no. 1, pp. 38–43, Jan. 2001, doi: 10.1097/00002060-200101000-00011.
[125] M. Schenkman *et al.*, “Exercise to Improve Spinal Flexibility and Function for People with Parkinson’s Disease: A Randomized, Controlled Trial,” *J Am Geriatr Soc*, vol. 46, no. 10, pp. 1207–1216, Oct. 1998, doi: 10.1111/j.1532-5415.1998.tb04535.x.
[126] N. B. Herz, S. H. Mehta, K. D. Sethi, P. Jackson, P. Hall, and J. C. Morgan, “Nintendo Wii rehabilitation (‘Wii-hab’) provides benefits in Parkinson’s disease,” *Parkinsonism Relat Disord*, vol. 19, no. 11, pp. 1039–1042, Nov. 2013, doi: 10.1016/j.parkreldis.2013.07.014.
[127] S. Summa, A. Basteris, E. Betti, and V. Sanguineti, “Adaptive training with full-body movements to reduce bradykinesia in persons with Parkinson’s disease: a pilot study,” *J Neuroeng Rehabil*, vol. 12, no. 1, p. 16, 2015, doi: 10.1186/s12984-015-0009-5.
[128] C. Pazzaglia *et al.*, “Comparison of virtual reality rehabilitation and conventional rehabilitation in Parkinson’s disease: a randomised controlled trial,” *Physiotherapy*, vol. 106, pp. 36–42, Mar. 2020, doi: 10.1016/j.physio.2019.12.007.
[129] K. Tanaka, A. C. de Quadros, R. F. Santos, F. Stella, L. T. B. Gobbi, and S. Gobbi, “Benefits of physical exercise on executive functions in older people with Parkinson’s disease,” *Brain Cogn*, vol. 69, no. 2, pp. 435–441, Mar. 2009, doi: 10.1016/j.bandc.2008.09.008.
[130] Sinforiani E, Banchieri L, Zucchella C, Pacchetti C, and Sandrini G, “Cognitive rehabilitation in Parkinson’s disease,” *Arch Gerontol Geriatr*, vol. 38, pp. 387–391, Jan. 2004, doi: 10.1016/j.archger.2004.04.049.
[131] R. Biundo, L. Weis, E. Fiorenzato, and A. Antonini, “Cognitive Rehabilitation in Parkinson’s Disease: Is it Feasible?,” *Archives of Clinical Neuropsychology*, vol. 32, no. 7, pp. 840–860, Nov. 2017, doi: 10.1093/arclin/acx092.
[132] M. Díez-Cirarda, N. Ibarretxe-Bilbao, J. Peña, and N. Ojeda, “Neurorehabilitation in Parkinson’s Disease: A Critical Review of Cognitive Rehabilitation Effects on Cognition and Brain,” *Neural Plast*, vol. 2018, pp. 1–12, 2018, doi: 10.1155/2018/2651918.
[133] A. Bogosian, L. Rixon, and C. S. Hurt, “Prioritising target non-pharmacological interventions for research in Parkinson’s disease: achieving consensus from key stakeholders,” *Res Involv Engagem*, vol. 6, no. 1, p. 35, Dec. 2020, doi: 10.1186/s40900-020-00212-7.
[134] G. Abbruzzese, R. Marchese, L. Avanzino, and E. Pelosin, “Rehabilitation for Parkinson’s disease: Current outlook and future challenges,” *Parkinsonism Relat Disord*, 2016, doi: 10.1016/j.parkreldis.2015.09.005.
[135] R. Marchese, M. Diverio, F. Zucchi, C. Lentino, and G. Abbruzzese, “The role of sensory cues in the rehabilitation of parkinsonian patients: A comparison of two physical therapy protocols,” *Movement Disorders*, vol. 15, no. 5, pp. 879–883, Sep. 2000, doi: 10.1002/1531-8257(200009)15:5<879::AID-MDS1018>3.0.CO;2-9.

[136] A. Nieuwboer *et al.*, “Cueing training in the home improves gait-related mobility in Parkinson’s disease: the RESCUE trial,” *J Neurol Neurosurg Psychiatry*, vol. 78, no. 2, pp. 134–140, Feb. 2007, doi: 10.1136/jnnp.200X.097923.
[137] Katherine Baker, Lynn Rochester, and Alice Nieuwboer, “The effect of cues on gait variability—Reducing the attentional cost of walking in people with Parkinson’s disease,” *Parkinsonism Relat Disord*, vol. 14, no. 4, pp. 314–320, May 2008, doi: 10.1016/j.parkreldis.2007.09.008.
[138] S. Vercruysse *et al.*, “Abnormalities and Cue Dependence of Rhythmical Upper-Limb Movements in Parkinson Patients With Freezing of Gait,” *Neurorehabil Neural Repair*, vol. 26, no. 6, pp. 636–645, Jul. 2012, doi: 10.1177/1545968311431964.
[139] E. Heremans *et al.*, “External Cueing Improves Motor Imagery Quality in Patients With Parkinson Disease,” *Neurorehabil Neural Repair*, vol. 26, no. 1, pp. 27–35, Jan. 2012, doi: 10.1177/1545968311411055.
[140] A. Nieuwboer, L. Rochester, L. Müncks, and S. P. Swinnen, “Motor learning in Parkinson’s disease: limitations and potential for rehabilitation,” *Parkinsonism Relat Disord*, vol. 15, pp. S53–S58, Dec. 2009, doi: 10.1016/S1353-8020(09)70781-3.
[141] G. Sharpe, A. Macerollo, M. Fabbri, and E. Tripoliti, “Non-pharmacological Treatment Challenges in Early Parkinson’s Disease for Axial and Cognitive Symptoms: A Mini Review,” *Front Neurol*, vol. 11, Sep. 2020, doi: 10.3389/fneur.2020.576569.
[142] F. A. dos S. Mendes *et al.*, “Motor learning, retention and transfer after virtual-reality-based training in Parkinson’s disease – effect of motor and cognitive demands of games: a longitudinal, controlled clinical study,” *Physiotherapy*, vol. 98, no. 3, pp. 217–223, Sep. 2012, doi: 10.1016/j.physio.2012.06.001.
[143] A. A. Kehagia, R. A. Barker, and T. W. Robbins, “Cognitive Impairment in Parkinson’s Disease: The Dual Syndrome Hypothesis,” *Neurodegener Dis*, vol. 11, no. 2, pp. 79–92, 2013, doi: 10.1159/000341998.
[144] M. S. Okun, “Management of Parkinson Disease in 2017,” *JAMA*, vol. 318, no. 9, p. 791, Sep. 2017, doi: 10.1001/jama.2017.7914.
[145] N. L. Diaz and C. H. Waters, “Current strategies in the treatment of Parkinson’s disease and a personalized approach to management,” *Expert Rev Neurother*, vol. 9, no. 12, pp. 1781–1789, Dec. 2009, doi: 10.1586/ern.09.117.
[146] G. Abbruzzese, R. Marchese, L. Avanzino, and E. Pelosin, “Rehabilitation for Parkinson’s disease: Current outlook and future challenges,” *Parkinsonism Relat Disord*, vol. 22, pp. S60–S64, Jan. 2016, doi: 10.1016/J.PARKRELDIS.2015.09.005.
[147] P. C. Poortvliet, K. O’Maley, P. A. Silburn, and G. D. Mellick, “Perspective: Current Pitfalls in the Search for Future Treatments and Prevention of Parkinson’s Disease,” *Front Neurol*, vol. 11, Jul. 2020, doi: 10.3389/fneur.2020.00686.
[148] M. Flanders, “What is the biological basis of sensorimotor integration?,” *Biol Cybern*, vol. 104, no. 1–2, pp. 1–8, Feb. 2011, doi: 10.1007/s00422-011-0419-9.
[149] S. Sangani, A. Lamontagne, and J. Fung, “Chapter 15 - Cortical mechanisms underlying sensorimotor enhancement promoted by walking with haptic inputs in a virtual environment,” in *Sensorimotor Rehabilitation*, in Progress in Brain Research, vol. 218. Elsevier, 2015, pp. 313–330. doi: https://doi.org/10.1016/bs.pbr.2014.12.003.
[150] M. O. Ernst and H. H. Bülthoff, “Merging the senses into a robust percept,” *Trends Cogn Sci*, vol. 8, no. 4, pp. 162–169, Apr. 2004, doi: 10.1016/j.tics.2004.02.002.
[151] B. E. Stein and M. A. Meredith, *The Merging of the Senses*. MIT Press, 1993.

[152] V. Gaveau *et al.*, “Automatic online control of motor adjustments in reaching and grasping,” *Neuropsychologia*, vol. 55, pp. 25–40, Mar. 2014, doi: 10.1016/j.neuropsychologia.2013.12.005.
[153] R. Shadmehr, M. A. Smith, and J. W. Krakauer, “Error Correction, Sensory Prediction, and Adaptation in Motor Control,” *Annu Rev Neurosci*, vol. 33, no. 1, pp. 89–108, Jun. 2010, doi: 10.1146/annurev-neuro-060909-153135.
[154] D. W. Franklin and D. M. Wolpert, “Computational Mechanisms of Sensorimotor Control,” *Neuron*, vol. 72, no. 3, pp. 425–442, Nov. 2011, doi: 10.1016/j.neuron.2011.10.006.
[155] S. H. Creem-Regehr, “Sensory-motor and cognitive functions of the human posterior parietal cortex involved in manual actions,” *Neurobiol Learn Mem*, 2009, doi: 10.1016/j.nlm.2008.10.004.
[156] B. L. Riemann and S. M. Lephart, “The sensorimotor system, part I: The physiologic basis of functional joint stability,” *J Athl Train*, 2002.
[157] S. E. D. C. Machado *et al.*, “Sensorimotor integration: Basic concepts, abnormalities related to movement disorders and sensorimotor training-induced cortical reorganization,” *Revista de Neurologia*. 2010. doi: 10.33588/rn.5107.2010228.
[158] O. Ciccarelli *et al.*, “Identifying brain regions for integrative sensorimotor processing with ankle movements,” *Exp Brain Res*, 2005, doi: 10.1007/s00221-005-2335-5.
[159] O. Baumann *et al.*, “Consensus Paper: The Role of the Cerebellum in Perceptual Processes,” *Cerebellum*, 2015, doi: 10.1007/s12311-014-0627-7.
[160] M. H. Monfils, E. J. Plautz, and J. A. Kleim, “In search of the motor engram: Motor map plasticity as a mechanism for encoding motor experience,” *Neuroscientist*. 2005. doi: 10.1177/1073858405278015.
[161] K. Sakai, O. Hikosaka, R. Takino, S. Miyauchi, M. Nielsen, and T. Tamada, “What and when: Parallel and convergent processing in motor control,” *Journal of Neuroscience*, 2000, doi: 10.1523/jneurosci.20-07-02691.2000.
[162] Q. J. Almeida *et al.*, “An evaluation of sensorimotor integration during locomotion toward a target in Parkinson’s disease,” *Neuroscience*, 2005, doi: 10.1016/j.neuroscience.2005.02.050.
[163] A. Nagy, G. Eördegh, Z. Paróczy, Z. Márkus, and G. Benedek, “Multisensory integration in the basal ganglia,” *European Journal of Neuroscience*, 2006, doi: 10.1111/j.1460-9568.2006.04942.x.
[164] M. A. Jabri, J. Huang, O. J. D. Coenen, and T. J. Sejnowski, “Models of basal ganglia and cerebellum for sensorimotor integration and predictive control,” *Sensor Fusion and Decentralized Control in Robotic Systems III*, vol. 4196, no. October 2000, pp. 125–137, 2000, doi: 10.1117/12.403711.
[165] M. O. Ernst, J.-P. Bresciani, K. Drewing, and H. H. Bülthoff, “Integration of Sensory Information Within Touch and Across Modalities,” *Proceedings of the 2004 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS 2004)*, 2004.
[166] M. O. Ernst and M. S. Banks, “Humans integrate visual and haptic information in a statistically optimal fashion,” *Nature*, 2002, doi: 10.1038/415429a.
[167] S. Deneve and A. Pouget, “Bayesian multisensory integration and cross-modal spatial links,” *J Physiol Paris*, 2004, doi: 10.1016/j.jphysparis.2004.03.011.
[168] D. R. Wozny, U. R. Beierholm, and L. Shams, “Probability matching as a computational strategy used in perception,” *PLoS Comput Biol*, 2010, doi: 10.1371/journal.pcbi.1000871.

[169] K. P. Körding, U. Beierholm, W. J. Ma, S. Quartz, J. B. Tenenbaum, and L. Shams, "Causal inference in multisensory perception," *PLoS One*, 2007, doi: 10.1371/journal.pone.0000943.
[170] M. Alex Meredith and B. E. Stein, "Spatial factors determine the activity of multisensory neurons in cat superior colliculus," *Brain Res*, 1986, doi: 10.1016/0006-8993(86)91648-3.
[171] M. A. Meredith, J. W. Nemitz, and B. E. Stein, "Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors.," *J Neurosci*, 1987, doi: 10.1523/jneurosci.07-10-03215.1987.
[172] R. B. Welch, L. D. DutionHurt, and D. H. Warren, "Contributions of audition and vision to temporal rate perception," *Percept Psychophys*, 1986, doi: 10.3758/BF03204939.
[173] R. B. Welch and D. H. Warren, "Immediate perceptual response to intersensory discrepancy," *Psychol Bull*, 1980, doi: 10.1037/0033-2909.88.3.638.
[174] M. Maschke, C. M. Gomez, P. J. Tuite, and J. Konczak, "Dysfunction of the basal ganglia, but not the cerebellum, impairs kinaesthesia," *Brain*, 2003, doi: 10.1093/brain/awg230.
[175] N. Putzki, P. Stude, J. Konczak, K. Graf, H. C. Diener, and M. Maschke, "Kinethesia is impaired in focal dystonia," *Movement Disorders*, 2006, doi: 10.1002/mds.20799.
[176] M. Fiorio *et al.*, "Defective temporal discrimination of passive movements in Parkinson's disease," *Neurosci Lett*, 2007, doi: 10.1016/j.neulet.2007.02.050.
[177] M. Demirci, S. Grill, L. McShane, and M. Hallett, "A mismatch between kinesthetic and visual perception in Parkinson's disease," *Ann Neurol*, vol. 41, no. 6, pp. 781–788, Jun. 1997, doi: 10.1002/ana.410410614.
[178] M. Maschke, P. J. Tuite, K. Krawczewski, K. Pickett, and J. Konczak, "Perception of heaviness in Parkinson's disease," *Movement Disorders*, 2006, doi: 10.1002/mds.20876.
[179] M. Maschke, C. M. Gomez, P. J. Tuite, K. Pickett, and J. Konczak, "Depth perception in cerebellar and basal ganglia disease," *Exp Brain Res*, 2006, doi: 10.1007/s00221-006-0535-2.
[180] E. Y. Uc, M. Rizzo, S. W. Anderson, S. Qian, R. L. Rodnitzky, and J. D. Dawson, "Visual dysfunction in Parkinson disease without dementia," *Neurology*, 2005, doi: 10.1212/01.wnl.0000191565.11065.11.
[181] C. Bulens, J. D. Meerwaldt, G. J. van der Wildt, and C. J. Keemink, "Contrast sensitivity in Parkinson's disease," *Neurology*, 1986, doi: 10.1212/wnl.36.8.1121.
[182] S. Adams, O. Haralabous, A. Page, K. Abrams, and M. Jog, "Effects of multi-talker background noise on the intensity of spoken in Parkinson's disease," *Can Acoust*, vol. 33, pp. 94–95, Aug. 2005.
[183] Z. Jafari, B. E. Kolb, and M. H. Mohajerani, "Auditory Dysfunction in Parkinson's Disease," *Movement Disorders*, vol. 35, no. 4, pp. 537–550, Apr. 2020, doi: 10.1002/mds.28000.
[184] G. Abbruzzese and A. Berardelli, "Sensorimotor integration in movement disorders," *Movement Disorders*. 2003. doi: 10.1002/mds.10327.
[185] R. Dubbioso, F. Manganelli, H. R. Siebner, and V. di Lazzaro, "Fast Intracortical Sensory-Motor Integration: A Window Into the Pathophysiology of Parkinson's Disease," *Front Hum Neurosci*, vol. 13, Apr. 2019, doi: 10.3389/fnhum.2019.00111.
[186] M. L. T. M. Müller *et al.*, "Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease," *Brain*, vol. 136, no. 11, pp. 3282–3289, Nov. 2013, doi: 10.1093/brain/awt247.

[187] J. P. Azulay, S. Mesure, B. Amblard, and J. Pouget, “Increased Visual Dependence in Parkinson’s Disease,” *Percept Mot Skills*, vol. 95, no. 3_suppl, pp. 1106–1114, Dec. 2002, doi: 10.2466/pms.2002.95.3f.1106.

[188] L. A. Brown *et al.*, “Parkinsonian deficits in sensory integration for postural control: Temporal response to changes in visual input,” *Parkinsonism Relat Disord*, vol. 12, no. 6, pp. 376–381, Sep. 2006, doi: 10.1016/j.parkreldis.2006.03.004.

[189] G. N. Lewis, “Altered sensorimotor integration in Parkinson’s disease,” *Brain*, vol. 125, no. 9, pp. 2089–2099, Sep. 2002, doi: 10.1093/brain/awf200.

[190] B. Müller, J. P. Larsen, T. Wentzel-Larsen, G. O. Skeie, and O.-B. Tysnes, “Autonomic and sensory symptoms and signs in incident, untreated Parkinson’s disease: Frequent but mild,” *Movement Disorders*, vol. 26, no. 1, pp. 65–72, Jan. 2011, doi: 10.1002/mds.23387.

[191] N. Patel, J. Jankovic, and M. Hallett, “Sensory aspects of movement disorders,” *The Lancet Neurology*. 2014. doi: 10.1016/S1474-4422(13)70213-8.

[192] T. Platz, R. G. Brown, and C. D. Marsden, “Training improves the speed of aimed movements in Parkinson’s disease.,” *Brain*, vol. 121 (Pt 3), pp. 505–14, Mar. 1998, doi: 10.1093/brain/121.3.505.

[193] Y. Broche-Pérez, L. F. Herrera Jiménez, and E. Omar-Martínez, “Neural substrates of decision-making,” *Neurologia*, 2016, doi: 10.1016/j.nrl.2015.03.001.

[194] H. G. Yeom, J. S. Kim, and C. K. Chung, “Brain mechanisms in motor control during reaching movements: Transition of functional connectivity according to movement states,” *Sci Rep*, 2020, doi: 10.1038/s41598-020-57489-7.

[195] R. Cunnington, C. Windischberger, L. Deecke, and E. Moser, “The preparation and execution of self-initiated and externally-triggered movement: A study of event-related fMRI,” *Neuroimage*, 2002, doi: 10.1006/nimg.2001.0976.

[196] R. Cunnington, C. Windischberger, L. Deecke, and E. Moser, “The preparation and readiness for voluntary movement: A high-field event-related fMRI study of the Bereitschafts-BOLD response,” *Neuroimage*, 2003, doi: 10.1016/S1053-8119(03)00291-X.

[197] R. E. Passingham, “Functional specialization of the supplementary motor area in monkeys and humans.,” *Advances in neurology*. 1996.

[198] S. Kakei, D. S. Hoffman, and P. L. Strick, “Muscle and movement representations in the primary motor cortex,” *Science (1979)*, 1999, doi: 10.1126/science.285.5436.2136.

[199] D. Farina, M. Fosci, and R. Merletti, “Motor unit recruitment strategies investigated by surface EMG variables,” *J Appl Physiol*, vol. 92, no. 1, pp. 235–247, Jan. 2002, doi: 10.1152/jappl.2002.92.1.235.

[200] O. Monchi, M. Petrides, A. P. Strafella, K. J. Worsley, and J. Doyon, “Functional role of the basal ganglia in the planning and execution of actions,” *Ann Neurol*, vol. 59, no. 2, pp. 257–264, Feb. 2006, doi: 10.1002/ana.20742.

[201] V. Menon, R. T. Anagnoson, G. H. Glover, and A. Pfefferbaum, “Basal ganglia involvement in memory-guided movement sequencing,” *Neuroreport*, vol. 11, no. 16, pp. 3641–3645, Nov. 2000, doi: 10.1097/00001756-200011090-00048.

[202] M. A. Farries, L. Ding, and D. J. Perkel, “Evidence for ‘direct’ and ‘indirect’ pathways through the song system basal ganglia,” *Journal of Comparative Neurology*, 2005, doi: 10.1002/cne.20464.

[203] K. Doya, “Complementary roles of basal ganglia and cerebellum in learning and motor control,” *Current Opinion in Neurobiology*. 2000. doi: 10.1016/S0959-4388(00)00153-7.

[204] H. Mushiake and P. L. Strick, “Pallidal neuron activity during sequential arm movements,” *J Neurophysiol*, 1995, doi: 10.1152/jn.1995.74.6.2754.
[205] R. S. Turner and M. Desmurget, “Basal ganglia contributions to motor control: A vigorous tutor,” *Current Opinion in Neurobiology*. 2010. doi: 10.1016/j.conb.2010.08.022.
[206] P. Redgrave, T. J. Prescott, and K. Gurney, “The basal ganglia: A vertebrate solution to the selection problem?,” *Neuroscience*. 1999. doi: 10.1016/S0306-4522(98)00319-4.
[207] J. C. Houk *et al.*, “Action selection and refinement in subcortical loops through basal ganglia and cerebellum,” *Philosophical Transactions of the Royal Society B: Biological Sciences*, 2007, doi: 10.1098/rstb.2007.2063.
[208] P. Romanelli, V. Esposito, D. W. Schaal, and G. Heit, “Somatotopy in the basal ganglia: Experimental and clinical evidence for segregated sensorimotor channels,” *Brain Research Reviews*. 2005. doi: 10.1016/j.brainresrev.2004.09.008.
[209] R. Shadmehr and J. W. Krakauer, “A computational neuroanatomy for motor control,” *Exp Brain Res*, vol. 185, no. 3, pp. 359–381, 2008, doi: 10.1007/s00221-008-1280-5.
[210] K. Gurney, T. J. Prescott, and P. Redgrave, “A computational model of action selection in the basal ganglia. I. A new functional anatomy,” *Biol Cybern*, 2001, doi: 10.1007/PL00007984.
[211] V. S. Chakravarthy, D. Joseph, and R. S. Bapi, “What do the basal ganglia do? A modeling perspective,” *Biol Cybern*, vol. 103, no. 3, pp. 237–253, Sep. 2010, doi: 10.1007/s00422-010-0401-y.
[212] F. C. Anderson and M. G. Pandy, “Dynamic optimization of human walking,” *J Biomech Eng*, 2001, doi: 10.1115/1.1392310.
[213] T. Flash and N. Hogan, “The coordination of arm movements: An experimentally confirmed mathematical model,” *Journal of Neuroscience*, 1985, doi: 10.1523/jneurosci.05-07-01688.1985.
[214] N. Hogan, “An organizing principle for a class of voluntary movements,” *Journal of Neuroscience*, 1984, doi: 10.1523/jneurosci.04-11-02745.1984.
[215] E. Nakano *et al.*, “Quantitative examinations of internal representations for arm trajectory planning: Minimum commanded torque change model,” *J Neurophysiol*, 1999, doi: 10.1152/jn.1999.81.5.2140.
[216] C. M. Harris and D. M. Wolpert, “Signal-dependent noise determines motor planning,” *Nature*, 1998, doi: 10.1038/29528.
[217] M. R. Harwood, L. E. Mezey, and C. M. Harris, “The spectral main sequence of human saccades,” *Journal of Neuroscience*, 1999, doi: 10.1523/jneurosci.19-20-09098.1999.
[218] P. M. Fitts, “The information capacity of the human motor system in controlling the amplitude of movement.,” *J Exp Psychol Gen*, vol. 121, no. 3, pp. 262–269, 1992, doi: 10.1037/0096-3445.121.3.262.
[219] R. Bogacz, E.-J. Wagenmakers, B. U. Forstmann, and S. Nieuwenhuis, “The neural basis of the speed–accuracy tradeoff,” *Trends Neurosci*, vol. 33, no. 1, pp. 10–16, Jan. 2010, doi: 10.1016/j.tins.2009.09.002.
[220] A. F. de C. Hamilton and D. M. Wolpert, “Controlling the Statistics of Action: Obstacle Avoidance,” *J Neurophysiol*, vol. 87, no. 5, pp. 2434–2440, May 2002, doi: 10.1152/jn.2002.87.5.2434.
[221] E. Todorov, “Optimality principles in sensorimotor control,” *Nature Neuroscience*. 2004. doi: 10.1038/nn1309.

[222] E. Todorov and M. I. Jordan, “Optimal feedback control as a theory of motor coordination,” *Nat Neurosci*, 2002, doi: 10.1038/nn963.
[223] J. P. Gallivan, C. S. Chapman, D. M. Wolpert, and J. R. Flanagan, “Decision-making in sensorimotor control,” *Nature Reviews Neuroscience*. 2018. doi: 10.1038/s41583-018-0045-9.
[224] M. Desmurget and S. Grafton, “Forward modeling allows feedback control for fast reaching movements,” *Trends in Cognitive Sciences*. 2000. doi: 10.1016/S1364-6613(00)01537-0.
[225] D. M. Wolpert and J. R. Flanagan, “Motor prediction.,” *Current biology : CB*. 2001. doi: 10.1016/s0960-9822(01)00432-8.
[226] M. Haruno, D. M. Wolpert, and M. Kawato, “MOSAIC Model for Sensorimotor Learning and Control,” *Neural Comput*, 2001, doi: 10.1162/089976601750541778.
[227] D. M. Wolpert, Z. Ghahramani, and M. I. Jordan, “An internal model for sensorimotor integration,” *Science (1979)*, 1995, doi: 10.1126/science.7569931.
[228] L. P. J. Selen, D. W. Franklin, and D. M. Wolpert, “Impedance control reduces instability that arises from motor noise,” *Journal of Neuroscience*, 2009, doi: 10.1523/JNEUROSCI.2826-09.2009.
[229] E. Burdet, R. Osu, D. W. Franklin, T. E. Milner, and M. Kawato, “The central nervous system stabilizes unstable dynamics by learning optimal impedance,” *Nature*, 2001, doi: 10.1038/35106566.
[230] A. Kadiallah, G. Liaw, E. Burdet, M. Kawato, and D. W. Franklin, “Impedance control is tuned to multiple directions of movement,” in *Proceedings of the 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS’08 - “Personalized Healthcare through Technology,”* 2008. doi: 10.1109/iembs.2008.4650425.
[231] L. J. Holmberg and A. Klarbring, “Muscle decomposition and recruitment criteria influence muscle force estimates,” *Multibody Syst Dyn*, vol. 28, no. 3, pp. 283–289, Sep. 2012, doi: 10.1007/s11044-011-9277-4.
[232] F. Michaud, M. Lamas, U. Lugrís, and J. Cuadrado, “A fair and EMG-validated comparison of recruitment criteria, musculotendon models and muscle coordination strategies, for the inverse-dynamics based optimization of muscle forces during gait,” *J Neuroeng Rehabil*, vol. 18, no. 1, p. 17, Dec. 2021, doi: 10.1186/s12984-021-00806-6.
[233] J. Rasmussen, M. Damsgaard, and M. Voigt, “Muscle recruitment by the min/max criterion - A comparative numerical study,” *J Biomech*, vol. 34, no. 3, pp. 409–415, 2001, doi: 10.1016/S0021-9290(00)00191-3.
[234] J. S. Schneider, S. Sendek, and C. Yang, “Relationship between motor symptoms, cognition, and demographic characteristics in treated mild/moderate Parkinson’s disease,” *PLoS One*, 2015, doi: 10.1371/journal.pone.0123231.
[235] D. Orcioli-Silva, R. Vitório, E. Lirani-Silva, P. C. R. Santos, V. S. Beretta, and L. T. B. Gobbi, “Objective measures of unobstructed walking and obstacle avoidance in Parkinson’s disease subtypes,” *Gait Posture*, 2018, doi: 10.1016/j.gaitpost.2018.03.046.
[236] C. Lu, E. Twedell, R. Elbasher, M. McCabe, C. D. MacKinnon, and S. E. Cooper, “Avoiding virtual obstacles during treadmill gait in Parkinson’s disease,” *Front Aging Neurosci*, 2019, doi: 10.3389/fnagi.2019.00076.

[237] M. Gentilucci and A. Negrotti, “Planning and executing an action in Parkinson’s disease,” *Movement Disorders*, 1999, doi: 10.1002/1531-8257(199901)14:1<69::AID-MDS1013>3.0.CO;2-M.

[238] B. C. Leis, M. K. Rand, A. W. A. van Gemmert, M. G. Longstaff, J. S. Lou, and G. E. Stelmach, “Movement precues in planning and execution of aiming movements in Parkinson’s disease,” *Exp Neurol*, 2005, doi: 10.1016/j.expneurol.2005.02.014.

[239] M. K. Y. Mak and C. W. Y. Hui-Chan, “Switching of movement direction is central to Parkinsonian bradykinesia in sit-to-stand,” *Movement Disorders*. 2002. doi: 10.1002/mds.10257.

[240] M. Desmurget, V. Gaveau, P. Vindras, R. S. Turner, E. Broussolle, and S. Thobois, “On-line motor control in patients with Parkinson’s disease,” *Brain*, 2004, doi: 10.1093/brain/awh206.

[241] D. Ferrazzoli, P. Ortelli, G. Madeo, N. Giladi, G. M. Petzinger, and G. Frazzitta, “Basal ganglia and beyond: The interplay between motor and cognitive aspects in Parkinson’s disease rehabilitation,” *Neurosci Biobehav Rev*, vol. 90, pp. 294–308, Jul. 2018, doi: 10.1016/j.neubiorev.2018.05.007.

[242] J. Koerts, L. Tucha, K. L. Leenders, M. van Beilen, W. H. Brouwer, and O. Tucha, “Subjective and objective assessment of executive functions in Parkinson’s disease,” *J Neurol Sci*, vol. 310, no. 1–2, pp. 172–175, Nov. 2011, doi: 10.1016/j.jns.2011.07.009.

[243] F. L. Pagan, “Improving outcomes through early diagnosis of Parkinson’s disease.,” *Am J Manag Care*, vol. 18, no. 7 Suppl, pp. S176-82, Sep. 2012.

[244] A. Conte, N. Khan, G. Defazio, J. C. Rothwell, and A. Berardelli, “Pathophysiology of somatosensory abnormalities in Parkinson disease,” *Nat Rev Neurol*, vol. 9, no. 12, pp. 687–697, Dec. 2013, doi: 10.1038/nrneurol.2013.224.

[245] S. O. Mittal, D. Machado, D. Richardson, D. Dubey, and B. Jabbari, “Botulinum Toxin in Parkinson Disease Tremor: A Randomized, Double-Blind, Placebo-Controlled Study With a Customized Injection Approach,” *Mayo Clin Proc*, 2017, doi: 10.1016/j.mayocp.2017.06.010.

[246] O. Samotus, J. Lee, and M. Jog, “Personalized Bilateral Upper Limb Essential Tremor Therapy with Botulinum Toxin Using Kinematics,” *Toxins (Basel)*, vol. 11, no. 2, p. 125, Feb. 2019, doi: 10.3390/toxins11020125.

Chapter 2

2 Materials and Methods

2.1 Design and Development of Robot-Based Tasks to Quantify Impairments due to Parkinson's Disease

The primary objective of the thesis is to quantify the SMI and SMC impairments presented due to PD, affecting the patient's ability to perform task-specific voluntary movements. To examine these impairments, we need:

1. Precise equipment that can accurately capture the upper-limb kinematic parameters of the participants when performing a task and also provide real-time multi-modal sensory feedback.
2. There is also a need to determine and design tasks suitable to assess the SMI and SMC performance of PD patients.
3. Since SMI and SMC broadly include the functioning of multiple domains, including motor, sensory and cognitive structures, the testing environment and sensory feedback should be varied so that the participants are assessed under differing motor, sensory and cognitive demands and conditions.
4. Finally, there is a need to design metrics or features that can be used to objectively evaluate the SMI and SMC performance.

This section discusses the methodology used to quantify the SMI and SMC impairments presented due to PD.

2.1.1 KINARM Endpoint Robot

With current technological advancements, robotic devices are the preferred option to develop a flexible virtual testing environment to accurately assess motor, sensory, and executive functions. Kinesiological Instruments for Normal and Altered Reaching Movement (KINARM) End-Point robot [1][2] is a robotic device that offers an interactive environment using a graspable robotic manipulandum coupled with a virtual reality display. KINARM end-point robot (BKIN Technologies Ltd, Kingston, ON, Canada) was used to assess the SMI and SMC impairments in PD patients. The robot includes two

primary components (i) a graspable robotic manipulandum and (ii) a 2-dimensional Virtual Reality (VR) display that is placed above the robotic manipulandum.

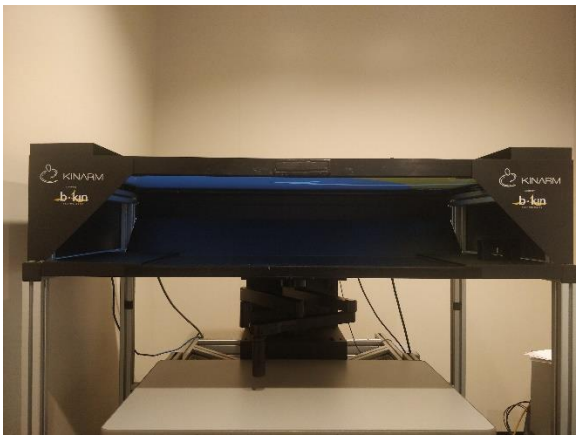


Figure 2.1: KINARM End-point robot comprising a robot handle and a virtual reality display

The VR display shows the virtual objects and the real-time fingertip position (as a white cursor or dot) of the participants when they held the robotic manipulandum. The participants can grasp the robotic manipulandum and interact with any virtual objects shown on the display by generating a planar movement and controlling the white cursor in real-time. Figures 2.1 and 2.2 show the image of the KINARM end-point robot. Through its flexible and programmable environment, several custom tasks with multi-modal sensory feedback and varying cognitive demands were designed and developed using MATLAB/Simulink (MathWorks, Inc.) [3] and Dexterit-E (BKIN Technologies, Ltd.) to investigate various aspects of SMI and SMC functions. The following sections provide a more comprehensive overview of the tasks designed for the robotic assessment and the corresponding sensory feedback and cognitive demands for each task. The primary outcome measure of the robotic assessment is the upper-limb kinematic and force data of the participants, which is collected by the real-time data acquisition system at 1kHz. The acquired kinematic and force data are used to extract multiple features for assessing the upper-limb motor control and higher-order functions, including executive and sensory performance. A list of features extracted as the performance metrics for each task is discussed in the later sections.

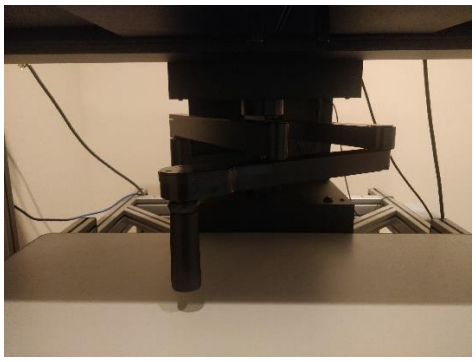


Figure 2.2: Robot handle

2.1.2 Experimental Setup

The participants (PD patients and Healthy controls) were seated in a deluxe chair with no armrest and positioned in front of the robot with their foreheads in the center of the visual field. The height of the chair was adjusted to ensure that the participants had a clear view of the entire VR display and also ensured that the robot manipulandum was in parallel to the subject's waist level. A black screen was placed between the VR display and the participant's arm to prevent the participants from seeing their arm when performing the robotic tasks. Figure 2.3 shows how the black screen was used to block the view of the participant's arm.

(a) **(b)**

Figure 2.3: Virtual reality display

Note: (a) The Virtual-Reality Display without using the Black Screen; The virtual reality display is transparent, as shown in the figure, and without the black screen, the participant

can see their arm. The black screen was pulled in to block the view of the participant's arm during the experiment. (b) The Virtual-Reality Display with the black screen; the black screen ensures that only the virtual objects are visible to the participant.

2.1.3 Task Design

In this study, tasks were designed and developed for the robotic device to investigate SMI and SMC performance of PD patients. The development of the tasks was done using MATLAB, Simulink and Stateflow. Figure 2.4 briefly outlines the tasks designed to evaluate SMI and SMC functions.

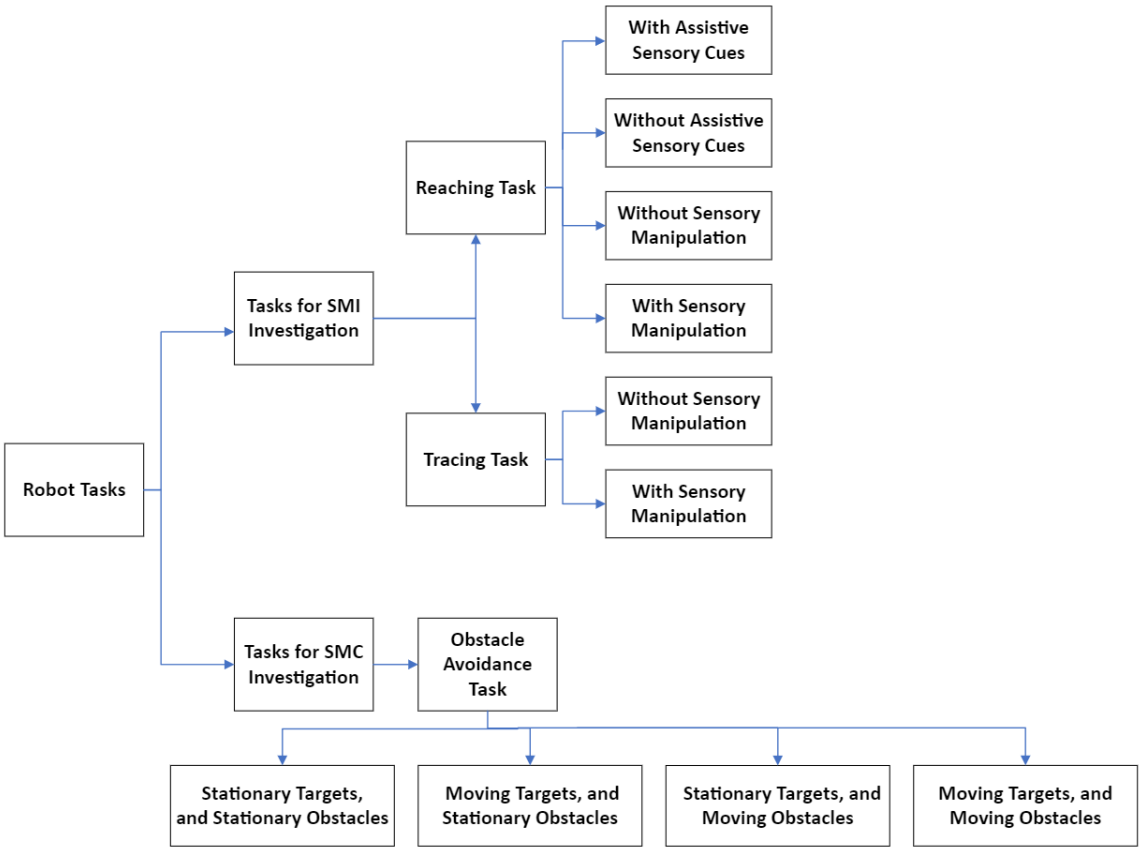


Figure 2.4: Robot tasks for SMI and SMC investigation

2.1.4 Task Protocol for Investigating Sensorimotor Integration

Tasks designed to investigate SMI functions in the participants are discussed in this section. The sensory conditions are varied in each task to understand how the task performance of the participants varies with differing sensory conditions. Variation in the sensory

conditions includes tasks with and without assistive multi-modal sensory feedback and tasks with and without sensory manipulation or disturbance. Multi-modal assistive feedback was provided to understand if the participants were able to integrate inputs from multiple modalities optimally and interpret the integrated sensory estimate accurately to improve their task performance. The inclusion of sensory manipulation was aimed at understanding if the participants could adapt to sensory disturbance or inaccuracies. Adapting to sensory manipulation requires optimal SMI functions to differentiate between accurate and inaccurate sensory feedback, and accordingly determine a strategy to optimally integrate sensory inputs and appropriately adjust their motor outputs to ensure that the task performance is not affected due to inaccurate sensory feedback. The participants were evaluated independently in each sensory condition to investigate and quantify any deficits associated with sensory integration and processing in PD patients.

2.1.4.1 Reaching Task

Performing a reaching movement is considered one of the fundamental features of human competence [4]. Optimal multisensory integration is necessary for accurately planning and executing reaching movements [5][6][7]. Earlier literature [8] has also discussed the possibility of evaluating SMI depending on how accurately and efficiently a reaching movement may be performed. Further, the reaching movement [9][10] is considered an essential component in performing any day-to-day activity including eating, interacting with objects, exploring the space around oneself, etc. Additionally, researchers [11] have also indicated that since reaching movements have a clear objective, they are well suited to study how the CNS may use the sensory inputs to complete the desired motor action. Therefore, in the current study, a reaching task is designed to quantify any SMI deficits in PD patients. Multi-sensory integration is investigated based on the participant's performance in the reaching task under four sensory conditions (with/without multi-modal assistive sensory cues and with/without sensory manipulation). Reaching tasks with and without multi-modal Assistive Sensory Cues (ASC) are used to assess visuomotor and sensorimotor performance. Sensory manipulation is also used to resemble the real-world scenario where the received sensory stimuli are often noisy or inaccurate. The results from the reaching task with sensory manipulation are essential in understanding how efficiently

the participants can integrate multiple modalities while considering the sensory disturbances. Studies [12] [13] have indicated that SMI processes may have flexible strategies during movement planning depending on the relevance and reliability of the information provided by the sensory modalities. Adapting SMI strategies based on the reliability of the received sensory inputs is vital to minimizing the error in the perceptual estimates, that are used to plan and execute a movement optimally. Investigating the performance of PD patients in the presence of a sensory manipulation or inaccurate sensory input may provide insights as to whether they can adapt their SMI strategies considering the unreliable sensory input.

The primary objective for the participants in the reaching task was to reach the targets (red dot) shown on the VR display using the robotic manipulandum within a given time. In other words, the white fingertip marker had to reach the red target for the participants to complete the reaching task successfully. The trial began when the participant's arm was located at the center of the screen, which was indicated by a marker dot. A red dot which is the target, was shown when the trial began, and the participants were given a specific amount of time to reach the target. The time limit to reach the target dot was six seconds. It should also be mentioned that the participants had to reach the targets and stay on the target for 3 seconds for it to be counted as a successful reaching action. The trial ended when the participants reached and were on the target dot for three seconds or if six seconds had passed without the participants reaching the target. Once the trial ended, a marker dot appeared in the center of the screen, and the participant had to reach the marker, at which point the subsequent trial began. Figure 2.5 shows the design of the reaching task. The reaching task encompassed four subtasks, each testing the participants in different sensory conditions (see Table 2.1). The protocol and specifications for each subtask are explained in the following sections.

Table 2.1: Subtasks of the reaching task

	Subtasks	Sensory Conditions
Reaching task (RT)	First subtask	Without Assistive Sensory Cues (ASC)
	Second subtask	With ASC
	Third subtask	With ASC and without sensory manipulation
	Fourth subtask (Mirror-reaching task)	With ASC and with sensory manipulation

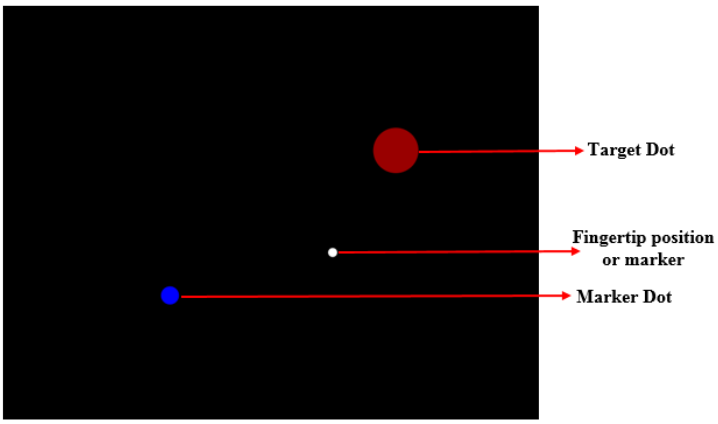


Figure 2.5: Reaching task

Note: The objective for the participant is to reach the target dot; The white dot indicates the fingertip position of the participant while holding the robotic handle.

2.1.4.1.1 First Subtask (Without Assistive Sensory Cues)

In this subtask for the reaching task, the participants only received visual input through the VR display. No multi-modal ASC was provided to assist the participants in accurately reaching the targets. Participants performed ten trials of this subtask. The size, location, and distance of the target from the center have been randomized across the ten trials to ensure that the participants do not predict the location of the target and initiate the movement before the target appears on the screen. Randomization of the task parameters also ensured that the trials were not the exact replica of each other and that the participants did not find the tasks repetitive, which may result in reduced task difficulty. Literature [14] have pointed out that repetitive task may require reduced cognitive and sensory effort than randomized tasks. Therefore, the randomized task would be more suitable for investigating the SMI functions as it demands optimal sensory integration, and any inaccuracies in SMI

would deteriorate the task performance. All targets are circular, and the target size ranges from 1 cm to 2.5 cm in radius. The distance between the screen center and the target ranges from 7 to 12.2 cm. The targets were spread out in all directions to pinpoint any bias in performance depending on the target direction.

2.1.4.1.2 Second Subtask (With Assistive Sensory Cues)

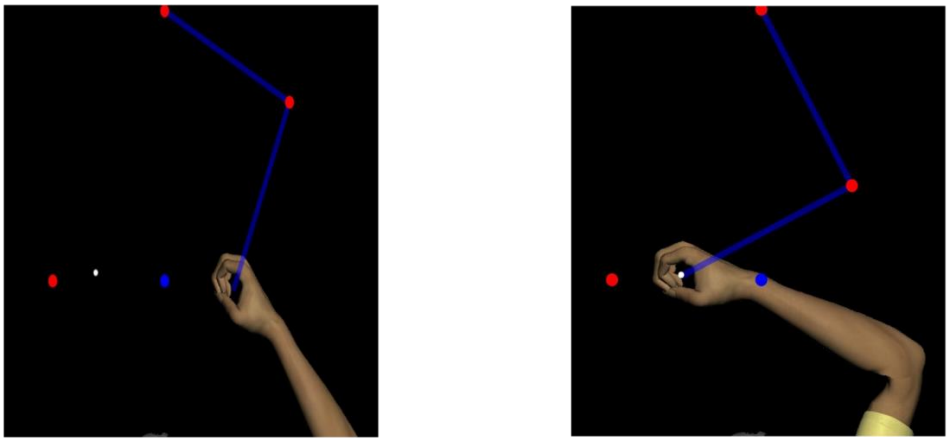
In addition to the visual input received through the VR display, participants also received multi-modal assistive sensory cues, which assisted the participants in reaching the target accurately. Multi-modal sensory inputs include vibrotactile and auditory input. These multi-modal sensory inputs were feedback provided by the robotic system to the participants when they reached the target so that they could stay on the target for 3 seconds to complete the task successfully. Vibrotactile and auditory sensory cues were provided to assist the participants in movement regulation and control. Integrating these ASC may improve the participant's task performance. Vibrotactile input is applied to the robot manipulandum, which the participant grasped. A separate speaker attached to the robotic system was used to provide an auditory input: a single beep sound when the participants reached the target. All the multi-modal inputs were provided in real-time with no delay. Participants performed a total of 10 trials, and the parameters used for this subtask were the same as the ones used in the first subtask.

2.1.4.1.3 Third Subtask (Without Sensory Manipulation)

This reaching subtask was done to evaluate the performance of the participants when performing the reaching action without any sensory manipulation or disturbance. In addition to the visual input, participants also received multi-modal assistive cues throughout this subtask. The earlier sub-section explains the parameters for the vibrotactile and auditory inputs and when these multi-modal inputs were evoked. The participants under this sensory condition performed a total of 33 trials. The target size ranges from 0.6 cm to 2.6 cm in radius, and the distance of the target from the screen center ranges from 20 cm to 40 cm.

2.1.4.1.4 Fourth Subtask (With Sensory Manipulation)

In this subtask, the participants encountered sensory manipulation or disturbance when performing the reaching movement. The visual input on the VR display was manipulated to investigate how the participants cope and adapt to sensory inaccuracies. To be specific, the fingertip position of the participant shown on the VR display was manipulated such that the fingertip position shown on the screen is a mirror image of the actual fingertip position of the participant. The fingertip movement shown on the screen moves in the mirror image of the actual movement made by the participant. For instance, if the participant moved to the left side, the marker indicating the fingertip position moved to the right, which is the direction opposite to that of the actual movement. If the participant moved in the upward direction, the marker indicating the fingertip position shifted in the downward direction. Therefore, the participant had to consider this visual manipulation when attempting to reach the target. For instance, If the target was located on the right side from the screen center, the participant had to move the robotic manipulandum to the left side for the marker indicating the fingertip position to move to the right side and reach the target accurately. Throughout this subtask, the participants received the vibrotactile and auditory assistive cues in addition to the manipulated visual input. However, the vibrotactile and auditory inputs were not manipulated. The parameters associated with the multi-modal assistive cues were mentioned in the earlier section. The target size and the distance from the screen center were the same as the third subtask. Figure 2.6 shows the reaching task with and without sensory manipulation. As shown in Figure 2.6(a), with sensory manipulation, the fingertip position (white dot) moves in the direction opposite to the participant's arm, whereas, in the three earlier subtasks without sensory manipulation, as shown in Figure 2.6(b), the fingertip position would move along with the participant's arm.



a) With sensory manipulation **b) Without sensory manipulation**

Figure 2.6: Reaching task with and without sensory manipulation
Note: This figure is captured from the analysis software to provide a better understanding of the task and does not indicate what the participants would see during the experiment. During the experiment, the participants would not see their arms or the blue line indicating the robot manipulandum. They would only see the fingertip position (white dot) and the virtual objects associated with the tasks.

2.1.4.2 Tracing Task

The difficulties experienced by PD patients in performing fine motor tasks that require smooth continuous movements have been extensively reported [15][16][17]. Generating multiple discrete sub-movements rather than a smooth continuous movement and an inability to adapt to the task requirement and demands of the environment during continuous motions have been widely discussed [18]. While the motor impairments such as rigidity could contribute to this difficulty, an impairment in SMI may also lead to inaccuracies and choppy movements when performing the continuous motion. A tracing task was designed and developed in this study to assess the deficits in sensorimotor abilities that may adversely affect motor control and smooth modulation of motor commands when performing continuous movements.

In the tracing task, a green circular path was shown in the center of the VR display. A marker dot was presented on the right half of the circular path. This marker dot was primarily used to determine when the trial could begin. When the participant was ready, they grasped the robotic manipulandum and reached the marker dot, at which point the trial started. Once the participants reached the marker dot, a red dot appeared just above the

marker dot and within the green circular path. The objective for the participant was to move in the clockwise direction or, in other words, go around the circular path and reach the red dot while staying within the green circular path. Any deviations from the green circular path were considered a violation or error, and the participants received sensory feedback indicating that the fingertip position was outside the green circular path. Figure 2.7 shows the design of the tracing task.

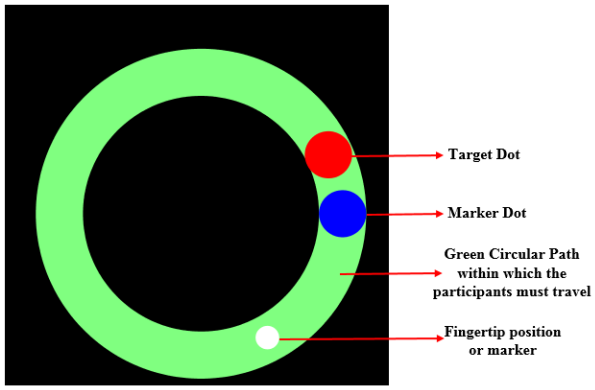


Figure 2.7: Tracing task

Note: The participants are only allowed to move in the clockwise direction when reaching the target dot and must stay within the green circular path

In addition to the visual feedback provided by the VR display, haptic and auditory feedback was also provided as ASC when the participants deviated from the green circular path. While the auditory feedback was the beep sound, the haptic feedback included a force input that pushed the participant's arm back into the green circular path. This sensory feedback was provided to assist the participants in performing the tasks more accurately and efficiently. Unlike the reaching task that had four subtasks, the tracing task only includes two subtasks (see Table 2.2): one with sensory manipulation and the other without sensory manipulation. This was done to reduce the amount of time it takes for the participants to complete all the tasks so as to ensure that the study's results are not unduly affected by fatigue. Earlier studies [19][20] have found that fatigue is a common problem in PD patients, and an increased assessment time may adversely affect a patient's performance due to fatigue.

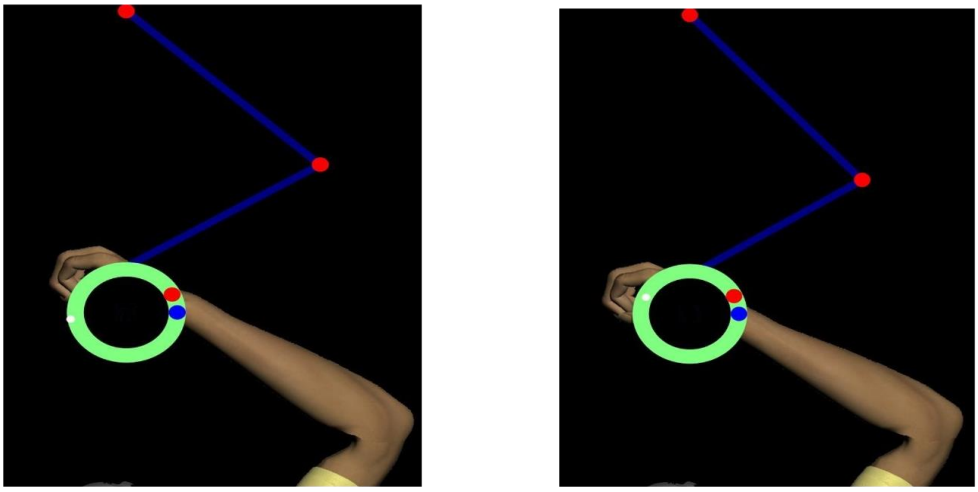
Table 2.2: Subtasks of the tracing task

	Subtasks	Sensory Conditions
Tracing task (TT)	First subtask (Tracing task without delay)	With ASC and without sensory manipulation
	Second subtask (Tracing task with delay)	With ASC and with sensory manipulation

2.1.4.2.1 First Subtask (Without Sensory Manipulation)

The trials in this subtask included no sensory manipulations. Participants performed a total of 12 trials, with the diameter of the green circular path varying randomly. The width of the circular path is 2.5 cm.

2.1.4.2.2 Second Subtask (With Sensory Manipulation)



a) With sensory manipulation **b) Without sensory manipulation**

Figure 2.8: Tracing task with and without sensory manipulation

Note: This figure is captured from the analysis software to provide a better understanding of the task to the audience and does not indicate what the participants would see during the experiment. The participant would not see their arm or the blue line indicating the robot manipulandum during the experiment. They would only see the fingertip position (white dot) and the virtual objects associated with the tasks.

In this subtask, the visual sensory input shown on the VR display was manipulated by adding a time delay of 1000 milliseconds to the visual input. In other words, the white dot indicating the fingertip position moves 1000 milliseconds after the participants have

moved. Adapting to the visual delay requires the optimal functioning of SMI and cognitive abilities. Literature [21][22] has suggested that an efficient strategy used by CNS when integrating multiple modalities is to determine the reliability of each modality and assign weights based on the reliability of the modality. Therefore, the participants needed to determine the reliability of the modalities taking into account the visual delay, to efficiently integrate these modalities and modulate the motor output accordingly. Furthermore, integrating multi-modal ASC is also essential to recognize and correct any errors committed due to this visual delay. Therefore, the performance of the participants when encountering visual delay could highlight any deficits in SMI. Similar to the first subtask, participants performed 12 trials per arm, with the width of the circular path being 2.5 cm. Figure 2.8 shows the tracing task with and without sensory manipulation. As shown in Figure 2.8(a), with sensory manipulation, the fingertip position indicated by a white dot is delayed compared to the participant's arm. It does not accurately show the exact fingertip position. However, in Figure 2.8(b), without sensory manipulation, the white dot accurately indicates the exact fingertip position of the participant's arm, as there is no delay between the fingertip marker and the participant's arm.

2.1.5 Task Protocol for Investigating Sensorimotor Control

Sensorimotor control is the ability to interpret the acquired sensory input and appropriately plan, update, and generate motor output to perform the desired movement considering the state of oneself and the world around us. Optimal motor, sensory and cognitive functioning is essential to perform two vital SMC functions: movement planning and online error correction. An obstacle avoidance task was built to investigate the impairments in multiple domains (motor, sensory or cognitive) that would adversely affect the functioning of SMC. An obstacle avoidance task was chosen to evaluate the SMC functions as it allows us to explore not only the motor planning ability in PD patients to reach the targets but also the ability to correct the planned strategy to avoid obstacles. Numerous studies [23][24] have also indicated obstacle avoidance tasks to be more suitable for evaluating SMC functions. Additionally, there have been many studies [25][26] that have used obstacle avoidance tasks to assess lower-limb motor control performance and to evaluate the effect of rehabilitation therapies on motor control. However, the obstacle avoidance task used in

most of these earlier studies neither included any sensory cues nor trials with varying cognitive loads. In our study, the obstacle avoidance task was aimed at testing movement planning and online error correction in participants under varying cognitive loads. Examining the participants under variable cognitive loads would help to understand the deterioration in performance as the tasks become more cognitively demanding. In addition to investigating the effect of motor and cognitive deficits on SMC, the sensory domain related to SMC was also investigated, i.e., if the SMC functions such as movement planning and error correction were affected by impairments in perceiving and interpreting sensory inputs. The protocol used in the obstacle avoidance task is explained in the next section. Figure 2.9 shows the task design of the obstacle avoidance task.

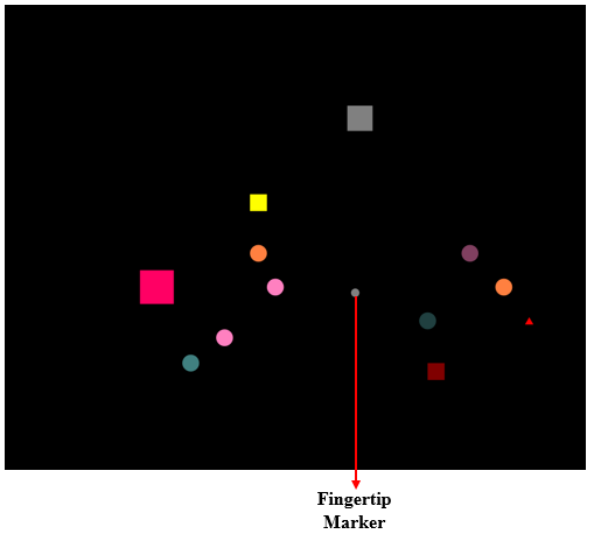


Figure 2.9: Obstacle avoidance task

Note: Targets are Square Shaped; Obstacles are in Circle and Triangle Shape; The objective of the participant is to move the fingertip marker using the robot handle to reach the targets and avoid the obstacles.

2.1.5.1 Obstacle Avoidance Task

Table 2.3: Levels in the obstacle avoidance task

Level	Target	Obstacle	Perturbations
Level – 1 (L-1)	Stationary	Stationary	None
Level – 2 (L-2)	Moving	Stationary	One (2 to 2.8 N)
Level – 3 (L-3)	Stationary	Moving	Two (3 to 4.2 N)
Level – 4 (L-4)	Moving	Moving	Three (4 to 5.6 N)

The objective for the participants was to reach all the targets while avoiding the obstacles simultaneously. Participants can differentiate an obstacle from the targets based on their shapes; while targets were square shaped, the obstacles were triangular and circles. The task was divided into four levels, with ten trials in each and 40 trials overall. To vary the cognitive load for the participants, the difficulty of the task was increased with each level by varying the state (stationary or moving) of the obstacles and targets. Each trial included eight obstacles and four targets, with a total of 160 targets and 320 obstacles throughout the task. The width of the obstacles and targets ranged from 1 to 6 cm. On average, the task takes about 6 to 8 minutes.

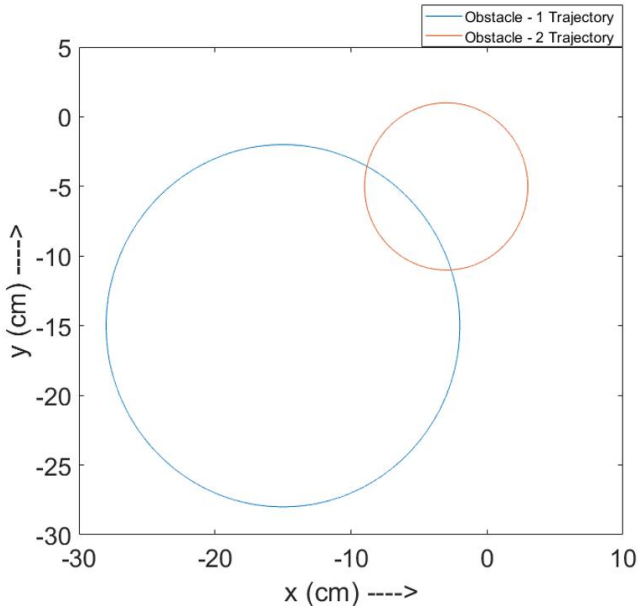


Figure 2.10: Trajectory of two different obstacles with varying radii and centers

Table 2.3 shows the state of the obstacles and targets at each level. The obstacles and targets might be stationary or moving depending on the level of the task. When the obstacles and targets were moving, they moved in a circular trajectory with the radius, speed, and center of these virtual objects varying from one another. Equations (2.01) and (2.02) show how the *x* and *y* coordinates of the virtual objects have been updated using Simulink. Figure 2.10 shows the trajectory of two obstacles with varying centers and radii. The speed of the obstacles and targets ranged from 1.8 to 22.8 cm/s, and this range remained constant for all moving virtual objects across all levels.

$$x\ coordinate = center + radius \times \cos(speed \times counter) \quad (2.01)$$
$$y\ coordinate = center + radius \times sin\ (speed \times counter) \quad (2.02)$$

A haptic (vibrotactile input to the robot handle) and auditory (beeping sound from a speaker) sensory cue were provided as a warning cue to the participants when they reached 2 to 2.5 cm from an obstacle. Understanding if the participants could use the external sensory cues to efficiently avoid obstacles would inform us of any impairments in the sensory domain and how they may affect the SMC functions.

Perception of force is also a vital component for the optimal functioning of SMC. While earlier studies have reported altered kinesthetic sensitivity [27], there has been a lack of understanding if PD also alters the detection threshold for force perception. Analyzing the participant's ability to perceive perturbations of varying force and appropriately correcting their planned strategy to account for this disturbance would shed light on any impairment in force perception and how it affects the SMC. Furthermore, this would also show that altered kinesthetic sensitivity is not specific to a single modality but a universal phenomenon that affects the sensitivity of multiple modalities due to a central processing deficit rather than an impairment related to a particular modality. Therefore, multiple mechanical perturbations separated by a few seconds were applied to the robot handle while the participants were performing the task. While there was no mechanical perturbation in level-1, there were one, two, and three mechanical perturbations in level-2, 3, and 4, respectively. In levels with multiple mechanical perturbations, each perturbation was separated by a few seconds. The magnitude of force applied to generate the perturbations increased as the levels increased.

Table 2.4: Direction of force used to generate perturbation

F_x	F_y
1	1
1	-1
-1	1
-1	-1
1	0
0	1

Note: A positive value applies a force in the positive direction of the *x* and *y* axes, and a negative value applies a force in the negative direction of the *x* and *y* axes. A zero value indicates no force in the x or y directions.

Let F_x and F_y be the force applied along the *x*- and *y*-axis, respectively. First, the directions of forces applied along the *x*- and *y*-axis were chosen, and then the force magnitude was determined based on the level. Table 2.4 shows the six directions in which the force may be applied, and one of these directions was chosen at random. A positive value for F_x indicates that the force was applied in the positive direction of the *x*-axis and vice versa. Once the force direction in the *x*- and the *y*-axis was chosen, the F_x and F_y was scaled based on the desired force magnitude. The scaling factor changed based on the level with force magnitude increasing with levels. The scaling factors used for level-2, level-3, and level-4 were 2, 3, and 4, respectively. For instance, if $F_x = 1$ and $F_y = -1$ was chosen as the force direction in level-2, it was then multiplied with the scaling factor of 2, resulting in $F_x = 2$ and $F_y = -2$. This will apply 2 newtons of force along the *x*-axis and -2 newtons of force along the *y*-axis. The overall force magnitude was calculated as shown in equation (2.03), and the force magnitude range for each level is shown in the Table 2.3.

$$F_{magnitude} = \sqrt{F_x^2 + F_y^2} \tag{2.03}$$

In levels 3 and 4, multiple perturbations were applied, with each perturbation separated by a few seconds. The time interval between subsequent perturbations was varied to ensure that the participants did not get used to the time interval between the perturbation and attempt to generate a corrective movement even before the perturbation was applied. Predicting the perturbation and generating corrective movements before the perturbation was applied might be counterproductive when attempting to investigate how the participants perceive the perturbation and correct for it after it has been applied. Therefore, a variation in the time interval between perturbations was included, and the interval between the perturbation ranged from 2.5 to 5 seconds.

2.2 Feature Extraction

Quantifying the SMI and SMC deficits in PD patients requires evaluating the performance of the participants in each of the tasks. While the KINARM provides the upper-limb kinematic data, it does not provide any insights into the participant's performance. Therefore, specific features were extracted during this study to be used as metrics in evaluating the performance of the participants. The features (performance metrics) extracted from the kinematic data vary from one task to another based on the nature and objective of a given task. This section discusses the features extracted for each task and how these features may be used to evaluate the SMI and SMC functions.

2.2.1 Parameters Extracted for Reaching Tasks

In reaching tasks, the objective for the participants was to reach the targets within a given amount of time. Therefore, the features were extracted to evaluate how accurately and efficiently the participants reached the targets. Table 2.5 shows the features extracted for the reaching task and the corresponding definitions for these features.

Table 2.5: Features extracted for the reaching task

Features	Definitions
Target reach	Mean percentage of targets reached
Mean endpoint error	Mean distance between the fingertip and center of the target when the subject reaches and stays at the target
Mean direction error	Mean distance traveled by the white dot, indicating the fingertip position, in the wrong direction, i.e., a direction in which there is no target.
Mean Deviation Error (MDE)	Mean deviation between the ideal and the actual path taken by the participants was calculated using the K-Nearest neighbor (K-NNR). A higher MDE indicates a lower efficiency.
Maximum endpoint error	Maximum distance between the fingertip and the center of the target when the subject reaches and stays at the target
Maximum direction error	Maximum distance travelled in the wrong direction
Mean velocity	Mean velocity when performing the reaching task

2.2.2 Parameters Extracted for Tracing Tasks

The tracing task requires the participants to stay within the green track and move in a clockwise direction to reach the targets. Therefore, extracted features for the tracing task

focus on whether the participants committed any violation by moving outside the green track and how efficiently they used the sensory cues to correct any violations. Furthermore, the smoothness and speed of the continuous movements were investigated. Table 2.6 shows the features extracted for the tracing task.

Table 2.6: Features extracted for the tracing task

Features	Definitions
Mean number of violations	Mean number of times the participants have moved outside the green track
Time spent under violation	Mean time spent by the participants outside the green track
Mean violation distance	Mean distance the participants have travelled or deviated from the green track
Mean Deviation Error (MDE)	Mean deviation between the ideal and the actual path calculated using K-NNR. In the tracing task, the ideal path is the center of the green track. A higher MDE indicates a lower efficiency.
Mean velocity	Mean velocity when performing the tracing task

2.2.3 Parameters Extracted for Obstacle Avoidance Task

Firstly, the objective for this task was to reach the targets while also avoiding obstacles. The extracted features focused on how efficiently and accurately the participants could avoid obstacles and reach the targets. Secondly, testing conditions were varied at each level to test the participants in varying cognitive loads. Therefore, features also focused on investigating if the participants' performance improved or deteriorated as the cognitive load has been varied to understand how the performance of PD patients may be affected as tasks become more complex.

Finally, it should also be noted that the obstacle avoidance task examined the SMC functions, such as movement planning and online error correction in PD patients. SMC is a complex network that requires multiple systems (motor, sensory and cognitive systems) working together [28][29][30]. To investigate the SMC deficits in PD patients, impairments that may adversely affect SMC functions in each domain (motor, sensory and cognitive) needed to be explored. Quantifying these impairments would show how these domain-specific impairments may have adversely affected the SMC functions. The role of

motor, sensory and cognitive domains in SMC and how an impairment in any of these domains may affect the overall SMC functionalities has been debated for years [31][32][33]. Therefore, all the features extracted for this task were assigned to assess a specific domain. We categorized the extracted features based on which domain (motor, sensory or cognitive) influences that feature the most. For instance, features such as speed and movement time were assigned to assess motor deficits, whereas components of testing that were not directly related to the generation of motion, but influenced the overall task performance through planning and correction of the movement were grouped as cognitive features. While the features may not be considered a pure measure of the respective domains that it was categorized to assess, the principal contributor to the improvement or deterioration of a feature would be the domain that it was assigned to evaluate. An in-depth explanation of how these features were grouped to assess motor, sensory or cognitive deficits is explained below. Table 2.7 shows all the features extracted for this task and which domain-specific impairment it was assigned to evaluate.

Table 2.7: Features extracted for the obstacle avoidance task

Features	Definitions	Purpose
Mean speed	Mean velocity throughout the task	Motor features
Peak speed	Maximum velocity throughout the task	Motor features
Time to reach maximum speed	Time taken to reach the peak velocity	Motor features
Movement area	Area covered during the task using convex hull	Motor features
Reaction time	Time required to reach 10 % of the total distance	Motor features
Speed peaks	Number of maxima in hand speed	Motor features
Movement time	Time taken from the movement onset to the end.	Motor features
Obstacle hit to warn ratio	Ratio of (i) number of obstacles hit in each trial. (ii) number of warnings provided through auditory, and vibrotactile sensory cues in each trial	Sensory features
Corrective time for perturbation	Time required to correct for any perturbation	Sensory features
Target reach percent	Mean percentage of targets reached	Cognitive features

Efficiency	Ratio of (i) distance travelled to reach a target, (ii) distance pertaining to the shortest path to reach a target	Cognitive features
Target order	Target order requiring participants to travel the least distance was considered the ideal target order. R^2 values were calculated between the ideal order and the order in which subjects reached the targets. The ideal target order was determined, taking into consideration the target and obstacle location.	Cognitive features
Endpoint error	Distance between the fingertip and center of the target when the subject reaches and stays at the target	Cognitive features
Mean obstacle hit proportion per trial	Mean proportion of obstacles hit during the trial	Cognitive features
Corrective movements	Number of corrective movements performed throughout the task	Cognitive features
Slope between performance and Index of Difficulty (ID)	ID was calculated using Fitts's law, and the performance indicator is taken as movement time per Fitts's law.	Cognitive features
Endpoint variance	Variance of the distance between the fingertip position and the target center	Features for computational model
Error-speed ratio	Ratio between Endpoint error and Mean speed. Rate at which the endpoint error increases for every 1cm/s increase in mean velocity	Features for computational model
(1) Correlation between the corrective movements and target reach (2) Correlation between the corrective movements and Obstacle hits	Correlation between different sets of variables was calculated.	Features for computational model
Correlation between Endpoint variance and Obstacle hit-to-warn ratio	A correlation between two error metrics was calculated to understand how efficiently the participants could optimize their movements.	Features for computational model

2.2.3.1 Motor Features

Certain features were aimed at investigating motor impairments that may affect SMC functions. These features were categorized to assess the motor domain based on earlier literature [34][35] that has used these features to evaluate motor performance in humans.

2.2.3.2 Sensory Features

There is a lack of objective assessment of sensory deficits that may adversely affect the SMC functions in PD patients. Therefore, the features were categorized based on earlier literature that explains the sensory abilities that might be vital in performing goal-directed movements. The sensory features were designed to provide an understanding of how the SMC functions might be affected due to impairments in the sensory domain [36][37][27]. This study explored the ability to interpret sensory inputs to avoid obstacles and the threshold to perceive force input. Consequently, the feature–corrective time for perturbation was extracted to understand if the threshold to perceive force inputs is altered in PD patients. This aspect of sensory function was explored to understand if a universal sensory dampening exists in PD patients across multiple modalities due to a central processing deficit [38] and how it affects SMC. Likewise, the obstacle hit-to-warn ratio is extracted to understand if the participants could interpret these sensory warning cues and use them efficiently to update their motor plan and avoid obstacles.

2.2.3.3 Cognitive Features

Certain features were categorized to evaluate any cognitive deficits impairing SMC functions. Cognitive deficits defined in this study may not directly align with the clinical definition of cognition but point towards the impairment in cognitive abilities related to movement planning and error correction. While the features used to evaluate motor performance were determined based on earlier literature, an objective investigation of cognitive ability, specifically executive functions in PD patients, has been lacking. However, earlier studies [39] have shown that cognitive abilities such as executive functions may be vital in planning and correcting the planned motor strategy during goal-directed movement. Therefore, features that captured and represented the participant's

cognitive performance (efficiency and accuracy of executive functions) that were essential to performing goal-directed movements were categorized as cognitive features.

2.2.3.4 Features to Compare with Computational Models

The strategies that may be employed by the CNS when performing an executive function have been discussed in Section 1.5.5 in Chapter 1. Multiple computational models have been hypothesized to explain the criterion used by the CNS to plan and correct any voluntary movement optimally. The criterion proposed by each model varies from one to another. Certain models also include cost functions that represent the criterion hypothesized to be used by the CNS. It has also been hypothesized that the CNS can adapt to dynamic environments through its flexibility in adjusting the SMC strategies. In other words, the CNS may use different criteria to accomplish optimal performance based on the demands of the environment and task at hand rather than using a fixed criterion [40][41][42]. While the exact functioning of the CNS is still largely unknown to the scientific community, and these computational models are not validated by clinicians, it does provide valuable insights into how the CNS may approach a movement planning or online error correction problem and the policy that the CNS may use to perform the SMC functions optimally. Therefore, to understand how PD may alter the criterion that may be used by the CNS to plan and correct movements, the performance of the participants was also compared from the perspective of the computational models. To this end, specific features that represent the criterion proposed by the computational models were calculated. For instance, as the criterion proposed by the minimum variance model is to minimize the fingertip variance, the endpoint variance, which was the fingertip variance in our task, was calculated for each group. These extracted features representing the criterion proposed by a computational model were then compared between the participants to understand which groups performed the best from the perspective of the computational models. In this study, six computational models were considered. Table 2.8 shows the six computational models, the objective or the criterion proposed by the models, and the features extracted to represent the criterion of each model.

Table 2.8: Computational models, their objectives, and the features extracted to compare a participant's performance from the perspective of the computational model

Computational models	Objectives or Criteria of the computational models to optimally plan or correct movements	Features used to compare the groups from the perspective of a given computational model
Minimum Variance Model	To increase the fingertip accuracy by reducing the fingertip variance	Endpoint Variance
Minimum Energy Model	To reduce the metabolic energy consumed when performing a given task by reducing any sub-movements	
Minimum Jerk Model	To reduce the jerkiness and generate a smooth trajectory from origin to target	Speed Peaks
Obstacle Avoidance Model	To reduce the (i) Mean Squared Error (MSE) between the actual and predicted arm position, (ii) Collision Probability	Correlation between the Endpoint Variance and Obstacle hit-to-warn ratio
Speed-to-accuracy Trade-off model	To reduce the ratio at which the movement error increases when the movement speed increase	Error-speed ratio (Ratio between the endpoint error and mean speed indicating the increase in endpoint error to every 1cm/s rise in mean speed)
Minimum Intervention Model	To perform corrective movements only for task-relevant errors (to avoid obstacles) by accurately distinguishing between the task-relevant and task-irrelevant errors	Two sets of correlation coefficients were used (i) correlation between corrective movements, and obstacle hits, (ii) correlation between corrective movements, and target reach

Models such as minimum variance [43] and minimum energy [44] were used to compare the performance of the participants. The objective of the minimum variance model is to reduce the fingertip variance, and thereby increase the fingertip accuracy. The energy model, which attempts to reduce metabolic energy spent in each task, also indirectly aims to reduce variance in the fingertip to preserve the energy that might be used for any corrective movements to compensate for the fingertip variance. Therefore, the objective of both these models is to minimize the fingertip variance. Correspondingly, the endpoint variance representing the fingertip variances was calculated to compare the participants'

performance based on these models. Flash et al. [45] and Hogan et al. [46] have discussed the minimum jerk model to plan arm movements, as the jerk in the movement may indicate uncertainty and the inability to generate a smooth trajectory leading to inaccuracies and inefficiencies. Therefore, the speed peaks, indicating the amount of jerkiness present in the subject's trajectory, were calculated to compare the participants' performance from the perspective of the minimum jerk model. Studies have also discussed the speed-to-accuracy trade-off model [43]. However, no study has so far explored the ratio of the trade-off between movement speed and accuracy, even in healthy subjects. To understand if this trade-off ratio has been altered due to PD, the error-speed ratio (the rate at which the endpoint error increases for a very cm/s increase in mean velocity) was calculated and used to compare the groups.

Apart from these generic models, a task-specific model was also considered. The cost function for the obstacle avoidance model [23] includes two criteria (1) minimize the mean squared error between the actual and predicted arm position and (2) minimize the collision probability with the obstacles. The endpoint variance represents the mean squared error between the actual and predicted arm position. The obstacle hit-warn ratio is used to evaluate the subject's ability to minimize the collision probability. The rationale is that if the subjects hit the obstacles even after the sensory warning cue indicating a higher probability of collision with the obstacles, then the subjects have failed to reduce the collision probability. A correlation coefficient was calculated between the variables representing the two criteria of the model (endpoint variance and obstacle hit-warn ratio). This correlation value was used to understand if subjects were to minimize at least one part of the cost function or were unable to reduce both parts of the cost function. Finally, to evaluate the participant's ability to correct errors, the performance of the participants was compared from the perspective of the minimum intervention model [42][47]. The objective or criteria of the model is to differentiate between task-relevant and task-irrelevant errors and efficiently correct only task-relevant errors. In the obstacle avoidance task, the task-relevant error is obstacle hit. Therefore, two correlation coefficients were calculated; one between obstacle hits and corrective movements; another between target reach and corrective movements. These correlation values would be used to evaluate if the corrective movements helped reduce the obstacle hit while also ensuring it did not adversely affect

the primary objective of the task, which was to reach the targets. It would help in understanding if the participants were able to optimally correct only the task-relevant errors without affecting their task performance.

2.3 Statistical Analyses

MATLAB was used to perform the statistical comparisons between the different groups to investigate the difference in the performance metrics calculated to evaluate the SMI and SMC functions of the participants. As the extracted features were found to be non-normal, non-parametric statistical tests were used in this study as these methods do not necessitate the assumption of normality. Furthermore, non-parametric tests were found to be more robust, especially in medical analysis, due to the limited sample size and the existence of skewness and outliers [48][49][50][51]. The Mann-Whitney-Wilcoxon test was used to compare the extracted features between unpaired groups, and the Wilcoxon signed-rank test was used to perform statistical comparisons between paired groups [52]. While the Mann-Whitney-Wilcoxon test was used for statistical comparison between PD patients in the ON and OFF states with the control subjects, the Wilcoxon signed-rank test was used to compare PD patients in the OFF state with PD patients in their ON state. Any within-group comparisons were done using the Wilcoxon signed-rank test. The null hypothesis for the statistical tests was that the two compared samples came from the same population with an equal median. The alternate hypothesis was that the two came from different populations with unequal medians. Since the risk of wrongly rejecting the null hypothesis increases as multiple statistical tests are conducted, Bonferroni's correction [53] was used to correct the acquired *p*-values for multiple comparisons. The *p*-values are corrected by multiplying it with a correction parameter to obtain the corrected *p*-values. The correction parameter was determined separately for each task depending on the number of statistical tests conducted for that task. The number of statistical tests for a given task rely on the number of features extracted for that task and the number of groups. While the number of groups for all the tasks remained constant, equal to three (PD patients in OFF medication state, PD patients in ON medication state, and control subjects), the number of features varied from one task to another. Only the *p*-values pertaining to statistical comparisons were corrected using Bonferroni's correction. A *p*-value of 0.05 was considered

statistically significant to reject the null hypothesis in Mann-Whitney-Wilcoxon and Wilcoxon signed-rank test. Finally, the relationship between the extracted features and the clinical scales was determined by measuring the correlation coefficient between the variables of interest. In this study, the correlation coefficient was calculated using the spearmen correlation [54]. A significance test was also done to determine if the correlation coefficient was statistically significant. A *p*-value of 0.05 was considered to be statistically significant. When calculating the correlation coefficient and its significance between extracted features and clinical scales, they were calculated separately for each level of the task. Fisher's Z transformation [55][56] was used to combine correlation coefficients obtained from multiple levels wherever needed. To combine *p*-values, the harmonic mean method [57] has been used.

2.4 Feature Selection and Pattern Recognition

The metrics developed to assess SMI and SMC functions may be a potential biomarker for an early diagnosis and may also be used in patient-specific analysis for a more efficient and individualized treatment approach. While the tools developed in the thesis may not be directly employed in a clinical environment, this may be considered a first step in using technology-driven tools to diagnose, monitor, and manage the disease efficiently. To this end, the metrics or features extracted from the robotic task needed to be analyzed to understand if they can be used to differentiate between the PD and control subject, which would imply that the metrics can be considered as a promising marker for diagnosis. This section focuses on using the extracted feature to classify between the PD and control subjects using pattern recognition algorithms. Pattern recognition [58] uses machine learning techniques to recognize the regularities and patterns in a dataset, which can then be used to determine the distribution to which a given data point belongs. In this study, neural network (NN) models have been used to determine if the patterns from the extracted features (informing us of SMI and SMC impairments) is sufficient to classify between a PD, and a control subject, thereby implying that these metrics may be considered a potential diagnostic variable. Before training the NN model, it is necessary to select the correct metrics that can be used for the training process. Filtering out irrelevant or redundant metrics and only choosing metrics that provide valuable and unique information

that is representative of the population is vital to the performance of the NN model. Therefore, we use feature selection methods [59] to determine the metrics that provide unique and necessary information about the population. This section explains the methodology involved in the feature selection process and the methodology involved in designing and training a NN model.

2.4.1 Feature Importance

Selecting the features needed to train a NN model is a critical step in preprocessing. It is necessary to only include features that contain unique and relevant information about the population and filter out the remaining features that may be irrelevant or noisy, that can affect the model's predictive accuracy. Furthermore, reducing the number of features would also help avoid the curse of dimensionality, which saves computational power and time.

In our study, a decision tree [60] was used to determine the importance of the features in accurately predicting and differentiating between the PD and control subjects. Based on the feature importance score provided by the decision tree, the most important features were used to train the NN model. The decision tree was used to determine the importance of the features separately for each task; accordingly, the selected features differ from task to task. This section discusses the technique involved in determining the importance of features using the decision tree. A decision tree is a non-parametric supervised learning method used for classification, where the data is split continuously based on a particular feature. Figure 2.11 shows the schematics associated with the decision tree.

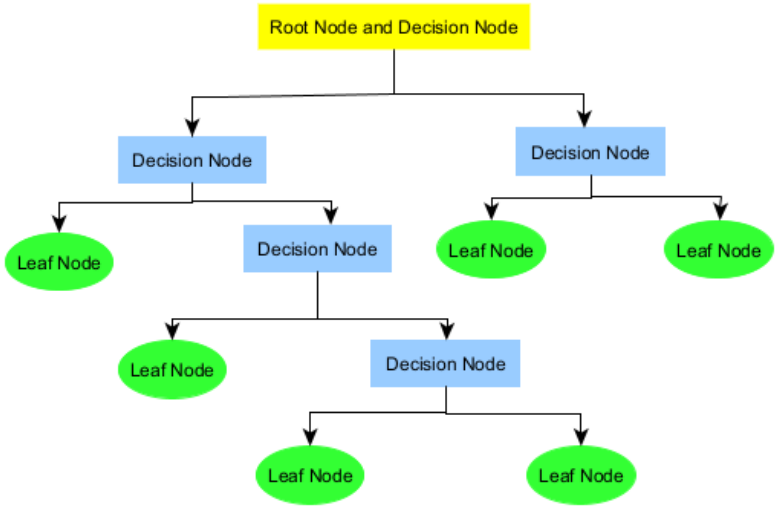


Figure 2.11: Schematic of the decision tree

The dataset is split continuously at each decision node down to the leaf node until all data is classified, and the dataset can no longer be split based on any feature. The decision node is where the features used to split the data points are decided, and the leaf nodes denote the output of those decisions. All data points in the leaf nodes are assigned to a specific class based on the split. The decision node uses a variable selection criterion to determine which feature may be used to split the data points. In this study, a Gini index [61] has been used to make this decision. The Gini index is an impurity measure that calculates the probability of a random data point being misclassified; therefore, a lower Gini index represents a lower likelihood of misclassification. Equation (2.04) shows the method to calculate the Gini index.

$$Gini\ index = 1 - \sum_{i=1}^{K} P(i)^2 \tag{2.04}$$

where K represents the number of classes and $P(i)$ is the probability of a data point belonging to i^{th} class. To determine which feature needs to be used for splitting the decision node, we calculate the Gini index of the potential child nodes (child nodes are the resulting nodes from the split of the parent node) if we are to pick a given feature as the splitting condition. This process is repeated for each feature, i.e., if there are *n* features, we calculate the Gini index for each feature. The objective is to pick the feature with the least

Gini index. Once a specific feature is picked, the decision node is split into multiple child nodes using the selected feature. This process continues until all data points are classified. Figure 2.12 explains the working of a decision tree.

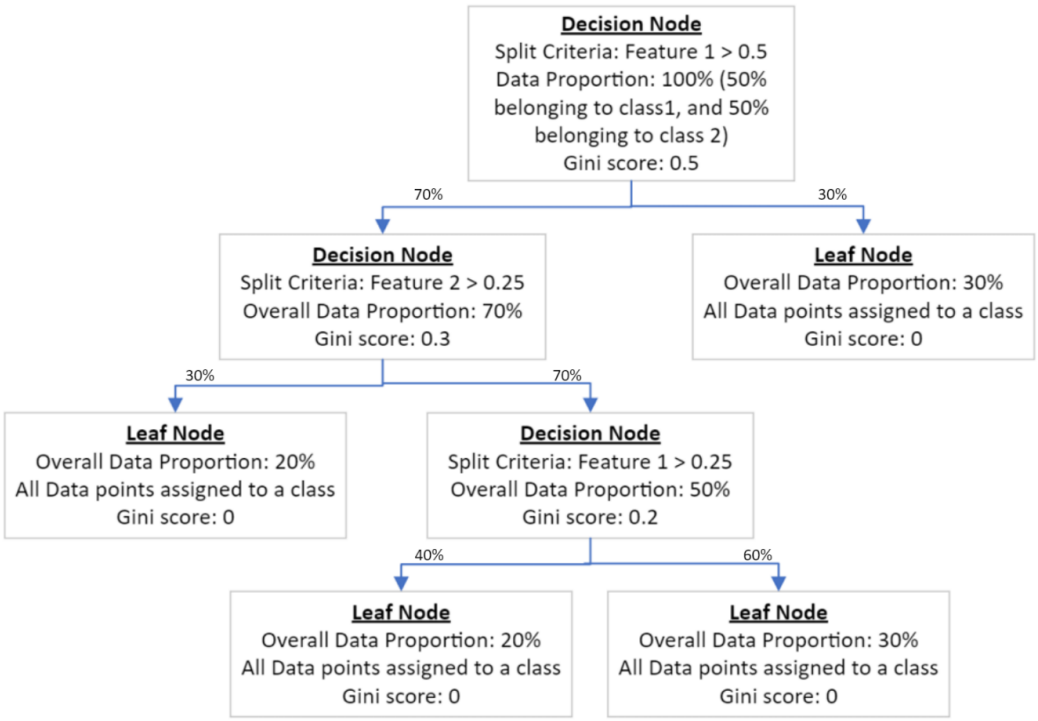


Figure 2.12: Working of a decision tree

This method is an efficient way to determine which features are most crucial for accurately classifying a data point between the PD and the control subject. The importance of each feature is calculated using the Gini index, as shown in equation (2.05).

$$I_i = \sum_{\substack{n \in T \\ i_n = i}} p(n)\Delta_{Gini}(n) \tag{2.05}$$

where I_i represents the importance of i^{th} feature, T represents the nodes that use feature i for splitting, $p(n)$ is the proportion of data points in node n, and $\Delta_{Gini}(n)$ represents the difference between the Gini score of node n and its child nodes.

2.4.2 Artificial Neural Network

Artificial neural networks (ANNs) belong to a class of systems based on the human brain and mimic how biological neurons communicate. Warren McCulloch and Walter Pitts [62],

in 1943, proposed the first artificial neuron, called the perceptron. Kustrin et al. [63] discusses the basic concepts of ANNs. An ANN usually comprises input layers, one or more hidden layers, and an output layer, each containing a defined number of neurons. Figures 2.13 and 2.14 show the working of a neuron and a simple NN model, respectively.

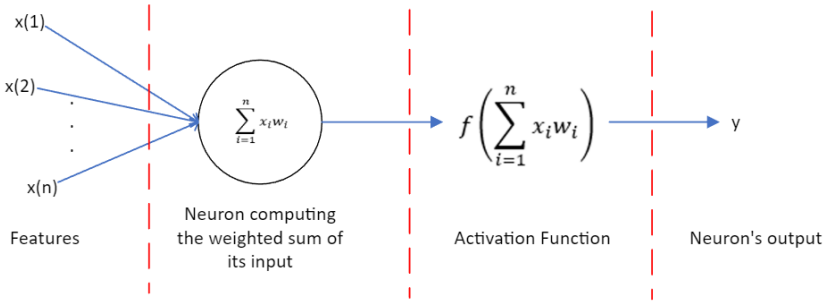


Figure 2.13: A single neuron and its computations

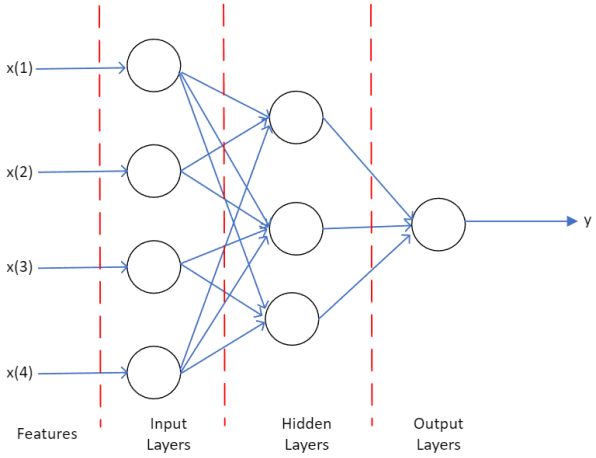


Figure 2.14: A simple Neural Network (NN) model with one hidden layer

2.4.2.1 Deep Learning Model

In this study, a deep-learning neural network (NN) model was implemented in python through the TensorFlow [64] backend and was used to differentiate between the two classes (PD patients in OFF medication state (PD-OFF) and Control subjects). The data from PD patients in ON medication state (PD-ON) was not included in the training or testing phase. Only the data from PD-OFF was included and therefore, the model can only classify between PD-OFF and control subjects. The data from PD-ON was not included in the deep

learning model because the goal of this model is to understand if the SMI/ SMC impairments are more commonly presented across PD patients in their baseline state and if these patterns can be detected using a neural network model. While numerous deep learning methods have been discussed in earlier studies [65] for the detection of PD, the features representing the SMI and SMC impairments have not been explored in these studies. Considering that the SMI and SMC impairments may be presented earlier in the disease, it might be beneficial to understand if a machine learning model could differentiate between a PD and a healthy control subject based on the features representing the SMI/SMC impairments. The proposed NN model had input layers equivalent to the number of features (one for each input feature), 8 hidden layers, and one output layer with two neurons, each representing one class (PD-OFF or control subject). A deep neural network was used because of the following advantages: (i) Its ability to learn complex nonlinear relationships; (ii) its capability for continuous learning; (iii) handling multi-modal datasets. While the model is currently trained using only the kinematic parameters obtained from the robot, the neural network model will be further expanded in future work and trained using data from other assessments. Some of these assessments could even provide image data, and unlike traditional machine learning models, a deep neural network is more customizable and is capable of being trained incrementally using newer data without the need to be re-trained from the scratch. Figure 2.15 shows the schematic of the NN model used in this study. The hyperparameters for the model are provided in Table 2.9.

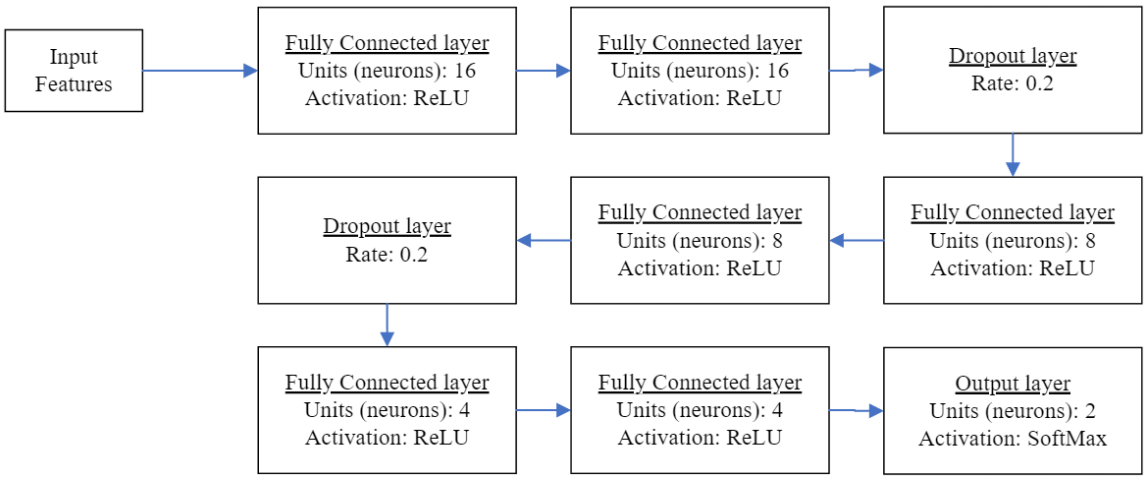


Figure 2.15: Schematic of the proposed NN Model

Table 2.9: Hyperparameters of the NN model

	Hyperparameters
Train-Validation-Test Split	70:15:15
Learning Rate	0.001
Optimization Algorithm	Adam
Activation function for hidden layers	ReLU
Activation function for the output layer	SoftMax
Loss function	Categorical Cross-entropy
Number of hidden layers	8
Drop-out rate	0.2

2.4.2.1.1 Activation Function

In this study, two different activation functions were used. The ReLU (Rectified Linear Unit) activation function was used on hidden layers. Equation (2.06) shows the mathematical representation of the ReLU activation function.

$$f(x) = \max(0, x) \tag{2.06}$$

where x is the weighted sum of the neuron's inputs. The SoftMax activation function was used on the output layer. Equation (2.07) shows the mathematical expression associated with the SoftMax function.

$$f(x_i) = \frac{e^{x_i}}{\sum_{j=1}^{K} e^{x_j}} \tag{2.07}$$

where x_i represents the output of i^{th} neuron in the output layer, and K represents the number of classes, which will be equivalent to the number of neurons in the output layer. In our case, there are two classes (PD and control) and, therefore, two neurons in the output layer.

2.4.2.1.2 Loss Function

This study used the categorical cross-entropy loss function to evaluate the model's performance during training. Equation (2.08) shows the mathematical expression for the loss function.

$$CE = -\sum_{i=1}^{N} y_i \log(\hat{y}_i) \tag{2.08}$$

where *CE* represents the Categorical Cross-entropy, *N* represents the number of classes, y_i indicates the prediction of the model, and $\hat{y}_i$ is the ground truth or the expected result from the model.

2.4.2.1.3 Optimizers

The Adam optimizer [66] was used in this study to optimize the loss function by updating the weights. Adam optimizer is an extension of two other gradient descent optimizers namely, gradient descent with momentum and Root Mean Square Propagation. It inherits the strengths of the two optimizers, which makes it more efficient in reaching the global minimum with the least oscillations and ensures that the algorithm does not get stuck in the local minima. Equation (2.09) shows how the network weights (w) may be updated using the algorithm.

$$w = w - \alpha \frac{V_{dw}}{\sqrt{S_{dw}} + \sigma} \tag{2.09}$$

$$V_{dw} = \beta_1 V_{dw} + (1 - \beta_1) dw \tag{2.10}$$

$$S_{dw} = \beta_2 S_{dw} + (1 - \beta_2)\, dw^2 \tag{2.11}$$

where α is the learning rate. β_1 and β_2 represents the decay rate of the moving average of gradients.

2.4.2.1.4 Performance Metrics

The NN's performance was determined using the following performance metrics: accuracy, recall, precision, and F-1 Score [67], as shown in equations (2.12) to (2.15).

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{2.12}$$

$$Recall = \frac{TP}{TP + FN} \tag{2.13}$$

$$Precision = \frac{TP}{TP + FP} \tag{2.14}$$

$$F-1\ score = \frac{2 * TP}{(2 * TP) + FP + FN} \tag{2.15}$$

where TP, TN, FP, FN represent the True Positive, True Negative, False Positive, and False Negative rates [67], respectively. Further, the area under the curve for the plot between the true positive rate and false positive rate was also calculated using Simpson's rule as a performance metric [68].

2.5 Musculoskeletal Model

In the recent past, patient-specific analysis and treatment have been gaining much attention as literature has shown that targeted therapies may be more efficacious than generic ones. While the KINARM provides upper-limb kinematic data that can be used to analyze sensory and cognitive networks, it still does not provide any information about the biomechanics of the movements, such as activity and contribution of individual muscles when performing a task. Earlier studies [69][70] have indicated an altered motor unit behavior, although the nature of this abnormality is unknown. Understanding the motor recruitment strategies in PD patients and how they may differ from healthy subjects may provide new insights into how PD may alter motor unit recruitments, which is an essential component in SMC functions. In addition to being used as an analysis tool, investigating the biomechanics of upper-limb movements in PD patients might be of clinical significance as the efficacy of certain treatments [71] that are now provided to mitigate motor symptoms require accurate estimation of biomechanical parameters, such as muscle activity and contribution.

Currently, the widely accepted method to measure muscle activity is surface electromyography (sEMG). While sEMG is considered the gold standard in measuring muscle activity, it has several inherent limitations. The primary limitation of sEMG is its inability to measure the activity of deep muscles, and the high chance of muscle crosstalk [72][73][74][75] when the superficial muscles are in close proximity to one another. This makes it difficult to accurately measure the activity of even the superficial muscles. Additionally, the output from the sEMG may also be contaminated with noise due to mechanical and motion artifacts [76], adversely affecting the quality of sEMG's output. Some of the limitations associated with sEMG may not apply to intramuscular EMG.

However, the intramuscular EMG is highly invasive and painful (in some cases, the patients need to be anesthetized) and is, therefore, seldom used [77][78]. Finally, while muscle activity can be measured using EMG despite its limitations, neither surface nor intramuscular EMG can be used to measure the relative contribution of individual muscles to a movement. While the most predominant methods for measuring muscle activity involve surface and intramuscular EMG, other methods such as ultrasonography (USG), radioligand imaging (18F- FDG PET/CT), and frequency analysis [71] have also been used. However, the accuracy and efficacy of these techniques have not been well established [79][80]. Finally, numerous muscle models [81][82] and machine learning models [83] have been discussed in earlier literature as an alternative to measuring muscle activities. However, these models suffer from a lack of detail (only a few muscles were designed in these models leaving out the remaining muscles) and lower prediction accuracy. These models are also not subject-specific, which may further reduce the accuracy of these models [84]. Therefore, there is a need for a detailed, accurate, patient-specific muscle model that can estimate the activity and contribution of individual muscles to analyze and effectively guide targeted therapies for treating PD. To this end, a musculoskeletal model was designed and developed to estimate the muscle activity and contribution, based on the upper-limb kinematic data. While the KINARM analysis involved extracting features using the acquired kinematic data, the musculoskeletal model can be considered an extension of this feature extraction as it uses the upper-limb joint data as an input to estimate the corresponding biomechanical parameters. The proposed muscle model has been validated using healthy subjects, and the result related to this validation are provided in the result section.

One potential application of this musculoskeletal model is to be used as a guiding tool for targeted therapies (lidocaine, botulinum toxin type A) [71]. Botulinum toxin injections are an effective targeted therapy in treating tremor in PD patients. It is ideally injected into the muscles that contribute to the tremor. As such, accurately identifying muscles that contribute to the tremor and how much each muscle contributes to this involuntary movement is necessary to determine the muscles that need to be injected and the dosage per muscle. Currently, muscle selection and dosage determination are made by intramuscular EMG and visual assessment [71][85]. However, this may not be an optimal

strategy because of the subjective nature of the visual assessment and the limitations of the intramuscular EMG discussed earlier. With the efficacy of the therapy heavily depending on whether the correct muscles are being injected with optimal dosage [86][87], the validated muscle may act as a guiding tool for dosage determination, which in turn may enhance the efficacy of the therapy. The methodology behind using the validated model to estimate the dosage has been explained in this chapter. Therefore, apart from being an in-depth analysis tool to study motor unit recruitments, this model can also be used to translate patient-specific information into a clinical setting, enhancing and optimizing the treatment plan for PD patients.

2.5.1 Design and Development of the Musculoskeletal Model

The musculoskeletal model discussed in this study was designed using the AnyBody Modeling System^{TM} (AMS^{TM}) (Version 7.2.3, AnyBody Technology) [88]. The model includes seven bones, 61 upper-limb muscles, and seven functional joints [89]. This section discusses the parameters used in designing each element of the model (bones, joints, and muscles) and the corresponding mathematical model. Figure 2.16 shows the upper-limb musculoskeletal model developed in this study.

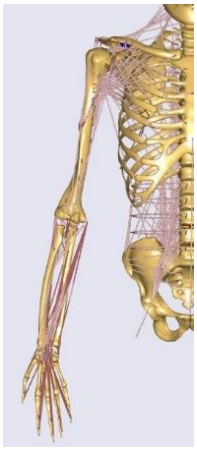


Figure 2.16: Musculoskeletal model

2.5.1.1 Bones

The model includes seven bone structures (rigid bodies): the humerus, radius, ulna, clavicle, scapula, hand, and thorax. When designing the rigid bodies, the effects of wobbly

masses of soft tissues were ignored. Equation (2.16) shows the position and orientation of an i^{th} rigid body [90]:

$$q_i = [r_i^T \quad p_i^T]^T \tag{2.16}$$

where r_i represents the position vector of the center of mass and p_i represents the four Euler parameters of the i^{th} rigid body. Further, the velocity of the i^{th} rigid body can be represented as shown in equation (2.17).

$$q_i = [\dot{r}_i^T \quad \omega'^T_i]^T \tag{2.17}$$

where $\dot{r}_i$ and ω'_i represents the linear and angular velocity of the i^{th} rigid body measured in the reference frame. Parameters such as length, mass, and radius of the rigid bodies also need to be set, and these parameters can be adjusted to fit the subjects.

2.5.1.2 Joints

Seven functional joints (wrist, elbow, radioulnar (forearm), glenohumeral (shoulder), scapulothoracic, acromioclavicular and sternoclavicular joints) were included in the model, which allows for the movement of the upper limb in multiple Degrees of Freedom (DOF). Each joint consists of two or more reference frames, which would be the rigid bodies (bones) connected to the joints. Table 2.10 shows the reference frames and the degree of freedom associated with each joint.

Table 2.10: Modeled joints, their corresponding DOF, and reference segments

Joints	Reference segments	DOF
Wrist	Radius and hand	2
Elbow	Humerus and ulna	1
Radioulnar	Radius and Ulna	1
Glenohumeral	Scapula and humerus	3
Acromioclavicular	Clavicula and scapula	3
Sternoclavicular	Thorax and clavicula	3
Scapulothoracic	Scapula and thorax	3

2.5.1.3 Muscles

Muscles facilitate joint movements, postural stability and maintain tone. In this study, 61 muscles critical to upper-limb movement were designed. Parameters such as PCSA, tendon slack length, neutral fiber length, and maximum isometric force must be estimated and inputted for each muscle. In this study, muscle parameters estimated through earlier cadaveric studies [91][92][93][94] were used to design the muscles and were kept constant throughout the study. While these parameters were kept constant, it is not a shortcoming of the model as it is possible to vary these parameters based on the subject. The model is capable of estimating activity taking into account the varying subject-specific parameters. The reason for keeping parameters such as PCSA constant is that calculating these parameters requires cost and time-intensive procedures such as MRI. To demonstrate the model's ability to predict activity for varying parameters, a separate section is included in Chapter-5, discussing the model's prediction for varying values of PCSA and neutral fiber length obtained from earlier studies. Table 2.11 shows the muscle parameters used in the model design.

Table 2.11: Muscle parameters

		PCSA (cm2)	**Tendon slack length (cm)**	**Neutral fiber length (cm)**	**Maximum isometric force (N)**
1	Biceps brachii caput breve	1.72	1.95E+01	1.50E+01	1.97E+02
2	Biceps brachii caput longum	1.78	2.75E+01	1.00E+01	1.89E+02
3	coracobrachialis	5.58E+00	7.82E+00	9.10E+00	524.3589
4	Deltoideus posterior	3.60E+00	3.41E+00	1.16E+01	338.2446
5	Deltoideus lateral	8.20E+00	5.96E+00	1.28E+01	770.446
6	Deltoideus anterior	5.44E+00	5.40E+00	1.40E+01	511.1251
7	Infraspinatus	8.16E+00	5.48E+00	6.50E+00	767.8152
8	Latissimus dorsi thoracic	1.302	12.6	14	122.4
9	Latissimus dorsi lumbar	2.48	22.7	14	233
10	Latissimus dorsi iliac	1.8	22.7	14	169
11	Levator scapulae	3.44E+00	6.23E+00	1.00E+01	323.3054
12	Pectoralis major clavicular part	2.60E+00	6.62E+00	1.20E+01	244.2877
13	Pectoralis major sternocostal part	3.90E+00	1.39E+01	1.20E+01	366.4316

14	Pectoralis major abdominal part	2.60E+00	1.43E+01	1.20E+01	244.2877
15	Pectoralis minor	3.43E+00	4.12E+00	8.00E+00	322.084
16	Rhomboid major	5.05E+00	9.14E+00	6.80E+00	474.1061
17	Rhomboid minor	2.52E+00	5.05E+00	6.80E+00	2.37E+02
18	Serratus Anterior superior part	3.81	12.25	7.3	358
19	Serratus Anterior middle part	1.905	8.86	7.3	179
20	Serratus Anterior inferior part	5.715	4.98	7.3	537
21	Subscapularis	1.50E+01	5.85E+00	8.00E+00	1409.352
22	Supraspinatus	4.68E+00	7.56E+00	4.70E+00	439.7179
23	Teres major	3.00E+00	7.24E+00	1.00E+01	281.8705
24	Teres minor	3.10E+00	5.04E+00	7.00E+00	290.8903
25	Trapezius ascending	4.37E+00	5.97E+00	9.81E+00	410.1215
26	Trapezius middle	4.37E+00	2.85E+00	9.89E+00	410.1215
27	Trapezius descending	8.73E+00	6.14E+00	1.00E+01	820.2431
28	Triceps long head	5.62E+00	2.38E+01	9.40E+00	744.138
29	Triceps lateral head	4.78E+00	1.01E+01	5.50E+00	719.7093
30	Triceps middle head	9.04E+00	7.41E+00	8.70E+00	986.5466
31	Brachialis	6.10E+00	7.39E-01	1.12E+01	573.5069
32	Brachioradialis	2.20E+00	1.48E+01	1.28E+01	206.7014
33	Anconeus	1.85E-01	3.32E+00	2.40E+00	112.0301
34	Pronator teres humeral head	1.86E+00	6.81E+00	6.65E+00	175.0883
35	Pronator teres Ulnar head	1.86E+00	6.49E+00	6.65E+00	1.75E+02
36	Supinator	1.19E+01	4.28E+00	4.00E+00	1118.62
37	pronator quadratus	2.18E+00	2.82E+00	2.00E+00	206.7014
38	Extensor Pollicis Longus	9.00E-01	15.272	5.5	8.46E+01
39	Extensor Pollicis Brevis	3.00E-01	6.253	6.8	2.82E+01
40	Abductor Pollicis Longus	1.30E+00	18.460	5.4	1.22E+02
41	Extensor Indicis	5.00E-01	16.540	5.9	4.70E+01
42	Extensor Carpi Ulnaris	2.10E+00	24.673	5.1	1.97E+02
43	Extensor Carpi Radialis Longus	2.20E+00	24.040	8.1	2.07E+02
44	Extensor Carpi Radialis Brevis	2.20E+00	24.445	5.9	2.07E+02
45	Flexor Carpi Radialis	1.60E+00	23.122	6.3	1.50E+02
46	Flexor Carpi Ulnaris	2.90E+00	23.972	5.1	2.72E+02
47	Palmaris Longus	6.00E-01	23.252	6.4	5.64E+01
48	Flexor Digitorum Superficialis Digit5	4.00E-01	33.284	5.2	3.76E+01

49	Flexor Digitorum Superficialis Digit4	1.30E+00	32.763	7.4	1.22E+02
50	Flexor Digitorum Superficialis Digit3	2.00E+00	33.294	7.5	1.88E+02
51	Flexor Digitorum Superficialis Digit2	1.40E+00	32.009	8.4	1.32E+02
52	Flexor Digitorum Profundus Digit5	1.80E+00	27.457	7.5	1.69E+02
53	Flexor Digitorum Profundus Digit4	1.40E+00	29.016	8	1.32E+02
54	Flexor Digitorum Profundus Digit3	1.80E+00	29.260	8.4	1.69E+02
55	Flexor Digitorum Profundus Digit2	1.50E+00	29.045	7.5	1.41E+02
56	Extensor Digitorum Digit5	3.00E-01	33.277	6.5	2.82E+01
57	Extensor Digitorum Digit4	8.00E-01	34.987	6.3	7.52E+01
58	Extensor Digitorum Digit3	8.00E-01	34.674	7.2	7.52E+01
59	Extensor Digitorum Digit2	4.00E-01	34.387	7	3.76E+01
60	Extensor Digiti Minimi	6.00E-01	35.265	6.8	5.64E+01
61	Flexor Pollicis Longus	1.70E+00	19.330	5.5	1.60E+02

Once the muscle parameters were set, the contact points for the muscles needed to be determined. Depending on the functionality and pathway of the muscles, either via-point or wrapping muscles were chosen when designing the muscles in the model. The final step was to determine how muscles needed to behave when performing a movement. In this study, a three-element hill muscle model [95] was chosen as it closely resembles the active and passive properties of the muscles in the human body. Figure 2.17 shows a schematic representation of the three-element muscle model. The L_m and L_t shown in Figure 2.17 represents the length of the muscle's contractile element and the tendon, respectively. As the name suggests, the model includes three crucial components: (i) a Contractile Component (CC) representing the active properties of the muscle, (ii) a Parallel Elastic Component (PEC) representing the passive properties of the muscle fibers (iii) a Serial Elastic Component (SEC) representing the elasticity of the tendon.

The active and passive components needed to be considered to accurately estimate the overall force generated by the muscle when performing a movement. Muscle force can be classified into two types (i) active force and (ii) passive force. The active force is required to carry out a task and is generated by the CC during muscle contraction. On the

other hand, passive tension arises from the PEC when the muscle is stretched beyond its resting length and is essential to maintaining the structural integrity of the muscle and bone. By considering the active and passive components of the muscle, the overall muscle force (F_m) can be calculated as shown in equation (2.18), which can then be used to estimate muscle activity and contribution.

$$F_m = F_P + F_A \cos\gamma \tag{2.18}$$

where F_P and F_A represent the passive and active forces, respectively. The γ represents the pennation angle of the muscle.

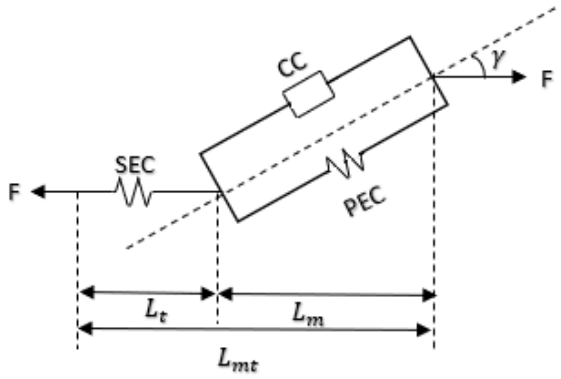


Figure 2.17: Three-element muscle model

2.5.2 Kinematic Analysis

This section discusses the kinematic analysis, i.e., how the joint kinematic data is used to replicate the movement imposed on the model. Based on the kinematic analysis, the inverse dynamics optimization algorithm (discussed in the next section) can determine the muscles needed to be recruited (activated) to perform the given movement. The kinematic analysis does not calculate the muscle force but only calculates the position, velocity, and acceleration of each rigid-body element, given the joint constraints while performing the movement.

The joint kinematic data was used as input to the model to perform the kinematic analysis. Each joint may contain more than one driver depending on the joint's DOF; therefore, the joint kinematic data must be provided for each driver assigned to the joints. For instance, a wrist joint had two drivers, one dedicated to flexion/extension movement

and the other reserved for abduction/adduction movement. Therefore, two sets of kinematic data pertaining to the wrist joint must be provided, one representing the wrist joint's flexion/ extension movement and the second representing the wrist joint's abduction/adduction movement. The modeling system uses system coordinate vectors, kinematic constraints, and Euler parameter constraints to perform its kinematic analysis. The nonlinear equation in (2.19) represents the constraints associated with drivers, Euler parameters, and holonomic joint constraints.

$$\Phi(q, t) = 0 \tag{2.19}$$

where t is explicit time and $q = [q_1^T \ldots\ldots q_n^T]^T$ is the coordinate vector for n rigid-body segments. For all the kinematically determinate problems [96], the modeling system performs the position analysis by solving the Jacobian constraint (Φ_q) using the Newton-Raphson scheme. Further, the velocity and acceleration constraints are solved using equations (2.20) and (2.21).

$$\emptyset_{q^*} v = -\emptyset_t \tag{2.20}$$

$$\emptyset_{q^*} \dot{v} = \gamma(q, v, t) \tag{2.21}$$

where $\emptyset_{q^*}$ is the transformed Jacobian with respect to q^*. By solving equations (2.20) and (2.21), the entire motion imposed by the joint kinematic data can be properly specified to the model to replicate the movement.

2.5.3 Motor Unit Recruitment

Human locomotion is achieved through the contraction of activated muscle fibers leading to the generation of force and power to overcome external resistive forces. While each muscle has multiple fibers that can contract to generate the force required to complete the desired task, selecting the appropriate muscles that need to be activated is crucial to the optimal execution of movements. The functional building blocks of muscles are motor units that activate the muscle fibers [97]. A single motor unit comprises a motor neuron and muscle fibers scattered across a localized region, with these muscle fibers innervated by the axon of the motor neuron. Motor unit recruitment is the phenomenon of different motor units recruited by the CNS, resulting in the corresponding muscle fibers being activated to exert the force required to perform the desired movement. Therefore, the CNS determines the force needed to perform a task and accordingly modulates the force exerted

by the muscle fibers through motor unit recruitment. The recruitment process is particularly complex due to the redundancy problem (humans have more muscles than strictly needed to perform specific tasks), as infinitely different sets of muscle groups can be recruited to perform a given action, and the CNS has to choose one of these muscle groups to drive the motion based on some rational criteria. Numerous studies [98][99][100][101] have attempted to explore the criteria used in the muscle recruitment process. However, currently, no optimal criterion is universally accepted as exactly explaining the criteria used by the CNS.

In this study, an inverse dynamics optimization algorithm [102][88] was used to determine the muscles that needed to be recruited and to estimate the corresponding muscle forces and moments based on the joint kinematic data and inertial forces. This muscle recruitment algorithm requires knowledge of the movements imposed on the model. The information from the kinematic analysis was used to determine the muscles that needed to be recruited and the force required to be generated to balance the external resistive force and successfully complete the imposed movement. The equilibrium equations in (2.22) and (2.23) represent the relation between the muscle and joint forces with the external and inertial forces. No additional external loads are applied in the study, and the gravity is compensated by simulating an equivalent load in the y-direction.

$$Cf = r \tag{2.22}$$

$$\begin{bmatrix} C^{(M)} & C^{(R)} \end{bmatrix} \begin{bmatrix} f^{(M)} \\ f^{(R)} \end{bmatrix} = r \tag{2.23}$$

where r represents the external forces and inertial forces, f is the vector containing the internal forces, which is divided between the muscle forces ($f^{(M)}$) and joint forces ($f^{(R)}$). Finally, C represents the coefficient matrix for the unknown muscle and joint forces. Any solution for muscle force must abide by this equilibrium equation. Equation (2.24) shows the non-negativity constraints on the estimated muscle force as the muscles can only pull and not push.

$$f_i^{(M)} \geq 0, i = 1, 2, n \tag{2.24}$$

Equation 2.22 shown above would provide infinitely many solutions for the muscle forces due to the redundancy problem explained earlier. Therefore, an objective function proposed by Rasmussen et al. [102] was used as a criterion to recruit muscles and estimate the optimal muscle forces pertaining to movement. Equations (2.25) and (2.26) show the optimization criteria used in this study.

$$Minimize\ G\left(f^{(M)}\right) \tag{2.25}$$

$$\begin{gathered} Subject\ to: \\ cf = r \\ f_i^{(M)} \geq 0, i = 1, 2, n \end{gathered} \tag{2.26}$$

G is the objective function that needs to be minimized to obtain the optimal solution for the muscle force. A polynomial criterion was used as the objective function (G), as shown in equation (2.27).

$$G = \sum_{i=1}^{n} \left(\frac{f_i^{(M)}}{N_i} \right)^P \tag{2.27}$$

In this study, N_i is the muscle strength and is used as a normalization factor in the objective function. This ensures that the larger and stronger muscles do more work and carry more load than the smaller and weaker muscles, which is physiologically reasonable. Through the normalization factor, the model also limits the maximum force that a muscle can produce at a given instant and considers the force-length-velocity relationship when predicting the muscle force. The normalization parameter, which is the time-dependent muscle strength parameter, is shown in equation (2.28).

$$N_i = F_0 \cos(\alpha) \widehat{F(l)} \widehat{F(v)} \tag{2.28}$$

where F_0 is the maximum isometric force for a muscle and adds a limit to the maximum force a given muscle can generate. $\widehat{F(l)}$ and $\widehat{F(v)}$ represent the normalized force-length and force-velocity relationship, thereby ensuring that any muscle force predicted using the objective function satisfies the force-velocity-length relationship. Finally, α represents the pennation angle of the muscle. The polynomial value (P) used in this study was three, as earlier studies [103] have suggested that a polynomial value of three had the least prediction error and promoted better muscle synergism.

2.5.4 Predicting Muscle Activity and Contribution

This section discusses how the active and passive forces predicted using the muscle recruitment criterion explained in the earlier section were used to estimate the activity and contribution of individual muscles.

2.5.4.1 Muscle Activity

Muscle activity can be defined as a representation of the percentage of fibers recruited in an individual muscle to enable a motion. Several studies [104] have discussed the relationship between muscle activity and active force produced by the muscle. One of the drawbacks of EMG activity is that it only represents the electrical activity of the muscle contraction and does take into consideration the mechanical aspects of the contraction. In this study, the muscle force has been estimated based on the objective function declared in the earlier section while considering the mechanical parameters, including the muscle's force-length-velocity relationship. Therefore, estimating muscle activity based on the predicted active force might accurately represent the percentage of muscle fibers recruited by CNS. As indicated earlier, muscle activity should indicate the percentage of muscle fibers recruited in an individual muscle. Therefore, the active force produced by the muscle was divided by the maximum force that could be produced during maximum voluntary contraction. Equation (2.29) shows how the individual muscle activity was estimated based on the active force.

$$MA_i = \frac{F_A^i}{F_{MVC}^i} \tag{2.29}$$

where F_A^i represents the active force generated by the i^{th} muscle at a given time instant, F_{MVC}^i indicates the force produced by the i^{th} muscle during maximum voluntary contraction and MA_i represents the activity of the i^{th} muscle. While the estimated muscle activity has numerous advantages over EMG activity owing to the accuracy and detail of the model, there also exist a few limitations. Since it is biologically possible that the muscle force may vary while the same volume of motor units is recruited by CNS, predicting the volume of recruited motor units based on the muscle force may lead to a mismatch between the predicted and actual activity. Therefore, some discrepancy between the EMG and

predicted activity can be attributed to this factor and needs further work for a more accurate estimation of the muscle activity.

2.5.4.2 Muscle Contribution

Muscle contribution is not a concept that has been widely explored in earlier studies. Neither the sEMG nor other existing methodologies can estimate the relative contribution of an individual muscle when performing a motion. In this study, muscle contribution represents the relative contribution of individual muscles in performing the imposed movement or maintaining joint stability. This is different from muscle activity as an activity only represents the percentage of fibers recruited in an individual muscle and does not provide any information about the relative contribution of a given muscle compared to other muscles that may be involved in the motion. However, the contribution indicates the relative percentage of an individual muscle's contribution while considering the other muscles involved in that movement. For instance, the biceps and brachioradialis might be involved in performing an elbow flexion. Activity only shows the fibers recruited by CNS in each of the two muscles; contribution provides information about how much each muscle has contributed to produce the force required to complete the elbow flexion. That is, it may be that 30% of the fibers from the biceps and 10% of the fibers from the brachioradialis were recruited to complete the flexion movement, and the muscle activity would represent this. On the other hand, the percentage that each muscle has contributed to performing the motion would be indicated in the muscle contribution. This would be different from muscle activity as the biceps, with their 30% of recruited fibers, may have produced 80% of the force required to complete the task, and 10% of the recruited brachioradialis fibers produced the remaining 20% of the force needed to complete the task. Equation (2.30) shows the methodology behind calculating the muscle contribution:

$$MC_j = \frac{\left(\overline{F_p^j} + \overline{F_A^j}\cos\,\gamma^j\right) * PCSA^j}{\sum_{k=1}^{n}\left(\overline{F_p^k} + \overline{F_A^k}\cos\,\gamma^k\right) * PCSA^k} \tag{2.30}$$

where $\overline{F_A^j}$, $\overline{F_P^j}$ represents the normalized active and passive forces for the j^{th} muscles respectively; $\overline{F_A^k}$, $\overline{F_P^k}$ represent the normalized active and passive forces for the k^{th} muscles respectively; $PCSA^k$ and $PCSA^j$ represent the PCSA for the k^{th} and j^{th} muscles

respectively; and γ^k and γ^j represent the pennation angles for the k^{th} and j^{th} muscles respectively.

2.5.5 Subject-Specific Modeling

The muscle model was designed to estimate muscle activity and contribution, taking into account the subject-specific parameters associated with bones, joints, and muscles. Studies [105][106][107] have shown that bone, joint, and muscle parameters influence the force produced by the muscles and, consequently, the activity and contribution of individual muscles. Furthermore, earlier literature [108][84] has also indicated that subject-specific muscle models may predict activity more accurately than generic models. Therefore, in this model, multiple parameters associated with bones, muscles, and joints may be altered based on the subjects. Table 2.12 shows all the parameters that may be altered to fit the subjects.

Table 2.12: Subject-specific parameters

	Bones	**Joints**	**Muscles**
Subject-Specific Parameters	a) Mass b) Radius c) Length d) Moment of Inertia	a) Joint Constraints (range of joint movements)	a) Muscle Path b) Insertion Point c) Origin Point d) Via Point e) Physiological Cross-Sectional Area (PCSA) f) Muscle Volume g) Fiber Length h) Tendon Length

2.5.5.1 Subject-Specific Bone Parameters

The major rigid body parameters that can be adjusted to fit the subjects are the radius, mass, and length of the rigid body. The length of the rigid body was estimated as a percentage of the subject's arm length and height. The mass of the rigid body was calculated as a percentage of the subject's overall body mass. The radius of the rigid body was calculated based on the estimated length and mass of the corresponding rigid body [109][110]. Finally, since the moment of inertia is a function of these parameters, the inertia was adjusted based on the subject's parameters.

2.5.5.2 Subject-Specific Joint Parameters

The joint parameters determine the constraints imposed on a given joint and the degrees of freedom associated with the attached rigid bodies. While these joint parameters may be kept constant for healthy subjects, patients with joint dysfunctions [111] or injuries [112] may have reduced joint mobility. Therefore, the joint constraints must be adjusted considering the injuries or dysfunctions.

2.5.5.3 Subject-Specific Muscle Parameters

Table 2.12 shows all the muscle parameters that can be altered in the muscle model to suit the subject. The two ends of the muscles attached to the rigid body – insertion and origin points have been adjusted based on the rigid body lengths. While all the parameters shown in Table 2.12 can be adjusted based on the subjects, estimating parameters such as muscle length, mass, volume, and PCSA requires extensive, time-consuming, and expensive techniques to be used. For instance, parameters such as PCSA can be estimated only through MRI, which is time-consuming and expensive. Therefore, throughout the study, these parameters were not altered. However, a separate result was included wherein these parameters were altered based on the existing dataset from earlier studies to showcase the model's ability to vary these parameters and take them into account when estimating the muscle force and, consequently, the muscle activity and contribution.

2.5.6 Model Validation

The overall working of the model is shown in Figure 2.18. The model used an inverse dynamics based optimization algorithm to estimate the muscle forces (as explained in Section 2.5.3) based on the joint kinematic data. The muscle force was then used to estimate the activity (explained in Section 2.5.4.1) and relative contribution (explained in Section 2.5.4.2) of individual muscles. The proposed model has been validated to determine the efficacy and accuracy of the model's output. Validation of the model was done by comparing the model's output with the sEMG output. The rationale behind using the normalized sEMG data to validate the proposed model was that while the sEMG does not provide an accurate representation of muscle activity, as discussed earlier, the sEMG is still the gold standard used in clinical practice. Therefore, despite the limitations of the

sEMG, the model's output was compared with the normalized sEMG data for validation. The sEMG data was only used to validate the model's output and does not play a role in the functioning of the model and in estimating the muscle force or activity.

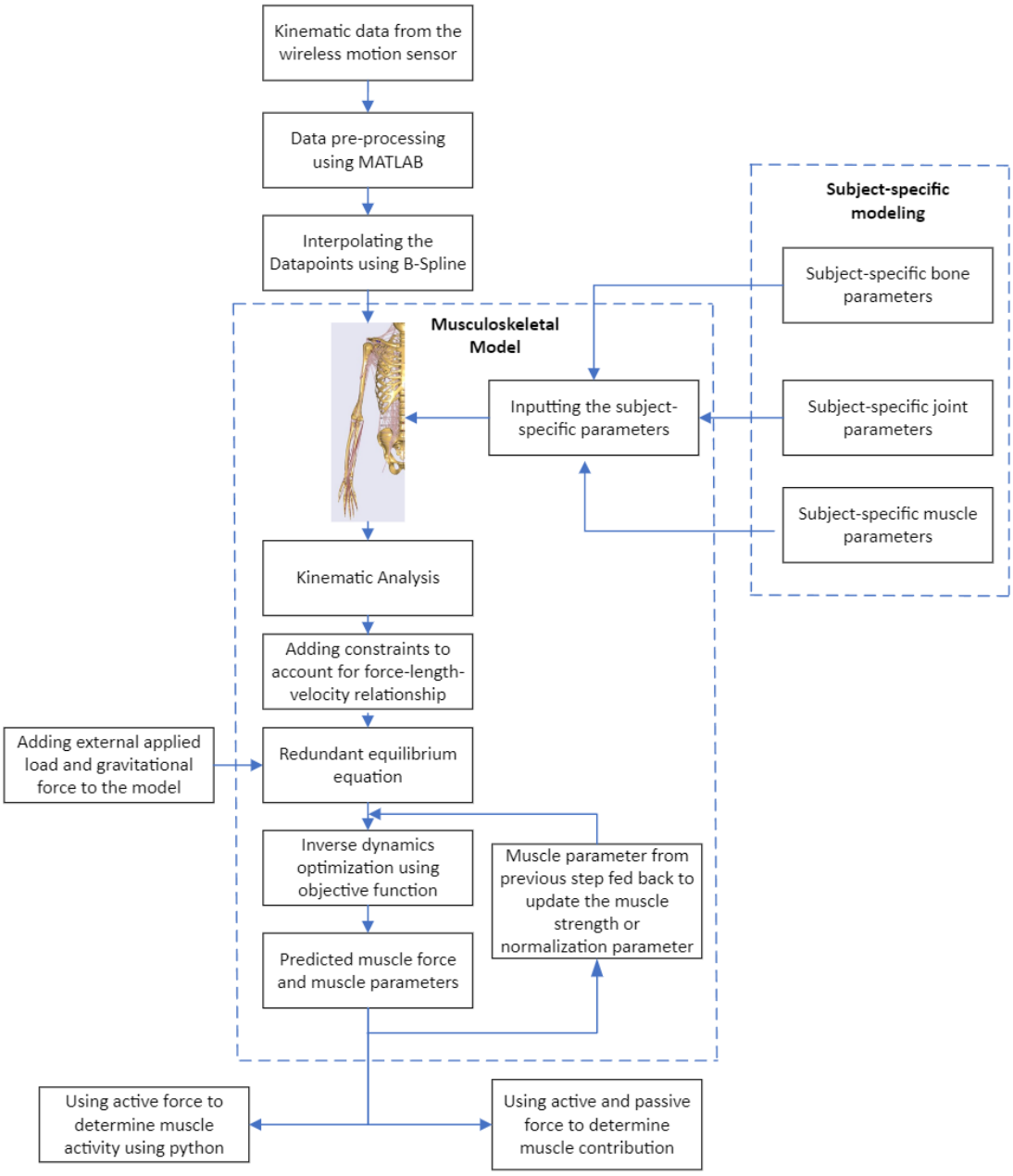


Figure 2.18: Flowchart indicating the working of the musculoskeletal model

Healthy subjects were recruited to perform five tasks involving a sequence of upper-limb movements requiring the motion of three different joints (wrist, elbow, and

shoulder). The subjects performed each task for five trials. The wireless motion sensors and sEMG sensors were attached to the healthy subjects when performing the sequence of movements. While the wireless motion sensors provided the joint kinematic data needed to drive the model, the sEMG sensors provided the normalized sEMG data required to validate the model's output. The model's output (muscle activity) pertaining to the upper-limb movements was compared with the normalized sEMG data corresponding to the exact motion. This section discusses the sequence of movements the subjects had to perform during the five tasks and how the kinematic joint data and normalized sEMG data was obtained when the subjects performed the upper-limb motions.

2.5.6.1 Kinematic Data Acquisition

Table 2.13: Placement of wireless sensors

Sensor	Placement
Wrist electro-goniometer	Posterior side of arm: third metacarpal and midline of the forearm
Forearm torsiometer	Anterior side of the forearm: mid-region of the forearm
Elbow electro-goniometer	Exterior side of the elbow: upper end of the forearm and lower end of the humerus
Shoulder electro-goniometer	Exterior side of shoulder: right over the deltoid muscle and between the shoulder point and neck joint

Electro-goniometers [113] and torsiometers were used to gather the joint kinematic data of the upper-limb joint. Three electro-goniometers were used, each gathering the joint data pertaining to the wrist, elbow, or shoulder movement. Additionally, one torsiometer was also used to capture the forearm movement. Table 2.13 shows the placement of the sensors on the upper limb. Figure 2.19 shows an image of the upper limb with the sensors attached to the joints. The data collected from the motion sensors were independent of each other [114].

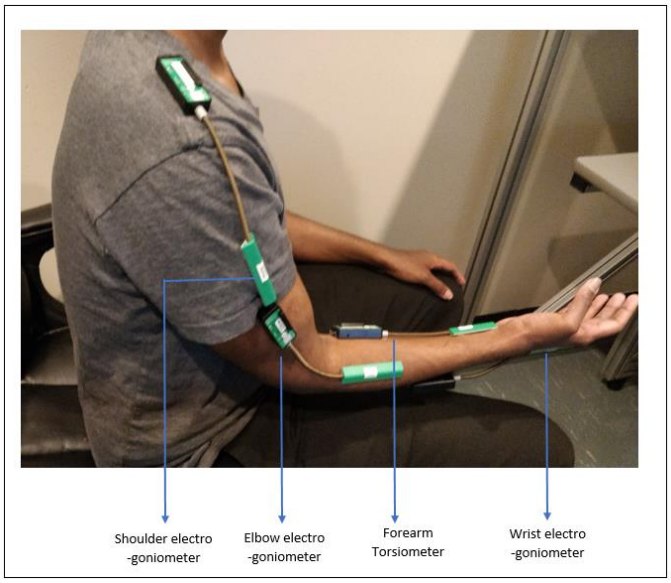


Figure 2.19: Placement of wireless motion sensors (electro-goniometers, torsiometer)

Before the joint kinematic data are used in the muscle model, the data needs to be pre-processed. In this study, the kinematic data obtained from the sensors were first filtered using a high pass filter to avoid any noise interference. Secondly and more importantly, there were offsets between the kinematic data collected from the sensors and what it may represent when fed into the muscle model. For instance, a fully flexed wrist in the muscle model corresponds to -90 degrees, and a fully extended wrist corresponds to 90 degrees. However, the kinematic data obtained from the sensor would be different as the range of values for the sensor may not be between -90 to 90 degrees. This offset was corrected after the filtering process for kinematic data pertaining to all joint movements. Table 2.14 shows the range of angles pertaining to every joint. Finally, a B-spline interpolation function [115][116] with an order of four was used on the kinematic data to obtain a smooth approximation of the data points.

Table 2.14: Range of joint angles

Movements	Joint angles (degrees)
Shoulder flexion/extension	-180 to 180
Shoulder abduction/adduction	0 to 180
Elbow flexion/extension	0 to 180
Forearm supination/pronation	-90 to 90
Wrist flexion/extension	-90 to 90
Wrist abduction/adduction	20 to -20

2.5.6.2 sEMG Data Acquisition

In this study, the sEMG data was collected at the same time the joint kinematic data was collected to ensure that both data correspond to the same motion. A Delsys multi-contact surface EMG sensor was used to calculate the muscle activity of eight superficial muscles (Biceps, Triceps, Flexor Carpi Radialis (FCR), Extensor Carpi Radialis (ECR), Deltoid, Teres Major, Pectoralis Major, Latissimus Dorsi) when the participants were performing the five different upper-limb tasks. To avoid noise and extract essential information, based on the recommendations in [117], the sampling rate was kept at 1000 Hz. Finally, the sEMG data was rectified and filtered using a second-order Butterworth filter with a cut-off frequency of 20 Hz [76]. The sEMG recordings obtained from the superficial muscles were normalized using the root mean squared value of the amplitude of sEMG data obtained at MVC.

2.5.6.3 Sequence of Movements

In this study, the participants performed five distinct tasks, each involving a sequence of upper-limb movements. Table 2.15 shows the five tasks that the participants performed during the study.

Table 2.15: Five tasks performed for model validation

	Movement sequence
Task 1	Shoulder flexion to 90 degrees with the fully supinated forearm – elbow flexion to 90 degrees – Maximum wrist flexion – Maximum wrist extension– Neutral wrist position– Elbow extension (neutral elbow position) - Shoulder extension (neutral shoulder position)
Task 2	Elbow flexion to 90 degrees with the fully supinated forearm– Forearm semi-pronation – Maximum forearm supination – Elbow extension (neutral elbow position)
Task 3	Shoulder abduction to 90 degrees with neutral forearm position – Maximum forearm supination – Maximum wrist abduction – Maximum wrist adduction – Neutral wrist position – Neutral forearm position (Semi-prone) – Shoulder adduction (neutral shoulder position)
Task 4	Shoulder abduction to 90 degrees with the fully supinated forearm – Wrist rotation – Shoulder adduction (neutral shoulder position)
Task 5	Elbow flexion to 90 degrees with neutral forearm position - Shoulder abduction to 90 degrees – Maximum wrist flexion – Neutral wrist position – Shoulder adduction (neutral shoulder position) – Elbow extension (neutral elbow position)

While the sequence of movements involves three functional joints and the corresponding rigid bodies, other rigid bodies that were not involved in this sequence of movements, such as the scapula and clavicle, were also modeled in this study. Furthermore, the muscle activity corresponding to the scapula or clavicle movements can also be calculated. Therefore, to showcase this ability of the model, an additional result is added in the result section wherein the clavicle and scapula movements, such as shoulder protraction/retraction and shoulder elevation/depression, were performed, and related muscle activity was shown.

2.5.6.4 Performance Metrics

Muscle activity predicted by the muscle model was compared with the normalized sEMG data obtained from the participants. It must be noted that the predicted and actual muscle activity was divided into sectors based on the timed change of the movements. Only the predicted activity of a specific sector was compared to the sEMG activity of the same sector. In this study, two metrics were used to evaluate the performance of the muscle model by comparing its output with normalized sEMG recordings. The Root Mean Squared Error (RMSE) was calculated separately for each sector between the predicted and actual activity pertaining to each of the eight superficial muscles. The RMSE from the sectors was then averaged together for each muscle. Equation (2.31) shows how RMSE was calculated using the actual and predicted activity.

$$RMSE = \sqrt{\overline{(MA_{EMG} - MA_{SIM})^2}} \tag{2.31}$$

where MA_{EMG} and MA_{SIM} indicate the sEMG activity and predicted activity, respectively. Similarly, the Pearson correlation coefficient between predicted and actual activity was computed for each sector and combined using the Fisher's Z transformation method [55][118] for each muscle. Finally, a test to determine the significance of the correlation coefficient [119][120] was calculated alongside the Pearson correlation coefficient, and the harmonic mean method [57] was used to combine the *p*-values. A *p*-value less than 0.05 was considered to be statistically significant. Equation (2.32) shows the method used to calculate the Pearson correlation coefficient.

$$r = \frac{\sum_{i=1}^{n}\left(MA_{EMG_i} - \overline{MA_{EMG}}\right)\left(MA_{SIM_i} - \overline{MA_{SIM}}\right)}{\sqrt{\sum_{i=1}^{n}\left(MA_{EMG_i} - \overline{MA_{EMG}}\right)^2}\sqrt{\sum_{i=1}^{n}\left(MA_{SIM_i} - \overline{MA_{SIM}}\right)^2}} \tag{2.32}$$

2.5.7 A Prospective Application of the Model

One of the primary reasons behind validating the muscle model was to ensure that it could be used in a clinical setting. Apart from using the muscle model as an analysis tool to study the muscle recruitment strategies, which are a vital part of SMC functions, the muscle model may also be used to improve the efficacy of certain PD-related treatments. This section discusses one potential application - the estimation of Botulinum toxin dosage using the muscle model. Identifying the correct muscles to be injected and the dosage per

muscle is vital to the success of the therapy. Using the muscle contribution and activity from the muscle model, a method was devised to estimate the dosage per muscle. The muscle contribution estimated by the model may be used to determine how much each muscle contributes to the tremor movement. The kinematic data of the PD patients undergoing the therapy was obtained. The methodology behind obtaining the kinematic data has been explained earlier. Based on the tremor movement imposed by the kinematic data, the muscle model predicted the muscle contribution using equation (2.30). A total of nine upper-limb muscles (prime movers of elbow, forearm, and wrist joint) were considered for injection. The dosage pertaining to these muscles was estimated based on the muscle contribution. As indicated earlier, all the PD patients involved in this part of the study were undergoing the therapy. Therefore, the actual dosage provided to the patients was used as a baseline to estimate future dosage using the muscle model. Equation (2.33) shows the methodology used to estimate the dosage of the elbow (Biceps, Triceps), wrist (FCR, ECR, FCU, ECU), and forearm (supinator, pronator teres (PT), pronator quadratus (PQ)) muscles.

$$Dosage\ of\ i^{th} Muscle = total\ dosage\ to\ the\ muscle\ groups * contribution\ of\ the\ i^{th}\ muscle \quad (2.33)$$

The total dosage to the muscle groups indicates the sum of all the dosages provided to the muscle group of interest during the previous clinic visit. The total dosage for the muscle groups was calculated based on the work of Samotus et al [114] [87]. For instance, when estimating the dosage of FCR (one of the prime movers of the wrist joint), the total dosage provided to all the prime movers (FCR, ECR, FCU, ECU) of the wrist joint corresponds to the total dosage of the muscle groups. Likewise, when estimating the dosage for the muscle responsible for forearm movement, the total dosage to the muscle groups would indicate the sum of the dosage provided to the supinator, PT, and PQ. Finally, to estimate the dosage for the muscles involved in elbow motion, the total dosage to the muscle groups would be the sum of the dosages provided to the biceps and triceps.

2.6 References

[1] C. S. Mang *et al.*, “Robotic Assessment of Motor, Sensory, and Cognitive Function in Acute Sport-Related Concussion and Recovery,” *J Neurotrauma*, vol. 36, no. 2, pp. 308–321, Jan. 2019, doi: 10.1089/neu.2017.5587.

[2] C. S. Mang *et al.*, “Test-retest reliability of the KINARM end-point robot for assessment of sensory, motor and neurocognitive function in young adult athletes,” *PLoS One*, 2018, doi: 10.1371/journal.pone.0196205.

[3] Documentation and Simulink, “Simulation and Model-Based Design,” *https://www.mathworks.com/products/simulink.html*, 2020.

[4] H. E. Kim, G. Avraham, and R. B. Ivry, “The Psychology of Reaching: Action Selection, Movement Implementation, and Sensorimotor Learning,” *Annu Rev Psychol*, vol. 72, no. 1, pp. 61–95, Jan. 2021, doi: 10.1146/annurev-psych-010419-051053.

[5] L. K. Chinn, M. Hoffmann, J. E. Leed, and J. J. Lockman, “Reaching with one arm to the other: Coordinating touch, proprioception, and action during infancy,” *J Exp Child Psychol*, vol. 183, pp. 19–32, Jul. 2019, doi: 10.1016/j.jecp.2019.01.014.

[6] P. N. Sabes, “Chapter 13 - Sensory integration for reaching: Models of optimality in the context of behavior and the underlying neural circuits,” in *Progress in Brain Research*, 2011, pp. 195–209. doi: 10.1016/B978-0-444-53752-2.00004-7.

[7] S. J. Sober and P. N. Sabes, “Flexible strategies for sensory integration during motor planning,” *Nat Neurosci*, vol. 8, no. 4, pp. 490–497, Apr. 2005, doi: 10.1038/nn1427.

[8] D. P. Sadaphal, A. Kumar, and P. K. Mutha, “Sensorimotor Learning in Response to Errors in Task Performance,” *eNeuro*, vol. 9, no. 2, Mar. 2022, doi: 10.1523/ENEURO.0371-21.2022.

[9] P. Sabes, “The planning and control of reaching movements,” *Curr Opin Neurobiol*, vol. 10, no. 6, pp. 740–746, Dec. 2000, doi: 10.1016/S0959-4388(00)00149-5.

[10] A. d’Avella, “Reaching Movements,” in *Encyclopedia of Neuroscience*, Berlin, Heidelberg: Springer Berlin Heidelberg, pp. 3363–3367. doi: 10.1007/978-3-540-29678-2_4936.

[11] J. F. Kalaska and D. J. Crammond, “Cerebral Cortical Mechanisms of Reaching Movements,” *Science (1979)*, vol. 255, no. 5051, pp. 1517–1523, Mar. 1992, doi: 10.1126/science.1549781.

[12] S. J. Sober and P. N. Sabes, “Flexible strategies for sensory integration during motor planning,” *Nat Neurosci*, vol. 8, no. 4, pp. 490–497, Apr. 2005, doi: 10.1038/nn1427.

[13] M. O. Ernst and H. H. Bülthoff, “Merging the senses into a robust percept,” *Trends Cogn Sci*, vol. 8, no. 4, pp. 162–169, Apr. 2004, doi: 10.1016/j.tics.2004.02.002.

[14] N. Lelis-Torres, H. Ugrinowitsch, T. Apolinário-Souza, R. N. Benda, and G. M. Lage, “Task engagement and mental workload involved in variation and repetition of a motor skill,” *Sci Rep*, vol. 7, no. 1, p. 14764, Dec. 2017, doi: 10.1038/s41598-017-15343-3.

[15] M. Thomas, A. Lenka, and P. Kumar Pal, “Handwriting Analysis in Parkinson’s Disease: Current Status and Future Directions,” *Mov Disord Clin Pract*, vol. 4, no. 6, pp. 806–818, Nov. 2017, doi: 10.1002/mdc3.12552.

[16] P. Dahdal *et al.*, “Fine Motor Function Skills in Patients with Parkinson Disease with and without Mild Cognitive Impairment,” *Dement Geriatr Cogn Disord*, vol. 42, no. 3–4, pp. 127–134, 2016, doi: 10.1159/000448751.

[17] H.-L. Teulings, J. L. Contreras-Vidal, G. E. Stelmach, and C. H. Adler, “Parkinsonism Reduces Coordination of Fingers, Wrist, and Arm in Fine Motor Control,” *Exp Neurol*, vol. 146, no. 1, pp. 159–170, Jul. 1997, doi: 10.1006/exnr.1997.6507.

[18] M. Desmurget, V. Gaveau, P. Vindras, R. S. Turner, E. Broussolle, and S. Thobois, “On-line motor control in patients with Parkinson’s disease,” *Brain*, 2004, doi: 10.1093/brain/awh206.

[19] K. Herlofson and B. M. Kluger, “Fatigue in Parkinson’s disease,” *J Neurol Sci*, vol. 374, pp. 38–41, Mar. 2017, doi: 10.1016/j.jns.2016.12.061.

[20] J. H. Friedman *et al.*, “Fatigue in Parkinson’s disease: A review,” *Movement Disorders*, vol. 22, no. 3, pp. 297–308, Feb. 2007, doi: 10.1002/mds.21240.

[21] M. O. Ernst and M. S. Banks, “Humans integrate visual and haptic information in a statistically optimal fashion,” *Nature*, 2002, doi: 10.1038/415429a.

[22] M. O. Ernst, J.-P. Bresciani, K. Drewing, and H. H. Bülthoff, “Integration of Sensory Information Within Touch and Across Modalities,” *Proceedings of the 2004 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS 2004)*, 2004.

[23] A. F. de C. Hamilton and D. M. Wolpert, “Controlling the Statistics of Action: Obstacle Avoidance,” *J Neurophysiol*, vol. 87, no. 5, pp. 2434–2440, May 2002, doi: 10.1152/jn.2002.87.5.2434.

[24] R. G. Cohen, J. C. Biddle, and D. A. Rosenbaum, “Manual obstacle avoidance takes into account visual uncertainty, motor noise, and biomechanical costs,” *Exp Brain Res*, vol. 201, no. 3, pp. 587–592, Mar. 2010, doi: 10.1007/s00221-009-2042-8.

[25] J. B. Doan, N. de Bruin, S. M. Pellis, O. Suchowersky, I. Q. Whishaw, and L. A. Brown, “Obstacle Avoidance amongst Parkinson Disease Patients Is Challenged in a Threatening Context,” *J Neurodegener Dis*, vol. 2013, pp. 1–8, May 2013, doi: 10.1155/2013/787861.

[26] D. Orcioli-Silva, R. Vitório, E. Lirani-Silva, P. C. R. Santos, V. S. Beretta, and L. T. B. Gobbi, “Objective measures of unobstructed walking and obstacle avoidance in Parkinson’s disease subtypes,” *Gait Posture*, vol. 62, pp. 405–408, May 2018, doi: 10.1016/j.gaitpost.2018.03.046.

[27] J. Konczak *et al.*, “Proprioception and Motor Control in Parkinson’s Disease,” *J Mot Behav*, vol. 41, no. 6, pp. 543–552, Nov. 2009, doi: 10.3200/35-09-002.

[28] D. W. Franklin and D. M. Wolpert, “Computational Mechanisms of Sensorimotor Control,” *Neuron*, vol. 72, no. 3, pp. 425–442, Nov. 2011, doi: 10.1016/j.neuron.2011.10.006.

[29] S. H. Creem-Regehr, “Sensory-motor and cognitive functions of the human posterior parietal cortex involved in manual actions,” *Neurobiol Learn Mem*, 2009, doi: 10.1016/j.nlm.2008.10.004.

[30] G. Abbruzzese, R. Marchese, L. Avanzino, and E. Pelosin, “Rehabilitation for Parkinson’s disease: Current outlook and future challenges,” *Parkinsonism Relat Disord*, 2016, doi: 10.1016/j.parkreldis.2015.09.005.

[31] L. Craighero, “The Role of the Sensorimotor System in Cognitive Functions,” *Brain Sci*, vol. 12, no. 5, p. 604, May 2022, doi: 10.3390/brainsci12050604.

[32] L. L. Edwards, E. M. King, C. M. Buetefisch, and M. R. Borich, “Putting the ‘Sensory’ Into Sensorimotor Control: The Role of Sensorimotor Integration in Goal-Directed Hand Movements After Stroke,” *Front Integr Neurosci*, vol. 13, May 2019, doi: 10.3389/fnint.2019.00016.

[33] S. Chivukula, M. Jafari, T. Aflalo, N. A. Yong, and N. Pouratian, "Cognition in Sensorimotor Control: Interfacing With the Posterior Parietal Cortex," *Front Neurosci*, vol. 13, Feb. 2019, doi: 10.3389/fnins.2019.00140.

[34] J. A. Semrau, T. M. Herter, J. M. Kenzie, S. E. Findlater, S. H. Scott, and S. P. Dukelow, "Robotic Characterization of Ipsilesional Motor Function in Subacute Stroke," *Neurorehabil Neural Repair*, vol. 31, no. 6, pp. 571–582, Jun. 2017, doi: 10.1177/1545968317704903.

[35] M. Zappia, R. Montesanti, R. Colao, and A. Quattrone, "Usefulness of movement time in the assessment of Parkinson's disease," *J Neurol*, vol. 241, no. 9, pp. 543–550, 1994, doi: 10.1007/BF00873517.

[36] M. Nolano *et al.*, "Sensory deficit in Parkinson's disease: Evidence of a cutaneous denervation," *Brain*, 2008, doi: 10.1093/brain/awn102.

[37] G. Abbruzzese and A. Berardelli, "Sensorimotor integration in movement disorders," *Movement Disorders*. 2003. doi: 10.1002/mds.10327.

[38] R. S. Weil, A. E. Schrag, J. D. Warren, S. J. Crutch, A. J. Lees, and H. R. Morris, "Visual dysfunction in Parkinson's disease," *Brain*, vol. 139, no. 11, pp. 2827–2843, Nov. 2016, doi: 10.1093/brain/aww175.

[39] B. Dubois and B. Pillon, "Cognitive deficits in Parkinson's disease," *J Neurol*, vol. 244, no. 1, pp. 2–8, Nov. 1996, doi: 10.1007/PL00007725.

[40] R. McN. Alexander, "A minimum energy cost hypothesis for human arm trajectories," *Biol Cybern*, vol. 76, no. 2, pp. 97–105, Feb. 1997, doi: 10.1007/s004220050324.

[41] T. F. Hornbein, B. D. Townes, R. B. Schoene, J. R. Sutton, and C. S. Houston, "The Cost to the Central Nervous System of Climbing to Extremely High Altitude," *New England Journal of Medicine*, vol. 321, no. 25, pp. 1714–1719, Dec. 1989, doi: 10.1056/NEJM198912213212505.

[42] E. Todorov, "Optimality principles in sensorimotor control," *Nature Neuroscience*. 2004. doi: 10.1038/nn1309.

[43] C. M. Harris and D. M. Wolpert, "Signal-dependent noise determines motor planning," *Nature*, 1998, doi: 10.1038/29528.

[44] F. C. Anderson and M. G. Pandy, "Dynamic optimization of human walking," *J Biomech Eng*, 2001, doi: 10.1115/1.1392310.

[45] T. Flash and N. Hogan, "The coordination of arm movements: An experimentally confirmed mathematical model," *Journal of Neuroscience*, 1985, doi: 10.1523/jneurosci.05-07-01688.1985.

[46] N. Hogan, "An organizing principle for a class of voluntary movements," *Journal of Neuroscience*, 1984, doi: 10.1523/jneurosci.04-11-02745.1984.

[47] E. Todorov and M. I. Jordan, "Optimal feedback control as a theory of motor coordination," *Nat Neurosci*, 2002, doi: 10.1038/nn963.

[48] C. M. R. Kitchen, "Nonparametric vs Parametric Tests of Location in Biomedical Research," *Am J Ophthalmol*, vol. 147, no. 4, pp. 571–572, Apr. 2009, doi: 10.1016/j.ajo.2008.06.031.

[49] N. Leech and A. Onwuegbuzie, "A Call for Greater Use of Nonparametric Statistics," *Annual Meeting of the Mid-South Educational Research Association*, Oct. 2002.

[50] D. W. Zimmerman, "Increasing the Power of Nonparametric Tests by Detecting and Downweighting Outliers," *The Journal of Experimental Education*, vol. 64, no. 1, pp. 71–78, Oct. 1995, doi: 10.1080/00220973.1995.9943796.

[51] D. W. Zimmerman, “A Note on the Influence of Outliers on Parametric and Nonparametric Tests,” *J Gen Psychol*, vol. 121, no. 4, pp. 391–401, Oct. 1994, doi: 10.1080/00221309.1994.9921213.

[52] K. F. Weaver, V. Morales, S. L. Dunn, K. Godde, and P. F. Weaver, “ Mann-Whitney U and Wilcoxon Signed-Rank ,” in *An Introduction to Statistical Analysis in Research*, 2017. doi: 10.1002/9781119454205.ch7.

[53] R. A. Armstrong, “When to use the Bonferroni correction,” *Ophthalmic and Physiological Optics*, vol. 34, no. 5, pp. 502–508, Sep. 2014, doi: 10.1111/opo.12131.

[54] A. J. Bishara and J. B. Hittner, “Testing the significance of a correlation with nonnormal data: Comparison of Pearson, Spearman, transformation, and resampling approaches.,” *Psychol Methods*, vol. 17, no. 3, pp. 399–417, Sep. 2012, doi: 10.1037/a0028087.

[55] N. C. Silver and W. P. Dunlap, “Averaging Correlation Coefficients: Should Fisher’s z Transformation Be Used?,” *Journal of Applied Psychology*, 1987, doi: 10.1037/0021-9010.72.1.146.

[56] L. Myers and M. J. Sirois, “Spearman Correlation Coefficients, Differences between,” in *Encyclopedia of Statistical Sciences*, Hoboken, NJ, USA: John Wiley & Sons, Inc., 2006. doi: 10.1002/0471667196.ess5050.pub2.

[57] D. J. Wilson, “The harmonic mean p-value for combining dependent tests,” *Proc Natl Acad Sci U S A*, 2019, doi: 10.1073/pnas.1814092116.

[58] A. K. Jain, P. W. Duin, and Jianchang Mao, “Statistical pattern recognition: a review,” *IEEE Trans Pattern Anal Mach Intell*, vol. 22, no. 1, pp. 4–37, 2000, doi: 10.1109/34.824819.

[59] B. Remeseiro and V. Bolon-Canedo, “A review of feature selection methods in medical applications,” *Comput Biol Med*, vol. 112, p. 103375, Sep. 2019, doi: 10.1016/j.compbiomed.2019.103375.

[60] C. Kingsford and S. L. Salzberg, “What are decision trees?,” *Nat Biotechnol*, vol. 26, no. 9, pp. 1011–1013, Sep. 2008, doi: 10.1038/nbt0908-1011.

[61] T. Daniya, M. Geetha, and K. Suresh Kumar, “Classification and Regression Trees with Gini Index,” *Advances in Mathematics: Scientific Journal*, vol. 9, no. 10, Sep. 2020, doi: 10.37418/amsj.9.10.53.

[62] W. S. McCulloch and W. Pitts, “A logical calculus of the ideas immanent in nervous activity,” *Bull Math Biophys*, vol. 5, no. 4, pp. 115–133, Dec. 1943, doi: 10.1007/BF02478259.

[63] S. Agatonovic-Kustrin and R. Beresford, “Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research,” *J Pharm Biomed Anal*, vol. 22, no. 5, pp. 717–727, Jun. 2000, doi: 10.1016/S0731-7085(99)00272-1.

[64] M. Abadi *et al.*, “TensorFlow: Large-Scale Machine Learning on Heterogeneous Distributed Systems,” *Preliminary White Paper*, Mar. 2016, Accessed: Mar. 26, 2023. [Online]. Available: http://download.tensorflow.org/paper/whitepaper2015.pdf

[65] M. S. Alzubaidi *et al.*, “The Role of Neural Network for the Detection of Parkinson’s Disease: A Scoping Review.,” *Healthcare (Basel)*, vol. 9, no. 6, Jun. 2021, doi: 10.3390/healthcare9060740.

[66] D. P. Kingma and J. Ba, “Adam: A Method for Stochastic Optimization,” *3rd International Conference for Learning Representations*, Dec. 2014.

[67] G. Canbek, S. Sagiroglu, T. T. Temizel, and N. Baykal, “Binary classification performance measures/metrics: A comprehensive visualized roadmap to gain new insights,” in *2017*

International Conference on Computer Science and Engineering (UBMK), IEEE, Oct. 2017. doi: 10.1109/UBMK.2017.8093539.

[68] A. P. Bradley, "The use of the area under the ROC curve in the evaluation of machine learning algorithms," *Pattern Recognit*, vol. 30, no. 7, pp. 1145–1159, Jul. 1997, doi: 10.1016/S0031-3203(96)00142-2.

[69] D. S. Glendinning and R. M. Enoka, "Motor Unit Behavior in Parkinson's Disease," *Phys Ther*, vol. 74, no. 1, pp. 61–70, Jan. 1994, doi: 10.1093/ptj/74.1.61.

[70] O. Darbin and E. B. Montgomery, "Challenges for future theories of Parkinson pathophysiology," *Neurosci Res*, vol. 177, pp. 1–7, Apr. 2022, doi: 10.1016/j.neures.2021.11.010.

[71] A. I. Grigoriu, M. Dinomais, O. Rémy-Néris, and S. Brochard, "Impact of injection-guiding techniques on the effectiveness of botulinum toxin for the treatment of focal spasticity and dystonia: A systematic review," *Ann Phys Rehabil Med*, 2015, doi: 10.1016/j.rehab.2015.07.193.

[72] R. V. Miller, "Electromyography; uses and limitations.," *Calif Med*, vol. 89, no. 4, pp. 250–252, 1958.

[73] Eleanor. Criswell and J. R. Cram, *Cram's introduction to surface electromyography*, vol. second edition. Jones and Bartlett, 2011.

[74] B. C. Fortune, L. R. McKenzie, L. T. Chatfield, and C. G. Pretty, "Crosstalk Removal in Stimulus-evoked Forearm Electromyography," *IFAC-PapersOnLine*, vol. 51, no. 27, pp. 315–320, 2018, doi: 10.1016/j.ifacol.2018.11.622.

[75] J. P. M. Mogk and P. J. Keir, "Crosstalk in surface electromyography of the proximal forearm during gripping tasks," *Journal of Electromyography and Kinesiology*, vol. 13, no. 1, pp. 63–71, Feb. 2003, doi: 10.1016/S1050-6411(02)00071-8.

[76] C. J. De Luca, L. Donald Gilmore, M. Kuznetsov, and S. H. Roy, "Filtering the surface EMG signal: Movement artifact and baseline noise contamination," *J Biomech*, vol. 43, no. 8, pp. 1573–1579, May 2010, doi: 10.1016/j.jbiomech.2010.01.027.

[77] R. H. Chowdhury, M. B. I. Reaz, M. A. bin Mohd Ali, A. A. A. Bakar, K. Chellappan, and T. G. Chang, "Surface electromyography signal processing and classification techniques," *Sensors (Switzerland)*. 2013. doi: 10.3390/s130912431.

[78] A. Péter *et al.*, "Comparing Surface and Fine-Wire Electromyography Activity of Lower Leg Muscles at Different Walking Speeds," *Front Physiol*, vol. 10, Oct. 2019, doi: 10.3389/fphys.2019.01283.

[79] I. H. Lee, Y. C. Yoon, D. H. Sung, J. W. Kwon, and J. Y. Jung, "Initial experience with imaging-guided intramuscular botulinum toxin injection in patients with idiopathic cervical dystonia," *American Journal of Roentgenology*, 2009, doi: 10.2214/AJR.08.1535.

[80] H. S. Duk *et al.*, "Localization of dystonic muscles with 18F-FDG PET/CT in idiopathic cervical dystonia," *Journal of Nuclear Medicine*, 2007, doi: 10.2967/jnumed.107.044024.

[81] E. Pennestrì, R. Stefanelli, P. P. Valentini, and L. Vita, "Virtual musculo-skeletal model for the biomechanical analysis of the upper limb," *J Biomech*, 2007, doi: 10.1016/j.jbiomech.2006.05.013.

[82] M. Millard, T. Uchida, A. Seth, and S. L. Delp, "Flexing computational muscle: Modeling and simulation of musculotendon dynamics," *J Biomech Eng*, 2013, doi: 10.1115/1.4023390.

[83] L. A. Johnson and A. J. Fuglevand, “Evaluation of probabilistic methods to predict muscle activity: Implications for neuroprosthetics,” *J Neural Eng*, 2009, doi: 10.1088/1741-2560/6/5/055008.

[84] R. Akhundov *et al.*, “Is subject-specific musculoskeletal modelling worth the extra effort or is generic modelling worth the shortcut?,” *PLoS One*, vol. 17, no. 1, p. e0262936, Jan. 2022, doi: 10.1371/journal.pone.0262936.

[85] O. Samotus, “Characterization and personalization of botulinum toxin type A therapy for upper limb tremor in Parkinson disease and Essential tremor patients using multi-sensor kinematic technology,” 2016. Accessed: Aug. 04, 2023. [Online]. Available: https://ir.lib.uwo.ca/etd/4035

[86] S. O. Mittal, D. Machado, D. Richardson, D. Dubey, and B. Jabbari, “Botulinum Toxin in Parkinson Disease Tremor: A Randomized, Double-Blind, Placebo-Controlled Study With a Customized Injection Approach,” *Mayo Clin Proc*, 2017, doi: 10.1016/j.mayocp.2017.06.010.

[87] O. Samotus, J. Lee, and M. Jog, “Personalized Bilateral Upper Limb Essential Tremor Therapy with Botulinum Toxin Using Kinematics,” *Toxins (Basel)*, vol. 11, no. 2, p. 125, Feb. 2019, doi: 10.3390/toxins11020125.

[88] J. Rasmussen, M. Damsgaard, E. Surma, S. T. Christensen, M. de Zee, and V. Vondrak, “AnyBody - a software system for ergonomic optimization,” *Fifth World Congress on Structural and Multidisciplinary Optimization, May 19-23, 2003, Lido di Jesolo - Venice, Italy*, 2003.

[89] Y. K. Tamilselvam, J. Ganguly, R. V. Patel, and M. Jog, “Musculoskeletal Model to Predict Muscle Activity During Upper Limb Movement,” *IEEE Access*, vol. 9, pp. 111472–111485, 2021, doi: 10.1109/ACCESS.2021.3103438.

[90] M. Damsgaard, J. Rasmussen, S. T. Christensen, E. Surma, and M. de Zee, “Analysis of musculoskeletal systems in the AnyBody Modeling System,” *Simul Model Pract Theory*, 2006, doi: 10.1016/j.simpat.2006.09.001.

[91] N. Bogduk, G. Johnson, and D. Spalding, “The morphology and biomechanics of latissimus dorsi,” *Clinical Biomechanics*, 1998, doi: 10.1016/S0268-0033(98)00102-8.

[92] R. L. Lieber, B. M. Fazeli, and M. J. Botte, “Architecture of selected wrist flexor and extensor muscles,” *Journal of Hand Surgery*, 1990, doi: 10.1016/0363-5023(90)90103-X.

[93] G. R. Johnson, D. Spalding, A. Nowitzke, and N. Bogduk, “Modelling the muscles of the scapula morphometric and coordinate data and functional implications,” *J Biomech*, 1996, doi: 10.1016/0021-9290(95)00176-X.

[94] F. C. T. van der Helm, H. E. J. Veeger, G. M. Pronk, L. H. V. van der Woude, and R. H. Rozendal, “Geometry parameters for musculoskeletal modelling of the shoulder system,” *J Biomech*, 1992, doi: 10.1016/0021-9290(92)90270-B.

[95] R. H. Miller, “Hill-Based Muscle Modeling,” *Handbook of Human Motion*, no. Cc, pp. 1–23, 2017, doi: 10.1007/978-3-319-30808-1_203-1.

[96] M. S. Andersen, M. Damsgaard, B. MacWilliams, and J. Rasmussen, “A computationally efficient optimisation-based method for parameter identification of kinematically determinate and over-determinate biomechanical systems,” *Comput Methods Biomech Biomed Engin*, vol. 13, no. 2, pp. 171–183, Apr. 2010, doi: 10.1080/10255840903067080.

[97] C. Gans, “Fiber architecture and muscle function,” *Exerc Sport Sci Rev*, 1982, doi: 10.1249/00003677-198201000-00006.

[98] L. J. Holmberg and A. Klarbring, “Muscle decomposition and recruitment criteria influence muscle force estimates,” *Multibody Syst Dyn*, vol. 28, no. 3, pp. 283–289, Sep. 2012, doi: 10.1007/s11044-011-9277-4.

[99] F. Michaud, M. Lamas, U. Lugrís, and J. Cuadrado, “A fair and EMG-validated comparison of recruitment criteria, musculotendon models and muscle coordination strategies, for the inverse-dynamics based optimization of muscle forces during gait,” *J Neuroeng Rehabil*, vol. 18, no. 1, p. 17, Dec. 2021, doi: 10.1186/s12984-021-00806-6.

[100] D. Farina, M. Fosci, and R. Merletti, “Motor unit recruitment strategies investigated by surface EMG variables,” *J Appl Physiol*, vol. 92, no. 1, pp. 235–247, Jan. 2002, doi: 10.1152/jappl.2002.92.1.235.

[101] J. Rasmussen, M. Damsgaard, and M. Voigt, “Muscle recruitment by the min/max criterion - A comparative numerical study,” *J Biomech*, vol. 34, no. 3, pp. 409–415, 2001, doi: 10.1016/S0021-9290(00)00191-3.

[102] J. Rasmussen, “The AnyBody Modeling System,” in *DHM and Posturography*, Elsevier, 2019, pp. 85–96. doi: 10.1016/B978-0-12-816713-7.00008-8.

[103] B. I. Prilutsky and R. J. Gregor, “Analysis of muscle coordination strategies in cycling,” *IEEE Transactions on Rehabilitation Engineering*, 2000, doi: 10.1109/86.867878.

[104] T. L. Hedrick, B. W. Tobalske, and A. A. Biewener, “How cockatiels (*Nymphicus hollandicus*) modulate pectoralis power output across flight speeds,” *Journal of Experimental Biology*, vol. 206, no. 8, pp. 1363–1378, Apr. 2003, doi: 10.1242/jeb.00272.

[105] T. J. Roberts and A. M. Gabaldon, “Interpreting muscle function from EMG: lessons learned from direct measurements of muscle force,” *Integr Comp Biol*, vol. 48, no. 2, Jun. 2008, doi: 10.1093/icb/icn056.

[106] H. Sugi and T. Ohno, “Physiological Significance of the Force-Velocity Relation in Skeletal Muscle and Muscle Fibers,” *Int J Mol Sci*, vol. 20, no. 12, Jun. 2019, doi: 10.3390/ijms20123075.

[107] E. Martín-Sosa, J. Martínez-Reina, J. Mayo, and J. Ojeda, “Influence of musculotendon geometry variability in muscle forces and hip bone-on-bone forces during walking,” *PLoS One*, vol. 14, no. 9, Sep. 2019, doi: 10.1371/journal.pone.0222491.

[108] L. Bosmans *et al.*, “Sensitivity of predicted muscle forces during gait to anatomical variability in musculotendon geometry,” *J Biomech*, vol. 48, no. 10, Jul. 2015, doi: 10.1016/j.jbiomech.2015.02.052.

[109] D. A. Winter, *Biomechanics and Motor Control of Human Movement: Fourth Edition*. 2009. doi: 10.1002/9780470549148.

[110] H. E. J. Veeger, B. Yu, K. N. An, and R. H. Rozendal, “Parameters for modeling the upper extremity,” *J Biomech*, 1997, doi: 10.1016/S0021-9290(97)00011-0.

[111] J. A. Buckwalter, C. Saltzman, and T. Brown, “The Impact of Osteoarthritis,” *Clin Orthop Relat Res*, vol. 427, Oct. 2004, doi: 10.1097/01.blo.0000143938.30681.9d.

[112] G. Verrall *et al.*, “Hip joint range of motion reduction in sports-related chronic groin injury diagnosed as pubic bone stress injury,” *J Sci Med Sport*, vol. 8, no. 1, Mar. 2005, doi: 10.1016/S1440-2440(05)80027-1.

[113] G. Legnani, B. Zappa, F. Casolo, R. Adamini, and P. L. Magnani, “A model of an electro-goniometer and its calibration for biomechanical applications,” *Med Eng Phys*, 2000, doi: 10.1016/S1350-4533(01)00009-1.

[114] F. Rahimi, O. Samotus, J. Lee, and M. Jog, “Effective Management of Upper Limb Parkinsonian Tremor by IncobotulinumtoxinA Injections Using Sensor-based

Biomechanical Patterns.," *Tremor Other Hyperkinet Mov (N Y)*, vol. 5, p. 348, 2015, doi: 10.7916/D8BP0270.

[115] H. S. Hou and H. C. Andrews, "Cubic Splines for Image Interpolation and Digital Filtering," *IEEE Trans Acoust*, 1978, doi: 10.1109/TASSP.1978.1163154.

[116] C. C. Leung, P. C. K. Kwok, K. Y. Zee, and F. H. Y. Chan, "B-spline interpolation for bend intra-oral radiographs," *Comput Biol Med*, 2007, doi: 10.1016/j.compbiomed.2007.02.004.

[117] J. C. Ives and J. K. Wigglesworth, "Sampling rate effects on surface EMG timing and amplitude measures," *Clinical Biomechanics*, 2003, doi: 10.1016/S0268-0033(03)00089-5.

[118] D. M. Corey, W. P. Dunlap, and M. J. Burke, "Averaging correlations: Expected values and bias in combined pearson rs and fisher's z transformations," *Journal of General Psychology*, 1998, doi: 10.1080/00221309809595548.

[119] E. I. Obilor and E. C. Amadi, "Test for significance of Pearson's correlation coefficient (r)," *International Journal of Innovative Mathematics, Statistics & Energy Policies*, 2018.

[120] E. S. Pearson, "The Test of Significance for the Correlation Coefficient," *J Am Stat Assoc*, 1931, doi: 10.1080/01621459.1931.10503208.

Chapter 3

3 Sensorimotor Integration in Parkinson's Disease

This chapter discusses the results pertaining to the evaluation of Sensorimotor Integration in patients diagnosed with Parkinson's Disease.

3.1 Introduction

Integration of sensory and motor systems is vital for accurate perception of the world and optimal execution of voluntary movements. The sensory system collects information from multiple modalities, which are processed and integrated to obtain a perceptual estimate, which informs us about the state of oneself and the properties of the environment. This information is used for determining the motor command needed to achieve the desired goal while also ensuring that the motor output meets the demands of the environment [1][2]. This integration between the sensory and motor system is called Sensorimotor Integration (SMI), and it has two principal facets: (1) multi-sensory integration (integration of sensory information obtained from multiple modalities) (2) modulation of motor output based on the perceptual estimate [3][4]. The process of SMI is vital in perceiving the world around us and completing daily activities accurately and efficiently. The neural bases for SMI have been discussed in Chapter 1 under Section 1.5.1. Studies [5][6] [7] [8] [9] have pointed to BG as a neural region that may be involved in the process of SMI, and therefore, dysfunctions in BG may affect SMI functionalities. Various computational models [10][11] have attempted to explain the criteria used by the CNS in SMI. However, no study is universally accepted to precisely describe the exact brain computation involved in SMI.

Parkinson's Disease, a neurodegenerative disorder that primarily leads to dysfunctions in BG, presents a cluster of motor and non-motor symptoms. Recent evidence suggests that the non-motor symptoms, specifically perceptual abnormalities, are presented much earlier than any motor deficits and may contribute to the motor deficits that arise later. Studies have reported perceptual deficits across multiple modalities in PD patients (kinesthetic [12][13], visual [14][15], haptic [16], and auditory perception [17]). The traditional view was that these deficits arise from a peripheral impairment due to PD.

However, with the perceptual deficits being experienced in multiple modalities, studies [18] point to a more central impairment in processing sensory inputs, leading to perceptual deficits. As discussed in section 1.3.2.2, an impairment in SMI may be a primary contributor to the perceptual deficits experienced by PD patients, leading to motor deficits later in the disease. The involvement of BG (an impaired region in PD) in the functioning of SMI also supports this hypothesis of SMI impairment. Therefore, impairments in SMI have been hypothesized to primarily contribute to perceptual abnormalities. Further, a deficit in the SMI process could substantially degrade the motor performance as modulation of motor output pertaining to voluntary movements heavily relies on the optimal functioning of SMI. Understanding the factors contributing to the perceptual abnormalities leading to motor deficits is necessary to better target these deficits. Recent evidence [19][20] suggests that a more targeted and patient-specific approach to managing the symptoms of PD may be more effective than a generic one and would, in turn, significantly improve the patient's quality of life. Additionally, studies [21][22] have discussed that the efficacy of rehabilitation therapy heavily depends on whether the sensory cues provided as part of the therapy are optimal and how the patients use the sensory cues during the therapy. Therefore, in-depth knowledge of how PD patients integrate the multi-modal sensory inputs to perceive the world around them as compared to a healthy subject may provide valuable insights about the nature and type of sensory cues that may be effective during the therapy. Furthermore, with SMI impairments presumably presented much earlier in the disease, a reliable method to detect these impairments may be useful to diagnose the disease at an early stage, which may help in better managing the disease. Finally, PD patients use pharmacological treatments to mitigate the symptoms of the disease. It is also vital to understand how medication commonly prescribed to patients alters SMI functioning. Understanding the complex effects of medication is important to optimize the treatment protocols and to plan or structure the rehabilitation therapy.

Currently, very little is known about how PD may alter the functioning of SMI. Only a few studies [23] [24] [25] [26][27] have explored the impairments of SMI in PD patients, although there are numerous limitations and literature gaps that need to be addressed. Most studies evaluating SMI examined the perceptual deficits associated with a single modality and failed to investigate the patient's ability to integrate multi-modal

inputs. Furthermore, the relationship between task-specific voluntary movements and multi-sensory integration in PD patients has not been studied extensively. This relationship between movement expression and sensory perception in PD patients must also be understood to better treat PD. Finally, the effect of dopaminergic medication on SMI performance is unknown. With certain studies [28][29][30] reporting adverse effects of medication on perception, it is vital to understand how SMI may be altered due to medication. Earlier studies on SMI functions in PD patients, followed by the literature gap and limitations, have been discussed in detail in Chapter 1 under section 1.5.3. Therefore, there is a need for an objective assessment of SMI in PD patients.

3.2 Methods

3.2.1 Participants

One hundred and twenty-five patients diagnosed with Parkinson's Disease and fifty age-equivalent healthy controls were recruited to investigate the SMI deficits caused due to PD. While all participants performed the reaching tasks, only seventy-four participants performed the tracing tasks. The participants were recruited through the Movement Disorders Clinic at University Hospital, London Health Sciences Centre in London, Ontario, Canada. Inclusion criteria for patients were diagnosis of PD, no injuries limiting upper-limb movements, and normal or corrected-to-normal vision. For the control subjects, the inclusion criteria were no known neurological or psychiatric disorders, no injuries limiting upper-limb movements, and normal or corrected-to-normal vision.

All participants performed the robotic assessment tasks using their right and left arms. While the control subjects had to perform these tasks once, the PD patients performed them twice, once in their medication OFF state and later in their medication ON state. In this thesis, the group of PD patients in their OFF state is referred as PD-OFF and that for PD patients in their ON state is referred as PD-ON. The first robotic assessment was done after overnight suspension of the dopaminergic medication to ensure that the PD patients were completely OFF medication. Once the assessments were completed in the OFF state, the patients were administered the same amount of medication prescribed by the clinicians to be taken every day. One hour after the administration of the medication, the patients

underwent the robotic assessment in their ON state. No dyskinesia was observed after medication in patients included in this study. Before the robotic assessments, the motor and cognitive status of the PD patients were assessed using clinical scales. Before each experimental session, section 3 (motor sub-scale) of the UPDRS was used to evaluate the motor complications and their severity in each patient. The UPDRS score was calculated before and one hour after the medication. Furthermore, the MoCA [31] was used to evaluate the cognitive status of PD patients during the ON state.

3.2.2 Ethics

The office of Human Research Ethics at Western University's Research Ethics Board approved the study protocol (protocol numbers: 115770, 108252) required for this work. The experiments in the study were conducted per the ethical standards laid down in the 1964 Declaration of Helsinki and the Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans in Canada. The letter of information detailing the nature of the study and consent forms were provided to the patients before their participation. All recruited participants provided their written and informed consent to participate in the study.

3.2.3 Testing Apparatus and Experiment Setup

The KINARM Endpoint robot was used to characterize the SMI deficits presented due to PD. The robot allows movement in two dimensions along a horizontal plane. The device includes a robotic handle and a VR display. The robotic handle is placed directly below the VR display, and the earlier figures (2.1, 2.2, and 2.3) show the robotic device used in the study. More information about the robotic device is provided in Chapter 2 under section 2.1.1. The participants sat upright in front of the KINARM Endpoint robot, holding the robot handle, and the height of the chair was adjusted to ensure optimal viewing of the entirety of the VR display. To ensure that the participants were only able to view the virtual objects displayed in the VR display and did not have a direct view of their arm, a black screen was placed between the VR display and the participant’s arm. Figures 3.1 and 3.2 shows the experimental setup for the reaching and tracing task, respectively.

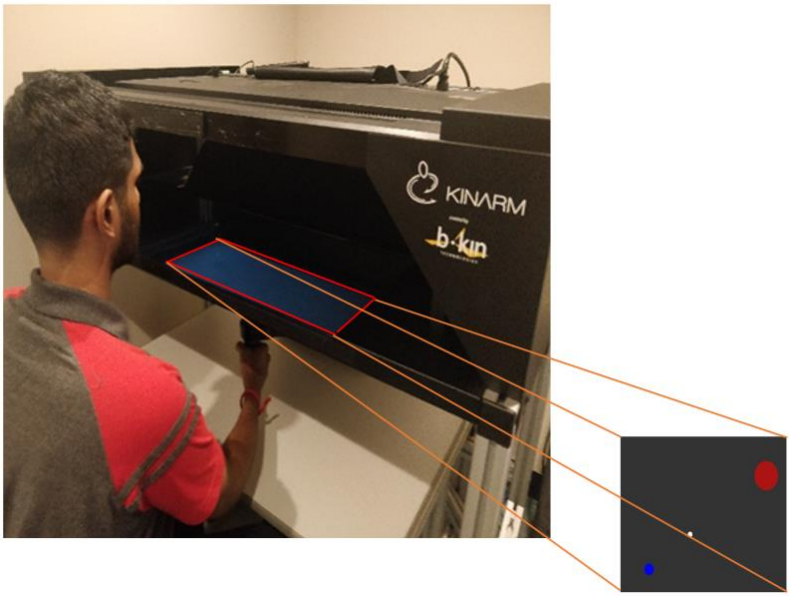


Figure 3.1: Experimental setup for the reaching task

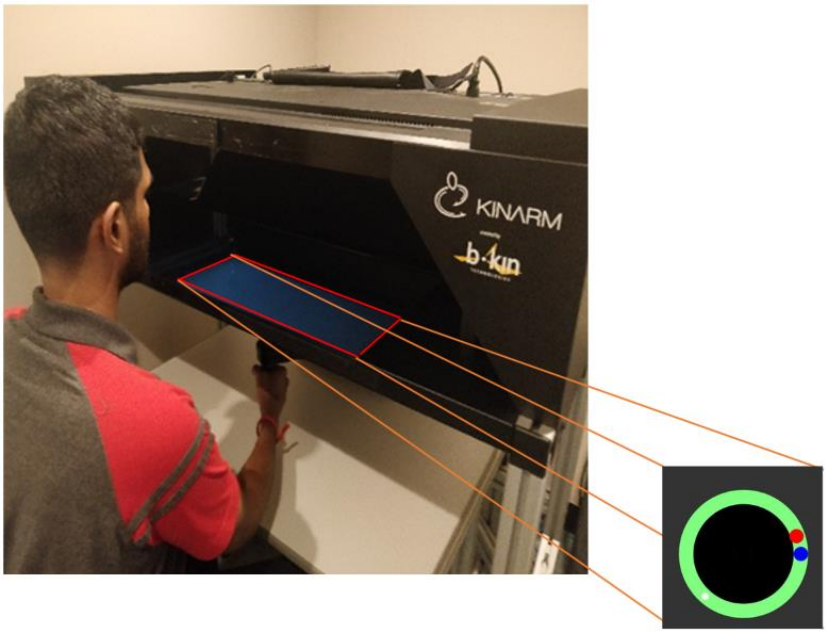


Figure 3.2: Experimental setup for the tracing task

3.2.4 Design and Development of Reaching and Tracing Tasks

To evaluate the SMI performance in PD patients, a set of reaching and tracing tasks were performed using the KINARM Endpoint robot [32]. The tasks used to assess the SMI were

discussed in Chapter 2 under Section 2.1.4. Further, the rationale behind the nature of the tasks and how they can be used to evaluate SMI performance is discussed in Chapter 2. Participants performed the reaching and tracing tasks under varying sensory conditions (with/without Assistive Sensory Cues (ASC) and with/without sensory manipulation). Tables 2.1 and 2.2 show the subtasks associated with the reaching and tracing tasks and the sensory condition related to each subtask. The ASC include a vibrotactile input given to the robotic handle held by the participant and an auditory cue (beep sound) provided to the participants through an external speaker. The multi-modal ASC provide additional information intending to assist the participants in performing the tasks more efficiently and accurately. Section 2.1.4 explains when the multi-modal ASC would be provided to the participants. Subtasks with and without ASC evaluate the participant's ability to integrate the multi-modal sensory inputs and use the resulting perceptual estimate to improve one's motor performance. Sensory manipulation was also included in specific subtasks of reaching and tracing subtasks. The nature of sensory manipulation is explained in section 2.1.4. Subtasks with sensory manipulation were used to evaluate the participant's ability to adapt to inaccurate sensory signals and filter them out. It would also provide insights into how voluntary movements may be affected by inaccurate sensory signals and if the participants can adapt and learn to improve their motor performance taking into consideration the inaccurate sensory information provided by the experimenter.

3.2.5 Feature Extraction and Analysis

The features extracted to analyze SMI performance in participants were described in Chapter 2 under section 2.2. Statistical analyses for comparing the performance of the groups were discussed in section 2.3. The feature extraction and statistical analyses were performed using MATLAB and Python. Additionally, a trial-by-trial analysis was performed using the extracted features discussed in section 2.2 to evaluate the motor learning ability of the participants. Motor learning is the ability to learn and improve motor performance over time using acquired sensory cues, and thereby heavily depends on the optimal functioning of the SMI. Therefore, the trial-by-trial analysis evaluates if impairment in SMI may affect motor learning ability and the extent to which it may be affected. In a trial-by-trial analysis, the performance of each group was averaged across an

individual trial for selected features. For instance, if the mean velocity is selected, we start by averaging the mean velocity across all the participants in the first trial of the task, subsequently, the second trial, and so on, and this was done individually for each group. Then the difference between the two groups in each trial was calculated. To understand if the difference between the two groups increased or decreased as they performed more trials, a correlation between the trial numbers and the difference between the groups was calculated. While a positive correlation indicates an increase in the difference between the groups, a negative correlation indicates a reduction in the difference between the groups. This provides insight into whether the participants can improve their task performance as they complete more trials. For instance, PD-OFF may have higher endpoint error than the control subjects. However, suppose the trial-by-trial analysis for the endpoint error between PD-OFF and the control subjects indicates a negative correlation. In that case, it suggests that PD-OFF reduced their endpoint error at later trials and improved their performance as they completed more trials. The trial-by-trial was performed only in tasks with sensory manipulation to understand if the participants could adapt to the incorrect sensory inputs and improve their performance over time. Therefore, the trial-by-trial analysis was performed on four error metrics (direction error, mean number of violations, mean violation distance, and time spent under violation) extracted from the reaching and tracing task with sensory manipulation.

3.3 Results

3.3.1 Demographic Data and Clinical Assessment

In this study, a hundred and twenty-five PD patients (81 males and 44 females) and fifty age-equivalent control subjects (37 males and 13 females) were recruited. The motor and cognitive status of the PD patients were assessed using the UPDRS and MoCA scales. Table 3.1 shows the demographic and clinical information pertaining to the participants.

Table 3.1: Demographic and clinical data for PD patients

Demographic Data	PD patients	Control subjects
Number of participants	125	50
Age (years) (Mean (Minimum - Maximum))	64 (38 – 79)	57 (30 - 81)
Gender (M/F)	81/44	37/13
Years with disease (Mean (Minimum - Maximum))	10 (2 -30)	N/A
Clinical Data		
MOCA (Mean (Minimum - Maximum))	25.0 (17- 30)	N/A
UPDRS motor sub-scale in OFF therapy (Mean (Minimum - Maximum))	39.8 (4 – 73)	N/A
UPDRS motor sub-scale in ON therapy (Mean (Minimum - Maximum))	23.5 (1 - 57)	N/A

3.3.2 Sensorimotor Integration: Within-Group Comparison

This section compares the performance of each group against their own performance under varying sensory conditions [32]. First, the performance of a given group with and without ASC was compared. Second, a comparison between the performance of each group with and without sensory manipulation was performed. Table 3.2 shows the performance of the groups in the features extracted for the reaching and tracing tasks. Table 3.3 shows the significance value for the within and between-group comparisons.

Table 3.2: Task performance of each group in reaching and tracing tasks

Parameters		PD-OFF (Median (Range))	PD-ON (Median (Range))	Control subjects (Median (Range))
Reaching Task				
Target Reach (%)	w.o. ASC	100 (80)	98 (33)	100 (0)
	w. ASC	97 (75)	99 (50)	100 (0)
	w.o. SM	96 (87)	98 (100)	100 (50)
	w. SM	93 (100)	90 (100)	100 (75)
Mean Endpoint error (cm)	w.o. ASC	0.477 (4.56)	0.435 (2.58)	0.374 (0.59)
	w. ASC	0.488 (3.94)	0.406 (1.79)	0.345 (0.75)
	w.o. SM	0.490 (13.5)	0.426 (10.4)	0.314 (4.04)
	w. SM	0.744 (22.3)	0.632 (17.4)	0.518 (11.15)
Mean Direction Error (cm)	w.o. ASC	0.009 (1.49)	0.008 (2.17)	0.002 (0.63)
	w. ASC	0.013 (1.68)	0.005 (0.74)	0.001 (0.38)
	w.o. SM	0.057 (15.7)	0.051 (6.14)	0.032 (4.74)
	w. SM	1.296 (14.4)	1.651 (19.1)	0.901 (7.34)
MDE (cm)	w.o. ASC	0.419 (1.44)	0.443 (1.23)	0.364 (1.03)

	w. ASC	0.425 (4.17)	0.412 (2.37)	0.341 (1.06)
	w.o. SM	0.436 (12.2)	0.448 (4.04)	0.360 (1.50)
	w. SM	0.605 (12.8)	0.642 (8.68)	0.494 (6.04)
Maximum Endpoint Error (cm)	w.o. ASC	4.971 (7.02)	*6.712* (6.75)	*1.576* (1.34)
	w. ASC	2.034 (12.5)	*3.035* (6.53)	*1.400* (1.83)
	w.o. SM	2.212 (26.1)	*1.884* (27.6)	*1.074* (19.8)
	w. SM	3.989 (28.5)	*5.476* (29.2)	*2.677* (16.3)
Maximum Direction Error (cm)	w.o. ASC	2.421 (4.48)	3.875 (6.52)	1.588 (2.53)
	w. ASC	1.067 (2.20)	2.959 (2.91)	0.427 (0.46)
	w.o. SM	1.588 (21.5)	2.613 (20.8)	1.009 (7.82)
	w. SM	4.187 (22.4)	5.329 (25.2)	3.790 (12.5)
Mean Velocity (cm/s)	w.o. ASC	0.036 (0.13)	0.038 (0.06)	0.040 (0.02)
	w. ASC	0.036 (0.10)	0.037 (0.05)	0.039 (0.02)
	w.o. SM	0.058 (0.12)	0.061 (0.10)	0.065 (0.08)
	w. SM	0.050 (0.09)	0.055 (0.14)	0.060 (0.09)
Tracing Task				
Mean Number of Violations	w.o. SM	0.60 (9.6)	0.35 (8)	0.25 (1.10)
	w. SM	2.12 (12.1)	2.57 (7.17)	1.60 (4.46)
Time Spent under Violation (s)	w.o. SM	0.08 (2.31)	0.16 (2.80)	0.03 (0.33)
	w. SM	1.05 (5.66)	1.32 (4.77)	0.59 (3.50)
Mean Violation Distance (cm)	w.o. SM	0.0008(0.35)	0.001 (0.24)	0.0003(0.007)
	w. SM	0.015 (0.44)	0.022 (1.06)	0.008 (0.157)
MDE (cm)	w.o. SM	0.421 (1.26)	0.478 (1.94)	0.343 (0.590)
	w. SM	0.669 (1.65)	0.700 (2.25)	0.578 (1.367)
Mean Velocity (cm/s)	w.o. SM	0.055 (0.08)	0.060 (0.05)	0.062 (0.06)
	w. SM	0.052 (0.07)	0.057 (0.07)	0.066 (0.04)

Note: w.o. ASC = without assistive sensory cues; w. ASC = with assistive sensory cues; w.o. SM = without sensory manipulation; w. SM = with sensory manipulation.

Table 3.3: Significance value for within and between-group comparisons

		Significance for within-group comparison			Significance for between-group comparison		
		PD-OFF	PD-ON	Control Subjects	PD-OFF vs. Control Subjects	PD-OFF vs. PD-ON	PD-ON vs. Control Subjects
Reaching Task							
Target Reach	w.o. ASC	$p = 0.0147$*	$p = 0.7087$	$p = 1$	$p = 0.6636$	$p = 0.0294$*	$p = 0.2419$
	w. ASC				$p = 0.0095$*	$p = 0.8945$	$p = 0.0764$
	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0260$*	$p < 0.0001$*	$p = 0.0604$	$p < 0.0001$*
	w. SM				$p < 0.0001$*	$p = 0.0506$	$p = 0.0001$*
Mean Endpoint Error	w.o. ASC	$p = 0.0057$*	$p = 0.1913$	$p = 0.2409$	$p < 0.0004$*	$p = 0.0688$	$p = 0.0011$*
	w. ASC				$p < 0.0001$*	$p = 0.1342$	$p = 0.0007$*
	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*
	w. SM				$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*
	w.o. ASC	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0106$*	$p = 0.0503$	$p = 0.5118$	$p = 0.0515$
	w. ASC				$p < 0.0001$*	$p = 0.9635$	$p = 0.0024$*

Mean Direction Error	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0022$*
	w. SM				$p = 0.1707$	$p < 0.0001$*	$p = 0.0027$*
MDE	w.o. ASC	$p = 0.5887$	$p = 0.6408$	$p = 0.9922$	$p < 0.0001$*	$p = 0.1149$	$p < 0.0001$*
	w. ASC				$p < 0.0001$*	$p = 0.0434$*	$p < 0.0001$*
	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*
	w. SM				$p < 0.0001$*	$p = 0.3702$	$p < 0.0001$*
Maximum Endpoint Error	w.o. ASC	$p = 0.0993$	$p = 0.4432$	$p = 0.4049$	$p < 0.0001$*	$p = 0.1080$	$p = 0.0036$*
	w. ASC				$p < 0.0001$*	$p = 0.0167$*	$p < 0.0001$*
	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*
	w. SM				$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*
Maximum Direction Error	w.o. ASC	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0046$*	$p = 0.0022$*	$p = 0.9598$	$p = 0.0505$
	w. ASC				$p < 0.0001$*	$p = 0.6599$	$p = 0.0031$*
	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0031$*	$p = 0.0034$*	$p = 0.0019$*
	w. SM				$p = 0.0686$	$p < 0.0001$*	$p = 0.0002$*
Mean Velocity	w.o. ASC	$p = 0.4055$	$p = 0.2536$	$p = 0.2835$	$p < 0.0001$*	$p = 0.0019$*	$p = 0.0068$*
	w. ASC				$p < 0.0001$*	$p = 0.0050$*	$p = 0.0009$*
	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0040$*
	w. SM				$p < 0.0001$*	$p < 0.0001$*	$p = 0.0021$*
Tracing Task							
Mean Number of Violations	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0012$*	$p = 0.0021$*	$p < 0.0001$*
	w. SM				$p = 0.0118$*	$p = 0.0694$	$p = 0.0019$*
Time Spent under Violation	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0009$*	$p < 0.0001$*
	w. SM				$p = 0.0020$*	$p = 0.0457$*	$p < 0.0001$*
Mean Violation Distance	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0001$*	$p < 0.0001$*	$p < 0.0001$*
	w. SM				$p = 0.0396$*	$p = 0.0070$*	$p = 0.0038$*
MDE	w.o. SM	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.0103$*	$p = 0.1817$	$p = 0.0001$*
	w. SM				$p = 0.0272$*	$p = 0.9335$	$p = 0.0477$*
Mean Velocity	w.o. SM	$p = 0.002$*	$p = 0.0042$*	$p < 0.0001$*	$p < 0.0001$*	$p < 0.0001$*	$p = 0.1800$
	w. SM				$p < 0.0001$*	$p < 0.0001$*	$p = 0.6622$

Note: w.o. ASC = without assistive sensory cues; w. ASC = with assistive sensory cues; w.o. SM = without sensory manipulation; w. SM = with sensory manipulation; * after the *p*-value indicates statistical significance

3.3.2.1 PD Patients in OFF state

Comparing the performance of PD patients in the OFF state with and without ASC, in the reaching task, the PD patients reached 3% fewer targets with ASC than without ASC. This decrease in reaching the target when provided with ASC was also statistically significant (see Table 3.3). Further, the PD patients were also less accurate when provided with ASC, as the endpoint error increased by 2% when encountering ASC compared to without ASC.

Similarly, the direction error has also increased by 36% when encountering ASC. Finally, the efficiency in reaching a target has also worsened with the inclusion of ASC. This is indicated by a 1.4% increase in MDE in trials with ASC compared to those without any sensory cues. Interestingly, the findings imply that the multi-modal sensory cues provided to help improve motor performance have adversely affected the performance of the PD patients in most features.

Moving to the within-group comparison between the performance in trials with and without sensory manipulation, the PD patient underwent both reaching and tracing tasks under these sensory conditions. In reaching tasks, the PD patients reached 3% more targets, far more accurately (41% less endpoint error and 183% less direction error), and more efficiently (32% less MDE) in trials without sensory manipulation than with sensory manipulation. Further, the PD patients were much faster without sensory manipulation, as shown by a 14% increase in mean velocity in trials without sensory manipulation than in trials with sensory manipulation. Across all the features, there is a statistically significant difference (see Table 3.3) when comparing the performance of the PD patient with and without sensory manipulation. This trend continues into the tracing tasks. In this task, the primary goal of the participants is to move in a clockwise direction to reach the target and stay within the green track when performing the task. Any deviation from the green track is referred to as a violation. The patients committed more violations and spent more time under violation before correcting the violation when encountering sensory manipulation compared to the task without sensory manipulation. Further, the mean violation distance, which indicates how far the patients have moved away from the green track they are instructed not to deviate from, is 179% higher in trials with sensory manipulation than in trials without any manipulation of sensory inputs. Similar to the reaching task, the MDE was higher when encountering sensory manipulation, with the difference in MDE between the trials with and without sensory manipulation being statistically significant (see Table 3.3). The findings from comparing the performance between trials with and without sensory manipulation were on the expected line. Manipulation of sensory inputs affected the perceptual estimates, which, in turn, affected the motor performance of PD patients. The more interesting question is if there is a difference in how PD patients adapt to sensory manipulation compared to control subjects. This is discussed in a later section.

3.3.2.2 PD Patients in ON state

In this section, the performance of PD patients in their ON state was compared under differing sensory conditions. Regarding reaching tasks with and without ASC, PD patients have shown marginal improvement when provided with ASC. A minor increase in the number of targets reached, followed by a minimal improvement in efficiency and accuracy, was observed when provided with ASC. However, apart from direction error, no statistically significant difference (see Table 3.3) was observed when comparing the performance with and without ASC. The study's findings reveal that the ASC neither improved nor deteriorated the motor performance of PD patients in their ON state. This may imply that the PD patients in their ON state could not benefit from the ASC provided to assist them and therefore did not improve their motor performance significantly. Furthermore, this may indicate that the effect of sensory cues or inputs on motor performance is minimal during the ON state, which may adversely affect specific aspects of the motor ability, such as adapting to the demands of the testing environment.

Comparing the performance with and without sensory manipulation, in reaching tasks, the PD patients in their ON state reached fewer targets, with their accuracy and efficiency worsening when encountering sensory manipulation. Regarding accuracy, the endpoint and direction errors were 38% and 188% higher in trials with sensory manipulation than without sensory manipulation. Similarly, the MDE increased by 35% when provided with sensory manipulation, indicating a worsening of efficiency with manipulation of sensory manipulation. When encountering sensory manipulation, there was statistically significant deterioration across all features (see Table 3.3). A similar trend was also observed when comparing performance in the tracing tasks with and without sensory manipulation. While the mean number of violations was 0.35 without sensory manipulation, the PD patients committed a significantly higher mean number of violations at 2.57 when encountering the manipulated sensory input. Further, there was a statistically significant deterioration (see Table 3.3) in the mean violation distance and time spent under violation in trials with sensory manipulation compared to trials in which the visual inputs were not manipulated. This performance deterioration was also carried over to the movement speed as the mean velocity decreased by 5% in trials with sensory manipulation

compared to those without sensory manipulation. Therefore, the sensory manipulation has affected the motor performance as expected. However, as indicated earlier, a more vital question may be answered through the between-group comparison that may indicate which group adapted to the sensory manipulation quickly and efficiently and, thereby, modulated their motor output using an integrated perceptual estimate that considers the inaccurate or unreliable sensory input.

3.3.2.3 Control Subjects

When comparing the tasks with and without ASC, the control subjects reached 100% of the targets in both sensory conditions. However, there was a difference in the accuracy and efficiency of the performance between the two conditions. The control subjects were more accurate in tasks with ASC, as indicated by a decrease in endpoint and direction error by 8% and 66% respectively when provided with ASC compared to without ASC. Further, the reduction in the direction error with ASC was also statistically significant (see Table 3.3). Regarding efficiency, there was a 6% reduction in MDE in tasks with ASC compared to without ASC. Therefore, it is pretty evident that the accuracy and efficiency improved when provided with ASC, implying that the control subjects benefitted from the multi-modal sensory inputs as they were able to construct a more informative and coherent perceptual estimate through their SMI process, which in turn improved their motor performance.

Regarding tasks with and without sensory manipulation, the findings were as expected: the control subjects performed better in the task without sensory manipulation compared to the task with sensory manipulation. In reaching tasks, the control subjects were less accurate and efficient in the task with sensory manipulation than without. Similarly, in tracing tasks, there was a statistically significant deterioration (see Table 3.3) in the performance of the control subjects when encountering the sensory manipulation. They committed more violations, spent more time outside the green track, and had higher mean violation distance in the task with sensory manipulation compared to those without manipulation of the sensory inputs. This indicates that the motor performance was negatively affected even in the control subjects when the sensory inputs were manipulated. While the relationship between sensory input and motor output has been discussed in

earlier studies [33], these findings further emphasize the importance of an accurate or reliable sensory input in optimally executing any voluntary movement.

3.3.3 Sensorimotor Integration: Healthy Controls vs. PD Patients in the OFF State (PD-OFF)

This section compares the performance of PD patients in their OFF state with the performance of the control subjects under differing sensory conditions. Table 3.4 shows the results from the trial-by-trial analysis. Figure 3.3 and Figure 3.4 compare the performance of all groups in reaching and tracing tasks respectively.

Table 3.4: Trial-by-trial analysis

	Trial-by-trial analysis between PD-OFF and Controls	Trial-by-trial analysis between PD-OFF and PD-ON	Trial-by-trial analysis between PD-ON and Controls
Mean Direction error	0.3302 (p = 0.0866)	0.1524 (p = 0.6362)	0.4136 (p = 0.0250)
Mean Number of Violations	-0.6781 (p = 0.015)	0.3676 (p = 0.1252)	-0.1740 (p = 0.5899)
Mean Violation Distance	0.1741 (p = 0.3885)	0.3961 (p = 0.2023)	0.3424 (p = 0.2758)
Time Spent under Violation	-0.4652 (p = 0.1354)	0.5921(p = 0.0429)	-0.0234 (p = 0.9423)

3.3.3.1 Tasks with and without ASC

In the reaching task without ASC, the accuracy of the control subjects was substantially better than PD-OFF. While PD-OFF had a 24% higher mean endpoint error than the control subjects, the direction error was 127% higher in PD-OFF compared to the control subjects. Furthermore, the efficiency also deteriorated in PD-OFF as the MDE for PD-OFF was 14% higher than the control subjects, with the difference being statistically significant. PD-OFF was also significantly slower as their mean velocity was 10% less than control subjects. For reaching tasks with ASC, the control subjects reached a higher number of targets than PD-OFF. Concerning the other metrics, PD-OFF were less accurate and efficient than the control subjects, with their endpoint error, direction error, and MDE being 34%, 171%, and 21% higher than the control subjects. The percentage difference between PD-OFF and the control subjects increased in tasks with ASC than without ASC. This may indicate that

the control subjects could effectively use the multi-modal inputs to improve their motor performance. However, an impairment in SMI among PD-OFF that adversely affects their ability to integrate multi-modal inputs leading to inaccurate perceptual estimates may have worsened their motor performance when provided with ASC. Therefore, there exists an impairment in SMI due to PD, which adversely affects the voluntary movements of PD patients during their OFF state.

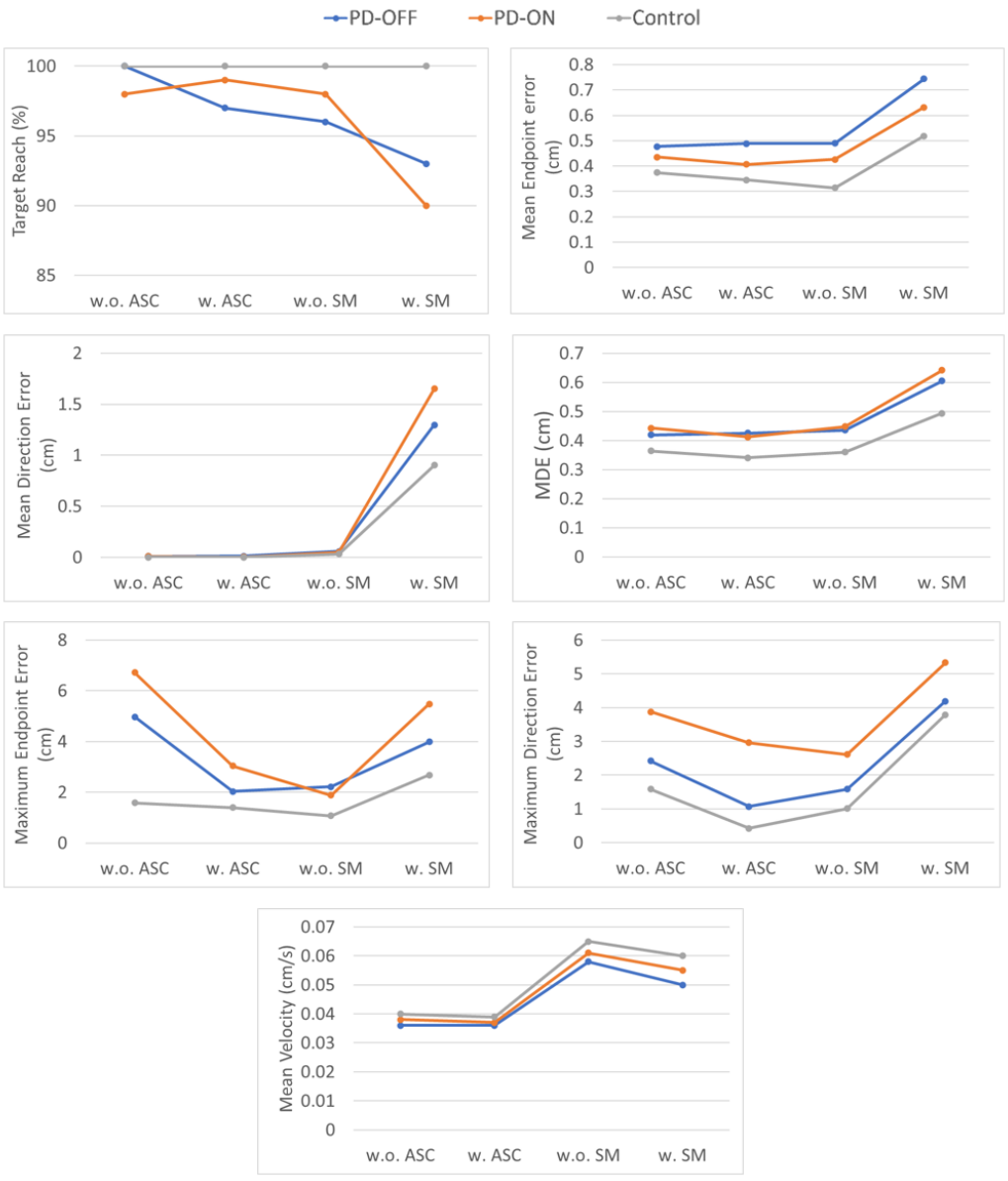


Figure 3.3: Features extracted from the reaching task for the three groups across all sensory conditions

Note: w.o. ASC = without assistive sensory cues; w. ASC = with assistive sensory cues; w.o. SM = without sensory manipulation; w. SM = with sensory manipulation.

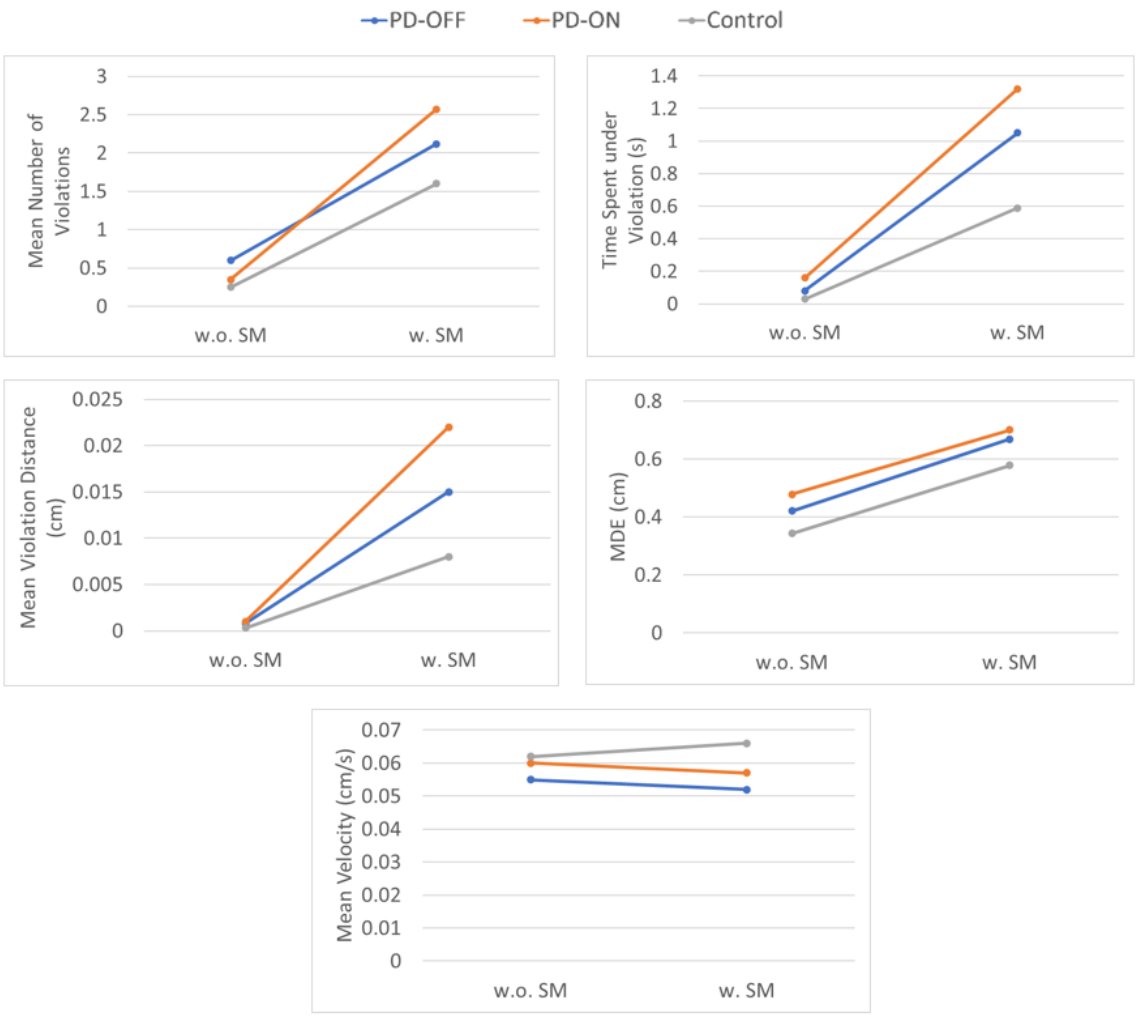


Figure 3.4: Features extracted from the tracing task for the three groups across all sensory conditions

Note: w.o. ASC = without assistive sensory cues; w. ASC = with assistive sensory cues; w.o. SM = without sensory manipulation; w. SM = with sensory manipulation.

3.3.3.2 Tasks with and without Sensory Manipulation

For the reaching task without sensory manipulation, the control subjects have once again outperformed PD-OFF across all features. The control subjects reached 4% more targets, 43% less endpoint error, 56% less direction error, and 19% less MDE than PD-OFF. Higher movement speed for the control subjects was also noticed, as their mean velocity was 11% higher than PD-OFF. Moving to the tracing task without sensory manipulation, PD-OFF suffered from higher inaccuracies than the control subjects. PD-OFF committed 82% more violations than the control subjects while spending 90% more time under violation than the control subjects. Furthermore, the mean violation distance for PD-OFF was substantially higher than the control subjects. Lastly, the MDE was 20% higher in PD-OFF than the control subjects, implying that PD-OFF were less efficient than the control subjects.

To evaluate the effect of sensory manipulation on these two groups, the performance of the groups when encountering sensory manipulation was compared. For the reaching task with sensory manipulation, PD-OFF had a statistically significant deterioration (see Table 3.3) in performance across most features. The number of targets reached by PD-OFF was 7% lower than the control subjects. PD-OFF were also significantly less accurate as their mean endpoint and direction errors were 35% and 36% higher than the control subjects. Finally, the efficiency of the reaching movement was also affected by the manipulation of sensory inputs, as PD-OFF had a statistically significant deterioration (see Table 3.3) in efficiency compared to the control subjects. Apart from the accuracy and efficiency, the mean velocity was also 18% lower for PD-OFF than the control subjects. Similarly, in tracing task with sensory manipulation, PD-OFF committed 27% more violations, and spent 56 % more time under violation than control subjects. The findings suggest an apparent impairment among PD-OFF in the ability to flexibly adapt the SMI strategy based on the reliability of the sensory inputs. It must be noted that the control subjects also performed worse when encountering sensory manipulation, as indicated in the within-group comparison of the control subjects (Section 3.3.2.3). However, the performance of PD-OFF was significantly worse than that of the control subjects when performing tasks with sensory manipulation. This may imply that while the motor performance of both groups was affected due to unreliable sensory inputs, the

control subjects could adapt their SMI strategies to account for the unreliable sensory inputs and improve their motor performance over time. In contrary, PD-OFF were either unable to or less efficient in adapting to the manipulation of sensory inputs by varying their strategy for the SMI process based on the reliability of the sensory inputs, implying an impairment in SMI due to PD.

In the case of trial-by-trial analysis (see Table 3.4) that evaluates the motor learning ability, a positive correlation (r = 0.3302) was observed for the mean direction error. However, a negative correlation was observed between the two groups for the mean number of violations (r = -0.6781) and time spent under violation (r = -0.4652). This implies that the difference between the groups in the two features reduced as they performed more trials.

3.3.4 Sensorimotor Integration: PD Patients in the ON State (PD-ON) vs. PD Patients in the OFF State (PD-OFF)

This section discusses the effect of medication on SMI and how it affects voluntary movements. Therefore, the performance of PD-OFF and PD-ON was compared under varying sensory conditions.

3.3.4.1 Tasks with and without ASC

In the reaching task without ASC, while PD-OFF reached 2% more targets and was more efficient than PD-ON, their mean endpoint and direction error were also 9% and 11% higher, respectively, than PD-ON. Interestingly, while the mean error for PD-OFF was higher than that for PD-ON, the latter had a substantially higher maximum endpoint and maximum direction error than PD-OFF. This may imply that while the frequency of error committed by PD-ON was less than by PD-OFF, they commit much bigger errors compared to PD-OFF when they do end up committing errors.

Moving to the reaching task with ASC, PD-ON reached 2% more targets, committed 18% less endpoint, and 88% less direction error than PD-OFF. However, the maximum endpoint and maximum direction error for PD-ON were 39% and 93% higher respectively than for PD-OFF. This finding aligns with the ones from the reaching task

without ASC. Finally, the efficiency of PD-ON was better as their MDE was 3% less than PD-OFF. An interesting finding was that the maximum error was higher for PD-ON, although their mean error was less than PD-OFF, which implies that the magnitude of error was much higher in PD-ON than PD-OFF, although the number of errors for PD-ON was less than PD-OFF. This may suggest that PD-ON struggled to correct errors once they had committed them as opposed to PD-OFF, who, despite committing more errors, could fix them; thereby, the magnitude of their errors was less. Correcting errors requires optimal integration of sensory inputs, proper interpretation of environmental properties, and appropriately modulating the motor outputs. It could be inferred that the medication may have affected the ability to use the sensory inputs to modulate the motor outputs, thereby being unable to correct errors once they have been committed.

3.3.4.2 Tasks with and without Sensory Manipulation

For tasks without sensory manipulation, in the reaching task, PD-ON reached 2% more targets, had 13% less endpoint error, and 11% less direction error than PD-OFF. Therefore, across most features, PD-ON performed better than PD-OFF. However, as it was observed earlier, while PD-ON performed better than PD-OFF across many features, PD-ON was much worse than PD-OFF in features such as maximum direction error. PD-ON had a 48% higher maximum direction error than PD-OFF. In the tracing task without sensory manipulation, PD-ON committed 52% fewer violations than PD-OFF. However, the time spent under violation and mean violation distance for PD-ON was 66% and 22% higher than PD-OFF, respectively. This further aligns with our earlier findings that PD-ON commits less violations or errors than PD-OFF. However, the magnitude of their violation was much higher than PD-OFF, owing to their inability to correct violations once they have been committed. PD-OFF also had better efficiency as PD-ON had 12% more MDE than PD-OFF. Finally, the mean velocity for both reaching and tracing tasks was 5% and 8% higher for PD-ON than PD-OFF.

For the tasks with sensory manipulation, in the reaching task, PD-OFF reached more targets than PD-ON, with the efficiency of PD-OFF being much higher than that of PD-ON, as indicated by an increase of 6% in MDE after medication. Mean direction error is an important performance indicator of how the participants can adapt to sensory

manipulation and appropriately modulate motor output. With the manipulation being the fingertip position moving in the opposite direction to actual movement, the ability to adapt to the manipulation of visual inputs is vital to determine the direction in which the movement needs to be made to reach the desired target. In this, PD-OFF was much better than PD-ON as the mean direction error for PD-OFF was 24% less than PD-ON. Similarly, the maximum direction error was also 24% less for PD-OFF than PD-ON. In the tracing task with sensory manipulation, PD-ON committed 19% more violations than PD-OFF, with the time spent under violation and mean violation distance for PD-ON being 22% and 37% more than that for PD-OFF. The efficiency in performing the tracing task with sensory manipulation was also much better for PD-OFF as their MDE was 4.5% less than PD-ON. In both reaching and tracing tasks with sensory manipulation, the mean velocity for PD-ON was 9.1% and 9.5% higher than PD-OFF, respectively. To summarize, PD-ON performed worse than PD-OFF across most features when encountering sensory manipulation. While the movement speed improved after medication, the overall task performance was adversely affected due to the poor accuracy and efficiency in performing the task after taking medication. The findings suggest that the medication affected the ability to adapt to sensory manipulation, and therefore, could not appropriately modulate the motor outputs to suit the demands of the environment. Furthermore, even without sensory manipulation, the PD patients in their ON state struggled to correct errors once committed. Putting these results together, it may be inferred that the medication worsened the SMI impairments in PD patients, adversely affecting their ability to use the multi-modal sensory inputs to correct errors and adapt to the sensory manipulation resulting in poor motor performance.

Discussing the trial-by-trial analysis (see Table 3.4) between PD-OFF and PD-ON groups, a positive correlation was observed across all four features (mean direction error, mean number of violations, time spent under violation, and mean violation distance). Further, the positive correlation observed in time spent under violation was statistically significant.

3.3.5 Sensorimotor Integration: PD Patients in the ON State (PD-ON) vs. Healthy Controls

This section compares the performance of PD patients in their ON state with control subjects.

3.3.5.1 Tasks with and without ASC

In tasks without ASC, the control subjects reached 2% more targets than PD-ON. Furthermore, the accuracy of the control subjects was also much better compared to PD-ON, as their mean endpoint error and mean direction error was 15% and 120% less than for PD-ON. The control subjects also had 19% less MDE than PD-ON, indicating a better efficiency for the control subjects than for PD-ON. The trend was similar in tasks with ASC as the control subjects reached more targets and had substantially less endpoint error and direction error than PD-ON. The efficiency of the control subjects was also better with ASC, as the MDE for PD-ON was 18% higher than that for the control subjects. In both tasks with ASC and without ASC, the mean velocity for the control subjects was 5.1% and 5.2% higher than for PD-ON, with the difference being statistically significant.

3.3.5.2 Tasks with and without Sensory Manipulation

In tasks without sensory manipulation, the control subjects outperformed PD-ON across all features for the reaching task. The control subjects reached 2% more targets, had 30% less endpoint error, 45% less direction error, and 21% less MDE than PD-ON, resulting in better accuracy and efficiency than PD-ON. Similarly, in tracing tasks, the control subjects committed 33% fewer violations than PD-ON, with the time spent under violation and mean violation distance for the control subjects being 136% and 107% less than PD-ON. MDE for the control subjects was 32% less than PD-ON, indicating better efficiency for the control subjects. Finally, PD-ON was substantially slower across both reaching and tracing tasks than the control subjects.

When encountering sensory manipulation in the reaching task, the performance of the control subjects was once again better than PD-ON across all features, with the control subjects reaching 10% more targets, committing 19% less endpoint error, 58% less direction error, and 26% less MDE than PD-ON. In the tracing task with sensory

manipulation, PD-ON committed substantially more violations than the control subjects. Furthermore, the time spent under violation and mean violation distance for PD-ON was 76% and 93% higher than the control subjects. The efficiency of PD-ON was also lower than the control subjects as the MDE was 19% lower for the control subjects compared to PD-ON. The mean movement speed for control subjects was 8% and 14% higher than PD-ON in reaching and tracing tasks with sensory manipulation, respectively. The comparison indicates that the control subjects performed far better than PD-ON across all tasks and sensory conditions. The medication did not normalize the task performance of PD-ON and, therefore, was still much worse than the control subjects across all features. Even the features such as mean velocity, which was seen to improve after medication as shown in the comparison between PD-OFF and PD-ON, did not get normalized to the pre-PD state resulting in PD-ON being substantially slower than the control subjects. Finally, in trial-by-trial analysis, a statistically significant positive correlation was observed between the two groups for mean direction error.

3.3.6 Feature Selection and Pattern Recognition

3.3.6.1 Selecting Features using the Decision Tree Algorithm

With two different tasks being used to investigate the SMI performance, the feature selection and NN training were done separately to understand if the metrics acquired from these tasks may be used to predict or diagnose PD. This is primarily because some patients who completed the reaching tasks did not complete the tracing task. Therefore, it was not possible to combine the features from the two tasks to train a single NN model. As such, the feature importance was calculated using the decision tree algorithm separately for each task. Figures 3.5 and 3.6 show the feature importance calculated for reaching and tracing tasks, respectively. Based on the importance value, four metrics (speed peaks, mean endpoint error, maximum direction error, and maximum endpoint error) obtained from the reaching task were selected to train the NN model. For the tracing task, the five metrics with the highest importance value (time taken, mean violation distance, median MDE, mean velocity, and mean number of violations) was used to train a separate NN model. As illustrated earlier, the participants performed vastly differently depending on the sensory conditions of the task. Therefore, the sensory conditions were also used as a feature when

training the NN model. For ease of training purposes, a feature indicating the sensory condition of each data point is used when training the model. This will ensure that the NN considers the sensory manipulation and learns the participants' behavior under varying sensory conditions.

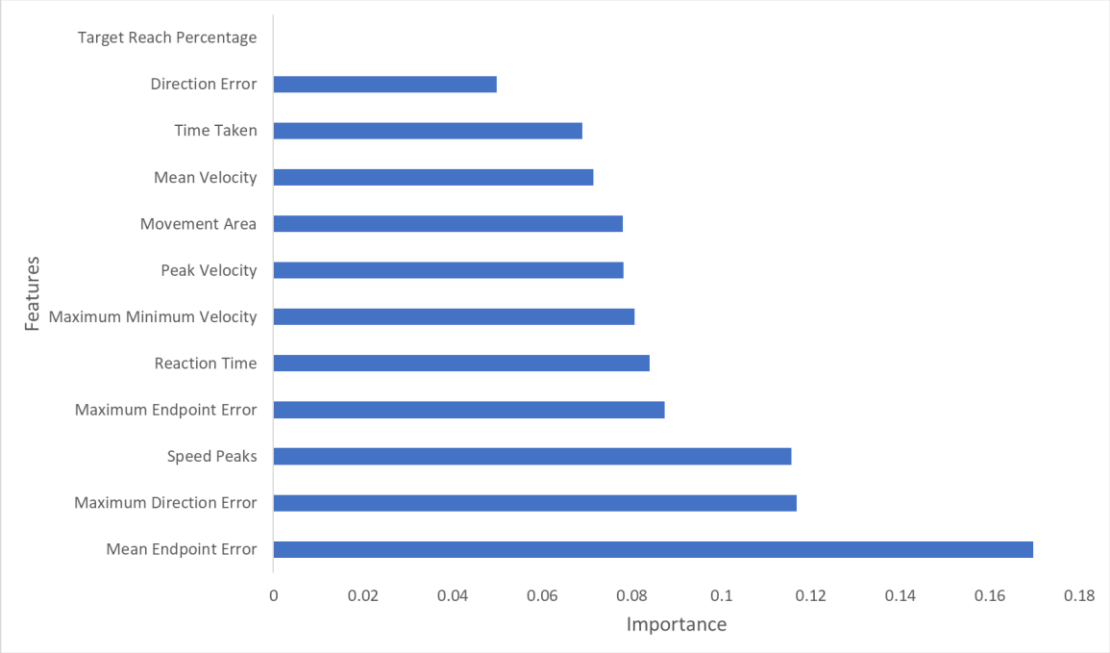


Figure 3.5: Feature importance score for the reaching task

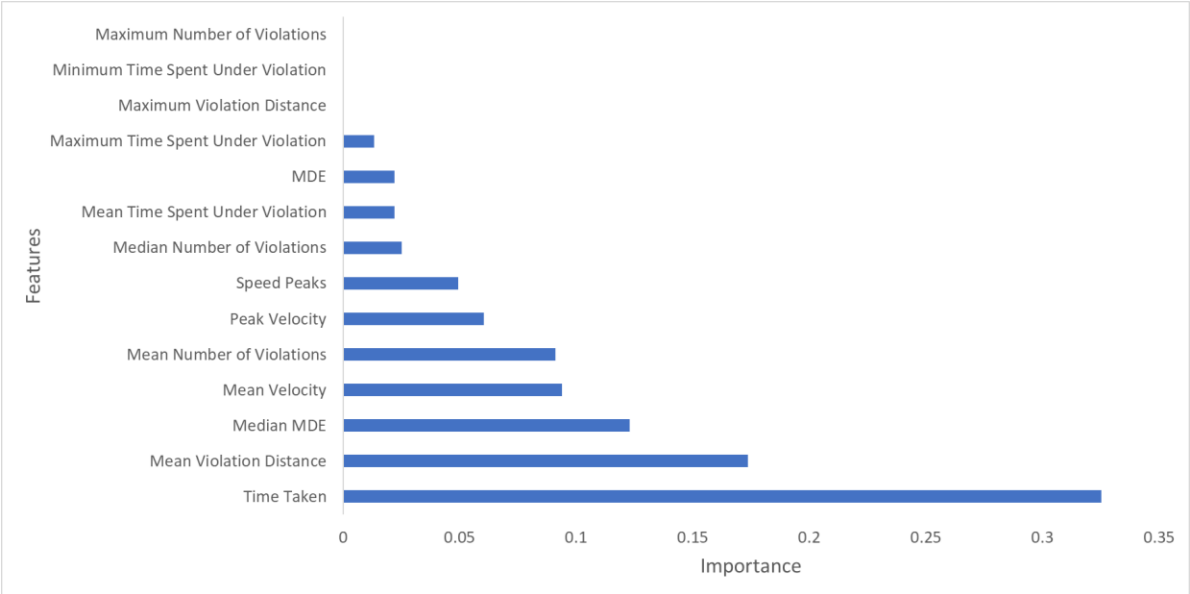


Figure 3.6: Feature importance score for the tracing task

3.3.6.2 Training and Testing of NN Models

Two different NN models were trained separately using the selected features. While one NN model was trained using features pertaining to the reaching task, another NN model was trained using the features pertaining to the tracing task. The architecture of the NN model is illustrated in Chapter 2 under section 2.4.2.1. In this study, 70% of the dataset was used to train the model, 15% of the data was used for validation, and 15% of the data was used to test the model's performance. Figures 3.7 and 3.8 show how the training loss was minimized in each NN model. The trained model was tested using the remaining dataset to evaluate if the model could accurately differentiate between the PD and control subjects. Five performance metrics were calculated to evaluate the model's performance and predictive accuracy. Tables 3.5 and 3.6 show the performance metrics of the NN model based on the reaching and tracing tasks, respectively. Both models have more than 80% accuracy, with the F-1 score of the NN for the tracing task being 0.87. This indicates that the model could differentiate between the PD and control subjects using the selected features.

Table 3.5: Performance metrics of the NN model for the reaching task

Accuracy (%)	Recall	Precision	F-1 Score	ROC-AUC
81.56	0.8156	0.8122	0.8137	0.7481

Table 3.6: Performance metrics of the NN model for the tracing task

Accuracy (%)	Recall	Precision	F-1 Score	ROC-AUC
88.27	0.8821	0.8813	0.8795	0.8359

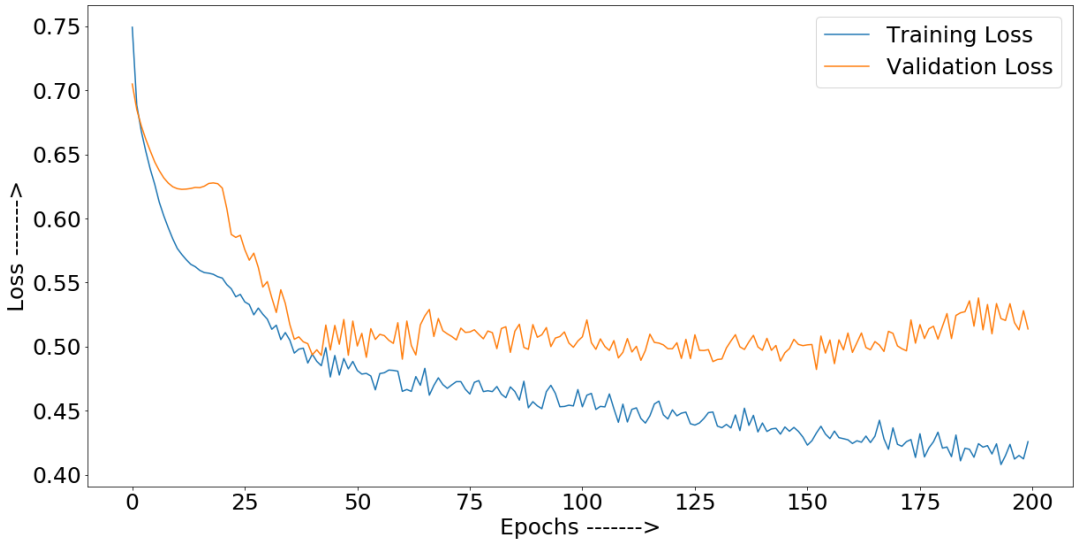


Figure 3.7: Training loss for the reaching task

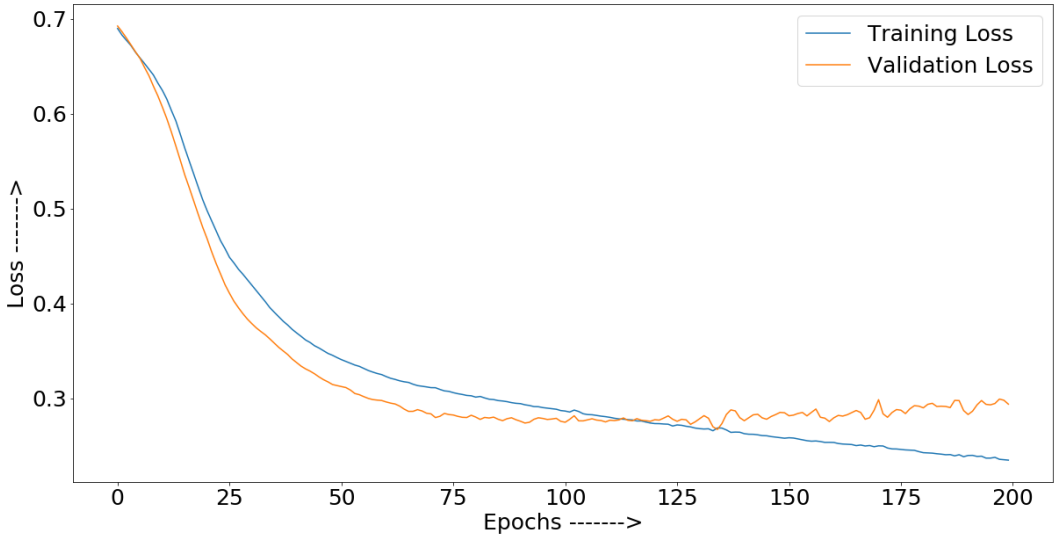


Figure 3.8: Training loss for the tracing task

3.4 Discussion

This section focuses on quantifying and characterizing any impairments in SMI caused due to PD and how dopaminergic medication may alter these impairments. To evaluate the SMI performance, the healthy subjects and PD patients in their OFF and ON state of medication performed a series of reaching and tracing tasks under differing sensory conditions. The participants were tested under four sensory conditions: (i) without ASC, (ii) with ASC, (iii)

without sensory manipulation (iv) with sensory manipulation. The kinematic data acquired from the robotic device were used to calculate the features that serve as metrics to evaluate the performance of the participants. Two different comparisons were made using the extracted features: (i) within-group comparison, and (ii) between-group comparison. These comparisons provide us information about the participant's ability to perform various facets of SMI appropriately: (i) integrate the multi-modal ASC, (ii) use the resulting perceptual estimates to modulate the motor output taking into account any changes in the testing environment or presence of sensory manipulation (inaccurate sensory inputs). Therefore, this objective investigation evaluated the SMI impairments in PD patients and the effect of dopaminergic medication. Furthermore, a trial-by-trial analysis was also performed to evaluate the motor learning ability, which is highly dependent on the proper functioning of SMI. The findings from this study may be used to understand and characterize the impairments in SMI that may contribute to the perceptual and motor deficits experienced by PD patients. Better knowledge about the contributing factor may enable us to target these deficits through a more systematic treatment regime. Furthermore, understanding the effect of medication would shed light on how the rehabilitation regimes needed to be planned and structured to be effective.

A within-group comparison for each group was done to evaluate how the performance of the participants changes with the sensory conditions. Firstly, across all groups (PD-OFF, PD-ON, control subjects), when performing a within-group comparison between tasks with and without sensory manipulation, the participants performed better in tasks without sensory manipulation than in tasks with sensory manipulation. Therefore, it can be concluded that both the PD and control subjects were affected to varying degrees due to the inaccurate sensory inputs provided in the task with sensory manipulation. Moving to the within-group comparison between the reaching task with ASC and without ASC, PD-OFF appeared to perform worse when provided with ASC than their performance without ASC. This suggests that the assistive cues provided to help the patients perform better have instead affected their performance, implying an impairment in integrating multi-modal sensory cues. The reasoning behind this inference is that in the task without ASC, the participants received only visual input with no ASC (haptic or auditory inputs) and therefore are not required to integrate the inputs from multiple modalities and can

perform motor movements or modulate motor outputs based on the perceptual estimates formed through just the visual inputs. However, in the task with ASC, sensory inputs were provided through multiple modalities. Therefore, the patients are required to integrate multi-modal inputs and filter out unnecessary inputs to form the perceptual estimate that would be used to modulate the motor outputs. Therefore, the performance deterioration in the task with ASC compared to without ASC implies an impairment in PD-OFF to integrate multi-modal sensory inputs, resulting in an inaccurate perceptual estimate when provided with ASC, which in turn led to the incorrect modulation of motor outputs and, consequently the motor underperformance. Moving to PD-ON, the results from the within-group comparison were not statistically significant. While PD-ON showed marginal improvement when provided with ASC, there was no substantial improvement in the performance, implying that the ASC neither significantly improved nor deteriorated their performance. This may indicate that the external sensory cues provided to assist the patients did not alter their motor performance in any significant way. Finally, for the control subjects, the performance marginally improved in the task with ASC compared to without ASC. It may be that the control subjects have been exhibiting close to optimal performance even without ASC as shown by the fact that they were able to reach 100 % targets even in task without ASC. The reason for control subjects showing only marginal improvement in certain features when provided with ASC may be due to the limits of human motor control precision. However, a marginal improvement was seen in control subjects across most features when provided with ASC. Therefore, the motor performance of the control subjects may have benefitted from the ASC as they could optimally integrate the multi-modal inputs to obtain an accurate perceptual estimate and modulate the motor outputs to suit the demands of the environment. The reason for their better motor performance in the task with ASC may be the additional information provided by the haptic and auditory inputs, which resulted in a more coherent and detailed perceptual estimate. However, in the task without ASC, with no multi-modal inputs, their perceptual estimate may not be as robust and accurate as the task with ASC. This may explain the improvement in performance when the control subjects received ASC compared to when they did not receive any ASC. Studies [34][35] have also indicated that the perceptual estimate formed through multi-modal inputs may be a more accurate, robust, and coherent representation of

oneself and the world around us than an estimate formed through a single modality. In conclusion, while PD-OFF exhibited deficits in integrating multi-modal inputs due to SMI impairment, the control subjects with their optimal SMI functioning have shown that the ASC provided in the task was able to elicit an improvement in their motor performance.

Moving to the comparison between PD-OFF and the control subjects, in tasks with and without ASC, the control subjects outperformed PD-OFF across all features. The underperformance by PD-OFF compared to the control subjects in the task without ASC (where the participants only had visual inputs) also aligns with earlier studies [36] [37] that reported abnormal vision-based spatial and temporal perception in PD patients. Additionally, while the control subjects performed better than PD-OFF with and without ASC, the difference in performance between the two groups was much higher in the task with ASC than in the task without ASC. The difference in endpoint error between the groups was 0.143 cm and 0.103 cm in tasks with and without ASC, respectively. Similarly, the difference in MDE between the groups was also 0.084 and 0.055 cm in tasks with and without ASC, respectively. Finally, while there was a statistically significant difference between the groups in features such as mean direction error and target reach in the task with ASC, there was no statistically significant difference between the groups in these features without ASC. This may be because the control subjects improved their motor performance when provided with ASC as opposed to PD-OFF, whose motor performance deteriorated in the task with ASC, resulting in a higher difference between the two groups. This opposing reaction between the two groups, when provided with ASC, was also observed in the within-group comparison. Therefore, this implies an impairment in one of the facets of SMI (multi-sensory integration) among PD patients. Computational models explaining how CNS may perform multi-sensory integration have been discussed in Chapter 1. The MLE model [10][11] indicates that a weight value is assigned to each input obtained from various modalities depending on the noise associated with that modality and then integrated. A modality with higher noise will receive a lower weight and vice versa. Interpreting the results from the perspective of the MLE model, there appears to be an impairment in determining the noise associated with a given modality and, therefore, could not assign appropriate weights to that modality during multi-sensory integration. Furthermore, apart from the noise associated with the modality, other factors, such as the

appropriateness of the information provided by a given modality to complete the task at hand, also needed to be considered based on earlier computational models [38][39]. This ability to determine which modality provides the most vital and accurate information necessary to complete a given task may be impaired in PD patients, leading to impairment in SMI. Studies [26] [27] have also suggested that an increased dependence on visual input among PD patients may indicate an apparent inability to rank the modality based on its importance and accuracy. This suggests that PD patients give higher importance to visual inputs irrespective of whether other modalities may provide equally or, if not more, vital information than the visual input due to an impaired multi-sensory integration process. However, it must be noted that while PD patients may rely more on visual inputs, they do not ignore the inputs from other modalities. This inference can be validated by examining the performance of PD-OFF in tasks with ASC, as the additional multi-modal inputs affected the motor performance and were not ignored by the PD patients. Therefore, while PD patients could utilize or consider the multi-modal inputs during the sensory integration process, there is an impairment in their ability to appropriately integrate multi-modal inputs as a result of CNS criteria for sensory integration being altered due to PD. Further work is still needed to understand how this multi-sensory integration criteria was altered in PD patients and if these criteria can be normalized through treatment strategies to better manage the sensory deficits in PD. Moving to tasks with and without sensory manipulation, the control subjects have again performed better than PD-OFF in tasks with and without sensory manipulation across all features. The findings from the reaching and tracing task without sensory manipulation further emphasizes our earlier inference that when provided with multi-modal ASC, the control subjects are better than PD-OFF in integrating inputs from multiple modalities and using the resulting perceptual estimate to modulate the motor outputs. In reaching and tracing tasks with sensory manipulation, while the control subjects performed better than PD-OFF, certain features that showed a statistically significant difference between the two groups in the task without sensory manipulation were not significant in the task with sensory manipulation. This may indicate that both groups were adversely affected due to sensory manipulation. Furthermore, this reduction in the difference between the two groups in the presence of sensory manipulation may also suggest that while PD-OFF may be more affected by the sensory manipulation, they were

able to improve their performance and get closer to the control subjects. This inference can be further validated by examining the trial-by-trial analysis, which evaluates the participant's ability to adapt to sensory manipulation, learn and improve their motor performance as they complete more trials. In the tracing task with sensory manipulation, a negative correlation was observed in features such as the mean number of violations and time spent under violation. This indicates that while the overall performance of the control subjects was better than PD-OFF, the difference in performance between PD-OFF and the control subjects reduced over time in these two features as they performed more trials. Since there is no evidence of the deterioration in the performance of the control subjects in later trials, the only explanation for this finding is that PD-OFF improved their performance and got closer to the control subjects. This indicates that PD-OFF can adapt to sensory manipulation and learn over time to improve their motor performance. Interestingly, while PD-OFF improved their performance over time in the tracing task with sensory manipulation, they failed to do so in the reaching task with sensory manipulation, as a positive correlation was observed in the trial-by-trial for the mean direction error, indicating that the difference between the two groups has increased over trials. An explanation for the difference in the ability to learn over trials may be that the nature of ASC provided during the tracing task was much more helpful and efficient in guiding the motor movements. While the ASC in the reaching task was provided only when the participants reached the target as a sign of confirmation, the ASC provided in the tracing tasks existed throughout the trial to ensure that the participant did not move out of the green track. Consequently, the ASC in the tracing task may be more efficient in guiding the participants, resulting in a more accurate and efficient motor performance than the reaching task with sensory manipulation. Therefore, the improvement observed in the trial-by-trial analysis may be attributed to the multi-modal ASC provided during the task. While examining the tasks with and without ASC, PD-OFF underperformed in the task with ASC due to the impairment in appropriately integrating the multi-modal inputs. However, in tasks with and without sensory manipulation, PD-OFF showed that despite the impaired SMI circuit, if provided with appropriate multi-modal inputs, PD-OFF is capable of improving their ability to integrate the multi-modal inputs over time and using the resulting perceptual estimate to improve their motor performance as they complete more trials. As

indicated earlier, the SMI has two facets (i) multi-sensory integration and (ii) modulation of motor outputs based on the resulting perceptual estimate. Taking these results together, while PD-OFF showed a deficit in the first facet of the SMI, they still retained the ability to modulate the motor outputs based on the perceptual estimate. This is why when they eventually improve their multi-sensory integration process over time, it gets translated into an improvement in motor performance. The findings suggest that if PD-OFF are provided with appropriate sensory inputs during their rehabilitation regimes, they can improve motor performance. However, retaining this improvement over a longer period is still a topic of debate.

A comparison was done between PD-OFF and PD-ON under different sensory conditions. In tasks with and without ASC, PD-ON performed better than PD-OFF across most features except for the maximum endpoint and direction errors. In both these sensory conditions, PD-ON exhibited higher maximum endpoint and maximum direction error than PD-OFF. However, PD-ON performed better than PD-OFF in mean endpoint and direction error. The findings suggest that while PD-ON may commit fewer errors than PD-OFF when PD-ON commits an error, PD-ON is less efficient in correcting it than PD-OFF. In the reaching task without sensory manipulation, PD-ON had performed better than PD-OFF except in maximum direction error. Again, while the mean error was less for PD-ON than PD-OFF, their maximum error was much higher than PD-OFF. Therefore, PD-OFF may be able to use the perceptual estimates obtained from an impaired SMI circuit to correct the errors. While this estimate may not be very accurate due to the SMI impairment, PD-OFF could still use it to correct errors, resulting in lower maximum endpoint and maximum direction errors. On the other hand, the results indicate that PD-ON may be unable to use the perceptual estimates to correct the endpoint and direction error committed during the task. For the tracing task without sensory manipulation, the findings show that while PD-ON had a less mean number of violations than PD-OFF, the time spent under violation, MDE, and the mean violation distance for PD-ON were much higher than PD-OFF. Congruent to our earlier conclusion, the results imply that while PD-ON committed fewer violations (deviating from the green track) than PD-OFF, when they do commit a violation, the magnitude of the violation is much higher due to their inability to modulate motor outputs based on perceptual estimates to correct the violation. Hence, the findings suggest

that the medication may impair the online motor control (ability to listen to the sensory inputs and appropriately adjust the motor outputs to suit the demands of the environment), which is vital to performing any task-specific voluntary movements. Finally, in the reaching task with sensory manipulation, PD-ON performed worse than PD-OFF across all features apart from mean velocity and mean endpoint error. The mean and maximum direction error, which evaluate one's ability to adapt to the sensory manipulation and adjust motor output, was statistically significantly worse in PD-ON compared to PD-OFF. This trend continued in the tracing task with sensory manipulation as PD-ON performed poorly across all features except the mean velocity compared to PD-OFF. Therefore, the patients in their medicated state struggled to adapt to the sensory manipulation compared to their unmedicated state. Earlier studies [10][11] [38][39] have shown that SMI is responsible for ranking the modalities based on their accuracy, reliability, and relevance to the task at hand and integrating them. Therefore, identifying and adapting to an inaccurate sensory input requires proper functioning of SMI. Considering the findings, it can be concluded that the medication has exacerbated the SMI deficits in PD patients. This may be why the inaccurate sensory inputs have negatively affected the performance of PD-ON much more than the performance of PD-OFF. Apart from this deficit in ranking the modality based on their accuracy, the more important finding is the worsening of the ability to modulate the motor outputs based on the perceptual estimate. Studies [40][41] have discussed an internal model that includes a forward and inverse model to explain how humans may perform online motor control (see Section 1.5.5). By comparing PD-OFF and PD-ON, it was evident that PD-ON was unable to recognize that they had committed an error. From the perspective of the internal model, there exists a deficit in PD-ON to appropriately use the perceptual estimates and understand that the motor outcome is not what was expected. As a result, they fail to recognize and correct the error. This impairment in correcting errors using perceptual estimates among PD-ON may also be the reason for why the magnitude of the error or violation committed by PD-ON is much worse than that by PD-OFF, although the number of errors committed by PD-OFF is higher than that by PD-ON. Therefore, it can be concluded that the medication has adversely affected online motor control ability, affecting task-specific voluntary movements. Any deficit in this ability would also adversely affect the performance when encountering sensory manipulation.

While PD-OFF did struggle when encountering sensory manipulation, as they retained the ability to recognize an error and adjust the motor output accordingly, their performance was better than PD-ON. However, PD-ON, due to their deficit in online motor control, could not use the perceptual estimate to appropriately determine an error and were far less efficient in correcting the error. The observation from within-group comparison was also in line with this inference as the motor performance of PD-ON was not impacted significantly when provided with ASC. This could also be attributed to the impaired online motor control as they could not use the additional information provided through multi-modal inputs to modulate the motor outputs. Finally, the motor learning was also evaluated between the two groups using trial-by-trial analysis, which indicated that a positive correlation was observed between the mean violation distance, time spent under violation, and mean number of violations in the tracing tasks with sensory manipulation. Therefore, in addition to PD-ON being worse than PD-OFF in these features, the difference between the two groups also increased as more trials were performed. This suggests that while PD-OFF improved their performance in these features when encountering sensory manipulation, PD-ON failed to do so. Therefore, motor learning, which is heavily dependent on SMI performance, was also affected due to medication. To summarize, numerous studies in the past have reported that the medication has mitigated the cardinal motor symptoms of PD. The result from our study also aligns with earlier studies as the movement speed improved after medication. However, there exists a distinction between the speed at which a task is performed and the quality (accuracy and/or efficiency) with which a task is performed. Optimally performing a task-specific voluntary movement requires constant learning, re-learning, and updating of motor outputs based on the changes in the environment and task at hand. These abilities depend on the proper functioning of SMI circuits, and any impairment in SMI functions may affect these abilities, resulting in poorer task performance. This is why an improvement in movement speed due to medication did not translate to improving task performance. While the medication improved the movement speed, it adversely affected certain aspects of the SMI, which impaired the ability to learn, re-learn, and modulate motor outputs to suit the demands of the testing environment. These impairments during the ON state led to a deterioration in task performance despite an improvement in movement speed. Therefore, on a cautionary

note, these findings imply that the medication may negatively impact various aspects of SMI, which in turn impairs the online motor control and motor learning abilities in PD patients. This effect of medication on the functioning of SMI needs to be considered when planning and structuring the rehabilitation regimes.

A comparison between the control subjects and PD-ON was performed. The results indicate that the control subjects performed better than PD-ON in both reaching and tracing under all sensory conditions. A few crucial findings needed to be discussed when comparing the two groups. While the medication improved the movement speed in PD patients, the control subjects were still faster than PD-ON, indicating the medication did not normalize the movement speed in PD patients. Comparing the performance of the two groups in tasks with and without ASC, the difference in error metrics between the two groups increased in the task with ASC compared to without ASC. This implies that the control subjects improved their motor performance because of multi-modal ASC as opposed to PD-ON who did not benefit substantially from the ASC. Additionally, the difference between the two groups in tasks with sensory manipulation was much higher for most features than for tasks without sensory manipulation. The finding suggests that the control subjects were better than PD-ON in adapting to sensory manipulation. Finally, a positive correlation was observed in the trial-by-trial analysis for mean violation distance, indicating the difference between the two groups increased. Considering that the control subjects performed better than PD-ON in tasks with sensory manipulation, the positive correlation implies that the control subjects improved their performance over time while PD-ON failed to do so. To conclude, compared to the control subjects, PD-ON showed deficits in SMI, which impaired their ability to use the ASC to exhibit any motor improvements, adapt to sensory manipulation, and learn to improve their motor performance over time.

Machine learning models were designed and trained to determine if the robotic tasks and the metrics may be used as a potential diagnostic tool to detect abnormalities in SMI and SMC functions. Two different NN models were tested using the metrics from the reaching, and tracing task, which indicated that the models could accurately predict and differentiate between the PD and control subjects. The NN models showed an accuracy,

and F-1 score of more than 80%, implying that the robotic task and metrics designed in this thesis were able to characterize the impairments caused due to PD accurately. The results from these tasks may be used to manage the disease better. Another notable finding is that the NN trained using the features related to the tracing task performed better than the NN trained using the features pertaining to the reaching task. This may suggest that the tracing task was more efficient in highlighting the difference between the PD and control subjects than the reaching task. Moving forward, it may be worthwhile to investigate if selected features from the objective analysis may be used in conjunction with the current clinical method to better diagnose and gauge the disease's severity and progression.

Summarizing the findings, PD-OFF exhibited clear impairments in integrating multi-modal sensory inputs, affecting the task-specific voluntary movements. As a result, PD patients were unable to benefit from the multi-modal ASC. From the perspective of computational models [11] [38], the PD appears to alter the criteria used by the CNS to rank modalities based on accuracy and appropriateness before integrating them. The studies [26][27] that discuss the increased visual dependence of PD patients also support this inference. This altered criterion may be the root cause of the SMI impairment, leading to perceptual and motor deficits. However, the PD patients still retained the ability to use the residual perceptual estimates formed using the impaired multi-sensory integration process to modulate the motor outputs based on the requirements of the testing environment. Therefore, while the first facet (multi-sensory integration) of SMI is impaired, the second facet (modulation of motor output) of SMI may be unaffected due to PD. Due to this, the PD patients were able to adapt to sensory manipulation, although they took more time than the control subjects to do so. Moreover, the PD patients were also able to learn and improve their performance over time, implying that they still retain their motor learning ability. With the motor learning ability being heavily reliant on the proper functioning of SMI, the PD patients, despite the impairment in the multi-sensory integration process, were able to improve on the SMI process as they completed more trials which in turn led to improvement in motor performance over time. Therefore, PD patients only exhibit deficits in one facet of the SMI. If provided with appropriate sensory cues that guide the patients throughout the task, they can improve their SMI performance over time. The effect of the medication on the PD patients was evaluated, which indicated that the

medication worsened the SMI impairments. The medication has disrupted the ability to use the perceptual estimate to modulate the motor outputs based on the changes in the environment and to learn or relearn any motor skills. Any task-specific voluntary movement, including daily activities such as driving or eating, requires the ability to use the perceptual estimates for constant updating of motor commands and the ability to learn new tasks or modify an already learned task to suit the demands of the environment. The worsening of the impairment due to medication affecting the integration between the sensory and motor system may have resulted in the motor system outputting a motor command without accurately considering the changes in the testing environment. This deficit in online motor control resulted in PD-ON being unable to benefit from the multi-modal ASC and has also exhibited a significant deterioration in motor performance when encountering sensory manipulation. Furthermore, the ability to learn and improve motor performance was also impaired as it requires optimal use of the acquired sensory inputs to continuously refine their skills and improve performance. Therefore, as opposed to PD-OFF (who were able to learn and improve over time), the worsening of impairment in the SMI due to medication affected the ability to use the sensory feedback to refine the motor skills, adversely affecting the motor learning ability. Although the medication improved the movement speed, it has substantially deteriorated the functioning of SMI, which led to a deterioration in the accuracy and efficiency of voluntary movements. While the improvement in movement speed helped the patients complete the tasks quicker, it negatively affected their overall task performance, owing to the worsening SMI impairment. Therefore, despite their impairment in multi-sensory integration, PD-OFF were better than PD-ON in using the sensory feedback to modulate the motor outputs, adapt to erratic testing conditions, and learn new motor skills. Studies [21] discussed the importance of providing appropriate sensory cues during rehabilitation regimes and the role of sensory cues in improving the efficacy of the regimes. Therefore, the ability to use sensory cues to improve motor performance is the key to the success of rehabilitation therapies. Taking these results together, the PD patients in their OFF state may benefit more from the therapy as they still retain the ability to modulate or learn motor skills based on sensory feedback. This would ensure that the sensory cues essential to the success of the therapies are utilized appropriately to improve motor performance, enhancing the

efficiency of therapy. On the other hand, the efficacy of the therapies may be negatively affected when the PD patients in their ON state are exposed to the rehabilitation regimes as they exhibit worsening SMI impairments and are unable to learn and improve motor performance using sensory cues. This inability to use sensory cues to better their motor performance may result in the patients not benefitting from the therapies. Therefore, it may be that rehabilitation therapies with an enriched sensory environment that provides useful and appropriate multi-modal inputs may be more beneficial to PD patients before medication. However, certain PD patients do experience severe motor symptoms during their OFF state, thereby affecting their ability to perform any motor tasks. Hence, the patient's motor symptoms during the OFF state also need to be considered when determining their rehabilitation strategy.

3.5 References

[1] V. Gaveau *et al.*, "Automatic online control of motor adjustments in reaching and grasping," *Neuropsychologia*, vol. 55, pp. 25–40, Mar. 2014, doi: 10.1016/j.neuropsychologia.2013.12.005.

[2] R. Shadmehr, M. A. Smith, and J. W. Krakauer, "Error Correction, Sensory Prediction, and Adaptation in Motor Control," *Annu Rev Neurosci*, vol. 33, no. 1, pp. 89–108, Jun. 2010, doi: 10.1146/annurev-neuro-060909-153135.

[3] M. Flanders, "What is the biological basis of sensorimotor integration?," *Biol Cybern*, vol. 104, no. 1–2, pp. 1–8, Feb. 2011, doi: 10.1007/s00422-011-0419-9.

[4] S. Sangani, A. Lamontagne, and J. Fung, "Chapter 15 - Cortical mechanisms underlying sensorimotor enhancement promoted by walking with haptic inputs in a virtual environment," in *Sensorimotor Rehabilitation*, in Progress in Brain Research, vol. 218. Elsevier, 2015, pp. 313–330. doi: https://doi.org/10.1016/bs.pbr.2014.12.003.

[5] R. Kaji and N. Murase, "Sensory function of basal ganglia," *Movement Disorders*, vol. 16, no. 4, pp. 593–594, Jul. 2001, doi: 10.1002/mds.1137.

[6] G. Abbruzzese and A. Berardelli, "Sensorimotor integration in movement disorders," *Movement Disorders*. 2003. doi: 10.1002/mds.10327.

[7] Q. J. Almeida *et al.*, "An evaluation of sensorimotor integration during locomotion toward a target in Parkinson's disease," *Neuroscience*, 2005, doi: 10.1016/j.neuroscience.2005.02.050.

[8] A. Nagy, G. Eördegh, Z. Paróczy, Z. Márkus, and G. Benedek, "Multisensory integration in the basal ganglia," *European Journal of Neuroscience*, 2006, doi: 10.1111/j.1460-9568.2006.04942.x.

[9] M. A. Jabri, J. Huang, O. J. D. Coenen, and T. J. Sejnowski, "Models of basal ganglia and cerebellum for sensorimotor integration and predictive control," *Sensor Fusion and Decentralized Control in Robotic Systems III*, vol. 4196, no. October 2000, pp. 125–137, 2000, doi: 10.1117/12.403711.

[10] M. O. Ernst, J.-P. Bresciani, K. Drewing, and H. H. Bülthoff, "Integration of Sensory Information Within Touch and Across Modalities," *Proceedings of the 2004 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS 2004)*, 2004.

[11] M. O. Ernst and M. S. Banks, "Humans integrate visual and haptic information in a statistically optimal fashion," *Nature*, 2002, doi: 10.1038/415429a.

[12] T. Klockgether and J. Dichgans, "Visual control of arm movement in Parkinson's disease," *Movement Disorders*, 1994, doi: 10.1002/mds.870090108.

[13] T. Klockgether, M. Borutta, H. Rapp, S. Spieker, and J. Dichgans, "A defect of kinesthesia in Parkinson's disease," *Movement Disorders*, vol. 10, no. 4, pp. 460–465, Jul. 1995, doi: 10.1002/mds.870100410.

[14] R. S. Weil, A. E. Schrag, J. D. Warren, S. J. Crutch, A. J. Lees, and H. R. Morris, "Visual dysfunction in Parkinson's disease.," *Brain*, vol. 139, no. 11, pp. 2827–2843, 2016, doi: 10.1093/brain/aww175.

[15] U. P. Mosimann, G. Mather, K. A. Wesnes, J. T. O'Brien, D. J. Burn, and I. G. McKeith, "Visual perception in Parkinson disease dementia and dementia with Lewy bodies," *Neurology*, vol. 63, no. 11, pp. 2091–2096, Dec. 2004, doi: 10.1212/01.WNL.0000145764.70698.4E.

[16] J. Konczak, K. Y. Li, P. J. Tuite, and H. Poizner, "Haptic perception of object curvature in Parkinson's disease," *PLoS One*, 2008, doi: 10.1371/journal.pone.0002625.

[17] Z. Jafari, B. E. Kolb, and M. H. Mohajerani, “Auditory Dysfunction in Parkinson’s Disease,” *Movement Disorders*, vol. 35, no. 4, pp. 537–550, Apr. 2020, doi: 10.1002/mds.28000.

[18] H. Shibasaki, S. Tsuji, and Y. Kuroiwa, “Oculomotor Abnormalities in Parkinson’s Disease,” *Arch Neurol*, vol. 36, no. 6, pp. 360–364, Jun. 1979, doi: 10.1001/archneur.1979.00500420070009.

[19] G. Abbruzzese, R. Marchese, L. Avanzino, and E. Pelosin, “Rehabilitation for Parkinson’s disease: Current outlook and future challenges,” *Parkinsonism Relat Disord*, 2016, doi: 10.1016/j.parkreldis.2015.09.005.

[20] T. K. Lee and E. L. Yankee, “A review on Parkinson’s disease treatment,” *Neuroimmunol Neuroinflamm*, vol. 8, p. 222, 2022, doi: 10.20517/2347-8659.2020.58.

[21] R. Marchese, M. Diverio, F. Zucchi, C. Lentino, and G. Abbruzzese, “The role of sensory cues in the rehabilitation of parkinsonian patients: A comparison of two physical therapy protocols,” *Movement Disorders*, vol. 15, no. 5, pp. 879–883, Sep. 2000, doi: 10.1002/1531-8257(200009)15:5<879::AID-MDS1018>3.0.CO;2-9.

[22] T. Platz, R. G. Brown, and C. D. Marsden, “Training improves the speed of aimed movements in Parkinson’s disease.,” *Brain*, vol. 121 (Pt 3), pp. 505–14, Mar. 1998, doi: 10.1093/brain/121.3.505.

[23] R. Dubbioso, F. Manganelli, H. R. Siebner, and V. di Lazzaro, “Fast Intracortical Sensory-Motor Integration: A Window Into the Pathophysiology of Parkinson’s Disease,” *Front Hum Neurosci*, vol. 13, Apr. 2019, doi: 10.3389/fnhum.2019.00111.

[24] M. L. T. M. Müller *et al.*, “Thalamic cholinergic innervation and postural sensory integration function in Parkinson’s disease,” *Brain*, vol. 136, no. 11, pp. 3282–3289, Nov. 2013, doi: 10.1093/brain/awt247.

[25] J. Konczak *et al.*, “Parkinson’s disease accelerates age-related decline in haptic perception by altering somatosensory integration,” *Brain*, vol. 135, no. 11, pp. 3371–3379, Nov. 2012, doi: 10.1093/brain/aws265.

[26] J. P. Azulay, S. Mesure, B. Amblard, and J. Pouget, “Increased Visual Dependence in Parkinson’s Disease,” *Percept Mot Skills*, vol. 95, no. 3_suppl, pp. 1106–1114, Dec. 2002, doi: 10.2466/pms.2002.95.3f.1106.

[27] L. A. Brown *et al.*, “Parkinsonian deficits in sensory integration for postural control: Temporal response to changes in visual input,” *Parkinsonism Relat Disord*, vol. 12, no. 6, pp. 376–381, Sep. 2006, doi: 10.1016/j.parkreldis.2006.03.004.

[28] P. O’Suilleabhain, J. Bullard, and R. B. Dewey, “Proprioception in Parkinson’s disease is acutely depressed by dopaminergic medications,” *J Neurol Neurosurg Psychiatry*, 2001, doi: 10.1136/jnnp.71.5.607.

[29] J. Konczak *et al.*, “Proprioception and Motor Control in Parkinson’s Disease,” *J Mot Behav*, vol. 41, no. 6, pp. 543–552, Nov. 2009, doi: 10.3200/35-09-002.

[30] D. Mongeon, P. Blanchet, and J. Messier, “Impact of Parkinson’s disease and dopaminergic medication on proprioceptive processing,” *Neuroscience*, vol. 158, no. 2, pp. 426–440, Jan. 2009, doi: 10.1016/j.neuroscience.2008.10.013.

[31] Z. S. Nasreddine *et al.*, “The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment,” *J Am Geriatr Soc*, vol. 53, no. 4, pp. 695–699, Apr. 2005, doi: 10.1111/j.1532-5415.2005.53221.x.

[32] Y. K. Tamilselvam, M. S. Jog, and R. V. Patel, “Robotics-Based Characterization of Sensorimotor Integration in Parkinson’s Disease and the Effect of Medication,” *IEEE*

Transactions on Neural Systems and Rehabilitation Engineering, vol. 31, pp. 3201–3211, 2023, doi: 10.1109/TNSRE.2023.3299884.

[33] L. L. Edwards, E. M. King, C. M. Buetefisch, and M. R. Borich, "Putting the 'Sensory' Into Sensorimotor Control: The Role of Sensorimotor Integration in Goal-Directed Hand Movements After Stroke," *Front Integr Neurosci*, vol. 13, May 2019, doi: 10.3389/fnint.2019.00016.

[34] M. O. Ernst and H. H. Bülthoff, "Merging the senses into a robust percept," *Trends Cogn Sci*, vol. 8, no. 4, pp. 162–169, Apr. 2004, doi: 10.1016/j.tics.2004.02.002.

[35] B. E. Stein and M. A. Meredith, *The Merging of the Senses*. MIT Press, 1993.

[36] M. Bernardinis, S. F. Atashzar, M. Jog, and R. V. Patel, "Visual Displacement Perception in Parkinson's Disease Analyzed Using a Computer-Generated Graphical Tool," in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, 2018. doi: 10.1109/EMBC.2018.8512754.

[37] M. Bernardinis, S. F. Atashzar, M. S. Jog, and R. V. Patel, "Differential Temporal Perception Abilities in Parkinson's Disease Patients Based on Timing Magnitude," *Sci Rep*, vol. 9, no. 1, p. 19638, Dec. 2019, doi: 10.1038/s41598-019-55827-y.

[38] R. B. Welch, L. D. DutionHurt, and D. H. Warren, "Contributions of audition and vision to temporal rate perception," *Percept Psychophys*, 1986, doi: 10.3758/BF03204939.

[39] R. B. Welch and D. H. Warren, "Immediate perceptual response to intersensory discrepancy," *Psychol Bull*, 1980, doi: 10.1037/0033-2909.88.3.638.

[40] D. M. Wolpert, Z. Ghahramani, and M. I. Jordan, "An internal model for sensorimotor integration," *Science (1979)*, 1995, doi: 10.1126/science.7569931.

[41] F. Yavari, F. Towhidkhah, and M. A. Ahmadi-Pajouh, "Are fast/slow process in motor adaptation and forward/inverse internal model two sides of the same coin?," *Med Hypotheses*, 2013, doi: 10.1016/j.mehy.2013.07.009.

Chapter 4

4 Sensorimotor Control in Parkinson's Disease: Abnormalities in Movement Planning and Online Error Correction

This chapter discusses results pertaining to the investigation of Sensorimotor Control (SMC) in Parkinson's Patients.

4.1 Introduction

Motor actions are the means through which humans physically interact with the world around them. Chapter 3 discusses Sensorimotor Integration, which provides the motor system with the necessary information about oneself and one's surroundings. However, humans still need to use this information and determine the best course of action to achieve the desired goal. In short, having the necessary information from the SMI process alone does not guarantee the proper execution of a motor task. Optimal planning and correction or updating of an existing motor plan are necessary for the optimal execution of a motor task in a dynamic environment. The ability to use and interpret the information obtained from the SMI process to plan, update, correct the motor strategies and generate the appropriate motor commands to achieve the desired outcome is called Sensorimotor Control (SMC). SMC encompasses a broad network of functions intertwined with each other that involves and requires multiple systems to work together. Therefore, in addition to the motor system, which plays a vital role in movement execution, and the sensory system, which provides the necessary information to perceive the world around oneself, the cognitive system also plays a crucial role in SMC as it aids in a series of decision-making processes involved in planning or correcting the motor strategies. Therefore, optimal functioning of SMC requires multiple systems (sensory, motor, and cognitive systems) communicating with each other in a closed loop. The neural and computational bases related to SMC functions were discussed in Chapter 1 under sections 1.5.4 and 1.5.5. Since almost all daily activities are performed in an environment that is constantly changing and sometimes unpredictable, i.e., a dynamic environment, executing any day-to-day task requires constant planning and updating of planned movements. Therefore,

SMC functions such as movement planning, and online error correction are vital for performing voluntary movements. Any disease affecting the domains (motor, sensory, and cognitive) related to the SMC functions may, in turn, severely impair the individual's ability to perform any voluntary movement, adversely affecting their quality of life.

Cardinal motor symptoms such as tremor, rigidity, and bradykinesia presented by PD have garnered a lot of attention over the years and have been associated with difficulties in movements. However, the planning and execution of motor actions are far more complex, as explained earlier, and may contribute to the difficulties in voluntary movements. It is well known that PD not only affects the motor systems but may also impair sensory or cognitive systems, which may lead to a disruption of fundamental processes involved in performing voluntary movements. SMC functions such as movement planning and online error correction, which act as building blocks for any motor action, may be impaired due to PD, adversely affecting the patient's ability to perform any day-to-day tasks. The neural regions involved in SMC functions are not yet fully understood, although numerous studies [1] [2] [3][4] have pointed to BG, the affected region in PD, having a vital role in movement planning and error correction. Therefore, the BG dysfunction due to PD may give rise to an impairment in SMC, which aligns with our earlier hypothesis stated in Chapter 1. It is important to characterize any impairments in SMC that may be presented due to PD and to understand the underlying mechanism as to how an impairment in a specific domain affects the SMC functions. To better understand the mechanisms or criteria associated with SMC that may be altered due to PD, it may be necessary to analyze the SMC functions of PD patients from the perspective of computational models that have been hypothesized to explain the functioning of SMC. This would shed light on how dysfunctions in PD may affect the CNS's criterion in executing an SMC function. So far, to the best of our knowledge, no study has evaluated the SMC performance of PD patients based on existing computational models. Furthermore, investigating the SMC impairments in PD patients using objective metrics would provide new insights into the factors contributing to motor dysfunctions. This may open new doors in patient-specific and domain-specific rehabilitation therapy to target SMC impairments using specific objective metrics that signify an improvement or deterioration in SMC performance due to the therapy. Using objective metrics in rehabilitation therapies would

provide a more tangible method to assess the patient's response to the therapy, thereby improving the efficacy of the therapy. Furthermore, with deficits in certain sensory and cognitive domains arising at an early stage, there is a need to objectively detect these deficits at an early stage. While clinical scales may be used to detect these deficits, some studies [5] discuss the limitations of subjective assessments, such as clinical scales, and recommend complementing these scales with objective metrics for more effective diagnosis and management of PD. Additionally, there is also a lack of clinical methods to evaluate SMI and SMC performance. Finally, there is also a need to understand the effect of medication on SMC function, as some studies [6][7][8] have reported that medication has mixed results on PD-related impairments. While it is well-known and even clinically established that the medication may mitigate cardinal motor symptoms, the studies in [6][7][8] show that the medication may have an adverse effect on the sensory, and cognitive systems, which are also vital for the proper functioning of SMC. Therefore, it is necessary to understand the effect of medication on SMC functions and how it may affect a patient's ability to perform voluntary movements.

Studies have discussed difficulties in performing motor functions and impairments in SMC among PD patients. A detailed discussion of existing studies on SMC impairments in PD patients is provided in Chapter 1 under section 1.5.6. However, several unanswered questions about movement planning and error correction aspects of SMC functions need to be explored. Most studies that examine SMC functionalities either do not use objective metrics to evaluate SMC functions or fail to individually explore all domains associated with SMC functions. Furthermore, to the best of our knowledge, no study has evaluated the functioning of SMC from the perspective of the computational model, which is also one of the objectives of this study. Therefore, it is essential to objectively investigate all domains involved in SMC functions (specifically movement planning and online error correction) and the effect of medication on these functions.

4.2 Methods

4.2.1 Participants

Fifty-six patients diagnosed with PD and twenty age-equivalent control subjects were recruited to evaluate the effects of PD on SMC. The patients were recruited at the Movement Disorders Clinic of the London Health Sciences Centre in London, Ontario, Canada. The Office of Human Research Ethics at Western University's Research Ethics Board approved this study (protocol numbers: 115770, 108252). The nature of the experiment was explained to the participants before the study through a letter of information, and all participants provided their informed consent before their participation. The experiments were conducted in accordance with the ethical standards indicated by the Declaration of Helsinki and the Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans in Canada. The robotic assessment for the OFF state was done after overnight suspension of the dopaminergic drugs. Later, the patients were administered the prescribed medication, and the robotic assessment was repeated one hour after the medication intake. Therefore, all PD patients underwent the robotic assessment in both OFF and ON states. The patients included in this study did not experience any dyskinesia after medication that affected their upper-limb movement. Furthermore, the control subjects and PD patients performed the robotic tasks separately using their right as well as left hands. Before the robotic assessment, motor complications, if any, were evaluated for each PD patient using section 3 (motor sub-scale) of UPDRS in both the OFF and ON states. The cognitive status of the PD patients was evaluated in the ON state using the MoCA scale.

4.2.2 Experimental Setup

During the robotic assessment, participants sat upright and comfortably on a wheelchair base facing the VR display. The height of the chair was adjusted such that the participant’s forehead was aligned with the fixed headrest ensuring optimal arm reach and screen visibility. The position of the chair was also adjusted so that the participants could comfortably grasp the robotic handle and move it across the entire workspace. Figure 4.1 shows the experimental setup.

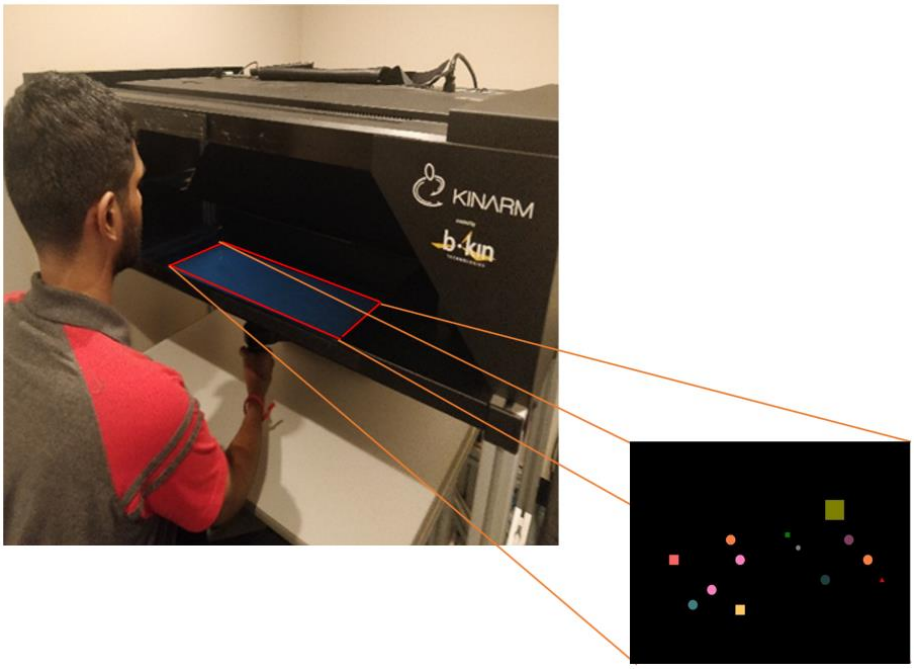


Figure 4.1: Experimental setup for the obstacle avoidance task

4.2.3 Design and Development of an Obstacle Avoidance Task

A custom-designed obstacle avoidance task was used to assess if sensorimotor control in PD patients is altered. Participants were tested under dynamic conditions to evaluate their sensory, motor, and cognitive performance, as the optimal functioning of SMC requires multiple systems (sensory, motor, and cognitive) working together. The primary objective for the participants was to reach all the targets within a given time while avoiding all the obstacles. Targets were square-shaped, and the obstacles were circle- or triangle-shaped. The testing conditions were varied by changing the state (moving or stationary) of the targets or obstacles and adding single or multiple mechanical perturbations. The task was divided into four levels, with the obstacles and targets either moving or stationary depending on the level of the task. Table 2.3 shows the testing conditions for each level of the task. Apart from these variations, the speed at which the objects may move and the objects' width were also randomly varied. Humans need to perform most day-to-day tasks in a dynamic environment. Optimally planning a movement in an environment where its properties are constantly changing and correcting or updating a planned motor strategy to adapt to the changes in the environment is essential to perform any daily activity.

Therefore, various aspects of the testing conditions were varied to evaluate the movement planning and online error correction ability of the participants in dynamic environments. Additionally, mechanical perturbations were added to understand if PD also alters the force sensitivity in individuals. Participants performed 40 trials, with each level containing ten trials. Finally, to evaluate the individual's ability to use multi-modal inputs, haptic and auditory inputs were provided to help the participants avoid obstacles. With the SMC network spanning multiple domains (cognitive, sensory, and motor), the task was designed to evaluate the SMC functions associated with each domain and individually characterize the SMC impairments in each domain. The obstacle avoidance task was explained in greater detail in Chapter 2 under Section 2.1.5.

4.2.4 Feature Extraction and Analysis

To quantitatively analyze the SMC performance of the participants, features were extracted using the kinematic data collected by the robotic device when the participants performed the obstacle avoidance task. The extracted features were used to evaluate each domain (sensory, motor, and cognitive) involved in SMC functionalities. Section 2.2.3 in Chapter 2 provides definitions for the extracted features and the rationale behind classifying them to evaluate a specific domain associated with SMC functions. Table 2.7 shows the extracted features and the domain that it evaluates. Furthermore, specific features were extracted to compare each group's performance from the perspective of six computational models that hypothesized the criteria CNS might use to optimally perform SMC functions such as movement planning and online error correction.

4.3 Results

4.3.1 Participant Demographics

This study tested twenty age-equivalent healthy controls (13 males and 7 females) and fifty-six PD patients (40 males and 16 females) in their OFF and ON states. The motor and cognitive status of all PD patients were examined using the section 3 motor subscale of UPDRS and MoCA, respectively. Table 4.1 shows the demographics and clinical data for PD patients and control participants.

Table 4.1: Demographic and clinical data for PD patients

Demographic Data	**PD patients**	**Control subjects**
Number of participants	56	20
Age (years) (Mean (Minimum - Maximum))	62 (49 – 78)	58 (46 – 74)
Gender (M/F)	40/16	13/7
Years with disease (Mean (Minimum - Maximum))	10 (2 -30)	N/A
Clinical Data		
MOCA (Mean (Minimum - Maximum))	26 (21 – 30)	N/A
UPDRS motor sub-scale in OFF therapy (Mean (Minimum - Maximum))	46 (6 – 73)	N/A
UPDRS motor sub-scale in ON therapy (Mean (Minimum - Maximum))	30 (4 – 51)	N/A

4.3.2 Sensorimotor Control: Healthy Controls vs. PD-OFF

This section compares the performance of the control subjects with the PD patients in their OFF state. The features extracted to evaluate each domain (sensory, motor, and cognitive) involved in SMC functionalities were compared between the two groups individually to understand and characterize any domain-specific impairments that may affect SMC functions, such as movement planning and online error correction. Furthermore, specific features were also used to compare the performance of the two groups from the perspective of computational models. Table 4.2 shows the performance of the groups in the features extracted for the obstacle avoidance task, and Table 4.3 shows the significance value obtained from comparing the performance of the groups [9].

Table 4.2: Task performance of the three groups in each level of the obstacle avoidance task

Parameters		**PD-OFF (Median (Range))**	**PD-ON (Median (Range))**	**Control (Median (Range))**
Mean speed (cm/s)	L-1	0.125 (0.127)	0.135 (0.123)	0.166 (0.076)
	L-2	0.154 (0.206)	0.176 (0.160)	0.214 (0.076)
	L-3	0.152 (0.169)	0.167 (0.151)	0.210 (0.097)
	L-4	0.159 (0.174)	0.178 (0.152)	0.235 (0.010)
Peak speed (cm/s)	L-1	0.563 (0.749)	0.570 (0.666)	0.887 (0.786)
	L-2	0.604 (0.815)	0.685 (0.770)	0.894 (0.624)
	L-3	0.629 (0.899)	0.679 (0.528)	1 (0.748)
	L-4	0.684 (0.759)	0.776 (0.671)	1.013 (0.666)
Time to reach maximum speed (s)	L-1	5.468 (6.086)	5.168 (6.529)	4.608 (5.008)
	L-1	626.4 (753)	644.9 (237)	737.5 (233)

Movement area (cm^2)	L-2	753.8 (1008)	852.5 (793)	954.9 (321)
	L-3	748.3 (561)	754.2 (361)	860.6 (557)
	L-4	714.1 (999)	860.1 (771)	1002 (328)
Reaction time (s)	L-1	1.571 (1.485)	1.334 (1.216)	1.295 (0.704)
Speed peaks	L-1	8 (10)	6 (8)	5 (2)
	L-2	14 (6)	12 (5)	10 (5)
	L-3	10 (9)	9 (6)	7 (2)
	L-4	13 (6)	13 (5)	11 (3)
Movement time (s)	L-1	8.969 (12.91)	7.756 (4.674)	7.484 (2.426)
	L-2	10.66 (3.351)	10.82 (4.601)	9.001 (3.414)
	L-3	8.645 (5.072)	7.964 (5.416)	7.326 (1.965)
	L-4	11.29 (3.183)	11.02 (4.083)	10.19 (2.830)
Obstacle hit-to-warn ratio	L-1	0.051 (0.300)	0.040 (0.233)	0.013 (0.144)
	L-2	0.055 (0.474)	0.043 (0.333)	0.018 (0.194)
	L-3	0.314 (0.574)	0.355 (0.300)	0.210 (0.259)
	L-4	0.300 (0.446)	0.323 (0.339)	0.145 (0.257)
Corrective time for perturbation (s)	L-2	0.196 (0.237)	0.192 (0.273)	0.162 (0.119)
	L-3	0.208 (0.127)	0.226 (0.184)	0.181 (0.113)
	L-4	0.216 (0.168)	0.238 (0.161)	0.203 (0.142)
Target reach percent (%)	L-1	91.2 (60.7)	97.5 (30.5)	98.6 (55)
	L-2	58.2 (72.2)	63.8 (71.0)	71.6 (38.8)
	L-3	92.3 (36.1)	96.8 (16.6)	100 (27)
	L-4	55.5 (61.1)	68.0 (52.7)	76.3 (22.2)
Efficiency	L-1	0.671 (0.546)	0.685 (0.410)	0.879 (0.167)
Target order	L-1	0.705 (0.577)	0.749 (0.392)	0.838 (0.278)
Endpoint error (cm)	L-1	0.454 (0.387)	0.462 (0.524)	0.257 (0.112)
	L-2	0.676 (0.541)	0.729 (0.672)	0.591 (0.510)
	L-3	0.421 (0.630)	0.396 (0.325)	0.272 (0.133)
	L-4	0.630 (0.409)	0.640 (0.550)	0.587 (0.361)
Mean obstacle hit proportion per trial	L-1	17.11 (26.25)	15.66 (24.43)	11.62 (10.90)
	L-2	45.68 (32.53)	46.27 (37.76)	26.76 (19.72)
	L-3	85.76 (63.33)	69.31 (58.31)	53.72 (43.28)
	L-4	86.87 (67.89)	89.46 (71.52)	56.67 (47.71)
Total Corrective movements	L-1	87 (141)	69 (83)	58 (14)
	L-2	111 (224)	105 (72)	65 (46)
	L-3	93 (122)	84 (98)	73 (34)
	L-4	127 (104)	121 (59)	115 (73)
Endpoint variance (cm)	L-1	0.556 (2.062)	0.517 (2.517)	0.133 (0.835)
	L-2	1.213 (5.096)	1.706 (6.245)	1.108 (3.353)
	L-3	0.488 (2.923)	0.445 (2.463)	0.201 (0.422)
	L-4	1.161 (4.451)	1.947 (5.220)	0.950 (2.475)
Slope between performance and ID	L-1	0.391 (0.284)	0.361 (0.249)	0.283 (0.198)
	L-2	0.904 (0.693)	0.940 (0.560)	0.791 (0.412)
	L-3	0.410 (0.346)	0.391 (0.331)	0.321 (0.351)
	L-4	0.927 (0.540)	0.876 (0.670)	0.827 (0.790)

Error-speed ratio	L-1	3.60 (16.2)	3.26 (9.34)	1.40 (1.57)
	L-2	4.51 (11.5)	4.10 (9.90)	2.87 (4.43)
	L-3	2.35 (9.95)	1.98 (6.04)	1.12 (1.52)
	L-4	3.48 (10.3)	3.47 (6.96)	2.26 (3.38)

Table 4.3: Comparing the three groups for statistical differences

Parameters		**Statistical Significance**		
		PD-OFF Vs. Controls	**PD-OFF Vs. PD-ON**	**PD-ON Vs. Controls**
Mean speed (cm/s)	L-1	$p = 0.0016$*	$p = 0.0879$	$p = 0.0139$*
	L-2	$p = 0.0014$*	$p = 0.0703$	$p = 0.0096$*
	L-3	$p = 0.0007$*	$p = 0.0062$*	$p = 0.0065$*
	L-4	$p = 0.0006$*	$p = 0.010$*	$p = 0.0057$*
Peak speed (cm/s)	L-1	$p = 0.0004$*	$p = 0.2343$	$p = 0.0008$*
	L-2	$p = 0.0031$*	$p = 0.071$	$p = 0.0157$*
	L-3	$p = 0.0006$*	$p = 0.032$*	$p = 0.0003$*
	L-4	$p = 0.0002$*	$p = 0.044$*	$p = 0.0056$*
Time to reach maximum speed (s)	L-1	$p = 0.43$	$p = 0.039$*	$p = 0.9480$
Movement area (cm^2)	L-1	$p = 0.0062$*	$p = 0.0836$	$p = 0.0050$*
	L-2	$p = 0.0442$*	$p = 0.024$*	$p = 0.2488$
	L-3	$p = 0.0385$*	$p = 0.212$	$p = 0.0348$*
	L-4	$p = 0.0048$*	$p = 0.08$	$p = 0.0938$
Reaction time (s)	L-1	$p = 0.010$*	$p = 0.0329$*	$p = 0.5280$
Speed peaks	L-1	$p = 0.0123$*	$p = 0.0654$	$p = 0.0973$
	L-2	$p = 0.0431$*	$p = 0.0811$	$p = 0.2142$
	L-3	$p = 0.0006$*	$p = 0.0035$*	$p = 0.0499$*
	L-4	$p = 0.1094$	$p = 0.160$	$p = 0.2723$
Movement time (s)	L-1	$p = 0.0027$*	$p = 0.0022$*	$p = 0.0231$*
	L-2	$p = 0.011$*	$p = 0.0062$*	$p = 0.3494$
	L-3	$p = 0.0004$*	$p = 0.0019$*	$p = 0.0856$
	L-4	$p = 0.0282$*	$p = 0.0401$*	$p = 0.6793$
Obstacle hit-to-warn ratio	L-1	$p = 0.0252$*	$p = 0.0203$*	$p = 0.0894$
	L-2	$p = 0.101$	$p = 0.255$	$p = 0.0642$
	L-3	$p = 0.0052$*	$p = 0.0935$	$p = 0.004$*
	L-4	$p = 0.4274$	$p = 0.7782$	$p = 0.6476$
Corrective time for perturbation (s)	L-2	$p = 0.040$*	$p = 0.2432$	$p = 0.0780$
	L-3	$p = 0.09$	$p = 0.2954$	$p = 0.0679$
	L-4	$p = 0.115$	$p = 0.967$	$p = 0.4208$
Target reach percent (%)	L-1	$p = 0.1438$	$p = 0.87$	$p = 0.09$
	L-2	$p = 0.0801$	$p = 0.0220$*	$p = 0.5413$
	L-3	$p = 0.0045$*	$p = 0.26$	$p = 0.0084$*
	L-4	$p = 0.010$*	$p = 0.0312$*	$p = 0.1211$
Efficiency	L-1	$p = 0.0359$*	$p = 0.936$	$p = 0.0223$*
Target order	L-1	$p = 0.029$*	$p = 0.935$	$p = 0.0489$*

Endpoint error (cm)	L-1	$p = 0.015$*	$p = 0.0879$	$p = 0.0065$*
	L-2	$p = 0.0425$*	$p = 0.0703$	$p = 0.0250$*
	L-3	$p = 0.018$*	$p = 0.012$*	$p = 0.0387$*
	L-4	$p = 0.0032$*	$p = 0.159$	$p = 0.0647$
Mean obstacle hit proportion per trial	L-1	$p = 0.284$	$p = 0.199$	$p = 0.294$
	L-2	$p = 0.313$	$p = 0.193$	$p = 0.311$
	L-3	$p = 0.0421$*	$p = 0.701$	$p = 0.5621$
	L-4	$p = 0.023$*	$p = 0.253$	$p = 0.0215$*
Total Corrective movements	L-1	$p = 0.0068$*	$p = 0.0021$*	$p = 0.2028$
	L-2	$p = 0.018$*	$p = 0.0329$*	$p = 0.8276$
	L-3	$p = 0.0003$*	$p = 0.018$*	$p = 0.0611$
	L-4	$p = 0.0449$*	$p = 0.0437$*	$p = 0.3378$
Endpoint variance (cm)	L-1	$p = 0.044$*	$p = 0.880$	$p = 0.0139$*
	L-2	$p = 0.056$	$p = 0.492$	$p = 0.0361$*
	L-3	$p = 0.0419$*	$p = 0.730$	$p = 0.0780$
	L-4	$p = 0.232$	$p = 0.0071$*	$p = 0.0616$
Slope between performance and ID	L-1	$p = 0.217$	$p = 0.0068$*	$p = 0.683$
	L-2	$p = 0.026$*	$p = 0.519$	$p = 0.0011$*
	L-3	$p = 0.028$*	$p = 0.277$	$p = 0.0021$*
	L-4	$p = 0.0097$*	$p = 0.687$	$p = 0.065$
Error-speed ratio	L-1	$p = 0.0009$*	$p = 0.212$	$p = 0.0012$*
	L-2	$p = 0.0268$*	$p = 0.076$	$p = 0.3275$
	L-3	$p = 0.0008$*	$p = 0.032$*	$p = 0.0057$*
	L-4	$p = 0.125$	$p = 0.398$	$p = 0.2314$

Note: * after the *p*-value indicates statistical significance

4.3.2.1 Motor Features

Figure 4.2 shows a comparison between the three groups across all motor features. Regarding motor performance, PD-OFF were much slower than the control subjects as their mean and peak speed were 32% and 41% less than for the control subjects across all levels of the task. Consequently, PD-OFF took 15% more time to complete a given trial at all levels than the control subjects. Across all levels, there was a statistically significant deterioration in mean speed (see Table 4.3) for PD-OFF compared to the control subjects. PD-OFF also took more time to react to the target once it appeared on the VR display. PD-OFF took 19% more time to react than the control subjects in level 1 of the task. Additionally, PD-OFF group also took 17% more time to reach the maximum speed than the control subjects, indicating the slowness in reacting to the target. Finally, the movement area for PD-OFF was 21% less than for the control subjects, with the difference between the groups being statistically significant across all levels (see Table 4.3).

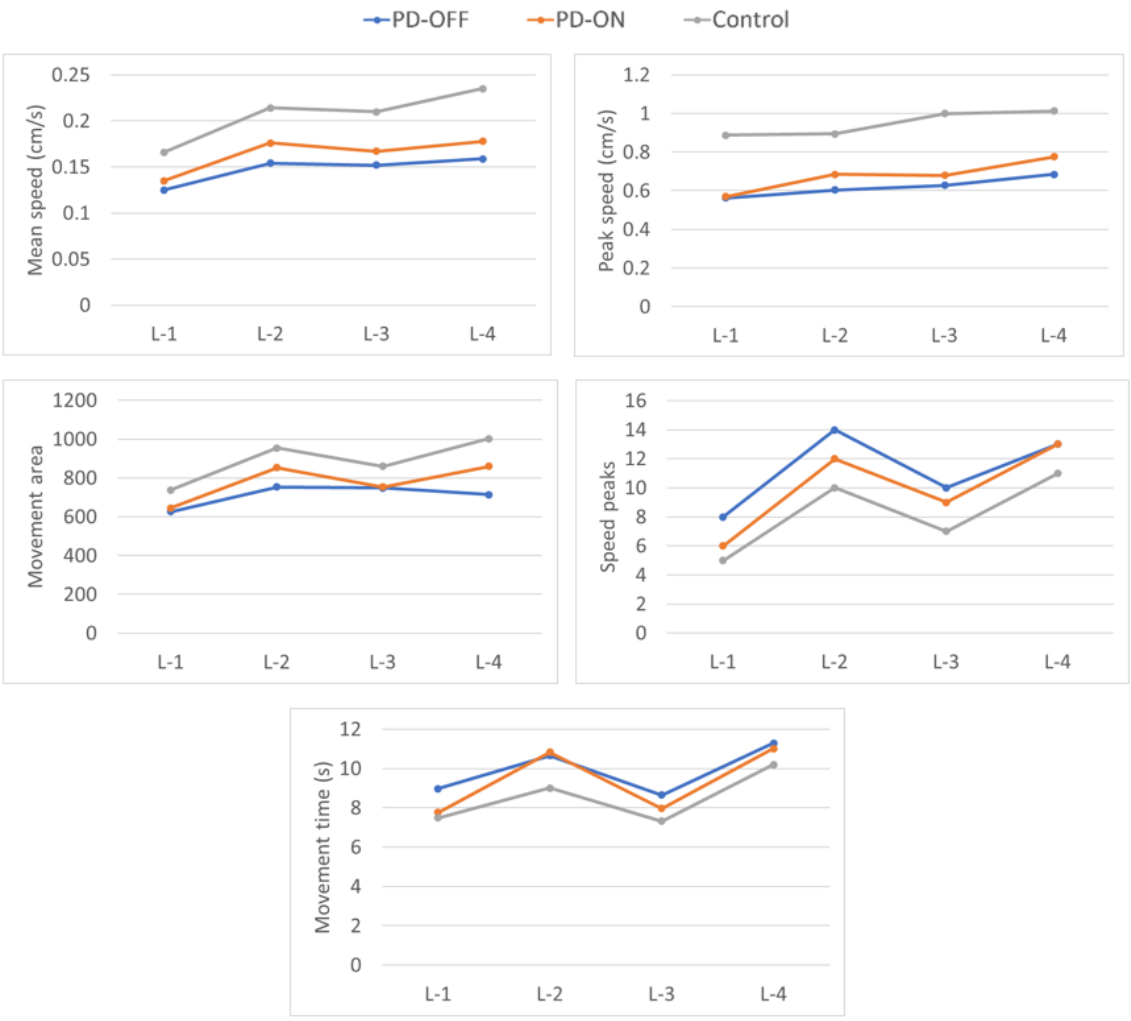


Figure 4.2: Motor features extracted from the three groups across all levels of the obstacle avoidance task.

Note: L-1 = Level-1; L-2 = Level-2; L-3 = Level-3; L-4 = Level-4.

4.3.2.2 Sensory Features

A plot comparing the three groups across all sensory features is given in Figure 4.3. Two features were used to assess the SMC functions of the sensory domains – (1) Obstacle hit-to-warn ratio, and (2) Corrective time for perturbation. The obstacle hit-to-warn ratio, which indicates if the participants could use the sensory warning cue to avoid hitting the obstacles, was 82% higher for PD-OFF than the control subjects across all levels. This implies that the control subjects could use the warning cues more effectively to avoid

obstacles than PD-OFF. The difference between the control subjects and PD-OFF was also statistically significant in levels where the targets were not moving (see Table 4.3). Additionally, PD-OFF took 13% more time to correct for the perturbation compared to the control subjects. Interestingly, the difference in the corrective time for perturbation between PD-OFF and control subjects reduced as the levels increased, although the control subjects were still better than PD-OFF in all levels. PD-OFF took 18%, 13%, and 6% less time to correct for perturbation than the control subjects in L-2, 3, and 4, respectively. Therefore, as the force applied to generate a perturbation increased with the increase in the task level, the performance of PD-OFF got better and became closer to the control subjects, resulting in a reduction in the difference between PD-OFF and the control subjects. Apart from increasing the applied force for the perturbations, the number of perturbations also increased as the levels increased, as shown in Table 2.3. The corrective time for individual perturbation was analyzed, indicating that PD-OFF took 2.54%, 7.12%, and 11.93% more time to correct for the first, second, and third perturbations, respectively, compared to the control subjects.

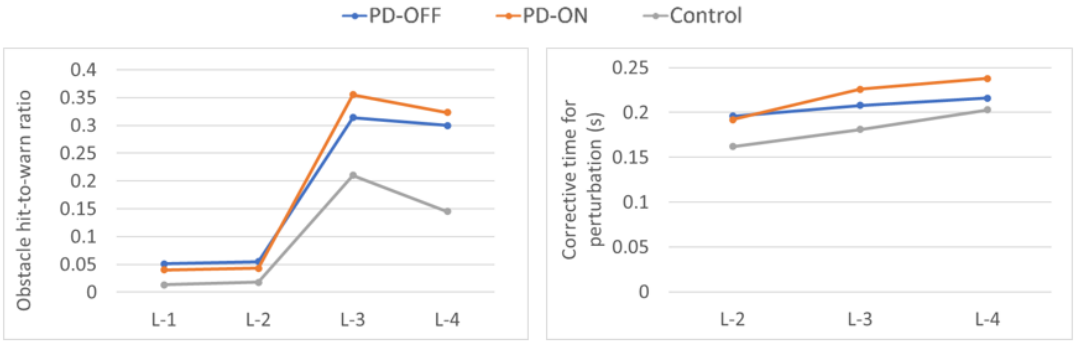


Figure 4.3: Sensory features extracted from the three groups across all levels of the obstacle avoidance task.

Note: L-1 = Level-1; L-2 = Level-2; L-3 = Level-3; L-4 = Level-4.

4.3.2.3 Cognitive Features

The performance of three groups across all cognitive features are compared and shown in Figure 4.4. The executive functions, a major component of the cognitive domain, play a vital role in using sensory information to devise a motor plan for accomplishing the primary

objectives of the task. This section evaluates the SMC functions associated with the cognitive domain. PD-OFF reached 17% fewer targets than the control subjects across all levels, with the difference being statistically significant in L-3 and L-4 (see Table 4.3). In analyzing the efficiency of the movement, PD-OFF was 26% less efficient than the control subjects in L-1. Moving to target order, this feature evaluates the participants' ability in higher-level planning. While the median R^2 value for PD-OFF was 0.705, the median R^2 value for the control subjects was 0.838, implying that the control subjects were closer to the ideal target order than PD-OFF. Moving to endpoint error, PD-OFF exhibited 29% higher endpoint error than the control subjects, with the difference being statistically significant across all levels (see Table 4.3). The difference in endpoint error between the groups varied notably depending on the state of the target. While PD-OFF exhibited 49% more endpoint error than the control subjects when the targets were stationary, this difference between the groups was reduced when the targets were moving, as PD-OFF only exhibited 10% more error than the control subjects in this condition. This may indicate that the endpoint error of even the control subjects increased during tougher levels when the targets were moving, resulting in the reduction of the difference between the groups. Apart from reaching targets, the participants were also tasked with avoiding obstacles. PD-OFF hit 44% more obstacles than the control subjects across all four levels. The difference between the groups was statistically significant in levels where the obstacles were moving (see Table 4.3). With the obstacles moving in the tougher levels, the control subjects did hit more obstacles compared to their own performance in simpler levels where obstacles were stationary. However, the findings suggest that the ability to adapt to a dynamic environment and appropriately plan a movement has deteriorated significantly in PD patients, resulting in a statistically significant increase in obstacle hits compared to the control subjects in L-3 and 4. This can be emphasized by comparing PD-OFF and the control subjects based on the next feature (slope between performance and ID). This feature explored the relationship between the participants' performance and task complexity by calculating a slope between the performance index and index of difficulty based on Fitts's law [10]. PD-OFF exhibited a 20% steeper deterioration in their performance as the task complexity increased compared to the control subjects.

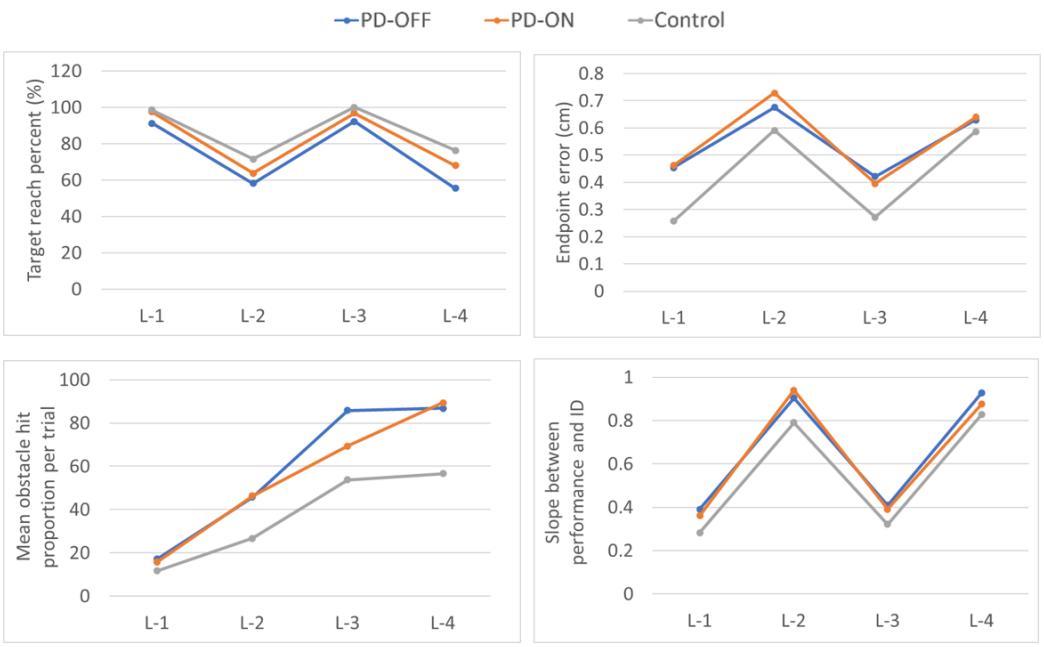


Figure 4.4: Cognitive features extracted from the three groups across all levels of the obstacle avoidance task.

Note: L-1 = Level-1; L-2 = Level-2; L-3 = Level-3; L-4 = Level-4.

4.3.2.4 Features to Compare with Computational Models

Table 4.4: Correlation between endpoint variance and obstacle hit-to-warn ratio

	PD-OFF	PD-ON	Control
L-1	-0.4497 (p = 0.0076*)	0.0966 (p = 0.6536)	-0.2143 (p = 0.0191*)
L-2	0.3764 (p = 0.0337*)	0.2501 (p = 0.0941)	-0.2857 (p = 0.0408*)
L-3	-0.2421 (p = 0.0394*)	0.3091 (p = 0.0416*)	-0.6429 (p = 0.0462*)
L-4	0.2153 (p = 0.0320*)	0.0853 (p = 0.6920)	0.4286 (p = 0.0299*)

Note: * after the p-value indicates statistical significance

Table 4.5: Correlation between corrective movements and target reach; Correlation between corrective movements and obstacle hits

Group	Corrective movements and Target reach		Corrective movements and Obstacle hit	
	Correlation coefficient	*p*	Correlation coefficient	*p*
PD-OFF	-0.6328	= 0.0003*	0.2771	= 0.024*
PD-ON	-0.6540	= 0.0039*	-0.0445	= 0.271
Control	-0.1183	= 0.0848	-0.3618	= 0.031*

Note: * after the p-value indicates statistical significance

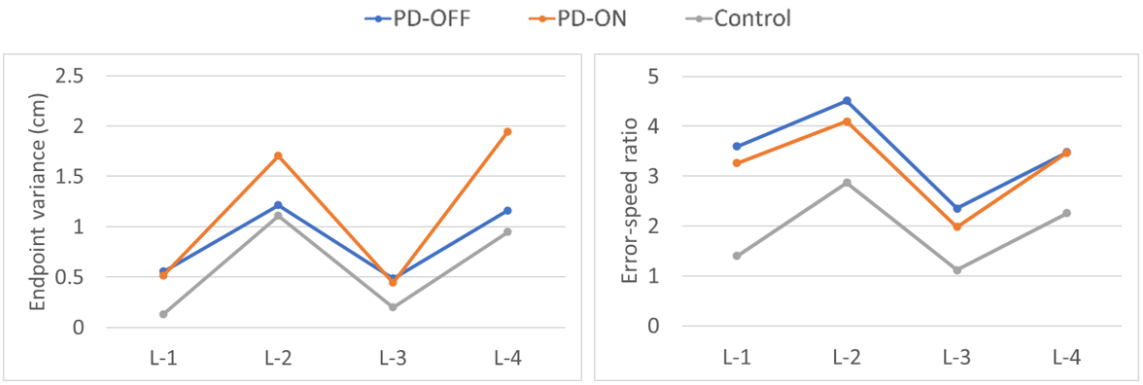


Figure 4.5: Features related to the computational models extracted from the three groups across all levels of the obstacle avoidance task.

Note: L-1 = Level-1; L-2 = Level-2; L-3 = Level-3; L-4 = Level-4.

Table 4.4, Table 4.5, and Figure 4.5 show the features used to compare the groups from the perspective of computational models. The performance of the two groups was compared from the perspective of the six computational models to understand if the performance of the participants aligns with the optimality principles proposed to explain SMC functions and to understand the specific metrics that can be targeted during treatments. Regarding the minimum energy and minimum variance model, PD-OFF exhibited 58% higher endpoint variance than the control subjects, implying that PD-OFF may exhibit less fingertip accuracy and spend more energy completing the given task than the control subjects. Comparing from the perspective of the minimum jerk model, PD-OFF had 32% higher speed peaks than the control subjects, indicating the control subjects may exhibit a smoother trajectory than PD-OFF. In terms of speed-to-accuracy trade-off, the ratio of increase in endpoint error to 1cm/s increase in mean velocity was almost two times higher for PD-OFF than the control subjects. The difference in error-speed ratio between the two groups was also statistically significant in the first three levels (see Table 4.3). Moving to the task-specific computational model, Table 4.4 shows the correlation between the two parts of the cost function (mean squared error between the actual and predicted arm position and collision probability) proposed by the obstacle avoidance computational model. Both control subjects and PD-OFF exhibited a positive correlation in L-4, although only PD-OFF exhibited a positive correlation in L-2. Therefore, while both groups let both

parts of the cost function increase in L-4, which is the most complex level of the task, only PD-OFF performed worse in L-2, allowing both parts of the cost function to increase. This may suggest that the difficulty threshold in reducing at least one part of the cost function is altered in PD patients, as, unlike control subjects, PD-OFF were unable to optimally reduce at least part of the cost function in L-2. Finally, to compare the two groups from the perspective of the minimum intervention model, two correlation coefficients were calculated, as shown in Table 4.5, to evaluate the ability of participants to effectively correct any errors in the motor plan. There was a positive correlation ($r = 0.2771$, $p < 0.05$) between the corrective movements and obstacle hits for PD-OFF, indicating that as they performed more corrective movements, they hit more obstacles. Furthermore, the corrective movements also negatively affected their ability to reach targets, as shown by the negative correlation ($r = -0.6328$, $p < 0.05$) between the corrective movements and target reach, implying that as they performed more corrective movements, they reached fewer targets. The results suggest that PD-OFF could not distinguish between the task-relevant and task-irrelevant errors. Therefore, the corrective movements performed by PD-OFF were counter-productive because when they performed corrective movements with the intent to avoid errors, they committed more task-relevant errors (hitting the obstacles) and also worsened their task performance (reaching fewer targets) significantly. However, a negative correlation ($r = -0.3618$, $p < 0.05$) was observed between the corrective movements, and the obstacle hits for the control subjects, indicating that the corrective movements performed by the control subjects helped them to avoid task-relevant errors (avoid obstacles). It needs to be noted that the corrective movements performed by the control subjects did marginally interfere with their ability to reach the targets, although it was not statistically significant.

4.3.3 Sensorimotor Control: PD-ON vs. PD-OFF

This section explores the effects of medication on each domain associated with the SMC functions by comparing the performance of PD-OFF with PD-ON.

4.3.3.1 Motor Features

Improvement in the movement speed after the medication was observed as the mean and peak velocity of PD-OFF was 10% and 8% less than for PD-ON, respectively, across all levels. There was a statistically significant improvement in mean and peak velocity (see Table 4.3) after medication at tougher levels. Consequently, the average movement time across all levels for PD-ON was 5.9% less than that for PD-OFF. The reaction and time to reach maximum speed were also 16% and 5.6% better in PD-ON compared to PD-OFF, indicating a marked improvement in reacting to the target once it appeared on the VR display. Finally, the movement area across all levels was 8.6% higher for PD-ON than PD-OFF, although a statistically significant difference was observed only in one level (L-2). The findings indicate that motor performance has benefitted from the medication as the treatment has effectively mitigated the motor deficits presented due to PD.

4.3.3.2 Sensory Features

Features evaluating the sensory domain associated with SMC were compared between PD-OFF and PD-ON. With regards to obstacle hit-to-warn ratio, while PD-ON performed better than PD-OFF in simpler levels when the obstacles were stationary (L-1 and L-2), the medication adversely affected the patients as PD-ON had 12% and 7% higher obstacle hit-to-warn ratio compared to PD-OFF in tougher levels when the obstacles were moving (L-3 and L-4). Moving to corrective time for perturbation, this trend continues as PD-ON took 8.2% and 9.6% more time to correct for the perturbation in L-3 and 4. However, their corrective time for perturbation was less than PD-OFF in a simpler level (L-2). This indicates that the medication has had an adverse effect on the patient's sensory domain, which is critical to the appropriate functioning of SMC. This worsening of sensory impairment has been amplified as the difficulty of the task increases, resulting in performance deterioration.

4.3.3.3 Cognitive Features

Analyzing the effect of medication on the cognitive ability to optimally plan goal-directed movement, PD-ON reached 10% more targets than PD-OFF at all levels. Likewise, the efficiency and target order in L-1 for PD-ON was 2% and 6% better than PD-OFF,

respectively. However, the medication has negatively affected the performance of the participants in tougher levels owing to higher cognitive load. PD-ON exhibited 7.5% and 1.5% higher endpoint error in L-2 and 4, respectively (levels with moving targets) compared to PD-OFF. Additionally, PD-ON also hit 1.2% and 2.9% more obstacles in L-2 and L-4. It must be noted that PD-ON had performed worse than PD-OFF only in complex and tougher levels, demanding higher cognitive resources. Concerning the slope between the performance index and index of difficulty, PD-ON showed a 3.9% steeper deterioration in L-2 compared to PD-OFF. The results suggest a deterioration in cognitive ability to appropriately plan or correct movements due to medication as the task became complex demanding higher cognitive resources.

4.3.3.4 Features to Compare with Computational Models

Comparing the two groups from the perspective of the computational models, in terms of minimum variance and minimum energy model, PD-ON had 33% and 50% worse endpoint variance than PD-OFF in L-2 and L-4 (levels with moving targets) respectively, with the difference being statistically significant in L-4 (see Table 4.3). This may imply a deterioration in fingertip accuracy and an increase in energy spent after medication in complex levels of the task. Regarding the minimum jerk model, PD-ON had fewer speed peaks than PD-OFF in L-1, 2, and 3, although this reduction in speed peaks could be attributed to the improvement in motor performance. Comparing from the perspective of the speed-to-accuracy trade-off, PD-ON had shown an improvement as their error-speed ratio was 9% better than PD-OFF across all levels. In terms of the obstacle avoidance model, while PD-OFF was able to reduce at least one part of the cost function in L-3 as shown by the negative correlation (r = -0.2421, $p < 0.05$), a positive correlation (r = 0.3091, $p < 0.05$) was observed in L-3 for PD-ON. This indicates that PD-ON was unable to reduce at least one part of the cost function proposed by the obstacle avoidance model. Finally, from the perspective of the minimum intervention model, while PD-OFF hit more obstacles as they performed more corrective movement, as shown by the positive correlation (r = 0.2771, $p < 0.05$), PD-ON may have shown improvement as a negative correlation (r = -0.0445, p = 0.271) was observed between the corrective movement and obstacle hit, although this correlation was not statistically significant.

4.3.4 Sensorimotor Control: PD-ON vs. Healthy Controls

This section discusses the comparison between PD-ON and the control subjects.

4.3.4.1 Motor Features

Comparing the motor features between PD-ON and the control subjects, PD-ON had 22% and 33% less mean and peak velocity, respectively, than the control subjects across all levels, with the difference between the two groups being statistically significant (see Table 4.3). Additionally, the movement time for the control subjects was 9% less than PD-ON. Furthermore, the control subjects were also able to react much more quickly to the targets than PD-ON. The reaction time and the time to reach maximum speed were 2.9% and 11% less for the control subjects than PD-ON. Finally, the movement area for control subjects was also 13% higher for the control subjects than for PD-ON. The findings indicate that despite the improvement in motor features due to medication, the control subjects have outperformed PD-ON across all features evaluating the motor performance.

4.3.4.2 Sensory Features

Comparing the two groups, the average obstacle hit-to-warn ratio across all levels for PD-ON was 77% higher than for the control subjects. Another sensory feature, the corrective time for perturbation, was again 18% lower for control subjects than for PD-ON across all levels. The results show that the control subjects performed much better than PD-ON across all sensory features, indicating that the sensory deficits affecting the SMC functions exist after medication.

4.3.4.3 Cognitive Features

Regarding the cognitive features, the control subjects reached 6.8% more targets across all levels than PD-ON. Furthermore, the efficiency and target order for the control subjects were 24% and 11% better than PD-ON, respectively, indicating that PD-ON struggled to efficiently plan or correct goal-directed voluntary movements. Additionally, the endpoint error and obstacle hits for PD-ON were 30% and 38% worse across all levels, respectively, compared to the control subjects. Finally, PD-ON also had a 16% steeper performance deterioration as the task complexity increased. Considering these results, the control

subjects outperformed PD-ON across all metrics evaluating the cognitive domain associated with the SMC functions. This implies that the medication did not normalize the cognitive ability to plan or correct voluntary movements in PD patients.

4.3.4.4 Features to Compare with Computational Models

Comparing the two groups from the perspective of the computational models, across all levels, PD-ON had 76% worse endpoint variance than the control subjects, implying that PD-ON may have poorer fingertip accuracy and spent more energy on a given task compared to the control subjects. Regarding the minimum jerk model, PD-ON had 19% more speed peaks than the control subjects, implying that the control subjects had the smoothest trajectory of the two groups. Furthermore, the ratio of increase in error for 1 cm/s increase in speed is higher for PD-ON as their error-speed ratio was 53% higher than that for the control subjects. Moving to task-specific computational models, PD-ON could not reduce both parts of the cost function in L-2 and 3 as opposed to the control subjects. Therefore, PD-ON performed worse than the control subjects in these two levels, although it must be noted that both PD-ON and control subjects were also unable to reduce both parts of the cost function in L-4, the most complex level of the task. This may point to a threshold of difficulty or complexity beyond which the participants were unable to reduce both parts of the cost function. While for the control subjects, this threshold appears to be the complexity exhibited in L-4 of the task, PD-ON seems to have an altered threshold of difficulty as they were unable to reduce both parts of the cost function even in levels (L-2 and L-3) that are less complex than L-4. Finally, from the perspective of the minimum intervention principle, the control subjects were able to efficiently correct only task-relevant errors, as indicated by the statistically significant negative correlation (r = -0.3618, $p < 0.05$) between the corrective movements and the obstacle hits. While a negative correlation (r = -0.0445, p = 0.271) was also observed between the corrective movements and obstacle hits for PD-ON, it is not statistically significant. This may imply that the control subjects were better than PD-ON in distinguishing between the task-relevant and irrelevant errors or were better equipped to correct errors optimally without affecting the task performance.

4.3.5 Correlation between Task Performance and Clinical Scores

The correlation between the extracted features and the clinical scores (UPDRS motor subscale and MoCA) was calculated. Table 4.6 shows the correlation between the extracted features and UPDRS. A predominant number of features that correlated with the UPDRS were motor features. Correlation between the features and UPDRS shows that 11 (out of which 7 are motor features) and 6 (all motor features) correlated with the UPDRS score in the OFF and ON states, respectively. Table 4.7 shows the correlation between the extracted features and MoCA. The features correlated with the MoCA score were predominantly cognitive features. While four features (out of which three are cognitive features) correlated with the MoCA score in the OFF state, five features (out of which four are cognitive features) correlated with the MoCA score in the ON state.

Table 4.6: Correlation between the extracted features, and UPDRS motor sub-scale

Features	Correlation with UPDRS score in OFF state	Correlation with UPDRS score in ON state
Mean speed	-0.4749 ($p < 0.05$)	-0.2322 ($p < 0.05$)
Peak speed	-0.3967 ($p < 0.05$)	-0.2295 ($p < 0.05$)
Time to reach maximum speed	0.3231 ($p < 0.05$)	0.3145 ($p < 0.05$)
Movement area	-0.3665 ($p < 0.05$)	-0.2310 ($p < 0.05$)
Reaction time	0.2926 ($p < 0.05$)	NS
Speed peaks	0.6417 ($p < 0.05$)	0.5124 ($p < 0.05$)
Movement time	0.3114 ($p < 0.05$)	0.4514 ($p < 0.05$)
Obstacle hit to warn ratio	NS	NS
Corrective time for perturbation	NS	NS
Target reach percent	-0.5717 ($p < 0.05$)	NS
Efficiency	-0.5253 ($p < 0.05$)	NS
Target order	NS	NS
Endpoint error	0.2975 ($p < 0.05$)	NS
Obstacle hit	NS	NS
Corrective movements	NS	NS
Endpoint variance	NS	NS
Slope between performance and index of difficulty	NS	NS
Error-speed Ratio	0.3528 ($p < 0.05$)	NS

Table 4.7: Correlation between the extracted features, and MoCA score

Features	Correlation with MoCA score in OFF state	Correlation with MoCA score in ON state
Mean speed	NS	NS
Peak speed	NS	NS
Time to reach maximum speed	NS	NS
Movement area	NS	NS
Reaction time	-0.3085 ($p < 0.05$)	-0.3146 ($p < 0.05$)
Speed peaks	NS	NS
Movement time	NS	NS
Obstacle hit to warn ratio	NS	NS
Corrective time for perturbation	NS	NS
Target reach percent	0.3571 ($p < 0.05$)	0.2988 ($p < 0.05$)
Efficiency	NS	0.3123 ($p < 0.05$)
Target order	NS	NS
Endpoint error	-0.2374 ($p < 0.05$)	-0.3908 ($p < 0.05$)
Obstacle hit	NS	NS
Corrective movements	NS	NS
Endpoint variance	-0.3339 ($p < 0.05$)	-0.4785 ($p < 0.05$)
Slope between performance and index of difficulty	NS	NS
Error-speed Ratio	NS	NS

4.3.6 Feature Selection and Pattern Recognition

4.3.6.1 Selecting Features Based on the Importance

As discussed earlier, the feature selection was done using the importance score of each feature obtained by fitting the data to the decision tree model. Firstly, the task used to investigate SMC had multiple levels; therefore, the participant's performance in each level was individually evaluated. A total of 15 features calculated separately in four levels of the task were considered. Figure 4.6 shows the importance score for each feature. Based on the score, the top six features (Maximum Minimum Velocity, Mean Velocity, Obstacle Hit-warn Ratio, Speed peaks, Target Reach Percentage, and Mean End Point Error) were selected to train the model. Since the performance of the participants, and by extension, the six selected features vary substantially depending on the level of the task, the level is also considered as a feature when training the neural network model. This allows the model to take into consideration the level of the task and learn how the participants from the two different classes may perform differently in various levels.

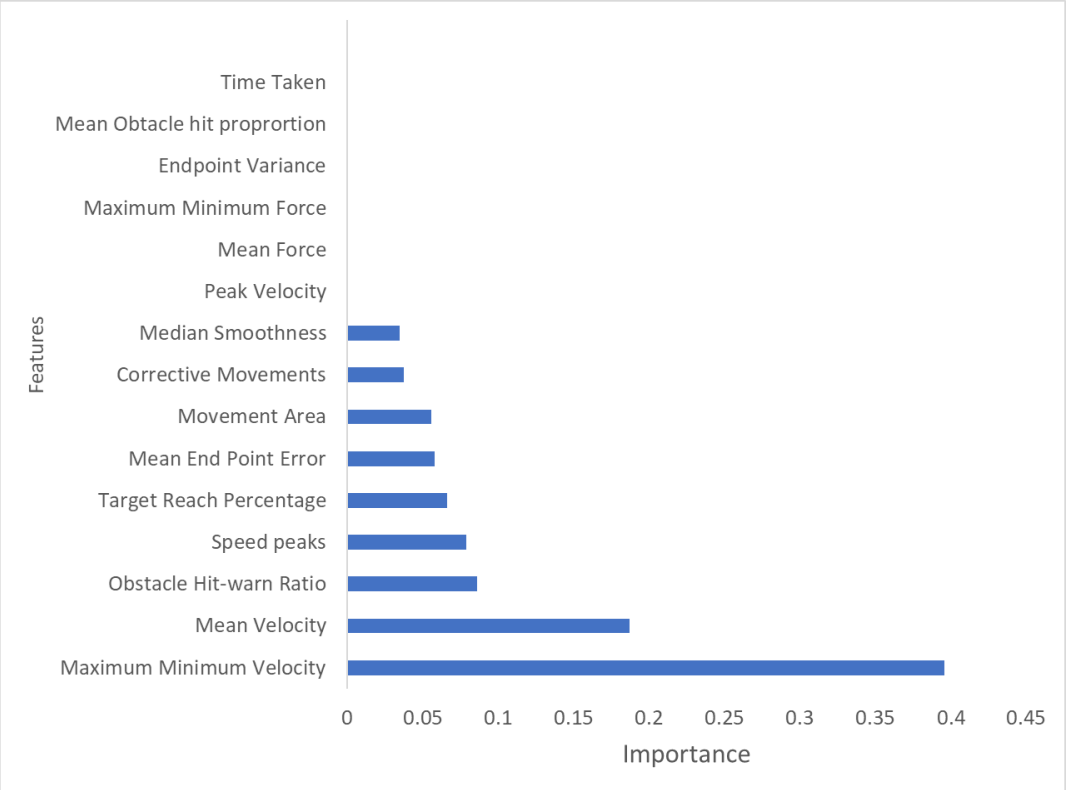


Figure 4.6: Feature importance score for the obstacle avoidance task

4.3.6.2 Training and Testing of the Neural Network Model

As discussed in Chapter 2 section 2.4.2.1, a neural network model was designed to classify PD and control subjects to understand if the KINARM features could be used to differentiate between two sets of participants. This may assist in detecting these novel impairments at an early stage. The dataset was split, with 70 % of data used for training the model, 15 % of data used for validation and 15 % of data used for testing the model. Figure 4.7 shows how the loss function was minimized during training to improve the model's accuracy. Once the model was trained, the trained model was then tested using the test dataset to determine if the neural network model could predict and differentiate between the PD and control subjects. Table 4.8 shows the performance metrics calculated to evaluate the model's performance based on its prediction. The results show that the model can predict and differentiate between the PD, and control subjects to an accuracy of 93.67%, implying the potential application of the neural network model in using the SMC features for an early clinical diagnosis of PD.

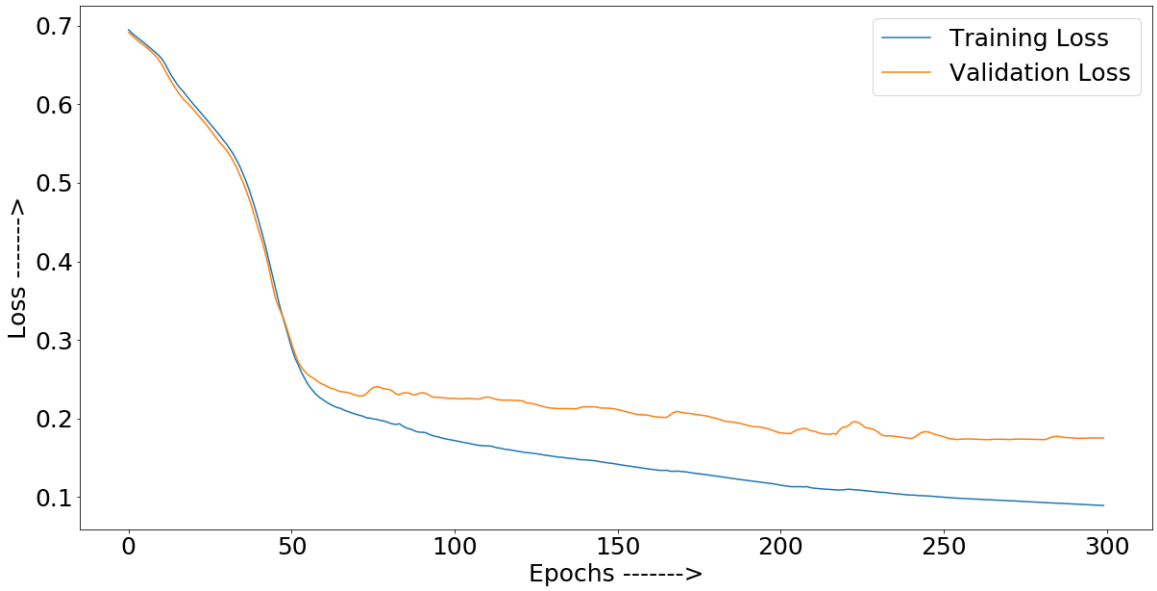


Figure 4.7: Training loss for the obstacle avoidance task

Table 4.8: Performance metrics of the NN model for the obstacle avoidance task

Accuracy (%)	Recall	Precision	F-1 Score	ROC-AUC
93.67	0.9367	0.9353	0.9350	0.8787

4.4 Discussion

The current work focused on exploring and characterizing the deficits presented due to PD in SMC functions such as movement planning and online error correction. Age-equivalent healthy control subjects and PD patients in their OFF and ON states performed a custom-designed obstacle avoidance task using a KINARM Endpoint robot [11]. The kinematic data acquired from the robot was used to extract features or metrics to analyze the SMC performance in PD patients before and after medication and how it may differ from that of the healthy subjects. Apart from individually studying each domain (Motor, Sensory, and Cognitive) associated with the SMC functions and comparing its performance among the groups (PD-OFF, PD-ON, and Control subjects), the participants were also compared from the perspective of six computational models using the features that closely resemble the cost functions proposed by the model. To the best of our knowledge, so far, no study has analyzed the deficits caused due to PD from the perspective of computational models. This computational model-based analysis may provide valuable insights into the SMC

impairments in PD and how they may be better managed. Therefore, in addition to characterizing the SMC deficits, the results obtained by comparing the participants from the perspective of computational models may help pinpoint the metrics that may lead to the deterioration in SMC performance. In the future, these metrics may be targeted through systematic rehabilitation regimes or treatments, thereby improving or mitigating SMC impairments.

To analyze the deficits in movement planning and online error correction, the performance associated with the motor, sensory and cognitive domains of PD-OFF and the control subjects were compared. The findings related to the motor domain were in line with the earlier studies [12] as PD-OFF were slower, took more time to react to targets, and covered a smaller area. It is evident from the results that motor performance is significantly deteriorated due to the onset of PD. This deterioration has adversely affected the role of the motor domain in SMC functions. Moving to the sensory domain associated with the SMC functions, PD-OFF could not use the warning sensory cue to effectively avoid obstacles as opposed to the control subjects. The findings demonstrate that PD may have affected the ability to process sensory information from multi-modal inputs and interpret the received information, which affected their ability to use the warning sensory cue to avoid obstacles, resulting in a higher obstacle hit-to-warn ratio than the control subjects. These deficits in processing or integrating multi-modal sensory inputs among PD patients have also been discussed in detail in the Chapter 3. Therefore, the impairment in SMI may have contributed to the higher obstacle hit-to-warn ratio among the PD patients, which has, in turn, affected SMC functions such as movement planning and error correction. Another deficit in the sensory domain that may have affected the SMC function may be the presence of sensory dampening in force perception. Overall, the control subjects were much quicker than PD-OFF in responding to the perturbations and correcting for force imposed on the robot handle across all levels. However, the difference in the corrective time for perturbation between PD-OFF and the control subjects decreased as the levels and the force applied to generate the perturbation increased. This may imply that PD-OFF were able to react to the stronger perturbation (perturbation with high force) much quicker than the weaker perturbation (perturbation with less force), resulting in less difference between PD-OFF and the control subjects at later levels. One inference could be the presence of sensory

dampening as PD-OFF were better at perceiving stronger sensory information than a weaker one, implying an altered threshold for force perception. This finding about force perception is also in line with a few other studies [13] discussing altered kinesthetic perception. Finally, as certain levels (L-3 and L-4) of the tasks included more than one perturbation, the time taken to correct for each perturbation was compared between the two groups. This indicated that the control subjects were more prepared to correct for the second or third perturbation once they had experienced the first perturbation, thereby correcting for the second or third perturbation much quicker than the first perturbation. In contrast, PD-OFF did not improve the corrective time for the second or third perturbation compared to their corrective time for the first perturbation. Evaluating the cognitive domain associated with the SMC functions, a similar trend was observed as the control subjects outperformed PD-OFF across all cognitive features, implying an impairment in cognitive abilities such as executive function. Impairments in executive functions [14] may severely affect an individual's ability to plan or correct goal-directed voluntary movements. Due to the impairments in cognitive ability (executive functions), PD-OFF could not reach the targets accurately and efficiently or avoid obstacles as well as the control subjects irrespective of the state (moving or stationary) of the target or obstacles. Additionally, the SMC deficits originating from the cognitive domain also appear to worsen with increased task complexity as PD-OFF has shown (see slope between performance index and index of difficulty) stepper deterioration in the performance as the complexity of the task, and consequently, the cognitive load increased. To put it together, the control subjects could handle high cognitive loads owing to increased task difficulty better than PD-OFF, as shown by their better performance in tougher levels than PD-OFF. It is well known that a relationship between cognitive load and performance exists even in healthy subjects, as humans tend to perform better in easier tasks than in difficult ones. However, the results imply that PD may alter this relationship between the cognitive load associated with a task and the performance of executive functions, leading to steeper performance deterioration as the cognitive load increases. Another notable finding is that while a predominant number of PD patients can be considered cognitively normal as indicated by their MoCA scores, impairments in cognitive ability, such as executive function, which affects movement planning and error correction, were observed. This points to the fact that the executive

dysfunctions were detected by the objective investigation performed in this study, even in patients who were deemed to be cognitively normal by the clinical scales (MoCA), implying that certain deficits that may not be detected by the subjective assessments such as clinical scales may be detected through objective assessments. Studies [15] have discussed the limitations of utilizing subjective techniques to evaluate the severity of the disease. They have also recommended [5] complementing the subjective assessment with objective testing and analysis for better diagnosis and management of the disease. Information acquired through objective assessments may provide valuable insights about the patient's condition, which may be vital in optimizing the treatment plan concerning the individual. Therefore, it may be beneficial to adopt and use objective metrics alongside subjective assessment to better quantify and characterize the cognitive deficits related to executive functions as deficits that may go unnoticed by one assessment, may be detected by the other. However, it must be noted on a cautionary note that the objective metrics used in this study were designed purely to evaluate the SMC deficits based on the task that was performed and needed to be validated by the clinicians and experts before being used in clinics. Moreover, the objective metrics should be considered a complementary tool to the subjective assessment and not a replacement for the existing clinical scales, as limitations associated with objective assessments also exist [16]. From the perspective of generic computational models (minimum energy model, minimum variance model, minimum jerk model, and speed-to-accuracy trade-off), the control subjects performed better than PD-OFF across all features representing the cost function associated with these models. These comparisons from the perspective of computational models provide valuable insights about the impairments presented due to PD and how it can be better targeted. The endpoint variance indicated that PD-OFF had a poorer fingertip accuracy, which is vital for accurately performing any reaching movement. Deterioration in fingertip accuracy among PD patients may result in increased variance in the endpoint. Therefore, the patients may perform more sub-movements than required to compensate and correct for the variance resulting in higher energy being spent to complete a given task. These metrics (endpoint variances) may be used to evaluate the fingertip accuracy before and after treatment or rehabilitation to understand if the treatment had improved the patient's ability to accurately perform reaching movements. Furthermore, the speed-to-accuracy trade-off model

indicates that the rate at which the error increases for 1 cm/s increase in velocity may have been altered in PD patients. This may imply a higher noise ratio in the neural control signal in PD patients compared to the control subjects. Studies [17] have shown that the increased signal-dependent noise may lead to poorer motor planning, and this alteration in the error-speed ratio may have contributed to the impairment in motor planning. Comparing PD-OFF and control subjects from the perspective of the obstacle avoidance model further emphasizes the earlier inference that PD alters the relationship between cognitive load and performance. While the control subjects and PD-OFF struggled to perform better from the perspective of the obstacle avoidance model in L-4, only PD-OFF performed poorly in L-2, which is far less complex than L-4. It needs to be understood that only PD-OFF performed poorly in L-2 (not the most complex level), although both PD-OFF and the control subjects performed poorly in L-4 (the most complex level of the task). One possible explanation could be that while the control subjects have a threshold of difficulty beyond which they fail to abide by the cost function, as shown by their performance in L-4, their threshold is much higher than PD-OFF, which explains why they were able to perform better in L-2 as opposed to PD-OFF. Therefore, aligning with the earlier inference, the threshold of difficulty until which an individual can efficiently reduce both parts of the cost function, thereby optimally planning or correcting movements, may be altered due to PD. Finally, from the perspective of the minimum intervention principle, it is evident that the control subjects were much better than PD-OFF in correcting any task-relevant errors without affecting their task performance. While PD-OFF performed corrective movements, it was counterproductive as the very corrective movements that needed to be aimed at reducing task-relevant errors resulted in increased task-relevant errors (hitting the obstacles). In addition to hitting more obstacles, the performance of corrective movements also adversely affected their primary objective for the task, which is to reach the targets. Therefore, PD-OFF may not be able to differentiate between the task-relevant and irrelevant errors and thereby may not abide by the minimum intervention principle. In contrast, the control subjects could distinguish between the task-relevant and irrelevant errors and corrected only to avoid task-relevant errors. As a result, the corrective movements performed by the control subjects were successful in avoiding obstacles, and as they performed more corrective movements, they avoided more obstacles. Considering

PD-OFF's deficit in generating corrective movements, it may be interesting and valuable to the clinical community to understand if rehabilitation regimes focused on assisting patients in differentiating between task-relevant and irrelevant errors may improve their ability to perform corrective movements.

The effect of medication on the various domains involved in SMC functionalities was investigated. In terms of the motor domain, the medication improved the performance of the patients across all motor features compared to their performance before the medication. This finding aligns with earlier results [18] that report mitigation of cardinal motor symptoms such as bradykinesia and rigidity due to medication, which may improve upper-limb movements. However, an improvement in pure motor metrics due to the mitigation of cardinal motor symptoms after medication may not translate to an improvement in movement planning or online error correction as it relies on the proper functioning of sensory and cognitive systems as well. To this end, features evaluating the sensory domain involved in the SMC functions were compared between PD-OFF and PD-ON. While the medication had improved motor features, it was accompanied by a worsening of performance in sensory features, especially in later levels that are designed to be more complex, resulting in higher sensory load. This was evident from the fact that PD-ON performed worse in higher levels than PD-OFF as their obstacle hit-to-warn ratio and corrective time for perturbation were much worse than PD-OFF in complex levels. Therefore, in addition to medication worsening the patient's ability to use warning cues to avoid obstacles, it has also worsened the sensory dampening that further altered the force perception threshold. The underperformance in sensory features when encountering higher levels of the task may be because the trials in the higher levels are more complex than the earlier ones. Due to this, the ability to perceive the imposed perturbation and correct for it or interpret the warning sensory cues provided by the experimenter to avoid obstacles becomes far more vital to the overall performance in complex levels compared to the simpler levels. While in simpler levels, due to the reduced complexity, it may be possible for participants to perform a given task without the use of any external stimuli and proper perception of the perturbations, the later levels with their high complexity might require accurate perception of the perturbations and warning sensory cues from the participants to appropriately complete the objectives of the task. Therefore, the worsening of the sensory

domain after medication becomes far more evident in higher levels than in simpler ones. The cognitive features between PD-OFF and PD-ON were compared to understand how the cognitive ability to plan or correct movements has been altered due to medication. Findings from cognitive features were similar to the results observed from sensory features. While PD-ON performed better than PD-OFF at simpler levels, the performance of PD-ON was much worse than PD-OFF at higher levels that were more cognitively demanding. The endpoint error in L-2, and L-4, obstacle hits in L-4 for PD-ON were worse than for PD-OFF. Therefore, in levels that included dynamic environments and required higher cognitive resources to plan and correct movements, PD-ON failed to accurately and efficiently complete the task compared to PD-OFF. The reasoning could again be that in simpler levels, the worsening of executive functions due to medication may not be highlighted as simpler levels do not require higher cognitive resources. On the other hand, the later levels that are far more complex, necessitating higher cognitive resources to complete the given task, accentuated the worsening of cognitive abilities due to medication. This also aligns with an earlier hypothesis that PD patients, after medication, may perform differently in a given task depending on the cognitive resource needed to complete that task. Kulisevsky et al. [19] inferred from their results that patients with stable motor responses to medication might perform differently on a given task when the complexity and the required cognitive resource go beyond a certain threshold needing a more flexible SMC strategy. However, they may show no difference when performing simpler tasks requiring lower resources. The literature also points to the possible adverse effects of medication on complex and highly demanding executive functions. This inference is further emphasized by our findings which showed a steeper deterioration in performance among PD-ON in certain complex levels (L-2), which again implied that when the complexity of the task goes beyond a certain threshold, PD-ON was far less efficient than PD-OFF in optimally planning or correcting voluntary movements. Analyzing the effect of the medication from the perspective of the computational models, PD-ON has once again performed poorly in terms of minimum energy and minimum variance model in cognitively demanding levels (L-2 and L-4). When viewed from the minimum jerk model, PD-ON was better than PD-OFF across all levels. However, these improvements in PD-ON may be due to the mitigation of cardinal motor symptoms and may not provide any insights into the

effect of medication on the sensory and cognitive domains. Moving to the speed-to-accuracy trade-off model, PD-ON improved the error-speed ratio across all levels. However, the difference between PD-OFF and PD-ON appears to reduce as the levels become more complex. Regarding the obstacle avoidance model, PD-ON could not reduce both parts of the cost function at all levels. Additionally, PD-ON had again performed poorer than PD-OFF in certain levels (L-3). While PD-OFF and PD-ON performed poorly in L-4, only PD-ON performed poorly in L-3. This again emphasizes our earlier inference about the threshold of difficulty that can be handled by the patients being negatively altered by the medication. Finally, in terms of the minimum intervention principle, as opposed to PD-OFF, a negative correlation was observed between the corrective movements and obstacle hits, although it was not statistically significant. To summarize, the findings reveal that while the medication improved the motor domain, it adversely affected PD patients' sensory and cognitive performance. This was especially true in complex levels that were more cognitively demanding and required participants to appropriately perceive and interpret sensory inputs to complete a given task. Furthermore, the worsening of SMI impairments after medication discussed in Chapter 3 may have also contributed to the underperformance of PD-ON in sensory and cognitive features compared to PD-OFF. While other studies [7][20][21] have explored the effect of medication on PD patients, the findings from this study provide new insights by individually evaluating the domains associated with the SMC functions and comparing their performance from the perspective of the computational model which was lacking in earlier studies.

Comparing the performance of PD-ON against the control subjects, the motor performance of the control subjects was far and above better than PD-ON. Across all motor features and all levels of the task, the control subjects exhibited substantially superior performance compared to PD-ON, with the difference between the two groups being statistically significant in certain features and levels. This implies that despite the improvements in the motor domain due to medication, the medication did not normalize the motor domain, resulting in PD-ON underperforming compared to the control subjects. Moving to the sensory features, based on the earlier comparison between PD-OFF and PD-ON, it was evident that the sensory domain was negatively affected after medication resulting in PD-ON performing worse than PD-OFF. Therefore, the results from the

comparison between PD-ON and the control subjects were along the expected lines. The control subjects had far less obstacle hit-to-warn ratio and corrective time for perturbation than PD-ON. However, a notable finding was that while the difference in the corrective time for perturbation between PD-OFF and control subjects decreased as the levels and force applied to the perturbations increased, the difference between PD-ON and the control subjects remained stable as the levels increased. Therefore, as indicated earlier, unlike PD-OFF, who improved their corrective time when perceiving stronger force, PD-ON did not improve their corrective time for perturbation even when the force applied to the perturbations increased. Similarly, the comparison between PD-ON and the control subjects based on cognitive features showed that the control subjects were much better than PD-ON across all cognitive features at all levels. Again, this is along the expected line, as the medication affected cognitive ability, as shown by the comparison between PD-OFF and PD-ON. Finally, comparing PD-ON and the control subjects from the perspective of the computational models, the endpoint variance for PD-ON was much higher than the control subjects, implying that the PD patients experienced a reduction in fingertip accuracy and an increase in energy consumption even after medication. In terms of the speed-to-accuracy trade-off model, while the medication had improved the error-speed ratio, the performance of PD-ON was still worse than the control subjects. This was the case in the minimum intervention model, which had shown a statistically insignificant improvement after medication. However, the control subjects were much better at correcting for task-relevant errors. Finally, in terms of the obstacle avoidance model, compared to the control subjects, PD-ON was worse than the control subjects at all levels. To summarize, the findings show that the current medication neither normalizes the motor domain involved in SMC functions nor normalizes the sensory or cognitive domains involved in SMC functions. While the medication mitigates the cardinal motor symptoms for a short time, it worsens the sensory and cognitive performance, therefore not enabling the PD patients to perform at the same level as the control subjects.

A correlation between the extracted features and the clinical scales was performed, which showed that most motor features correlated well with the UPDRS motor subscale. Most cognitive features had a statistically significant correlation with the MoCA scores, which evaluates the participants' cognitive status. This may validate the approach used to

classify features based on the domain. Additionally, the sensory and cognitive features did not have any statistically significant correlation with the UPDRS motor subscale, implying that the progression of motor, sensory, and cognitive features may vary from each other. This progression of motor deficits differing from the progression of sensory and cognitive deficits has been hypothesized in earlier studies [22][23], and our findings align with them.

Moving to the results associated with machine learning, a neural network was trained using six features extracted from the obstacle avoidance model to determine if the model can use features pertaining to SMC deficits to differentiate between the PD and control subjects. The machine learning model had a predictive accuracy of over 90%, implying that the tasks developed in this study could characterize the SMC deficits specific to PD patients. With the possible early onset of SMI and SMC deficits, a neural network model that can differentiate between the PD and control subjects based on the features characterizing an individual's SMI and SMC performance may be considered as a potential early diagnostic tool. Therefore, the neural network model proposed in this chapter showed that the NN model was able to detect these novel impairments and differentiate between the control and PD subjects. However, it must be stated on a cautionary note that while the machine learning models could differentiate between the two cohorts, this needs to be considered only as a first step in utilizing objective metrics for clinical diagnosis. More work is required before these diagnostic tools can be used in a clinical setting.

To summarize the study’s findings, in addition to the motor impairments among PD patients, the results also point to an apparent deficit in sensory and cognitive domains associated with the SMC functionalities. PD-OFF demonstrates deficits in the sensory domain, such as the inability to use multi-modal warning cues to avoid obstacles and an altered force perception or sensory dampening. The deficit in using sensory cues to adjust motor outputs has also been discussed in Chapter 3. Therefore, the high obstacle hit-to-warn ratio in PD patients may be due to impairments in multi-sensory integration (explained in Chapter 3). Furthermore, cognitive abilities, such as executive functions, may also be impaired in PD patients, affecting their ability to plan or correct a movement, especially at cognitively demanding levels. PD-OFF have shown impairment in handling high cognitive and sensory loads, as shown by their steep deterioration in SMC

performance during complex levels of the task. Finally, PD-OFF also failed to optimally plan or correct movement when compared from the perspective of existing computational models. The medication improved the motor features in the PD patients, although a deterioration in sensory and cognitive features compared to their performance in the OFF state was observed in complex levels of the task. The deterioration in sensory and cognitive performance after the medication was mainly observed in later levels of the task. This is because these levels were far more complex than the earlier ones and necessitated an appropriate functioning of the sensory and cognitive domains to optimally plan or correct movements. The findings imply that the threshold of difficulty above which the PD patients were unable to appropriately plan or correct movements was altered due to medication. While earlier findings show that this threshold has already been altered due to PD, the medication has further worsened this impairment. Therefore, while the improvement in the motor domain was observed in PD patients, a deterioration in cognitive and sensory domains was also observed, which exacerbated the SMC impairments and affected the task performance. These complex, multi-modal medication effects must be considered during patient assessment and medication optimization. Additionally, the improvement in motor features after medication does not indicate a normalization of motor performance in PD patients, as the control subjects were still significantly better than PD-ON across all features (motor, sensory, and cognitive). Therefore, the study provided new insights into understanding the deficits in SMC and the effect of medication. Moreover, it also explored how these deficits may affect movement expression. Earlier studies [24] have indicated that understanding the relationship between movement expression with executive and sensory dysfunction may assist in tailoring a more targeted, efficient rehabilitation program. To aid in designing a more targeted treatment approach, the metrics developed to evaluate performance based on the computational models may also be used to target and improve specific variables, which in turn may enhance the overall SMC performance. Finally, an interesting observation was that the objective testing and analysis detected impairments in cognitive abilities, such as executive function, even in patients deemed cognitively normal by clinical scales such as MoCA. Therefore, an objective assessment such as the one described in this study may complement a subjective assessment to better evaluate a PD patient’s condition, which may enhance the management of the disease.

Furthermore, past studies [25] have also stressed the importance of a more patient-specific approach to diagnosis and treatment. A machine learning model was discussed, which showed that the metrics designed in this study might be improved upon and used for an early diagnosis of PD. Therefore, the metrics and experiment used in this study to evaluate various domains of the SMC functions may be adopted as a patient-specific tool to better diagnose and target the deficits through a systematic rehabilitation regime.

4.5 References

[1] O. Monchi, M. Petrides, A. P. Strafella, K. J. Worsley, and J. Doyon, "Functional role of the basal ganglia in the planning and execution of actions," *Ann Neurol*, vol. 59, no. 2, pp. 257–264, Feb. 2006, doi: 10.1002/ana.20742.

[2] V. Menon, R. T. Anagnoson, G. H. Glover, and A. Pfefferbaum, "Basal ganglia involvement in memory-guided movement sequencing," *Neuroreport*, vol. 11, no. 16, pp. 3641–3645, Nov. 2000, doi: 10.1097/00001756-200011090-00048.

[3] P. Redgrave, T. J. Prescott, and K. Gurney, "The basal ganglia: A vertebrate solution to the selection problem?," *Neuroscience*. 1999. doi: 10.1016/S0306-4522(98)00319-4.

[4] J. C. Houk, C. Bastianen, D. Fansler, A. Fishbach, D. Fraser, P. J. Reber, S. A. Roy, and L. S. Simo, "Action selection and refinement in subcortical loops through basal ganglia and cerebellum," *Philosophical Transactions of the Royal Society B: Biological Sciences*, 2007, doi: 10.1098/rstb.2007.2063.

[5] J. Koerts, L. Tucha, K. L. Leenders, M. van Beilen, W. H. Brouwer, and O. Tucha, "Subjective and objective assessment of executive functions in Parkinson's disease," *J Neurol Sci*, vol. 310, no. 1–2, pp. 172–175, Nov. 2011, doi: 10.1016/j.jns.2011.07.009.

[6] A. Steinke, F. Lange, C. Seer, M. K. Hendel, and B. Kopp, "Computational Modeling for Neuropsychological Assessment of Bradyphrenia in Parkinson's Disease," *J Clin Med*, vol. 9, no. 4, p. 1158, Apr. 2020, doi: 10.3390/jcm9041158.

[7] P. O'Suilleabhain, J. Bullard, and R. B. Dewey, "Proprioception in Parkinson's disease is acutely depressed by dopaminergic medications," *J Neurol Neurosurg Psychiatry*, 2001, doi: 10.1136/jnnp.71.5.607.

[8] R. Weil and S. Reeves, "Hallucinations in Parkinson's disease: new insights into mechanisms and treatments," *Advances in Clinical Neuroscience & Rehabilitation*, vol. 19, no. 4, pp. 20–22, 2020, doi: 10.47795/ONNS5189.

[9] Y. K. Tamilselvam, M. Jog, and R. V. Patel, "Robot-assisted investigation of sensorimotor control in Parkinson's disease," *Sci Rep*, vol. 13, no. 1, p. 4751, Mar. 2023, doi: 10.1038/s41598-023-31299-z.

[10] I. S. MacKenzie and W. Buxton, "Extending Fitts' law to two-dimensional tasks," in *Conference on Human Factors in Computing Systems - Proceedings*, 1992, pp. 219–226. doi: 10.1145/142750.142794.

[11] C. S. Mang, T. A. Whitten, M. S. Cosh, S. H. Scott, J. P. Wiley, C. T. Debert, S. P. Dukelow, and B. W. Benson, "Test-retest reliability of the KINARM end-point robot for assessment of sensory, motor and neurocognitive function in young adult athletes," *PLoS One*, 2018, doi: 10.1371/journal.pone.0196205.

[12] A. A. Moustafa, S. Chakravarthy, J. R. Phillips, A. Gupta, S. Keri, B. Polner, M. J. Frank, and M. Jahanshahi, "Motor symptoms in Parkinson's disease: A unified framework," *Neurosci Biobehav Rev*, vol. 68, pp. 727–740, Sep. 2016, doi: 10.1016/j.neubiorev.2016.07.010.

[13] J. Konczak, D. M. Corcos, F. Horak, H. Poizner, M. Shapiro, P. Tuite, J. Volkmann, and M. Maschke, "Proprioception and Motor Control in Parkinson's Disease," *J Mot Behav*, vol. 41, no. 6, pp. 543–552, Nov. 2009, doi: 10.3200/35-09-002.

[14] J. Grafman and I. Litvan, "Importance of deficits in executive functions," *The Lancet*, vol. 354, no. 9194, pp. 1921–1923, Dec. 1999, doi: 10.1016/S0140-6736(99)90438-5.

[15] M. Knudson, T. H. Thomsen, and T. W. Kjaer, “Comparing Objective and Subjective Measures of Parkinson’s Disease Using the Parkinson’s KinetiGraph,” *Front Neurol*, vol. 11, Nov. 2020, doi: 10.3389/fneur.2020.570833.

[16] K. Yang, W.-X. Xiong, F.-T. Liu, Y.-M. Sun, S. Luo, Z.-T. Ding, J.-J. Wu, and J. Wang, “Objective and quantitative assessment of motor function in Parkinson’s disease—from the perspective of practical applications,” *Ann Transl Med*, vol. 4, no. 5, pp. 90–90, Mar. 2016, doi: 10.21037/atm.2016.03.09.

[17] C. M. Harris and D. M. Wolpert, “Signal-dependent noise determines motor planning,” *Nature*, 1998, doi: 10.1038/29528.

[18] P. Rizek, N. Kumar, and M. S. Jog, “An update on the diagnosis and treatment of Parkinson disease,” *Can Med Assoc J*, vol. 188, no. 16, pp. 1157–1165, Nov. 2016, doi: 10.1503/cmaj.151179.

[19] J. Kulisevsky, A. Avila, M. Barbanoj, R. Antonijoan, M. L. Berthier, and A. Gironell, “Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson’s disease patients at different levodopa plasma levels,” *Brain*, 1996, doi: 10.1093/brain/119.6.2121.

[20] F. Girotti, F. Carella, M. P. Grassi, P. Soliveri, R. Marano, and T. Caraceni, “Motor and cognitive performances of Parkinsonian patients in the on and off phases of the disease,” *J Neurol Neurosurg Psychiatry*, 1986, doi: 10.1136/jnnp.49.6.657.

[21] S. E. Starkstein, M. Esteguy, M. L. Berthier, H. Garcia, and R. Leiguarda, “Evoked potentials, reaction time and cognitive performance in on and off phases of Parkinson’s disease,” *J Neurol Neurosurg Psychiatry*, 1989, doi: 10.1136/jnnp.52.3.338.

[22] R. Xia and Z.-H. Mao, “Progression of motor symptoms in Parkinson’s disease,” *Neurosci Bull*, vol. 28, no. 1, pp. 39–48, Feb. 2012, doi: 10.1007/s12264-012-1050-z.

[23] M. Lawton, Y. Ben-Shlomo, M. T. May, *et al.*, “Developing and validating Parkinson’s disease subtypes and their motor and cognitive progression,” *J Neurol Neurosurg Psychiatry*, vol. 89, no. 12, pp. 1279–1287, Dec. 2018, doi: 10.1136/jnnp-2018-318337.

[24] D. Ferrazzoli, P. Ortelli, G. Madeo, N. Giladi, G. M. Petzinger, and G. Frazzitta, “Basal ganglia and beyond: The interplay between motor and cognitive aspects in Parkinson’s disease rehabilitation,” *Neurosci Biobehav Rev*, vol. 90, pp. 294–308, Jul. 2018, doi: 10.1016/j.neubiorev.2018.05.007.

[25] G. Abbruzzese, R. Marchese, L. Avanzino, and E. Pelosin, “Rehabilitation for Parkinson’s disease: Current outlook and future challenges,” *Parkinsonism Relat Disord*, 2016, doi: 10.1016/j.parkreldis.2015.09.005.

Chapter 5

5 Subject-Specific Musculoskeletal Model to Analyze Muscle Recruitment Strategies

This Chapter discusses the results pertaining to the validation of the proposed musculoskeletal model and its application in PD-related therapies.

5.1 Introduction

SMC functions not only involve planning or correcting movement but also involve determining the force required to perform the desired movement and recruiting the necessary muscles [1][2][3]. Generating the desired force requires recruiting or activating the most relevant muscles to complete a given task. The contraction of these recruited muscle fibers leads to the generation of the necessary force in the appropriate direction to overcome the external resistive loads and perform the desired movement. This recruitment process occurs through the motor units that include a motor neuron that innervates the muscle fibers within a localized region [4] [5]. The recruitment of this motor unit and its corresponding muscle fibers is called motor unit recruitment, an essential component of SMC functions [1] [5]. Any modulation or generation of motor output can only be achieved by successive activation and deactivation of the muscle fibers. Therefore, the kinematic and dynamic variables related to the motion of interest depend on the muscle fibers recruited by the CNS. There are numerous studies [6][7][8] that hypothesize the strategies or criteria that CNS may employ in determining the motor units that need to be recruited. However, no one criterion is universally accepted by experts in the field to correctly explain the SMC criterion for muscle recruitment. Exploring the muscle activations and contributions in performing a given movement may be valuable in understanding the CNS's criteria for recruiting muscles. Abnormalities in motor unit behavior due to PD have also been discussed in earlier studies [9][10], and these abnormalities may contribute to motor deficits. A tool to understand how PD may affect the muscle recruitment process due to an impaired SMC circuit, while expanding our knowledge, could be helpful in efficiently guiding certain PD-related therapies.

Techniques such as musculoskeletal and machine learning models have been developed in recent years to study the functioning of motor unit recruitment and how it may differ in patients diagnosed with neurodegeneration and neuromuscular disease. A muscle model comprising 22 functional muscles with 74 muscle elements and six functional joints was proposed by Quental et al. [11][12]. To verify the model's accuracy, its output was also compared with that from sEMG, which indicated a correlation of 0.9 with the sEMG data. Nikooyan et al. [13][14] proposed the Delft shoulder and elbow model that includes 31 muscles and five functional joints, which yielded a correlation of 0.66 with the sEMG data. Another muscle model was proposed by Wu et al. [15] and comprised 26 muscle-tendon units. The authors also indicated that their model was subject-specific, so certain parameters can be adjusted to fit the subject. However, the model's output was not validated by comparing its results with any clinically accepted method. Klemt et al. [16] proposed in-depth and comprehensive techniques to construct 10 MRI-based shoulder models. The authors designed individual models based on the parameters measured from 10 subjects using the MRI. The models included a total of 87 muscle elements and five functional joints. Another upper-limb model that comprised 24 muscle elements was discussed by Pennestri et al. [17]. While there are numerous simulated muscle models that have been designed over the years, all of which are not discussed here, there are a few limitations in the existing models. One of the primary limitations is the lack of detail in the model, i.e., only a few specific muscles have been included. This limits the model's ability to estimate the activity of smaller and deeper muscles. Another limitation is that there is a lack of subject-specific models, with the few models that are subject-specific comprising only a smaller set of muscles and a lower prediction accuracy. The prediction accuracy of certain models was also not measured, and therefore, the output of these models was not validated. Apart from the model that uses the kinematic data as input to analyze the biomechanics of the upper limb, a few models also use the sEMG activity data as inputs to predict the corresponding muscle forces. Buchanan et al. [18] discussed a model that predicts the force exerted by four muscles based on the sEMG recording of that muscle. However, these sEMG-driven models would suffer from the same limitation (mechanical, motion artifacts, muscle crosstalk, inability to measure the activity of deeper muscles) as the sEMG discussed earlier in Section 2.5 of Chapter 2. Moving away from the virtual

muscle models, numerous machine learning models have also been proposed to examine and study the muscle recruitment process. Johnson et al. [19] have proposed a probabilistic model to predict the activity of 12 upper-limb muscles. Another machine learning-based approach to predicting muscle activity was discussed by Nardo et al. [20]. However, this model was again fed with sEMG data as input to train the model and, therefore, may suffer from its limitations. Further, apart from measuring muscle activity, there are currently no techniques that evaluate each muscle's relative contribution when performing a movement. Understanding and knowing the contribution of each muscle in relation to other muscles may be useful in improving the efficacy of targeted therapies, such as injections of botulinum toxin used to mitigate PD-related symptoms. Furthermore, how the CNS solves muscle redundancy is still a topic of debate, although it is hypothesized that the CNS promotes muscle synergism. Studying the relative contribution of each muscle may provide new insights into how the CNS recruits and the ratio in which it shares the workload with multiple sets of muscles. Hence, there is a need for a more detailed, accurate, and subject-specific muscle model that can estimate muscle activity and the relative contribution of muscles. A detailed, accurate muscle model may be useful in studying how PD alters the muscle recruitment processes and to better guide targeted therapies. This study aims to develop a detailed, accurate musculoskeletal model to study the muscle recruitment strategies and validate its output using the current gold standard methods used in clinics to measure muscle activations.

As discussed earlier, apart from studying the muscle recruitment strategies, the muscle model may also be useful in guiding targeted therapies such as injections of botulinum toxin. Apart from discussing the muscle model validation, this chapter also discusses the potential of the muscle model to be adopted as an alternative guiding tool for the targeted therapies used to mitigate Parkinsonian tremor. Typically, the tremor in PD patients occurs at rest at a frequency of 4 to 6 Hz [21], affecting the patient’s ability to perform even day-to-day activities [22][23]. Targeted therapies such as botulinum toxin injections are safer, have the least side effects, and have shown clinically meaningful improvement in mitigating tremor [24]. A specific dosage of botulinum toxin is injected into targeted muscles that contribute to the tremor. While botulinum toxin injection is considered a promising treatment for tremor, studies [25][26] have shown that the efficacy

of the injections heavily depends on optimizing the injection patterns, i.e., selecting the muscles that need to be injected and determining the optimal dosage per muscle. Muscle selection and dosage determination require an accurate estimation of muscle activity and its relative contribution to the tremor. The current methods for dosage determination (subjective visual assessment or intramuscular EMG) suffer from numerous limitations [27] [28] [29] [30]. Therefore, there is a need for an objective method to determine the injection sites accurately and the dosage per muscle that could help improve the efficacy of the treatment. The muscle activity and contribution provided by the validated muscle model may be used to better select the muscles and the dosage per muscle. As such, the model's output was used to estimate the dosage for nine upper-limb muscles in 47 PD patients undergoing the therapy. The methodology used to estimate the dosage is given in section 2.5.7 of Chapter 2. The estimated dosage, actual dosage, and the tremor in the follow-up visits were compared to understand the model's potential for this application. It should be indicated on a cautionary note that the dosage estimated by the model was never used to inject patients in real-time, and neither has the validated model been used in a clinical setting so far. The study to evaluate the model's ability to estimate dosage is a first step towards using novel techniques to improve the efficacy of the targeted therapies.

5.2 Methods

5.2.1 Participants

5.2.1.1 Model Validation

Six healthy subjects were recruited in this study to validate the accuracy of the musculoskeletal model. Only subjects with no injuries limiting their upper-limb movements were recruited. The arm was divided into three sections: (i) tip of the middle finger to the wrist joint, (ii) wrist joint to the elbow joint, and (iii) elbow joint to the shoulder joint. The length pertaining to each section of the arm was measured. These values for a given subject were entered into the muscle model when inputting the kinematic data collected from that subject. This was done to ensure that the bone parameters were adjusted to fit the subjects when predicting muscle activity. Table 5.1 shows the average subject-specific bone parameters used in this study. No joint parameters were varied, as the subjects

did not suffer from joint dysfunctions. Finally, the muscle parameters such as PCSA and muscle fiber length were not measured due to the amount of time and complexity involved in the process.

Table 5.1: Average of the subject-specific bone parameters

	Mean length (m)	**Mean mass (kg)**	**Mean radius (m)**	**Mean inertia**		
				I_{xx} (kg m^2)	**I_{yy} (kg m^2)**	**I_{zz} (kg m^2)**
Humerus	0.3132	2.282	0.0481	0.01990	0.00264	0.01990
Radius	0.2454	1.304	0.0411	0.00110	0.00709	0.00709
Ulna	0.2610	1.304	0.0398	0.00792	0.00103	0.00792
Clavicle	0.1522	0.532	0.0333	0.00029	0.00117	0.00117
Scapula	0.0120	0.532	0.1180	0.00188	0.00188	0.00375
Hand	0.1717	0.489	0.0301	0.00131	0.00022	0.00131

5.2.1.2 Application of the Model

One of the prospective applications of the model was to estimate the dosage of botulinum toxin to improve the efficacy of the therapy. A total of forty-seven patients were recruited for this study. All patients had undergone botulinum toxin therapy to treat hand tremors. The patients were asked to come for two visits. In the first visit, the patients were injected with the dosage determined through visual assessment or EMG. In the second visit (follow-up), the patient's tremor was assessed using joint kinematic data to understand if the injection mitigated the tremor.

5.2.2 Ethics

The Office of Human Research Ethics at Western University's Research Ethics Board (REB) approved this study protocol (protocol number: 108252). All the participants provided their informed consent before the study. The experiment was conducted per the ethical standards laid down by the Declaration of Helsinki and the Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans in Canada.

5.2.3 Experiment

5.2.3.1 Model Validation

The participants performed five distinct upper-limb movements involving three upper-limb joints (shoulder, elbow, and wrist). All participants completed the tasks in the right hand. Table 2.15, in Chapter 2, indicates the sequence of five tasks performed during the study. Each participant performed each of the five tasks for a total of five trials.

5.2.3.2 Application of the Model

The PD patients undergoing the therapy to mitigate rest tremors were asked to sit upright with their elbows bent to 90 degrees and resting on their legs when the kinematic data was acquired. The data collection was done during both visits of the patient.

5.2.4 Study Design

5.2.4.1 Model Validation

As indicated earlier, the kinematic and sEMG data was collected when the participants performed the five tasks to capture joint movements and muscle activation, respectively. The Kinematic and sEMG data was collected simultaneously to ensure that the collected data corresponded to the same motion. The kinematic data was collected using wireless sensors (three electrogoniometers and one torsiometer) placed at the joint of interest. The procedure involved in collecting and processing the joint kinematic data is given in Chapter 2 under section 2.5.6.1. Figure 5.1 shows the sample joint kinematic data collected from the participants when performing the five tasks [31]. These joint kinematic data was provided as input to the muscle model.

The sEMG recordings were rectified and filtered using a Butterworth filter with a cut-off frequency of 20 Hz [32]. The filtered sEMG data was normalized using the root mean squared value of the amplitude of the sEMG recordings obtained at MVC. The normalized sEMG data for eight superficial muscles (Biceps, Triceps, FCR, ECR, Deltoid, Teres Major, Pectoralis Major, Latissimus Dorsi) was obtained using the Delsys Multi-Contact sEMG sensor. The procedure involved in collecting and processing the sEMG recordings is explained in Chapter 2 under section 2.5.6.2. As discussed earlier, the

participants performed each task for five trials. Therefore, the normalized sEMG data was divided into sectors depending on the timed change of the movement. The normalized sEMG data belonging to each sector were then averaged across the five trials. A similar exercise was carried out for the predicted muscle activity. Finally, the averaged normalized sEMG data and predicted activity was compared to validate the muscle model. As mentioned in section 2.5.6, the normalized sEMG data was calculated only for the purpose of muscle validation and was not provided to the muscle model during its prediction phase. In other words, the sEMG data does not have any role to play in the functioning of the muscle model or in its prediction of the muscle activity. It was only used to compare the model's predicted activity with the sEMG's measured activity to understand if there is a correlation between the model's output and the sEMG's output.

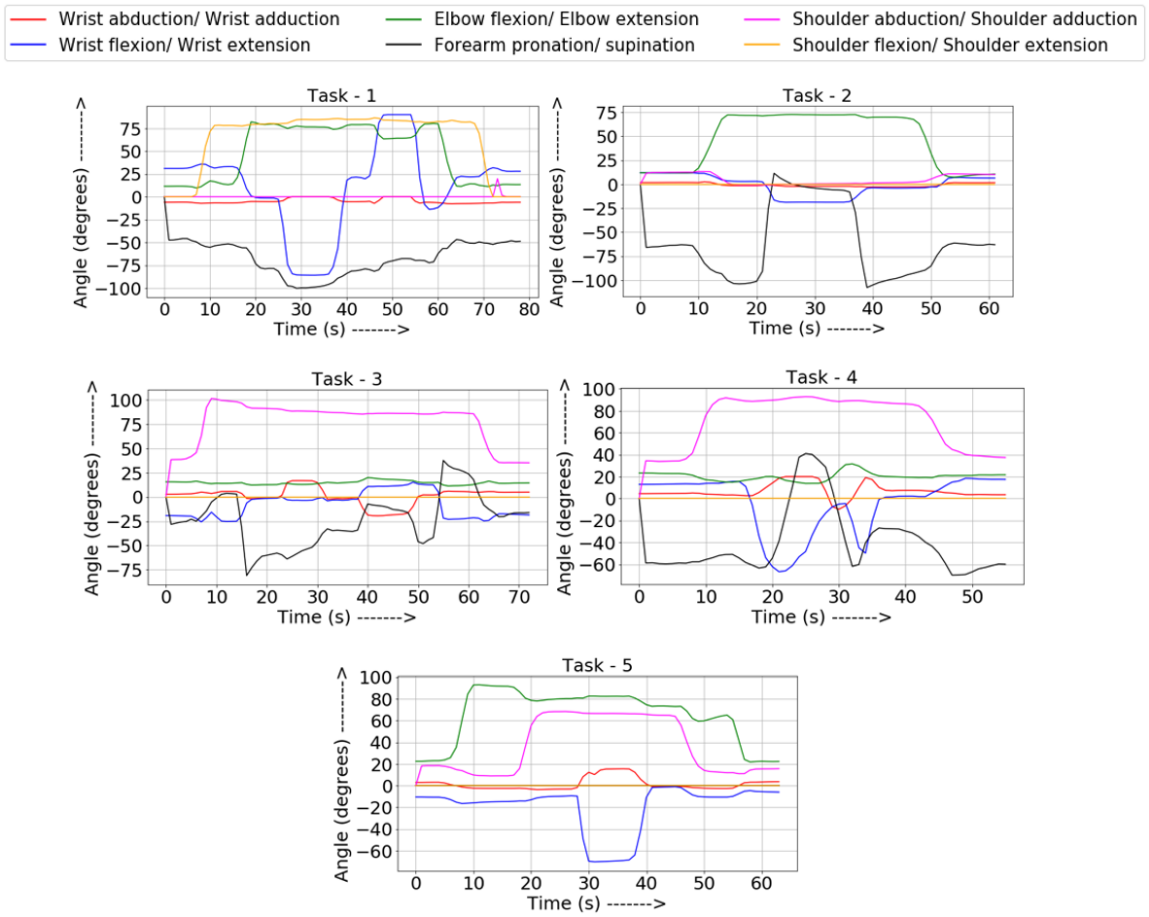


Figure 5.1: Kinematic data collected for the five tasks

5.2.4.2 Application of the Model

The placement of the wireless sensors remains the same as mentioned in the previous section. The kinematic data collected from the PD patients were used to predict the activity and contribution of individual muscles using the model, which is then used to estimate the dosage for nine upper-limb muscles (Biceps, Triceps, FCR, ECR, FCU, ECU, Supinator, Pronator teres (PT) and quadratus (PQ)).

The first step in dosage determination is to estimate the overall dosage for all the muscles involved in a joint movement. This is done by calculating the tremor amplitude pertaining to each joint, i.e., elbow, wrist, and forearm. Once the tremor amplitude for each joint was calculated, the overall dosage pertaining to that joint was determined based on the work of Samotus et al [26]. For instance, four muscles (FCR, ECR, FCU, and ECU) are prime movers for the wrist joint. Therefore, the wrist tremor amplitude can be used to determine the total dosage across the four muscles. This is carried out separately for muscle groups that move each joint. While this step can provide the total dosage for each muscle group, it does not indicate the exact dosage for individual muscles. It is not an efficient strategy to divide the dosage across all muscles equally, as each muscle in the group may contribute differently to the joint movement. Therefore, the muscle contribution, indicating the percentage of individual muscle contribution towards the tremor movement, was used to determine the dosage per muscle. Section 2.5.7 discusses further the methodology used to predict dosage per muscle.

5.2.5 Analysis

5.2.5.1 Model Validation

This study validated the proposed musculoskeletal model by comparing the predicted muscle activity from the muscle model with the calculated muscle activity from the sEMG. Therefore, two performance metrics, namely RMSE and Pearson Correlation (r), were calculated to compare the predicted and sEMG activity and evaluate the accuracy of the proposed model. Furthermore, the coefficient of determination was also calculated by squaring the correlation value. The equations associated with these performance metrics are provided in Chapter 2.

5.2.5.2 Application of the Model

Two different analyses were done to demonstrate the effectiveness of the muscle model in being used to estimate the dosage of Botulinum Toxin: (1) a comparison between the dosage predicted by the muscle model with the actual dosage prescribed by the clinicians, (2) Correlation analysis between the dosage difference and the tremor experienced by the patients after receiving the injection during their follow-up visit. Since the model's accuracy has already been validated, a higher difference between the actual and predicted dosage indicates that the dosage currently provided to the patients through visual assessment or EMG is very different from the optimized dosage obtained from the muscle model. Secondly, a positive correlation between dosage difference and tremor during the follow-up visit may imply that the therapeutic efficacy may improve by using the dosage predicted by the muscle model. The reason is that a high tremor amplitude during the follow-up visit indicates that the dosage obtained through conventional methods did not mitigate the tremor, indicating that the dosage per muscle needs to be changed. It can be assumed that this change in dosage would have to be proportional to the tremor amplitude, i.e., if a high amplitude of tremor exists, the dosage needs to be varied by a large margin and vice versa. Therefore, a positive correlation would indicate that when a high amplitude of tremor still exists, the predicted dosage varied by a large margin compared to the actual dosage and vice versa. This may indicate that the predicted dosage is the optimized dosage per muscle and may yield a better result than the dosage currently determined through conventional methods. Therefore, a correlation was calculated between the dosage difference for a given muscle and the tremor amplitude pertaining to the joint that is moved by the muscle of interest. For instance, a correlation between the FCR and the tremor amplitude pertaining to the wrist was calculated. This was because the FCR was one of the prime movers of the wrist. Furthermore, a correlation between the summed dosage difference of a muscle group and the tremor amplitude of the corresponding joint was also calculated. For instance, a correlation between wrist tremor and the summed difference in dosage across all prime movers of the wrist (FCR, ECR, ECU, FCU) was calculated.

5.3 Results

5.3.1 Validating the Musculoskeletal Model

In this section, the musculoskeletal model proposed as a tool to evaluate the motor unit recruitment, which may also assist in improving the efficacy of targeted therapies, is validated [31]. The validation is done by comparing the muscle activity predicted by the model with the measured activity obtained from the sEMG. Apart from the model validation, the model's ability to predict muscle activity and contribution, taking into account the subject-specific bone, joint, and muscle parameters, is also discussed.

5.3.1.1 Comparing the Measured (sEMG) and Estimated Muscle Activity

As discussed earlier, the model is validated by comparing the measured (from the sEMG recordings) and estimated (from the muscle model) muscle activity. Only activity from eight muscles was recorded using the sEMG due to the limitations of the device (the sEMG device can only record accurate activities from large superficial muscles). Therefore, only the activity from these muscles was compared for model validation. However, the musculoskeletal model can estimate activity for all deep and superficial muscles in the upper limb, which is one of the model's advantages over conventional methods. To generalize the results across multiple subjects, the predicted and measured activity obtained from each subject was averaged together to obtain the mean predicted and measured activity pertaining to a given task. Appendix C shows the mean predicted activity across six subjects for various muscles when performing the five tasks. The muscle activity is dimensionless and ranges from 0 to 1, with 0 indicating no activity and 1 indicating maximum activity. Additionally, the muscle model can also estimate the muscle contribution, represented in percentages. Appendix D shows the mean contribution averaged across six subjects of various muscles when performing the five tasks.

To compare the predicted output with the normalized sEMG activity, performance metrics, namely RMSE and correlation value, were calculated. These performance metrics were used to evaluate if the predicted muscle activity aligns with the measured activity to validate the model's accuracy. Table 5.2 shows the muscle-wise performance metrics

comparing the measured and predicted activity values [31]. The results indicate that the average R^2 value between the measured and predicted activity across the eight muscles was 0.8190, implying that the two activity values are closely related and increase or decrease at the same rate. The mean correlation value was 0.906, indicating a linear relationship between the measured and predicted activity. Additionally, the overall p-value for the correlation across all muscles was $p < 0.0001$. Therefore, the correlation between the two activity values was also statistically significant. Furthermore, the RMSE value averaged across the eight muscles was also 0.1031, which falls within an acceptable range of discrepancy between the predicted and measured values. The RMSE value indicates the difference between the predicted and measured value was about 10% of the maximum activity value. This RMSE value may be considered acceptable because even the sEMG values recorded across multiple trials for the same motion had a minor difference from each other. The RMSE value for the sEMG data between two trials of the same task was found to be 0.04485, which is about 4% of the maximum activity value. It must be noted that while the difference between the two sEMG recordings was only 4% as opposed to the 10% between the measured and predicted value, the sEMG comes with many limitations that affect its accuracy, which was the motivation behind designing this muscle model.

Table 5.2: Muscle-wise performance metrics when comparing the predicted and measured (sEMG) activity

Muscle	Root Mean Squared Error (RMSE)	Pearson's correlation	Coefficient of Determination (R^2)	P-value
Biceps	0.014185	0.9297	0.8643	< 0.0001
Triceps	0.003462	0.8982	0.8067	< 0.0001
FCR	0.046810	0.8922	0.7715	< 0.0001
ECR	0.024805	0.9139	0.8352	< 0.0001
Deltoid	0.083255	0.9293	0.8635	< 0.0001
Latissimus dorsi	0.190851	0.9042	0.8175	< 0.0001
Teres Major	0.134105	0.8575	0.7353	< 0.0001
Pectoralis Major	0.327439	0.9034	0.8161	< 0.0001

The five tasks only involve the three joints of the upper limb. However, the model has other functional joints which are not involved in the five tasks. Therefore, a secondary result was added where the movement, such as shoulder retraction/ protraction and

shoulder elevation/ depression involving the acromioclavicular, scapulothoracic, and sternoclavicular joints, were performed in the model, and the corresponding activity was predicted. No kinematic data was collected during the movement as the wireless sensors are not equipped to collect data from these joints. Hence, the shoulder protraction/retraction and shoulder elevation/ depression were directly simulated in the muscle model. For shoulder protraction/ retraction, the shoulder was simulated to protract initially, followed by a retraction, and finally back to the shoulder's neutral position. Figure 5.2 shows the activity predicted by the muscle model for the four muscles primarily involved in this action. Moving to the shoulder elevation/ depression movement, the shoulder was simulated to perform a shoulder elevation, followed by a depression, and back to the shoulder's neutral position. Figure 5.3 shows the predicted activity of four muscles primarily involved in shoulder elevation/ depression motion [31].

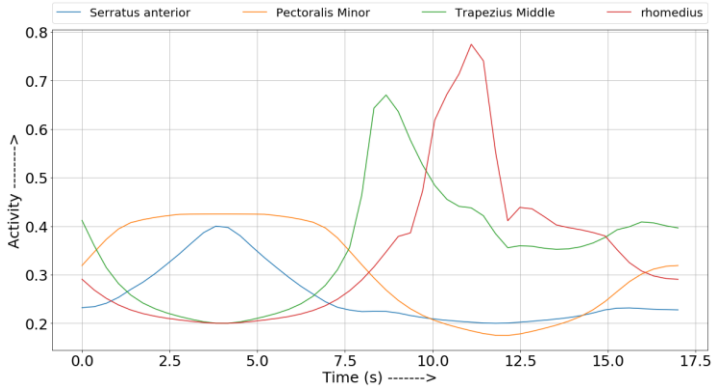


Figure 5.2: Predicted activity for shoulder protraction and retraction

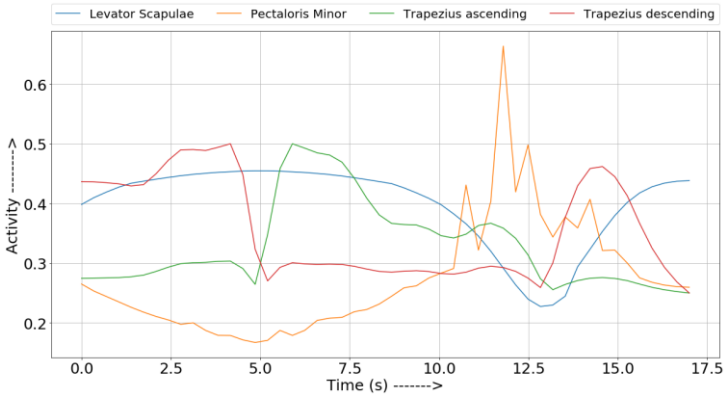


Figure 5.3: Predicted activity for shoulder elevation and depression

5.3.1.2 Subject-specific Muscle Activity and Contribution

One of the model's advantages is that the model's parameters can be varied to suit the subjects to obtain a subject-specific activity prediction. During the model validation using healthy subjects, the bone parameters were varied to fit the subjects. Consequently, certain muscle parameters, such as the insertion and origin points, also varied according to the length of the bones. This section showcases the model's ability to consider the subject-specific parameters when predicting muscle activity. While the earlier section compared the intra-subject predicted activity with the sEMG data, this section compares the inter-subject predicted activity with one another to show that the predicted activity varies based on the subject-specific parameters.

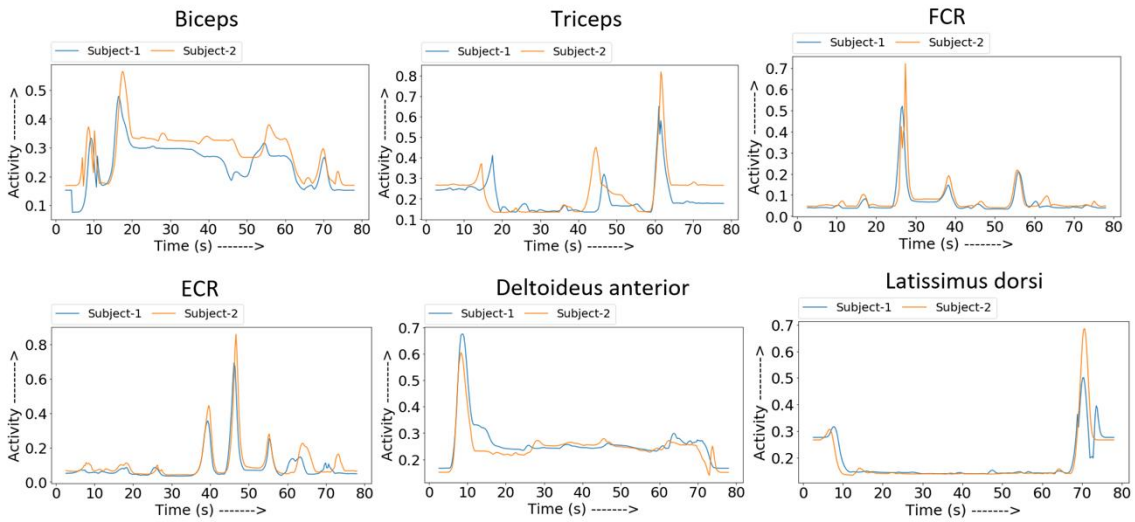
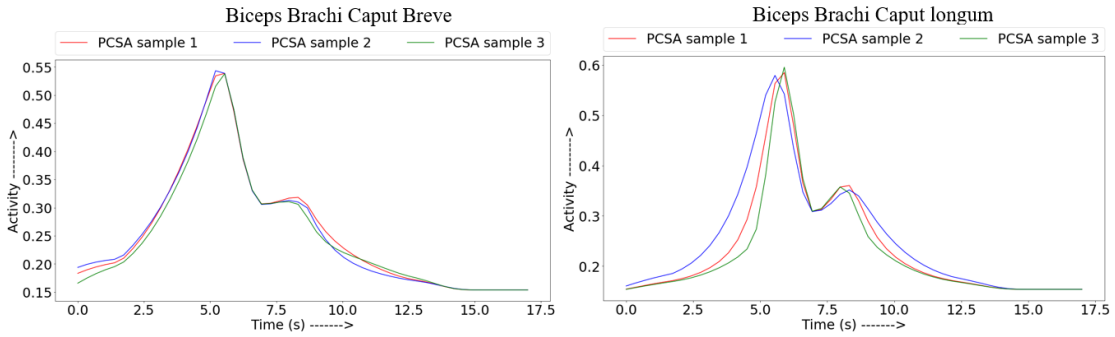


Figure 5.4: Subject-specific muscle activity for the task - 1

Two subjects were considered to understand the model's sensitivity to the subject-specific parameters. The bone parameters of the two subjects varied. The average mass, length, and radius of the bones for subject 1 was 15.9%, 8.95%, and 3.15% lower than subject 2. The predicted activity for both subjects in task 1 for the six muscles is shown in Figure 5.4. It can be seen that, while the predicted activity closely aligns between the subjects, there are a few variations in activity between the subjects when performing certain regions of the task. The minor difference in muscle activity between the two subjects may be attributed to the difference in the inertia tensor matrix of the rigid bodies. The reason

why the muscle activity between the two subjects was not vastly different from one another is because of the method used to determine the activity of muscles. The predicted muscle activity was obtained by normalizing the model's output using the force generated by that subject at MVC. This mirrors the procedure to obtain normalized sEMG data where the sEMG recordings were normalized using the sEMG recordings obtained at MVC. This may be the reason why the differences between the subjects were not substantially different. However, this difference in the activity between the subjects might be more evident when used on patients with varying degrees of movement disorders or varying severity of disease or joint dysfunctions.

Finally, the model's muscle parameters, such as PCSA, can also be varied depending on the subject. Although, due to the time and cost-intensive nature of measuring the muscle volume and fiber length, which are necessary to calculate the PCSA of the muscles, a subject-specific PCSA for each muscle was not calculated and used in the model during validation. However, three sets of muscle parameters were obtained from earlier cadaveric studies [33][34] and used in the model to demonstrate the model's ability to adjust the muscle parameters and accordingly predict the activity. Table 5.3 shows the three sets of PCSA and optimal fiber length values for the biceps and triceps fascicles obtained from earlier studies. Using each parameter set, the model predicts the muscle activity for an elbow flexion/extension movement. Figure 5.5 shows the muscle activity of two biceps and three triceps fascicles when performing the same movement using three sets of muscle parameters. While the trend of activity was the same, irrespective of the muscle parameters, the muscle activation values varied based on the parameters. This implies that the prediction made by the model takes into account the subject-specific muscle parameters.



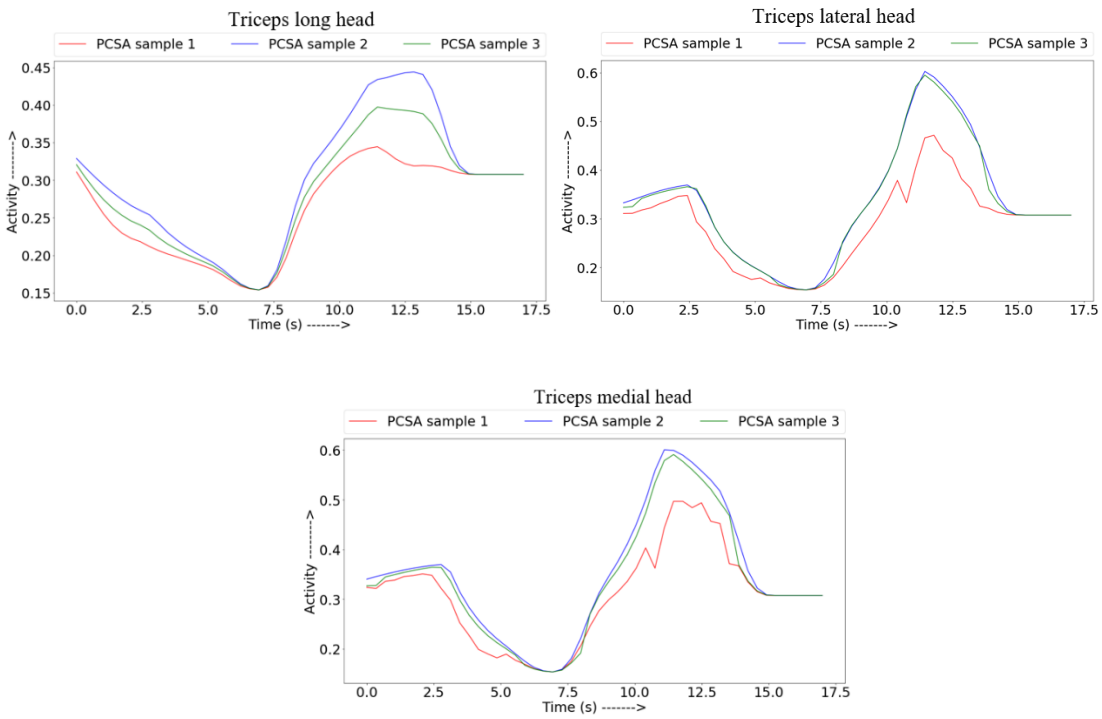


Figure 5.5: Muscle activity of biceps and triceps fascicles with varying muscle parameters

Table 5.3: Three sets of muscle parameters

	Set – 1		Set – 2		Set - 3	
	PCSA (cm^2)	**Neutral fiber length (cm)**	**PCSA (cm^2)**	**Neutral fiber length (cm)**	**PCSA (cm^2)**	**Neutral fiber length (cm)**
Biceps Brachi Caput Breve	1.72	15	1.75	18	3.1	13.2
Biceps Brachi Caput longum	1.78	10	1.57	15.6	4.5	11.6
Triceps lateral head	4.78	5.5	4.13	10.2	4.5	11.4
Triceps long head	5.62	9.4	3.6	17.6	5.7	13.4
Triceps medial head	9.04	8.7	3.21	14.4	4.5	11.4

5.3.2 Towards Estimating Dosage of Botulinum Toxin for Parkinson's Patients: A Prospective Application

The objective of the section is to propose the muscle model as a more effective alternative to determining the botulinum toxin dosage per muscle, which in turn would enhance the efficacy of the treatment. The muscle activity and contribution predicted by the model were used to estimate the dosage for nine upper-limb muscles for 47 PD patients undergoing botulinum toxin therapy. Further, the model's potential to be used for this application was also explored.

5.3.2.1 Calculating the Dosage based on Muscle Activity and Contribution

Table 5.4: Difference between the estimated and actual dosage

Muscles	Number of patients with a change in dosage (Out of 47 patients)	Percentage difference between the estimated and actual dosage	Significance
Biceps	22	11.77	$p = 0.1643$
Triceps	22	20.78	$p = 0.0070$*
FCR	20	55.79	$p = 0.0437$*
FCU	15	14.82	$p = 0.0707$
ECR	21	33.76	$p = 0.0002$*
ECU	22	22.10	$p = 0.8414$
Supinator	30	196.96	$p = 0.0014$*
Pronator Teres	13	15.71	$p = 0.0022$*
Pronator Quadratus	13	50.72	$p = 0.1655$

Note: * after the *p*-value indicates statistical significance

The kinematic data collected from the PD patients was used to predict the muscle activity and contribution, which was then used to estimate the dosage per muscle. The difference between the predicted and actual dosage for each muscle across the 47 PD patients was evaluated to understand if there was a statistically significant difference between the actual and predicted dosage. Table 5.4 shows that the predicted dosage for five out of nine upper-limb muscles was statistically significantly different from the actual dosage.

5.3.2.2 Correlation between the Dosage Difference and the Tremor Amplitude

A correlation between the dosage difference and the amplitude of the tremor in the patient's follow-up visit was performed. This was done to understand if the model's prediction differed from the actual dosage only when the treatment with the actual dosage did not mitigate the tremor, resulting in a higher tremor amplitude. Table 5.5 shows the correlation between the muscles and the tremor amplitude of the corresponding joint. A positive correlation between the tremor amplitude of the joint and the muscles was observed. The positive correlation was statistically significant for all muscles except the ECR and Pronator Quadratus. This implies that the predicted dosage was substantially different from the actual dosage when the tremor amplitude of the corresponding joint was high. Furthermore, Table 5.6 shows the correlation between the joint's tremor amplitude and the total dosage difference across every muscle in a given muscle group involved in moving the joint. Once again, a statistically significant correlation was observed between the tremor amplitude and the corresponding muscle group. There is a positive correlation of 0.5317, 0.4176, and 0.3075 between the wrist, forearm, and elbow muscle groups and the tremor amplitude of the wrist, forearm, and elbow joints. Combining all muscle groups and tremor amplitudes of all joints, a positive correlation of 0.5570 was observed and was statistically significant.

Table 5.5: Correlation between the difference in dosage of individual muscle and tremor amplitude of the joint moved by a given muscle

Muscles	Correlation	Significance
Biceps	0.3075	$p < 0.05$
Triceps	0.3075	$p < 0.05$
FCR	0.4984	$p < 0.05$
FCU	0.5318	$p < 0.05$
ECR	0.1848	NS
ECU	0.2981	$p < 0.05$
Supinator	0.3398	$p < 0.05$
Pronator Teres	0.3020	$p < 0.05$
Pronator Quadratus	0.2114	NS

Table 5.6: Correlation between the tremor amplitude of the joints and the difference in dosage among the muscle groups responsible for the joint movement

Muscle groups	Correlation	Significance
Wrist muscle group	0.5317	$p < 0.05$
Forearm muscle group	0.4176	$p < 0.05$
Elbow muscle group	0.3075	$p < 0.05$
All muscles	0.5570	$p < 0.05$

5.4 Discussion

The work described in this chapter focused on designing a musculoskeletal model to examine the muscle recruitment strategies, which may assist in understanding the muscle activation patterns in PD patients and act as a guiding tool to individualize and improve the efficacy of targeted therapies. Earlier literature [9][6] [25][26][35] has discussed the importance of studying muscle recruitment strategies and individualizing the targeted therapies to enhance their effectiveness. Due to the limitations in the earlier simulation or machine learning models [19] [11] [13] developed to examine the muscle activation patterns, there is a need for a subject-specific musculoskeletal model that is far more detailed and accurate. The proposed upper-limb musculoskeletal model comprises 61 muscles, seven functional joints, and seven rigid bones, making it more detailed than earlier models. Furthermore, to perform a patient-specific analysis of the muscle activation patterns, the model's parameters can be varied to suit the patient's bone, muscle, and joint parameters. The muscle model uses the joint kinematic data as input and outputs the muscle force using the inverse dynamics optimization algorithm. The muscle force is then used to estimate the activity and relative contribution of individual muscles. To validate the muscle model, the model's output (muscle activity) for healthy subjects was compared with the activity measured from the sEMG, which is currently considered the gold standard for measuring the activity of superficial muscles. While the muscle model may be used to study the muscle activation patterns in PD patients, an important application of this model was to better guide targeted therapies such as botulinum toxin injections. Therefore, the model's output (muscle activity and contribution) for the kinematic data obtained from PD patients were used to estimate the botulinum toxin dosage per muscle. Furthermore, to explore the model's potential as an effective tool to estimate dosage per muscle, the

difference between the actual and estimated dosage was correlated with the tremor experienced by the patients in the follow-up visits. This would indicate if there was a substantial difference between the actual and estimated dosage only when the dosage provided to the patients through subjective methods was ineffective, leading to tremor not being mitigated in the follow-up visit.

Discussing the model validation, the muscle activity predicted by the model was compared with the normalized sEMG activity for superficial muscles. Across the eight superficial muscles, the average RMSE was 0.1031, and further, a statistically significant correlation was observed between the measured and estimated activity. Therefore, the performance metrics show that the activity predicted by the muscle model closely resembled the normalized sEMG data. This close alignment with the sEMG, which is currently considered the gold standard in clinics to measure the activity of superficial muscles, validates the output of the muscle model. While the model's output for superficial muscles may align with the sEMG recordings, the model also has several benefits over conventional methods as it can measure the activity of even the deeper and smaller muscles without the need for any invasive procedures such as intramuscular EMG. Furthermore, while the earlier methods are not equipped to calculate the relative contribution of muscles, the proposed model can determine the contribution of each muscle pertaining to a motion.

Another significant aspect that needed to be considered when designing the model was the detail, i.e., the number of muscles included in the model. One of the objectives was to develop a model that is more detailed than existing models. A discussion on the existing simulation and machine learning models has been provided in the introduction. To this end, the proposed model is more detailed than the earlier models as it includes 61 upper-limb muscles.

The study was also aimed at adapting the model to suit the subject of interest. Therefore, the bone, joint, and muscle parameters can be varied depending on the subject. The model's ability to vary the bone parameters was showcased when validating the model's output using healthy subjects. A comparison between the model's output for two healthy subjects was also performed, which indicated that the activity estimated for the

healthy subjects was not substantially different, although their subject-specific parameters were different. This may be because the estimated activity used for validation was obtained by normalizing the muscle force with force generated by that subject at MVC. Therefore, the difference in the parameters may have been canceled out during the normalization; thereby, the activity patterns were not significantly different even though the subject-specific parameters were different. While the bone parameters were measured for each subject and varied during the model validation, the muscle parameters such as PCSA, muscle volume, and fiber length were not measured as they may require time and cost-intensive procedures such as MRI. However, to validate the model's ability to take the different muscle parameters into account when estimating the muscle activity, three sets of muscle parameters from earlier cadaveric studies [33][34] were used on the model to estimate the activity for the simulated elbow flexion/ extension movement. The results showed a variation in the muscle activity of the biceps and triceps, which implied that the model's prediction accounts for the subject-specific parameters.

Finally, a potential application for the model, which was to guide and individualize the targeted therapies, such as botulinum toxin, to improve its efficacy, was studied. The kinematic data collected from the PD patients undergoing botulinum toxin therapy was used to estimate the muscle contribution and then predict the dosage for nine upper-limb muscles. There was a statistically significant difference between the actual and predicted dosage. Considering that the model's output was validated, the significant difference in the predicted and actual dosage may imply that the dosing patterns may be further optimized to improve the effectiveness of the therapy. To explore the model's potential for this application, a correlation was calculated between the difference in the dosage and the tremor observed during the follow-up visit. A positive correlation was observed between the difference in the dosage and the tremor during the follow-up visit. This indicates that as the tremor in the follow-up visit increased, the difference between the predicted and actual dosage also increased. The result implies that only when the dosing patterns derived using conventional methods failed to effectively mitigate the tremor, the model predicted a substantially different dosage from the actual one. Therefore, taking these results together, the muscle model may be considered a potential alternative or a complementary method to better guide the therapies. However, while the model's output was validated by

comparing it with sEMG, the model's ability to predict the optimized dosage (the dosage that yields the best results for the patient) is yet to be validated. The muscle model has significant advantages over conventional methods. However, adopting the muscle model to guide the targeted therapies requires testing in a clinical setting and consensus from the experts in the field.

The work described in this chapter was aimed at designing and developing an accurate, detailed, and subject-specific musculoskeletal model that can be used to study the muscle activation patterns in PD patients and better guide PD-related therapies. To validate the accuracy of the muscle model, the activity estimated by the model for eight upper-limb muscles was compared with the normalized sEMG activity. The results showed that the muscle activity estimated by the model correlated with the sEMG recordings, thereby validating the model's output. Several studies [35] have indicated the need for a more targeted and patient-specific approach to improving the quality of care for PD patients. Therefore, to ensure that the model can be used for patient-specific analysis, the model's ability to adjust the parameters and take them into account when estimating muscle activity and contribution was also demonstrated. Hence, the model's accuracy and ability to be subject-specific have been validated through a set of experiments discussed earlier. Further, a potential application for the model was discussed. The activity and relative contribution were used to predict the botulinum toxin dosage per muscle to efficiently mitigate the rest tremor in PD patients. A statistically significant difference between the predicted and actual dosage was observed. Furthermore, a positive correlation was observed between the tremor in the follow-up visit and the dosage difference. This implies that the predicted dosage is substantially different from the actual dosage only in instances that necessitate a large change in actual dosage to optimize the treatment. Therefore, the results show that the muscle model has the potential to be used as a guiding tool in targeted therapies such as botulinum toxin injections. However, it must be indicated on a cautionary note that while the model's ability to estimate the muscle activity and contribution was validated, no validation was done to ensure that the model predicts the optimized botulinum toxin dosage. The correlation between the dosage difference and the tremor only shows that the model predicted a vastly different dosage when the tremor was not mitigated using the actual dosage. The findings still do not indicate if the dose estimated for each muscle is

optimized to effectively mitigate the rest tremor in PD patients. This may require clinical testing and analysis to understand if the predicted dosage improves the therapy's efficacy and does not lead to any side effects, including muscle weakness. Therefore, the work described here may act as the first step in objectively and accurately guiding targeted therapies. However, before adopting the muscle model in a clinical setting, there is a need for an extensive clinical trial or study, and it requires consensus from clinicians to understand its suitability for the application.

5.5 References

[1] S. E. Goodman and C. J. Hasson, “Elucidating Sensorimotor Control Principles with Myoelectric Musculoskeletal Models,” *Front Hum Neurosci*, vol. 11, Nov. 2017, doi: 10.3389/fnhum.2017.00531.

[2] P. M. Bays and D. M. Wolpert, “Computational principles of sensorimotor control that minimize uncertainty and variability,” *J Physiol*, vol. 578, no. 2, pp. 387–396, Jan. 2007, doi: 10.1113/jphysiol.2006.120121.

[3] D. W. Franklin, “Impedance control: Learning stability in human sensorimotor control,” in *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, IEEE, Aug. 2015, pp. 1421–1424. doi: 10.1109/EMBC.2015.7318636.

[4] C. Gans, “Fiber architecture and muscle function,” *Exerc Sport Sci Rev*, 1982, doi: 10.1249/00003677-198201000-00006.

[5] C. J. Heckman and R. M. Enoka, “Motor Unit,” in *Comprehensive Physiology*, Wiley, 2012, pp. 2629–2682. doi: 10.1002/cphy.c100087.

[6] D. Farina, M. Fosci, and R. Merletti, “Motor unit recruitment strategies investigated by surface EMG variables,” *J Appl Physiol*, vol. 92, no. 1, pp. 235–247, Jan. 2002, doi: 10.1152/jappl.2002.92.1.235.

[7] M. Hirashima and T. Oya, “How does the brain solve muscle redundancy? Filling the gap between optimization and muscle synergy hypotheses,” *Neurosci Res*, vol. 104, pp. 80–87, Mar. 2016, doi: 10.1016/j.neures.2015.12.008.

[8] R. Sharif Razavian, B. Ghannadi, and J. McPhee, “On the Relationship Between Muscle Synergies and Redundant Degrees of Freedom in Musculoskeletal Systems,” *Front Comput Neurosci*, vol. 13, Apr. 2019, doi: 10.3389/fncom.2019.00023.

[9] D. S. Glendinning and R. M. Enoka, “Motor Unit Behavior in Parkinson’s Disease,” *Phys Ther*, vol. 74, no. 1, pp. 61–70, Jan. 1994, doi: 10.1093/ptj/74.1.61.

[10] O. Darbin and E. B. Montgomery, “Challenges for future theories of Parkinson pathophysiology,” *Neurosci Res*, vol. 177, pp. 1–7, Apr. 2022, doi: 10.1016/j.neures.2021.11.010.

[11] Q. Carlos, A. Margarida, A. Jorge, S. B. Goncalves, and F. Joaõ, “Influence of the Musculotendon Dynamics on the Muscle Force-Sharing Problem of the Shoulder-A Fully Inverse Dynamics Approach,” *J Biomech Eng*, 2018, doi: 10.1115/1.4039675.

[12] C. Quental, J. Folgado, and J. Ambrósio, “A window moving inverse dynamics optimization for biomechanics of motion,” *Multibody Syst Dyn*, 2016, doi: 10.1007/s11044-016-9529-4.

[13] A. Asadi Nikooyan, H. E. J. Veeger, E. K. J. Chadwick, M. Praagman, and F. C. T. van der Helm, “Development of a comprehensive musculoskeletal model of the shoulder and elbow,” *Med Biol Eng Comput*, 2011, doi: 10.1007/s11517-011-0839-7.

[14] A. A. Nikooyan, H. E. J. Veeger, P. Westerhoff, F. Graichen, G. Bergmann, and F. C. T. van der Helm, “Validation of the Delft Shoulder and Elbow Model using in-vivo glenohumeral joint contact forces,” *J Biomech*, 2010, doi: 10.1016/j.jbiomech.2010.06.015.

[15] W. Wu, P. V. S. Lee, A. L. Bryant, M. Galea, and D. C. Ackland, “Subject-specific musculoskeletal modeling in the evaluation of shoulder muscle and joint function,” *J Biomech*, 2016, doi: 10.1016/j.jbiomech.2016.09.025.

[16] C. Klemt *et al.*, "Anthropometric Scaling of Anatomical Datasets for Subject-Specific Musculoskeletal Modelling of the Shoulder," *Ann Biomed Eng*, 2019, doi: 10.1007/s10439-019-02207-2.

[17] E. Pennestrì, R. Stefanelli, P. P. Valentini, and L. Vita, "Virtual musculo-skeletal model for the biomechanical analysis of the upper limb," *J Biomech*, 2007, doi: 10.1016/j.jbiomech.2006.05.013.

[18] T. S. Buchanan, D. G. Lloyd, K. Manal, and T. F. Besier, "Estimation of muscle forces and joint moments using a forward-inverse dynamics model," in *Medicine and Science in Sports and Exercise*, 2005. doi: 10.1249/01.mss.0000176684.24008.6f.

[19] L. A. Johnson and A. J. Fuglevand, "Evaluation of probabilistic methods to predict muscle activity: Implications for neuroprosthetics," *J Neural Eng*, 2009, doi: 10.1088/1741-2560/6/5/055008.

[20] F. di Nardo, A. Nocera, A. Cucchiarelli, S. Fioretti, and C. Morbidoni, "Machine Learning for Detection of Muscular Activity from Surface EMG Signals," *Sensors*, vol. 22, no. 9, p. 3393, Apr. 2022, doi: 10.3390/s22093393.

[21] M. F. Dirkx and M. Bologna, "The pathophysiology of Parkinson's disease tremor," *J Neurol Sci*, vol. 435, p. 120196, Apr. 2022, doi: 10.1016/j.jns.2022.120196.

[22] L. E. Heusinkveld, M. L. Hacker, M. Turchan, T. L. Davis, and D. Charles, "Impact of Tremor on Patients With Early Stage Parkinson's Disease," *Front Neurol*, vol. 9, Aug. 2018, doi: 10.3389/fneur.2018.00628.

[23] E. D. Louis and D. G. Machado, "Tremor-related quality of life: A comparison of essential tremor vs. Parkinson's disease patients," *Parkinsonism Relat Disord*, vol. 21, no. 7, pp. 729–735, Jul. 2015, doi: 10.1016/j.parkreldis.2015.04.019.

[24] N. Niemann and J. Jankovic, "Botulinum toxin for the treatment of hand tremor," *Toxins (Basel)*, 2018, doi: 10.3390/toxins10070299.

[25] S. O. Mittal, D. Machado, D. Richardson, D. Dubey, and B. Jabbari, "Botulinum Toxin in Parkinson Disease Tremor: A Randomized, Double-Blind, Placebo-Controlled Study With a Customized Injection Approach," *Mayo Clin Proc*, 2017, doi: 10.1016/j.mayocp.2017.06.010.

[26] O. Samotus, J. Lee, and M. Jog, "Personalized Bilateral Upper Limb Essential Tremor Therapy with Botulinum Toxin Using Kinematics," *Toxins (Basel)*, vol. 11, no. 2, p. 125, Feb. 2019, doi: 10.3390/toxins11020125.

[27] A. I. Grigoriu, M. Dinomais, O. Rémy-Néris, and S. Brochard, "Impact of injection-guiding techniques on the effectiveness of botulinum toxin for the treatment of focal spasticity and dystonia: A systematic review," *Ann Phys Rehabil Med*, 2015, doi: 10.1016/j.rehab.2015.07.193.

[28] C. Disselhorst-Klug, T. Schmitz-Rode, and G. Rau, "Surface electromyography and muscle force: Limits in sEMG-force relationship and new approaches for applications," *Clinical Biomechanics*. 2009. doi: 10.1016/j.clinbiomech.2008.08.003.

[29] O. Samotus, J. Lee, and M. Jog, "Personalized botulinum toxin type A therapy for cervical dystonia based on kinematic guidance," *J Neurol*, vol. 265, no. 6, pp. 1269–1278, Jun. 2018, doi: 10.1007/s00415-018-8819-6.

[30] O. Samotus, "Characterization and personalization of botulinum toxin type A therapy for upper limb tremor in Parkinson disease and Essential tremor patients using multi-sensor kinematic technology," 2016. Accessed: Aug. 04, 2023. [Online]. Available: https://ir.lib.uwo.ca/etd/4035

[31] Y. K. Tamilselvam, J. Ganguly, R. V. Patel, and M. Jog, “Musculoskeletal Model to Predict Muscle Activity During Upper Limb Movement,” *IEEE Access*, vol. 9, pp. 111472–111485, 2021, doi: 10.1109/ACCESS.2021.3103438.

[32] C. J. De Luca, L. Donald Gilmore, M. Kuznetsov, and S. H. Roy, “Filtering the surface EMG signal: Movement artifact and baseline noise contamination,” *J Biomech*, vol. 43, no. 8, pp. 1573–1579, May 2010, doi: 10.1016/j.jbiomech.2010.01.027.

[33] K. R. S. Holzbaur, W. M. Murray, and S. L. Delp, “A model of the upper extremity for simulating musculoskeletal surgery and analyzing neuromuscular control,” *Ann Biomed Eng*, 2005, doi: 10.1007/s10439-005-3320-7.

[34] J. Langenderfer, S. A. Jerabek, V. B. Thangamani, J. E. Kuhn, and R. E. Hughes, “Musculoskeletal parameters of muscles crossing the shoulder and elbow and the effect of sarcomere length sample size on estimation of optimal muscle length,” *Clinical Biomechanics*, 2004, doi: 10.1016/j.clinbiomech.2004.04.009.

[35] G. Abbruzzese, R. Marchese, L. Avanzino, and E. Pelosin, “Rehabilitation for Parkinson’s disease: Current outlook and future challenges,” *Parkinsonism Relat Disord*, 2016, doi: 10.1016/j.parkreldis.2015.09.005.

Chapter 6

6 Discussion

This thesis explored how PD could alter SMI and SMC functions and how objective disease diagnostic and management techniques could be developed. Following the objectives described in Section 1.8 in Chapter 1, the thesis was divided into four chapters, with Chapter 2 containing the methodology, followed by Chapters 3, 4, and 5 focusing respectively on the evaluation of the performance of SMI and SMC using robot-based tasks, and designing of a musculoskeletal model to analyze muscle activation patterns. While the deficits in perception and motor functions have been widely studied, the factors contributing to these deficits must be understood to better optimize the treatments. It has been hypothesized that an impairment in SMI and SMC in PD patients may lead to perceptual deficits, leading to motor dysfunctions. However, the exact nature and extent of these impairments are not fully understood. Therefore, multiple custom-built upper-limb tasks and corresponding features were designed and developed to evaluate and characterize various aspects of SMI and SMC impairments in PD. The extracted features were used to expand our knowledge about the SMI and SMC impairments in PD patients and the effect of dopaminergic medication. These tasks and the corresponding metrics were also designed to be used as an objective clinical assessment tool of the SMI and SMC impairments in PD patients, which may provide clinicians with vital information to optimize the treatments. The tool described in this thesis is a foundation for our research goal of developing an objective technique that can complement the existing subjective assessments, such as clinical scales, for better diagnosis and management of the disease. With studies [1][2][3] indicating that non-motor symptoms, such as perceptual deficits, are presented earlier than motor symptoms, this tool may be used to detect SMI and SMC impairments that lead to perceptual deficits at an earlier stage of the disease, thereby aiding in early disease diagnosis. To demonstrate the potential of the tool in differentiating PD and healthy subjects, a machine learning model was also trained and tested using the features extracted from the robotic device. Finally, in Chapter 5, another tool, a subject-specific musculoskeletal model, was developed to analyze a specific aspect of SMC functions: muscle activation and recruitment patterns in PD and healthy subjects. Unlike the robot-

based tool, the musculoskeletal model was not used to investigate specific impairments. However, the model may be considered a potential tool to better guide targeted therapies and improve their efficacy, enhancing the patient's quality of life. Therefore, the work described in this thesis focuses on developing objective tools and performing patient-specific analysis to quantify and characterize SMI and SMC performance in PD patients. These tools lay the foundation for future work that focuses on developing a fully objective diagnosis and management tool for neurological disorders, which takes into account the diverse nature of the disorders and provides a more individualized, targeted treatment approach.

6.1 Summary of Findings

6.1.1 Quantification of SMI impairments in PD patients

- PD patients underperformed in tasks with only visual input compared to controls, implying a deficit in visual perception.

- The deterioration in the performance of the PD patients in tasks with ASC compared to without ASC implies an impairment in integrating multi-modal sensory inputs.

- The discussion of the findings based on the computational models indicates that PD may adversely affect the ability to rank modalities based on reliability, and appropriateness, thereby affecting their ability to assign weights to the modalities during multi-sensory integration, leading to impaired SMI functioning.

- The increased visual dependence in PD patients may be a symptom of impaired SMI function.

- Considering the earlier two points, PD may alter the CNS's criteria in integrating multi-modal inputs.

- PD patients may retain their ability to adjust motor outputs using the perceptual estimates obtained from the impaired multi-sensory integration process.

- The ability to modulate the motor outputs may not be completely unimpaired in PD patients. However, any impairment in this aspect may be purely a motor component rather than a deficit in using the sensory inputs to update a motor command to suit the demands of the testing environment.

- The retention of the PD patients' ability to modulate motor output based on perceptual estimates ensured that the patients took into account the changes in the testing environment when performing a movement. However, the perceptual estimates being inaccurate due to the impaired multi-sensory integration process led to inaccuracies in the modulation of motor output resulting in performance deterioration compared to control subjects.

- The PD patients were also able to learn over multiple trials and improve their motor performance. This implies that despite the impaired SMI functions, the PD patients improved their SMI performance over time which translates into an improvement in motor performance. However, the PD patients took more time than the control subjects to learn and adapt to changes in the environment.

- The PD patients were able to improve their sensory integration and motor performance over time when provided with appropriate sensory inputs that assisted the participants through a task.

- Overall, while the second facet of SMI (modulating the motor outputs using perceptual estimates) is largely retained, the first facet of SMI (multi-sensory integration) appears to be impaired due to PD altering the CNS's criteria in integrating multi-modal sensory inputs. However, PD patients improved their impaired SMI process over time.

6.1.2 Effect of Medication on SMI Impairments

- The ASC did not yield a statistically significant improvement in the performance of PD-ON, as shown by the within-group comparison.

- PD-ON committed fewer errors than PD-OFF, although PD-ON struggled to correct errors once they had committed them. While the number of errors committed by PD-ON was less, the magnitude of error for PD-ON was much higher than for PD-OFF. This implies that the medication worsened the ability to adjust motor outputs using the perceptual estimates, resulting in an inability to modulate motor commands to correct the errors that have been committed.

- The earlier inference is validated by the two findings in tasks without sensory manipulation (i) Higher maximum error for PD-ON than PD-OFF while having lower mean error than for PD-OFF, (ii) Higher mean violation distance and time spent under violation for PD-ON than for PD-OFF, while the mean number of violation was lower than for PD-OFF.

- PD-ON performed worse than PD-OFF when encountering sensory manipulation, which aligns with our earlier inference that the online motor control may be affected due to medication, which may negatively affect the ability to perform task-specific voluntary movements.

- Interpreting the results from the perspective of the internal model, due to disruption in the sensory-motor coupling, PD-ON did not consider that the preceding motor output failed to yield the desired results, leading to an error. Therefore, the motor output was modulated without fully considering why the preceding motor output resulted in an error and how the successive output needed to be modulated to attain the desired result.

- The findings indicate that the medication also worsens motor learning ability. With motor learning ability highly dependent on how an individual uses the sensory input to learn or re-learn to modify and refine an already learned task, the deterioration in motor learning may be attributed to the worsening of SMI deficit due to medication.

- Taking these results together, the medication has disrupted the coupling between the sensory and motor systems. SMI requires proper communication and

coordination between the motor and sensory systems in a closed loop. The motor system must modulate its output based on the sensory inputs that inform us about any potential error or environmental changes. However, the medication affected the ability of the motor system to "listen" to the sensory inputs when generating or modulating its output, thereby making it unable to consider the errors that needed to be corrected or changes in the environment when performing a movement.

- Despite the improvement in movement speed after medication, the worsening of SMI impairments, specifically the ability to modulate motor outputs based on perceptual estimates due to medication, resulted in PD-ON's poorer overall task performance than that of PD-OFF.

- Furthermore, while the medication improves the movement speed, it does not normalize it, as the control subjects were significantly faster than PD-ON.

6.1.3 Quantification of SMC impairments in PD patients

- The PD patients exhibited impairments in the motor domain of SMC, which aligns with earlier studies.

- In the sensory domain of SMC, PD patients exhibited deficits in interpreting and using the multi-modal sensory inputs to avoid errors, implying impaired processing of sensory inputs. This deficit in the sensory domain of SMC may be attributed to the SMI impairment discussed earlier.

- The PD has altered the threshold for force perception, leading to sensory dampening, as the difference in the time taken to correct for perturbations between PD patients and control subjects was less for stronger perturbations (perturbation with high force) than for weaker perturbations (perturbation with low force). This implies that PD patients could perceive and correct for stronger perturbations better and more quickly than for weaker perturbations.

- Regarding the cognitive domain associated with SMC, PD patients exhibited impairments in executive functions such as movement planning or online error correction.

- Furthermore, the decline in cognitive function worsens as the complexity of the task increases, implying that PD patients may exhibit steeper deterioration in performance compared to control subjects as the cognitive load associated with a given task increases.

- The impairments in executive functions were also observed in patients deemed cognitively normal by the clinical scales.

- The PD patients performed worse than the control subjects when compared from the perspective of generic and task-specific computational models related to movement planning.

- Concerning the speed-to-accuracy trade-off model, the PD patients exhibited increased signal-dependent noise, which may adversely affect motor planning. This aligns with our earlier findings from the cognitive domain, which also demonstrated impaired movement planning in PD patients.

- Finally, in terms of the minimum intervention model, the PD patients exhibited deficits in distinguishing between the task-relevant, and task-irrelevant errors, leading to their corrective movements increasing the number of obstacle hits rather than decreasing it.

6.1.4 Effect of Medication on SMC Impairments

- The medication has improved all motor features, implying an improvement in the motor domains of SMC.

- The obstacle hit-to-warn ratio and corrective time for perturbation worsened after medication in complex levels of the task.

- The worsening of the sensory domain due to medication was evident only in complex levels because the simpler levels may not require proper usage of multi-modal sensory inputs and appropriate force perception to optimally plan or correct movement. However, due to high complexity, the later levels might require accurate sensory perception for movement planning and error correction. Therefore, the worsening of the sensory domain may be specifically highlighted in the later levels of the task.

- Interpreting the earlier point, the medication worsened the ability to interpret sensory inputs to adjust the motor output. This result also aligns with the worsening of SMI impairment after medication, which was discussed earlier. Additionally, the medication has further negatively altered the force perception threshold.

- Regarding the cognitive domain associated with SMC, the medication worsened the executive functions, leading to PD-ON exhibiting poorer movement planning and error correction in cognitively demanding levels of the task compared to PD-OFF. Worsening of executive functions after the medication was only highlighted in complex levels of the task as these levels require high cognitive resources necessitating complex planning or correction of movement. In contrast, the simpler levels requiring low cognitive resources may not highlight the effect of medication on the cognitive domain associated with SMC. This inference that PD-ON may perform differently depending on the required cognitive resource also aligns with an earlier study [4].

- Compared to SMC-based computational models, the medication worsened the fingertip accuracy (endpoint variance) at cognitively demanding levels. However, the performance of PD-ON in the minimum intervention model and speed-to-accuracy trade-off model was better compared to PD-OFF. Therefore, the effect of medication based on the computational models was mixed.

- In conclusion, while the medication improved the motor domain, it worsened the sensory and cognitive domains of SMC, especially at cognitively demanding levels.

- The worsening of SMI impairments after medication may have a role to play in the deterioration of the sensory domain associated with SMC after medication.

- While the medication improved the motor domain associated with SMC, it did not normalize its functions, as the control subjects still performed better than PD-ON across all motor features.

6.1.5 Robotic Tools and Metrics to Analyze SMI and SMC Impairments

Currently, no objective tool is available to evaluate SMI and SMC performance. The robotic tool developed in this study may be the first step in complementing the existing subjective scales with an objective technique to better analyze, manage, and diagnose the disease. With the burden on medical responses predicted to increase due to the rising number of PD patients globally, the robotic tasks and metrics may be improved upon for use in a clinical setting for earlier diagnosis or to assist in creating a more sophisticated, efficient, and targeted treatment approach, that could reduce the stress on the health care system. The tool described in this thesis has several advantages (described below) over the conventional methods.

- The functioning of SMI and SMC plays a vital role in performing day-to-day tasks, and impairments in SMI and SMC may severely affect the patient's quality of life. While there are numerous clinical scales to evaluate the cardinal motor and non-motor symptoms, there is currently no objective method to evaluate the SMI and SMC impairments that contribute to perceptual and motor dysfunctions in PD patients. The robotic tool discussed in this thesis may be used to examine SMI and SMC impairments, which would assist in efficiently managing these impairments, thereby improving a PD patient's quality of life.

- Three neural network models were developed to understand if the metrics obtained from the robotic tasks may be improved in the future as a potential diagnostic tool. All three models demonstrated an accuracy of over 80% in differentiating between PD and control subjects. With SMI and SMC deficits arising earlier in the disease leading to perceptual deficits, the result may imply that the metrics examining SMI

and SMC performance may be used in conjunction with the current clinical methods to efficiently diagnose PD at an early stage.

- While PD is considered a heterogeneous disease that presents symptoms differently to different patients, the neural network model was able to detect the SMI and SMC impairments commonly across most PD patients (around 80%). Therefore, abnormalities in SMI and SMC may be considered a potential biomarker for diagnosis of PD.

- In evaluating SMC, the objective metrics were divided into motor, sensory, and cognitive features. These features may be used to individually assess each domain associated with SMC and target the domain-specific impairments through systematic rehabilitation regimes. Currently, no study has evaluated each domain of the SMC functionalities individually.

- During SMC assessment, the cognitive features detected numerous impairments in the cognitive domain of the PD patients deemed cognitively normal by the subjective clinical scales. Therefore, the objective metrics could detect certain impairments in executive functions that the clinical scales could not detect. Considering this, it might be beneficial to complement the existing subjective scales with objective metrics and testing to better diagnose and manage the disease.

- The robotic tool is also capable of testing the patients in dynamic environments. This includes varying the sensory conditions as it was done when assessing SMI or changing the nature of the task that demands varying cognitive resources from the patients, like the task used in SMC assessment. Therefore, the techniques developed in this thesis may be used to understand how PD patients may perform differently in a diverse environment. This may be important to examine as any day-to-day activity needs to be performed in a constantly changing or dynamic environment.

- The objective metrics may also be used to understand if a rehabilitation regime or a targeted treatment improved SMI or SMC functionalities and how the treatments need to be optimized.

- As discussed earlier, the robotic tool could evaluate the effects of the medication on SMI and SMC functions in PD patients. Considering the heterogeneous nature of PD, the complex and multi-modal effect of medication needs to be considered individually for each patient for better optimization of the treatment and patient assessment. The robotic task and metrics may therefore be used to understand the patient-specific effects of the medication, which is vital for treatment optimization.

- Metrics were developed to examine the participants from the perspective of existing computational models. The metrics for the computational model provide valuable insights into how PD may alter the CNS's criteria for movement planning or error correction. These metrics are developed based on the cost function of the models, and optimizing these cost-functions-based metrics is assumed to be vital for appropriate motor functions. Therefore, the treatment or rehabilitation regimes targeted at improving or optimizing these cost-function-based metrics may, in turn, improve overall task performance. Currently, no study has evaluated PD patients using computational models.

- These metrics may also be used to evaluate healthy subjects to expand our knowledge about how the CNS may optimally plan or correct motor movements.

6.1.6 Subject-specific Musculoskeletal Model

The musculoskeletal model was developed to be more detailed, accurate, and subject-specific compared to existing models. While the robotic tool evaluates the movement performed under dynamic environments, the muscle model was developed to examine another aspect of SMC function: the muscle recruitment process.

- The muscle model comprised 61 muscles, seven functional joints, and seven rigid bones, making it more detailed than existing upper-limb models.

- The model's accuracy was validated by comparing the muscle activity estimated by the model with the sEMG activity recorded for eight superficial muscles. The findings indicate that the estimated and measured activity for eight muscles have a

statistically significant correlation with each other, thereby validating the model's output.

- Studies [5][6] have emphasized a need for a more subject-specific model as the prediction accuracy of the subject-specific may be better than a generic model. To this end, the proposed model was developed to be subject-specific as the parameters associated with bones, muscles, and joints may be varied depending on the subject's parameters.

- Experiments were conducted to demonstrate that the model considers the subject-specific parameters when estimating the activity.

- Currently, there are no models or techniques that can estimate the relative contribution of each muscle when performing a motion. Therefore, the muscle contribution estimated by the proposed model may provide valuable insights into the criterion that the CNS employs in recruiting the muscles and how the workload is shared among the muscles.

- Muscle recruitment is an essential SMC function to successfully perform any motion. The validated muscle model developed in this study may be used to understand if PD alters the muscle recruitment strategies compared to those of healthy subjects.

- The outputs from the muscle model may also be used to guide certain targeted therapies, to enhance their efficacy. One potential application is discussed in this study, which is to use the muscle model to determine and optimize the botulinum toxin dosage per muscle, thereby improving the efficacy of the therapy.

- With the model being subject-specific, the outputs from the muscle model may also be used for a more patient-specific treatment or therapy, as studies [7][8][9] have indicated the importance of a patient-specific approach in managing neurological disorders more effectively. Therefore, the muscle model may be considered a first

step in providing an individualized analysis and treatment for neurological disorders.

6.2 Novel Contributions

To highlight the study's contributions, this section summarizes the novel contributions of the thesis and how the objectives mentioned in the Section 1.8 were achieved. The novel contributions of work described in the thesis are as follows:

Development of robot-based tools to evaluate SMI and SMC impairments in PD Patients: While there are several assessment tools available for evaluating the cardinal motor symptoms in PD, there is a lack of assessment tools to explicitly evaluate the SMI and SMC impairments caused due to PD. With impairments in SMI and SMC functions possibly contributing to the motor, sensory and cognitive deficits in PD patients, there is a need for an efficient and accurate method to assess SMI and SMC functions. Therefore, in the work described in this thesis, a set of robot-based assessment tasks were developed to evaluate SMI and SMC functions. Further, a neural network model was designed to analyze PD patients' performance, which indicated that the abnormalities in SMI and SMC functions were seen more commonly across PD patients, thereby validating the hypothesis mentioned in Section 1.7. So far, PD has been considered a heterogeneous disease since the symptoms presented by the disease vary from one patient to another. However, our findings may suggest that despite the heterogeneous nature of the disease, there may be some aspects of PD that are common across multiple patients such as impairments in SMI and SMC. As such, these abnormalities in SMI and SMC may also be considered a potential biomarker for early detection of the disease. Therefore, in addition to these tools being used to evaluate SMI and SMC functions to facilitate better understanding of the disease, they may also assist in an early diagnosis of the disease by detecting abnormalities in SMI and SMC at an early stage.

Characterization of SMI deficits in PD patients: In the PD literature, the impact of PD on SMI has been somewhat unclear. An understanding of how PD affects the SMI process is necessary to understand how an impairment in SMI contributes to perceptual deficits and how it can be treated through targeted therapies. Therefore, there is a need to characterize

SMI impairments in PD patients before a treatment protocol can be designed to target these impairments. In this thesis, using the robot-based tasks, SMI impairments caused due to PD were characterized. The findings show that the PD negatively affects SMI functions, especially the ability to integrate inputs from multiple modalities. To quantify and characterize the impairments, the patients were also tested under different sensory conditions. Therefore, in addition to the novel contribution of characterizing SMI deficits in PD patients, the results provide insights as to how rehabilitation therapies may be structured taking into account the SMI impairments.

Characterization of SMC deficits in PD patients: SMC functionalities such as movement planning and online error correction are critical to performing any motor movements. As such, it is vital to understand how PD may affect these abilities. While there are some studies that explore the impact of PD on SMC. As mentioned in Section 1.5.6, there are several limitations that needed to be addressed to obtain a more comprehensive understanding of SMC impairments in PD patients. To this end, in our study, an obstacle avoidance task was used to assess SMC functions under varying cognitive loads. The study's results are useful in characterizing SMC impairments in PD patients. Apart from this contribution, another novelty in our assessment of SMC functions is that each domain (motor, sensory and cognitive) associated with SMC was evaluated individually. This sheds light on how PD may impact different domains in SMC differently. Further, multiple SMC-based computational models were also used to better understand SMC impairments in PD patients and the metrics associated with these computational models may also be used to target specific aspects of SMC through rehabilitation therapies. So far, to the best of our knowledge, no study has evaluated SMC functions in PD patients from the perspective of using computational models.

Understanding the effect of medication on SMI and SMC: The effect of medication on perception and cognition has long been mixed and to some extent controversial. Therefore, understanding the effects of medication on SMI/ SMC which may contribute to deficits in perception and executive functions was necessary to ensure better treatment optimization. One of the novel contributions of the thesis is that the effect of dopaminergic medication on SMI and SMC was explored using the robot-based tasks. The findings revealed that

while medication improved motor features such as speed, the medication also adversely affected certain aspects of SMI/SMC functions, especially sensory and cognitive functions. These findings need to be taken into account during treatment optimization as deterioration of sensory and cognitive functions may have detrimental effects on PD patients' quality of life.

Development of patient-specific musculoskeletal model: The final contribution of the thesis was the development of a novel patient-specific muscle model, which is more detailed and accurate than earlier models. The muscle model has been validated using sEMG. However, unlike the sEMG, the developed model can also estimate activity of deep muscles and calculate the relative contributions of individual muscles. The muscle model was developed as a tool to explore and study SMC functions such as muscle recruitment strategies and how these strategies may be impacted by PD. Further, the muscle model may also be used as a guiding tool to improve efficacy of the targeted therapies. As such, one application of the model (improving the efficacy of botulinum toxin injections using the muscle model) was also explored. This provides new insights into how technology-driven tools may be used in a clinical environment to improve the efficiency of treatment.

6.3 Future Work

The findings from the study reported in this thesis provide valuable insights into SMI and SMC impairments in PD and how to manage them better. However, the thesis does not explore all areas of PD, and these gaps in our understanding need to be addressed through future work. The following are the few areas of future work.

Discussing the task design and experimental setup, one direction for future work may be to explore and understand the nature of certain perceptual deficits, such as the scaling of sensory inputs [10] or sensory overload, reported in PD patients. An altered threshold for force perception was also found in this thesis; however, the extent of this alteration is yet unknown. Fully understanding the extent and nature of the perceptual abnormalities would enable us to design targeted treatments and optimize the existing therapies. While the thesis studied the effect of sensory cues on PD patients, it did not investigate how a change in sensory cues may affect the motor performance of PD patients.

Exploring the relationship between the intensity and nature of sensory cues with movement expression may help determine the optimal sensory environment for rehabilitation programs to enhance therapeutic efficacy. Further, when providing ASC, inputs from multiple modalities (visual, haptic, and auditory) were provided to assess the impact of multi-modal inputs on motor performance. In future studies, it may be beneficial to understand how inputs from dual modalities (visual and haptic or visual and auditory) rather than multiple modalities may influence movement patterns. This would help to determine which modality is most effective in guiding the participants and improving their performance. Future work may also focus on understanding how the order in which the assessments are conducted affects the results of the assessments. In this study, the OFF-ON testing was conducted such that the PD patients were first assessed in their OFF state and then later assessed in their ON state, which has been the common practice for OFF-ON testing even in earlier studies [11][12][13]. However, it may be beneficial to repeat these experiments in the reverse order, i.e., testing the patients in the ON state and then in the OFF state. This would help understand if the order in which the assessment was conducted may have influenced the results of the experiment. Additionally, the impact of fatigue on the performance of the patients in assessment tasks also needs to be further explored. Earlier studies [14][15] have mentioned that the fatigue due to extended physical work may be a common problem in PD patients. Future work may focus on how to tackle this limitation and take into account the fatigue factor when assessing a PD patient's condition.

Moving to feature design and extraction, the thesis compares the performance of SMI and SMC from the perspective of computational models, which provides valuable information as to how PD alters the CNS criteria. However, it needs to be stated that although the computational models discussed in this thesis do a fine job of describing and hypothesizing the criteria used by the CNS in SMI and SMC, there is still no validated and clinically accepted model to explain the functioning of SMI, SMC, and the associated brain computations. More work is needed to understand the criteria used by the CNS in vital processes such as multi-sensory integration, movement planning, and error correction. This may shed light on how PD alters these functions from the perspective of the CNS criteria, and this knowledge can then be used to better target the deficits. This study investigated

domain-specific SMC impairments by using features primarily influenced by a specific domain (motor, sensory, and cognitive). Features were classified into motor, sensory, and cognitive to analyze domain-specific impairments. The feature classification is justified through earlier literature and validated through correlation with the clinical scales. While this classifying of features based on domain has not been done before and provided us with useful information, there is a possibility of minor domain overlap, i.e., features assigned to assess a specific domain may, to a small extent, be influenced by other domains. This is one of the limitations of the study. However, it is essential that various aspects of SMC need to be analyzed separately, considering the diverse nature of the disease. Therefore, future work could focus on better validating these domain-specific features and designing more in-depth features to evaluate the motor, sensory, and cognitive domains of SMC. To analyze motor learning, a trial-by-trial analysis was performed to understand if the difference between the groups reduced over time. It was taken that the target group (PD-OFF or PD-ON) was able to learn if the difference between the target group and controls reduced over time. However, if the learning rate for the two groups involved in the trial-by-trial analysis remained the same, there may not be any reduction in the difference between the performance of the two groups. Future work can focus on an in-depth study of motor learning skills in PD patients. Finally, as mentioned earlier, the robotic tools and features designed in this study may be improved to monitor and manage the symptoms of PD. The robotic and simulation tools developed in the study lay a foundation for a detailed and objective analysis of the symptoms and an equally efficient technology-driven technique to design patient-specific treatment strategies. With the advancements in robotics, virtual reality, and machine learning, future work may focus on developing more sophisticated methods and refining the tools developed in this thesis to increase the diagnostic range and management capabilities. Developing and refining technology-driven solutions for an earlier diagnosis and improved disease management may, in the long run, enable us to employ these technologies in a clinical setting. However, this is a long-term goal as considerable effort is needed from the research community to design and validate these devices.

Focusing on early diagnosis of PD, the thesis has developed neural network models that can detect abnormal SMI/ SMC functions and classify participants based on their SMI/

SMC characteristics. Future work could focus on recruiting participants who have high risk of developing PD [16] [17] [18] [19], and determine if the neural network models can detect any abnormal SMI/ SMC functions in these participants. This may make it possible to use the neural network model as a platform for early diagnosis of PD and in considering SMI/ SMC characteristics as a potential biomarker for PD. Finally, as indicated earlier, the robotics task developed in this study only assessed a few aspects of SMI and SMC functions and the neural network model is only trained on features representing limited SMI and SMC behavior. Improving and increasing the number of assessment tasks that consider a wider range of SMI/ SMC functions, and using features from these tasks to update or retrain the neural network models would enable the models to detect a large class of abnormalities in SMI/ SMC functions. This is also one of the reasons why the use of a neural network was chosen as a preferred machine learning algorithm since it allows for incremental and transfer learning. The performance of the neural network can be improved and/or generalized by including new features that represent a wider spectrum of SMI and SMC functions.

6.4 Conclusion

This thesis focused on developing tools to characterize SMI and SMC impairments that contribute to perceptual and motor abnormalities. Furthermore, the objective tool was also used to study the effects of medication on SMI and SMC impairments. The PD patients were tested under varying sensory conditions to explore how the disease may alter the SMI functions and their ability to adapt to a dynamic sensory environment. The findings showed a substantial deterioration in multi-sensory integration, although the patients could improve their performance over time. However, the medication appears to have worsened the SMI deficits. With regard to the findings from the SMC investigation, the patients were tested using an obstacle avoidance task necessitating varying degrees of cognitive resources to complete the task. The study explored multiple domains associated with SMC functions, which assisted in characterizing the domain-specific impairments associated with SMC. Furthermore, existing computational models were used to evaluate the performance of PD patients. The results indicated that the PD patients suffered significant SMC impairments, affecting their voluntary movements. The medication worsened the impairments associated

with sensory and cognitive domains of the SMC function, especially in cognitively demanding tasks. Further, the ability to perform reaching movements, smooth continuous movements as necessitated by tracing tasks, and the skill to avoid obstacles as necessitated by obstacle avoidance tasks are essential components in performing numerous activities of daily living. Therefore, the results from the study may also be generalized to explain the performance of PD patients in everyday tasks under dynamic sensory and cognitive conditions. Finally, a muscle model was developed and validated to examine the muscle recruitment patterns, an essential component of the SMC function. The proposed model may be used to better target and guide PD-related therapies, which in turn may improve the efficacy of the treatments; a potential application of the proposed model to improve the benefits of targeted therapy was also discussed. In addition to these tools being used in a research capacity to expand our knowledge, the potential for the robotic task, metrics, and muscle model to be used in a clinical environment in conjunction with existing diagnostic and management tools has been discussed. With SMI and SMC impairments contributing to non-motor symptoms that severely affect a PD patient's quality of life, a patient-specific tool described in this study to assess these impairments under varying sensory and cognitive conditions may assist clinicians in better evaluating and targeting non-motor deficits through systematic treatments. Furthermore, considering that the non-motor deficits are presented much earlier in the disease, making them a promising biomarker for earlier diagnosis, an objective tool to assess the contributors to non-motor deficits may also be beneficial as a diagnostic tool. With the global rise in the prevalence of PD, placing the healthcare system under stress, there is a need for an early diagnosis and a more targeted treatment to provide an efficient quality of care, thereby reducing the burden on medical responses. We hope that the tools used in this thesis may be improved upon further to complement the existing subjective scales to better diagnose and manage the disease, thereby improving a PD patient's quality of life.

The results of this thesis are significant considering the unmet need to better understand non-motor symptoms, such as perceptual or cognitive abnormalities, and examine these impairments through an objective analysis. The findings from the study inform us about the factors contributing to perceptual and cognitive abnormalities, enabling us to target these deficits through systematic and patient-specific treatment protocols.

Furthermore, the study also explores the effect of dopaminergic medication on SMI and SMC, which is useful for optimizing therapeutic interventions. Finally, in addition to investigating SMI and SMC, the study also developed robotic and simulation tools that may be improved upon and used in conjunction with clinical scales to better analyze, diagnose, and treat PD.

6.5 References

[1] M. Bernardinis, S. F. Atashzar, M. S. Jog, and R. V. Patel, "Differential Temporal Perception Abilities in Parkinson's Disease Patients Based on Timing Magnitude," *Sci Rep*, vol. 9, no. 1, p. 19638, Dec. 2019, doi: 10.1038/s41598-019-55827-y.

[2] N. Patel, J. Jankovic, and M. Hallett, "Sensory aspects of movement disorders," *The Lancet Neurology*. 2014. doi: 10.1016/S1474-4422(13)70213-8.

[3] P. C. Poortvliet, K. O'Maley, P. A. Silburn, and G. D. Mellick, "Perspective: Current Pitfalls in the Search for Future Treatments and Prevention of Parkinson's Disease," *Front Neurol*, vol. 11, Jul. 2020, doi: 10.3389/fneur.2020.00686.

[4] J. Kulisevsky, A. Avila, M. Barbanoj, R. Antonijoan, M. L. Berthier, and A. Gironell, "Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels," *Brain*, 1996, doi: 10.1093/brain/119.6.2121.

[5] L. Bosmans *et al.*, "Sensitivity of predicted muscle forces during gait to anatomical variability in musculotendon geometry," *J Biomech*, vol. 48, no. 10, Jul. 2015, doi: 10.1016/j.jbiomech.2015.02.052.

[6] R. Akhundov *et al.*, "Is subject-specific musculoskeletal modelling worth the extra effort or is generic modelling worth the shortcut?," *PLoS One*, vol. 17, no. 1, p. e0262936, Jan. 2022, doi: 10.1371/journal.pone.0262936.

[7] S. O. Mittal, D. Machado, D. Richardson, D. Dubey, and B. Jabbari, "Botulinum Toxin in Parkinson Disease Tremor: A Randomized, Double-Blind, Placebo-Controlled Study With a Customized Injection Approach," *Mayo Clin Proc*, 2017, doi: 10.1016/j.mayocp.2017.06.010.

[8] O. Samotus, J. Lee, and M. Jog, "Personalized Bilateral Upper Limb Essential Tremor Therapy with Botulinum Toxin Using Kinematics," *Toxins (Basel)*, vol. 11, no. 2, p. 125, Feb. 2019, doi: 10.3390/toxins11020125.

[9] G. Abbruzzese, R. Marchese, L. Avanzino, and E. Pelosin, "Rehabilitation for Parkinson's disease: Current outlook and future challenges," *Parkinsonism Relat Disord*, 2016, doi: 10.1016/j.parkreldis.2015.09.005.

[10] M. Demirci, S. Grill, L. McShane, and M. Hallett, "A mismatch between kinesthetic and visual perception in Parkinson's disease," *Ann Neurol*, vol. 41, no. 6, pp. 781–788, Jun. 1997, doi: 10.1002/ana.410410614.

[11] U. Castiello, K. M. B. Bennett, C. Bonfiglioli, and R. F. Peppard, "The reach-to-grasp movement in Parkinson's disease before and after dopaminergic medication," *Neuropsychologia*, vol. 38, no. 1, pp. 46–59, Jan. 2000, doi: 10.1016/S0028-3932(99)00049-4.

[12] P. O'Suilleabhain, J. Bullard, and R. B. Dewey, "Proprioception in Parkinson's disease is acutely depressed by dopaminergic medications," *J Neurol Neurosurg Psychiatry*, 2001, doi: 10.1136/jnnp.71.5.607.

[13] J. A. Robichaud, K. D. Pfann, C. L. Comella, and D. M. Corcos, "Effect of medication on EMG patterns in individuals with Parkinson's disease," *Movement Disorders*, vol. 17, no. 5, pp. 950–960, Sep. 2002, doi: 10.1002/mds.10218.

[14] J. H. Friedman *et al.*, "Fatigue in Parkinson's disease: A review," *Movement Disorders*, vol. 22, no. 3, pp. 297–308, Feb. 2007, doi: 10.1002/mds.21240.

[15] K. Herlofson and B. M. Kluger, "Fatigue in Parkinson's disease," *J Neurol Sci*, vol. 374, pp. 38–41, Mar. 2017, doi: 10.1016/j.jns.2016.12.061.

[16] J. A. Driver, G. Logroscino, J. M. Gaziano, and T. Kurth, “Incidence and remaining lifetime risk of Parkinson disease in advanced age,” *Neurology*, vol. 72, no. 5, pp. 432–438, Feb. 2009, doi: 10.1212/01.wnl.0000341769.50075.bb.

[17] E. Broussolle and S. Thobois, “Genetics and environmental factors of Parkinson disease,” *Rev Neurol (Paris)*, vol. 158 Spec no 1, p. S11—23, Dec. 2002, [Online]. Available: http://europepmc.org/abstract/MED/12690660

[18] G. Hu, P. Jousilahti, A. Nissinen, R. Antikainen, M. Kivipelto, and J. Tuomilehto, “Body mass index and the risk of Parkinson disease,” *Neurology*, vol. 67, no. 11, pp. 1955–1959, Dec. 2006, doi: 10.1212/01.wnl.0000247052.18422.e5.

[19] G. E. Nam *et al.*, “Metabolic syndrome and risk of Parkinson disease: A nationwide cohort study,” *PLoS Med*, vol. 15, no. 8, p. e1002640, Aug. 2018, doi: 10.1371/journal.pmed.1002640.

Appendices

Appendix A: Ethics Approval (Protocol number: 108252)

LAWSON
HEALTH RESEARCH INSTITUTE

LAWSON FINAL APPROVAL NOTICE

LAWSON APPROVAL NUMBER: R-17-016

PROJECT TITLE: Observation of Movement Disorders using Kinematics

PRINCIPAL INVESTIGATOR: Dr. Mandar Jog

LAWSON APPROVAL DATE: Monday, 8 January 2018

Health Sciences REB#: 108252

ReDA ID: 1813

Please be advised the above project was reviewed by Lawson Administration and the project:

Was Approved

Please provide your Lawson Approval Number (R#) to the appropriate contact(s) in supporting departments (eg. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Lawson Approval Number and should be directed to Sherry Paiva, Research Approval Officer, Lawson Health Research Institute, 750 Baseline Road, East, Suite 300.

cc: Administration

Appendix B: Ethics Approval (Protocol number: 115770)

LAWSON
HEALTH RESEARCH INSTITUTE

LAWSON FINAL APPROVAL NOTICE

LAWSON APPROVAL NUMBER: R-21-151

PROJECT TITLE: STRAT-PARK: a prospective multimodal cohort study to stratify Parkinson's disease

PRINCIPAL INVESTIGATOR: Dr. Mandar Jog

LAWSON APPROVAL DATE: 23/03/2021

ReDA ID: 9885

Overall Study Status: Active

Please be advised that the above project was reviewed by Lawson Administration and the project was approved.

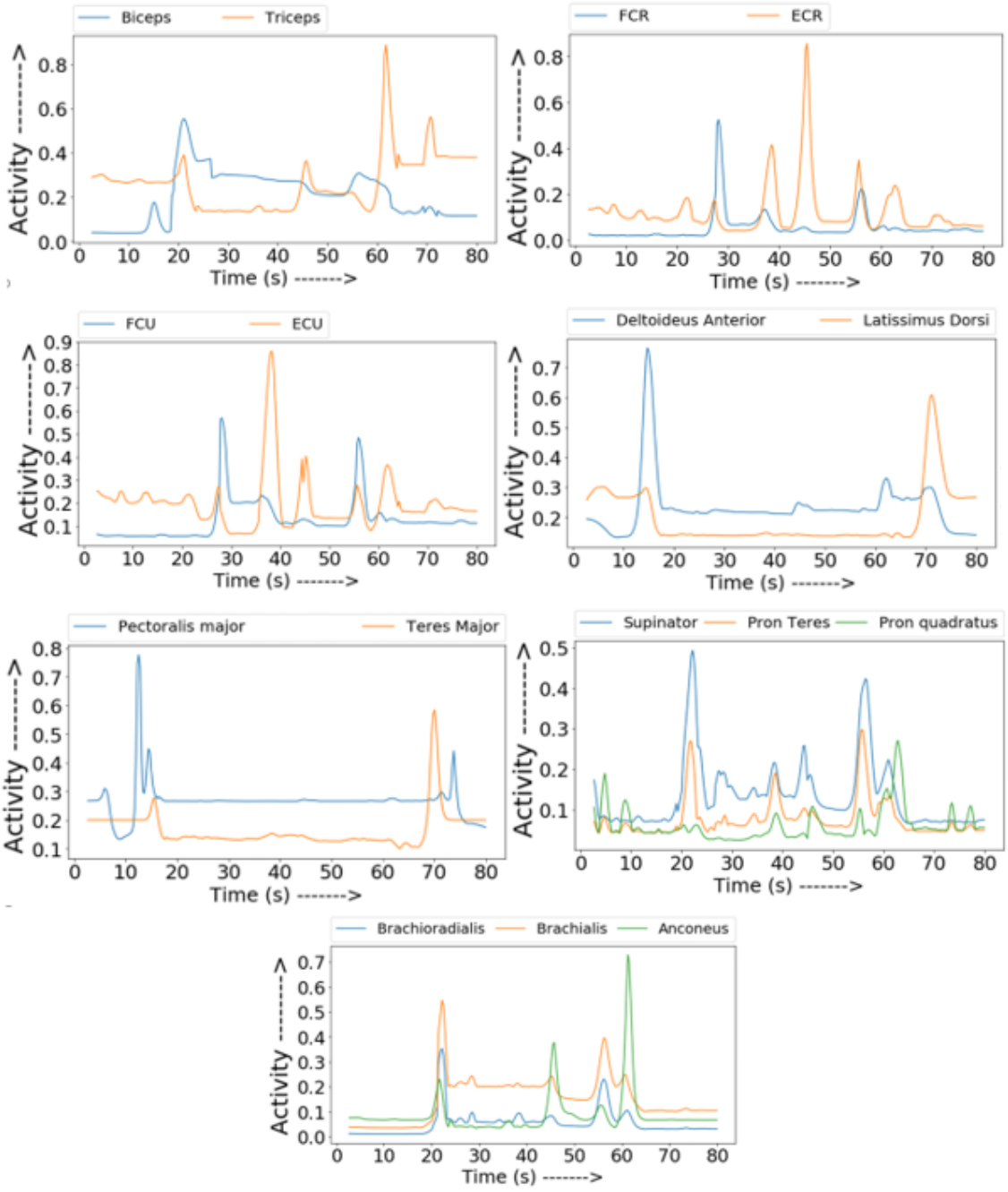
"COVID-19: Please note that Lawson is continuing to review and approve research studies. However, this does not mean the study can be implemented during the COVID-19 pandemic. Principal Investigators, in consultation with their program leader or Chair/Chief, should use their judgment and consult Lawson's research directive and guidelines to determine the appropriateness of starting the study. Compliance with hospital, Lawson, and government public health directives and participant and research team safety supersede Lawson Approval."

Please provide your Lawson Approval Number (R#) to the appropriate contact(s) in supporting departments (eg. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.

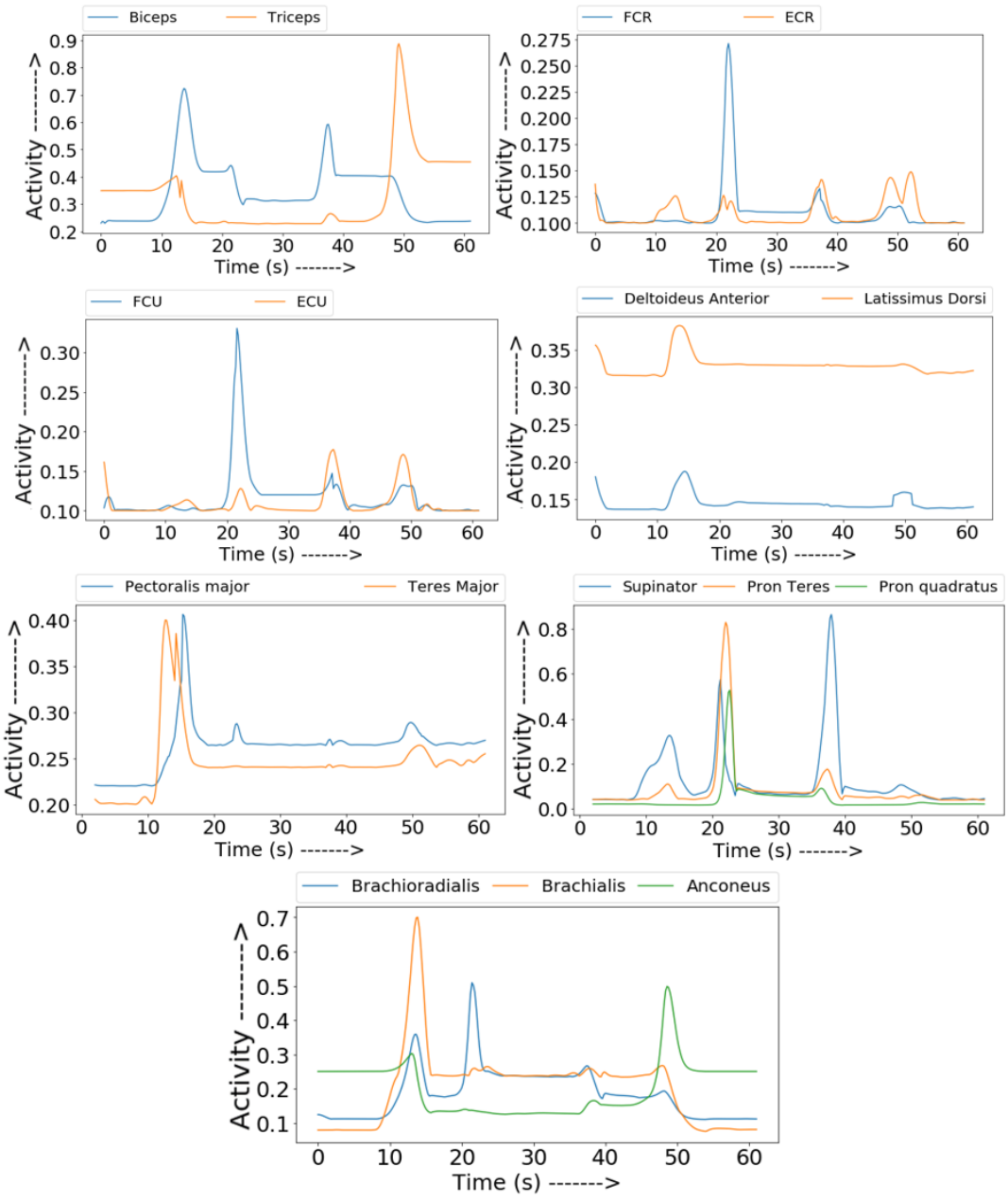
Dr. David Hill
V.P. Research
Lawson Health Research Institute

Appendix C: Mean activity predicted by the muscle model for sixteen upper-limb muscles when performing the five tasks

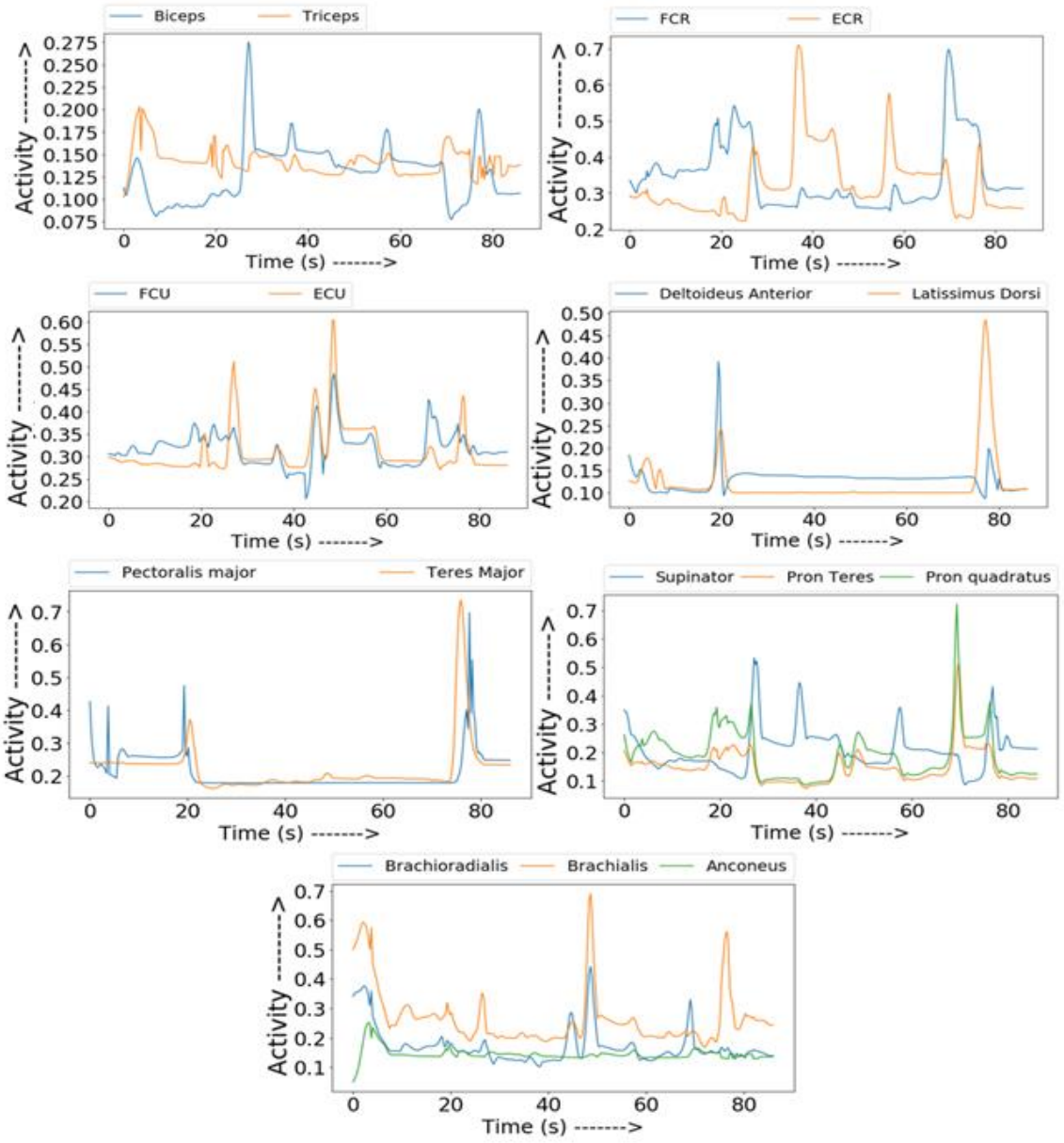
Overall muscle activity for the task - 1



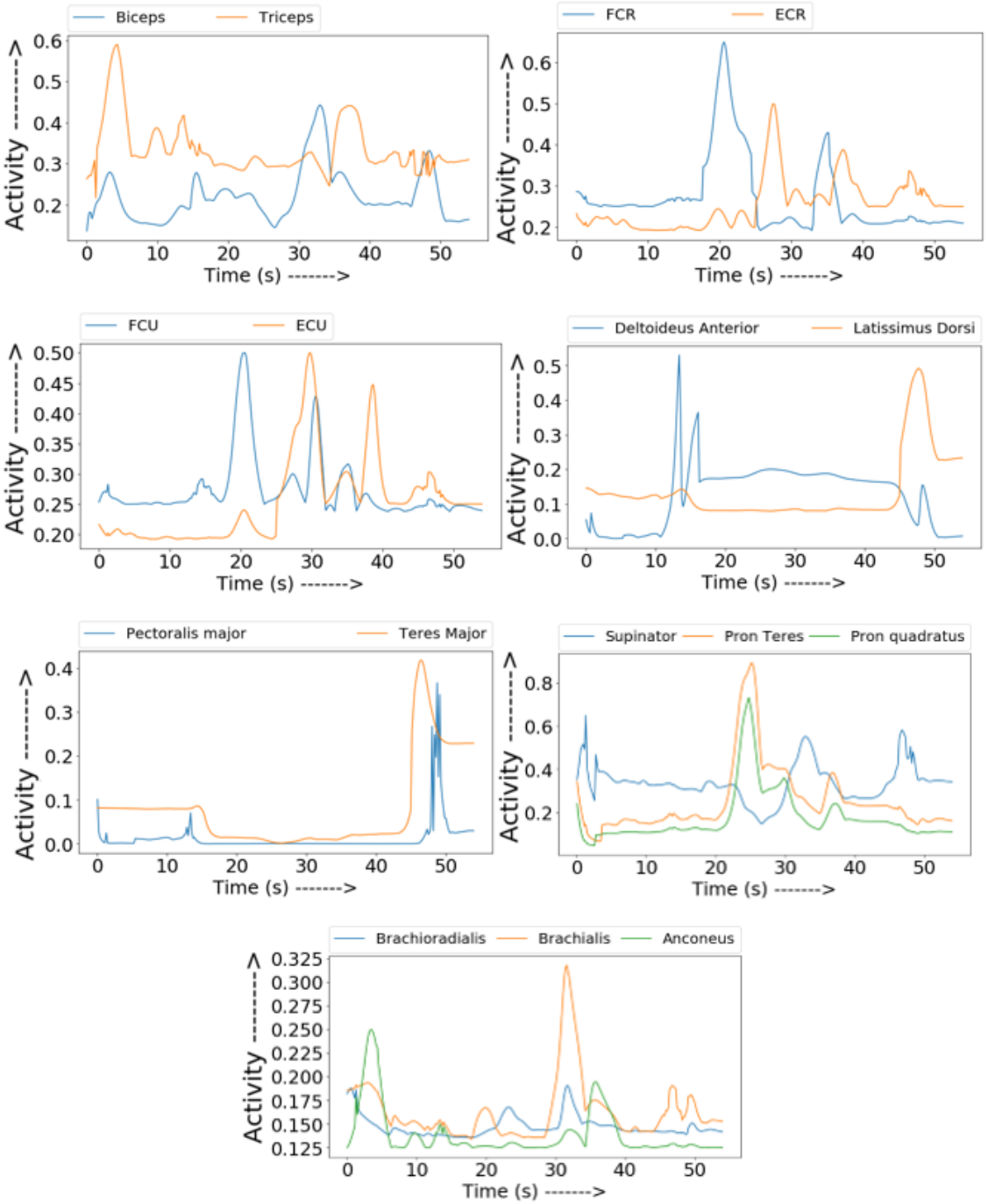
Overall muscle activity for the task - 2



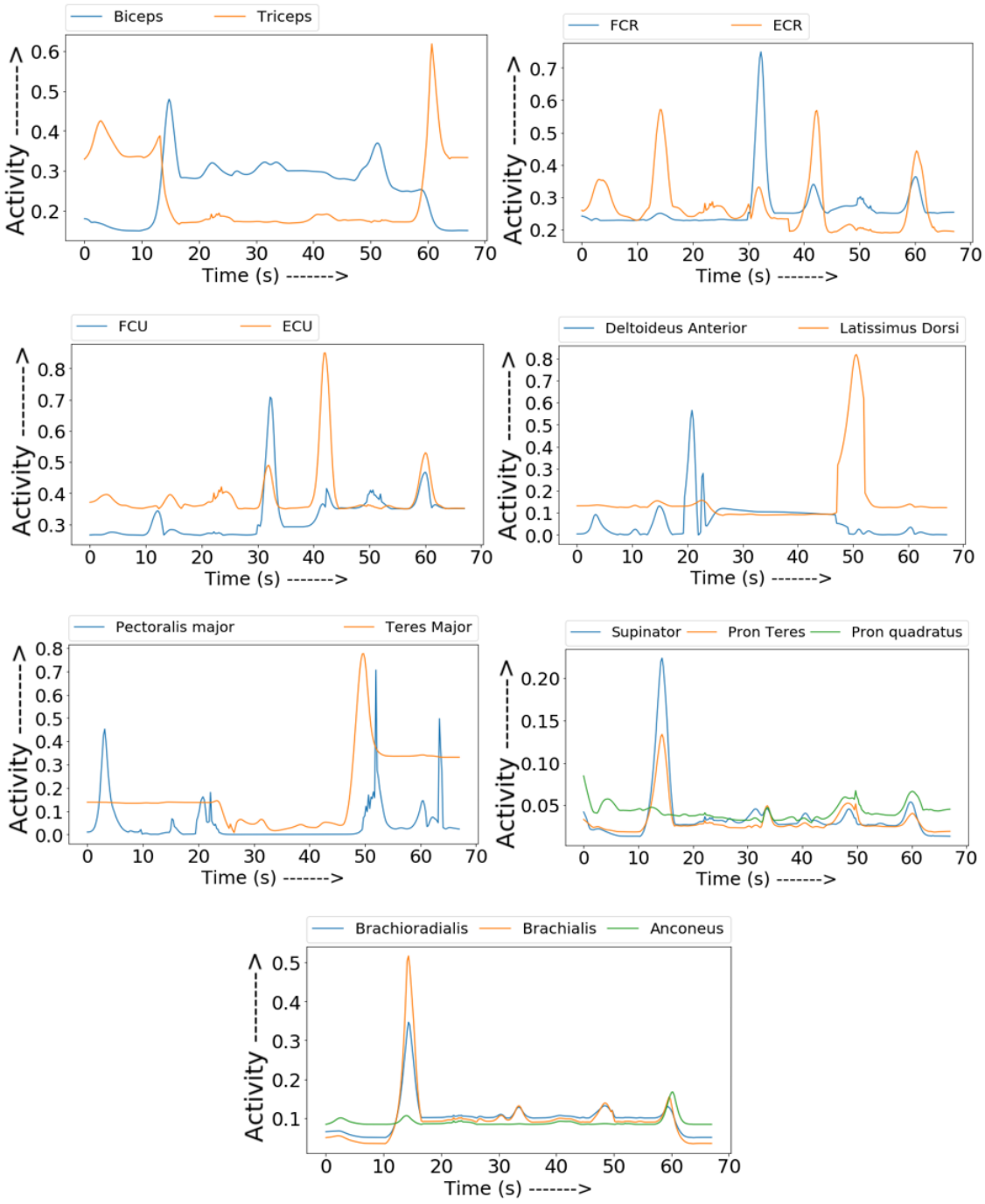
Overall muscle activity for the task - 3



Overall muscle activity for the task - 4

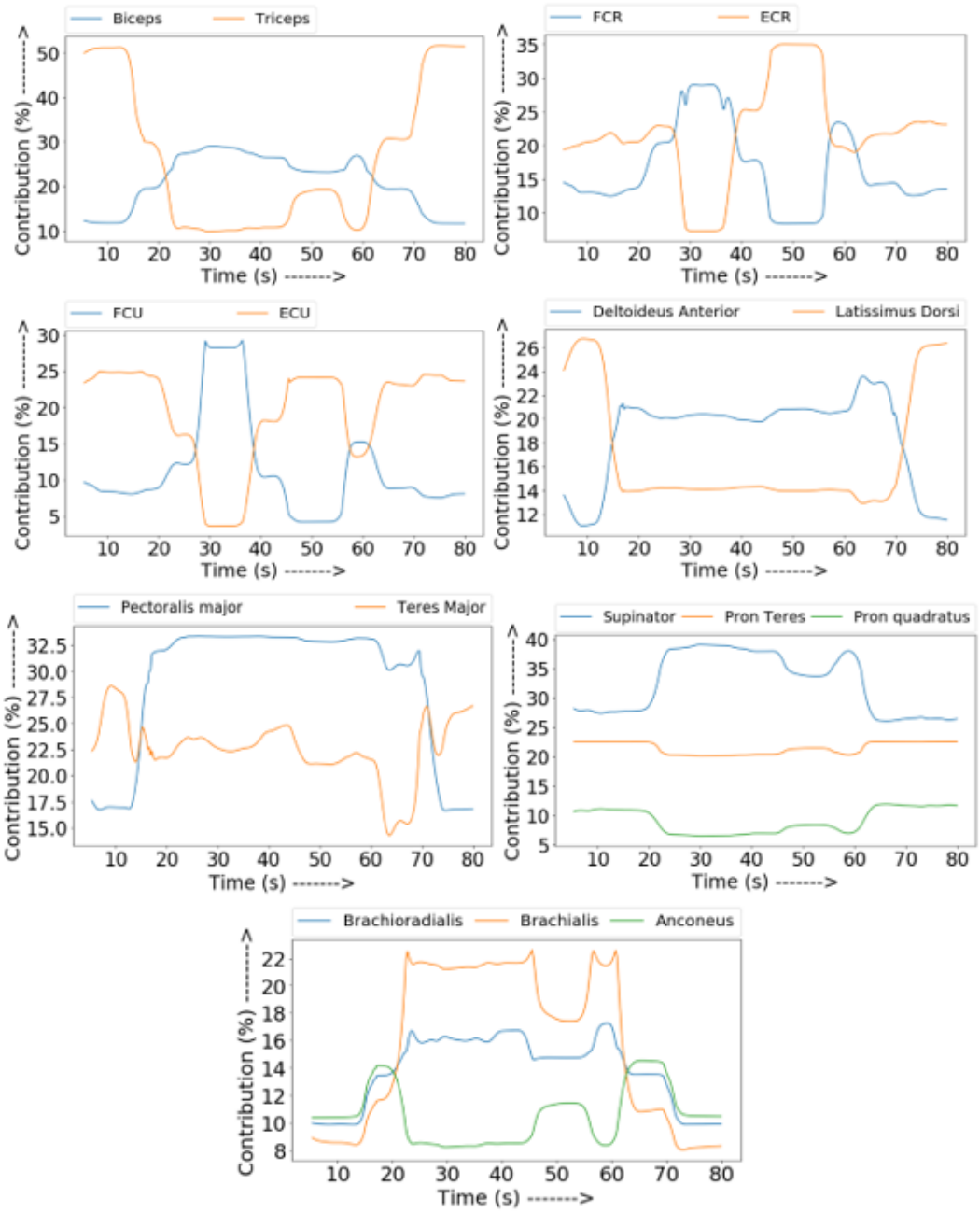


Overall muscle activity for the task - 5

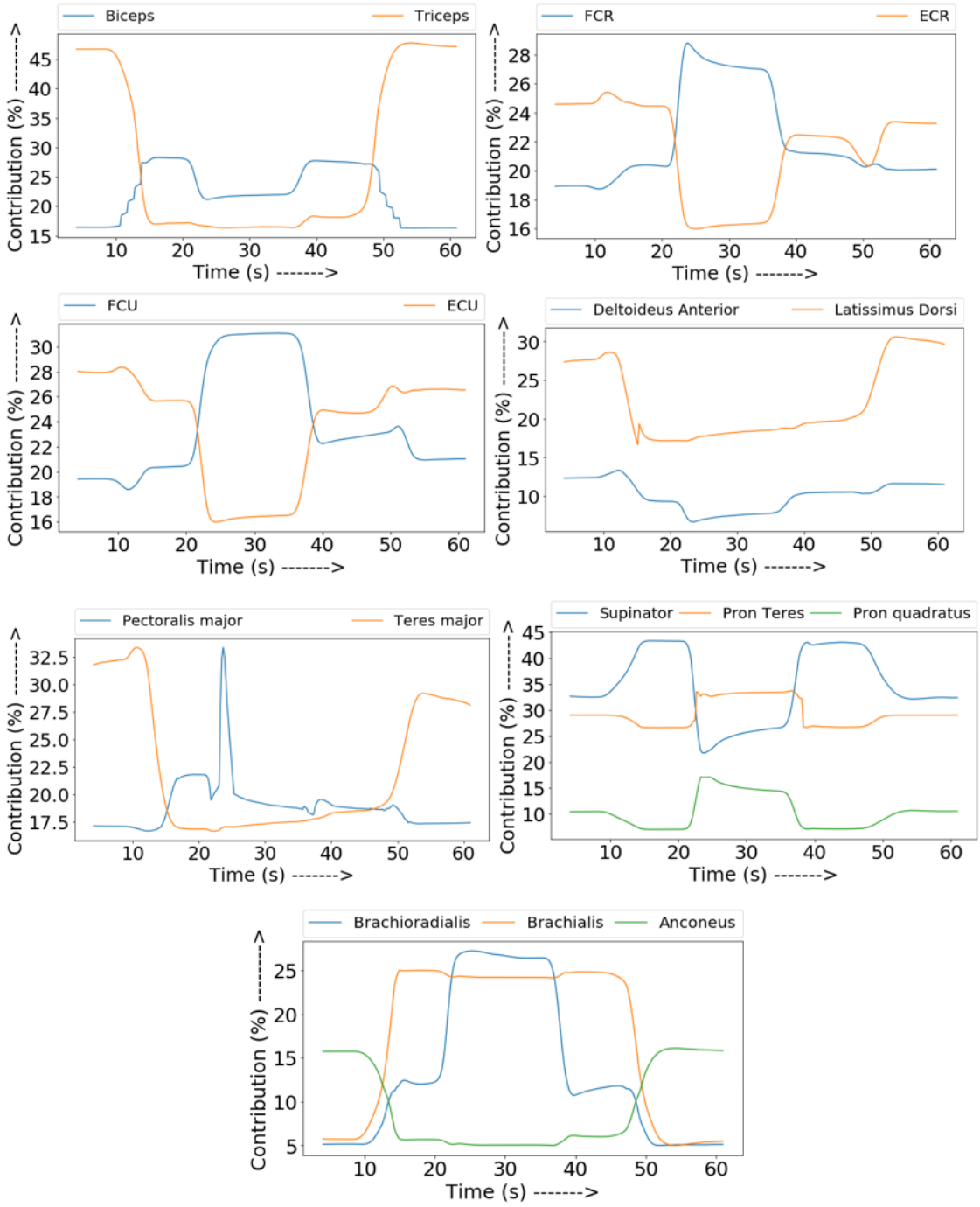


Appendix D: Mean contribution predicted by the muscle model for sixteen upper-limb muscles when performing the five tasks

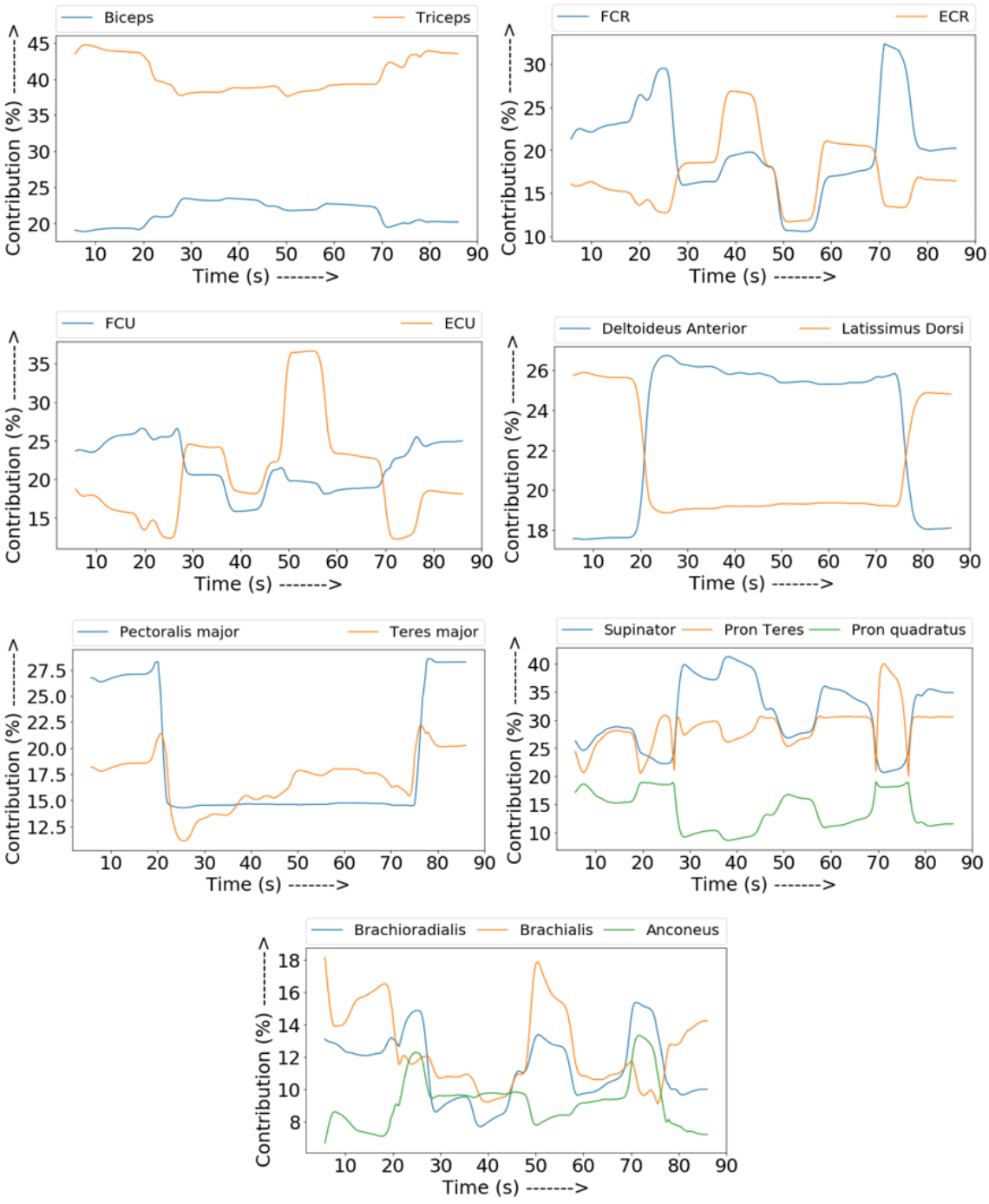
Overall muscle contribution for task - 1



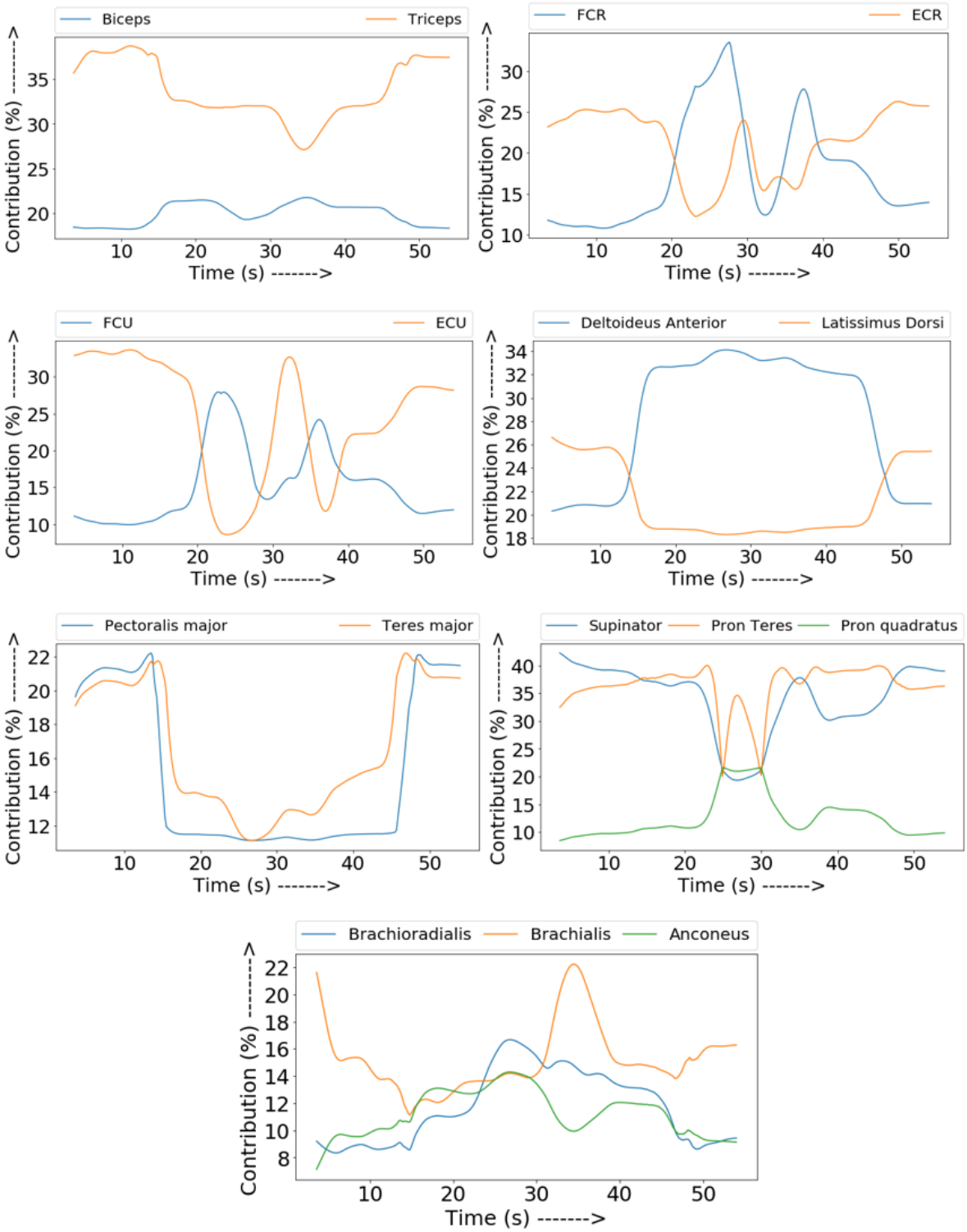
Overall muscle contribution for task - 2



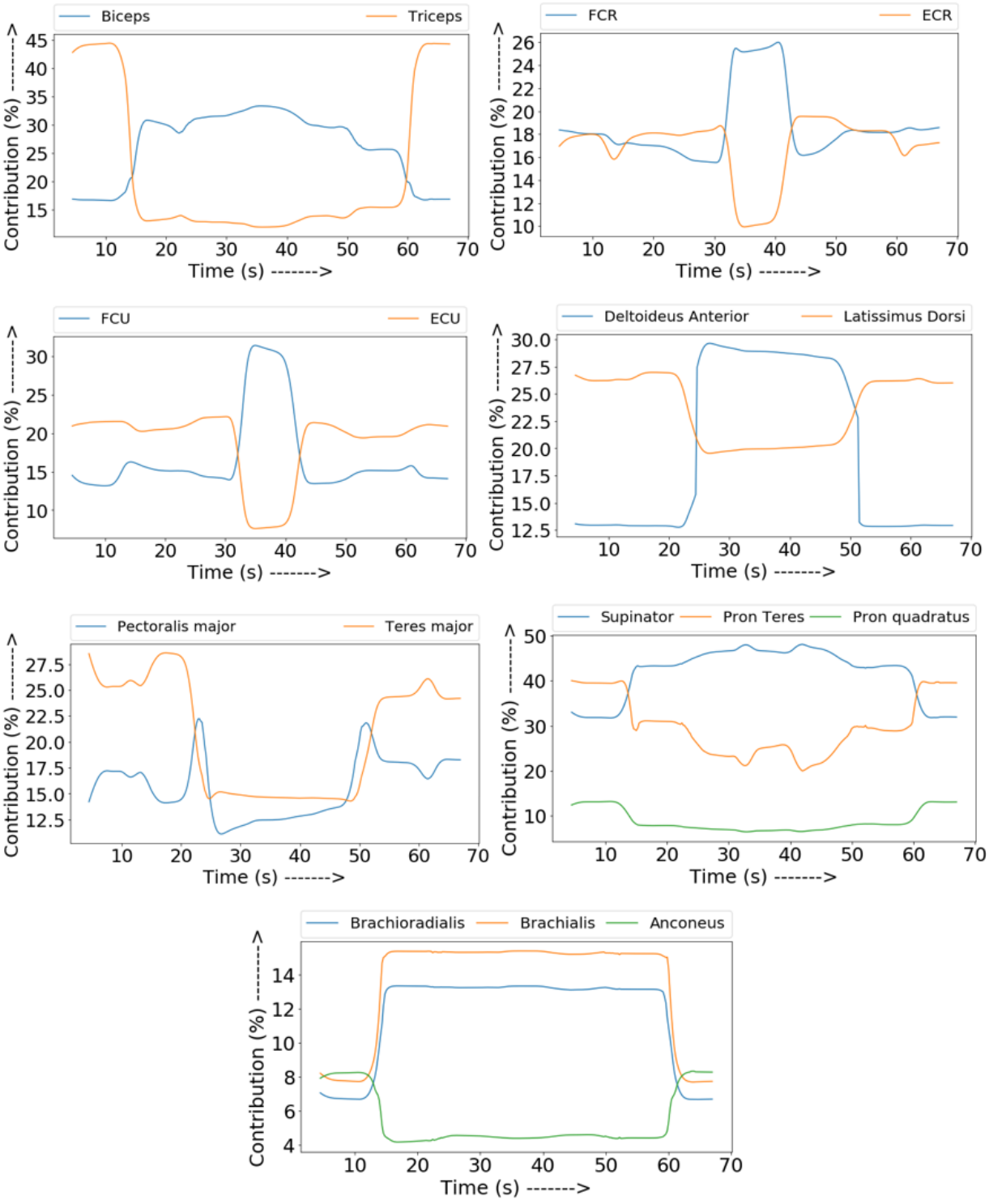
Overall muscle contribution for task - 3



Overall muscle contribution for task - 4



Overall muscle contribution for task - 5



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Y. K. Tamilselvam, M. Jog, and R. V. Patel (2023), "Robot-Assisted Investigation of Sensorimotor Control in Parkinson's Disease," *Nature Scientific Reports*, 13(1), 4751. https://doi.org/10.1038/s41598-023-31299-z

Y. K. Tamilselvam, M. S. Jog, and R. V. Patel, "Robotics-Based Characterization of Sensorimotor Integration in Parkinson's Disease and the Effect of Medication," IEEE Transactions on Neural Systems and Rehabilitation Engineering, vol. 31, pp. 3201–3211, 2023, doi: 10.1109/TNSRE.2023.3299884.