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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

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Abstract

Tremor commonly affects the upper extremities in essential tremor (ET) and Parkinson disease (PD) patients where many experience functional disability and ultimately seek therapy. As ET and PD tremor features overlap and clinical assessment is challenging due to its highly complex nature, misdiagnosis is common resulting in unsuitable therapies and prognosis. Current treatment options for ET and PD tremor include pharmacotherapy, focal therapy with botulinum toxin type A (BoNT-A) injections, and surgical interventions which provide modest relief of tremor. However, such therapies are commonly associated with significant adverse events and lack long-term efficacy and tolerability. Hence lack of standardized, objective measures of tremor and suboptimal treatment options are two significant unmet needs faced by neurologists today. The hypothesis of this thesis was to determine whether joint tremor amplitude can differentiate between ET and PD tremor types and can be applied towards improving BoNT-A tremor therapy. The first objective was to apply motion sensor kinematic technology to investigate the role of paired tasks in modulating tremor biomechanics in 24 ET and 28 PD participants. Paired tasks involved variating limb positioning while at rest, posture, and under weight-bearing conditions. Motion sensor devices were placed over the wrist, elbow and shoulder joints capturing joint angular tremor amplitude in multiple degrees of freedom (DOF). Kinematic measures of tremor allowed detailed segmentation of tremor into directional components, which cannot be performed visually. The relationship of joint tremor severity between paired tasks and across all tasks generated unique tremor profiles and provided a simple method to differentiate ET and PD tremor types. The second objective was to apply tremor kinematics to better tailor BoNT-A injection parameters. Participants were injected in the upper limb, which exhibited their most bothersome tremor, every 16 weeks, a total of 3 injection cycles, and attended follow-up visits six weeks following treatment, for a total of 6 study visits. Clinical rating scales and kinematic recordings were conducted at each visit. Dosing was based on clinician's experience and kinematic data, and muscle site of injection was determined kinematically. A significant decrease in mean clinical tremor rating scores during rest and action tasks and significant improvement in arm function was observed at week 6 and continued throughout the study in both ET and PD individuals. Ten PD participants and eight ET participants reported mild weakness in injected muscles that had no interference with arm function. Kinematic technology is a promising method for standardizing assessments and for personalizing BoNT-A therapy.

Keywords

Parkinson's disease, Essential tremor, kinematics, upper limb, biomechanics, focal therapy, botulinum toxin type A

List of Abbreviations

Abd/Add	Abduction/adduction shoulder degree of freedom
BG	Basal ganglia
BoNT-A	Botulinum toxin type A; incobotulinumtoxinA
DOF	Degree of freedom
ET	Essential tremor
F/E	Flexion/extension degree of freedom at wrist/elbow/shoulder
FTM	Fahn-Tolosa-Marin Tremor Rating Scale
L1	"Load-1" kinematic scripted task
L2	"Load-2" kinematic scripted task
MMT	Manual muscle testing
P1	"Posture-1" kinematic scripted task
P2	"Posture-2" kinematic scripted task
PD	Parkinson's disease
PIGD	Postural instability and gait disturbance
P/S	Pronation/supination degree of freedom at wrist
R1	"Rest-1" kinematic scripted task
R2	"Rest-2" kinematic scripted task
RMS	Root mean square
R/U	Radial/ulnar degree of freedom at wrist
QUEST	Quality of Life in Essential Tremor Questionnaire
UPDRS	Unified Parkinson's Disease Rating Scale

The Co-Authorship Statement

This integrated thesis contains two peer-reviewed publications, in chapters 3 and 4. Chapter 3, entitled "Functional ability improved in Essential Tremor by incobotulinumtoxinA injections using kinematically determined biomechanical patterns – A made to measure therapy" was written by Olivia Samotus *et al*. Olivia Samotus was involved in study supervision, coordination, writing and editing of the entire manuscript, analysis and interpretation of data, and statistical analysis. Fariborz Rahimi was involved in the study concept and design. Jack Lee was involved in editing of the manuscript and obtaining of funding. Mandar Jog was the senior responsible author involved in study concept and design, study supervision, editing of manuscript, and obtaining of funding.

Chapter 4, entitled "Effective management of upper limb parkinsonian tremor by botulinum toxin type A injections using sensor-based biomechanical patterns" was co-authored by Fariborz Rahimi and Olivia Samotus *et al.* Fariborz Rahimi was denoted as a co-author due to the involvement in study concept and design. Olivia Samotus was involved in study supervision and coordination, and writing and editing of the entire manuscript. Olivia was also involved in statistical analysis and interpretation of the data. Jack Lee was involved in editing of the manuscript and obtaining of funding. Mandar Jog was the senior responsible author involved in study concept and design, study supervision, editing of manuscript, and obtaining of funding.

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Preface

Tremor is the most common movement disorder encountered by clinicians today and is one of the most challenging symptoms to treat. Despite the high prevalence of tremor, limited progress has been made in treating tremor due to the relatively unclear understanding of many underlying conditions, such as PD and ET. The prevalence of ET markedly increases with age approximately affecting 6.3% globally and 14.3% in Canada of those aged > 65 years old[1] and more than 70% of PD patients have tremor as the presenting feature. As there is no standardized technique to distinguish among common tremor types, misdiagnosis rates in PD and ET are as high as one-third and hence lies a great interest in developing simple, objective techniques to distinguish such tremor types. All traditional pharmacological agents recommended for tremor therapy in PD and ET patients are approved to treat other conditions (e.g. anticonvulsants, beta-blockers) and thus produce suboptimal tremor relief coupled with significant adverse effects. A focal therapy with BoNT-A injected into tremulous muscles has shown past success in tremor relief although prominent muscle weakness has resulted in early discontinuation of therapy. This thesis demonstrates that accurate and intelligent kinematic measurement addresses the significant unmet need for more objective measures to differentiate tremor types and facilitate advances in tremor therapy.

Chapter 1 is an account of what has been published regarding upper limb tremor in PD and ET and current practices involved with tremor therapy. The aim of this thesis was to develop wearable technology that was feasible to differentiate tremor profiles and to improve focal therapy by individualization of BoNT-A injection parameters.

Chapter 2 is a report of the differentiation of ET and PD tremor types in the upper limb by weight-loading and paired task variations using angle-based kinematic technology.

Chapter 3 and 4 summarize the use of kinematic technology to measure tremor biomechanics and to enhance efficacy and tolerability of BoNT-A for ET and PD tremor. Tremor kinematic measures from each individual were utilized for muscle selection and calculating BoNT-A dosages thereby ultimately personalizing therapy.

Chapter 5 states the key findings from **Chapters 2, 3 and 4** and the concluding statements regarding the impact in the advancement of tremor therapy and future directions.

1. Introduction

1.1. Parkinson's disease: the importance of tremor and its pathogenesis

More than 10 million people worldwide suffer from a major neurodegenerative disease including Alzheimer's disease, multiple sclerosis, and PD, which is expected to grow significantly as the aging population lives longer and grows over the next few decades. Affecting 1% of the population older than 60 years, PD is a chronic, neurodegenerative disease with a broad spectrum of motor and non-motor features.[2] The prevalence of PD increases with age and is projected to continue to rise in parallel with our aging population. While the neuropathology is generally well understood, the etiology remains a mystery.

A 60-80% loss of dopaminergic neurons within the substantia nigra pars compacta (SNc) of the lateral ventral tier located in the basal ganglia (BG) and presence of Lewy bodies are significant pathological findings in PD.[2,3] A lack of dopamine producing neurons leads to dopamine depletion in the striatum, particularly in the dorsolateral putamen. Genetic mutations, mishandling of misfolded proteins ubiquitin–proteasome, the autophagy–lysosomal systems, mitochondrial dysfunction and increased oxidative stress are identified as contributing mechanisms underlying the death of dopaminergic and non-dopaminergic cells in PD.[4] Early in the disease, dopamine deficiency is the predominant neurochemical abnormality and is thought to be strongly linked to bradykinesia and rigidity, unlike the generation of tremor which remains unclear. As the disease progresses, involvement of non-dopaminergic brain regions results in levodopa (dopamine)-resistant motor and non-motor symptoms.[2] Even though the first descriptive account of PD was written in 1817 by James Parkinson, there is still an uncertain understanding of the mechanisms behind the occurrence of dopaminergic deficiencies in PD.[5] A better understanding of underlying mechanisms could help offer new possibilities for symptomatic treatments aimed to improve function and quality of life in PD patients.

PD presents in a sporadic, idiopathic fashion.[6] It is marked by primary motor symptoms of bradykinesia (slow voluntary movement), muscle rigidity and tremor often with postural instability and gait disturbance (PIGD) occurring later in the disease course. Non-motor

symptoms experienced by PD patients may include mood disorders, cognitive disorders and sleep disorders. The progression of PD and the manifestation of motor and non-motor symptoms vary considerably from patient to patient although 69% of patients reveal tremor at disease onset and 75% of patients will develop tremor during the course of their disease.[7,8] Tremor is clinically and pathologically distinctive from the other parkinsonian features. Tremor expression and severity may be associated with a genetic background and can also be associated with disease course and prognosis.[8] PD patients with a tremor-dominance show evidence of a milder disease course and a better prognosis in terms of life expectancy compared to patients with predominant PIGD symptom profiles.[8,9] The PIGD subtype has a larger annual increase in symptom severity, faster progression to Hoehn and Yahr grade 4, worse cognitive performance, and a higher degree of disability at 5 and 8 years of disease, compared to the tremor-dominant subtype.[7] Despite these differences, both PD subtypes have a similar disease duration at the time of death and thus tremor is not predictive of longer survival rates.[9] It is unclear whether resting, postural/action tremor or a combination of the two tremors best describes this tremor-dominant subtype.

Tremor pathogenesis in both PD and ET are linked with elevated activity within the cerebello-thalamo-cortical circuit. However, in PD, it is thought that dopaminergic dysfunction of the pallidum, particularly originating from the loss of dopaminergic projections from the retrorubral area, generates this increased activity.[7,9] Tremor severity is not related to the amount of dopamine deficiency in the SNc determined pathologically.[10] Anatomically, the BG and cerebellar circuits are connected. The cerebellar nuclei project glutamatergic, excitatory projections to the posterior part of the ventrolateral thalamus whereas the globus pallidus interna (GPi) within the BG projects GABAergic, inhibitory projections to the anterior part of the ventrolateral thalamus. Hence, motor cortical activity is facilitated by activity of the cerebellar outputs and inhibited by GPi outputs. In addition, the cerebellar nuclei have GABAergic, inhibitory projections to the inferior olive which sends excitatory projections to Purkinje cells in the cerebellar cortex and cerebellar nuclei.[7] BG and thalamus activity are synchronous with tremor, though the region in which this occurs varies. High synchronous activity with tremor has been found in posterior ventrolateral thalamus

neurons.[11] These findings propose that the driving force of rest tremor is not within the BG but is from the posterior ventrolateral thalamus.[12] A metabolic imaging study using positron emission tomography (PET) outlined the sensorimotor cortex, rostral cerebellum, dentate nucleus, and putamen regions synchronous with tremor, which correlated with clinical tremor scores, in those with the tremor-dominant subtype.[13] In 2011, Mure and colleagues reported that posterior ventrolateral stimulation reduced tremor amplitude and reduced the metabolic activity in both the cortico-cerebellar circuit and within the BG suggesting a relationship to tremor severity and a convergence in the motor cortex.[13] Currently, there are three hypotheses regarding the cause of PD resting tremor: the thalamic pacemaker hypothesis, the basal ganglia pacemaker hypothesis, and the dimmer-switch hypothesis.[7,9]

The basis of the thalamic pacemaker hypothesis originates from studies observing the intrinsic biophysical properties of guinea pig thalamic neurons which are single cell oscillators at distinct frequencies, 9-10 Hz and 4-6 Hz, when neurons are slightly depolarized producing low-threshold calcium spikes (LTS) or hyperpolarized, respectively.[7] These frequency ranges within the ventrolateral thalamus are similar to the frequency of PD tremor and the presence of LTS in the thalamus was also identified in PD patients. However, the presence of LTS may not be tremor-related as LTS was observed in both PD subtypes and tremor-dominant patients exhibited "tremor-locked bursts" without LTS. In contrast, "tremor-locked bursts" may be formed by LTS in the thalamocortical circuit.[14] It is thought that LTS may be generated by the increased inhibitory activity from the GPi to the thalamus which would suggest tremor production occurs in the anterior ventrolateral thalamus.[14] This hypothesis contrasts the effect of tremor suppression by targeting the posterior ventrolateral thalamus with deep brain stimulation (DBS). As there may be other brain regions that hyperpolarize thalamic neurons, this hypothesis does not explain why stimulating the BG reduces tremor. The advantage of this model is that it illustrates the fundamental role of the posterior ventrolateral thalamus.

The BG pacemaker hypothesis identifies the BG as the area of excessive synchronization which results in tremor. This hypothesis proposes that striatal inhibition of globus pallidus externa (GPe) neurons and the excitatory subthalamic nucleus (STN) generate the pacemaker by forming a feedback system that engages in synchronized bursting.[7,15] Previously described with in vitro data, the frequency of BG oscillations is between 0.4 and 1.8 Hz, which is lower than the associated frequency ranges of PD tremor.[7] A computational model demonstrated that STN and GPe are prone to LTS bursts due to the increased feedback of the dopamine depleted BG circuitry. This model definably explains the role of dopamine depletion within the BG but fails to elucidate the causal role of tremorgenesis by the cerebellothalamocortical circuit.

The dimmer-switch hypothesis is based on imaging studies in tremor-dominant and non-tremor PD patients and suggests that the BG triggers tremor episodes and the cerebellothalamocortical circuit modulates tremor amplitude. Data indicates that dopamine depletion in the pallidum correlates with tremor severity and that the tremor-dominant subtype has increased functional connectivity between the BG and the cerebellothalamocortical circuit. This model explains why DBS in the BG (GPi or STN) or in the ventrolateral thalamus can suppress tremor. [7]

1.1.1. Classification of PD tremor

Tremor is an involuntary, rhythmic movement affecting one or more body parts but most commonly affects the upper limbs and hands. Tremor varies depending on the circumstances under which they occur. PD patients with tremor can demonstrate different types of tremor: at rest, with posture, action/kinetic or orthostatic. Typical PD tremor is observed unilaterally or asymmetrically in the upper limb at rest, while the body part is completely supported by gravity, with a frequency between 4 and 6 Hz. However, in more advanced disease, tremor may appear bilaterally in the upper limbs. Approximately 34-60% of PD patients may also present with a tremor produced by a voluntary contraction called a postural tremor, when arms are outstretched in front of the chest.[16] Kinetic tremor occurs during any voluntary

movement including non-target directed and intention tremor where the amplitude increases towards the target. Postural and action tremors are typically delayed compared to ET, and is described as a re-emergent tremor (with a mean delay of ±10 seconds);[16] tremor frequency is higher than 1.5 Hz and is within a similar frequency range as a resting tremor.[16] As the frequency of resting and re-emergent tremors is similar, this suggests that both tremors originate from similar pathophysiological processes. Aside from tremor in the arms, patients may exhibit rest tremor in the lips, jaw or in the lower extremities.

Isolated postural and action tremors can occur in PD with a frequency varying between 4 and 9 Hz.[9] Postural tremor without parkinsonian features is often diagnosed as ET and is observed more frequently in those patients with a family history of PD.[16] Some PD patients have postural tremor similar to ET for many years before the onset of PD features suggesting that ET is a potential risk factor for PD.[4] Orthostatic tremor, a position-dependent postural tremor, can be isolated or co-exist with resting tremor with different frequency ranges (4-6, 8-9 or 13-18 Hz) and responds to dopaminergic treatment suggesting that it is a manifestation of PD rather than an association of ET and PD tremor types.[9] In some cases, postural and kinetic tremors can be more disabling than rest tremor and may present as an initial symptom prior to diagnosis.[4]

Tremor is a unique symptom of PD in that the rate of tremor progression and severity is unlike the other PD symptoms such as bradykinesia, rigidity, balance and gait. Tremor is complex to visually assess and the manifestations of tremor can challenge proper diagnosis and ultimate prognosis triggering high misdiagnosis rates when using the current classification system by the Movement Disorders Society (MDS).[17]

1.1.2. Current treatments of PD tremor

Investigations into understanding the pathogenesis of PD and providing new insights into the mechanism of cell death, connectivity of the BG, epidemiology, genetics, pharmacology and

neurosurgery has driven the focus of scientific advancement. While some of these advances are translating novel therapeutics into clinical practice, true pathogenesis targeted treatments are still lacking. This may be in part due to the need for better animal models that can better mimic the progression of the disease. There is a lack of success for neuroprotective strategies due to the scarce understanding of the various genetic, environmental, and other mechanisms contributing to neurodegeneration in PD. Efficacy of therapeutics is tested using evidence-based medicine designed to control for placebo effects. However, there are limitations to placebo-controlled randomized trials due to the inhomogeneous population of included patients, the short-term nature of these studies and specified patient demographics, which is not representative of clinical practice. This leads many physicians to rely on their own experience and best clinical judgement in selecting the optimal treatment option and for the therapeutic plans with patients.

Various treatment options are available to alleviate symptoms associated with PD. First line therapy is the use of oral pharmacological agents while surgical intervention is generally reserved for drug refractory PD. Generally, initiation of therapy is often delayed until symptoms are functionally disabling and interfere with activities of daily living (ADLs) or the patient's vocation.[18] Choice in therapeutics heavily depends on the patient's age, dominant symptoms, disease stage and cognitive state. Treatments are titrated and adjusted to changes in patient symptomatologies. Approximately 10% of patients are selected for surgical therapies.[6]

1.1.2.1. Pharmacotherapy agents

Pharmacological treatments seek to correct the imbalance within the BG due to the loss of dopamine producing neurons. There are many classes of dopamine replacement medications that ultimately seek to alleviate motor impairments in PD.

If motor symptoms are mild and require therapy, dopamine agonists (pramipexole and ropinirole), levodopa, or a monoamine oxidase type B inhibitor (MAOBI; selegiline or rasagiline) can be administered to produce symptomatic benefit.[2] Past studies show the use of beta-blockers, often propranolol, may improve PD tremor and motor function; anticholinergic medications are more effective than placebo for improving motor function but are inconclusive as a tremor therapy and frequent adverse events, such as cognitive impairments, dizziness, fatigue, tachycardia, lead to discontinuation.[2] Clozapine has been shown to improve bothersome or disabling PD tremor when used for tremor resistant to other therapies though significant adverse events such as agranulocytosis, myocarditis, seizures and sedation can occur.[19] Six, small class 3 randomized-control trials have shown mixed evidence for the possible efficacy of amantadine as a monotherapy or as an adjunct therapy due to the poor quality of studies.[2]

Levodopa or dopamine agonists are prescribed for patients with more severe symptoms and impairment in ADLs. Levodopa remains the gold standard in providing the greatest symptomatic benefit for PD and is linked to lower incidences of freezing, hallucinations, somnolence, impulse control disorders, and edema than initial treatment with dopamine agonists. However, dopamine agonists greatly benefit patients younger than 60 years of age or with younger-onset of disease and are associated with fewer dopaminergic motor complications associated with levodopa, such as dyskinesia which can be more disabling than the PD symptoms.[2,20] A meta-analysis showed the long-term benefits of levodopa-sparing versus levodopa as an initial treatment and concluded that levodopa alone was more effective in reducing Unified Parkinson's Disease Rating Scale (UPDRS) parts I-III scores though levodopa alone group were at a higher risk of developing dyskinesia and wearing-off phenomenon.[21] Interestingly, a study demonstrated that more than triple of patients receiving levodopa-sparing therapy discontinued prematurely due to adverse events compared to patients receiving levodopa alone therapy.[21] New evidence shows that the early advantage of dopamine agonists over levodopa diminishes over time (estimated 10 years).[19] Those with tremor as the initial manifestation of PD or having a tremor-dominant subtype have a lower probability of developing levodopa-induced dyskinesia.[22] Older, tremor-dominant PD

patients would benefit from starting with levodopa compared with dopamine agonists. Thus, levodopa and dopamine agonists appear to be reasonable options for initiating dopaminergic replacement therapy but are associated with different efficacy and adverse effects.[20]

Unfortunately, levodopa and dopamine-replacement therapies do not target tremor and tend to produce suboptimal tremor relief, and in some cases may worsen tremor. Additionally, it is often tremor that is sub-optimally alleviated or is a persistent tremor despite improvement in other cardinal PD symptoms, such as bradykinesia and rigidity, which are optimally managed by levodopa therapy. Recent studies have reported that tremor is high up among the key symptoms found to be one of the most bothersome symptoms experienced by patients.[23,24] Many clinicians are inclined to simply increase medication dosages or introduce adjunctive therapies. Dopamine agonists and anticholinergic medications can be used concomitantly with levodopa to treat tremor but may be accompanied by neuropsychiatric and cognitive side effects.[18] In double-blind studies, levodopa combined with carbidopa known to increase availability of levodopa in the brain, improves resting tremor by more than 50%, as well as bradykinesia and rigidity compared to using levodopa alone.[18] Efficacy of levodopa/carbidopa formulations and dopamine agonists have been reported to reduce rest and postural tremors to a similar level; however poor long-term efficacy and adverse events arise.[18] To reduce the incidence of adverse event profiles of oral, anti-tremor medications, a focal therapy with BoNT-A has been suggested to be efficacious in providing tremor reduction at the source, given the focal and asymmetric presentation of tremor.[25]

1.1.2.2. Botulinum toxin type A focal tremor therapy

Treating upper limb tremor with BoNT-A has not been widely adopted in clinical practice. However, BoNT-A is used to treat a wide variety of symptoms related to PD such as foot and hand dystonias, blepharospasm, lid apraxia, sialorrhea, hyperhidrosis, and jaw tremor. When injected intramuscularly, BoNT-A inhibits the release of acetylcholine (ACh) at the neuromuscular junction resulting in the blockade of neuromuscular conduction and reduced muscle activity/contraction. The release of ACh at the neuromuscular junction occurs by the

synaptic fusion complex of ACh vesicles bound to the pre-synaptic membrane by soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins. SNARE proteins mediate the docking and exocytosis of ACh vesicles at the presynaptic nerve terminal. The proteolytic action of BoNT-A cleaves SNAP-25, one of the three proteins which form SNARE, preventing the release of ACh into the synaptic cleft.[26] BoNT-A at the neuromuscular junction interrupts neurotransmitter release thereby causing muscle paralysis. Thus, when BoNT-A is injected into muscles contributing to tremor, effective alleviation of tremor can be achieved.[27]

There are limited number of studies reporting the efficacy of BoNT-A for PD tremor[25] though the success of BoNT-A lies in individualizing therapy by accurately distinguishing tremulous muscles.[27] However most past studies treating ET, dystonic tremor, or PD tremor used randomized or fixed dosing regimens based on visual/clinical assessments, which has led to early discontinuation of therapy due to bothersome, dose-dependent muscle weakness.[28–30] The use of accelerometry and surface electromyography to identify arm muscles with tremorogenic activity reduced incidence of weakness and improved functional outcomes in ET.[31] However, accelerometry provides an overall tremor severity score and is not capable of providing a more detailed breakdown regarding which degree of freedom (DOF) tremor is acting in.

1.1.2.3. Surgical intervention

Stereotactic surgery is the next treatment option for patients with disabling tremor resistant to pharmacotherapy. Tremor can be effectively reduced following DBS implantation or lesional therapy.

1.1.2.3.1. Deep brain stimulation

DBS is a surgical technique involving the implantation of electrodes in specific brain regions. DBS has proven to be effective for controlling rest and postural tremor in PD.[32] DBS is

known to be more effective than oral medication in reducing rest tremor severity and frequency.[33] A recent study has shown that patients with early motor complications who underwent DBS and medical therapy have significant improvements in ADLs and relief of motor disability for two years compared to patients with medical therapy alone.[34] DBS significantly improved survival of severe, late-stage patients and reduced admittance to long-term care facilities compared to patients with no DBS.[35]

The electrodes are connected to a device called an implanted pulse generator (IPG) that delivers electrical stimuli to brain regions in order to modulate or disrupt patterns of neuronal activity associated to PD. Three specific sites in the brain are most commonly targeted for DBS in PD: STN and GPi nuclei in the BG where much of the physiological modulation occurs in PD, and in the ventro-intermediate thalamic nucleus (Vim).[32] Bilateral DBS of the STN (STN-DBS) is performed in patients who are levodopa responsive with persistent motor symptoms despite optimal medical therapy. However, only a fraction of PD patients are eligible for this neurosurgical intervention. Surgical selection criteria include patients experiencing motor complications refractory to best medical treatment, who are levodopa-responsive, less than 65 years of age, with no mental health issues (depression, dementia) and have had PD for more than 7 years. In addition, intracranial hemorrhage, infection, and post-operative seizures are the most common adverse events[33] and impairments in gait, speech, and balance have been shown to have less chance of improvement and in some cases may worsen.[6] When the DBS is turned on about 2-4 weeks following surgery, most patients may require a reduction in medication dosages as the presence or severity of side effects such as dyskinesias increase.

Electrical stimuli promote neurogenesis, increased blood flow to stimulated areas, and astrocytes to release calcium and neurotransmitters including adenosine and glutamate.[6] However, the exact mechanism of how DBS alleviates PD symptoms is not yet clear despite these physical and physiological changes.[32] High frequency STN-DBS suppresses the excessive beta-frequency synchronization in PD patients, in a similar way to how levodopa

reduces synchronous beta-frequency oscillations.[36,37] However, the effect of how DBS intervention improves appendicular symptoms such as tremor, rigidity, and bradykinesia remains elusive.[38]

1.1.2.3.2. Lesional therapy

A surgical procedure involving lesioning the GPi reduces motor fluctuations, tremor and dyskinesias as the GPi is thought to be overactive in PD. This procedure, pallidotomy, is performed unilaterally as bilateral procedures rarely occur due to high incidence of severe adverse events including cognitive impairment, dysarthria, and dysphagia.[6] The reduction in PD symptoms by pallidotomy is not as great as DBS intervention.[32] Suppression of tremor, rigidity, dyskinesia and bradykinesia has been reported for five years following surgery however bradykinesia gradually reoccurs with freezing of gait at a 10-year follow-up.[6] In addition, cognitive and executive functions are reduced after five and 10 year follow-ups and thus, pallidotomy is an alternative to DBS or when DBS is no longer effective.[6]

An invasive procedure called thermal radiofrequency thalamotomy involves the passage of a probe into the VIM nucleus of the thalamus, an area understood to be involved in the tremor cerebello-rubro-thalamo-cortical circuit, and performing a lesion to the side contralateral to the tremor. Bilateral thalamotomy may affect executive function by disrupting neuroanatomical pathways between subcortical and prefrontal cortical areas. Unilateral thalamotomy significantly improves PD symptoms of tremor, rigidity, mobility, well-being, and ADLs.[6] The use of transcranial magnetic resonance imaging (MRI)-guided high intensity focused ultrasound to perform thalamotomy has reduced complications involving hemorrhages, motor deficits and post-operative cognitive impairment.[39] However, side effects including paraesthesia of lips, tongue and fingers, nausea and pain at one year follow-up do arise.

Gamma knife is a non-invasive surgical approach involving the emission of highly focused gamma radiation beams at a target within the brain pinpointed using imaging scans.[6]

Improvements in tremor and ADLs have been demonstrated though benefits take several months to appear. There are contrasting results on the effectiveness of gamma knife in reducing rest, postural, action and head tremor. Gamma knife lacks the accuracy observed in invasive procedures since there is no intraoperative electrophysiological confirmation of target site.[6] A large spectrum of possible complications involving the delayed effects of radiation necrosis and thus such procedures are reserved for PD patients with severe disabling symptoms who fail to adequately respond to pharmacotherapy.

1.2. Essential tremor: symptoms and etiology

ET is the most common adult-onset movement disorder after restless legs syndrome.[1] The prevalence of ET increases with age, affecting approximately 1% of the general population and 2.3-14.3% of those aged 60 years and older.[1] Approximately 70-80% of people with mild ET do not seek therapy and go undiagnosed and thus, prevalence is underestimated. The course of ET varies widely as in some patients the tremor remains mild while in others it becomes progressively and functionally disabling that many seek effective treatment. The slow, progressive nature of ET may evolve to more body parts/areas, increasing in amplitude and frequency.[40] The age of onset is a bimodal distribution with peaks at early childhood and around the age of 60 years of age.[41] A family history of ET and aging are risk factors for ET. The etiology of ET is genetic by inheritance in a Mendelian autosomal dominant fashion in approximately 50% of patients increasing the prevalence of ET within certain families [42] although, specific genes have not been identified.[42] A positive family history is very common and these ET patients have a younger age at onset.[43] Non-genetic and environmental factors are possible causes of ET yet are much less extensively studied.

ET is characterized by bilateral tremor during voluntary movement occurring most frequently in the hands and arms in absence of other medications or neurological signs that might cause tremor. Isolated head tremor with no signs of dystonia fall under ET. For definite certainty of ET, ET must be present for over five years with thorough exclusion of other causes. ET is now widely recognized as a condition associated with significant physical and psychosocial

disability and over the past 20 years, investigators have sought to better classify and define ET as growing literature considers ET to be a family of diseases.[44] ET as a monosymptomatic disorder has been challenged, as disturbances in gait, mood, cognition and hearing have been observed and linked to thalamic and cerebellar dysfunction.[44] Problems with postural stability and gait are evident in patients with longer disease time. Nevertheless, ET is a clinical syndrome of action tremor in the upper limbs (at least 95% of patients) and less commonly in the head (at least 34%), face/jaw (7%), voice (at least 12%), tongue (30%), trunk (5%), and lower limbs (30%).[44]

The pathophysiology of ET remains largely unknown as there is no known pathological or biochemical findings, no suitable animal model and hence most knowledge about ET is gathered from clinical studies. The frequency of ET ranges between 4 and 12 Hz and is thought to emerge from neuronal oscillation in the cortico-bulbo-cerebello-thalamo-cortical loop but the cause is unknown.[44] Low frequency repetitive transcranial magnetic stimulation (rTMS) over the posterior cerebellar cortex modulates the cerebello-thalamo-cortical circuit resulting in significant reduction in tremor severity for three weeks.[45] Oscillation in the cortico-bulbo-cerebello-thalamo-cortical loop is also observed in PD, Wilson disease and rhythmic cortical myoclonus. [40] The frequency of ET is associated with the dysfunction in the central component as several central lesions in the pons, internal capsule, cerebellum and frontal/sub-cortex modify ET. The peripheral component of ET modifies amplitude and is linked to adrenergic mechanisms in the muscle spindle.[46] A recent morphometric study reported all ET cases present with histological change, 24% of ET showed Lewy body inclusions and 76% had cerebellar pathology (Purkinje cell loss).[47] Some studies report altered gamma amino-butyric acid (GABA) function in ET.[40]

1.2.1. Classification of ET

Classical ET is bilateral, largely symmetrical, postural and/or kinetic tremor – although one limb may be more pronounced than the other. Postural tremor is provoked when arms are fully extended in front of the body though more pronounced tremor is observed when the shoulder is abducted, elbow is flexed and hands are held under the chin.[40] Kinetic tremor is more pronounced when nearing the target and is called an intention or terminal tremor. This

is tested by asking the patient to go back and forth between touching their nose and the target. Completing Archimedes spiral and line drawings, pouring, and writing tasks are other methods for testing action tremor.

Many ET patients are incorrectly diagnosed with PD.[40] PD tremor during the early course of PD may present as an action tremor without rest tremor, bradykinesia or rigidity thus making it extremely difficult to distinguish early PD from ET. However, postural tremor in ET manifests immediately on positioning arms horizontally where PD postural tremor has delayed onset. Additionally, classical PD tremor is at rest however one-third of ET patients have rest tremor which typically manifests later in the disease course.[40] Rest tremor can be elicited by physical or emotional stress and thus definite rest tremor should be evident when the patient is lying down with the arms fully supported. Rest tremor is not a feature of cerebellar disorders. Cerebellar tremor is slower than ET with variable amplitude, irregular rhythm and is primarily a proximal, upper limb tremor, in contrast to the distal tremor of ET. Dystonia with associated tremor is typically jerky and irregular occurring commonly in the head and is most prominent when the body part is positioned in a direction opposite to the direction of the dystonic side and thus may be considered a postural/kinetic tremor. A sensory trick alleviates dystonia but does not improve ET. Physiological tremor occurs under stressful situations and is non-progressive though frequency ranges from 8 to 12 Hz. Writing tremor may be a feature of ET but is better associated with the dystonic posturing of the hand classifying it as a dystonic tremor. Thus, proper positioning and tests are required in these movement disorders as ataxic or dystonic features can be misinterpreted for tremor.

1.2.2. Current treatments of ET

As the basic neuropathology and neurotransmitter deficits in ET are largely unknown, no disease-specific drug is available and all traditional oral agents used in treating ET were primarily developed for other diseases.[48] Treatment options currently available for ET include oral pharmacotherapy, botulinum toxin A (BoNT-A) injection, and stereotactic surgery, including DBS and thalamotomy.[48–50] Various drugs, including propranolol, which

is the only pharmacotherapy approved by the US Food and Drug Administration to date, primidone, benzodiazepines, gabapentin, pregabalin, topiramate, and nimodipine are used in the treatment of ET, with an average tremor reduction of 50% or less.[48,50,51] Poor efficacy is frequently coupled with dose limiting side-effects, such as drowsiness with primidone, bradycardia, syncope, fatigue, and erectile dysfunction with propranolol. Additionally, tolerance to the initial benefit often leads to the discontinuation of drugs in 56.3% of patients.[50] DBS of the VIM nucleus of the thalamus may benefit patients with disabling ET, though only a fraction of patients are eligible for this highly invasive procedure that may produce lasting neurological side-effects, including paresthesias (6-36%), dysarthria (3-18%), ataxia (6%), limb weakness (4-8%), balance disturbance (3-8%) and dystonia (2-9%).[49,50] Efficacy and risks of gamma knife thalamotomy is comparable to VIM-DBS.[49] Ultrasound guided thalamotomy can be performed only unilaterally and again carries the same potential risks as gamma-knife surgery and thus large, randomized, controlled trials are required to assess the procedure's efficacy and safety.[39,52,53] A review of the current, recommended treatment options for ET is summarized in Table 1-1.

Table 1-1. Treatment options for ET.

Drug Name	Drug Class	Level	Total Daily Dosage (mg/d)	Sample size	Efficacy (compared to baseline)	Adverse Effects	Reference
Propranolol	Beta blocker	A	40 - 320	533	~50% of patients respond. Those that respond experience a 50-60% reduction in tremor.	Nausea, vomiting, bradycardia, diarrhoea, hypotension, drowsiness, fatigue, light-headedness, weakness and paraesthesia	54,55

Primidone	Anticonvulsant	A	50 - 1000	218	50% mean improvement rated by clinical scales and accelerometry	Ataxia, vertigo, nausea, vomiting, fatigue, malaise, dizziness, unsteadiness, confusion, impotence, rash	51,54,55
Atenolol	Beta blocker	B	50 - 150	79	25% mean improvement by clinical scales, 37% mean improvement by accelerometry	Light-headedness, nausea, cough, dry mouth, sleepiness, decreased pulse and blood pressure	51,54
Alprazolam	Benzodiazepine	B	0.125 - 3	46	25-37% mean improvement by clinical scales	Mild sedative and fatigue effects	51,54
Gabapentin (monotherapy)	Anticonvulsant	B	1200 - 1800	61	Drowsiness, fatigue, dizziness, nervousness, shortness of breath, reduced libido	33% improvement by clinical scales, 77% improvement by accelerometry	51,54,55
Sotalol	Beta-adrenergic receptor antagonist	B	75 - 240	50	28% mean improvement in clinical scales	Serious ventricular arrhythmias, dose-related QT interval prolongation, reduced alertness	51,52,54
Topiramate	Anticonvulsant	B	25 - 300	335	29% improvement in clinical scales (mean dose=292 mg/d); 30% improvement in tremor (up to 400 mg/d) with a 32% attrition rate due to adverse events	Dizziness, disorientation, paraesthesia, weight loss, memory difficult, appetite suppression, cognitive difficulties, upper respiratory tract infection, taste perversion, fatigue, nausea, headache, somnolence	51,55

Nimodipine	Calcium channel blockers	C	120	16	45% improvement by clinical scales and 53% improvement by accelerometry (n=14)	Headache, heartburn, hypotension	51,54
Clonazepam	Benzodiazepine	C	0.5 - 6	44	45% improvement by accelerometry	Drowsiness, depression, cognitive and behavioural impairments	51,54
BoNT-A	Neurotoxin	C	50 - 300 U/arm[a]	283	20-27% improvement by clinical scales (n=133)	Dose-dependent muscle weakness occurred in 30% of patients, reduced grip strength, stiffness, cramping, pain at injection site	51,54,56
DBS	Unilateral or bilateral VIM-DBS; STN-DBS	C		398	40-90% improvement by clinical scales up to 3 years. Chronic stimulation gradually worsens efficacy leading to loss of tremor suppression in about 70% of patients	Dysarthria, disequilibrium, paresthesias, weakness, headache, intracranial hemorrhage, subdural hemorrhage, lead dislodgement, generalized motor seizures. About 18% experience equipment malfunction or lead displacement	54,56
Thalamotomy	Gamma-knife; MRI-guided Focused Ultrasound	C		181	55-90% improvement by clinical scales	Hemiparesis, transient problems with speech, motor function, dysarthria, verbal/cognitive deficit, weakness,	51,53,54

	(MRgFUS)	confusion, facial paresis. About 7% experience permanent complications (hemorrhage and infection).

[a]BoNT-A units are in mouse units from mouse lethality assay

In addition to pharmacotherapy and surgical intervention for ET, BoNT-A injected into tremulous muscles has demonstrated modest effect in reducing arm tremor in ET and similarly for PD rest tremor. A randomized, double-blind study by Brin and colleagues demonstrated in 133 ET patients a significant improvement in postural tremor up to 16 weeks and kinetic tremor improvement for 6 weeks without any improvements in motor tasks and functional disability.[28] Common side effects such as hand muscle weakness restrict its application as patients found the weakness more disabling than their tremor. The randomized injection regimen is the probable cause of the resulting dose-dependent muscle weakness. In fact, muscle weakness is often cited as the main and most severe adverse event of this therapy reducing efficacy and ease of use in 45-60% of patients.[29,30,57] Pacchetti and colleagues identified tremulous wrist flexor/extensor and bicep muscles by more objective measures such as accelerometry and surface EMG to better target BoNT-A; this resulted in significant reduction in tremor amplitude and improved ADLs scores in 20 patients.[31] Yet, practice guidelines score a level C recommendation and believe BoNT-A has a modest effect at best.[48]

1.3. Rationale

1.3.1. Using technology to differentiate ET and PD tremor types

There are no biochemical or radiological biomarkers in PD and ET and thus proper diagnosis heavily relies on clinical observation. As ET and PD tremor have overlapping tremor features and may occur in the same circumstances, reliable and accurate methods for differentiating these tremor types are important. Possible biomarkers involving MRI, PET and SPECT

scans, movements about the wrist, olfactory deficits, and REM sleep disorders have been proposed for PD but none are satifactory.[58] The criterion for ET is based on clinical assessment of tremor however patients usually present with more than one type of tremor and it is not clear whether ET is separable from different types of tremor.[59] A study failed to differentiate ET and PD tremor by combining EMG and kinematic analysis.[58] As both diseases are incurable and therapy is focused on alleviating symptoms and improving quality of life, there is a great interest in differentiating between these diseases for proper symptomatic management and reducing the economic burden to healthcare utilization, caregiver costs and lost productivity.[60]

To quantify tremor in the clinical setting, standardized clinical rating scales such as the Fahn-Tolosa-Marin (FTM) tremor rating scale, the Washington Heights-Inwood Genetic Study of ET rating scale, Whiget tremor rating scale and UPDRS part III for the tremor motor symptoms can be used in ET and PD.[61] The FTM uses a 5-point scale rating tremor severity based on tremor amplitude from 0 (no tremor) to 4 (severe tremor) in each part of the body.[62] UPDRS ratings use an integer scale (0-4) to assess severity of motor functions rather than a quantitative, ratio-based approach.[63] UPDRS maintains high subjectivity as intra-individual ratings vary, limiting its accuracy and value as a measure for clinical diagnosis and in clinical trials/studies.[64] In addition, questions and phrases used in scales are ambiguous, the sensitivity of scores to change in clinical trials, and the differences in ratings between patients and assessors needs to be revised.[61,65] Tremor rating scales also lack good inter-rater reliability and continuous/repetitive monitoring capabilities remain a concern. Thus there is a need for more objective outcomes that can be applicable to clinical practice.[66]

Several targeted and sensor-based methods for monitoring and for analysis of tremor have been developed over the past decades. Advantages in these emerging techniques include high accuracy, repetitiveness and reliability of measurements and that the devices are small, non-invasive and are easy to use.[67] The use of surface or needle-EMG involves electrical contacts fixed on the skin or using a needle placed in a muscle to analyze duration of EMG activity bursts. Patterns of muscle co-contractions can be observed and recent work has proven EMG

recordings can classify ET apart from parkinsonian tremor.[67] However, EMG analysis takes a skillset and may not be practical in clinical practice. Gyroscopes and accelerometers are low in cost, small, and are convenient to measure useful parameters such as frequency and amplitude of tremulous body segments. Unfortunately, such tools have really only been applied for clinical management and have not been successful in distinguishing pathological tremor types. Flexible angular sensors called goniometers measure joint angles and are frequently used in sports and rehabilitation [67] Currently, goniometers have not yet been applied in large scale studies of tremor and thus it is unknown whether these sensors can detect differences between tremor characteristics in PD and ET patients.[67] However, recent studies have demonstrated that kinematic technology for tremor characterization is a reliable and feasible methodology and have generated the ability to distinguish tremulous muscle groups.[68–71]

Owing to the lack of standardized methodologies to measure upper limb tremor, this current thesis focused on the use of wearable, motion sensor technology to quantify the tremor biomechanics at each arm joint in PD and ET individuals while individuals were in their best medically managed state. By deconstructing joint tremor amplitudes in each individual over a series of tasks, differences in tremor profiles were established thereby enabling an objective, simple method to distinguish between ET and PD tremor types.

1.3.2. Using technology to personalize therapy

Many tremor analysis tools are very expensive and are generally non-portable, such as an optical motion capture system.[67] Multi-sensor motion recordings, wearable accelerometers/gyrostats, and tremor apps for smartphones (based on accelerometry) to measure tremor have been established and are available for the general public. Such technological advances allow in-home monitoring, individualized therapy titrations, and is a diagnostic insight for clinicians.[72] However, wearable devices are not reliable measures in distinguishing tremulous muscles and do not provide accurate or diagnostically relevant information about tremor. Therefore, those who use these apps and wearable devices for

patient care or as outcome measures in clinical studies should exercise caution as there are a limited number of studies investigating the validity of these devices for tremor analysis.

Current research focuses on the use of portable and simple to use devices that provide applicable information for clinicians to better individualize therapy. One study extracted tremor characteristics, such as frequency, direction and amplitude, from spiral drawing on a digitizing tablet. Writing and spiral drawing tasks have recently been used as an objective measure of proximal versus distal arm tremor severity.[73] However tremor characteristics during rest or other functional tasks could not be measured.[72]

While BoNT-A injection in the upper extremities is a viable treatment option as a monotherapy or adjunctive therapy for ET and PD tremor, limited functional efficacy due to dose-dependent wrist and finger muscle weakness remain a concern. The use of injection protocols involving fixed BoNT-A dosages and predetermined muscle sites, regardless of patient's unique tremor characteristics are probable reasons for this problem.[74,28] During a tremor assessment, the characterization of the movement dynamics along the whole arm, muscle selection, dosing and proper muscle localization during injection are important considerations when utilizing BoNT-A to enhance arm function and to minimize likelihood of weakness.[27,68,69] While clinical knowledge and use of technologies, such as EMG or ultrasound aid in muscle localization and injection, visually-guided assessments to characterize tremulous movements at various joints are likely to fail due to the variability and complexity of tremor and the difficulty in accurately separating multi-joint, whole arm movements. Thus, the lack of adequate tremor assessment tools and poor injection guidelines have limited the use of BoNT-A for ET and PD tremor.[27,69,75] Ultimately, it is of great interest to improve the efficacy and tolerability of BoNT-A therapy by applying kinematic tremor biomechanics captured from each individual in order to better target BoNT-A to muscles contributing to the overall joint tremor.

1.4. Summary

The focus of this thesis is to apply commercially available motion sensor technology to measure the variation in joint tremor amplitude brought out by various scripted tasks to generate unique, correlational tremor profiles of PD and ET tremor types. Kinematic tremor assessments employing rest and postural paired tasks is simple, quick and could be translated to the clinic setting as a diagnostic aid, The use of multi-sensor kinematic technology addresses the significant unmet need in tremor therapy by pairing BoNT-A injections with individualized, multi-joint movement patterns. This combination has shown to alleviate tremor severity, improve the functional efficacy of BoNT-A while limiting the likelihood of dose-dependent weakness perceivable by patients.

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2. Differentiating parkinsonian tremor and essential tremor by the variation in tremor amplitude denoted in paired rest, postural and weight-bearing tasks

2.1. Introduction

Since tremor is the most common movement disorder, there are many different types of tremor that are often mistaken for one another.[1] Most errors in interpretation are essential tremor (ET) misdiagnosed as parkinsonian tremor, although distinguishing other tremors is also difficult.[2] Both ET and Parkinson's disease (PD) tremors have overlapping features that lead to high misdiagnosis rates which commonly occurs when other parkinsonian symptoms such as bradykinesia, rigidity and postural instability are not evident.[3] Such misdiagnosis can have a significant impact on the patient's state of mind. ET is a heterogeneous condition characterized by a postural or action tremor that typically affects both of the upper limbs (at least 95%) and less commonly the head (≥34%), voice (≥12%), and lower extremities (30%).[3] The location, amplitude and frequency of tremor along the whole arm vary among patients and while the condition is considered "benign", it frequently results in significant physical and psychosocial disability and many ultimately seek symptomatic treatment. Parkinson's disease (PD) patients also experience tremor which can be quite bothersome as more than 75% of patients develop tremor over the disease course. Classic PD tremor is typically asymmetrical, unilateral, and occurs at rest affecting the fingers, hand and wrist. However, PD tremor may be bilateral, affect the proximal upper limb and manifest itself during voluntary movements, although with delayed onset. Current literature reports that frequency-tolerance distinguishes between ET and PD tremor.[4] However, it is unknown how variations of clinically relevant static tasks such as rest and posture positions (e.g. forearm is resting fully pronated versus supinated) modulate tremor amplitude and the composition of tremor along the whole-arm, rather than at the wrist only.[5] Additionally, it is of interest to determine whether this information can be used to differentiate between these tremor types as current techniques of assessing tremor heavily depend on clinical expertise, and the use of clinician-based ratings and clinical scales.[6] Individual clinical tremor ratings can vary causing poor inter-rater reliability. Additionally, tremor rating scales contain an integer rating system (0-4) which lacks the accuracy of a more specific quantitative approach, a necessity in the field of movement disorders. There are many different methods of evaluating tremor but they are often complex, unavailable, and are developed for a specific tremor type.[6]

The use of gyroscopes, accelerometers, and magnetometers have advanced the field of objective movement in all facets of everyday life but particularly in monitoring whole-body movements in patients with movement disorders such as PD.[7] Such devices can measure overall tremor severity and can aid clinicians in understanding the variability in tremor when the patient is outside the clinic setting.[7-9] However, these medical devices are not necessarily regulated by the Food and Drug Administration (FDA) to assure effectiveness, safety, accuracy and ease of use of such medical devices and mobile device apps. Thus, caution is required as such wearable devices do not provide accurate and diagnostically relevant information and translation to the clinical setting may not be easy.[7] Thus, the purpose of this study is to utilize objective measures of joint tremor, by goniometers and a torsiometer, to explore the relationship of tremor amplitude, composition, and variability between different rest, postural and weight-bearing scripted tasks in ET and PD individuals. This study aims to determine whether changes in tremor by task variation are exclusive to either ET or PD, as this would be a novel and simple way to distinguish these tremor types in a clinical setting.

2.2. Methods[1,2]

2.2.1. Study timeline

This single-centre, pilot study recruited a convenience sampling of 24 ET participants and 28 PD participants from the London Movement Disorder Centre who completed a single study visit. The study visit consisted of clinical scales and kinematic tremor measurements. Medication was not withheld from participants during the assessment. The tremor dominant limb was assessed in all participants.

2.2.2. Study Criteria

[1] A version of parts of this chapter has been published (Samotus O, Rahimi F, Lee J, Jog M (2016) Functional Ability Improved in Essential Tremor by IncobotulinumtoxinA Injections Using Kinematically Determined Biomechanical Patterns – A New Future. PLoS ONE 11(4): e0153739. doi: 10.1371/journal.pone.0153739

[2] A version of parts of this chapter has been published (*Rahimi F, *Samotus O, Lee J, et al. Effective management of upper limb parkinsonian tremor by BoNT-A injections using sensor-based biomechanical patterns. Tremor Other Hyperkinet Mov. 2015; 5. doi: 10.7916/D8BP0270)

This study protocol was approved by Western University Health Sciences Research Ethics Board (REB#18445) on March 28, 2012 (see Appendix A for the approval letter and Appendix B for the full REB protocol). Participants provided written consent to participate in this study by signing the study's consent form. The ethics committee provided full board approval for this study protocol and consent procedure was approved as required in the consent documentation checklist, submitted with the full study protocol. All ongoing and related trials for this drug/intervention are registered (ClinicalTrials.gov Identifier: NCT02427646).

2.2.2.1. Study criteria for ET participants

The inclusion criteria consisted of male and female participants, aged 18 to 80 years diagnosed with ET with upper limb tremor as their primary and most bothersome symptom for at least two years, BoNT-A naïve, on stable medication management for a minimum of six months prior to study enrolment, with none withheld or adjusted during the study. At enrollment, participants were either stable on their anti-tremor medications, unable to tolerate oral medications, or unwilling to comply due to side effects. Exclusion criteria were those who had a history of stroke, contraindications per the BoNT-A monograph, pregnancy, and existing pharmacological therapy with tremor-inducing side effects (e.g. lithium, valproate, steroids, amiodarone, or beta-adrenergic agonists such as salbutamol).

2.2.2.2. Study criteria for PD participants

Inclusion criteria were: consenting male and female participants diagnosed with PD by UK Brain Bank Criteria with H&Y stage 1-3 disease, aged 18 to 80 years, having tremor as their most bothersome and important symptom while on stable medication management for at least six months prior to enrolment, with none withheld or adjusted during the time of the study, and BoNT-A naïve. Participant criteria excluded those who had a history of stroke, contraindications per the BoNT-A drug monograph, pregnancy, and existing pharmacological therapy with tremor-inducing side effects (e.g. lithium, valproate, steroids, amiodarone, or beta-adrenergic agonists such as salbutamol).

2.2.3. Kinematic assessment

2.2.3.1. Kinematic experimental tasks

PD and ET participants performed a series of scripted, paired tasks designed to study the effect of task variation on upper limb tremor. Paired tasks involved two rest positions (focusing on flexion/extension (F/E) and pronation/supination (P/S) movements), two postural positions (focusing on F/E and radial/ulnar (R/U) movements), and two weight-bearing tasks to simulate daily activities such as eating and drinking (Figure 2-1). These tasks were completed thrice in series and 20 seconds were allotted for each task. Rest tasks, denoted “Rest-1” and “Rest-2” were performed with a distraction (Figure 2-1a-b). Postural tasks involved the participant to extend both arms outstretched in front of their body with palms facing downwards or inwards, denoted “posture-1” (arms outstretched, palms down) and “posture-2” (palms facing inwards; Figure 2-1c-d). Weight-bearing tasks involved the participant holding an empty cup, “load-1”, or a cup with a 1-lb weight, “load-2”, with their shoulder abducted, elbow flexed with the cup held in front of the body or below the mouth (Figure 2-1e-f).

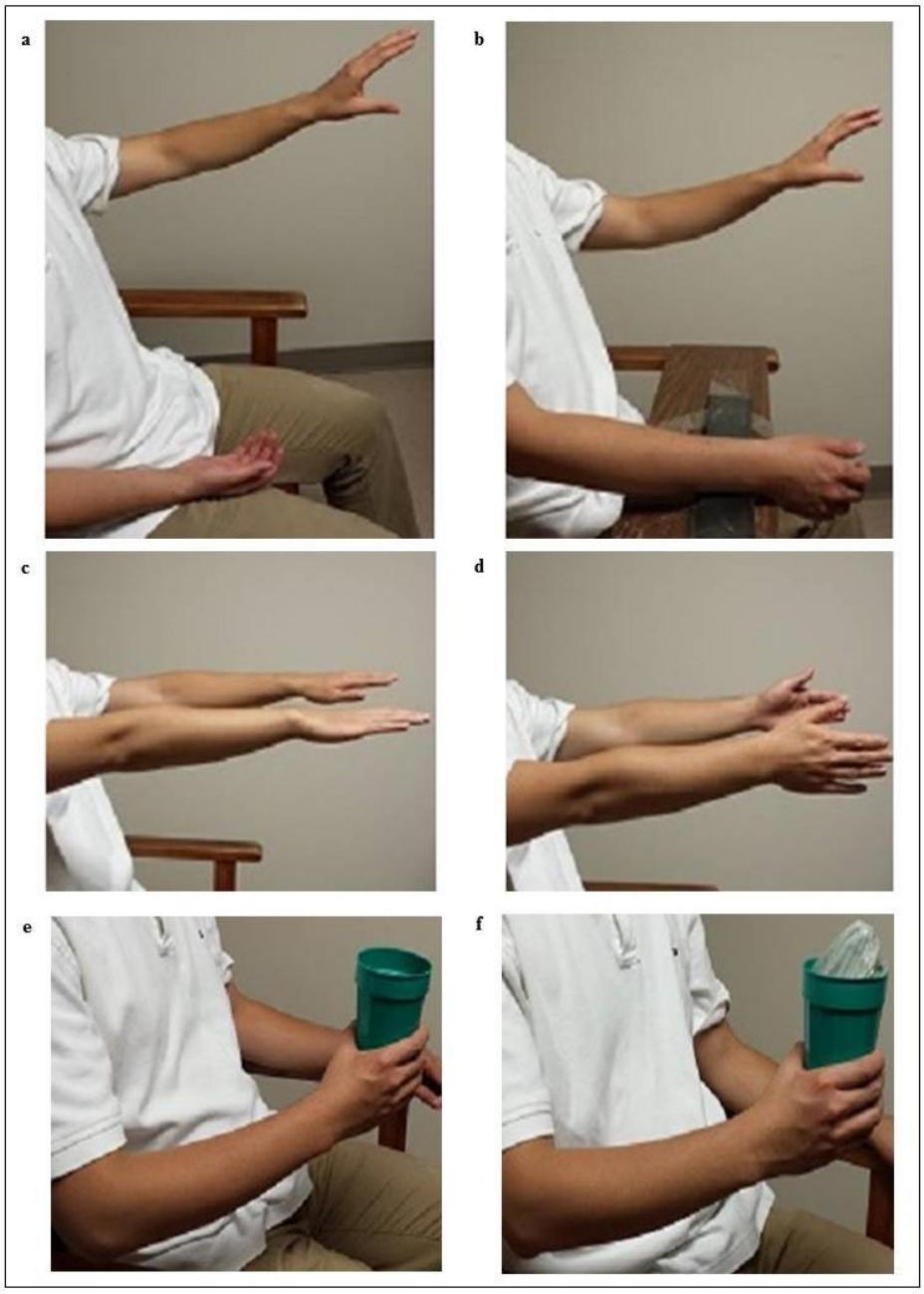

Figure 2-1. Images depicting three static, scripted task variations during rest, posture, and weight-bearing paired tasks.
(a) Rest position ("rest-1") with relaxed forearm in lap measuring F/E wrist movements. (b) Rest position ("rest-2") with arm supported measuring P/E movements. (c) Postural position ("posture-1") with shoulders flexed at 90° with arms extended anteriorly and pronated (palms facing downwards). (d) Postural position ("posture-2") position with shoulders flexed at 90° with arms extended anteriorly, palms facing inwards. (e) Functional task ("load-1") with the participant holding an empty cup in front of body with elbow and proximal arm unsupported (f) Functional task ("load-2") holding a cup with a one-pound weight in front of body with elbow and proximal arm unsupported.

2.2.3.2. Kinematic sensor set-up

Figure 2-2 displays the placement of a total of four motion recording sensors attached over the wrist, elbow, and shoulder arm joints. Motion sensor devices were placed over each the forearm, wrist, elbow and shoulder joints capturing tremor severity in angular root mean square (RMS) amplitude simultaneously in multiple degrees of freedom (DOF). Electrogoniometers measured wrist tremor, by angular position, in two degrees of freedom, F/E and R/U deviations (SG150, Biometrics Ltd). Wrist tremor in the P/S plane was measured by a torsiometer placed on the dorsal surface of the forearm (Q150, Biometrics Ltd.). Thus, the torsiometer provided the third angular degree of freedom of rotational motion about the wrist. Elbow tremor was captured an electrogoniometer in one degree of freedom, F/E. An electrogoniometer placed on the shoulder measured two degrees of freedom, F/E and abduction/adduction (Abd/Add). Internal/external shoulder rotation was not feasible to kinematically measure. Sensors were attached using 3M hypoallergenic micropore medical grade tape (Ref#: 1530–1).

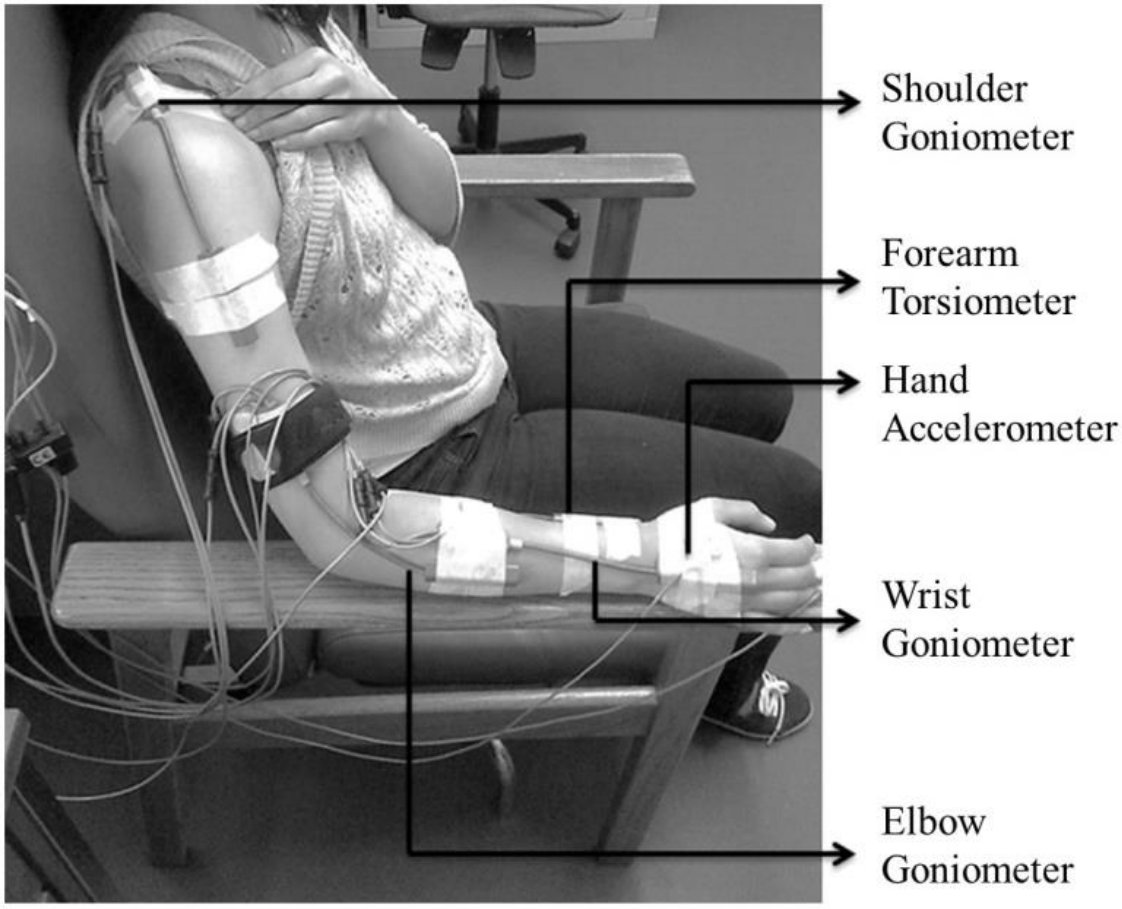

Figure 2-2. Images depicting sensor placement.
Placement of Biometric® motion sensors along arm: shoulder electrogoniometer, elbow electrogoniometer, wrist electrogoniometer, accelerometers placed on forearm, hand and third finger.

Sensor calibration was completed with the forearm supported and with the hand fixed against a vertical plane in neutral F/E, R/U, and P/S positions, and was held for five seconds. Additional sensor calibration was performed with the participant's arm held straight while standing, elbow extended with fingers pointing down for five seconds. Motion sensor data was collected at 1500Hz by TeleMyo™ 2400T G2 and PC interface (MyoResearch XP Master Edition 1.08.09, Noraxon®). Recordings at each joint were mutually exclusive with each sensor recording data only from a particular joint.

2.2.3.3. Kinematic tremor analysis output

Custom written software in MatLab® (R2011a) processed raw angular signal data captured by the motion sensors.[10] The interpreted data displayed tremor severity, as total angular RMS amplitude, in each DOF during each task in each arm joint. The software provided a percentage contribution of the directional movements in the wrist and shoulder joint as further tremor segmentation was not achievable at the elbow that deviates only in F/E DOF.

2.2.4. Statistical analyses

IBM® SPSS version 20 was the statistical program used to investigate the relationship of tremor severity in ET and PD across paired scripted tasks. Each task was performed thrice in series per kinematic recording session. The mean angular RMS tremor amplitude across three trials for each task per study visit was log-transformed as tremor amplitudes generated skewed distributions. The dispersion of the data from the mean was displayed as standard deviation of the population. Pearson's product-moment correlation was conducted to observe the relationship of joint tremor amplitudes between paired tasks and across non-paired tasks within ET and PD populations, and between ET and PD population groups. A paired t-test was performed to assess the statistical difference in tremor amplitudes across tasks within ET and PD populations. An independent t-test was conducted to determine whether a correlation (r value) was statistically significantly different between ET and PD groups. Similar statistical tests were conducted on the percent contribution of tremor in each DOF to the overall wrist tremor.

2.3. Results

2.3.1. Study demographics

The demographics of the ET participants are found in Table 3-1 in section 3.3.1 in Chapter 3. The demographics of the PD participants are found in Table 4-1 in section 4.3.1 in Chapter 4.

2.3.2. Effect of task variation on joint tremor severity

2.3.2.1. Essential Tremor

Mean tremor amplitude correlations were substantial in each joint across tasks (Figure 2-3). Mean tremor amplitude at the wrist, elbow or shoulder during "rest-1" or "load-1" led to a strongly correlated increase in tremor amplitude in the paired task ("rest-2" or "load-2"; $r>0.5$, $p<0.05$). However, this was not evident between "posture-1" and "posture-2" tasks indicating postural task variation significantly modulates tremor amplitude in all joints. A paired samples t-test revealed mean wrist tremor amplitude in tasks "posture-1" and "load-1" was significantly increased by 61.6% in "posture-2" [$t(23)=2.81$,$p=0.01$,95%CI -0.57 to 0.87 log-RMS degrees] and by 20.9% in "load-2" [$t(23)=2.912$,$p=0.008$,95%CI -0.31 to -0.05 log-RMS degrees], respectively, indicating forearm supination and additional weight increases wrist tremor amplitude in ET. Mean wrist tremor amplitude from tasks "posture-2" and "load-2" was statistically, strongly correlated [$r(24)=0.60$,$p=0.002$] though was not statistically different [$t(23)=0.61$,$p>0.05$,95%CI -0.32 to 0.57 log-RMS degrees] indicating these two arm positions produced similar wrist tremor severities.

Task variation (paired tasks) did not significantly change elbow tremor amplitude. However, mean elbow amplitudes during "posture-1" and "posture-2" were weakly correlated, as similarly seen in the wrist joint. Interestingly, mean elbow tremor amplitude in "posture-2" compared to both load tasks were strongly correlated and following a paired samples t-test, mean elbow tremor amplitude during "posture-2" was significantly lower by 58.3% compared to "load-2", indicating weight increases elbow tremor but not wrist tremor [$t(23)=1.408$,$p=0.17$,95%CI -0.30 to 0.06]. Mean shoulder tremor amplitudes did not significantly change between all tasks. However, tremor amplitude was strongly correlated between rest tasks, between load tasks, and between "posture-2" and load tasks, as seen in both the wrist and elbow joints.

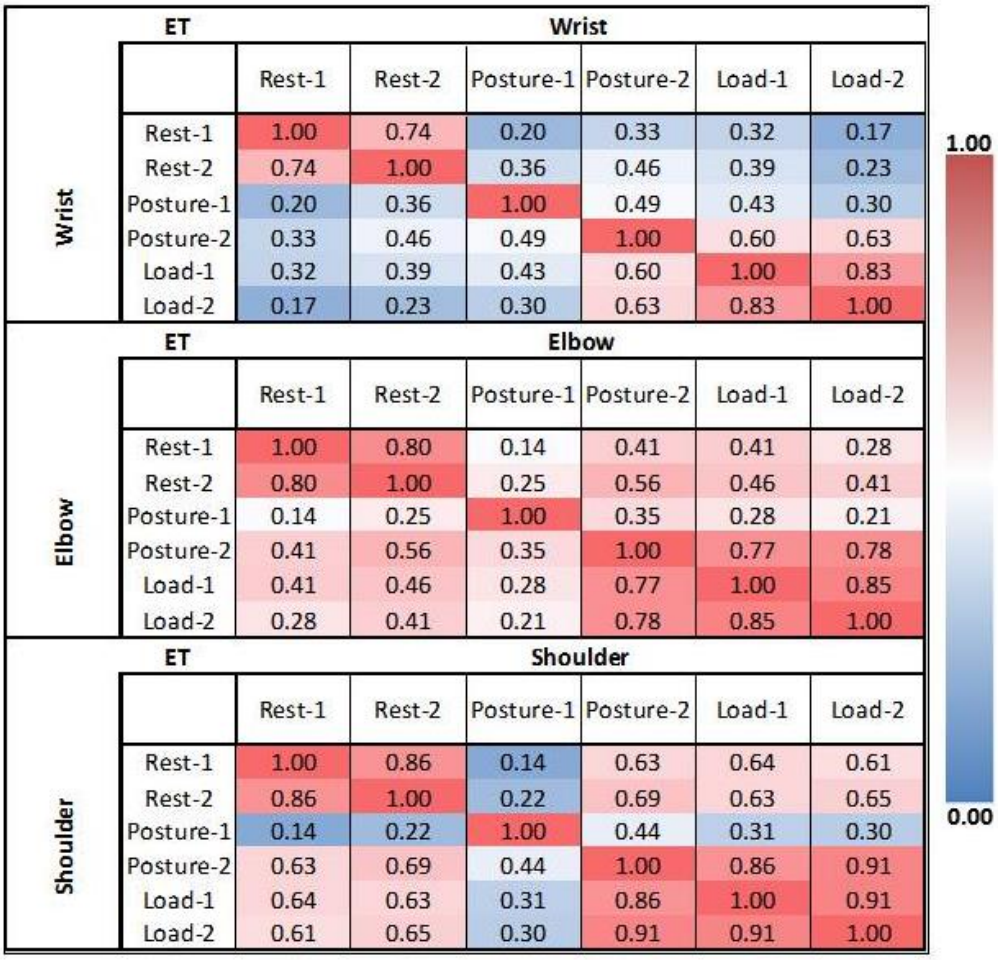

Figure 2-3. Pearson's coefficient correlation heat map of mean tremor amplitude in the wrist (top), elbow (middle) and shoulder (bottom) across all scripted tasks in ET participants.

Mean wrist and elbow tremor amplitudes during both rest tasks were significantly correlated (Figure 2-4). In addition, mean elbow tremor amplitude was strongly correlated [r=0.718; p<0.0005] to wrist tremor amplitude in "posture-1" (when the elbow is fully extended) yet was weakly correlated to wrist tremor during "posture-2" [r=0.23, p=0.342] and both load tasks [r=0.27 and r=0.24, p>0.05]. Tremor amplitude captured at the wrist and elbow during "posture-2" and both load tasks (with elbow flexion involvement) were strongly correlated (r values range from 0.665 to 0.891), suggesting a significant linear relationship between wrist and elbow tremor measured during tasks involving elbow flexion when the limb is unsupported and held against gravity.

Figure 2-4. Pearson's coefficient correlation map of mean wrist and elbow tremor amplitudes across all scripted tasks in ET participants.

2.3.2.2. Parkinson Disease

In PD participants, there was a strong, positive correlation of wrist tremor amplitude between paired tasks [$r(24)>0.6, p<0.0005$] (Figure 2-5). A paired samples t-test revealed the mean wrist tremor amplitude in "rest-1" was significantly increased by 69.7% in "rest-2" task [$t(23)=2.869, p=0.009$,95%CI -0.40 to -0.06 log-RMS degrees]. However, tremor amplitude was highly correlated yet was not significantly different between postural and load paired tasks ($p>0.05$). This signified that task variation when the arm is at rest significantly modulated wrist tremor which was not observed during postural or weight-bearing paired tasks. Observing mean wrist tremor across all tasks, mean wrist tremor during "rest-2" and "posture-1" was strongly correlated ($r=0.616; p=0.001$) and a paired samples t-test revealed mean wrist tremor amplitude in "rest-2" was significantly reduced by 42.4% in "posture-1" [$t(25)=2.132, p=0.043$,95%CI 0.01 to 0.34 log-RMS degrees] and by 46.6% in "load-2" task [$t(25)=2.661, p=0.013$,95%CI 0.07 to 0.54 log-RMS degrees]. This indicated that voluntary wrist extension observed in "posture-1" (holding palms facing downwards) and in "load-2" (when gripping a weighted cup) significantly reduced wrist tremor.

Mean elbow tremor amplitude between paired tasks was strongly and statistically correlated (Figure 2-5). Mean elbow tremor in "rest-2" was significantly increased by 45.5% when compared to tremor amplitude during "rest-1" task [$t(24)=2.400, p=0.025$,95%CI -0.27 to -0.02 log-RMS degrees], similarly observed in the wrist joint; however mean elbow tremor

amplitude in “rest-1” was significantly increased by 54.9% in “load-1” [$t(24)=2.198, p=0.038$, 95%CI -0.45 to -0.01 log-RMS degrees], but was not significantly different in “load-2” [$t(24)=-1.972, p=0.060$, 95%CI -0.48 to 0.01 log-RMS degrees]. This signifies that elbow flexion in “load-1” increases elbow tremor severity and additional weight reduces elbow tremor severity, when compared to tremor severity at rest (when arm is fully supinated in lap). There were no correlations or significant differences in mean shoulder tremor amplitude across all tasks.

PD — Wrist

Wrist	Rest-1	Rest-2	Posture-1	Posture-2	Load-1	Load-2
Rest-1	1.00	0.68	0.30	0.31	0.19	0.08
Rest-2	0.68	1.00	0.64	0.53	0.41	0.31
Posture-1	0.30	0.64	1.00	0.82	0.73	0.58
Posture-2	0.31	0.53	0.82	1.00	0.73	0.78
Load-1	0.19	0.41	0.73	0.73	1.00	0.66
Load-2	0.08	0.31	0.58	0.78	0.66	1.00

PD — Elbow

Elbow	Rest-1	Rest-2	Posture-1	Posture-2	Load-1	Load-2
Rest-1	1.00	0.76	0.37	0.43	0.47	0.28
Rest-2	0.76	1.00	0.47	0.42	0.41	0.35
Posture-1	0.37	0.47	1.00	0.84	0.83	0.70
Posture-2	0.43	0.42	0.84	1.00	0.90	0.78
Load-1	0.47	0.41	0.83	0.90	1.00	0.76
Load-2	0.28	0.35	0.70	0.78	0.76	1.00

PD — Shoulder

Shoulder	Rest-1	Rest-2	Posture-1	Posture-2	Load-1	Load-2
Rest-1	1.00	0.71	0.61	0.69	0.67	0.59
Rest-2	0.71	1.00	0.54	0.49	0.49	0.42
Posture-1	0.61	0.54	1.00	0.87	0.86	0.69
Posture-2	0.69	0.49	0.87	1.00	0.87	0.78
Load-1	0.67	0.49	0.86	0.87	1.00	0.78
Load-2	0.59	0.42	0.69	0.78	0.78	1.00

1.00

0.00

Figure 2-5. Pearson’s coefficient correlation heat map of mean tremor amplitude in the wrist (top), elbow (middle) and shoulder (bottom) across all scripted tasks in PD participants.

Mean wrist and elbow tremor amplitudes were strongly correlated between all posture and load tasks and between "rest-1" and "rest-2" tasks (Figure 2-6).

		Elbow					
	Task	Rest-1	Rest-2	Posture-1	Posture-2	Load-1	Load-2
Wrist	Rest-1	0.84	0.64	0.10	0.17	0.17	0.03
	Rest-2	0.58	0.84	0.26	0.20	0.20	0.25
	Posture-1	0.35	0.66	0.62	0.60	0.56	0.48
	Posture-2	0.35	0.55	0.57	0.75	0.60	0.63
	Load-1	0.34	0.43	0.63	0.74	0.81	0.60
	Load-2	0.19	0.33	0.53	0.70	0.60	0.88

1.00

0.00

Figure 2-6. Pearson's coefficient correlation map of mean wrist and elbow tremor amplitudes across all scripted tasks in PD participants.

2.3.2.3. Comparing Essential Tremor and Parkinson Disease profiles

Mean wrist tremor amplitude was significantly higher in PD participants than ET participants during "rest-1", "rest-2" and "posture-1" tasks (Figure 2-7). There was no significant difference in wrist or elbow tremor amplitudes captured in PD and ET participants during "posture-2", "load-1" and "load-2" tasks.

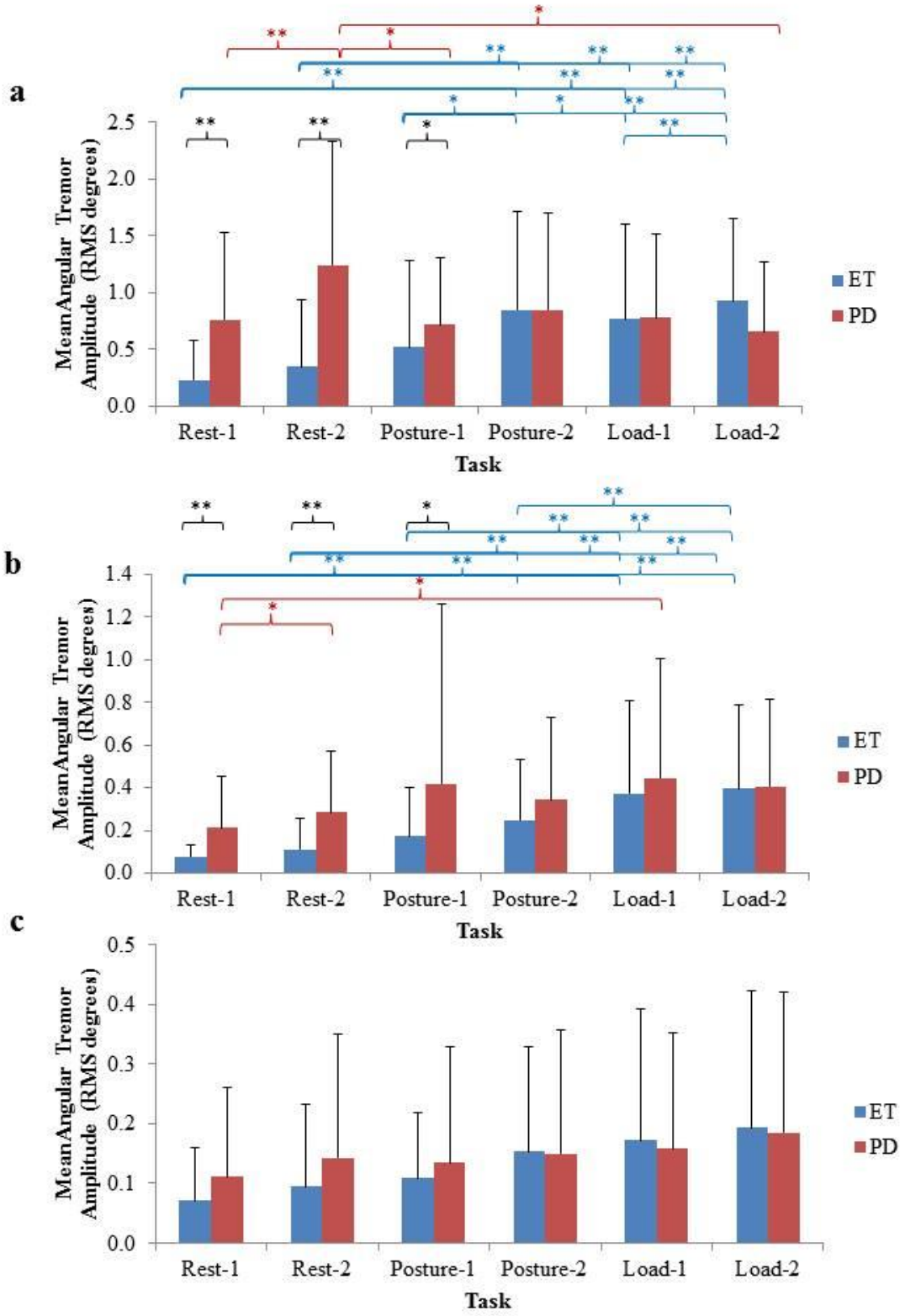

Figure 2-7. Mean joint tremor amplitude in ET and PD participants quantified in each scripted task. Error bars represent standard deviation of population.

Error bars represent standard deviation of population. Black brackets indicate between group comparisons; blue brackets indicate within ET group comparisons; red brackets indicate within PD group comparison. * represent p-value < 0.05 and ** represent p-value < 0.01 following an independent samples t-test (between groups) or a paired samples t-test (within group).

No significant correlations were found in wrist or shoulder tremor amplitudes between ET and PD participants across all tasks (Figure 2-8). However, mean elbow tremor amplitude during "posture-1" in ET participants was moderately correlated to mean elbow tremor amplitude in tasks "posture-2" (r=0.45) and "load-1" (r=0.42) and was not correlated in "load-2" in PD.

	Wrist	PD					
		Rest-1	Rest-2	Posture-1	Posture-2	Load-1	Load-2
ET	Rest-1	0.36	-0.07	-0.34	-0.26	-0.12	-0.22
	Rest-2	0.21	-0.10	-0.24	-0.24	-0.11	-0.17
	Posture-1	0.28	0.22	0.20	0.16	0.21	-0.08
	Posture-2	0.11	0.18	-0.10	-0.11	0.01	-0.15
	Load-1	0.28	0.23	0.01	0.06	0.10	0.12
	Load-2	0.11	0.32	0.12	0.19	0.26	0.20

	Elbow	PD					
		Rest-1	Rest-2	Posture-1	Posture-2	Load-1	Load-2
ET	Rest-1	-0.02	-0.26	-0.18	-0.11	0.00	-0.26
	Rest-2	0.13	0.00	0.13	0.13	0.25	0.03
	Posture-1	0.17	0.12	0.39	0.45	0.42	0.18
	Posture-2	-0.03	-0.11	0.02	0.24	0.20	0.16
	Load-1	0.09	0.09	0.13	0.26	0.22	0.21
	Load-2	0.04	0.18	0.13	0.22	0.11	0.18

	Shoulder	PD					
		Rest-1	Rest-2	Posture-1	Posture-2	Load-1	Load-2
ET	Rest-1	-0.10	-0.19	-0.08	-0.19	-0.06	-0.30
	Rest-2	0.04	-0.03	0.19	0.08	0.17	-0.06
	Posture-1	0.15	0.04	0.23	0.22	0.26	-0.03
	Posture-2	0.03	-0.10	0.08	0.12	0.18	-0.04
	Load-1	0.02	-0.15	0.11	0.15	0.16	0.10
	Load-2	-0.01	-0.01	0.05	0.10	0.13	0.02

Figure 2-8. Pearson's coefficient correlation map of mean tremor amplitude at the wrist (top), elbow (middle) and shoulder (bottom) across all scripted tasks between ET and PD participants.

2.3.3. Effect of task variation on wrist tremor composition

In ET participants, mean percent contribution of wrist tremor in the F/E DOF was significantly increased from 27.4±6.4% in "rest-1" to 33.5±8.7% in "rest-2" (Figure 2-9). Additionally, the mean F/E percent contribution was significantly reduced in "posture-2" and "load-2" compared to "posture-1" and "load-1", respectively. However, mean percent contribution of tremor in the P/S and R/U DOFs did not significantly change as a result of task variation.

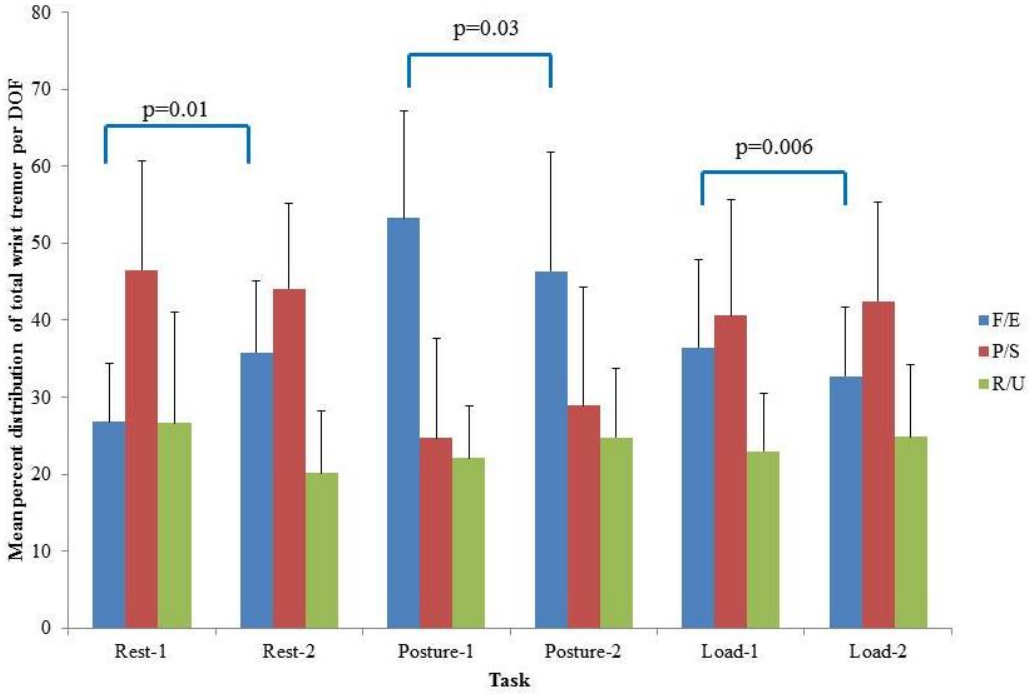

Figure 2-9. Task variation significantly modulated the mean percent distribution of wrist tremor in the F/E DOF between all paired tasks in ET participants.
P-values <0.05 represents the statistically significant mean difference.

Likewise in PD participants, the mean percent contribution to the total tremor in the F/E DOF significantly increased in "rest-2" and was reduced in "posture-2" and "load-2" tasks when compared to "rest-1" task (Figure 2-10). In addition, the amount of tremor originating from the R/U DOF significantly increased from 22.8±11.7% in "posture-1" to 28.8± 13.9% in "posture-2" [$t(25)=3.628, p=0.001$,95%CI -9.4 to -2.6], which was not observed in ET participants.

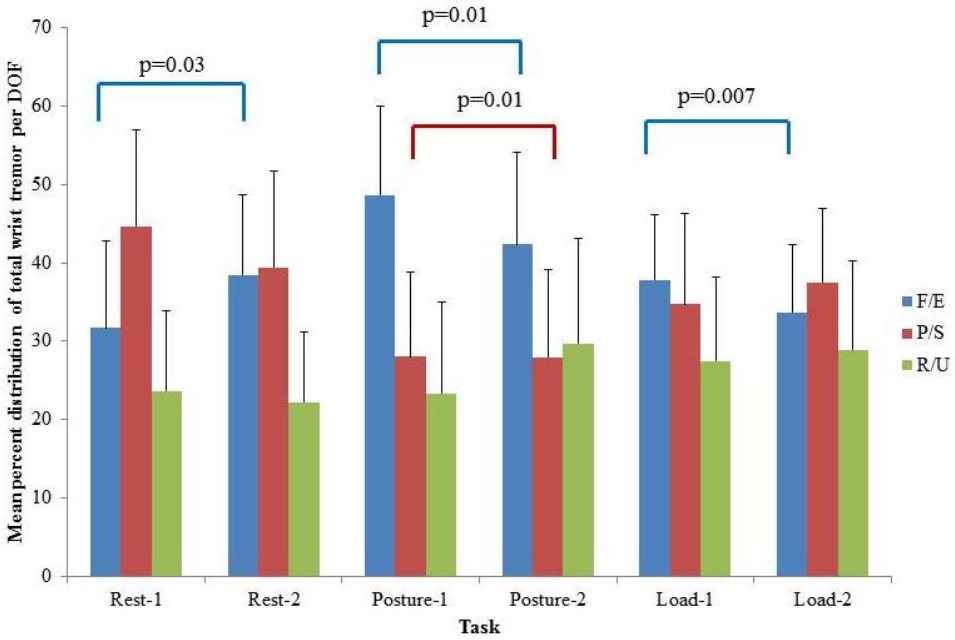

Figure 2-10. Task variation significantly modulated the mean percent distribution of wrist tremor in the F/E DOF between all paired tasks in PD participants.
P-values <0.05 represents the statistically significant mean difference of an independent samples t-test.

2.4. Discussion

This study demonstrated that multi-sensor kinematics quantified joint tremor amplitude to generate different tremor profiles based on the effect of paired tasks that alter limb positioning. As literature suggests there is a peripheral component of tremor that lies within the adrenergic mechanisms in muscle spindles, this study applied task variation to understand how modulating limb positioning can influence tremor amplitude and tremor distribution in ET and PD participants.[14,15] Detailed clinical examinations focusing on specific tremor features including amplitude, frequency, distribution and pattern, and associated clinical history can aid in further distinguishing between these two diseases.[11] However, studies of quantitative tremor analysis involving surface EMG and accelerometry have concluded that tremor frequency ranges between ET and PD are somewhat different yet there is considerable overlap.[12] Furthermore, PD and ET tremor amplitudes are similar during most positions and surface EMG studies identify patterns in PD and ET cases but these methods do not distinguish tremor types due to too much variability.[11,12] Thus, evaluation of tremor in

different limb postures has proven to be imperative in diagnostic studies as tremor features are strongly influenced by the method of measurement.[13]

Within ET participants, there was a significant and strong correlation of joint tremor amplitudes, either in the wrist, elbow or shoulder, between rest tasks and between load tasks. However, this was not observed between posture tasks, a distinctive feature of ET (Figure 2-3). Furthermore, the amplitude of wrist tremor during "posture-1" in PD was significantly higher than in ET participants, which was similar to a previous report by Jankovic in 1999.[11,16] In PD participants, mean joint tremor amplitude was significantly correlated between postural and load tasks but this was not observed between rest tasks, contrasting ET (Figure 2-5). Additionally, the effect of rest task variation significantly alters PD tremor in the wrist and elbow joint, though this was not observed in ET participants. Thus, not only does the latency of tremor onset when assuming horizontal postures differentiate PD and ET tremor types,[16] but also this study demonstrated that postural or rest task variations influenced tremor amplitudes in ET or PD participants, respectively.

Burne J et al reported that PD and ET tremor amplitudes were similar in most positions.[12] In accordance with past studies, mean tremor amplitudes in the wrist and elbow during tasks "posture-2", "load-1" and "load-2" were not statistically different and were strongly correlated between ET and PD participants (Figure 2-7). It was also interesting to observe that mean wrist tremor severity during "posture-2" and in both load tasks was strongly correlated to mean elbow tremor amplitude in both ET and PD; however, a strong correlation between wrist and elbow tremor amplitudes in "posture-1" was observed in PD but not in ET. This suggested that ET may be more susceptible to peripheral reflex modification than PD tremor when the limb is held in postural positions.[13]

Past studies observed variation of tremor amplitude during weight-bearing tasks to distinguish between pathological tremors and physiological tremor; however the effect of

weight-loading has not been utilized to distinguish ET and PD tremor types.[11,13,17] In PD, mean elbow tremor amplitude during "rest-1" was significantly lower than in "load-1" however mean elbow tremor amplitudes in "rest-1" and "load-2" tasks were statistically similar. On the other-hand in ET, mean elbow tremor amplitude was significantly greater in "posture-2" and in both load tasks when compared to "posture-1" and both rest tasks. This emphasises that greater elbow flexion increased elbow tremor in PD and ET patients but added weight reduced elbow tremor amplitude in PD and significantly increased mean elbow tremor amplitude in ET. Interestingly the increase in ET elbow tremor during "load-2" was not accompanied by a significant increase in wrist tremor however this was not the case for PD participants. Thus, this demonstrated that tremor amplitude in ET was more sensitive to the effects of change to the mechanical state of the limb.[17]

In both PD and ET participants, there was a significant change in the amount of tremor originating in the F/E DOF due to task variation (between paired tasks). In addition to change in percent contribution from the F/E DOF, a significant reduction in wrist tremor originating in the R/U DOF was observed in PD between postural tasks. A possible explanation to the significant change seen in F/E DOF as opposed to P/S DOF may be due to the greater use of wrist extensors/flexors during tasks such as: assuming palms facing downwards with arms outstretched in "posture-1", gripping a weighted cup close to chest in "load-2", and restricted wrist extensor range of motion in "rest-1" task. The analysis of the percent contribution of tremor was not considered a distinctive element of PD or ET and hence may not be diagnostically useful in the clinic setting. However, such joint tremor segmentation would be advantageous for individualizing focal therapy of tremor with BoNT-A injections.[10] In addition, this study concluded that the segmentation of shoulder tremor would also be beneficial for BoNT-A therapy as shoulder tremor analysis cannot be used to distinguish between ET and PD tremor types.

2.5. Conclusion

This thesis chapter demonstrated how task variation and limb positioning can influence unique ET and PD tremor profiles. These tremor profiles can be used to distinguish between ET and PD tremor types. The use of objective measures to quantify the relationship of wrist and elbow tremor amplitudes between paired tasks is a simple and easy method that can be applied in the clinic setting in order to aid in improving diagnostic certainty and personalizing treatments.

2.6. References

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3. Functional ability improved in Essential Tremor by incobotulinumtoxinA injections using kinematically determined biomechanical patterns – A made to measure therapy[3]

3.1. Introduction

One of the most prevalent movement disorders is essential tremor (ET), affecting 4.6% of people aged 65 and older.[1] ET is visually characterized by persistent, bilateral, mainly symmetrical postural or kinetic tremor involving distal and/or proximal arm muscles. The severity of ET gradually increases over time that may cause significant difficulty with daily tasks such as eating, grooming and other fine motor tasks. Functional disability due to tremor greatly affects the quality of life in patients who subsequently seek treatment. The most effective oral medications to symptomatically treat mild or moderate ET are primidone, an anticonvulsant, and propranolol, a beta-adrenergic receptor antagonist.[2] Although these agents reduce tremor amplitude by approximately 50%, they provide limited functional benefit and adverse side effects such as dizziness, fatigue, and bradycardia commonly occur.[3] In addition, 30% of patients have no therapeutic benefit leaving a large population with severe ET untreated.[4] Surgical therapy with thalamotomy or unilateral/bilateral thalamic deep brain stimulation is safe, although possibly effective (Level C recommendation) and is performed in patients under the age of 75 where post-operative device programming remains unclear.[2,5] Thus, a new approach for treating debilitating tremor is still a significant unmet need.

Botulinum neurotoxin type A (BoNT-A) intramuscular injections are commonly used to treat various movement disorders, such as focal dystonias, and may provide modest beneficial effects in essential tremor patients who are unresponsive to conventional pharmacotherapies.[6,7] Prior studies have reported that BoNT-A therapy reduces the severity of postural tremor with minimal improvements in clinical scores.[8-10] Despite this modest clinical benefit, BoNT-A therapy has not been widely adopted due to risk of significant hand

[3] A version of this chapter has been published (Samotus O, Rahimi F, Lee J, Jog M (2016) Functional Ability Improved in Essential Tremor by IncobotulinumtoxinA Injections Using Kinematically Determined Biomechanical Patterns – A New Future. PLoS ONE 11(4): e0153739. doi: 10.1371/journal.pone.0153739)

and wrist weakness causing functional limb impairment.[7] The primary drawback of these prior studies was utilizing a rigid dosing regimen which did not individualize and target appropriate muscles nor were appropriate BoNT-A dosages applied which failed to provide functional benefit. The fixed dosing regimen considers that tremor is similar across patients and across joints thereby defeats the advantage of using BoNT-A as a targeted and individualized focal therapy. The variation in tremor dynamics is considerable and multiple joints, wrist, elbow and shoulder, can be involved to differing degrees making visual assessments a significant challenge. Hence, it is clear that proper identification of the dynamics of the tremulous joints would allow individualization of muscle selection necessary to optimize injection pattern and outcomes.

Subjective tremor assessment tools, such as clinical rating scales are inaccurate methods of clinical evaluation that are not specific to tremor type. Characterization of tremor by kinematic methodology is objective and superior to visual inspection alone, a challenging task for a clinician. Preliminary work shows that identification of tremulous joints and muscles by accelerometers and by surface EMG can reduce the occurrence of muscle weakness.[11] Minimization of dose-dependent weakness is achievable by utilizing such objective methods to deliver individualized injection patterns.[12,13]

Multi-sensor technology has been well established, is becoming very affordable and is capable of characterizing tremor at the wrist, elbow, and shoulder.[14,15] Objective measures of the severity and direction of tremulous movements along the whole limb can be used for selecting injection sites and BoNT-A dose per muscle. Recent work in treatment of Parkinson disease (PD) tremor using methodology discussed in this paper has been successful.[16] However, clinical and biomechanical features of PD tremor are distinctly different from those seen in ET. In addition, the postural and kinetic nature of ET tremor results in different joint biomechanics and the individualization of injection patterns based upon kinematics are considerably different than in PD tremor. The current paper shows results of a first of its kind study use a kinematically guided, individualized, multi joint upper limb injection approach to

determine the efficacy and safety of incobotulinumtoxinA as a focal treatment in the longest, 38-week duration open label study involving ET participants.

3.2. Methods

3.2.1. Study Timeline

This single-centre, single-injector, open label (Health Canada CTA# 178589) pilot study recruited a convenience sampling of 24 ET participants from the London Movement Disorder Centre who completed six study visits at weeks 0, 6, 16, 22, 32, and 38 and were injected at weeks 0, 16, and 32. Assessments were carried out at all visits and peak dose effects were measured at 6 weeks after each visit. As prior studies have stated that BoNT-A peak effect is evident approximately 2 weeks to 8 weeks post-injection, the designated time-point for a follow-up visit occurred 6 weeks post-injection to encompass the peak effect.[17] Treatments were administered every 4 months instead of every 3 months, which is typically followed in the clinic setting, to incorporate a BoNT-A washout period of 1 month.[17] Each study visit consisted of clinical scales and kinematic tremor measurements. Medication was not withheld from participants during study visits. The tremor dominant limb was injected with incobotulinumtoxinA (0.5 mL of saline per 100 unit vial) using needle electromyographic (EMG) guidance (1" long 30 g injectable EMG needle using a Clavis® portable EMG machine.

3.2.2. Study Criteria

This study protocol was approved by Western University Health Sciences Research Ethics Board (REB#18445) on March 28, 2012 as a clinical phase IIb pilot study, see Appendix A. The letter of information for this study is located in Appendix B. The power calculation provided in the ethics study protocol submission suggested a target sample size of 35 ET participants, though this calculation was based on literature which did not incorporate kinematics or any objective data for guiding BoNT-A injections for tremor. As this is an open-label pilot study with no randomization, a convenience sampling was reported for those that were screened (n=25) and for those that participated in the study (n=24). Additionally, the duration of the study stated in the approved protocol is for a 96-week study over thirteen

study visits. However, the current results were significant at the timeline reported in the manuscript (six study visits over 38 weeks) as serial BoNT-A for upper limb tremor have been sparsely reported in this manner. Participants provided written consent to participate in this study by signing the study's consent form. The ethics committee provided full board approval for this study protocol and consent procedure was approved as required in the consent documentation checklist, submitted with the full study protocol. Registration with a clinical trial registry was not a requirement for ethics approval to perform the study at this institution. The authors confirm that all ongoing and related trials for this drug/intervention are now registered (ClinicalTrials.gov Identifier: NCT02427646). See Figure 3-1 for the CONSORT flowchart. The inclusion/exclusion criteria stated in Chapter 2, section 2.2.2.1 was used in this study.

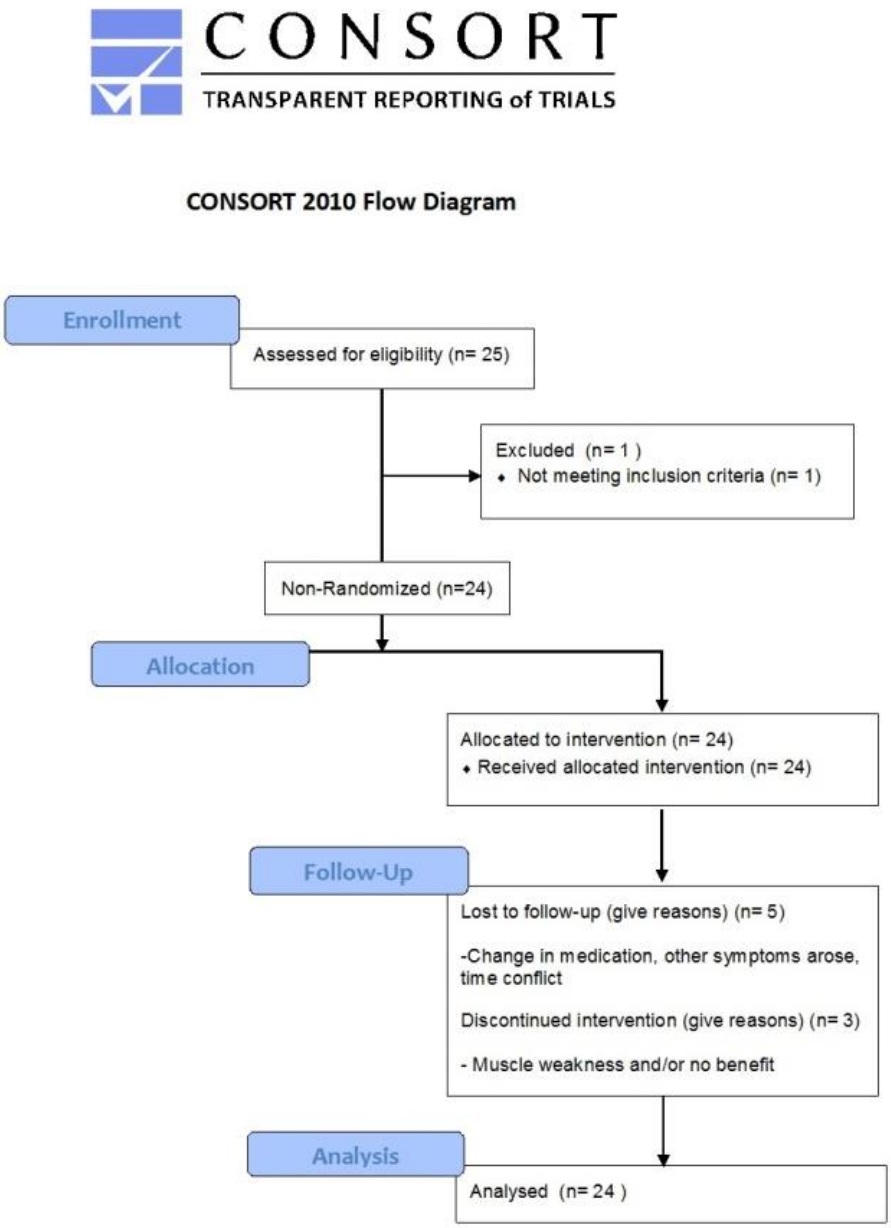

Figure 3-1. CONSORT flow diagram displaying the progress of the study's design.

3.2.3. Kinematic Assessment

3.2.3.1. Kinematic Experimental Tasks

Kinematic assessments were conducted when participants were on their anti-tremor medications as this state was deemed to be best determined after taking into account the optimal medication response. The sensor calibration tasks and a series of two postural and

two weight-bearing scripted tasks, previously described in Chapter 2 (Figure 2-1c-f), were performed by each participant while seated with motion sensor devices placed over each arm joint, as pictured in Figure 2-2 in Chapter 2. The same custom-written Matlab® code, described in Chapter 2, was used to extract angular position and angular tremor amplitude in RMS degrees from each DOF per arm joint.

3.2.4. Injection Determination

Custom written software in MatLab® (R2011a) processed raw angular signal data captured by the motion sensors was analyzed using the same methodology as in Chapter 2, section 2.2.3.3. The interpreted data displayed tremor severity, as total angular RMS amplitude, in each DOF during each task in each arm joint that was reviewed by a clinician prior to injection. The software provided a percentage contribution of the directional movements. Based upon the experienced clinician's best judgment, a preselected total dose based on tremor amplitude was divided using the percentage contribution data and was allocated to appropriate muscles for injection. Muscles selected for injection were based upon well-known anatomical basis of movement at each joint. Dosages for subsequent injection visits were based upon comparisons of kinematics at that visit to prior kinematic data. This approach allowed the experienced clinician to use the kinematic data to tailor the injections at each joint and to ensure the most appropriate muscles were selected, making the approach generalizable in the experienced clinician's hands.

3.2.5. Clinical Scale Assessment

Validated tremor severity and functional rating scales were used as primary endpoints for measuring efficacy and safety of incobotulinumtoxinA treatments. Participants completed the Fahn-Tolosa-Marin (FTM) Scale[18] consisting of parts A-C rating tremor severity, writing and functional disability caused by tremor, and the Quality of Life for Essential Tremor (QUEST)[19] questionnaire encompassing 30-items rating physical, psychosocial, communication, hobbies/leisure, and work/finance, the response to the 30-items, ranging from never = 0, rarely = 1, sometimes = 2, frequently = 3, and always = 4, were tallied for

each participant for each study visit. The assessor monitored strength in participant's fingers, distal, and proximal arm muscles by manual muscle testing (MMT), and by maximal grip strength, using a dynamometer.[20] Muscle weakness reported by participant was assessed using a Likert scale (ranging from 0 = no weakness to 4 = severe weakness in whole arm). The movement disorder neurologist, blinded to prior results, assessed tremor using UPDRS (items 20 and 21) during injection visits.[21] The FTM, QUEST, MMT and UPDRS scales are displayed in the Appendix sections C-F.

3.2.6. Statistical Analyses

IBM® SPSS® statistics version 20 was used to analyze both kinematic and clinical data using one-way repeated measures analysis of variance (ANOVA) using confidence intervals of 95% ($\alpha = 0.05$) with post hoc Bonferroni corrections for multiple comparisons performed across all time-points. Missing of random value analysis was conducted for all independent variables to ensure incomplete data sets were missing completely at random and multiple imputation method was not utilized for this dataset. Participant clinical rating scores from each time-point were analyzed by mean and dispersion of the data from the mean, standard deviation of the population. The mean angular RMS tremor amplitude across three trials for each task per study visit was log-transformed as tremor amplitudes generated skewed distributions. Acceleration values were computed by averaging the acceleration in X-axis, Y-axis and Z-axis for each task per participant at a visit. Each task was performed thrice in series per kinematic recording session. The means from each clinical rating scale and from the kinematic tremor analyses that met criteria were tested for normality using the Shapiro-Wilk test and z-score for skewness and kurtosis. The means which met criteria for parametric analysis underwent parametric ANOVA tests to investigate the presence of significant changes between time-points. If the means did not meet criteria for parametric analysis, the Friedman ANOVA test was conducted. A p-value < 0.05 for the Mauchly's test of sphericity indicated that the assumption of sphericity had been violated. The Greenhouse-Geisser correction of this bias was used when the estimated epsilon (ε) was less than 0.75 or by the Huynh-Feldt correction if estimated epsilon (ε) was greater than 0.75. Partial eta-squared (partial η^2) was reported as an estimate of the population effect size.

3.3. Results

3.3.1. Participant Demographics

Demographics and baseline clinical rating scores of the 24 ET participants are summarized in Table 3-1. 25.0% of participants (6/24) were being treated with primidone (mean dose of 125 mg/day). 4.2% of participants (1/24) withdrew following week 22 due to a myocardial infarction, unrelated to the study intervention. At week 38, 4.2% of participants (1/24) were withdrawn due to failed attendance and 4.2% of participants (1/24) withdrew due to unwanted weakness.

Table 3-1. ET participant demographics and baseline UPDRS, QUEST and FTM parts A to C scores

							Injected Limb								
ID	**Sex**	**Age**	**Weight (lbs)**	**Medications[a]**	**Motor Dominant Limb**	**Injected Limb**	**QUEST Score**	**UPDRS Item 20 (/4)**	**UPDRS Item 21 (/4)**	**FTM Part A Rest Tremor (/4)**	**FTM Part A Postural Tremor (/4)**	**FTM Part A Action Tremor (/4)**	**FTM Part B Spirals (/8)**	**FTM Part B Lines (/4)**	**FTM Part C Functional Disability (/28)**
1	M	76	175	Primidone (125 mg)	R	R	31	1	3	2	2	3	6	2	14
2	F	74	165	Primidone (125mg)	R	R	27	1	2	1	2	2	4	1	11
3	M	67	270	N/A	R	R	39	1	3	2	4	2	4	1	14
4	M	76	223	Primidone (125 mg)	R	R	49	2	2.5	1	3	3	6	2	20
5	M	78	220	Primidone (125mg)	R	R	27	0	3	0	3	3	2	1	17
6	M	84	225	Propranolol (180mg), primidone (250mg)	R	R	30	2	2.5	2	3	3	5	2	22
7	F	64	120	N/A	R	R	49	0	3.5	2	3	3	5	3	21
8	F	71	140	N/A	R	R	48	1	3.5	1	4	0	6	3	10

9	M	61	167	N/A	R	R	61	0	2.5	2	3	3	4	3	18
10	F	82	120	N/A	R	L	22	0	3	0	0	3	8	2	15
11	F	68	205	Quetiapine (400mg), Omeprazole (40mg),	L	L	49	0	3	3	3	3	7	4	17
12	M	85	221	N/A	R	R	5	0	2.5	3	2	2	5	1	14
13	F	51	160	N/A	R	R	40	1	2	1	1	0	3	2	13
14	F	66	300	N/A	R	R	61	0	3	1	3	1	7	3	23
15	F	78	155	N/A	R	R	47	0	2	2	2	1	2	2	14
16	F	65	270	N/A	R	R	42	0	3	1	2	1	4	2	12
17	M	80	175	N/A	R	R	76	0	3.5	0	3	2	8	4	29
18	F	80	130	N/A	R	R	64	1	2	1	2	1	2	2	17
19	M	61	270	N/A	R	R	44	0	2	2	2	1	2	1	13
20	F	73	200	N/A	R	R	22	0	2	2	2	1	2	1	12
21	M	84	175	N/A	R	R	39	0	2	0	1	2	8	1	20
22	M	59	227	N/A	R	R	31	0	2	1	1	1	2	1	11
23	M	71	237	N/A	L	L	30	0	3	0	3	2	4	2	19
24	M	73	197	N/A	R	R	35	0	2	2	1	1	2	2	13
Mean ± SD	11F	72.0 ± 8.9	197.8 ± 50.1	-	2L	3L	40.3 ± 15.8	0.4 ± 0.7	2.6 ± 0.6	1.3 ± 0.9	2.3 ± 1.0	1.8 ± 1.0	4.5 ± 2.1	2.0 ± 0.9	16.2 ± 4.6
Median	-	73.0	198.5	-	-	-	39.5	0.0	2.5	1.0	2.0	2.0	4.0	2.0	14.5
Range (low)	-	51.0	120.0	-	-	-	5.0	0.0	2.0	0.0	0.0	0.0	2.0	1.0	10.0
Range (high)	-	85.0	300.0	-	-	-	76.0	2.0	3.5	3.0	4.0	3.0	8.0	4.0	29.0

SD represents standard deviation of population; items 20 and 21 represent rest and action tremor UPDRS ratings. Weight data was collected as a correlational measure towards each individual's total injected joint dose and is reserved for reference for future pilot studies.

[a]Medication doses represent total daily doses. Medications listed represent current, concomitant treatment at the time of incobotulinumtoxinA therapy.

3.3.2. Selection and Administration of IncobotulinumtoxinA Treatments

Kinematics captured severity of tremor (angular RMS amplitude) and direction of the tremulous movement at each arm joint during each task. Figure 3-2a displays sample kinematic tremor measures showing quantification of tremor severity in wrist, elbow and shoulder joints (plots 1). For the wrist and shoulder joints, an additional plot calculated the distribution of the total tremor present in each degree of freedom that every joint moves in. Figure 3-2b demonstrates the injector's interpretation of the kinematics showing that the selection of the total dose was based on total tremor severity and the muscles selected were based on the distribution of tremor at each arm joint during a task. In the example in Figure 3-2a, posture-2 task generated the most severe tremor in the wrist, and load-2 induced the largest tremor amplitude in elbow and shoulder joints. Muscle groups, which generate these fundamental movements, were then injected (Figure 3-2b). Thus, the kinematic measures for all participants and their individualized injection parameters ultimately developed a dosing table from the movement disorder's clinical experience for each muscle and the dynamics of the movement at each joint.

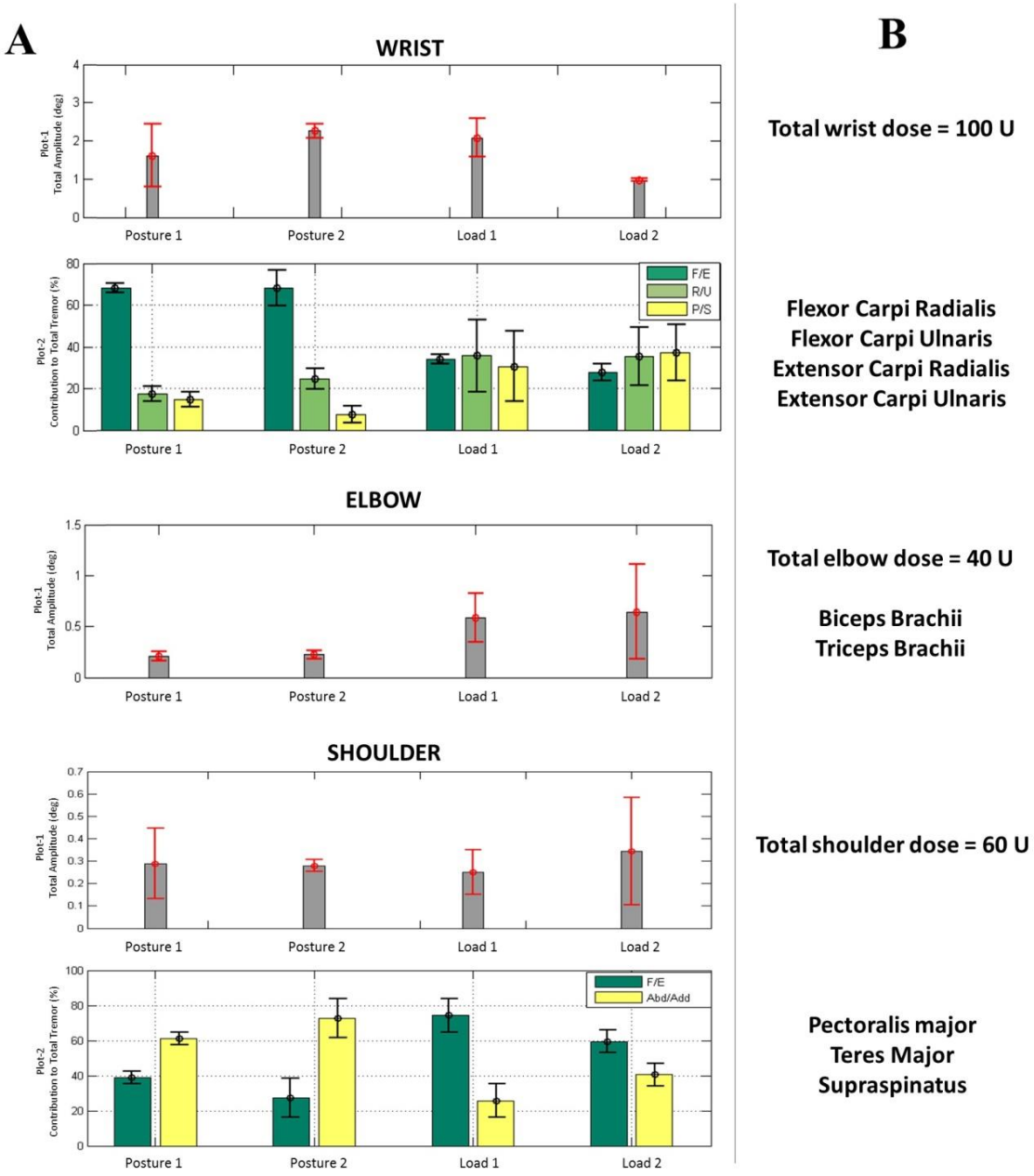

Figure 3-2. Sample kinematic data showing (A) presence of tremor in the wrist, elbow and shoulder joints and (B) the ideal injection parameters determined using the kinematics with the injector's best clinical judgement.

(A) Total tremor severity (plot 1) is displayed in angular RMS amplitude and the percent distribution of tremulous movement (plot 2) by 3 DOFs in the wrist and by 2 DOFs in the shoulder joint. Error bars indicate standard deviation over three trials. (B) Injector's interpretation of the kinematic results showing selection of total dose allocated to wrist, elbow and shoulder muscle groups based on tremor severity and the muscles selected based on the amount of tremor present in each degree of freedom that each arm joint moves in.

For optimizing this therapy, a comparison in the change in tremor, measured kinematically, from pre-injection to six weeks (BoNT-A peak effect) and to sixteen weeks post-treatment was solely used to determine whether the BoNT-A dose or muscle sites needed to be altered. A reduction in total tremor at the six week follow-up indicated the appropriate muscles were targeted. An increase in BoNT-A dose was administered if the tremor could have been reduced further, as quantified by kinematics at post-injection assessments, and no side effects were perceived by participant (outlined in the Likert scale). A reduction in dose was indicated by the participant experiencing side effects, muscle weakness, as rated by the Likert scale for muscle weakness, a rating of 3+ or lower at the wrist flexion-extension and elbow flexion-extension using manual muscle testing, which indicates weakness in injected muscles lasting more than 4 weeks, and a significant difference in maximal grip strength when compared to baseline scores.

Participants (n=24) were injected in their most bothersome arm. The mean total dose of incobotulinumtoxinA administered at the first treatment (week 0) was 169.0±62.9 U in 8.8±2.0 muscles (Table 3-2). The total dose for the second treatment was increased for 50.0% of participants (11/22), reduced for 13.6% of participants (3/22), and remained unchanged for 36.4% of participants (8/22). Between the second and third treatments, the total dose increased for 22.2% of participants (4/18), reduced for 11.1% of participants (2/18), and remained unchanged for 66.7% of participants (12/18). For the second treatment, the number of injected muscle sites increased to 10.1±2.0 muscles, which remained unchanged at the third treatment.

Table 3-2. Total injected dosage and number of muscles injected as determined by injector across all participants

	Week 0 (First Injection)	**Week 16 (Second Injection)**	**Week 32 (Third Injection)**

Patient ID	BoNT-A dose (U)	Num. of muscles injected	BoNT-A dose (U)	Num. of muscles injected	BoNT-A dose (U)	Num. of muscles injected
1	95	7	160	8	No injection[a]	
2	100	6	200	13	No injection[a]	
3	160	8	290	13	290	13
4	70	4	200	8	No injection[a]	
5	170	6	No injection[a]		No injection[a]	
6	300	9	300	9	300	9
7	200	11	100	11	100	11
8	200	9	150	9	150	9
9	195	9	300	12	300	7
10	185	10	185	10	200	13
11	100	8	200	11	200	11
12	200	8	185	9	185	9
13	170	10	170	10	165	10
14	200	11	260	11	300	11
15	100	9	No injection[b]		Withdrawn[c]	
16	200	10	200	10	260	13
17	300	11	300	14	Withdrawn[d]	
18	200	11	200	11	200	11
19	100	8	100	8	100	8
20	180	9	180	9	180	9
21	235	12	300	12	255	12
22	95	6	130	6	130	6
23	200	10	280	11	300	11
24	100	8	145	8	145	8
Mean ± SD	169.0 ± 62.9	8.8 ± 2.0	206.1 ± 65.8	10.1 ± 2.0	208.9 ± 71.0	10.1 ± 2.1

Dosing was in incobotulinumtoxinA units.

[a] = Participants presented with minimal tremor at visit and injector made a clinical judgment against injection.
[b] = Participants were not injected due to unattended study visit.
[c] = Participant withdrew from study due to other health issues.
[d] = Participant withdrew from study due to unwanted weakness.

The muscles selected and mean doses injected per muscle are listed in Table 3-3. The most frequently injected muscles during the first treatment were FCR and ECR (91.7%, 22/24). All participants were injected in the biceps for the second and third treatments.

Table 3-3. Mean injected dosage per arm muscle treated at each treatment time-point.

	Week 0 (First Injection)		**Week 16 (Second Injection)**		**Week 32 (Third Injection)**	
Muscles Injected	**Mean ± SD**	**Num. of Patients (n = 24)**	**Mean ± SD**	**Num. of Patients (n = 22)**	**Mean ± SD**	**Num. of Patients (n = 18)**
Flexor carpi radialis (FCR)	13.9 ± 4.9	22	14.5 ± 5.4	20	12.0 ± 5.6	15
Flexor carpi ulnaris (FCU)	12.4 ± 3.0	21	14.5 ± 5.8	20	12.3 ± 5.3	15
Brachioradialis	20.0 ± 0.0	2	27.5 ± 3.5	2	20.0 ± 0.0	1
Extensor carpi radialis longus (ECR)	15.7 ±5.4	22	16.5 ± 5.6	20	14.7 ± 6.7	15
Extensor carpi ulnaris (ECU)	16.2 ± 5.5	21	16.75 ± 5.9	20	15.7 ± 6.8	15
Pronator teres (PT)	15.3 ± 5.6	19	16.0 ± 5.8	21	15.3 ± 6.5	17
Pronator quadratus (PQ)	15.3 ± 5.6	19	16.0 ± 5.8	21	15.3 ± 6.5	17
Supinator	15.3 ± 5.7	17	18.2 ± 6.7	19	15.3 ± 6.7	16
Biceps brachii	28.6 ± 8.4	21	30.9 ± 8.5	22	30.3 ± 9.6	18
Triceps	28.7 ± 6.1	15	29.4 ± 7.8	18	30.6 ± 9.1	16
Pectoralis major	25.4 ± 6.3	13	25.7 ± 7.3	15	29.6 ± 10.7	13

Teres major	24.6 ± 7.5	12	25.0 ± 8.3	14	29.6 ± 11.4	12
Deltoid	28.0 ± 7.6	5	22.5 ± 5.2	6	30.0 ± 6.1	5
Supraspinatus	26.0 ± 9.6	5	21.7 ± 6.1	6	30.0 ± 8.4	6
Infraspinatus	0.0 ± 0.0	0	0.0	0	50 ± 0.0	1

All the dosages are in units of incobotulinumtoxinA. The mean values represent the average dose administered over the number of participants injected in the particular muscle. SD values represent standard deviation of population.

3.3.3. Clinical and Kinematic Efficacy Results

Over the 38-week period comprising of three injection cycles, severity of action tremor (UPDRS item 21) was statistically significantly reduced [$\chi^2(2)=17.836, p<0.0005$] from 2.6±0.5 at week 0 to 1.7±0.9 at week 16 ($p<0.0005$) and to 1.6±1.1 at week 32 ($p=0.001$). Tremor severity in the untreated limb like rest tremor (UPDRS item 20) did not significantly change during study course.

Figure 3-3a illustrates the significant decline in FTM part A score assessing tremor severity during rest, posture, and action positions. Compared to week 0, means for FTM part A score for rest tremor did not meet normal distribution, thus Friedman's test was utilized. Rest tremor was statistically significantly reduced during the BoNT-A treatment course, [$\chi^2(5)=13.809, p=0.017$]. Post hoc analysis revealed statistically significant reductions [$\chi^2(5)=37.568, p<0.0005$] in postural tremor at baseline (median:2.0) to week 6 (median:1.0;$p=0.015$), week 16 (median:1.0;$p=0.003$), week 22 (median:1.0;$p=0.007$), week 32 (median:1.0;$p<0.0005$) and to week 38 (median:1.0;$p<0.0005$). Action tremor, by post hoc analysis [$\chi2(5)=21.348, p=0.001$], demonstrated significantly decreased changes in tremor from baseline (median:2.0) to week 38 (median:0.0;$p=0.002$).

Total FTM part B sub-categorical scores rating the ability to write [$F(5,95)=2.286, p=0.049$, partial $\eta^2=0.107$] and to pour liquids with both upper limbs was statistically significantly reduced [$F(5,95)=5.867, p<0.0005$, partial $\eta^2=0.236$] by a mean

difference of 4.40±1.19 FTM points at week 22 (p=0.23), 4.45±1.25 at week 32 (p=0.31), and by 5.70±1.35 FTM points at week 38 (p=0.007) when compared to week 0 (Figure 3-3b). Total FTM part C score, rating functional ability in eight categories, was significantly reduced [$F(5,95)=11.584, p<0.0005$, partial $\eta^2=0.379$] at all time-points with a final total FTM part C sub-score of 9.5 ±6.3 ($p<0.0005$), plotted in Figure 3-3b. Post hoc analysis revealed a decrease in functional disability caused by tremor by a mean difference in FTM part C sub-score of 5.25±0.943 at week 6 ($p<0.0005$), 3.95±0.82 at week 16 (p=0.002), 5.65±0.92 at week 22 ($p<0.0005$), 4.25±0.96 at week 32 (p=0.004), and 6.05±1.12 at week 38 ($p<0.0005$). The most disabling tasks at week 0 were drinking (2.8±0.8 FTM score) and working (2.5±1.0 FTM score). Across all participants, drinking ability was significantly improved by a mean difference of 0.95±0.29 at week 6 (p=0.05) and by 0.95±0.21 at week 38 (p=0.004). Working performance was statistically significantly improved at all time-points [$F(5,90)=4.751, p=0.001$, partial $\eta^2=0.209$]. Other FTM categories such as eating, dressing and hygienic activities significantly improved and functional disability due to tremor did not return to baseline severity. ET participants reported elevated quality of life, measured by QUEST (Figure 3-3c). Mean total QUEST score was significantly reduced [$F(5,95)=4.620, p=0.001$, partial $\eta^2=0.196$]; post hoc analysis showed quality of life significantly improved at the time of and following the third treatment, by a mean difference of 9.45±2.69 at week 32 (p=0.035) and by 10.50±2.91 at week 38 (p=0.028), when compared to baseline.

Kinematic tremor assessments allowed objective monitoring of tremor severity before and after incobotulinumtoxinA therapy. Figure 3-3d displays angular tremor RMS amplitude and acceleration captured at the finger and hand values analyzed together over two postural (”posture-1” and “posture-2”) and two weight-bearing (”load-1” and “load-2”) tasks. Though joint angles and acceleration, which is quantified by the sum of acceleration in the X-, Y- and Z- axis, indicate different characteristics, they both represent tremor severity. Mean wrist RMS amplitude was significantly reduced [$F(2.297,85)=7.594, p=0.001$, partial $\eta^2=0.309$] by mean difference of 0.39±0.10 at week 6 (p=0.014), by 0.43±0.12 at week 22 (p=0.027) and by 0.41±0.09 at week 32 (p=0.005). Mean elbow tremor amplitude during both weight-

bearing tasks (load-1: $\chi^2(5) = 13.587$, p =0.018; load-2: $\chi^2(5) = 11.714$, p =0.039] produced statistically significantly different changes over treatment course. Mean elbow tremor during posture-2 (arms outstretched with palms facing inwards) [$\chi^2(5)=14.413$,p =0.013] demonstrated a significant decrease in tremor by a mean difference of 2.278±0.62 at week 32 (p=0.004). Hand tremor acceleration significantly decreased [$\chi^2(5)=27.937$,p<0.0005] across all time-points except at week 16, correlating to the change in wrist tremor amplitude (Figure 3-3d). Weight-bearing tasks produced the largest acceleration at the finger and hand.

Analyzing tremor per task (Figure 3-3e), load-2 produced the largest mean tremor amplitude of 0.9±0.7 RMS degrees (median: 0.81) in the wrist at week 0 which was significantly reduced [$\chi^2(5)=20.667$,p=0.001] to 0.5±0.6 degrees at week 6 (median:0.34;p<0.0005). Similar reduction in wrist tremor was observed during posture-1 [$\chi^2(5)=18.921$,p=0.002], posture-2 [$\chi^2(5)=22.636$,p <0.0005], and load-1 [$\chi^2(5)=22.635$,p <0.0005] tasks for all time-points excluding week 38 for posture-1 and for load-1.

Significant change in maximal grip strength [$F(2.730, 49.132)=11.155$,p <0.0005,partial $\eta^2=0.383$] coincided with peak effect of toxin but did not affect arm functionality or quality of life (Figure 4-5f). Maximal grip strength was significantly reduced from 24.7±10.7 kg at week 0 to 18.5±12.4 kg at week 6 (mean difference of 6.51±1.54; p=0.007). A significant reduction in maximal grip strength however did not indicate any impact on arm function, demonstrated on a Likert scale for self-reported perceived muscle weakness (Figure 3-3f, red line). At week 6, 12 participants (50%) reported a Likert score of 0, no weakness, two participants (8.3%) reported a 1, mild weakness with no loss in function, seven participants (29.1%) reported a 2, moderate weakness in injected muscles, and three participants (12.5%) reported a 3 indicating marked arm weakness. Following third treatment at week 38, eight participants (40%) experienced no weakness; eight and four participants reported a score of 1 and 2, respectively.

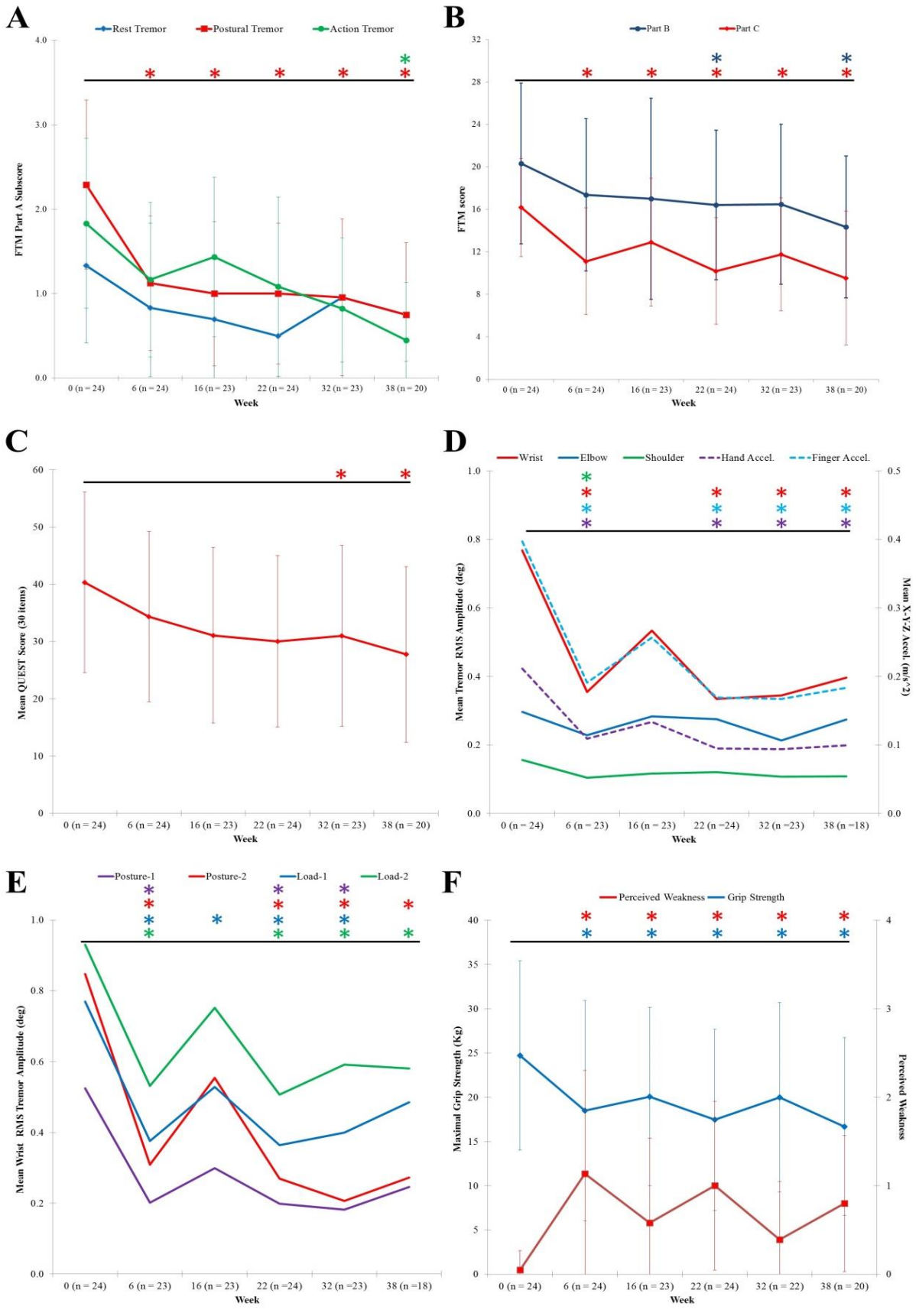
A
Rest Tremor
Postural Tremor
Action Tremor
FTM Part A Subscore
Week
0 (n = 24)
6 (n = 24)
16 (n = 23)
22 (n = 24)
32 (n = 23)
38 (n = 20)
B
Part B
Part C
FTM score
C
Mean QUEST Score (30 items)
D
Wrist
Elbow
Shoulder
Hand Accel.
Finger Accel.
Mean Tremor RMS Amplitude (deg)
Mean X-Y-Z Accel. (m/s^2)
0 (n = 24)
6 (n = 23)
16 (n = 23)
22 (n =24)
32 (n =23)
38 (n =18)
E
Posture-1
Posture-2
Load-1
Load-2
Mean Wrist RMS Tremor Amplitude (deg)
F
Perceived Weakness
Grip Strength
Maximal Grip Strength (Kg)
Perceived Weakness
32 (n = 22)

Figure 3-3. IncobotulinumtoxinA treatments significantly reduced severity of tremor and provided functional benefit for fine and gross motor tasks with mild muscle weakness in treated muscles.
(A) Tremor severity, FTM part A sub-category score (max: /4 per task), significantly decreased. (B) Handwriting, spiral and line writing tasks showed significant improvement, signified by FTM part B summed score, and functional disability, FTM part C summed score (max: /4 per category, 8 categories in total), was significantly reduced. (C) Quality of life, measured by QUEST tallied 30-items (max: /4 per item), significantly increased. (D) Angular RMS tremor amplitude (primary y-axis) and hand and finger acceleration values (secondary y-axis) at each arm joint was averaged per time-point. Significant reductions in wrist and shoulder tremor amplitudes resembled change in hand and finger acceleration values. (E) Angular wrist tremor RMS amplitude for each scripted-task was significantly reduced. (F) Maximal grip strength (blue) was significantly reduced, but did not impair function, and perceived muscle weakness (red) yielded no significant change at injection visits. All plotted values are means for all participants per each time-point. Asterisks represented statistical significant change ($p<0.05$) compared to baseline. Error bars represent standard deviation of population.

3.4. Discussion

This is the first study that uses whole limb kinematics to segment complex movements at multiple joints comprising of tremor in order to determine if efficacy and tolerability of incobotulinumtoxinA (BoNT-A) as a focal therapy is achievable. Kinematics provides an objective readout of the angular motion of tremor acting at each joint during a variety of tasks thereby providing the composition of tremor. This composition is unique for every patient and thus the selection of contributing joints, muscles that move the joint in the affected degrees of freedom and the dosing of these muscles can be individualized. An objective, repeatable platform of measuring the biomechanical properties of the tremor means that the same measurements can be carried out at any time point after the injection to determine the effect of injection. Such tools can record motion at multiple joints simultaneously, for an extended period of time, that can be averaged and thereby give a comprehensive dynamic view of the tremor. Visual assessment does not meet any of these criteria.

In the process of injection determination, the injector initially chooses a total dose based on the kinematic readout thus permitting dose allocation to muscles selected kinematically. Such targeting immediately individualizes the injections to the kinematic signature of the patient. Subsequent optimization by measuring the effect of the injection at subsequent visits is also possible, as demonstrated in this study. This longitudinal study demonstrates for the first time sustained relief of tremor and functional interference caused by ET by employing kinematics in personalizing injection parameters with a low incidence of weakness. By using such technology, a standardized method to assess tremor has been established and these results can be used to improve focal therapy thereby paving a way to offer clinicians and patients with alternate options for treating tremor.

ET patients who seek treatment suffer from functionally disabling tremor which restricts performance of every-day activities.[1] As 30% of patients do not respond to standard pharmacological medication and yet another 30% who start drug therapy will discontinue treatment due to side effects, an effective tremor therapy is needed.[4,6] Thalamotomy and thalamic stimulation is often age restricted, has strict guidelines including cognitive status, and is not accessible to many due to the requirements for a specialized centre. In addition, significant irreversible complications including dysarthria and gait difficulties can occur. As such surgical therapies are often restricted to a small group of severally disabled patients, which highlights the need for a targeted treatment such as BoNT-A injections. Prior studies have utilized BoNT–A injections as focal treatment, though significant finger and wrist muscle weakness has curtailed its use, despite its promising clinical benefit.[10,11,22–24] To improve BoNT–A efficacy and to reduce incidence of unwanted effects, this study addressed several major prior study limitations. These limitations include inability to determine the joints and their dynamics for the involved tremor, fixed and/or randomized dosing, subjective and/or fixed number of muscles selected, lack of individualization of injections to the participant's tremor, and number of injection cycles.

Accurate measurement of movement in multiple degrees of freedom at each upper limb joint is the first unmet need that has been addressed by our technology. Selection of tremulous muscles has previously been established by using a fixed method, injecting only flexor and extensor wrist muscles,[10,22,23] by using single joint surface EMG electrodes,[8] or by combining accelerometry and surface EMG.[11] The assumption here is that the tremor at the wrist is mainly unidirectional (F/E) and contributions from the elbow and shoulder joints are not measurable. Hence, accurate localization or segmentation of tremor at wrist, elbow and shoulder joints was not performed. This creates significant segmentation errors as a significant portion of the tremor originates from movements other than wrist F/E and indeed from proximal joints. Unlike accelerometers which provide tremor amplitude data for the entire arm, the sensors employed in this study allowed independent characterization of motion at the wrist, elbow, and shoulder joints, which is a difficult task by visual assessment or accelerometric and surface EMG measurements alone.[13,15,16] Based upon the composition of movement dynamics at multiple joints and in multiple directions at each joint, the contributing muscles were selected (Figure 3-2a). Injection patterns are thus tailored to each participant's kinematics (Figure 3-2b) instead of using visual methods or by standard set of injections, utilized in prior studies.

Fixed and randomized dosing, preselected muscles that may not actually be involved, while allowing a standardized approach to injection, fails to take into account an important aspect of significant individual variation in tremor. Applying objective kinematic technology to every patient uniquely provides a "read-out" of the patient's own tremor. This approach can thus reduce potential unwarranted weakness and indeed improve efficacy as the correct joints and muscles are targeted. Dose-dependent limb weakness limited functional efficacy of BoNT–A as shown in several earlier studies that utilized a fixed- or randomized-dosing method.[10,22-24] In addition, Brin MF and colleagues did display reduced postural tremor severity by using accelerometers, but could not show functional benefit following a BoNT–A treatment.[10] Hence, in this study, individualizing injection patterns optimized tremor therapy by characterizing the joints involved and by quantifying the angular displacement of tremor in each degree of freedom, an analysis only capable by the use of kinematics. Based upon the

clinician's judgment, muscles predominantly contributing to the total tremor were selected, though these muscles may vary somewhat depending upon the personal choices of the clinician.

An important unmet need with clinical assessments is the ability to change the dosing at a subsequent visit. Since visual assessment does not provide an objective record of the patient's prior limb motion, there is no objective way to compare the limb motion at subsequent visits. Kinematics is quantitative and repeatable, thereby providing a simple way for the clinician to determine the pattern of the original joint involvement and then continue optimization at any visit that is desired after that. In this study, we were able to achieve this optimization. Changes in BoNT-A dosages between treatments were calculated to optimize response by comparing the severity of tremor pre- and post-injection solely using kinematics, a personalized, targeted therapy unachievable by oral medications.

By using kinematic methodology, statistical significant functional benefit, particularly for eating, drinking and working performance reported in the FTM scale, was achieved six weeks following the first treatment and throughout the study course along with reductions in tremor severity during rest, postural, and action tasks (Figure 3-3a-e). These benefits generated a statistical significant improvement in quality of life scores, ranging across physical, psychosocial, communication, hobbies/leisure, and work/finance activities, at week 32 and 38 (Figure 3-3c), which has not been achieved in any of the prior BoNT-A studies for upper limb essential tremor.[1] Along with these physical and functional benefits, maximal grip strength was statistically significantly reduced at study visits, but functional strength was only minimally affected as demonstrated by the Likert perceived weakness scale (Figure 3-3f). A mild decrease in maximal grip strength was attributed to a modest toxin effect to the neighboring finger flexors by transfascial diffusion and/or to other synergistic muscles. Finger muscles were not directly treated because the kinematic tremor analysis did not include finger sensors. Thus, benefits of using kinematically-guided injections indicated relief of tremor, functional benefit and demonstrated less muscle weakness compared to prior

studies. These results indicate that incobotulinumtoxinA injection parameters determined using kinematics can effectively and tolerably reduce upper limb tremor, while keeping weakness related side-effects low. A clinician familiar with the anatomy and who is knowledgeable about BoNT-A dosages typically given to these muscles for other indications, such as spasticity, now has the ability to confidently treat tremor using kinematics as guidance. By accurately pinpointing joint dynamics in ET, individualization and optimization of tremor treatment is a possibility.

3.4.1. Study Limitations

Non-blinded injections and no treatment comparator were limitations of this study. However, in this longitudinal study, outcomes were kinematically and objectively determined with serial injections and hence a persistent placebo response is unlikely. Blinded studies with BoNT–A are difficult as weakness is obvious and easily perceived by participants and investigators. Similarly, cross-over designs are challenging as it is impossible to determine a true return to baseline in injected participants for accurate cross-over time. Final muscle injection pattern was determined by the treating physician and may vary. However, this allows even better individualization and flexibility. The study did not compare visually guided versus kinematically guided injections as the lack of tolerability and efficacy with injections based on visual assessments has already been demonstrated in the literature. Sample size was similar to previous literature.[10,23] As tremor is variable throughout a given day and participants were assessed while on their anti-tremor medications, severity fluctuations could have introduced error during each visit. Thus, participants were assessed around the same time of day.

It is also important to note that only one of the arms was injected to allow participants' functionality of at least one limb in case of unwarranted side effects of weakness. Although the most affected arm for functionality was treated, it is possible that even further improvements in quality of life can be achieved if both arms had been injected from the start.

3.5. Conclusion

This study clearly demonstrates that utilizing an objective, kinematically-based assessment of upper limb tremor provides a clinician with critical guidance for selecting which joints are affected and in what proportion. This allows for targeted, individualized muscle selection to significantly improve efficacy of consecutive incobotulinumtoxinA injections for tremor. For the first time, incobotulinumtoxinA injections have effectively treated essential tremor and enhanced the quality of life of patients suffering with essential tremor by improving functional ability of their whole arm.

3.6. References

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4. Effective management of upper limb parkinsonian tremor by botulinum toxin type A injections using sensor-based biomechanical patterns[4]

4.1. Introduction

Tremor is a cardinal sign of Parkinson disease (PD) and is one of the most challenging symptoms to treat. In PD patients, tremor is predominantly present at rest as compared to posture or task-specific movement.[1-3] Tremor causes difficulty in performing daily activities and significantly affects quality of life.[4] Levodopa remains the most potent drug for managing PD symptoms yet it results in significant complications such as "wearing off" motor fluctuations and dyskinesia and thus its use as a starting therapy for PD tremor is discouraged.[5-7] Dopamine agonists and anticholinergic medications can be used concomitantly with levodopa to treat tremor but may be accompanied by neuropsychiatric and cognitive side effects.[8,9] Deep brain stimulation (DBS) is an effective treatment for treating recalcitrant PD tremor though this is an invasive procedure and optimization of programming parameters still remain unclear. Therefore, physicians and patients are reluctant to use conventional pharmacotherapy as the first line of defense for tremor. Alternative methods for treating tremor must be considered, as an effective therapy is an enormous unmet need in tremor dominant PD patients.

Visual assessment of upper limb tremor is restricted by the difficultly to separate multi-joint, whole-arm movements. Characteristics of tremor such as severity at the fingers, wrist, elbow, and shoulder vary per patient and voluntary tasks alter upper limb biomechanics.[2] Wrist tremor is complicated by the wrist's ability to simultaneously flex-extend, pronate-supinate, and deviate from side to side, commonly seen during rest and described as a "pill-rolling" action in the hand.[10] Elbow and shoulder tremors are challenging to segment due to the size of these joints and consequently their small amplitude movements make significant impact at the most distal part of the arm. Similar to the wrist, the biomechanics of the shoulder simultaneously moves in two directions, abduction-adduction and flexion-extension.[11] Thus,

[4] A version of this chapter has been published for publication (*Rahimi F, *Samotus O, Lee J, et al. Effective management of upper limb parkinsonian tremor by BoNT-A injections using sensor-based biomechanical patterns. Tremor Other Hyperkinet Mov. 2015; 5. doi: 10.7916/D8BP0270. *co-authors).

understanding tremor biomechanics is crucial for targeting specific muscle groups for effective symptomatic treatment by incobotulinumtoxinA (BoNT-A) injections.

Treating upper limb tremor with BoNT-A intramuscular injection has not been widely adopted in clinical practice in PD tremor, despite some success in reducing tremor severity and improving functional rating scores.[12,13] Limited improvements were attributed to mainly muscle weakness. Significant muscle weakness from rigid protocols using a fixed dose and pre-determined group of muscles to inject, regardless of the patient's tremor characteristics, may contribute to limb weakness and subsequent loss of function.[14,15] Even with techniques such as electromyography- or ultrasound-guided needle injections that minimize toxin spread, muscle weakness can still occur.[16] Another factor contributing to the low efficacy reported in prior studies may have been due to only having one or two treatment cycles with short follow-up visits.[17,18] The lack of objective tremor assessments to monitor the dynamic movements at each joint may also be a factor hindering optimization capability and therapeutic outcome. Ultimately the selection of appropriate muscles to inject at each joint remains the most important issue which kinematics can solve by simplifying assessment of tremor and guide therapy.

Kinematic technology has been used to study the biomechanics of motion in many scenarios including gait and whole body characteristics.[19,20] The use of such multi-sensor motion recordings for tremor feature extraction is well understood.[21] Successful focal tremor therapy has recently been performed by using the biomechanics of tremor at each of the three arm joints for standardizing selection of injection parameters.[21] Thus, efficacious use of incobotulinumtoxinA, as a focal treatment, requires appropriately determined injection sites and dosage per muscle.[22] To determine these parameters, a clinician can use kinematic characterization of a patient's upper limb tremor to select muscles known to contribute to the joint movement. This was investigated in the longest-to-date open label study involving 28 PD participants who received three incobotulinumtoxinA injection treatments based upon

kinematically guided muscle selection criteria for upper limb PD tremor every 16 weeks over a 38-week duration.

4.2. Methods

4.2.1. Study Criteria and Timeline

This open label, single-centre, single-injector study (Health Canada CTA# 178589) recruited a convenience sampling of 28 PD participants from the London Movement Disorders Centre in London, Ontario who provided written consent and attended six study visits at weeks 0, 6, 16, 22, 32, and 38 and were treated with incobotulinumtoxinA (Xeomin®) at weeks 0, 16, and 32. Treatment-naïve participants were maintained on monotherapy of incobotulinumtoxinA injections for their PD throughout the study while participants on treatment did not change their medications throughout the study. Participants on stable PD medication, with inadequate tremor relief, were assessed in the "ON" state during, and at approximately the same time of the day at all study visits. Each study visit involved completion of clinical scales and kinematic tremor measurements. IncobotulinumtoxinA (0.5 mL of saline per 100 unit vial) was injected into the tremor dominant limb under electromyographic (EMG) guidance using a Clavis® portable EMG device (1" long 30 g injectable EMG needle).

4.2.2. Study Inclusion/Exclusion Criteria

The Western University Health Sciences Research Ethics Board approved this clinical phase IIb pilot study protocol (REB#18445). All ongoing and related trials for this drug/intervention are registered (ClinicalTrials.gov Identifier: NCT02427646). The study's progress is outlined in the CONSORT flowchart displayed in Figure 4-1. The inclusion/exclusion criteria outlined in Chapter 2, section 2.2.2.2 were used for this study.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

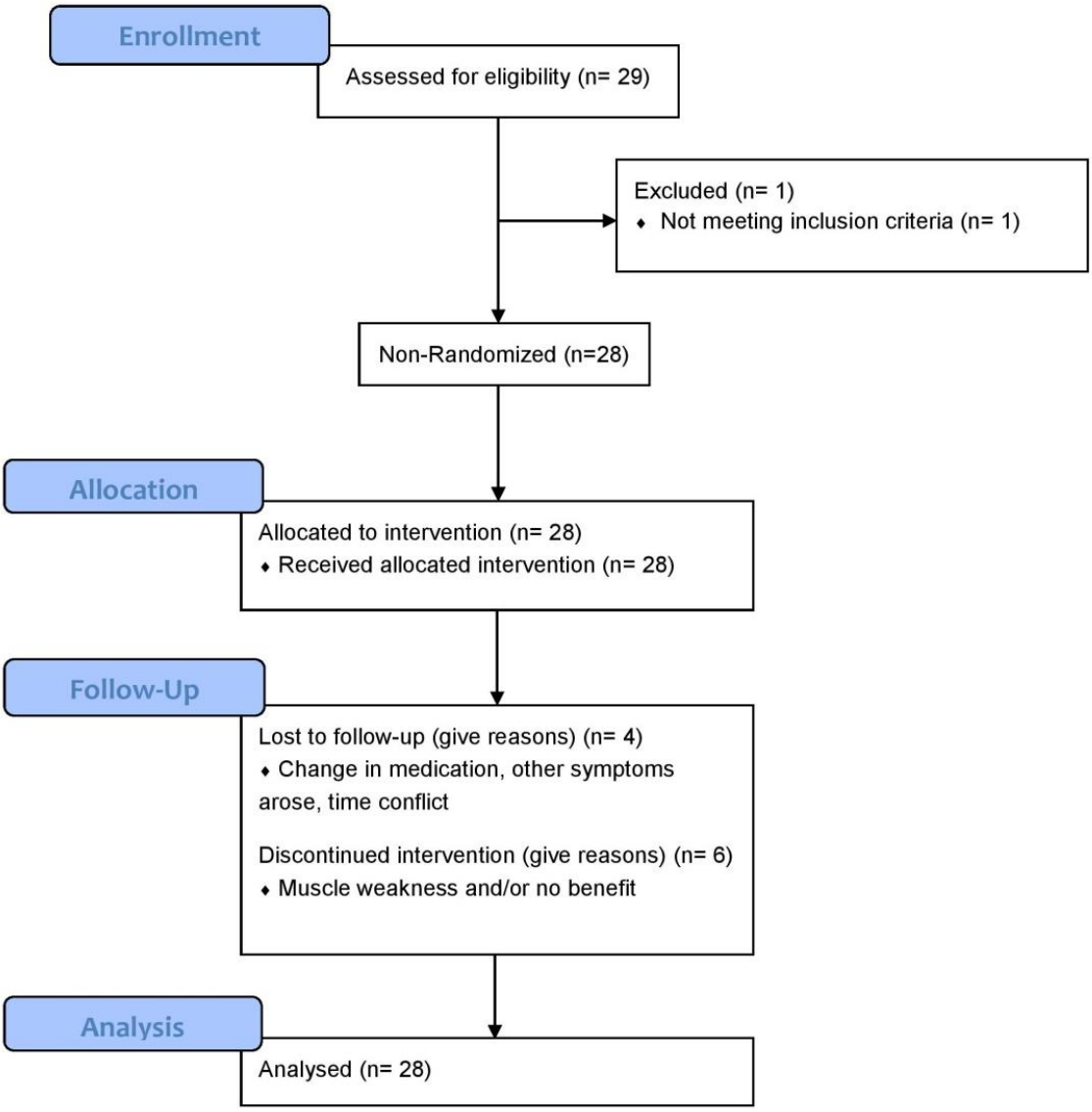

Figure 4-1. CONSORT Flow Diagram Displaying the Progress of the Study Design. Progress through the various stages of a trial including flow of participants, number of participants and reasoning of withdrawals and the number of participants included for analysis.

4.2.3. Clinical Scale Assessment

The same standardized questionnaires and clinical scales used in Chapter 3 were used for the data discussed in this current chapter (see section 3.2.5).

4.2.4. Kinematic Assessment

Kinematic measures of tremor were conducted while participants were in their "ON" state rather than their "OFF" state to reduce any overestimation of tremor severity. As participants were already stable on their oral medications, kinematic assessment was deemed to be best determined after taking into account the optimal medication response which was in the "ON" state. The sensor calibration tasks and a series of two rest and two postural scripted tasks, previously described in Chapter 2 (Figure 2-1a-d), were performed by each participant while seated with motion sensor devices placed over each arm joint, as pictured in Figure 2-2 in Chapter 2. The same custom-written Matlab® code, described in Chapter 2, was used to extract angular position and angular tremor amplitude in RMS degrees from each DOF per arm joint.

4.2.5. Injection Determination

This study followed the same protocol described in Chapter 3, section 3.2.4.

4.2.6. Statistical Analyses

The means and standard deviations of both kinematic and clinical data were analyzed using SPSS® statistics version 21 by performing one-way repeated measures ANOVA using confidence intervals of 95% (α=0.05) with post hoc Bonferroni corrections for multiple

comparisons performed across all time-points. Clinical scales were represented by mean and dispersion of the data from the mean, standard deviations of the population, for each time-point. The mean angular RMS tremor amplitude for all three trials per task at each time-point was log-transformed as tremor amplitudes generated positively skewed distributions. Tremor accelerometry values captured in the X-axis, Y-axis and Z-axis for each task were averaged per participant at each time-point. Missing of random value analysis was conducted for all independent variables to ensure incomplete data sets were missing completely at random and multiple imputation method was not utilized for this dataset. The means from each clinical rating scale and from the kinematic tremor analyses that met criteria were tested for normality using the Shaprio-Wilk test and z-score for skewness and kurtosis. The means that met parametric analysis criteria underwent parametric ANOVA tests to determine the presence of significant changes between time-points when compared to week 0. Means which did not meet parametric test criteria were tested using the Friedman's test. Partial eta-squared (partial η^2) was reported as an estimate of the population effect size.

4.3. Results

4.3.1. Participant Demographics

Demographics and baseline clinical scores of the 28 PD study participants are shown in Table 4-1. Following the first treatment at week 16, 11% of participants (3/28) withdrew due to experiencing both inadequate functional benefit and bothersome muscle weakness. Following the second treatment at week 32 and focusing on the remaining 89% of participants (25/28), one participant withdrew due to unwanted weakness, and two participants failed to maintain inclusion criteria such as lack of study attendance and medication change. Of the remaining participants (22/28), four did not continue past week 32 due to: unwanted weakness (9%, 2/22), failed study attendance (4%, 1/22), and change in other PD symptoms (4%, 1/22). Thus, only a total of six PD participants (21%) experienced unwanted weakness warranting study withdrawal following three treatments. However, this implies that 79% of patients did not have enough weakness to discontinue participation in the study.

Table 4-1. PD participant demographics and baseline UPDRS scores.

							Baseline Scores		
Patient ID	**Gender**	**Age**	**Years with tremor**	**Injected limb**	**Dominant limb**	**Weight (lbs)**	**Item 20 Non-treated arm (/4)**	**Item 20 Treated arm (/4)**	**Item 21 Non-treated arm (/4)**	**Item 21 Treated arm (/4)**
1	F	71	11	L	R	170	0	2	1	2
2	M	35	7	R	R	350	0	2	0	3
3	M	62	7	R	R	175	0	3	0	0
4	M	79	7	R	R	165	2	3.5	1	1
5	M	53	10	L	R	-	2	3	1	2.5
6	M	43	5	L	R	-	1	2	1	2
7	M	60	7	R	R	225	1	3	1	2.5
8	M	79	14	R	R	-	4	4	2	2
9	M	59	11	R	R	275	2	2	1	1
10	F	77	9	L	R	185	1	3	1	2
11	M	62	5	R	R	203	2	3	0	0
12	M	66	7	R	R	185	0	2.5	1	1
13	M	76	6	R	R	152	1	2	0	1
14	F	54	6	R	R	140	0	2	1	0
15	F	50	-	R	R	-	0	3	0	2
16	F	75	-	R	R	-	0	3	2	2
17	F	62	8	L	R	152	2	3.5	1	2.5
18	F	47	14	R	R	193	1	2	1	2
19	F	71	-	R	R	-	0	2.5	1	2
20	M	80	9	R	R	150	0	3.5	0	0
21	M	59	7	L	R	170	0	3	0	2

22	M	69	6	R	R	234	0	3.5	0	2.5
23	F	70	6	R	R	165	2	2	2.5	2.5
24	M	68	14	R	R	160	3	3	1	1
25	M	70	7	R	R	165	0	3.5	0	3.5
26	M	69	-	L	R	215	0	2	0	1
27	F	80	5	R	R	150	1	2.5	1	1
28	F	66	-	L	R	168	1	2.5	0	1
Mean	7F	65.5	7.5	8L	1L	188.2	0.9	2.7	0.7	1.6
± SD		± 11.5	± 3.1			± 47.5	± 1.0	± 0.6	± 0.7	± 0.9

Weight data was collected as a correlational measure towards each individual's total injected joint dose and is reserved for reference for future pilot studies. F, Female; L, Left; M, Male; PD, Parkinson's Disease; R, Right; SD, Standard Deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

4.3.2. Selecting Kinematically-Based IncobotulinumtoxinA Injection Parameters

Kinematics was utilized to quantify two key characteristics of tremor for optimizing incobotulinumtoxinA therapy: severity of total tremor (angular RMS amplitude) and directional contribution of the tremor at each arm joint. Figure 4-2a displays a sample participant's kinematic tremor measures during each of the four tasks by plotting the total tremor severity (plots 1) in the wrist, elbow and shoulder joints and segmenting total tremor in the wrist and shoulder joints by directional movements of the total tremor (plots 2). The task with the largest tremor amplitude served as a biomechanical basis for determining BoNT-A injection parameters. The movement disorders neurologist interpreted the kinematics by basing the total dose on total tremor severity (plots 1). This total dose was ultimately divided amongst select muscles which generated these fundamental tremulous movements, focusing on the distribution of the total tremor in each DOF (plots 2) at each arm joint (Figure 4-2b). In the example in Figure 4-2a, "rest-2" task, with forearm supported, generated the largest tremor severity at the wrist, elbow and shoulder joints. Thus, allocation of the total dose was distributed according to the division of the total tremor, illustrated in plot 2 for wrist and shoulder joints in Figure 4-2a.

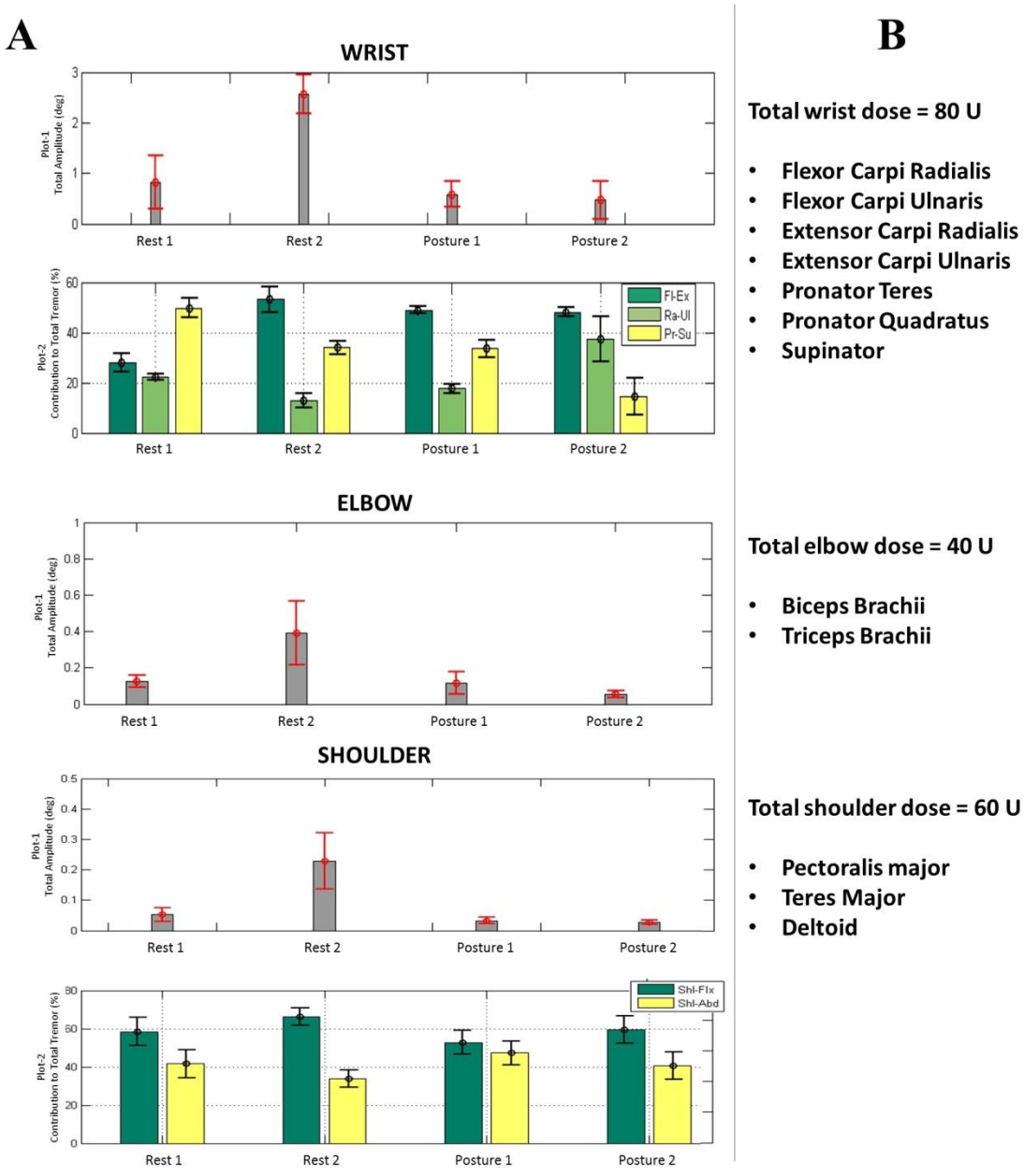

Figure 4-2. Sample participant kinematic data readout of tremor generated from the wrist, elbow and shoulder joints and individualized muscle selection based on both kinematic tremor profile and the injector's best clinical judgement.
(A) Total tremor severity (plot 1) is displayed in angular RMS amplitude and the percent directional contribution of tremulous movement (plot 2) by 3 DOFs in the wrist and by 2 DOFs in the shoulder joint. Error bars indicate standard deviation over three trials. (B) Injector's interpretation of the kinematic results showing selection of total dose allocated to wrist, elbow and shoulder muscle groups based on tremor severity and the muscles selected based on the amount of tremor present in each degree of freedom each arm joint moves in.

Injection parameters were optimized solely using kinematics by comparing the change in tremor at baseline to kinematic measures of tremor at six weeks and sixteen weeks post-treatment. A reduction in total tremor during a task at the six week follow-up visit indicated the appropriate muscles were targeted. An increase in BoNT-A dose was required if the tremor could have been reduced further, as quantified by kinematics at post-treatment assessments, and no presence of side effects as perceived by participant (reported in the Likert scale). A reduction in dose was indicated by the participant experiencing prolonged muscle weakness in injected muscles lasting more than one month, as rated by the Likert scale for muscle weakness, and reporting weakness as functionally bothersome.

The mean total dose per arm did not significantly change between the first and third treatments, however the mean number of injected muscles gradually increased, shown in Table 4-2. The total dose for the second treatment was increased for 47.6% of participants (10/21) and was reduced for 14.2% (3/21). Of those who required an increased BoNT-A dosing at the second treatment, at the third treatment, 10% of participants (1/10) required a reversal of the increased BoNT-A reverting to the original parameters and 20% of participants (2/10) required an additional increase in the total dose. One participant whose total dose increased at the second treatment was not injected at the third treatment due to prolonged moderate muscle weakness. The total dose was reduced for 13.3% of participants (2/15) whose parameters were not altered during the second treatment though required a reduced total dose at the third treatment.

Table 4-2. Total injected dosage and number of muscles injected as determined by injector across all participants

	Week 0 (First Injection)		Week 16 (Second Injection)		Week 32 (Third Injection)	
Patient ID	BoNT-A dose (U)	Num. of muscles	BoNT-A dose (U)	Num. of muscles	BoNT-A dose (U)	Num. of muscles

		injected		injected		injected
1	100	6	No Injection*		75	8
2	200	7	200	7	No Injection*	
3	100	6	100	6	No Injection*	
4	100	8	200	8	No Injection*	
5	100	8	100	8	No Injection*	
6	100	6	Withdrawn[#]		Withdrawn[#]	
7	200	8	No Injection*		200	8
8	275	8	Withdrawn[#]		Withdrawn[#]	
9	260	9	390	11	No Injection*	
10	125	7	No Injection**		125	7
11	140	8	175	9	No Injection***	
12	100	8	170	8	100	8
13	175	8	175	8	135	8
14	95	7	95	7	95	7
15	320	11	350	11	Withdrawn[#]	
16	200	11	Withdrawn[##]		Withdrawn[##]	
17	200	11	280	9	300	8
18	200	10	200	10	200	10
19	200	6	Withdrawn[#]		Withdrawn[#]	
20	265	13	300	13	300	13
21	200	8	280	12	300	13
22	200	8	100	8	100	8
23	190	11	170	11	170	11

24	200	8	200	8	200	11
25	300	12	300	12	300	12
26	100	7	200	9	Withdrawn[##]	
27	130	9	200	11	200	11
28	100	6	80	6	Withdrawn[###]	
Mean ± SD	174.1 ± 66.8	8.4 ± 1.9	203.1 ± 84.4	9.1 ± 2.0	186.7 ± 79.5	9.5 ± 2.1

Dosing was in incobotulinumtoxinA units. * = Participant presented with minimal tremor at visit and injector made a clinical judgment against injection. ** = Participants subjectively reported prolonged mild unwanted weakness in non-injected muscles in treated arm, but had functional benefit. *** = Participant perceived prolonged moderate wrist extensor weakness with limited functional benefit. [#] = Participant withdrew from study due to wrist extensor weakness. [##]= Participant withdrew from study due to lack of time commitment. [###] = Participant withdrew from study due to changes in PD symptoms and met exclusion criteria.

Muscles selected and mean administered dose per muscle are summarized in Table 4-3. For the first treatment, all participants were injected in FCU and ECU. The most frequently injected muscles during the second injection cycle (20/21) were ECU, PT and PQ and FCR, ECR, PT, PQ and supinator during the third treatment (14/15).

Table 4- 3: Mean injection dosage by arm muscle treated at each treatment time-point.

	First injection (Week 0)		**Second injection (Week 16)**		**Third injection (Week 32)**	
Muscles injected	**Mean ± SD**	**Num. of patients (n = 28)**	**Mean ± SD**	**Num. of patients (n = 21)**	**Mean ± SD**	**Num. of patients (n = 15)**
Flexor carpi radialis (FCR)	16.3 ± 7.0	24	15.6 ± 5.7	17	13.6 ± 5.8	14
Flexor carpi ulnaris (FCU)	16.8 ± 6.7	28	16.1 ± 5.8	19	14.2 ± 5.5	13
Brachioradialis	20.0 ± 0.0	1	20.0 ± 0.0	1	20.0 ± 0.0	1
Extensor carpi	18.5 ± 8.2	24	17.5 ± 5.8	18	16.1 ± 5.4	14

radialis longus (ECR)						
Extensor carpi ulnaris (ECU)	18.6 ± 7.9	28	17.5 ± 5.8	20	16.5 ± 5.3	13
Pronator teres (PT)	17.4 ± 5.1	25	17.8 ± 4.9	20	15.7 ± 4.2	14
Pronator quadratus (PQ)	16.0 ± 4.9	25	17.3 ± 5.1	20	15.4 ± 4.8	14
Supinator	17.3 ± 4.5	22	18.1 ± 4.8	18	16.8 ± 7.0	14
Biceps brachii	33.9 ± 10.3	23	36.3 ± 10.4	19	30.4 ± 9.7	12
Triceps	29.5 ± 10.1	10	32.7 ± 9.6	11	28.1 ± 9.3	8
Pectoralis major	33.3 ± 8.8	9	34.5 ± 13.0	11	28.1 ± 9.3	6
Teres major	25.8 ± 6.7	6	30.0 ± 12.2	8	29.2 ± 10.6	8
Deltoid	30.0 ± 9.4	4	32.0 ± 9.3	5	30.0 ± 5.5	5
Supraspinatus	28.0 ± 2.4	5	30.0 ± 5.5	5	27.5 ± 2.5	4

All the dosages are in units of incobotulinumtoxinA. The mean values represent the average dose administered over the number of participants injected in the particular muscle. SD value represents standard deviation of population.

4.3.3. Clinical and Kinematic Efficacy Results

Severity of rest tremor (UPDRS item 20) in treated arm was significantly reduced [$F(2,40)=8.378$,$p=0.001$, partial $\eta^2=0.295$] from 2.7±0.6 at week 0 to 2.0±0.8 at week 16 [$p=0.006$] and to 2.1±0.7 at week 32 [$p=0.014$]. Action tremor (UPDRS item 21) was reduced in the treated arm from 1.6±0.9 at week 0 to 0.9±1.0 [$p=0.09$] at week 16 and to 1.0±0.8 at week 32, though this was not statistically significant [$F(2,40)=2.832$,$p=0.071$, partial $\eta^2=0.124$] (Figure 5a).

FTM part A score, indicating tremor severity, significantly reduced [$F(5,65)=2.043$,$p=0.024$, partial $\eta^2=0.136$] at week 6, compared to week 0 (Figure 5b). Though mean total FTM part B

score assessing handwriting and pouring function did not produce a significant reduction [$F(5,60)=1.820, p=0.123$, partial $\eta^2=0.132$]. 25% of participants (7/28) indicated their arm tremor was the root source of functional disability, as opposed to other PD symptoms interfering with ADLs including eating, drinking, and working tasks (Figure 5b). For these participants, eating (solid food) FTM subcategory score was significantly reduced [$F(5,30)=2.558, p=0.048$, partial $\eta^2=0.299$] and produced strong evidence of functional improvement from 2.3±0.4 at week 0 to 1.3±0.7 [p=0.056] at week 38, though this was not significant as demonstrated by Bonferroni pairwise comparisons.

Kinematics displayed a significant reduction in tremor severity at each arm joint during rest and postural states over the treatment course (Figure 5c). By analyzing tremor severity over all of the four tasks, a statistically significant reduction in RMS tremor amplitude [$F(5,65)=7.096, p<0.0005$, partial $\eta^2=0.353$], captured by motion-sensor devices, was displayed in the wrist alone (Figure 3c); this was observed following the initial treatment at week 6 [p=0.004], at week 32 [p=0.032], and following the third treatment at week 38 [p=0.003]. Though tremor acceleration, averaged X-, Y- and Z-axis values, and joint amplitudes both measure tremor severity, they indicate different characteristics. Mean finger acceleration over the four tasks resembled a similar change in tremor severity to wrist joint angles and significantly decreased [$F(5,65)=9.057, p<0.0005$, partial $\eta^2=0.411$] following first injection at week 6 [p=0.001], following the second treatment at week 22 [p=0.028], at week 32 [p=0.03] and following the third treatment at week 38 [p=0.003] (Figure 3c). Likewise, tremor accelerometry captured at the hand demonstrated significant reduction [$F(5,65)=7.786, p<0.0005$, partial $\eta^2=0.375$] at week 6 [p=0.003], week 22 [p=0.006], week 32 [p=0.003], and at week 38 [p=0.003] (Figure 5c). The severity of elbow tremor amplitude significantly decreased [$F(5,65)=3.962, p=0.003$, partial $\eta^2=0.234$] from 0.46±1.240 at week 0 to 0.08±0.272 RMS at week 6 (p=0.029) (Figure 5c). Shoulder RMS tremor amplitude did not significantly change over study course.

Analyzing tremor severity per task, mean wrist RMS amplitude during "rest-1, supinated hand laying on participant's lap, did not significantly change [$F(5,65)=1.422$,$p=0.228$, partial $\eta2=0.099$] (Figure 5d). Though RMS tremor measured during "rest-2", forearm partly pronated while supported, was significantly reduced ([$F(5, 65) = 3.740$, $p=0.005$, partial $\eta^2=0.223$] from 1.2±1.2 at baseline to 0.7±1.1 at week 6 [$p=0.045$] and to 0.6±0.7 at week 32 [$p=0.004$]. Mean wrist RMS amplitude during "posture-1" was significantly reduced [$F(5,65)=7.410$,$p<0.0005$, partial $\eta2=0.363$] at week 6 [$p=0.003$], week 22 [$p=0.026$], and at week 32 [$p=0.05$]. Wrist tremor amplitude captured during "posture-2" was significantly reduced [$F(5,65)=4.205$, $p=0.002$, partial $\eta^2=0.244$] at week 6 [$p=0.013$]. Finger acceleration significantly decreased [$F(5,65)=8.538$,$p<0.0005$, partial $\eta^2=0.396$] during "posture-1" at week 6 [$p=0.005$], week 22 [$p=0.009$], week 32 [$p=0.23$] and at week 38 [$p=0.027$] (Figure 5e). Likewise, finger acceleration during "posture-2" decreased [$F(3.025,40.112)=4.589$,$p=0.007$, partial $\eta^2=0.261$] at week 6 [$p=0.025$]. During "rest-2", finger tremor acceleration significantly reduced [$F(5,65)=3.876$,$p=0.004$, partial $\eta^2=0.230$] at week 6 [$p=0.023$] and at week 38 [$p=0.005$].

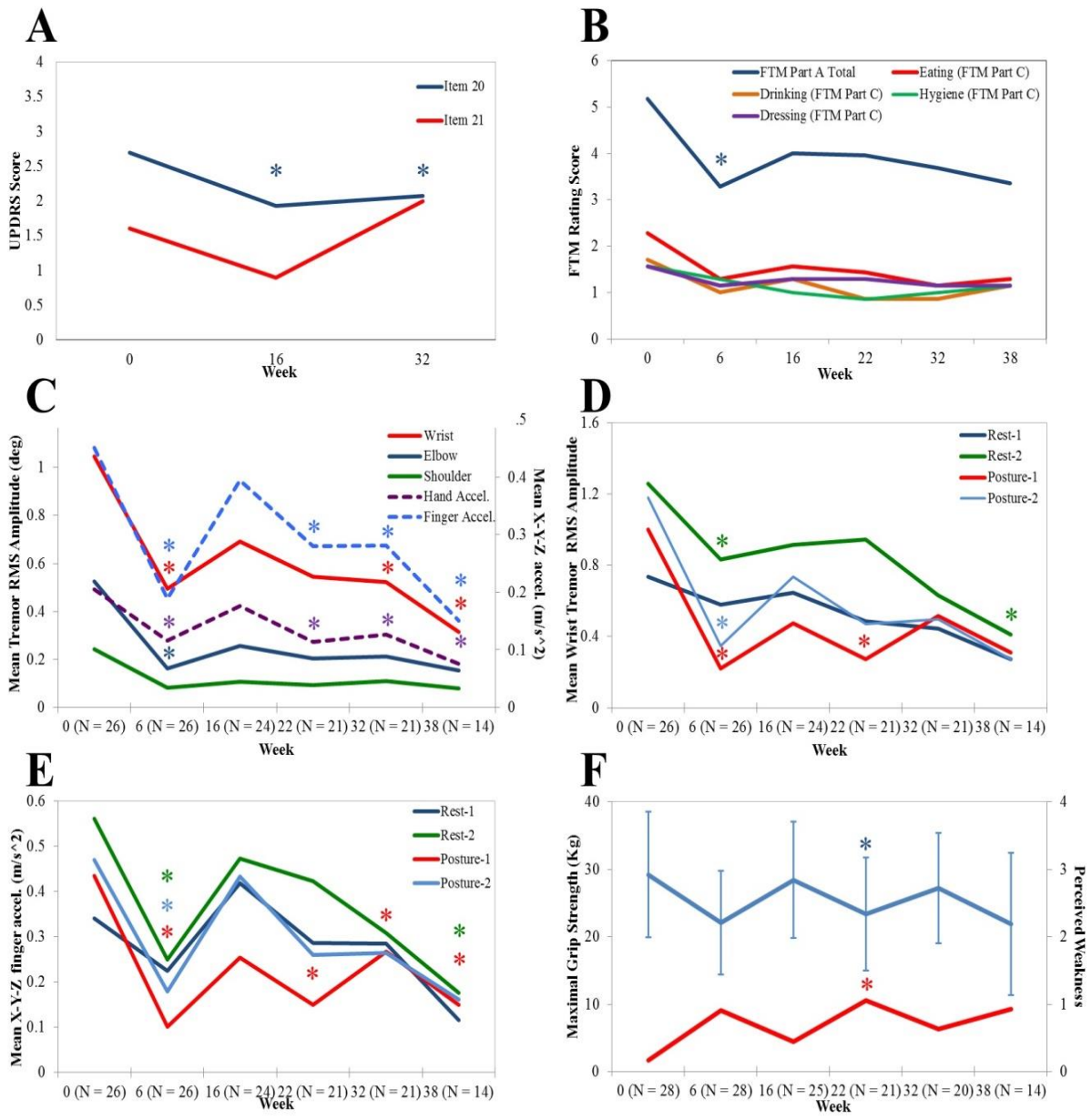

Figure 4-3. IncobotulinumtoxinA treatments significantly reduced tremor severity and improved arm function in the treated arm of PD participants reported qualitatively and quantitatively.

(A) UPDRS item 20 and 21 mean scores (max: 4/arm) for rest and action tremor, respectively. (B) FTM part A score (max: 12/arm), sum tremor severity during rest, posture and action tasks, significantly decreased. FTM part C score (max: 4/category), functional disability, was significantly reduced for eating tasks (N=7). (C) Angular RMS tremor amplitude (primary y-axis) and hand and finger accelerometer values (secondary y-axis) for each arm joint were averaged over 2 rest and 2 postural tasks per time-point. Significant

reductions in wrist amplitude and finger accelerometry were observed. (D) Angular wrist tremor RMS amplitude displayed for each rest and postural task showed significant reduction. (E) Maximal grip strength (blue) and perceived muscle weakness (red) yielded significant change at week 22. Asterisks represent statistically significant change ($p<0.05$) compared to baseline. Error bars represent standard deviation of population. Sample size (N) shown in brackets displayed on the x-axis.

4.3.4. Side Effects

Maximal grip strength was significantly reduced [$F(5,60)=6.350, p<0.0005$, partial $\eta^2=0.346$] from 29.2±9.5 kg at week 0 to 21.8±9.4 kg at week 22 [$p=0.05$] and returned to baseline strength of 24.4±8.8 kg at week 32 (Figure 5f). Significant change in maximal grip strength was perceived as mild weakness in injected muscles by participants, a mean rating of 1 out of 4 on the Likert scale of muscle weakness. Though significant change in perceived weakness occurred following the second treatment, an increase from 0.2±0.4 at week 0 to 1.1±0.6 at week 22 [$p=0.03$]. This coincided with the peak effect of incobotulinumtoxinA. Mean maximal grip strength of the untreated arm was 32.3±11.1 kg at week 0 and remained unchanged over the treatment course. Severity and frequency of perceived weakness reported in the Likert scale for each time-point is summarized below in Table 4.

Table 4-4. Number of participants who perceived weakness using a Likert scale over the treatment course

Time	Number of participants per Likert score				
	0	**1**	**2**	**3**	**4**
Week 0 (n = 18)	15	3	-	-	-
Week 6 (n = 21)	9	6	5	1	-
Week 16 (n = 18)	11	6	1	-	-
Week 22 (n = 17)	4	8	5	-	-
Week 32 (n = 19)	9	8	2	-	-

Week 38 (n = 14)	4	8	1	1	-

Note: Likert scale scores ranged from 0 = no weakness, 1 = mild weakness in non-injected muscles, 2 = mild weakness in injected muscles, 3 = moderate weakness in injected muscles and 4 = severe weakness in injected muscles.

4.4. Discussion

Although tremor is not the most disabling symptom in PD, patients perceive tremor as an important symptom that requires treatment.[4] Benefits from recommended treatments for PD tremor are often unsatisfactory and result in side effects of these medications.[23] In addition, for PD patients with tremor as their only troublesome symptom, treatment with current oral medications becomes a therapeutic dilemma as these drugs may contribute to motor fluctuations and dyskinesia later in life. Hence, levodopa sparing becomes an important variable to consider in treatment of tremor. Previous studies have shown botulinum neurotoxin type A (BoNT-A) injections as a possible focal treatment for tremor, although finger and wrist extensor muscle weakness and dose-dependent limb weakness frequently occurred.[14,15,18,24,25] Brin MF et al and Pullman SL et al applied a fixed-dosing regimen and subjectively determined injection sites which resulted in the occurrence of dose-dependent hand weakness thereby reducing any functional efficacy of BoNT-A.[14,15] Trosch RM and Pullman SL demonstrated in an open label study that five of the ten PD patients moderately improved in clinical tremor scores though accelerometry measures for rest tremor did not significantly change.[18] The limitations of these prior studies that reduced the effectiveness of BoNT-A therapy were attributed to single injection studies, visually selecting muscles to inject or using fixed-dosing parameters regardless of the patient's tremor severity. As such, BoNT-A for PD tremor is not widely adopted in clinical practice based on these past results.

The present study demonstrates that by individualizing BoNT-A injection parameters based on the biomechanical pattern of tremor at the wrist, elbow and shoulder joints, targeted focal therapy greatly improved efficacy without impairing arm function. As accelerometers placed on the hand/fingers cannot distinguish and segment tremor originating from wrist, elbow, or shoulder joints,[26] this study simplified the complexity of tremor by utilizing sensor-based

recordings in conjunction with custom-written software to characterize each patient's tremor profile.[27] Kinematics allows independent and separate characterization of joint motion along the arm for every patient, which is not possible with visual assessments. Furthermore, injection patterns can be tailored to each patient's kinematics (Figure 4) instead of depending on visual methods or using a standard set of injections, as employed in prior studies.[14]

The significant, palliative effect of incobotulinumtoxinA on whole arm tremor severity was clearly demonstrated both clinically and kinematically (Figure 5). Kinematically determined BoNT-A parameters showed efficacious results by observing a significant decrease in (UPDRS item 20) for all study time-points following the first treatment. Action tremor (UPDRS item 21) severity demonstrated a trending decline in rating though this was not significant (Figure 5a). Likewise, FTM tremor severity score displayed significant improvement in rest, postural and action tremor at week six which continued to week 38. Those seven participants who found tremor to be functionally bothersome at baseline demonstrated significantly improved eating and function of daily tasks, a significant enhancement in quality of life (Figure 5b). These functionally beneficial improvements in fine and gross motor skills continued to occur following the peak effect of BoNT-A. Reduced maximal grip strength during peak activity of BoNT-A (Figure 5f) was not perceived to be functionally bothersome as participants rated such weakness as a 1 out of 4 on the Likert scale, indicating mild weakness in injected muscles. Though maximal grip strength decreased by 25% following the first treatment and 57% of participants (12/21) experienced third finger extensor weakness, this was perceived as slight to mild weakness though these effects were reported as not troublesome. This demonstrated that kinematically-based BoNT-A injection patterns minimize the likelihood of adverse functional impairments.[14] As weakness in non-injected muscles (e.g. finger extensors) and in injected wrist muscle groups did occasionally occur, a need for further refinement of injection techniques is required for future studies, such as incorporating ultrasound-guided injections could be considered.[16]

Dosages per muscle, in particular elbow and shoulder muscle groups (Table 3), were substantially lower than previous studies involving treatment of PD, cerebellar and essential tremor.[15] As dosing was calculated based upon the quantified tremor amplitude, the best medicated i.e. "ON" state was chosen. Thus, tremor treatment with BoNT-A was provided concomitantly over and above the best treated oral medication state. An average of eight muscles was injected, which was more than prior literature reported value.[24,25] It is possible that kinematic determination of joint dynamics of tremor would allow better optimization of injections, thereby reducing muscle weakness.[15]

4.4.1. Study Limitations

Study limitations were non-blinded injections and having no treatment comparator and as this was an open-label study, results are subject to bias. As outcomes in this longitudinal study are both qualitative and quantitative, a persistent placebo response is unlikely. Since weakness is obvious to perceive by both the clinician and the participant, long-term blinded studies with BoNT-A are challenging to conduct. Validated clinical rating scales were used as primary endpoints of this study, though a need for better functional assessment scales, such as a patient global impression of change, could be incorporated for future studies. Comparative studies investigating the use of surface electromyographic (EMG) alone versus kinematics for tremor localization and assessment may also be useful to confirm this study's results. In addition, since tremor is variable, fluctuations in severity during each visit introduced error. However, participants were assessed around the same time of day and in the "ON" state. Visually-based versus kinematically-based treatments were not compared as the prior studies have already shown the lack of reproducibility and tolerability using visually guided, fixed schedule injections.[11-15,17,18] Sample size is similar to other reported studies in literature discussed.[2,11-15,18,21,24,25,27]

4.5. Conclusion

This study shows that individual, objective measurement of tremor at each joint in the upper limb affected by tremor allows for proper characterization and treatment of PD patients.

When achieved, such characterization can be used to guide the clinician's muscle selection for treatment of tremor. In PD tremor, individualized and optimized dosages of incobotulinumtoxinA can be used successfully and without significant severe weakness over a series of injections.

4.6. References

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5. General Discussion and Conclusion

The current thesis demonstrated the insight of measuring the biomechanics of limb tremor at each joint in ET and tremor-dominant patients with PD. Wearable, multi-sensor kinematics provided the ability to differentiate ET and PD kinematic tremor profiles and apply kinematic analysis to personalize BoNT-A focal therapy by guiding muscle selection and dosing. These findings revealed any changes in wrist or elbow tremor amplitude were related to shifts in limb position either between paired rest tasks in PD or between paired postural tasks in ET. In addition, detailed segmentation of joint tremor allowed individualization of BoNT-A therapy and optimization of BoNT-A parameters over serial treatments thereby minimizing the likelihood of side effects, mainly muscle weakness. This pilot study established an innovative method that can easily be translated into the clinical setting as an objective diagnostic aid, and when utilized by a clinician to monitor changes in symptoms to improve focal therapy.

5.1. Technology for differentiating pathological tremor forms

The peak frequency of pathological tremor forms, such as ET and PD tremors, tends to remain unchanged between different limb positions and under loaded conditions.[1] It is possible that tremors with similar frequencies may arise from similar central generators.[2] Due to the involuntary nature of tremor and its widespread appearance during various motor activities, literature suggests that tremor may be a derivative of corticomotor pathways.[2] Oscillations in the motor cortex have been shown to modulate descending corticospinal pathways which could manifest in the muscle's EMG and produce oscillatory movements.[2] In addition, as motor deficits and pathological tremors go hand in hand, it is considered that unlike physiological tremor, pathological tremors could be modulated peripherally.[2] The magnitude of pathological tremors, such as ET and PD tremors, are sensitive to somesthetic inputs.[1,3] It has been noted that ET and cerebellar tremors are more inclined to be influenced by peripheral reflex modifications than PD tremor.[2,3] Consistent with this evidence, it was observed, from the results presented in this thesis, that limb positioning and weight-bearing tasks modulate tremor amplitude in ET more than in PD. The findings discussed in Chapter 2 demonstrated that weakly correlated wrist or elbow tremor amplitude between posture tasks

was distinctive to ET, as this was not observed in PD participants. In addition, when the elbow is maximally flexed and the hand is positioned near the chest holding a weighted object, there was a significant increase in elbow tremor amplitude in ET participants only. As the pattern of agonist-antagonist muscle bursting has limited diagnostic value, these results have demonstrated that observing correlations of joint tremor amplitude during various limb positioning and weight-bearing paired tasks is an useful method to distinguish between ET and PD tremor forms. However, solely observing tremor amplitude was not sufficient in further advancing the knowledge of the pathogenesis of these tremors. Pairing EMG analysis, kinematic tremor analysis and new recording techniques such as magnetoencephalography may be useful to correlate the nature of central oscillatory activity with peripheral manifestations.

5.2. Personalization of BoNT-A therapy using kinematics

The success in the use of BoNT-A as a focal therapy for upper limb tremor has been limited due to the inaccuracies of visual assessments in determining muscles contributing to tremor and the appropriate dosages administered to alleviate tremor amplitudes. Past studies have used objective measures such as accelerometers and magnetometers to quantify overall joint tremor, however further segmentation of joint tremor is necessary for muscle selection. Kinematic technology has advanced the ability to distinguish tremulous movements at each arm joint. The findings in this thesis demonstrated that when kinematic tremor analysis is in the hands of a clinician, this simplified establishing which muscles to target and the necessary BoNT-A dose to administer. A reduction in both tremor amplitudes and functional disability caused by tremor was observed in PD and ET participants. In addition to determining initial BoNT-A parameters, this study also demonstrated that kinematics can play a major role in optimizing or modifying BoNT-A dosages for long-term, stable management of tremor over serial BoNT-A treatments. Thus, the use of kinematics provided a standardized method for both assessing and treating upper limb tremor in ET and PD participants.

5.3. Future directions

Effective management and development of new treatment strategies for disabling and degenerative diseases remains a significant unmet need as relevant cures or neuroprotective strategies are limited in the movement disorders field. The use of objective, wearable devices in medicine has significantly advanced over the past decades and has been applied in all facets of everyday life allowing accurate ratings/assessments and long-term monitoring of clinical symptoms. As this thesis demonstrated that wearable technology can be used to differentiate between PD and ET tremor forms and can be applied to improve localized therapeutic regimens, it is of current interest to use kinematic technology to better classify other pathological tremor types. Misdiagnosis rates in tremors are high due to the difficulty to classify several forms of tremor using the current MDS classification system. Clinical diagnosis cases with solely PD with rest tremor without convincing other signs of PD can be misinterpreted as essential tremor with rest tremor, dystonic tremor, Holmes or thalamic tremor or a few even rarer conditions.[4] Many patients with primary tremor, such as asymmetric rest and postural tremor, may not fit the current MDS criteria for other tremor entities and are ultimately termed "undetermined tremors".[4] Thus, the use of kinematics has a bright future in the hopes that a more comprehensive semiology and better separation of different tremors can be achieved.

5.4. References

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Appendix A: Ethics Initial Approval

Research Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Mandar Jog
Review Number:18445
Review Level: Full Board
Approved Local Adult Participants:70
Approved Local Minor Participants:0
Protocol Title: Use of kinematic assessment of hand tremor pre- and post- treatment with botulinum toxin type A in essential tremor and Parkinson disease
Department & Institution: Schulich School of Medicine and Dentistry\Clinical Neurological Sciences,London Health Sciences Centre
Sponsor:MERZ PHARMA

Ethics Approval Date: March 28, 2012
Ethics Expiry Date: December 31, 2014

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Western University Protocol	(including instruments noted in section 8.1)	
Letter of Information & Consent	Version 2.0	

This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

Appendix B: Letter of Information

Letter of Information

Study Title: Use of kinematic assessment of hand tremor pre- and post- treatment with botulinum toxin type A in essential tremor and Parkinson disease

Principal investigator: Dr. Mandar Jog, London Health Science Movement Disorders Clinic, UWO

Introduction

We are inviting you to voluntarily participate in a research project designed to evaluate hand tremor. Hand tremor is an unintentional, rhythmical, shaking of one or both hands. This project aims to study tremor before and after injection of a medication called Xeomin® (a form of botulinum toxin A), which can be used to manage tremor.

Study Funding

The study is funded by a research grant from Merz Pharma, which is the company that produces the medication used in this study.

Nature of the research project and tasks involved

We are looking to investigate tremor in participants with tremor either because of Parkinson disease or Essential tremor recruited from the Movement Disorders Clinic at London Health Sciences Centre (LHSC). This study requires you to attend a total of **9 visits** over the course of **96 weeks**. **IF the previous 96-week (extended) study treatment has benefited you, you have the option to continue in this study for an additional 8 more injection cycles for another 2 years.**

You will not have to change taking your medications in any way for this study. Participation in this study will not affect the routine management of your Parkinson disease or Essential Tremor. Scheduling of your routine clinic visits will not change.

You will be required to bring your Parkinson disease medications with you to each visit so that you may take them in accordance with your routine scheduled times.

You are eligible for the study based on the following: 1) a diagnosis of Parkinson disease with tremor as the predominant symptom or Essential Tremor and 2) hand tremor severe enough that it affects your quality of life and 3) you are a candidate for tremor treatment using Xeomin®, a formulation of botulinum toxin A as determined by your movement disorders neurologist. 4) Experienced a beneficial reduction in tremor using Xeomin® and would like to continue receiving injection treatments.

Pregnancy: If you are pregnant then you CANNOT BE IN THIS STUDY. Pregnancy screening will take place before study admission by the physician, Dr. Jog. A researcher will ask you about pregnancy at every study visit. Please notify the research team if you are presently pregnant or if you are attempting to become pregnant or if you become pregnant at any time during the course of the study. If this becomes the case, participation in this study may be terminated.

***Other Muscle/Nerve diseases*:** If you have a disease called Myasthenia Gravis or Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease) then you CANNOT BE IN THIS STUDY. Please notify the research team if you have these conditions.

***Previous side effects to botulinum toxin*:** If you have had a previous allergic reaction or side effect to botulinum toxin then you CANNOT BE IN THIS STUDY. Pease notify the research team if you have had a previous reaction/side effects from injection of botulinum toxin.

The research visits will require you to come to Dr. Jog's research facilities located at University Hospital London, Ontario.

At each visit you will be asked to complete the following tasks, which are described in detail below:

Complete an assessment of your motor function

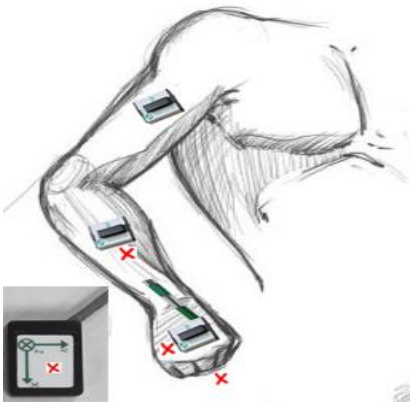
Complete an assessment of the severity of your tremor

Complete an assessment of how your tremor affects your quality of life

4) IF injection parameters are not reducing tremor to an acceptable level, a project member will perform a kinematic assessment of your tremor to modify injection sites, upon approval by Dr. Jog

Kinematic Assessment of Tremor:

You will be asked to change into a hospital gown (top only you will not have to take off your pants/skirt) so that the researchers may examine your full arm. You will have sensors placed (using tape that is safe for your skin) onto your arm and hand in order to measure the tremor (see picture below). In addition to the sensors that record the frequency (rate) and amplitude (size) of your tremor movements, we will also use video cameras to record what your tremor looks like.



You will be asked to do several tasks such as resting your arms in your lap, extending your arms out in front of you, pouring water, etc. so that your tremor can be measured across a variety of postures/activities. This will take approximately 20 minutes.

Motor function:

During each visit, a researcher will complete the United Parkinson's Disease Rating Scale (UPDRS). This is the same assessment that your neurologist completes with you during your routine clinic visit. It measures aspects of motor function such as: stiffness, tremor, walking, activities of daily living, speech, etc. It is a non-invasive assessment and will take approximately 10 minutes to complete. We will also measure the strength in your hand and fingers at each session.

Tremor Severity:

During each visit a researcher will complete the Fahn, Tolosa, Marin Tremor Rating Scale. It rates the severity of your tremor and during activities such as writing and asks you to rate the severity of your tremor during different daily activities. It is a non-invasive assessment and will take approximately 10-minutes to complete.

Tremor Quality of Life:

During each visit a researcher will complete a questionnaire called QUEST with you. Goal attainment scale for tremor (GAST) will be completed by you and a care-giver, if applicable. It asks you to rate how your tremor affects your quality of life. It is a non-invasive assessment and will take approximately 10-15 minutes to complete.

Xeomin® Injections: At each study visit, you will receive injections of Xeomin for the treatment of your tremor symptoms. **IF you choose to continue this study after completion of the initial 13 visits, you can receive 8 more injection cycles at 3 months apart for another 2 years.** Dr. Jog will inject the muscles that are involved in your tremor movements based on information from the kinematic assessment.

Injections are made using a small needle. The amount of Xeomin injected and the number of different muscles injected varies with each individual and each muscle and is done at the clinical discretion of Dr. Jog based on accepted clinical practice.

IF sufficient reduction in tremor is not at an acceptable level, Dr. Jog may make modifications to the amount and site of injections. This decision will be based in part on your

response to the previous injections and your perception of improvement in your tremor. This will be done to try and achieve the best response in reduction of tremor with the medication.

Benefits, risks and inconveniences

You may not benefit directly from participation in this study. However, the results may contribute to treatment of tremor. The cost of the medication will be covered during the course of the study.

Some individuals may be uncomfortable with being video taped. However, the research team is only recording your arms in an attempt to study your tremor.

Some individuals may be uncomfortable with having to change into a hospital gown. However, a private change area will be provided.

Risks associated with Xeomin

As with any medication call your doctor or get medical help right away if you have any side effects. Prior to being eligible for this study, your movement disorders neurologist has made the decision to start you on this medication as a part of a plan to manage your tremor. As with starting any new medication, questions regarding taking this medicine or side effects should be addressed with either your physician or your pharmacist prior to starting this medication.

Xeomin® may cause serious side effects that can be life threatening.

Problems with swallowing, speaking, or breathing. These problems can happen hours to weeks after an injection of Xeomin® if the muscles that you use to breathe and swallow become weak after the injection.

People with certain breathing problems may need to use muscles in their neck to help them breathe. These patients may be at greater risk for serious breathing problems with Xeomin®.

Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or

liquids may go into your lungs. **People who already have swallowing or breathing problems before receiving Xeomin® have the highest risk of getting these problems.**

Spread of toxin effects. In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:

loss of strength and muscle weakness all over the body

double vision

blurred vision and drooping eyelids

hoarseness or change or loss of voice

trouble saying words clearly

loss of bladder control

trouble breathing

trouble swallowing

Xeomin® may cause other serious side effects including allergic reactions. Symptoms of an allergic reaction to Xeomin® may include: itching, rash, redness, swelling, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you get wheezing or asthma symptoms, or if you get dizzy or faint.

The most common side effects of Xeomin® include:

dry mouth (up to 5%)

discomfort or pain at the injection site (up to 5%)

tiredness (less than 1%)

headache (less than 1%)

neck pain (up to 5%)

muscle weakness of injected muscles (less than 1% at a distant site)

eye problems, including: double vision, blurred vision, drooping eyelids, swelling of your eyelids, and dry eyes. Reduced blinking can also occur. Tell your doctor or get medical help right away if you have eye pain or irritation following treatment. (up to 5%)

While the above side effects can occur **side effects are usually linked to site of injection and therefore vary widely among people** depending on where they are injected and for what reason. For injections in the hand/arm the most common side effect is weakness in the hand or arm muscles. Tell your doctor if you have any side effect that bothers you or that does not go away.

Data collection and use of information

Participation is voluntary. Information and data obtained in the study will not be labeled with any of your personal information (name, initials, date of birth, medical record number, etc.).

The data from the study will be kept electronically and securely using the LHSC computer network. At all times, the data will be in the possession of one of the investigators of this study and will not be stored off-site.

For the purposes of contacting you to arrange the data collection sessions and linking your data from the multiple visits, we will keep a master list of all participants. This list will contain your first name, telephone number, address, the dates you completed your sessions, and a number that we will assign to you that will also appear on your data recordings. At the conclusion of this study, this master list will be destroyed.

Your signed consent, which will have your name on it, will not be stored with the data collected from the study and will not be connected to the data collected. The master list with your contact information on it will also be stored separately from the data collected to avoid linking your personal information to your data recordings. Consent forms and the master list will be stored in a secure location in the Movement Disorders Laboratory of Dr. Jog at University Hospital.

Any use of this information for publication in scientific journals or presentation at professional conferences, will not contain any of your personal information that could be linked back to you or to your health information.

You will receive a copy of this information letter for your records.

Withdrawal from the study by the investigator

The investigator may decide to take you off the study if he feels your continued participation would impair your wellbeing.

Monetary compensation

You will not be paid for participation in this study. Parking will however be compensated at $20.00 for each visit required by the study.

Confidentiality

In order to preserve your confidentiality, only the investigators in this study will have access to your research information. No personal information will be collected or retained with your data. AT NO TIME, will your name be used in scientific presentations or publications. The recorded data will remain secure, accessible only to research personnel.

Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or may require access to your study related records to monitor the conduct of the research.

Voluntary participation

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care.

You will be able to withdraw from the study at any point in time. However, to protect the integrity of the study the data collected up to the point of your withdrawal will remain a part of the study. You will not have the option of withdrawing your data once it has been collected even if you choose to withdraw from the study.

PATIENT CONSENT FORM

STUDY TITLE

Use of kinematic assessment of hand tremor pre- and post-treatment with botulinum toxin type A in essential tremor and Parkinson disease

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Signature of Research subject	Printed Name	Date

Signature of Investigator	Printed Name	Date

Signature of Person Obtaining Consent	Printed Name	Date

Appendix C: Fahn-Tolosa-Marin Rating Scale

Visit (weeks): _____ Date: ____/____/____
(dd / mm / yyyy)

Tremor Rating Scale

Study Name: _____

Participant #: _____ Diagnosis: _____

Age: _____ Gender: _____ R / L Handed

Have you had caffeine during the past 8 hr? YES NO

Have you had alcohol during the past 8 hr? YES NO

PART A: Tremor Location/Severity Rating

Location	Rest	Posture	Action/Intention	Total
1. Face tremor			XXXXXXXXXXXX	
2. Tongue tremor			XXXXXXXXXXXX	
3. Voice tremor	XXXXXX			
4. Head tremor			XXXXXXXXXXXX	
5. Right upper extremity				
6. Left upper extremity				
7. Trunk tremor			XXXXXXXXXXXX	
8. Right lower extremity				
9. Left lower extremity				
10. Orthostatic (trunk/legs when standing)	XXXXXX		XXXXXXXXXXXX	

Subtotal A: _____

0 = Normal
1 = Slight; barely perceivable. May be intermittent.
2 = Moderate; amplitude <2 cm. May be intermittent.
3 = Marked; amplitude 2–4 cm.
4 = Severe; amplitude >4 cm.

LIST OF MEDICATIONS:

COMMENTS:

PART B: Specific Motor Tasks/Function Rating

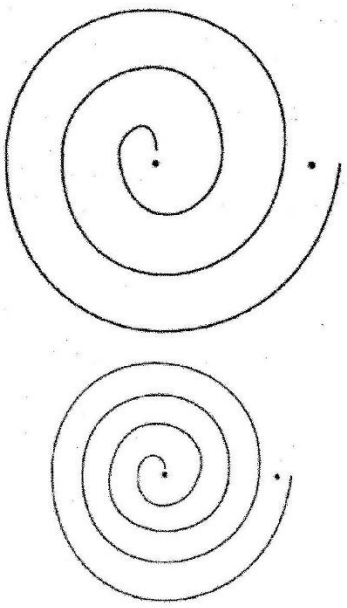
Motor Task	Right	Left	Total
11. Handwriting (*dominant hand only) Have the patient write the standard sentence "This is a sample of my best handwriting," sign his or her name and write the date. 0 = Normal 1 = Mildly abnormal. Slightly untidy, tremulous. 2 = Moderately abnormal. Legible, but with considerable tremor. 3 = Markedly abnormal. Illegible 4 = Severely abnormal. Unable to keep pencil or pen on paper without holding hand down with the other hand.			
12. Drawing A (large spiral) Ask the patient to join both points of the large spiral without crossing the lines, and starting from the inside of the spiral. Test each hand, beginning with the lesser involved, without leaning the hand or arm on the table. 0 = Normal 1 = Slightly tremulous. May cross lines occasionally. 2 = Moderately tremulous or crosses lines frequently. 3 = Accomplishes the task with great difficulty. Many errors. 4 = Unable to complete drawing.			
13. Drawing B (small spiral) Ask the patient to join both points of the small spiral without crossing the lines, and starting from the inside of the spiral. Test each hand, beginning with the lesser involved, without leaning the hand or arm on the table. 0 = Normal 1 = Slightly tremulous. May cross lines occasionally. 2 = Moderately tremulous or crosses lines frequently. 3 = Accomplishes the task with great difficulty. Many errors. 4 = Unable to complete drawing.			
14. Drawing C (line drawing) Ask the patient to join both points without crossing the lines. Test each hand, beginning with the lesser involved, without leaning the hand or arm on the table. 0 = Normal 1 = Slightly tremulous. May cross lines occasionally. 2 = Moderately tremulous or crosses lines frequently. 3 = Accomplishes the task with great difficulty. Many errors. 4 = Unable to complete drawing.			
15. Pouring Use firm plastic cups (8 cm tall), filled with water to 1 cm from top. Ask patient to pour water from one cup to another. Test each hand separately. 0 = Normal 1 = More careful than a person without tremor, but no water is spilled. 2 = Spills a small amount of water (up to 10% of total amount) 3 = Spills a considerable amount of water (10-50%). 4 = Unable to pour without spilling most of the water			

Subtotal B: _____

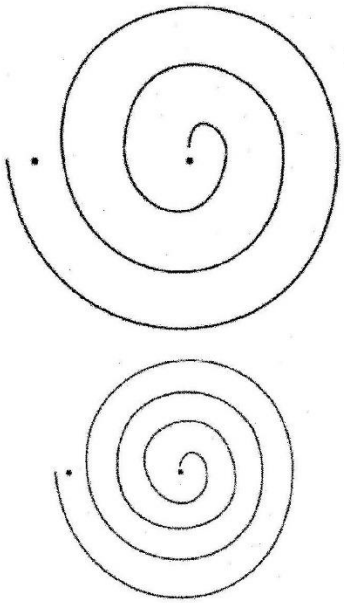
HANDWRITING (dominant hand only)

Signature: _____

LEFT HAND:



RIGHT HAND:



RIGHT HAND:

LEFT HAND:

PART C: Functional Disabilities Resulting from Tremor

Motor Task	Rating
16. Speaking This includes spastic dysphonia if present. 0 = Normal 1 = Mild voice tremulousness when nervous only. 2 = Mild voice tremor, constant. 3 = Moderate voice tremor. 4 = Severe voice tremor. Some words difficult to understand.	
17. Eating (other than liquids) 0 = Normal 1 = Mildly abnormal. Can bring all solids to mouth, spilling only rarely. 2 = Moderately abnormal. Frequent spills of peas and similar foods. May bring head at least halfway to meet food. 3 = Markedly abnormal. Unable to cut or uses two hands to feed. 4 = Severely abnormal. Needs help to feed.	
18. Drinking (bringing liquids to mouth) 0 = Normal 1 = Mildly abnormal. Can still use a spoon, but not if it is completely full. 2 = Moderately abnormal. Unable to use a spoon. Uses cup or glass. 3 = Markedly abnormal. Can drink from cup or glass, but needs two hands. 4 = Severely abnormal. Must use a straw.	
19. Hygiene 0 = Normal 1 = Mildly abnormal. Able to do everything, but is more careful than the average person. 2 = Moderately abnormal. Able to do everything, but with errors; uses electric razor because of tremor. 3 = Markedly abnormal. Unable to do most fine tasks, such as putting on lipstick or shaving (even with electric shaver), unless using two hands. 4 = Severely abnormal. Unable to do any fine-movement tasks.	
20. Dressing 0 = Normal 1 = Mildly abnormal. Able to do everything, but is more careful than the average person. 2 = Moderately abnormal. Able to do everything, but with errors. 3 = Markedly abnormal. Needs some assistance with buttoning or other activities, such as tying shoelaces. 4 = Severely abnormal. Requires assistance even for gross motor activities.	
21. Writing 0 = Normal 1 = Mildly abnormal. Legible. Continues to write letters. 2 = Moderately abnormal. Legible, but no longer writes letters. 3 = Markedly abnormal. Illegible. 4 = Severely abnormal. Unable to sign checks or other documents requiring signature.	
22. Working 0 = Tremor does not interfere with the job. 1 = Able to work, but needs to be more useful than the average person. 2 = Able to do everything, but with errors. Poorer than usual performance because of tremor. 3 = Unable to do regular job. May have changed to a different job because of tremor. Tremor limits housework, such as ironing. 4 = Unable to do any outside job; housework very limited.	
23. Social Activities 0 = No changes 1 = Minimal change in social activities, still socializes. 2 = Moderate change in social activities, avoids encounters with strangers. 3 = Marked change in social activities, avoids encounters with friends. 4 = Severe change in social activities, avoid any public encounters.	

Subtotal C: _____

TOTAL SCORE: _____

Appendix D: Unified Parkinson's Disease Rating Scale

Unified Parkinson's Disease Rating Scale

[redacted] [redacted]

	Date																	
	DOPA mg/day	hrs DOPA lasts																
			On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off
1	Mentation																	
2	Thought Disorder																	
3	Depression																	
4	Motivation/Initiative																	
	Subtotal 1–4 (maximum=16)																	
5	Speech																	
6	Salivation																	
7	Swallowing																	
8	Handwriting																	
9	Cutting food																	
10	Dressing																	
11	Hygiene																	
12	Turning in bed																	
13	Falling																	
14	Freezing																	
15	Walking																	
16	Tremor																	
17	Sensory symptoms																	
	Subtotal 5–17 (maximum=52)																	
18	Speech																	
19	Facial expression																	
20	Tremor at rest: face, lips, chin																	
	Hands:	right																
		left																
	Feet:	right																
		left																
21	Action tremor:	right																
		left																
22	Rigidity:	neck																
	Upper extremity:	right																
		left																
	Lower extremity:	right																
		left																

		Date																			
		[redacted]	Off		On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	
23	Finger taps:	right																			
		left																			
24	Hand grips:	right																			
		left																			
25	Hand pronate/supinate:	right																			
		left																			
26	Leg agility:	right																			
		left																			
27	Arise from chair																				
28	Posture																				
29	Gait																				
30	Postural stability																				
31	Body bradykinesia																				
	Sub-total: 18–31 (maximum=108)																				
	Total points: 1–31 (maximum=176)																				
32	Dyskinesia (duration)																				
33	Dyskinesia (disability)																				
34	Dyskinesia (pain)																				
35	Early morning dystonia																				
36	"Offs" (predictable)																				
37	"Offs" (unpredictable)																				
38	"Offs" (sudden)																				
39	"Offs" (duration)																				
40	Anorexia, nausea, vomiting																				
41	Sleep disturbance																				
42	Symptomatic orthostasis																				
	Blood Pressure:	seated																			
		supine																			
		standing																			
	Weight																				
	Pulse:	seated																			
		standing																			
	Name of Examiner ▸																				

		Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst
	Hoehn & Yahr Stage																
	% ADL Score (PD)																
	% ADL (with dyskinesia)																

Fahn S, Elton R, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease*, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, pp 153-163, 293-304.

Appendix E: Quality of Life in Essential Tremor Questionnaire

Quality of Life in Essential Tremor Questionnaire (QUEST)

Visit (weeks) _____ ID: _____ Date: ____/___/___

Gender: ☐ Male ☐ Female Date of Birth: ____/___/___

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction? Y N

In the past month, have you had side effects from tremor medications? Y N

In the past month, have you been satisfied with the tremor control achieved by your medications? Y N

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	Head	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	Right arm/hand	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	Right leg/foot	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: [N] [R] [S] [F] [A]

N = Never
R = Rarely
S = Sometimes
F = Frequently
A = Always
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.	N R S F A
2.	My tremor interferes with my ability to maintain conversations with others.	N R S F A
3.	It is difficult for others to understand my speech because of my tremor.	N R S F A
4.	My tremor interferes with my job or profession.	NA N R S F A
5.	I have had to change jobs because of my tremor.	NA N R S F A
6.	I had to retire or take early retirement because of my tremor.	N
7.	I am only working part time because of my tremor.	NA N
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA N R S F A
9.	My tremor has led to financial problems or concerns.	N R S F A
10.	I have lost interest in my hobbies because of my tremor.	N R S F A
11.	I have quit some of my hobbies because of my tremor.	N
12.	I have had to change or develop new hobbies because of my tremor.	N
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).	N R S F A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA N R S F
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).	N R S F A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).	N R S F A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).	N R S F A
18.	My tremor interferes with brushing or flossing my teeth.	N R S F A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).	N R S F A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).	N R S F A
21.	My tremor interferes with reading or holding reading material.	N R S F A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).	N R S F A
23.	My tremor makes me feel negative about myself.	N R S F A
24.	I am embarrassed about my tremor.	N R S F A
25.	I am depressed because of my tremor.	N R S F A
26.	I feel isolated or lonely because of my tremor.	N R S F A
27.	I worry about the future due to my tremor.	N R S F A
28.	I am nervous or anxious.	N R S F A
29.	I use alcohol more frequently than I would like to because of my tremor.	N R S F A
30.	I have difficulty concentrating because of my tremor.	N R S F A

THANK YOU!

Appendix F: Manual Muscle Testing

Participant ID: MT –_____ Visit: 1 2 3 4 5

Manual Muscle Testing – RIGHT HAND

R1	MCP Flexion	**0**	**1**	**2 –**	**2**	**2 +**	**3 –**	**3**	**3 +**	**4 –**	**4**	**4 +**	**5**
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
R2	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
R3	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
R4	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
R5	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
Hand	Abduction	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	Adduction	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
Wrist	Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
Bicep	Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5

Manual Muscle Testing – LEFT HAND

L1	MCP Flexion	**0**	**1**	**2 –**	**2**	**2 +**	**3 –**	**3**	**3 +**	**4 –**	**4**	**4 +**	**5**
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
L2	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
L3	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
L4	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
L5	MCP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	MCP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	PIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	DIP Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
Hand	Abduction	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	Adduction	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
Wrist	Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
Bicep	Flexion	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5
	Extension	0	1	2 –	2	2 +	3 –	3	3 +	4 –	4	4 +	5

Appendix G: Curriculum Vitae

Name:	Olivia Samotus
Post-secondary Education and Degrees:	University of Ottawa Ottawa, Ontario, Canada 2008 – 2013 Hon. B.Sc. Spec. Biochemistry with Co-Op
Honours and Awards:	Western Graduate Research 2014-2015, 2015-2016 Mitacs-Accelerate, Canada's Graduate Research Internship Program 2014-2015 University of Ottawa Dean's Honours List 2010-2011
Related Work Experience	Teaching Assistant Western University 2015 Clinical Research Associate London Health Sciences Centre 2013-2014

Peer-reviewed Publications:

1. Atashzar S., Shahbazi M., Samotus O., Tavkoli M., Jog M., Patel RV. Characterization of upper-limb involuntary movements in pathological tremor patients: application to design

of an augmented haptic rehabilitation system. Accepted for publication in IEEE Journal of Selected Topics in Signal Processing. 2016 June.

2. Samotus O., Rahimi F., Lee J., Jog M. Functional ability improved in Essential tremor by incobotulinumtoxinA injections using kinematically determined biomechanical patterns – A new future. PLoS ONE. 2016 April. 11(4): e0153739. doi:10.1371/journal.
3. Atashzar SF., Shahbazi M., Ward C., Samotus O., Delrobaei M., Rahimi F., Lee J., Jackman M., Jog M., Patel RV. Haptic feedback manipulation during botulinum toxin injection therapy for focal hand dystonia patients: possibility of a new assistive strategy. Accepted for publication in IEEE Transactions on Haptics. 2016 March.
4. Rahimi F*, Samotus O*, Lee J, Jog M. Effective Management of Upper Limb Parkinsonian Tremor by IncobotulinumtoxinA Injections Using Sensor-based Biomechanical Patterns. Tremor Other Hyperkinet Mov (N Y). 2015 Oct 30;5:348. doi: 10.7916/D8BP0270. eCollection 2015. PubMed PMID: 26566459; PubMed Central. PMCID: PMC4636031. * co-authors.

Conference/Abstract Publications:

1. Samotus O., Moradi H., Jog M. Individualized botulinum toxin type A therapy of bilateral upper limb essential tremor by multi-sensor kinematic technology. Poster accepted for presentation at the 20th MDS conference in Berlin, Germany. June 21, 2016.
2. Samotus O., Moradi H., Jog M. Personalized botulinum toxin type A therapy for bilateral upper limb essential tremor using multi-sensor kinematic technology. Poster presented at the Canadian Association of Neuroscience in Toronto. May 29 to June 1, 2016.
3. Samotus O., Moradi H., Jog M. Kinematic measures of bilateral upper limb essential tremor personalize botulinum toxin type A therapy. Poster presented at the Western University Resident Research Day Conference in London, Ontario. May 2016.
4. Samotus O., Moradi H., Jog M. Personalized botulinum toxin type A therapy for bilateral upper limb essential tremor using multi-sensor kinematic technology. Poster presented at the CNS departmental research day at the Bellamere Winery. April 26, 2016.
5. Samotus O., Moradi H., Lee J., Rahimi F., Jog M. Function improved in essential tremor by incobotulinumtoxinA injection patterns using upper limb biomechanical characterization. Presented at the 45th International Society of Neuroscience Conference. October 19, 2015.
6. Samotus O., Moradi H., Rahimi F., Jog M. Multi-sensor based biomechanical characterization of cervical dystonia determines optimal onabotulinumtoxinA treatment parameters. Presented at the 45th International Society of Neuroscience Conference. October 20, 2015.
7. Samotus O., Lee J., Rahimi F., Jog M. Longitudinal kinematic characterization of upper limb essential tremor to effectively guide incobotulinumtoxinA treatment. Presented at the 19th International Parkinson and Movement Disorder Society. June 18, 2015.
8. Samotus O., Lee J., Rahimi F., Jog M. Upper limb kinematics guides longitudinal, incobotulinumtoxinA therapy of Parkinson disease tremor. Presented at the 19th International Parkinson and Movement Disorder Society. June 18, 2015.

9. Samotus O., Vafadar H., Rahimi F., Jog M. Kinematic biomechanical characterization guides incobotulinumtoxinA treatment in cervical dystonia patients. Presented at the 19th International Parkinson and Movement Disorder Society. June 18, 2015.
10. Samotus O., Moradi H., Rahimi F., Jog M. Kinematic characterization successfully guides onabotulinumtoxinA treatment in cervical dystonia patients. Presented at the London Health Research Day. April 1, 2015. Poster #154
11. Samotus O., Lee J., Rahimi F., Jog M. Longitudinal kinematic characterization of upper limb essential tremor to effectively guide incobotulinumtoxinA treatment. Presented at the London Health Research Day. April 1, 2015. Poster #148
12. Samotus O., Lee J., Rahimi F., Jog M. Upper limb kinematics guides longitudinal, incobotulinumtoxinA therapy of Parkinson disease tremor. Presented at the London Health Research Day. April 1, 2015. Poster #131
13. Samotus O., Vafadar H., Rahimi F., Lee J., Jackman M., Jog M. Kinematic motion sensors objectively characterize neck movements in cervical dystonia. Presented at the 44th Society of Neuroscience Conference Washington, DC, USA. 2014 November. Poster#:47.12.
14. Lee J., Rahimi F., Samotus O., Jackman M., Jog M. Kinematic assessments effectively guide longitudinal treatment of Parkinson disease tremor. Presented at the 44th Society of Neuroscience Conference Washington, DC, USA. 2014 November.
15. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Characterization of essential tremor by kinematic assessments in the upper limb. Presented at the 44th Society of Neuroscience Conference Washington, DC, USA. 2014 November. Poster#697.18.
16. Samotus O., Vafadar H., Rahimi F., Lee J., Jackman M., Jog M. Kinematic motion sensors objectively characterize neck movements in cervical dystonia. Presented at the IEEE EMBS Brain Grand Challenge Conference Washington, DC, USA. 2014 November.
17. Lee J., Rahimi F., Samotus O., Jackman M., Jog M. Kinematic assessments effectively guide longitudinal treatment of Parkinson disease tremor. Presented at the IEEE EMBS Brain Grand Challenge Conference Washington, DC, USA. 2014 November.
18. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Characterization of essential tremor by kinematic assessments in the upper limb. Presented at the IEEE EMBS Brain Grand Challenge Conference Washington, DC, USA. 2014 November.
19. Rahimi F., Samotus O., Lee J., Jackman M., Jog MS. Kinematic Assessments Effectively Guide Botulinum Neurotoxin Type A Injections For Essential Tremor Treatment. Poster accepted for presentation at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden, 2014 June.
20. Lee J, Rahimi F, Samotus O, Jackman M, Jog MS. Effective Long-term Upper-Limb Tremor Treatment in Parkinson Disease Patients. Poster accepted for presentation at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden, 2014 June.
21. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Objective kinematic assessment of torticollis using motion sensors. Poster accepted for presentation at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden, 2014 June.
22. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Objective kinematic assessment of torticollis using motion sensors. Poster accepted for presentation at the Canadian Association for Neuroscience, Montreal, Canada, 2014 May.

23. Lee J., Rahimi F., Samotus O., Jackman M., Jog MS. Effective Long-term Upper-Limb Tremor Treatment in Parkinson Disease Patients. Poster accepted for presentation at the Canadian Association for Neuroscience, Montreal, Canada, 2014 May.
24. Rahimi F., Samotus O., Lee J., Jackman M., Jog MS. Kinematic Assessment Effectively Guide Botulinum Neurotoxin Type A Injections for Essential Tremor Treatment. Poster accepted for presentation at the Canadian Association for Neuroscience, Montreal, Canada, 2014 May.
25. Samotus O., Rahimi F., Lee J., Jog MS. Kinematic Assessment Effectively Guide Botulinum Neurotoxin Type A Injections for Essential Tremor Treatment. Poster accepted to be presented at the 44th American Academy of Neurology, Philadelphia, PA, 2014 April.