IMPAIRMENTS IN PRECISION GRIP FORCE CONTROL IN INDIVIDUALS WITH PARKINSON'S DISEASE.

by

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IMPAIRMENTS IN PRECISION GRIP FORCE CONTROL IN SUBJECTS WITH PARKINSON'S DISEASE.

Sujata Pradhan, M.S. (PT)

University of Pittsburgh, 2007.

Purpose: The purpose of our study is to identify impairments in fine motor control in individuals with Parkinson's disease(PD) during a force-tracking task using force sensors and comparing that to the fine motor control in age-matched controls. We also observed differences in fine motor coordination across a spectrum of patients with varying severity of disease **Methods:** 30 subjects with Parkinson's disease and 30 age-matched controls participated. Commercially available six-axes force sensors were used to provide an interface for interaction between the subject and the force-tracking task. Subjects tracked a moving sine wave on a computer screen by controlling the amount of force exerted between their index finger and thumb. The two digits were attached to the force sensors that are capable of recording the amounts of force exerted by the subject. During a part of the task, a simultaneous mental activity was introduced and the effect of this distraction was evaluated. Performance of the task was also evaluated using a pseudorandom wave for another three minutes including the distraction components. **Results:** We compared results between subjects and controls using univariate analysis of variance. Association between the motor score of the Unified Parkinson's disease Rating Scale (UPDRS) and the force tracking variables as well as that between the force tracking variables and chronicity of the disease was evaluated using multiple regression analyses. Individuals with PD showed greater amounts of error, lesser coordination and greater amounts of lag compared to controls. Distraction significantly affected individuals with PD to a greater extent compared to controls. The test showed no association with chronicity of the disease and showed a moderate association to function based on the UPDRS. **Clinical Relevance:** Deficient hand function in activities that involve fine motor coordination is one of the chief complaints of individuals with Parkinson's disease. The ability to perform activities that involve precision grip depends on the capacity to make fine adjustments to forces in response to the demands placed by complex environments with a number of distractions. Individuals with PD performed with greater deficits on our test especially during the distraction component of the task.

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PREFACE

I would like to thank my committee members for their guidance during my past years as a graduate student. Dr Delitto, who I consider my mentor and guide, has always had a watchful presence over me, letting me manage work, time and problems independently but stepping in exactly when I needed him to. Dr Carvell was the one who encouraged me to pursue doctoral studies. I am grateful for all the encouragement and the teaching opportunities that he has provided that have helped me learn better. Taking on a project that had such a huge technical aspect would have been impossible without all the patience that Dr Sparto and Dr Brewer had with all my questions. I am grateful for all the time that both of them spent with me during the analysis of the data and for contributing considerably to improving my writing skills. It was a privilege to have Dr Zigmond and Dr Matsuoka on my committee. I thank them for their input on my dissertation.

I would also like to thank all the participants who volunteered to participate in my study, people with Parkinson's disease, especially for staying off medications for 12 hours and letting me see them at possibly their worst. I am grateful for that. Likewise, all the people in the control group, some of whom were friends and family of people in our department. Thank you for participating with the sole intention of helping me out.

On a personal note, everything that my sister and I are today is because of my parents. Providing a good education was always the top priority in their lives. My father for the love of books that he instilled in us and teaching us not to worry about results as long as we had done the best that we could. My mother for devoting all her time to making learning fun when we were growing up and teaching us that nothing is impossible to achieve. From my sister, I have learnt how to persevere, work hard and never to give up.

Last but definitely not the least; I could not have done this without my husband Vikram by my side, who makes every day more joyful. I could not have gotten through some of the crazy times during these years without his sense of humor and his belief in me.

1.0 INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the degeneration of the nigrostriatal dopaminergic pathways within the basal ganglia (BG). Clinically the disease is characterized by bradykinesia (slowness of movement), akinesia, resting tremor, and rigidity[1-4]. This disease affects 0.3 % of the entire population and 1% of the people over 60 years in industrialized countries. This is an age related disease which is rare before age of 50 yrs and the prevalence increases to up to 4 % in higher age groups.[5]

Pathologic studies have shown that by the time the disease is diagnosed clinically, there is over 40% loss of dopaminergic neurons. The disease has a preclinical duration of about six years with the rate of progression being higher in the initial six years.[6;7].Involvement of the hand in Parkinson's disease, in terms of motor dysfunction has been documented in the literature[8-16]. There is also documentation of self reported early involvement of the hand in subjects with Parkinson's disease[17]. A majority of the population with Parkinson's disease is high functioning in terms of their activities of daily living, especially under the influence of medication. Impairments in hand function are difficult to demonstrate using common clinical measures like the Unified Parkinson's Disease Rating Scale in this population when they are on medication, since most patients are at a ceiling on these clinical instruments. Also, early on in the disease, many patients tend to underestimate their disability[18]. Consequently, the main motivation for this study is to identify motor impairments that contribute to deficits in hand function and to study

their relation to progression of the disease with the help of sensitive and accurate methods will help us understand the effects of the disease on fine motor coordination in this population.

2.0 SPECIFIC AIMS AND HYPOTHESES

2.1 SPECIFIC AIM 1

To design a force tracking task involving precision grip and increasing amounts of cognitive distraction.

2.2 SPECIFIC AIM 2

To identify impairments in fine motor control in patients with Parkinson's disease and age-matched controls during a force tracking task with and without interference from a simultaneous distracting cognitive task.

2.2.1 Hypothesis for Aim 2

Individuals with PD will show greater deficits in fine motor coordination during the force-tracking task compared to older adults without PD. Furthermore, when the task is made more challenging by adding a cognitive task, the deterioration in performance especially during the mental distraction part of the task will be even greater in individuals with PD.

2.3 SPECIFIC AIM 3

To explore the association between variables calculated from the force tracking task and progression of the disease based on the combined activities of daily living (ADL) and motor score of the Unified Parkinson's Disease Rating Scale (UPDRS) and number of years from initial diagnosis in individuals with Parkinson's disease.

2.3.1 Hypothesis for Aim 3

Subjects with greater deficits in fine motor coordination on the force-tracking task will have worse performance on the ADL and motor score of the UPDRS.

3.0 BACKGROUND AND SIGNIFICANCE

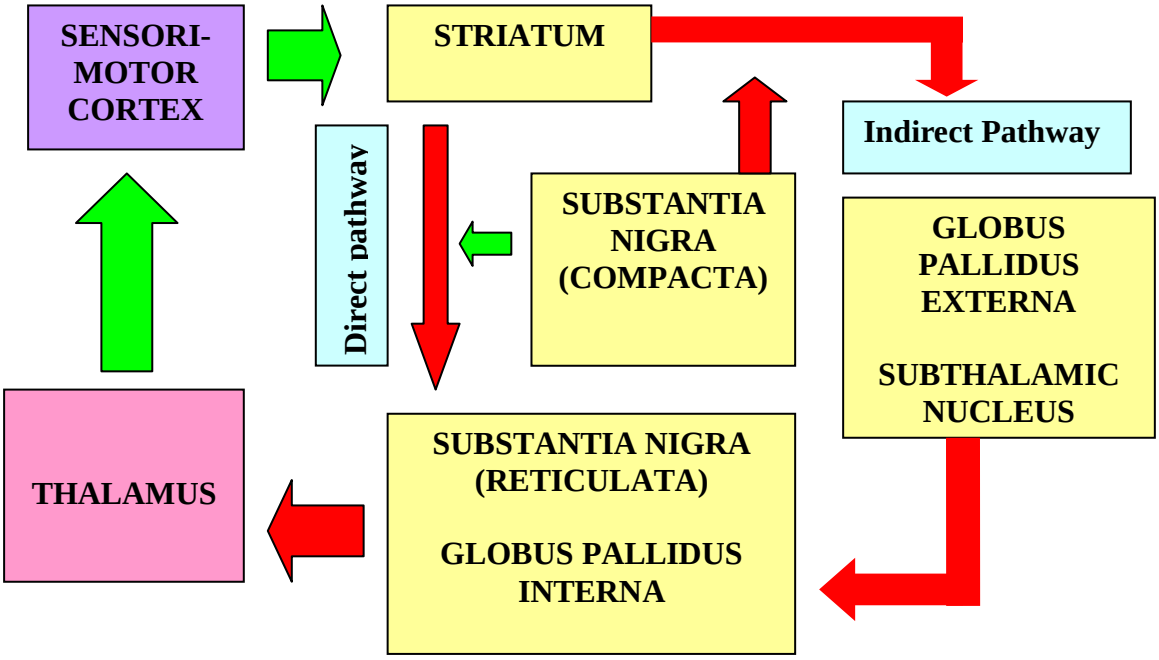
3.1 ROLE OF THE BASAL GANGLIA IN NORMAL MOVEMENT:

The basal ganglia (BG) comprising of the caudate nucleus, putamen (together known as the striatum), subthalamic nucleus and the substantia nigra (functionally) are part of the cortico-basal ganglia-thalamo-cortical circuits. Each circuit is named after the primary function of the cortical area (motor, oculomotor, association or limbic) associated with that circuit. The control of movement is primarily the function of the motor circuit within the basal ganglia.

The striatum (mainly the putamen) receives input from the pre and post central sensori-motor areas of the cortex. Striatal output is then directed to the internal globus pallidus (GPi) and the substantia nigra (SNr) via two pathways: a direct pathway and an indirect pathway via the subthalamic nucleus (STN) and the external globus pallidus (GPe). The output from the GPi and SNr is then directed to that ventral anterior and ventral lateral nucleus of the thalamus. The circuit is completed by the thalamocortical projection neurons.

Most intrinsic and output neurons of the BG are GABA-ergic and thus inhibitory. Thalamocortical neurons in contrast are excitatory (glutamatergic).The BG thus have a tonic inhibitor effect on the thalamocortical connections. The activity of the striato-pallidal connections is regulated by the nigro-striatal dopaminergic system. Dopamine has a inhibitory effect on the indirect pathway via the D2 receptor and an excitatory effect on the direct pathway

via the D1 receptors. The overall effect of dopamine is to reduce the BG output, leading to increased activity in the thalamo-cortical connections. Phasic activation of the direct pathway thus causes disinhibition of the thalamocortical loop and facilitation of movement. Phasic activation of the indirect pathway causes increased BG output that causes tonic inhibition of the thalamocortical connections and thus suppression of movement [19].



3-1 Cortico-Basal ganglia-cortical loop (Motor loop)

Basal ganglia dysfunction in PD:

Loss of dopaminergic neuron leads to excessive inhibition of the thalamocortical connections leading to inhibition of movement whereas excitation of the thalamocortical

connections via the indirect pathways leads to release of unwanted movements normally inhibited by this pathway.

Compensatory overactivity in other areas of the central nervous system:

A compensatory increase in activation of the cerebellum bilaterally and activation of the primary motor cortex has been observed in patients with rigidity[20] . An increased activation of ipsilateral premotor areas has also been observed during performance of a pre-learned sequential motor task [21].

3.2 RELEVANT ASPECTS OF MOVEMENT CONTROL BY THE BASAL GANGLIA

3.2.1 Self initiated versus externally triggered movements

A number of studies have found that the basal ganglia are involved in control of self initiated movements to a greater extent compared to externally triggered movements [22]. There were moderate to strong associations between the supplementary motor areas to the sensorimotor cortex via the putamen and the thalamus during self initiated movements, whereas during the externally triggered movements these interactions were found only in the premotor cortex to sensorimotor cortex and from the sensorimotor cortex to the putamen [23;24]. This suggests that planning and execution of voluntary movements requires proper functioning in the supplementary motor area that has extensive connections with the BG whereas when movement is made in response to an external cue, the movement is planned and executed by the premotor cortex that is under significantly less control by the BG [25].

3.2.2 Role of the BG in force control

Movements that require internal regulation of the rate of change of force pose increased metabolic demands on the BG specifically the internal component of the globus pallidus and the subthalamic nucleus [26]. Specific areas of the BG and their contributions to the control of force during precision tasks have also been identified. The caudate nucleus is responsible for selection of force amplitude. The STN and posterior putamen are active during force production and not during force amplitude selection [27]. It has also been documented that abnormalities in grip force are an intrinsic feature of the pathophysiology of PD and not an effect or side effect of the medications [28].

3.2.3 Role of the BG in fine motor coordination

A number of studies have shown deficient fine motor control in individuals with PD. Hejdukova et al showed grip force abnormalities during a task involving precision grip during components that require self initiation are affected to a greater extent as compared to other components of the task [29]. Agostino et al showed that there was a greater impairment of individual finger movements and grips involving two digits compared to multidigit grasping [8]. There is also reduced coordination between the fingers and the wrist [30]. The role of the cortex in the control of fractionated movements and precision activities is well known [31-33]. Difficulties with precision grip activities in patients with PD might reflect the failure of the BG to reinforce the cortical mechanisms that are responsible for executing fractionated movements during fine motor coordination. This notion is supported in part by the fact that there is increased cortico-

cortical activation during performance of sequential finger movements to compensate for the striatal dysfunction [12].

A number of other studies have reported that patients with Parkinson's disease (PD) experience difficulties with fine motor coordination in the upper extremity[4;8;14;28;30;34]. In spite of the extensive research in this area, there is inconclusive evidence about the exact nature of the impairments in fine motor coordination in patients with Parkinson's disease and their contribution to disability.

Various components of upper extremity fine motor skill dysfunction in PD have been identified. These include dysfunction in kinetic parameters such as higher grip force production, prolongation of movement phase,[14] irregular force profile, increase in peak movement velocity, inability to modulate movement parameters[4] and kinematic parameters such as decrease in maximum grip aperture, target overshoot[4] and absence of corrective sub movements[35]. It has also been shown that sequential, complex movements are affected to a greater degree compared to simple repetitive movement. Self initiated movements are affected to a greater degree as compared to externally triggered movements[36;37]. Patients with PD also show an impaired capability to process motor responses simultaneously when 2 stimuli are presented in rapid succession.[38]. Deficits have been shown in patients with PD in activities that involve switching between motor programs[39]. PD patients have significant difficulty when they have to perform multiple motor acts one after another in a sequence [34;36]. This difficulty is in part attributed to the difficulty to switch from one motor program to another during transition from one movement component to another [40].

Thus complex environments that require simultaneous attention to various components and switching between motor programs are difficult tasks for patients with PD. Also if there is a terminal accuracy requirement, the performance deteriorates considerably[41].

3.3 SIGNIFICANCE OF OUR STUDY

Although all these individual deficits in upper extremity motor control in patients with PD have been identified, there are no studies to date that integrate this information taking into consideration the effects of drugs, context and the environment to eavaluate the effects of these impairments on functional tasks. In addition, existing studies of patients with PD have compared their motor deficits to normal control subjects. To date there have not been studies that have observed differences in motor function across groups of patients with varying severity of the disease. We have created a computer-generated force-tracking task that requires the subject to attend to the dynamic changes that occur on the screen and modify their responses accordingly. An understanding of the association between the kinetic characteristics of the force-tracking task using precision grip, and disease progression, as well as with interference due to a mental task will help us understand the effects of the disease without the influence of medications. Data from this study will assess the effect of divided attention on fine motor coordination in these subjects.

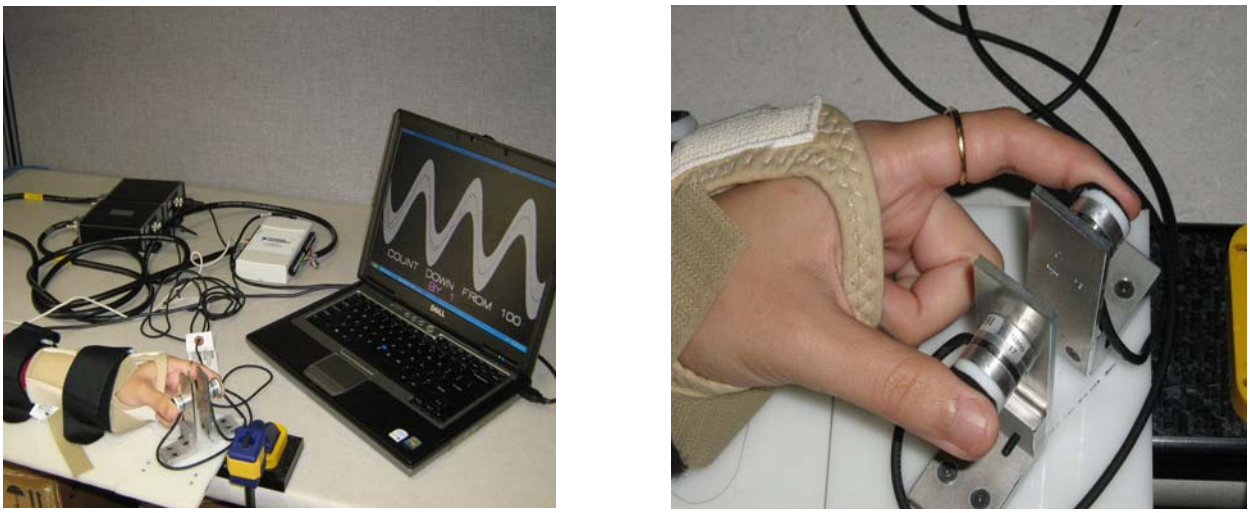
The purpose of this study is to identify impairments in fine motor coordination using a precision grip force-tracking task in subjects with Parkinson's disease. We focused on a task that involves precision grip and involves attention, concentration, is sequential and dynamic so that it would incorporate important components of a functional task in the upper extremity. Our methodology is based on creating a force-tracking task for the upper extremity that has some

characteristics of a functional task, using a computer display for the visual information and multi axial force transducers mounted on a steel plate. This will allow us to document fine motor impairments in the upper extremity in our subjects as well as help us understand the relation of these impairments to functional capabilities of these individuals without the interference of the effect of medications.

4.0 METHODS

4.1 DESIGNING THE TEST TASK

We used two six-axial force sensors (nano-17, ATI automation Industries, Birmingham, AL, USA) that are capable of sensing forces and torque each along three axes. For our study, we were interested in looking at the force data only. The sensors have a resolution for force of 0.003 N. These were mounted on two steel plates. The steel plates were mounted vertically on a plastic board at an angle of 45 degrees to the long axis of the forearm. The plastic board can be fixed to the edge of any table with the help of clamps. The experimental set up of the equipment is shown in figure 4-1.



4-1 Experimental Setup

For the first trial of the force tracking task, we displayed a sine wave at a frequency of 0.2 Hz moving across the screen with a black line running through its centre, which posed an accuracy requirement. The sine wave pattern was chosen since it provided a continuous, dynamic, sequential activity (gradual and smooth transition between task components). The participants also had to switch between motor programs of creating gradually increasing amounts of force (in the up-going part of the wave) to the motor program for creating gradually decreasing amounts of force (in the down-going part of the wave). The amount of force required to track the target wave was set to six Newton at the highest peak of the wave and two Newton at the lowest trough of the wave. This range of force is comparable to normal amounts of forces required during performance of everyday activities involving precision grip.[42]

The practice session consisted of patterns that were straight, up going or down going, to give the participants a feel for the resolution of the sensors. We gave each participant a practice for two minutes. The practice session did not have any mental distraction component.

The test task had a total time of 200 seconds. The first 20 seconds of the display were a constant value of 4 N for the participants to adjust to the tracking. The next 1 minute was pure tracking without any mental distraction. At the end of minute 1 the participants saw a display on the screen that said “Count backwards from 100 by 1”. At this time, the participants were asked to count aloud backwards consecutively by one. At the end of minute 2 they saw a sign on the screen saying” Count backwards from 100 by 3”. At this point, we asked them to count aloud backwards from 100 subtracting 3 every time. If the participants made a mistake greater than five numbers, we corrected it and they continued to count backwards from the corrected number. If the mistake was lesser than five numbers, they continued counting.

For the other force tracking task, the participants performed on another three minutes of trial with the counting sessions remaining the same: minute1 – only tracking, minute 2 – tracking with counting backwards consecutively and minute 3- tracking and counting backwards by threes. The subjects matched their force to a waveform generated by the derivative of a pseudorandom ternary sequence. The wave display on the screen was pseudo-random in nature, meaning it had a low frequency (0.01 Hz) pattern and some high frequency (2.5 Hz) components. The subjects were shown only part of the wave on the screen and were asked to track it as it appeared on the screen. The subjects were thus unaware of the upcoming force requirements, introducing an unpredictable component to the task. Our aim in doing the latter part of the trial was to see how well the subjects could make adjustments in their force without being able to use visual prediction.

4.2 TESTING THE FORCE-TRACKING TASK IN INDIVIDUALS WITH PARKINSON'S DISEASE AND AGE-MATCHED CONTROLS.

We tested the performance of 30 individuals with Parkinson's disease and 30 age-appropriate controls on the force-tracking task created. Participants were tested on both, the sine as well as the pseudorandom trial, using their right and left extremities. Ten controls were tested twice on the sine trial to measure the test-retest reliability of the primary outcome variable. Five cases with PD were tested twice on the sine trial for the left side, once with the mental distraction component and once without it to test whether the performance deteriorates over time in the absence of mental distraction.

4.2.1 Subjects

We used advertisements (see appendix B) posted throughout the communications of The Parkinson's Chapter of Greater Pittsburgh, National Parkinson's Foundation to recruit subjects for this research study. Individuals who contacted the research staff and met the preliminary inclusion criteria (diagnosis of Parkinson's disease, a history of signs and symptoms of the disease, and ≥18 years of age, were scheduled for the research study. Participants were asked to bring along a friend, spouse or acquaintance that was within 10 years of age as them, who is ready to participate for the purposes of getting age-matched data. Potential subjects who were unable to get a control were still eligible to participate.

Inclusion Criteria

1. Previously established diagnosis of Parkinson's disease (noted by a physician) and a reported history of symptoms of slowed movement, tremor, difficulty initiating movement for a minimum of one year and/or Hoehn and Yahr scale[43] rating documented by the participants neurologist.
2. Age ≥18 years of age
3. Subject is without profound movement dysfunction associated with Parkinson's disease, including severe bradykinesia, shuffling gait, etc., and also does not experience abnormal movements including dyskinesia and other involuntary movements.
4. Score of 27 or greater on the Mini Mental State Exam indicating that they are free of dementia. [44].
5. No history of concurrent CNS disease.

Exclusion Criteria

1. Restriction of movement in the upper extremities.
2. Sensory loss in the hand, as determined by superficial sensory testing.
3. Loss of vibration sense in the hand.
4. Subjects unable to stay off medications 12 hours prior to the appointment.
5. Deep Brain Stimulator implanted.

4.2.2 Procedures

4.2.2.1 Pre-screening

Individuals that contacted us on the phone were asked a few questions on the phone to verify if they qualify for participation in our study. A telephone screening questionnaire is attached in Appendix A.

4.2.2.2 Screening:

Individuals that qualified for the study based on the pre-screening process were scheduled for an appointment for testing. The testing was carried out at the department of Physical Therapy at the University of Pittsburgh. Because of the portable nature of the equipment, participants also had the option of being tested at home. Participants with PD were instructed to refrain from taking PD medications for 12 hours prior to the scheduled examination. The testing and experimental procedures were explained to the subject as soon as they came in. A signed informed consent was obtained. Basic demographic information (age, race, gender, education level) was collected on all individuals who consented to participate. All individuals who consented to participate also underwent a physical function screening examination to determine if they were eligible for the study. The physical function screening included a medical history, a review of systems including such things as assessment of vital signs (heart rate and blood pressure), assessment of upper and lower extremity range of motion, strength, and sensation (superficial light touch tested with a paper clip on the areas listed in Appendix C, cranial nerve screening (CN 2, 3, 4, 6, and 8) to assess vision, eye movements and hearing, assessment of postural responses (righting responses),

and an assessment of cognitive status (Mini-Mental State Examination). This part of the examination required about 40 minutes. Vibration sense was tested by placing a vibrating tuning fork with the subject's eyes closed on various bony prominences listed in appendix A6-5. The examiner stops the vibration of the fork randomly during the test and the subjects need to identify when the fork stops vibrating. The examiner then immediately places the fork on her own self to confirm a negative test. Individuals who were eligible for the study (i.e., meet all inclusion and exclusion criteria) underwent a comprehensive assessment. A description of items in this assessment is listed below. Anyone not eligible because of medical screening results was encouraged to contact their primary care physician for further work-up.

4.2.2.3 Comprehensive Exam

This included administering of the outcome measure questionnaire – the UPDRS and the experimental procedures.

Persons were instructed to refrain from taking PD medications for 12 hours prior to the scheduled examination.

Outcome Measures:

Measure of Disease Severity:

Unified Parkinson's Disease Rating Scale (UPDRS)[45]. The UPDRS is an instrument used for rating symptom severity in Parkinson's disease based on history (2 sections) and physical examination (one section). Symptom severity is rated on 45 items in 3 sections; individual items are rated on a scale of 0 to 4, and total possible scores range from 0 to 180 with higher scores

indicating greater severity of disease. The UPDRS has been widely used in clinical studies of Parkinson's disease as a reliable composite scale of physical function in this population[46;47].

Experimental Procedures

The testing was carried out at the department of Physical Therapy at the University of Pittsburgh. Subjects also had the option of being tested at home.

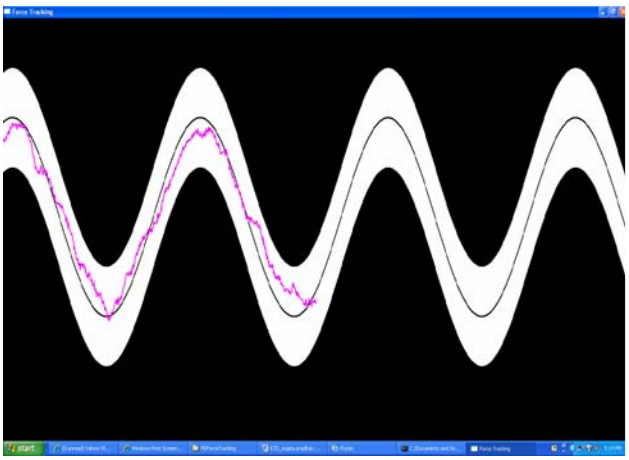
Reaction Time testing

The subject is seated in front of a computer screen with his/her dominant hand resting on the space bar of the keyboard. They are instructed to press the space bar to begin the test. The subject sees a red circle on the screen and is instructed to press the space bar again as soon as the color changes. This is repeated for five times and the average time is calculated from the five readings.

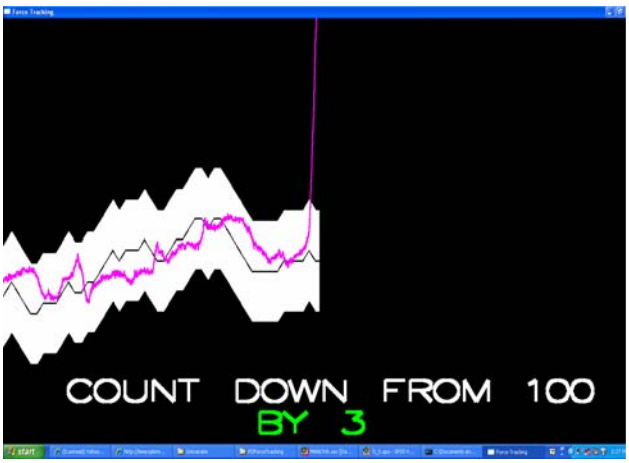
4.2.2.4 Force transducer testing

The examiner demonstrated the task to be performed to the subject. The subject is seated with the forearm and wrist supported and strapped with the index finger and thumb grasping the sensors mounted on a steel plate (See figure 4.1). As the subjects pinched on the sensors they create a pink line that rises up in proportion to the amount of force exerted on the sensors and falls as the subject relaxes. The subject is shown a moving pathway in the shape of a sine wave on a computer screen with a black line running through its centre. The subject is asked to adjust the force that he creates on the sensors such that the pink line stays as close as possible to the black line in the centre of the pathway (figure 2). The amount of force that the subject is

expected to produce is no higher that that required to draw a line on a paper with a pen (2-6 Newton).



4-2 Display for Sine wave trial



4-3 Display for Pseudo-Random trial

They continue the activity for a total of three minutes. In the first minute the subject will only track the sine wave. In the second minute, the subjects were asked to count backwards from 100 during the task to observe effects of multitasking. In the third minute we asked the subjects to count backwards from one hundred, subtracting three from it successively each time. A record of the number of mistakes made was kept. The subjects were given a practice trial before recording the test trial. The subjects were given a rest for 5 minutes after which the same protocol was repeated with the sine wave being unpredictable in its frequency for another three minutes (Figure 4- 3). The same procedures were repeated for the left side.

For ten of the control subjects, we performed the sine trial twice for the left side to test for test-retest reliability. For five of the case subjects with PD, we tested the left side twice, once with the distraction and once without, to compare if the deterioration was due to the effect of

distraction or due to degradation of the motor program, an established phenomenon in this population.

4.2.3 Data collection Record

The data collected on each subject as well as each control included the following:

4.2.3.1 Demographics

Includes questions about age, race, gender, education level etc. Appendix C.1

4.2.3.2 Medical Screening form

Includes questions about present and past medical history. . Appendix C.2

4.2.3.3 Vital signs and Cranial nerve testing

Involves testing heart rate, blood pressure and cranial nerve testing for cranial nerves 2,3,4,6, and 8 to assess vision, eye movements and hearing. Appendix C.3

4.2.3.4 Sensory & motor exam of the hand

This involved assessment of upper extremity range of motion, strength, and sensation (superficial light touch tested with a paper clip on the areas listed in Appendix C.4

4.2.3.5 Somatosensory testing : (Vibration testing) .

Vibration sense was tested by placing a vibrating tuning fork with the subject's eyes closed on various bony prominences listed in Appendix C.5.

4.2.3.6 Mini mental state exam (MMSE)

The MMSE is a series of questions and tests, each of which scores points if answered correctly. If every answer is correct, a maximum score of 30 points is possible. Simple questions regarding date, location, basic memory tests etc are part of the MMSE. A copy of the test is attached in the appendix. Appendix C.8

5.0 DATA ANALYSIS

5.1 DATA PROCESSING

We used Matlab version R2007a to process the raw data obtained from the force transducers. The data file was split into 3 parts each 60 seconds long: Min1 (pure tracking without mental distraction), min2 (tracking with counting backwards consecutively from 100) and min3 (Subtracting 3 backwards from 100).

The data were then analyzed for their frequency content. Visual inspection of the force output revealed significant high frequency components. Frequency analysis of the data resulted in the determination that the high frequency force output was concentrated in the range of 2 to 8 Hz, which is the characteristic frequency of the tremor for individuals with PD (see figure 5.1 and 5.2). The amount of tremor was quantified as an integral of the area between 2 and 8 Hz on the power spectral density plot. Because this was unintended force output, we filtered this component before performing subsequent data analyses. The data were filtered with a Butterworth low pass filter (2^{nd} order, cutoff frequency 2 Hz, dual pass). Variables like Root mean square error, Coefficient of coordination and amount of lag were calculated from the filtered data as follows:

5.1.1 Root mean square Error (RMSE)

The root mean square error is a measure of accuracy. The lower the root mean square error, the more accurate the tracking. It was calculated separately (using the equation below) for each minute for the sine and pseudorandom trials.

$$\sqrt{1/N \sum (F_T(t) - F_S(t))^2}$$

where F_T = Target force

F_S= Force produced by the subject.

5.1.2 Coefficient of coordination (Kc)

The grip force coordination was quantified by the coefficient of coordination (Kc)[48;49], defined by the product of 2 correlations(1). Correlation between target force (F_T) and response force (F_S) and (2).Correlation between the derivatives of the target and response forces. A Kc value closer to one suggests enhanced coordination of the pinch force.

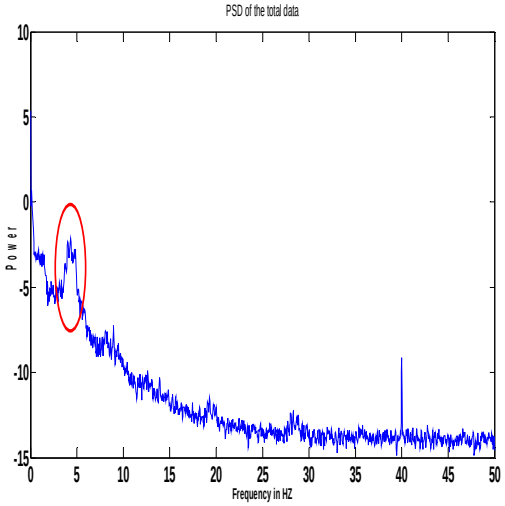
$$K_C = \text{Corrcoeff}\,(F_T, F_S)\ .\ \text{Corrcoeff}\,(F_T/dt\ ,\ F_S/dt\ )$$

where F_T = Target force

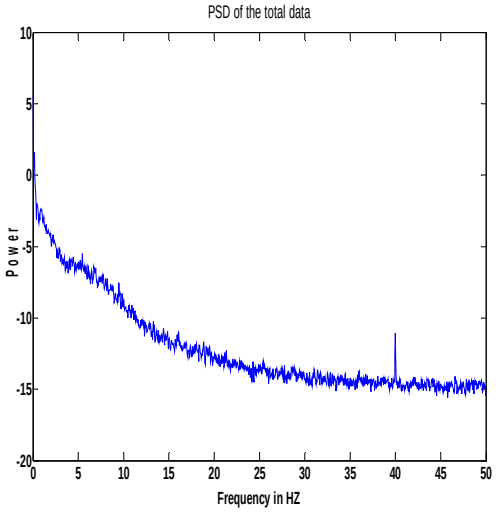
F_S= Force produced by the subject.

5.1.3 Tremor Integral (TR)

This was calculated as the integral of the power spectral density plot between 2 and 8 Hz of the unfiltered response force. It was calculated separately for the sine and pseudorandom trials. The spike at 40 Hz represents electrical noise.



5-1 Tremor peak around 5 Hz in the group with PD



5-2 Absence of tremor peak in Controls

5.1.4 Lag (lag)

The lag was calculated as the time period that maximized the covariance between the target and the response force based on the pseudorandom trial. We used the following matlab function to calculate the maxlag and then determined the corresponding time to get the lag in seconds.

[c,lags] = xcov (x, y, maxlags, 'unbiased')

where x=filtered response force and y=target force

If the covariance was very low, the subjects did not follow the pattern at all, so calculating the lag was not meaningful.

Thus if the covariance was <0.35, the lag was set to a maximum of 1.5 sec for the sine trial and 5 sec for the pseudorandom trial. The maximum lag cutoff value was decided based on the spread of that data, that minimized the number of cases being assigned a maximum lag value artificially.

5.2 STATISTICAL ANALYSIS

We used SPSS 11.0 to analyze the processed variables. Variables like Root mean square error, Coefficient of coordination, Tremor integral and amount of lag were entered into SPSS for the min1, min2 and min3 parts of the test for subjects as well as controls according to the side of testing.

5.2.1 Hypothesis for Specific Aim 2

Descriptive statistics, including frequency counts for categorical variables and measures of central tendency and dispersion for continuous variables were calculated to summarize the data.

A univariate mixed models analysis of variance was performed with presence of Parkinson's disease as the between group variable and the minute (min1, min2, min3) as well as side of involvement (better performed, worse performed) as repeated measures variables. We decided to use sides of better or worse performance for comparisons between controls and subjects with PD

since many of the participants in the group with PD had asymmetrical involvement and comparing the corresponding sides of controls was not always fair considering the issue of dominance simultaneously. The side of involvement was decided based on mean RMSE scores for the sine wave as well as the pseudorandom trial combined. The dependant variables were root mean square error, coefficient of coordination, amount of tremor and amount of lag. Pairwise comparisons were analyzed for each of the dependant variables across the three minutes comparing performance during min1 to performance during min3 and comparison between minute2 and minute3. Bonferronis' correction was used to control for alpha for multiple comparisons.

We were interested in the main effect of PD which would tell us whether there was an effect of having the disease on performance based on the variables of interest, and the interaction effect of PD and minute suggesting that individuals with and without PD performed differently according to each minute in testing.

5.2.2 Hypothesis for Specific Aim 3

Descriptive statistics, including frequency counts for categorical variables and measures of central tendency and dispersion for continuous variables were calculated to summarize the data.

The association between characteristics of fine motor function calculated from output data from the force transducers and the combined ADL and motor score of the UPDRS were investigated with a stepwise multiple regression. The combined ADL and motor score of the UPDRS was included as the dependant variable and the variables calculated from the force transducer output were included as the independent (predictor) variables. Before performing the

regression analysis, regression diagnostics were performed. Descriptive statistics and partial correlation among the variables were analyzed. We calculated partial correlations, instead of zero order correlations, to determine the independent strength of the relationships between the independent and each criterion variable. The probability of the F value was set at 0.05 to enter into and 0.10 to remove the measured variable from the model. R^2 values were calculated for the independent variable, reflecting the goodness of fit of the linear model in the equation. Significance of the linear association of each variable at each step was tested. Beta coefficients for the variable in the final model were calculated and their statistical significance were tested under the null hypothesis that the coefficient is not different from zero.

6.0 RESULTS

6.1 TEST-RETEST RELIABILITY IN CONTROL SUBJECTS USING THE SINE WAVE TRIAL

All participants performed the sine trial for the right hand followed by the pseudo-random trial for the right side and then the sine and pseudo-random trials for the left side. Ten control subjects performed an additional sine trial for the left side. We analyzed the two left sine trials for the ten control subjects for test-retest reliability of the equipment.

Test re-test reliability was calculated for the variable of Root Mean Square Error. The calculations are based on data from the two sine trials for the left side of ten control subjects.

Shrout and Fleiss describe three models for calculation of reliability coefficients[50]. We used Model 3 since it uses a repeated measures ANOVA design and hence is appropriate for testing reliability among multiple scores from the same rater.

Table 6-1 Reliability coefficients for RMSE_S

Minute	Intraclass correlation coefficient	Df	Sig
1	0.957	9	0.000
2	0.894	9	0.002
3	0.962	9	0.000

6.2 DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

	PD	Controls
Age (yrs)		
Mean(SD)	65 (10)	70 (10) (p=0.069)
Gender (M/F)	23/7	12/18
Handedness R/L	24/6	22/8
No of yrs since Dx	6 (1)	NA
Hoehn-Yahr stage	1-3	NA

6.3 CLINICAL TEST RESULTS FOR ALL PARTICIPANTS

	PD	Controls	p<0.05
	Mean (SD)	Mean (SD)	
Reaction time(sec)	0.36(0.15)	0.31(0.06)	0.15
GPT – BP(sec)	150 (69)	101 (25)	0.00
GPT –WP(sec)	159 (77)	95 (17)	0.00
FT – BP (/10 sec)	46 (13)	38 (10)	0.01
FT – WP (/10 sec)	46 (11)	41 (11)	0.07
UPDRS Total	26(15)	NA	
UPDRS (ADL+Motor)	21(12)	NA	

GPT : Grooved Pegboard test, FT: Finger Tapper,

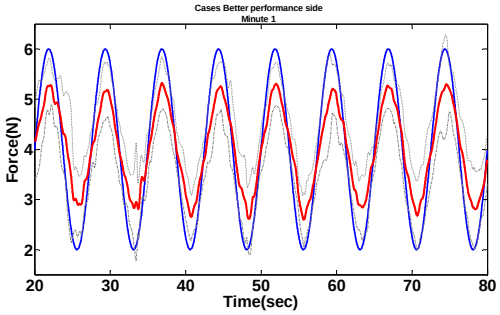
BP: Better performance side, WP: Worse performance side

6.4 BETWEEN GROUP DIFFERENCES ON THE DEPENDANT VARIABLES

6.4.1 Descriptive Statistics

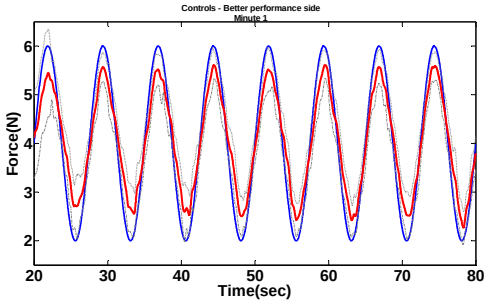
Descriptive statistics (Mean, standard deviation and 95% CI for the mean) are reported for each of the dependant variables. Performance of subjects with PD and controls averaged across 30 participants in each group is depicted in figures 6-1 to 6-24. The figures depict relation of the variables across minute 1, minute 2 and minute 3 between subject groups of with and without PD for sides of better or worse performance. The blue trace, in each instance, represents the target wave shown on the screen and the red trace is the response from the participants. The dotted traces represent one standard deviations for the response force in either direction. An expanded version of the traces is attached in Appendix D.

Average performance of 30 cases and 30 controls on the Sine trial for the side of better performance



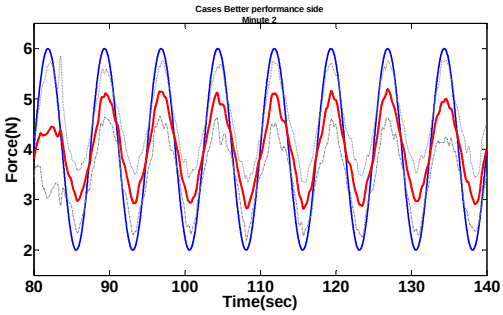
6-1 30 Cases - Min 1

[Click here for an enlarged version]



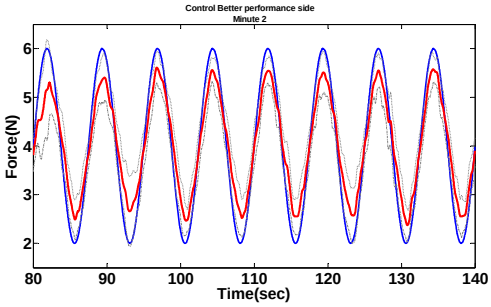
6-2 30 Controls - Min 1

[Click here for an enlarged version]



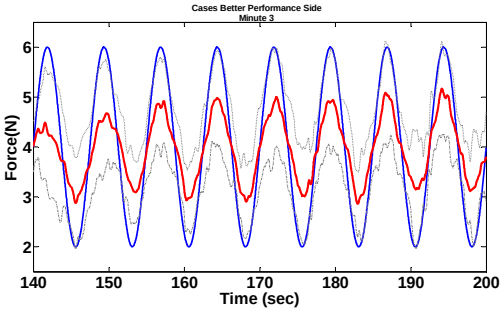
6-3 30 Cases - Min 2

[Click here for an enlarged version]



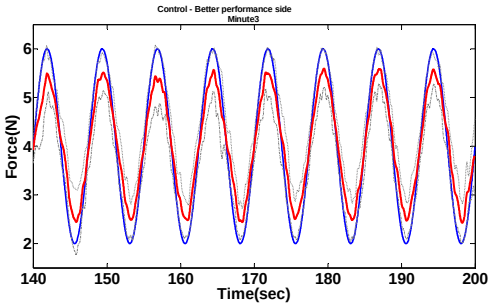
6-4 30 Controls - Min 2

[Click here for an enlarged version]



6-5 30Cases - Min 3

[Click here for an enlarged version]

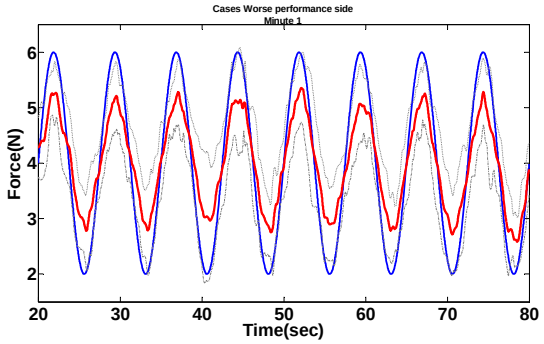


6-6 30Controls - Min 3

[Click here for an enlarged version]

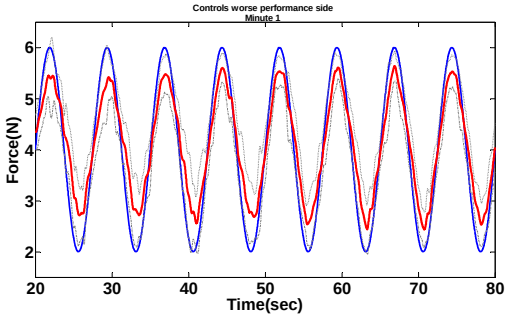
Blue Trace represents the Target force, Red Trace represents the ensemble response and the gray lines represent ± 1 Standard deviation

Average performance of 30 cases and 30 controls on the Sine trial for the side of worse performance



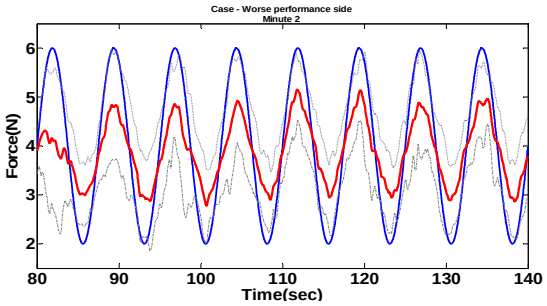
6-7 30 Cases - Min 1

[Click here for an enlarged version]



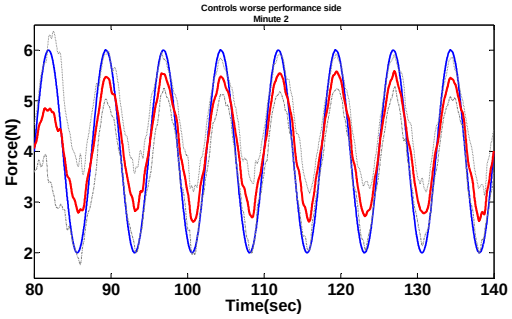
6-8 30 Controls - Min

[Click here for an enlarged version]



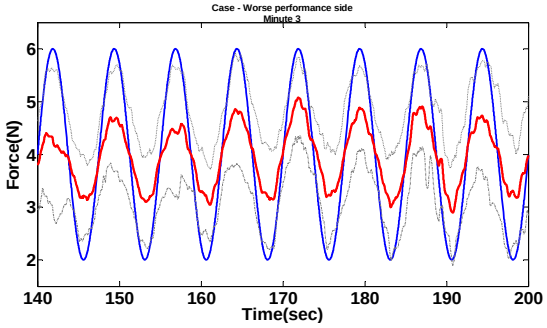
6-9 30 Cases - Min 2

[Click here for an enlarged version]



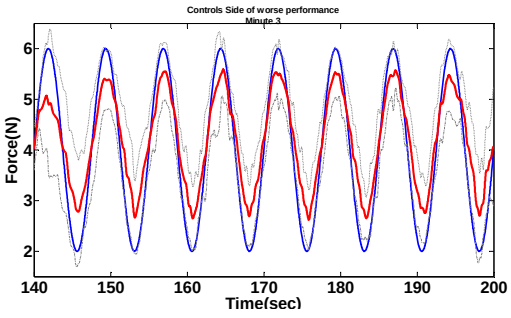
6-10 30 Controls - Min 2

[Click here for an enlarged version]



6-11 30 Cases - Min 3

[Click here for an enlarged version]

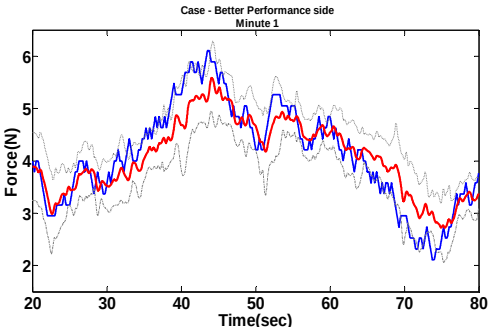


6-12 30 Controls - Min 3

[Click here for an enlarged version]

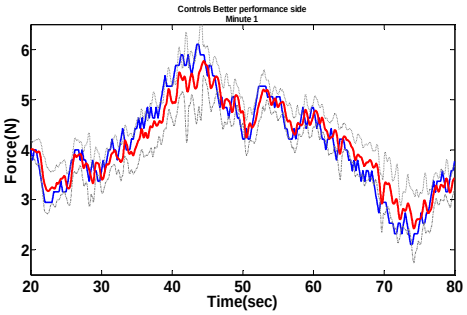
Blue Trace represents the Target force, Red Trace represents the ensemble response and the gray lines represent ± 1 Standard deviation

Average performance of 30 cases and 30 controls on the Pseudorandom trial for the side of better performance



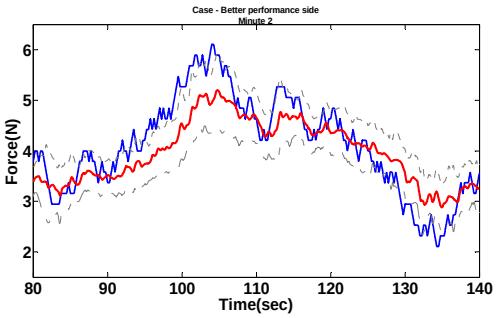
6-13 30 Cases - Min 1

[Click here for an enlarged version]



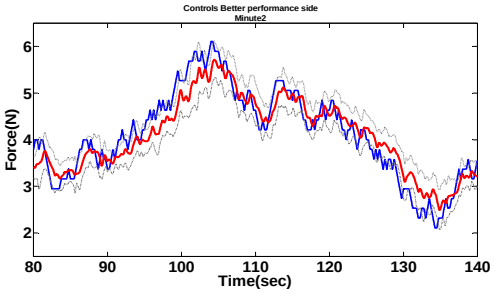
6-14 30 Controls - Min 1

[Click here for an enlarged version]



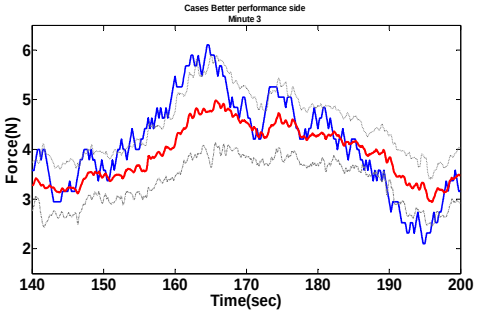
6-15 30 Cases - Min 2

[Click here for an enlarged version]



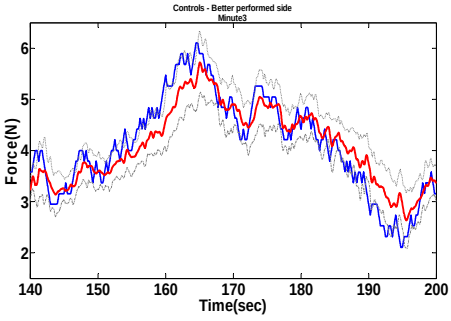
6-16 30 Controls - Min 2

[Click here for an enlarged version]



6-17 30 Cases - Min 3

[Click here for an enlarged version]

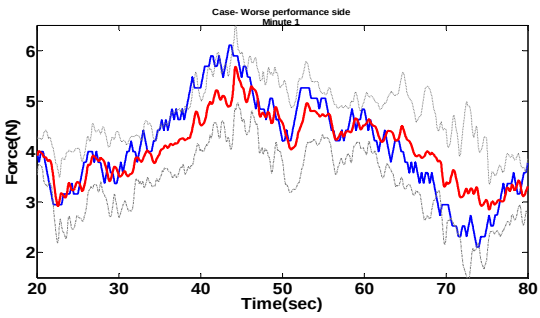


6-18 30 Controls - Min 3

[Click here for an enlarged version]

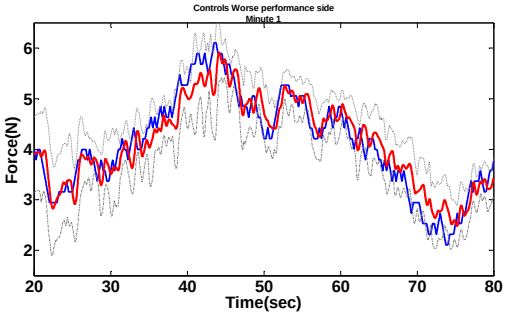
Blue Trace represents the Target force, Red Trace represents the ensemble response and the gray lines represent ± 1 Standard deviation

Average performance of 30 cases and 30 controls on the Sine trial for the side of worse performance



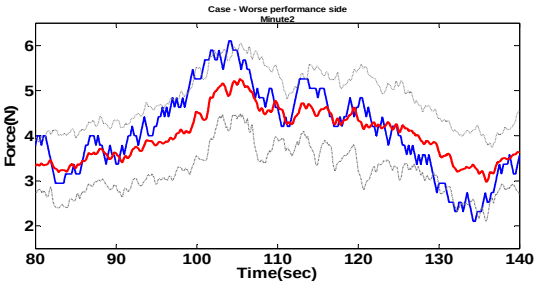
6-19 30 Cases - Min 1

[Click here for an enlarged version]



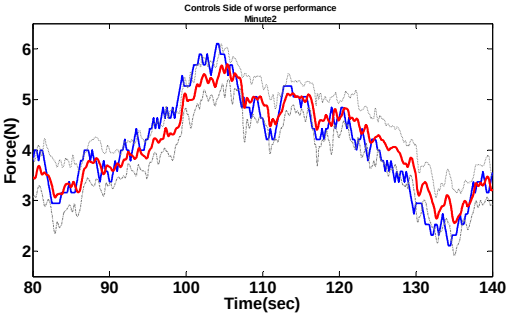
6-20 30 Controls - Min 1

[Click here for an enlarged version]



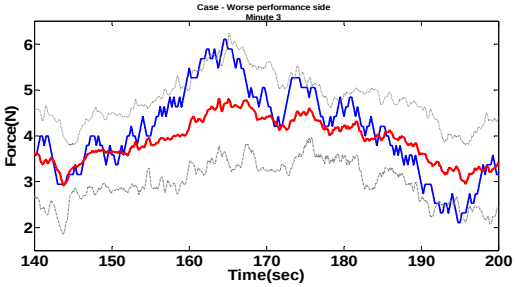
6-21 30 Cases - Min 2

[Click here for an enlarged version]



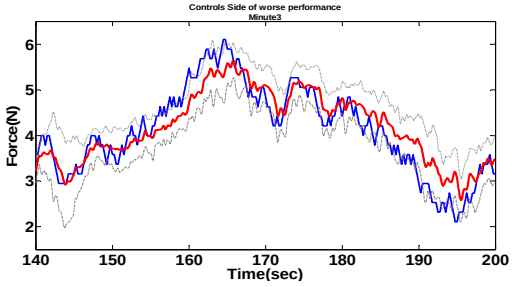
6-22 30 Controls - Min 2

[Click here for an enlarged version]



6-23 30 Cases - Min 3

[Click here for an enlarged version]



6-24 30 Controls - Min 3

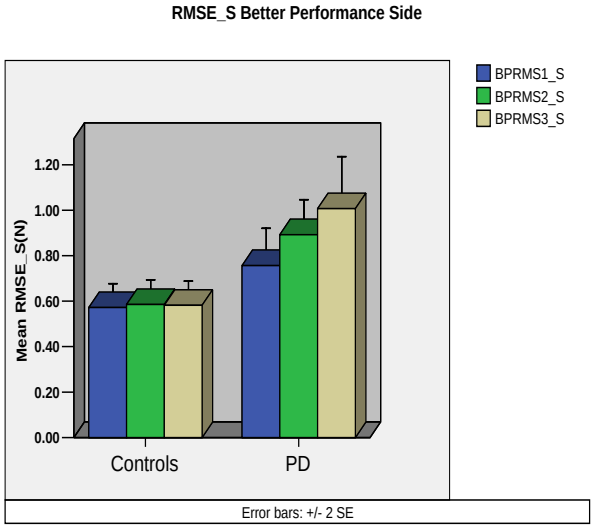
[Click here for an enlarged version]

Blue Trace represents the Target force, Red Trace represents the ensemble response and the gray lines represent ± 1 Standard deviation

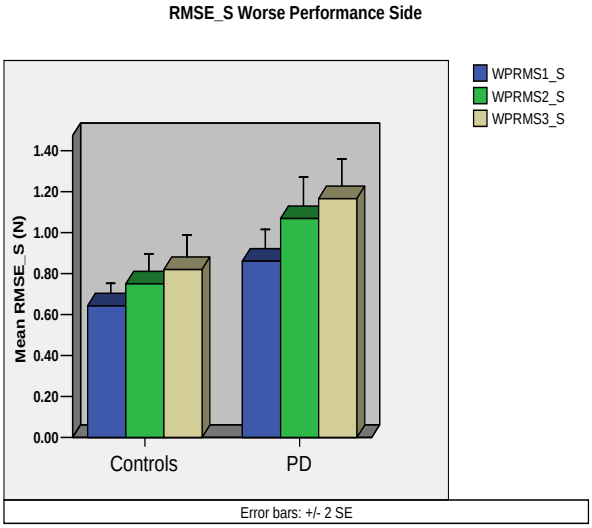
6.4.1.1 Root Mean Square Error for the Sine Trial (RMSE_S)

Table 6-2 Descriptive Statistics for RMSE_S

Dependant variables	Minute 1 Mean (SD) PD	Minute 1 Mean (SD) Controls	Minute 2 Mean (SD) PD	Minute 2 Mean (SD) Controls	Minute 3 Mean (SD) PD	Minute 3 Mean (SD) Controls
BPRMSE_S	**0.76(0.35)**	**0.58(0.2)**	**0.89(0.33)**	**0.58(0.20)**	**1.01(0.53)**	**0.58(0.20)**
95%CI	**0.62-0.89**	**0.50-0.64**	**0.77-1.01**	**0.51-0.66**	**0.81-1.21**	**0.51-0.65**
WPRMSE_S	**0.86(0.34)**	**0.64(0.22)**	**1.07(0.47)**	**0.75(0.32)**	**1.16(0.45)**	**0.82(0.38)**
95%CI	**0.73-0.99**	**0.56-0.72**	**0.89-1.24**	**0.63-0.87**	**1.00-1.33**	**0.68-0.96**



6-25 RMSE_Sine-Better Performance

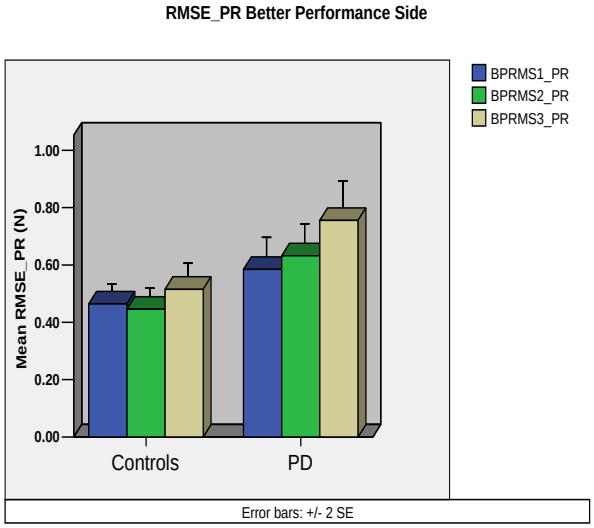


6-26 RMSE_Sine- Worse Performance

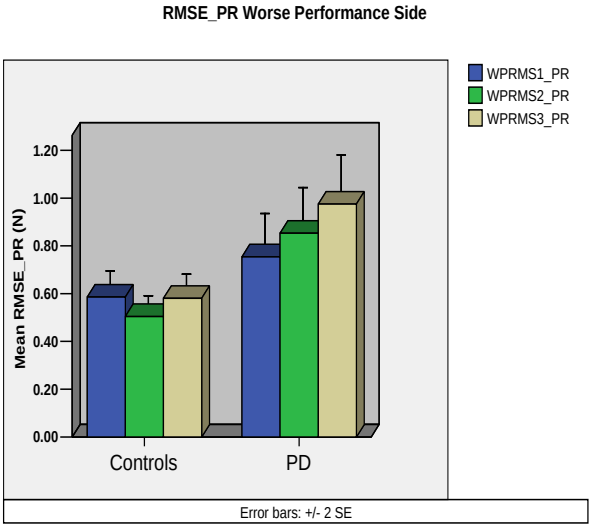
6.4.1.2 Root Mean Square error for the Pseudo-Random Trial (RMSE_PR)

Table 6-3 Descriptive Statistics for RMSE_PR

Dependant variables	Minute 1 Mean (SD) PD	Minute 1 Mean (SD) Controls	Minute 2 Mean (SD) PD	Minute 2 Mean (SD) Controls	Minute 3 Mean (SD) PD	Minute 3 Mean (SD) Controls
BPRMSE_PR	**0.58(0.24)**	**0.46(0.13)**	**0.63(0.24)**	**0.44(0.14)**	**0.75(0.31)**	**0.51(0.19)**
95%CI	**0.49-0.68**	**0.41-0.51**	**0.54-0.72**	**0.39-0.50**	**0.64-0.87**	**0.44-0.58**
WPRMSE_PR	**0.75(0.42)**	**0.58(0.23)**	**0.85(0.45)**	**0.50(0.17)**	**0.97(0.49)**	**0.58(0.20)**
95%CI	**0.60-0.91**	**0.50-0.67**	**0.68-1.02**	**0.44-0.57**	**0.79-1.56**	**0.50-0.66**



6-27 RMSE_Pseudo-Random-Better Performance



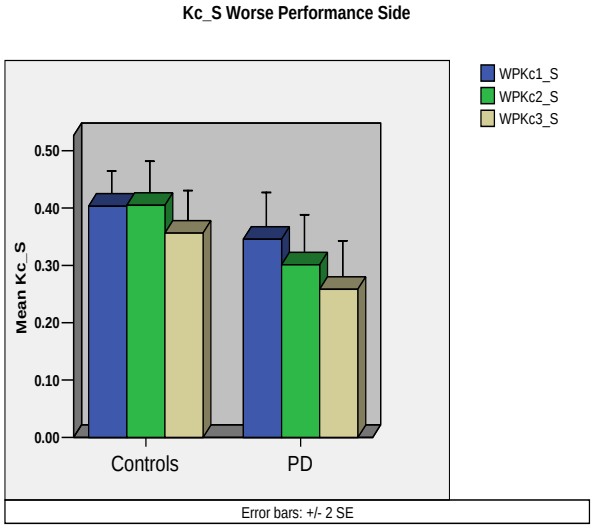
6-28 RMSE_Pseudo-Random-Worse Performance

6.4.1.3 Coefficient of coordination for the Sine Trial (Kc_S)

Table 6-4 Descriptive Statistics for Kc_S

Dependant variables	Minute 1 Mean (SD) PD	Minute 1 Mean (SD) Controls	Minute 2 Mean (SD) PD	Minute 2 Mean (SD) Controls	Minute 3 Mean (SD) PD	Minute 3 Mean (SD) Controls
BPKc_S	**0.43(0.21)**	**0.46((0.14)**	**0.37(0.23)**	**0.50(0.17)**	**0.35(0.24)**	**0.47(0.17)**
95%CI	**0.35-0.51**	**0.41-0.52**	**0.29-0.45**	**0.43-0.56**	**0.26-0.44**	**0.40-0.53**
WPKc_S	**0.34(0.19)**	**0.40(0.14)**	**0.30(0.21)**	**0.40(0.18)**	**0.26(0.20)**	**0.36(0.17)**
95%CI	**0.27-0.42**	**0.35-0.45**	**0.22-0.38**	**0.34-0.47**	**0.18-0.33**	**0.29-0.42**

6-29 Kc_Sine – Better Performance



6-30 Kc_Sine- Worse Performance

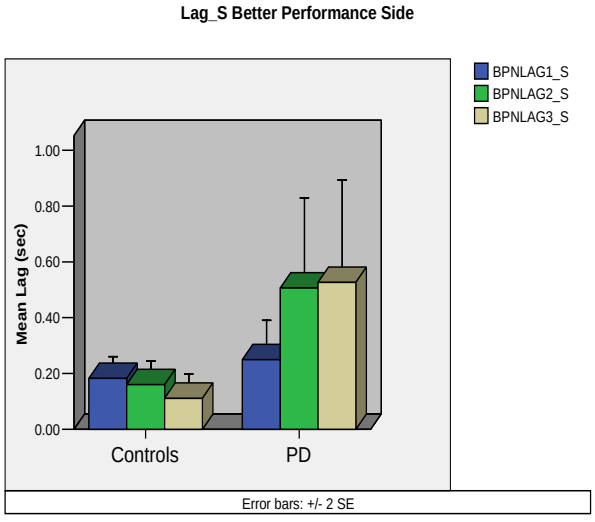
Coefficient of Coordination was also calculated for the pseudorandom trial but since the subjects were unaware about the direction in which the wave would move, the correlation between the

rates of production of the target and response forces was negative in many instances, which rendered the interpretation of the Kc_PR meaningless.

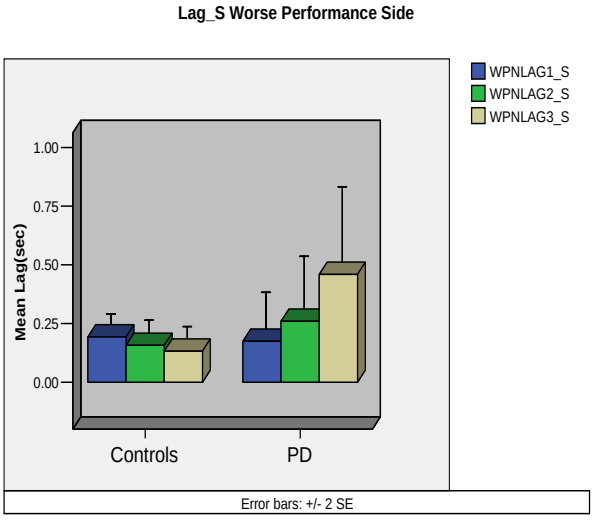
6.4.1.4 Lag from the Pseudo-Random Trial (Lag_S)

Table 6-5 Descriptive Statistics for Lag_S

Dependant variables	Minute 1 Mean (SD) PD	Minute 1 Mean (SD) Controls	Minute 2 Mean (SD) PD	Minute 2 Mean (SD) Controls	Minute 3 Mean (SD) PD	Minute 3 Mean (SD) Controls
BPLag_S	**0.25(0.31)**	**0.18 (0.14)**	**0.51(0.81)**	**0.16(0.15)**	**0.53(0.93)**	**0.11(0.16)**
95%CI	**0.13-0.36**	**0.13-0.23**	**0.20-0.81**	**0.10-0.22**	**0.18-0.87**	**0.05-0.17**
WPLag_S	**0.17(0.50)**	**0.19(0.19)**	**0.26(0.68)**	**0.16(0.22)**	**0.46(0.95)**	**0.13(0.22)**
95%CI	**-0.03-0.36**	**0.12-0.26**	**0.00-0.51**	**0.07-0.24**	**0.10-0.81**	**0.05-0.21**



6-31 Lag_Sine-Better Performance

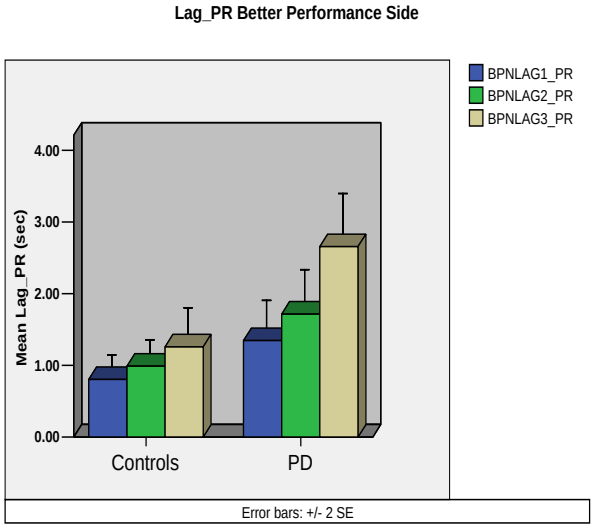


6-32 Lag_Sine-Worse Performance

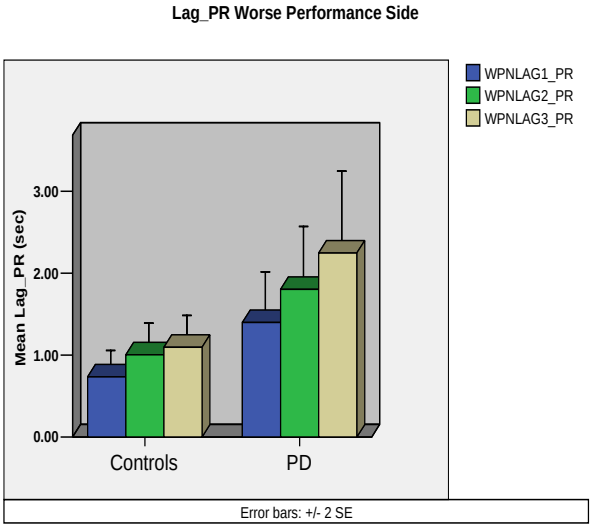
6.4.1.5 Lag from the Pseudo-Random Trial (Lag_PR)

Table 6-6 Descriptive Statistics for Lag_PR

Dependant variables	Minute 1 Mean (SD) PD	Minute 1 Mean (SD) Controls	Minute 2 Mean (SD) PD	Minute 2 Mean (SD) Controls	Minute 3 Mean (SD) PD	Minute 3 Mean (SD) Controls
BPLag_PR	**1.34(1.29)**	**0.80(0.69)**	**1.71(1.45)**	**0.99(0.77)**	**2.65(1.79)**	**1.26(1.26)**
95%CI	**0.86-1.83**	**0.54-1.06**	**1.17-2.26**	**0.70-1.27**	**1.98-3.32**	**0.79-1.73**
WPLag_PR	**1.40(1.48)**	**0.73(0.67)**	**1.80(1.89)**	**1.00(0.85)**	**2.25(2.53)**	**1.09(0.86)**
95%CI	**0.85-1.95**	**0.48-0.98**	**1.09-2.51**	**0.69-1.32**	**1.30-3.19**	**0.77-1.41**



6-33 Lag_Pseudo-Random-Better Performance

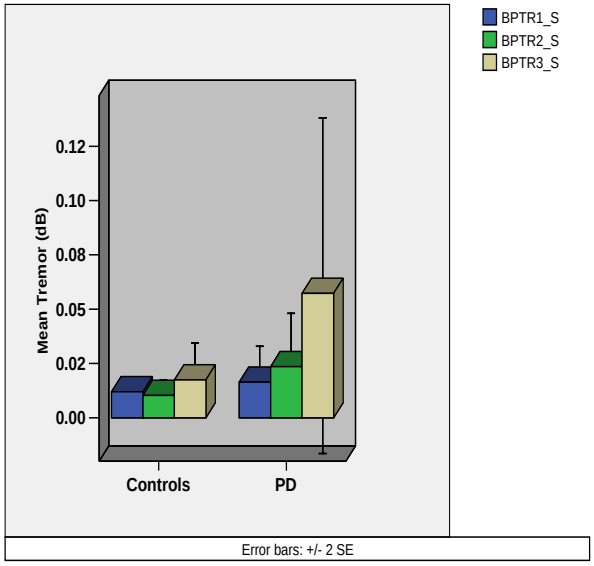


6-34 Lag_Pseudo-Random-Worse Performance

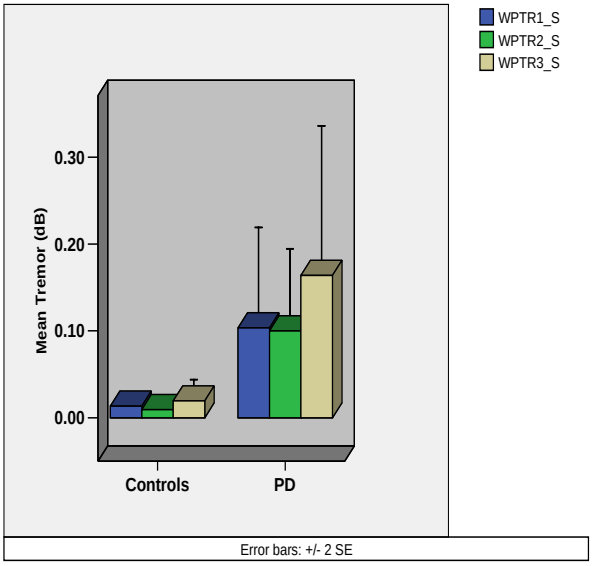
6.4.1.6 Tremor from the Sine Trial (TR_S)

Table 6-7 Descriptive Statistics for TR_S

Dependant variables	Minute 1 Mean (SD) PD	Minute 1 Mean (SD) Controls	Minute 2 Mean (SD) PD	Minute 2 Mean (SD) Controls	Minute 3 Mean (SD) PD	Minute 3 Mean (SD) Controls
BPTR_S	**0.02(0.03)**	**0.01(0.01)**	**0.02(0.06)**	**0.01(0.01)**	**0.06(0.21)**	**0.02(0.04)**
95%CI	**0.00-0.03**	**0.01-0.01**	**0.00-0.04**	**0.01-0.01**	**-0.02-0.14**	**0.00-0.03**
WPTR_S	**0.10(0.29)**	**0.01(0.01)**	**0.10(0.23)**	**0.01(0.01)**	**0.16(0.45)**	**0.02(0.04)**
95%CI	**-0.00-0.21**	**0.01-0.02**	**0.12-0.19**	**0.01-0.01**	**-0.00-0.33**	**0.00-0.03**



6-35 TR_Sine-Better Performance

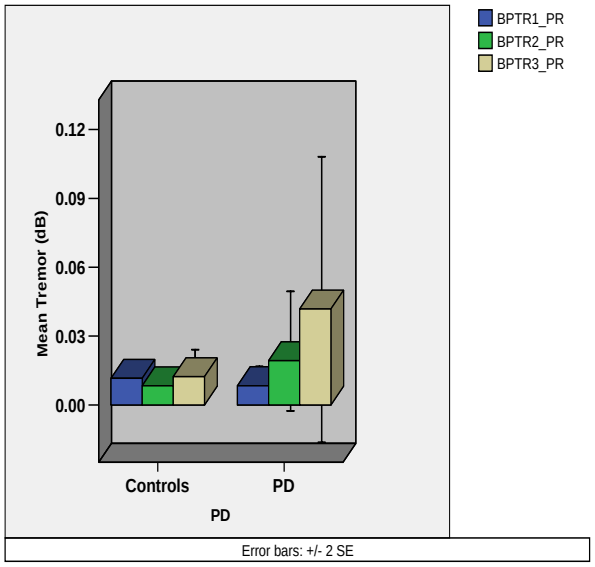


6-36 TR_Sine- Worse Performance

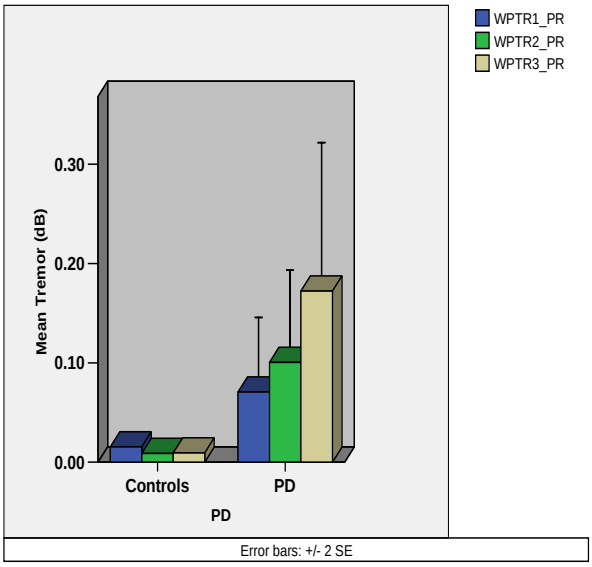
6.4.1.7 Tremor from the Pseudo-Random Trial (TR_PR)

Table 6-8 Descriptive Statistics for TR_PR

Dependant variables	Minute 1 Mean (SD) PD	Minute 1 Mean (SD) Controls	Minute 2 Mean (SD) PD	Minute 2 Mean (SD) Controls	Minute 3 Mean (SD) PD	Minute 3 Mean (SD) Controls
BPTR_PR	**0.01(0.01)**	**0.01(0.01)**	**0.02(0.07)**	**0.01(0.00)**	**0.04(0.17)**	**0.01(0.02)**
95%CI	**0.00-0.01**	**0.01-0.01**	**-0.00-0.04**	**0.01-0.01**	**-0.02-0.10**	**0.00-0.20**
WPTR_PR	**0.07(0.18)**	**0.01(0.01)**	**0.10(0.23)**	**0.01(0.01)**	**0.17(0.39)**	**0.01(0.01)**
95%CI	**0.00-0.14**	**0.01-0.01**	**0.01-0.19**	**0.00-0.01**	**0.03-0.32**	**0.00-0.01**



6-37 TR_Pseudo-Random -Better performance



6-38 TR_Pseudo-Random-Worse Performance

6.4.2 Repeated Measures Multivariate Analysis of Variance

We planned to perform a repeated measures multivariate analysis of variance (MANOVA) with presence of PD as the between subjects factor and three levels of minute (Minute1, minute2, minute3), as well as the two levels of side of performance (better or worse) as the repeated measures factor. On exploring the data we found that the assumption of multivariate normality was not met. Since univariate tests are robust to both non-normality and heterogeneity of variances (using the Greenhouse-Geisser correction for degrees of freedom) we decided to do a univariate tests for each dependant variable separately.

6.4.3 Repeated measures Univariate Analysis of variance results

A univariate analysis of variance (ANOVA) was performed for each of the dependant variables. We entered presence of PD as the between subjects factor and three levels of minute (Minute1, minute2, minute3), as well as the two levels of side of performance (better or worse) as the repeated measures factor.

Mauchley's test indicated that the assumption of sphericity was violated for the main effects as well as the interaction effects. Therefore, the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity.

6.4.3.1 Root Mean Square Error for the Sine Trial (RMSE_S)

A significant between subjects effect was seen for presence or absence of PD indicating that people with PD had a greater RMS error. There was a significant interaction of PD and minute suggesting that people with and without PD responded differently on the measure of RMSE during the sine trial depending on what minute they were performing in. RMS error increased during minute 2 and minute 3 of the task (Refer to table 6-2 and figures 6-25 and 6-26).

Pair wise comparisons of mean RMSE_S during min1, min2 and min3 showed significant differences between min1 and min2, min3 and min1 for both sides as well as min3 and min2 for side of worse performance in subjects with PD. In the control group, there were significant differences only between min1 and min2 as well as min 1 and min3 for the worse performed side only.

Table 6-9 ANOVA results for RMSE_S

Source	F	df	Sig
PD	**14.7**	**1,58**	**0.001**
min	**25.4**	**1.4, 83.4**	**0.001**
side	**39.8**	**1,58**	**0.001**
PD*min	**6.2**	**1.4, 83.4**	**0.010**
PD*side	**0.06**	**1,58**	**0.810**
side*min	**4.4**	**1.8, 103.8**	**0.022**

Table 6-10 Pairwise comparisons for RMSE_S (alpha<0.01)

Contrast	PD		Controls	
Side of performance	BP	WP	BP	WP
Min1 vs Min2 (p)	**0.001**	**0.001**	**0.583**	**0.005**
Min2 vs Min3 (p)	**0.035**	**0.009**	**0.872**	**0.213**
Min1 vs Min3 (p)	**0.001**	**0.001**	**0.771**	**0.001**

6.4.3.2 Root Mean Square error for the Pseudo-Random Trial (RMSE_PR)

A significant between subjects effect was seen for presence or absence of PD indicating that people with PD had a greater RMS error. There was a significant interaction of PD and minute suggesting that people with and without PD responded differently on the measure of RMSE during the sine trial depending on what minute they were performing in. RMS error increased during minute 2 and minute 3 of the task (Refer to table 6-3 and figures 6-27 and 6-28).

Pair wise comparisons of mean RMSE_PR during min1, min2 and min3 showed significant differences between min2 and min3 for the better performance side, as well as min3 and min1 but not between min1 and min2 for both sides in the group with PD. For the controls, there were differences between min2 and min3 for both sides, and min1 and min2 for the worse performance side. No differences were found between min1 and 3 in controls for either side.

Table 6-11 ANOVA results for RMSE_PR

Source	F	Df	Sig
PD	**15.8**	**1,58**	**0.001**
min	**11.5**	**1.4, 83.4**	**0.001**
side	**27.8**	**1,58**	**0.001**
PD*min	**6.3**	**1.4, 83.4**	**0.010**
PD*side	**5.0**	**1,58**	**0.032**
Side*min	**0.01**	**1.8, 102.1**	**0.981**

Table 6-12 Pairwise comparisons for RMSE_PR (alpha<0.01)

Contrast	PD		Controls	
Side of performance	BP	WP	BP	WP
Min1 vs Min2 (p)	**0.182**	**0.152**	**0.490**	**0.010**
Min2 vs Min3 (p)	**0.001**	**0.042**	**0.001**	**0.001**
Min1 vs Min3 (p)	**0.001**	**0.011**	**0.121**	**0.884**

6.4.3.3 Coefficient of coordination for the Sine Trial (Kc_S)

A significant between subjects effect was seen for presence or absence of PD showing that people with PD had a lesser coordination. There was a significant interaction of PD and minute suggesting that people with and without PD responded differently on the measure of Kc during the sine trial depending on what minute they were performing in. Kc decreased during minute 2 and minute 3 of the task (Refer to table 6-4 and figures 6-29 and 6-30).

Pair wise comparisons of mean Kc_S during min1, min2 and min3 showed significant differences between min1 and min2 for the better performance side, and min3 and min1 for both sides. No significant differences were found between min2 and min3 for either side. For the control group no significant differences were found between any of the minute pairs.

Table 6-13 ANOVA results for Kc_S

Source	F	df	Sig
PD	**4.02**	**1, 58**	**0.050**
min	**13.27**	**1.7, 98.4**	**0.001**
side	**34.9**	**1,58**	**0.001**
PD*min	**6.8**	**1.7,98.4**	**0.002**
PD*side	**0.023**	**1, 58**	**0.881**
Side*min	**1.7**	**1.9, 112.1**	**0.184**

Table 6-14 Pairwise comparisons for Kc_S (alpha<0.01)

Contrast	PD		Controls	
Side of performance	BP	WP	BP	WP
Min1 vs Min2 (p)	**0.001**	**0.064**	**0.073**	**0.943**
Min2 vs Min3 (p)	**0.252**	**0.052**	**0.052**	**0.021**
Min1 vs Min3 (p)	**0.003**	**0.002**	**0.855**	**0.032**

6.4.3.4 Lag from the Sine Trial (Lag_S)

A significant between subjects effect was seen for presence or absence of PD showing that people with PD had a greater lag. There was a significant interaction of PD and minute suggesting that people with and without PD responded differently on the measure of lag during the sine trial depending on what minute they were performing in. Lag increased during minute 2 and minute 3 of the task (Refer to table 6-5 and figures 6-31 and 6-32).

Pair wise comparisons of mean Lag_S during min1, min2 and min3 showed significant differences between min1 and min2, for controls only on the better performance side.

Table 6-15 ANOVA Results for Lag_S

Source	F	df	Sig
PD	**3.9**	**1,58**	**0.051**
min	**1.9**	**1.5, 87.8**	**0.173**
side	**2.5**	**1, 58**	**0.122**
PD*min	**4.8**	**1.5, 87.8**	**0.023**
PD*side	**3.4**	**1,58**	**0.072**
Side*min	**0.67**	**1.7, 101.4**	**0.411**

Table 6-16 Pairwise comparisons for Lag_S (alpha<0.01)

Contrast	PD		Controls	
Side of performance	BP	WP	BP	WP
Min1 vs Min2 (p)	**0.041**	**0.364**	**0.001**	**0.342**
Min2 vs Min3 (p)	**0.884**	**0.202**	**0.021**	**0.643**
Min1 vs Min3 (p)	**0.052**	**0.112**	**0.234**	**0.082**

6.4.3.5 Lag from the Pseudo-Random Trial (Lag_PR)

A significant between subjects effect was seen for presence or absence of PD. There was no significant interaction of PD and minute suggesting that people with and without PD behaved similarly on the measure of lag as they transitioned from min1 to min2 to min3. A significant

between subjects effect was seen for presence or absence of PD showing that people with PD had a greater lag. (Refer to table 6-6 and figures 6-33 and 6-34).

Pair wise comparisons of mean Lag_PR during min1, min2 and min3 showed significant differences between min1 and min3, min2 and min3 for the better performance side in the group with PD. In the control group, significant differences were found only between min1 and min3 on the worse performance side.

Table 6-17 ANOVA Results for Lag_PR

Source	F	df	Sig
PD	**11.0**	**1,58**	**0.021**
min	**10.9**	**1.7, 97.8**	**0.001**
side	**0.7**	**1,58**	**0.403**
PD*min	**2.4**	**1.7, 97.8**	**0.105**
PD*side	**0.0**	**1, 58**	**0.931**
Side*min	**1.18**	**1.8, 106.4**	**0.313**

Table 6-18 Pairwise comparisons for Lag_PR (alpha<0.01)

Contrast	PD		Controls	
Side of performance	BP	WP	BP	WP
Min1 vs Min2 (p)	**0.182**	**0.201**	**0.262**	**0.051**
Min2 vs Min3 (p)	**0.001**	**0.323**	**0.122**	**0.461**
Min1 vs Min3 (p)	**0.002**	**0.112**	**0.053**	**0.002**

6.4.3.6 Tremor from the Sine Trial (TR_S)

A significant between subjects effect was seen for presence or absence of PD. There was no significant interaction of PD and minute suggesting that people with and without PD responded similarly on the measure of TR during the sine trial depending on what minute they were performing in. A significant between subjects effect was seen for presence or absence of

PD showing that people with PD had a greater tremor. (Refer to table 6-7 and figures 6-35 and 6-36).

All pairwise comparisons were non-significant except that between min1 and min2 on the worse performance side in the control group.

Table 6-19 ANOVA Results for TR_S

Source	F	df	Sig
PD	**4.00**	**1,58**	**0.051**
min	**1.24**	**1.05,60.73**	**0.272**
side	**4.24**	**1,58**	**0.042**
PD*min	**0.70**	**1.05,60.73**	**0.413**
PD*side	**4.09**	**1,58**	**0.051**
Side*min	**0.41**	**1.18,68.35**	**0.552**

Table 6-20 Pairwise comparisons for TR_S (alpha<0.01)

Contrast	PD		Controls	
Side of performance	BP	WP	BP	WP
Min1 vs Min2 (p)	**0.401**	**0.886**	**0.314**	**0.001**
Min2 vs Min3 (p)	**0.302**	**0.305**	**0.183**	**0.172**
Min1 vs Min3 (p)	**0.221**	**0.442**	**0.432**	**0.421**

6.4.3.7 Tremor from the Pseudo-Random Trial (TR_PR)

A significant between subjects effect was seen for presence or absence of PD. There was no significant interaction of PD and minute suggesting that people with and without PD responded similarly on the measure of TR during the pseudorandom trial depending on what minute they were performing in. A significant between subjects effect was seen for presence or absence of PD showing that people with PD had a greater tremor. (Refer to table 6-8 and figures 6-37 and 6-38).

Pairwise comparisons showed significant differences between min1 and min2 for both sides in the control group and between min 1 and min3 for the worse performed side in the control group.

Table 6-21 ANOVA Results for TR_PR

Source	F	df	Sig
PD	**4.21**	**1,58**	**0.042**
min	**2.44**	**1.11,64.02**	**0.121**
side	**6.17**	**1,58**	**0.022**
PD*min	**2.71**	**1.11,64.20**	**0.104**
PD*side	**6.06**	**1,58**	**0.012**
Side*min	**2.15**	**1.18,75.00**	**0.141**

Table 6-22 Pairwise comparisons for TR_PR (alpha<0.01)

Contrast	PD		Controls	
Side of performance	BP	WP	BP	WP
Min1 vs Min2 (p)	**0.372**	**0.234**	**0.010**	**0.001**
Min2 vs Min3 (p)	**0.221**	**0.103**	**0.243**	**0.762**
Min1 vs Min3 (p)	**0.273**	**0.084**	**0.862**	**0.002**

6.5 ASSOCIATION BETWEEN FORCE VARIABLES AND PROGRESSION OF THE DISEASE

We calculated the RMSE_S with the effect of mental distraction due to subtraction as RMSE3_S – RMSE1_S and named it RMSE_S_3_1. RMSE_PR_3_1 was calculated similarly by subtracting RMSE1_PR from RMSE3_PR.

Kc_S_3_1, TR_S_3_1, TR_PR_3_1 and Lag_PR_3_1 were calculated similarly for the better and worse performed sides (BP and WP).

Bivariate correlations were computed between the UPDRS (motor + ADL) score and the *_3_1 variables .Variables that correlated significantly (BPKc_S_3_1, WPKc_S_3_1 and BPRMSE_S_3_1) were entered as independent variables in the multiple regression model.

A first multiple regression model used number of years from initial diagnosis as the dependant variable but no association was found between the force tracking variables and chronicity based on number of years from initial diagnosis.

A second multivariate stepwise regression model was used with the UPDRS (motor +ADL) scores as the dependent variable. Independent variables were entered in two stepwise blocks. The first block had the grooved pegboard and the finger tapper scores for the better as well as the worse performed sides. The second block had the force variables (BPKc_S_3_1, WPKc_S_3_1, BPRMSE_S_3_1) that correlated significantly with the UPDRS-AM.

The multiple regression demonstrated that the grooved pegboard score on the better performed side along with the finger tapper score on the worse performance side explained 68% of the variance in the UPDRS-AM (F=32.2, df=2,27, p=0.000). An additional 5% could be explained by the variable BPKc_S_3_1 (F=26.9, df=3, 26, p=0.000)

Table 6-23 Regression Model to predict UPDRS - AM score

Model	R	R-sq	Adj R-Sq	R-Sq Change	Significant F Change
1[a]	**0.76**	**0.57**	**0.56**	**0.57**	**0.000**
2[b]	**0.84**	**0.70**	**0.68**	**0.13**	**0.002**
3[c]	**0.87**	**0.76**	**0.73**	**0.05**	**0.026**

a. Predictors: BPGPT

b. Predictors: BPGPT, WPFT

c. Predictors: BPGPT, WPFT, BPKc_S_3_1

7.0 DISCUSSION

We have created a force tracking task that involves precision grip to document fine motor coordination. Performance of this task was significantly different between groups of individuals with and without PD. The primary variable of interest (RMSE) showed a reliability of alpha=0.96 for the first minute of performance, alpha=0.89 for the second minute and alpha=0.95 for the third minute.

Our task included an accuracy requirement during a sequential activity (with smooth transitions between task components). The task also required a constant switching movement direction from gradually increasing amounts of force to gradually decreasing the amount of force. There was a multitasking component during the last two third of the task where there was increasing amounts of mental distraction during the force tracking.

Individuals with PD demonstrated difficulty on performance of tasks that had each of these characteristics individually. It is known that individuals with PD show deficits in performance of sequential movements[36] , have difficulty switching between two motor programs[38] and have deterioration of motor performance deteriorates when an accuracy constraint is imposed[41].

We hypothesized that a task that integrates all these characteristics would be more difficult for people with PD to perform compared to age-appropriate controls. The between group effects confirmed our hypothesis. Individuals with PD showed significantly greater

amounts of error in their performance, a significant decline in coordination between rates of production of target and response forces, a significantly greater amounts of time lag in tracking, all of which worsened largely with mental distraction when compared to age-appropriate controls.

The overall mean error was less in the pseudorandom trial compared to the sine trial. We were expecting greater amounts of error in the pseudorandom trial due to its unpredictable nature. However due to the very low frequency of the pseudorandom wave (0.01Hz) the rate at which the force was ramped up or down during this trial was considerably slower compared to the sine trial (frequency of 0.2 Hz). Thus we were asking the participants to make comparatively gradual increases and decreases in the amounts of force created, thus reducing error during this part of the test.

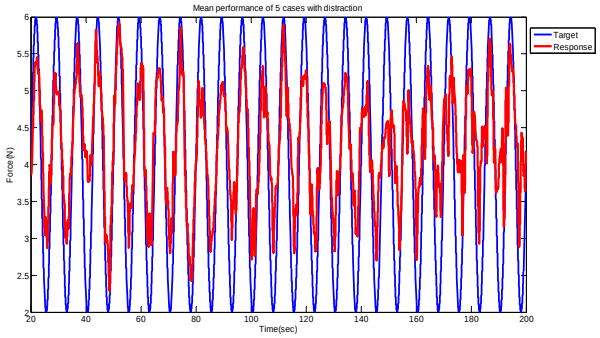
There was a large variability in the amount of tremor within groups. Many of our participants with PD (23.3%) did not have tremor. Of the participants that had tremor, 43% had tremor only on one side. Thus we may have lacked the necessary power to detect a difference within groups in spite of the trend towards increasing amounts of tremor during the second and third minutes.

Participants in the PD group showed greater amounts of lag during the pseudorandom trial of the study. This can be attributed to the unpredictable nature of the task. Several studies have shown that individuals with PD show a shift of control from feedforward to feedback mode. This implies an inability to use anticipatory control mechanisms [51] or a deficiency in predictive capability during everyday activities [52]. Some researchers have attributed this to the decaying of the motor program during execution and its reprogramming [53;54]. Desmurget et al have

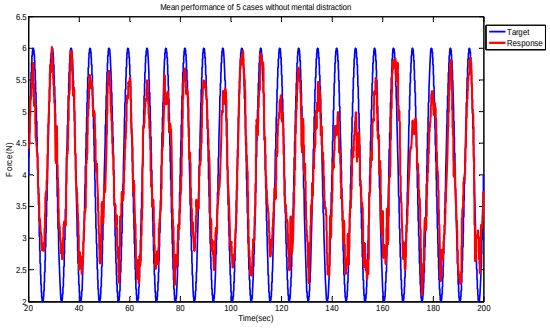
demonstrated that online corrections during ongoing movements are deficient in patients with PD [35].

Deterioration in performance during the latter two-thirds of the task could be attributed to fatigue with time. Although this could be a possibility, we did not anticipate the participants to be fatigued by the amount of force (2-6 N, where the maximum voluntary contraction for similar precision grip tasks is in the range of 50-60 N) required or the amount of time they were asked to sustain it (2.5 sec of increasing force followed by 2.5 sec of relaxation).Also the decline in performance is distinctly different for each minute in contrast to the gradual setting in of fatigue.

It is possible that the deterioration of performance of the group with PD during the second and third minute was not due to mental distraction but was due to degradation of the motor program, an established phenomenon seen in this population[53]. We tested five of the subjects with PD twice on the sine trial for the left side, once with the distraction and once without. We found that the deterioration was evident only in the distraction trial (Figure7-1) and not in the one without (Figure 7-2).



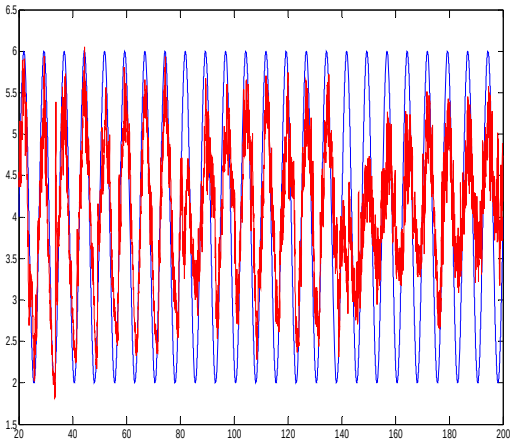
7-1 Mean sine trial for 5 cases with distraction



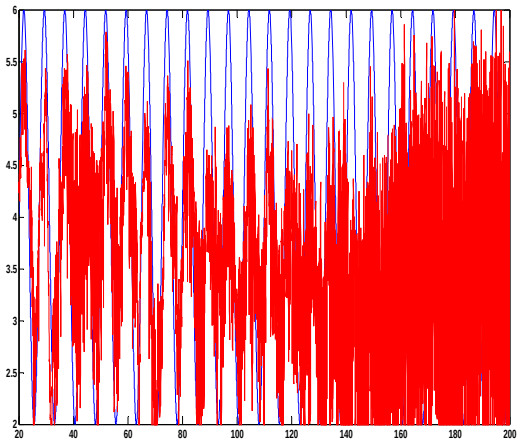
7-2 Mean sine trial for 5 cases without distraction

We found no significant difference between groups with and without PD on the test of reaction time. This may be due to the fact that our test reflected a measure of simple reaction time without the requirement of accuracy or that of making a choice during responding. Our test also did not include any movement time since the participants were already positioned with their fingers on the space bar to be pressed.

We also hypothesized that the force tracking variables would be strongly associated with progression of the disease based on the UPDRS (ADL+ motor scores). The data however showed that the coordination coefficient calculated from the force data was able to explain an additional 5% of the variance in the UPDRS-AM over and above what was explained by the grooved pegboard and the finger tapper. This implies that the task developed needs further refinement with addition of other variables associated with motor control of everyday activities like visuo-spatial coordination, multi-digit interactions and multi-directional movement. Refining the task further by incorporating some of these characteristics in addition to the existing ones might better predict progression of the disease based on a clinical rating scale. Inspite of its weak association with the UPDRS in comparison to the Grooved pegboard test, there is additional information that the test provides especially since the grooved pegboard provides only the total time taken to complete the test and does not provide any information about the quality of the movement. In addition, since some of the participants show a ceiling effect at 300 sec on the grooved pegboard test, we were still able to measure differences amongst them in terms of their tracking ability. The figures below show two participants from the PD group that had a ceiling on the Grooved pegboard test (300 sec). Inspite of scoring the same on the pegboard test, they had a significant difference in the quality of movement based on the force sensor testing.



7-3 Case 1 with a ceiling effect on the Grooved Pegboard Test



7-4 Case 2 with ceiling effect on the Grooved Pegboard Test

The force tracking variables did not show any association with chronicity of the disease based on number of years from initial diagnosis. This is in concurrence with other investigators that have found a non-linear progression of motor symptoms as well as neurophysiological aspects of the disease[55;56].

8.0 CONCLUSIONS

Individuals with PD showed significant difficulty performing a force tracking task that involved precision grip compared to age-appropriate controls. This difficulty was more pronounced in the presence of mental distraction caused by counting backwards consecutively from hundred as well as subtracting three backwards from hundred.

The force tracking variables showed a moderate association with progression of the disease based on the UPDRS (ADL+Motor) score. This suggests that inspite of the fact that the ability to control small amounts of force between fingers is an important component of fine motor coordination, the ability to perform precision grip activities of daily living requires numerous other components like visuo-spatial coordination, multi-digit interactions and multi-directional movement.

9.0 CLINICAL RELEVANCE AND FUTURE DIRECTION

Involvement of the hand in Parkinson's disease, in terms of motor dysfunction has been documented in the literature[8-15]. There is also documentation of self reported early involvement of the hand in subjects with Parkinson's disease[17]. Sensitive measures that would clinically detect early impairments in hand function will prove to be helpful for early clinical diagnosis of the disease. A majority of the population with Parkinson's disease is high functioning in terms of their activities of daily living that require good hand function especially so under the influence of medication. Consequently, most of the research so far has focused on posture, gait and balance in this population[57-61]. Impairments in hand function are difficult to demonstrate using common clinical measures like the Unified Parkinson's Disease Rating Scale in this population when they are on medication, since most patients are at a floor on these clinical instruments during the early stages of the disease. Early on in the disease, many patients tend to underestimate their disability[18]. Identification of variables that determine fine motor control will equip us with a sensitive and accurate measure of hand coordination in this population.

Fine motor coordination during a force-tracking task is significantly affected in individuals with PD. Mental distraction during the task significantly affects individuals with PD largely compared to age-matched controls.

Due to the limited sample size of our study, we were restricted in the number of predictors that could be entered into the regression model to predict the UPDRS (ADL+Motor)

scores. In a secondary analysis of the data, we plan to use machine learning techniques to develop a composite score of performance taking into account the individual contributions of each of the variables defined by this study. This composite score might be able to explain the variance in the UPDRS score better in comparison to individual variables.

We plan to replicate our results using a cohort of individuals with various stages of PD and test them at two time points to document the relation of the force-tracking variables to progression of the disease. We also plan to test a cross section of people with PD at various stages of the disease that have PET scans. This will help us understand if our test shows association with neuro-physiological changes in the brain. This will also help us develop our test into a progression biomarker for Parkinson's disease.

Developing tests that can be used as biomarkers in either a diagnostic or a progression capacity will help early diagnosis for early intervention, but also to monitor the rate of progression of the disease or the slowing in the rate of progression after administering possible neuro-protective therapies.

We plan to investigate the potential of this test as a biomarker by following one of two paths:

Development as a diagnostic biomarker:

We will use existing data and employ machine learning techniques to develop an algorithm to differentiate people with and without the disease by comparing characteristics of fine motor control between the affected side in individuals with asymmetrical or unilateral involvement and age-matched controls. This algorithm will then be tested on the uninvolved sides of the participants to check if the algorithm can correctly classify these individuals as having early preclinical signs of PD.

Progression biomarker:

Our test can be further refined by including spatial measures into a test that associates closely with the UPDRS. This will help us develop it further into a test of progression of the disease. Alternatively we could compare performance on our test of individuals with different stages of PD that have PET scans available .This will help us establish criterion-related validity of our test for progression of the disease and help in development of an alternative test that captures additional movement characteristics that the UPDRS currently fails to capture.

Current Biomarkers in use:

An excellent review by Michell et al[62]has listed the following biomarkers that have been investigated thus far:

Imaging as a biomarker:

PET and SPECT imaging studies have been the most widely studied testes to determine functional status of the BG by following the decline in neurotransmitter function, examining metabolic activity and monitoring regional blood flow. PET scans have greater spatial resolution compared to SPECT but SPECT scanning is cheaper and widely available. However the results can be confounded by numerous factors such as compensatory down regulation of DAT receptors or the effect of medication.

Other potential biomarkers:

These include, tests of olfaction, neuropsycholocical testing for depression, transcranial ultrasound, cardiac scintigraphy and tests of clinical neurophysiology of long latency reflexes, surface EMG and Bereitschaftspotentials. A number of biochemical (CSF testing) and genetic tests have also been investigated. All these have met pitfalls during establishing specificity in diagnosis of PD or the confounding effects of variable rates of progression and effects of

medication. Various attempts at using tests of motor performance as biomarker[63-65] have not had much success thus far since the motor task selected as a part of these tests were gross motor activities that did not place additional attentional or cognitive demands. We believe that due to the complex nature of the disease a combination of high level activities requiring attention will improve efficiency of such attempts. Advances in machine learning techniques to develop algorithms might help make the process faster by using relatively small amounts of data.

We realize that the development of our test into a potential biomarker that will be cheap, easily administered and non-invasive, will have to undergo rigorous testing in various populations to assure that impairments seen on this test are specific to PD.

APPENDIX A TELEPHONE SCREENING SCRIPT

TELEPHONE SCREENING INTERVIEW SCRIPT

Thank you for calling to find out more about our research study. My name is Sujata Pradhan (or name of Coordinator) and I am a physical therapist and research assistant working on this study. The purpose of our study is to identify impairments in fine motor coordination in subjects with Parkinson's disease. In order to determine if you are eligible to participate in the study, we would like to ask you a few questions about your medical history, the types of symptoms you may have. It is always possible that some of the questions may make you feel uncomfortable. You don't have to answer any of those questions if you don't want to. There is also a rare possibility (less than 1% or 1 in 100 people) that confidentiality of this phone conversation could be breached, however, the information that I receive from you by phone were kept confidential. The purpose of these questions is only to determine whether you are eligible for our study. If you are eligible for the study, we will schedule an appointment for testing with you at the end of this phone call. Remember, your participation is voluntary; you do not have to complete these questions. If it is determined that you are ineligible for the study, all information obtained during this phone conversation were immediately destroyed.

Do I have your permission to ask you these questions?

{If No}: Thank you very much for calling.

{If yes}:

If you qualify to participate in our study based on the questions that I am about to ask, you will have to come to the Carnegie Mellon University for testing. You also have the option to be tested at your home. If you do not qualify for the study based on the questions, or if you decide not to participate, all the information that you provide today will be destroyed with immediate effect.

Have you been diagnosed with Parkinson's disease by a doctor?

Are you ambulatory (with or without a straight cane, without the assistance of another person)?

Are you interested in participating in a study to examine hand function in people with Parkinson's disease?

What is your name?

What is your age?

What is your address?

What is your phone number?

Thank you for answering these questions. Do you have any other questions for me?

APPENDIX B ADVERTISEMENTS TO SEEK SUBJECTS

ADVERTISEMENT TO SEEK SUBJECTS

VOLUNTEERS NEEDED FOR RESEARCH STUDY TO EVALUATE HAND FUNCTION IN PARKINSON'S DISEASE

The University of Pittsburgh Department of Physical Therapy is currently conducting a research study to examine hand function in patients with Parkinson's disease. Participants will be tested at the robotics institute (at Carnegie Mellon University) or at home.

You may be eligible to participate in this study if you:

- Are 18 years of age or older,
- Have been diagnosed by your physician with Parkinson's disease.
- Are ambulatory (with or without a straight cane, without the assistance of another person)
- Are under a stable medication schedule for your Parkinson's disease

If you are interested in finding out more about this study or would like to participate, please call 412-383-6645.

APPENDIX C EXAMINATION FORMS

EXAMINATION FORMS

C.1 DEMOGRAPHICS

Gender:

0. Male
1. Female

Race:

0. Caucasian
1. African American
2. Other _____

What is your birth date? ____/_____/_____

What is your age? _____

What is your marital status? Are you…?

0. Never married
1. married
2. widowed
3. divorced
4. separated

Do you live alone?

0. No
1. Yes

Are you currently employed or do volunteer work?

0. No
1. Yes
   A. What do you do? _____

   B. How many hours per week? _____

What is the highest grade or year of school you completed?

0. no formal education
1. Did not complete high school
2. Completed high school
3. Vocational/trade school
4. Some college/Associate degree
5. College graduate
6. Graduate school or professional degree
7. refused

Do you currently smoke?

0. no
1. yes
   How long have you been smoking? _____

Did you ever smoke?

0. no
1. yes
   How many years did you smoke? _____

   How many years ago did you quit? _____

C.2 SCREENING MEDIICAL HISTORY

Health History:

Do you now have or have you recently had any of the following conditions?

___ Heart Disease

___ Stroke

___ Transient ischemic attack (TIA)

___ Heart attack

___ Angina

___ High Blood Pressure

___ Low Blood Pressure

___ Lung Disease

___ Diabetes

___ Ulcer or stomach disease

___ Kidney Disease

___ Liver Disease

___ Anemia or other blood disease

___ Cancer

___ Anxiety Disorder or Depression

___ Seizures

___ Dizziness or Vertigo

___ Fainting

___ Nerve Disease or Disorder

___ Hearing Loss

___ Eye Disease or Injury

___ Arthritis

___ Neck or Back Injury

___ Allergies

___ Skin Disease

___ Other Medical Problems_____

Are you currently taking any medications for the above conditions?

___ No

___ Yes (please provide a list of medications you are taking)

Medication list:	Time of day taken:
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Have you had surgery within the past year?

___ No

___ Yes (please list date and type of surgery) _____

_____

_____

Have you had any of the following procedures?

___ Angioplasty or balloon angioplasty

___ Stent procedure

Screening Vital Signs

Seated Resting Heart rate: _____BPM (Normal 60-100 BPM)

Seated Blood Pressure _____mmHg (normal 110-139/60-89 mmHg)

Assessment of Postural Stability

Reaction to an unexpected shoulder pull:

0= Normal, may take 2 steps to recover

1= Takes 3 or more steps to recover; recovers unaided

2= Would fall if not caught

3= Spontaneous tendency to fall or unstable to unaided (test not executable)

Cranial Nerve Screen

	NORMAL	ABNORMAL	COMMENTS
Cranial Nerve II			
Acuity			
Visual fields			
Light reflex			
Cranial NervesIII, IV,and VI			
Cranial Nerve VIII			

C.4 SENSORY AND MOTOR EXAMINATION

Sensory Exam:

	RIGHT			LEFT		
Level	Absent	Dim	WNL	Absent	Dim	WNL
C5(lat elbow)						
C6(lat thumb & index)						
C7(middle finger)						
C8(little finger)						
T1(medial forearm)						
T2(medial arm)						

Motor exam:

	RIGHT		LEFT	
Muscle test	Dim	WNL	Dim	WNL
Finger Flexion				
Finger Extension				

Finger abduction				
Finger adduction				
Thumb opposition				

ROM

	RIGHT		LEFT	
	Dim	WNL	Dim	WNL
MCPjoints				
PIP joints				
DIP joints				
Thumb opposition				

C.5 SOMATOSENSORY TESTING

Vibration

Right Great toe

0. absent

1. diminished

2. intact

Left Great toe

0. absent

1.diminished

2.intact

Right malleolus

0. absent

1. diminished

2. intact

Left malleolus

0. absent

1.diminished

2.intact

Right patella

0. absent

1. diminished

2. intact

Left patella

0.absent

1.diminished

2.intact

Right thumb

0. absent

1. diminished

Left thumb

0.absent

1.diminished

2. intact 2.intact

Right ulnar tubercle Left ulnar tubercle

0. absent 0.absent

1. diminished 1.diminished

2. intact 2.intact

Right medial humeral condyle Left medial humeral condyle

0. absent 0.absent

1. diminished 1.diminished

2. intact 2.intact

C.6 MINI MENTAL SCALE EXAMINATION

Patient Name: _____

Rater Name: _____

Date: _____

Activity Score

ORIENTATION – one point for each answer

Ask: “What is the: (year)(season)(date)(day)(month)?” ____

Ask: “Where are we: (state)(county)(town)(hospital)(floor)?” ____

REGISTRATION – score 1,2,3 points according to how many are repeated

Name three objects: Give the patient one second to say each.

Ask the patient to: repeat all three after you have said them.

Repeat them until the patient learns all three. ____

ATTENTION AND CALCULATION – one point for each correct subtraction

Ask the patient to: begin from 100 and count backwards by 7.

Stop after 5 answers. (93, 86, 79, 72, 65) ____

RECALL – one point for each correct answer

Ask the patient to: name the three objects from above. ____

LANGUAGE

Ask the patient to: identify and name a pencil and a watch. (2 points) ____

Ask the patient to: repeat the phrase “No ifs, ands, or buts.” (1 point) ____

Ask the patient to: “Take a paper in your right hand, fold it in half,

and put it on the floor “ (1 point for each task completed properly) ____

Ask the patient to: read and obey the following: “Close your eyes.” (1 point) ____

Ask the patient to: write a sentence. (1 point) ____

Ask the patient to: copy a complex diagram of two interlocking pentagons. (1 point) ____

TOTAL (0–30): ____

C.7 UNIFIED PARKINSON'S DISEASE RATING SCALE

A. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

B. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

C. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

D. COMPLICATIONS OF THERAPY (In the past week)

i. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

ii. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

iii. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

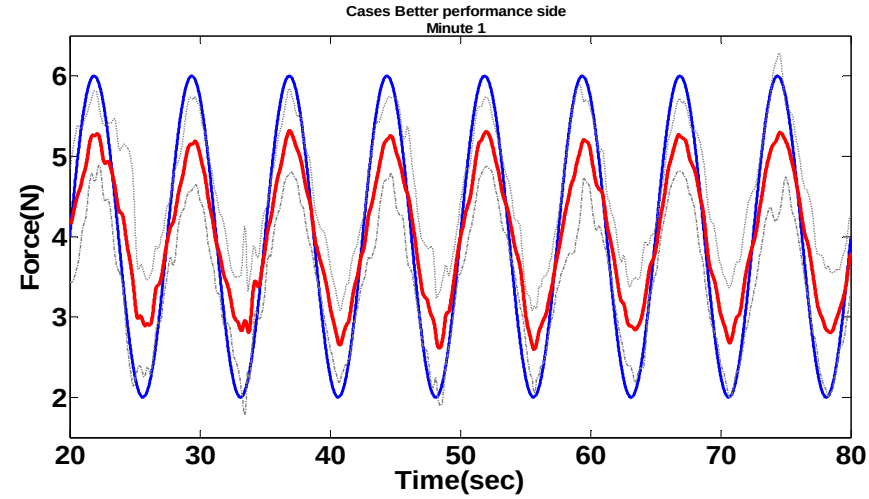
42. Does the patient have symptomatic orthostasis?
(Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

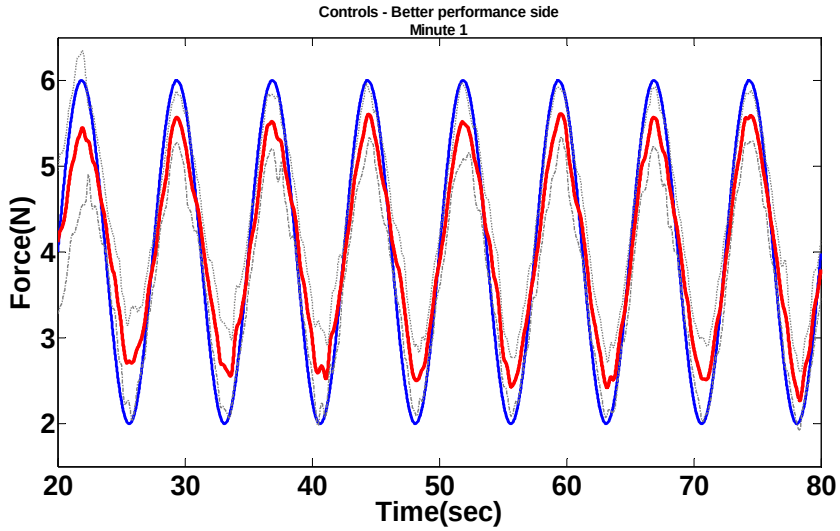
C.8 HOEHN-YAHR STAGING

Hoehn and Yahr Staging of Parkinson's Disease

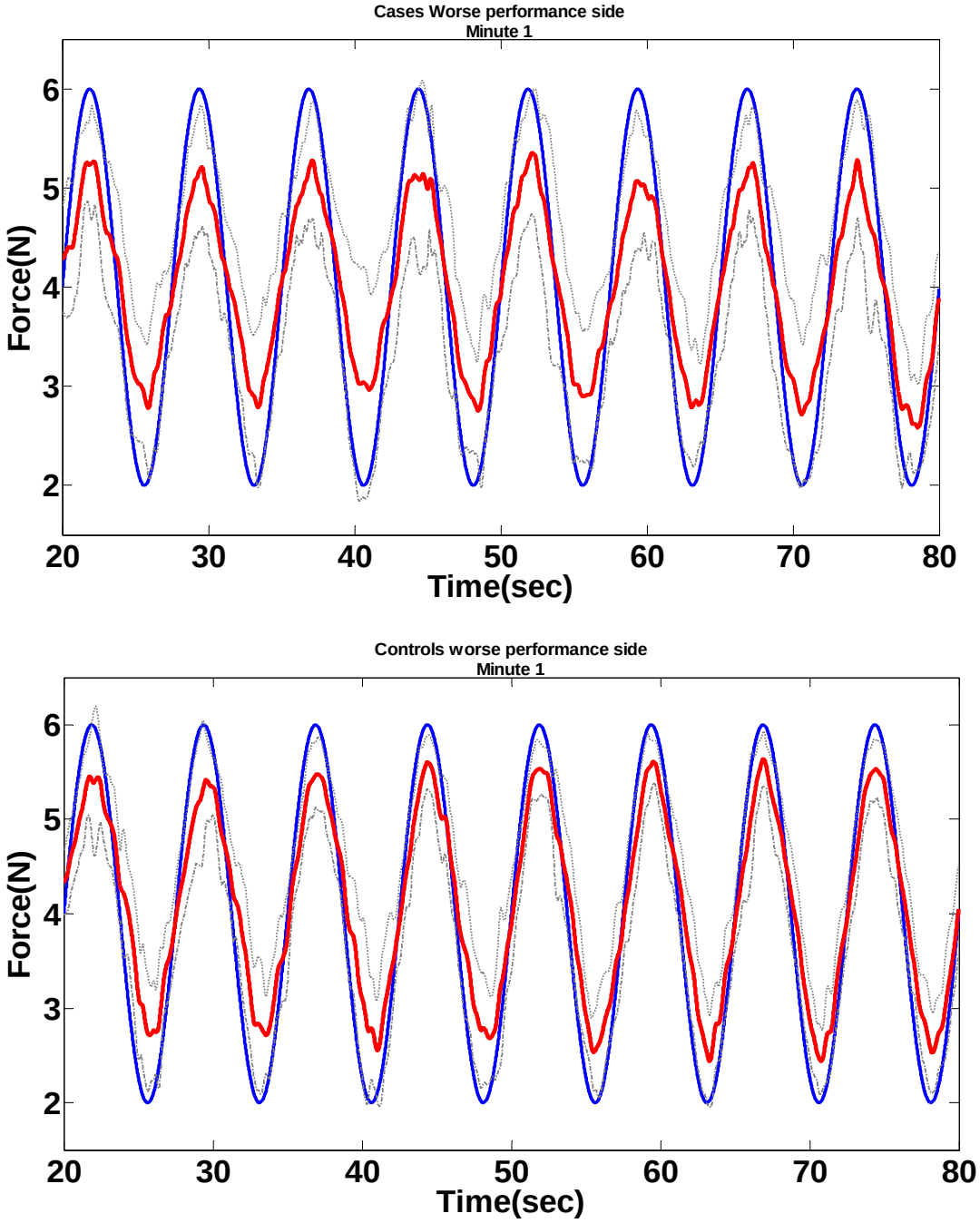
1. Stage One
    1. Signs and symptoms on one side only
    2. Symptoms mild
    3. Symptoms inconvenient but not disabling
    4. Usually presents with tremor of one limb
    5. Friends have noticed changes in posture, locomotion and facial expression
2. Stage Two
    1. Symptoms are bilateral
    2. Minimal disability
    3. Posture and gait affected
3. Stage Three
    1. Significant slowing of body movements
    2. Early impairment of equilibrium on walking or standing
    3. Generalized dysfunction that is moderately severe
4. Stage Four
    1. Severe symptoms
    2. Can still walk to a limited extent
    3. Rigidity and bradykinesia
    4. No longer able to live alone
    5. Tremor may be less than earlier stages
5. Stage Five
    1. Cachectic stage
    2. Invalidism complete
    3. Cannot stand or walk
    4. Requires constant nursing care

APPENDIX D FORCE TRACINGS AVERAGED ACROSS 30 PARTICIPANTS

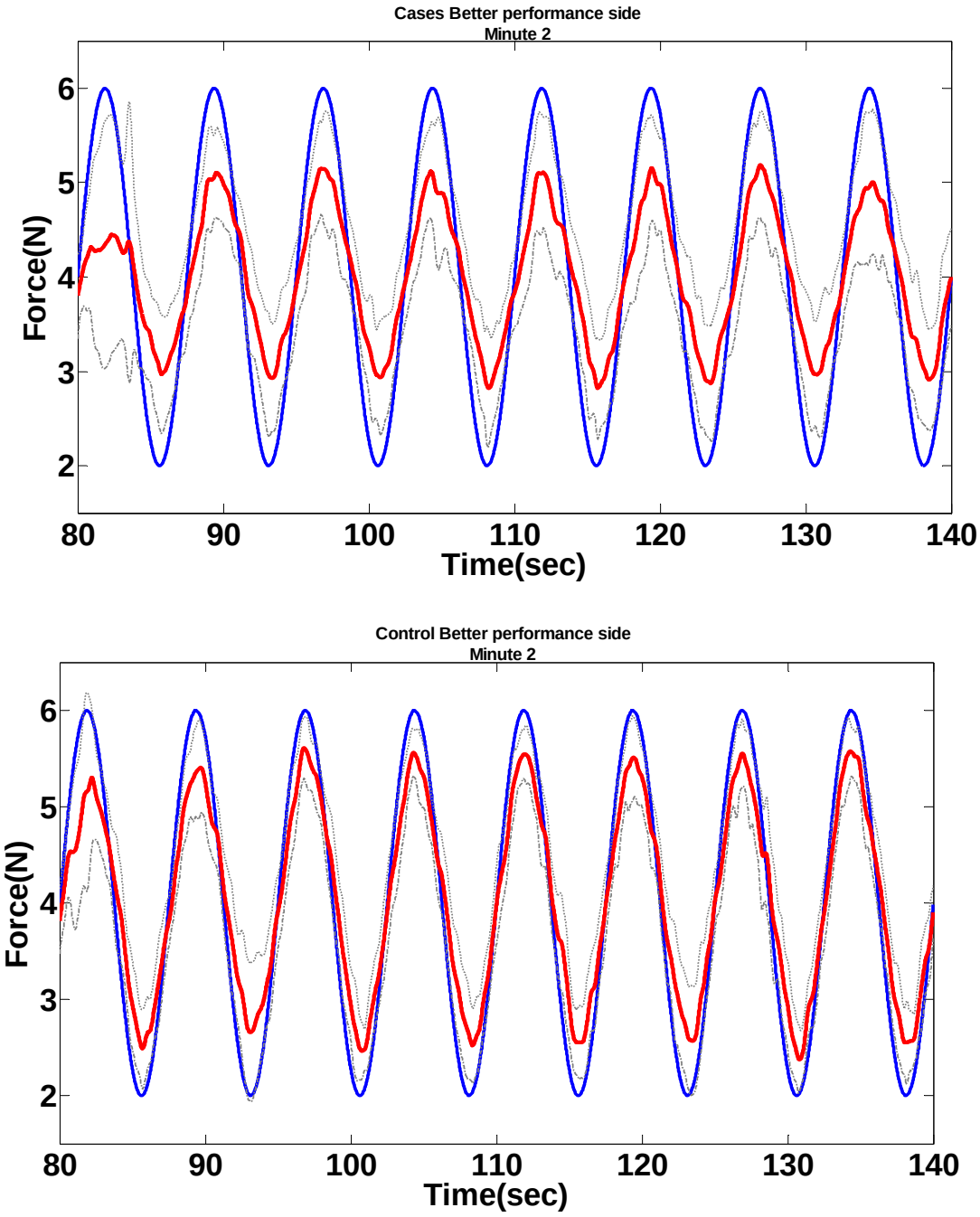




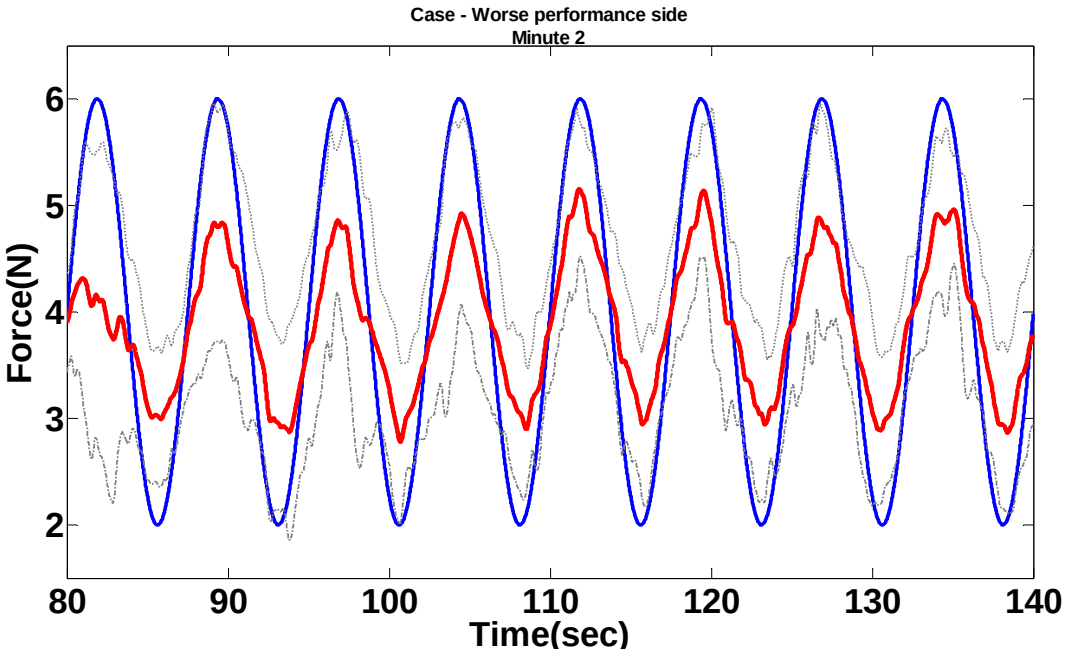
Blue Trace represents the Target force, Red Trace represents the ensemble response and the gray lines represent ± 1 Standard deviation

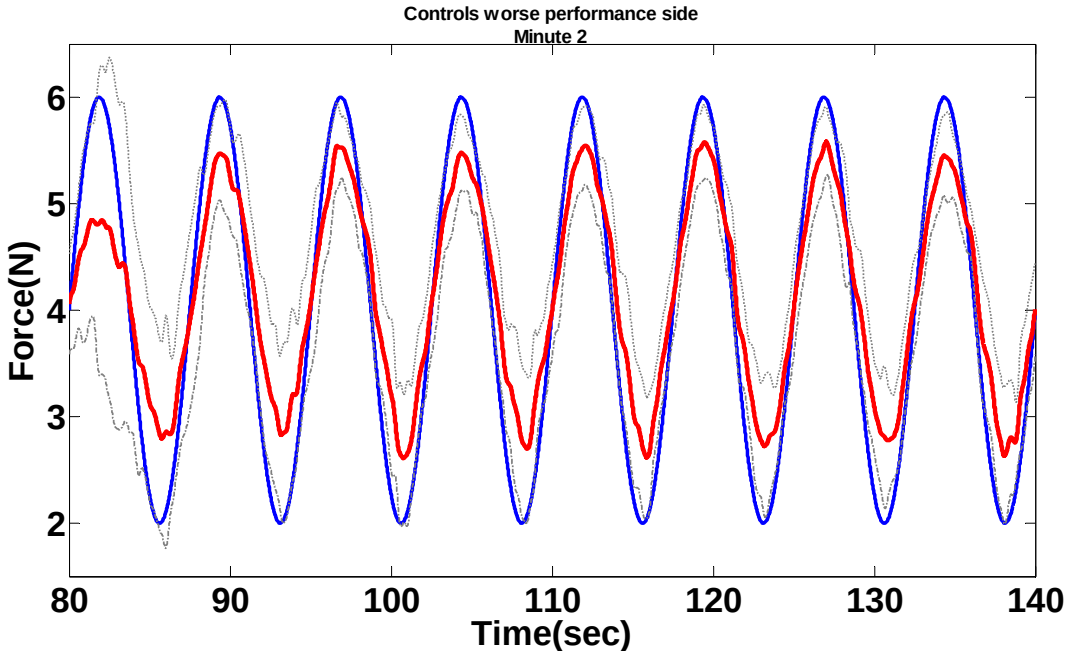


Blue Trace represents the Target force, Red Trace represents the ensemble response and the gray lines represent ± 1 Standard deviation



Blue Trace represents the Target force, Red Trace represents the ensemble response and the gray lines represent ± 1 Standard deviation





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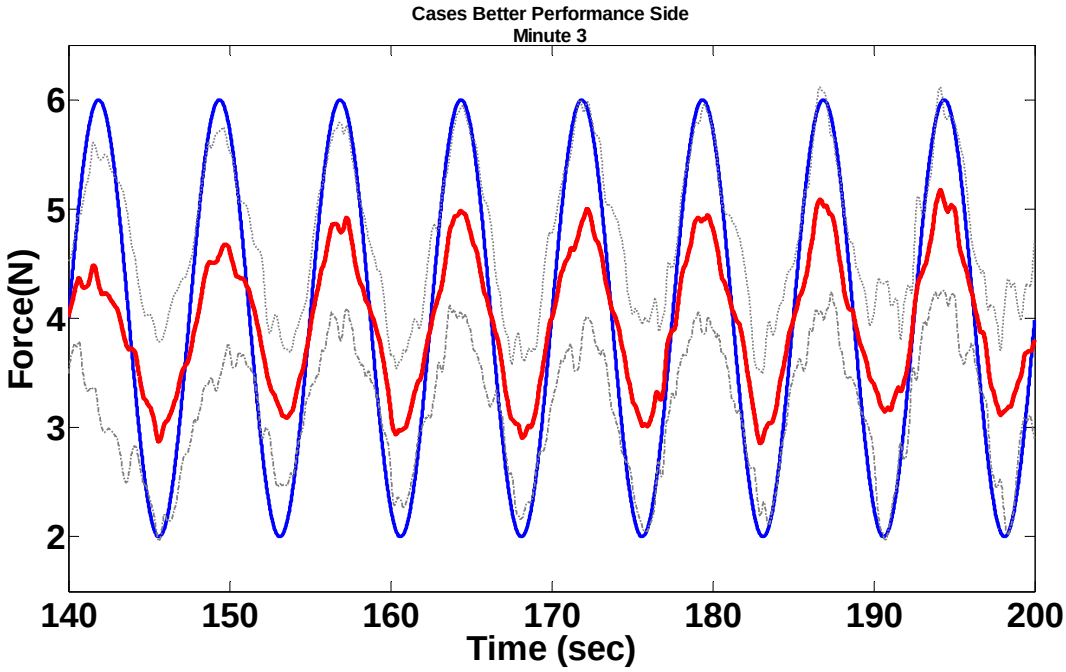

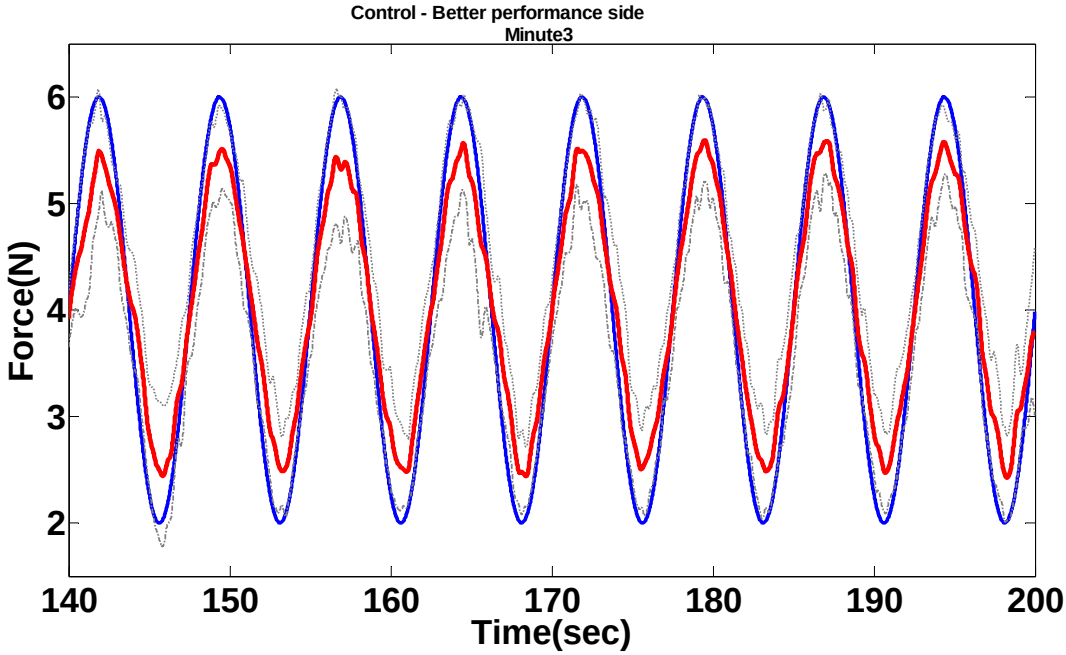

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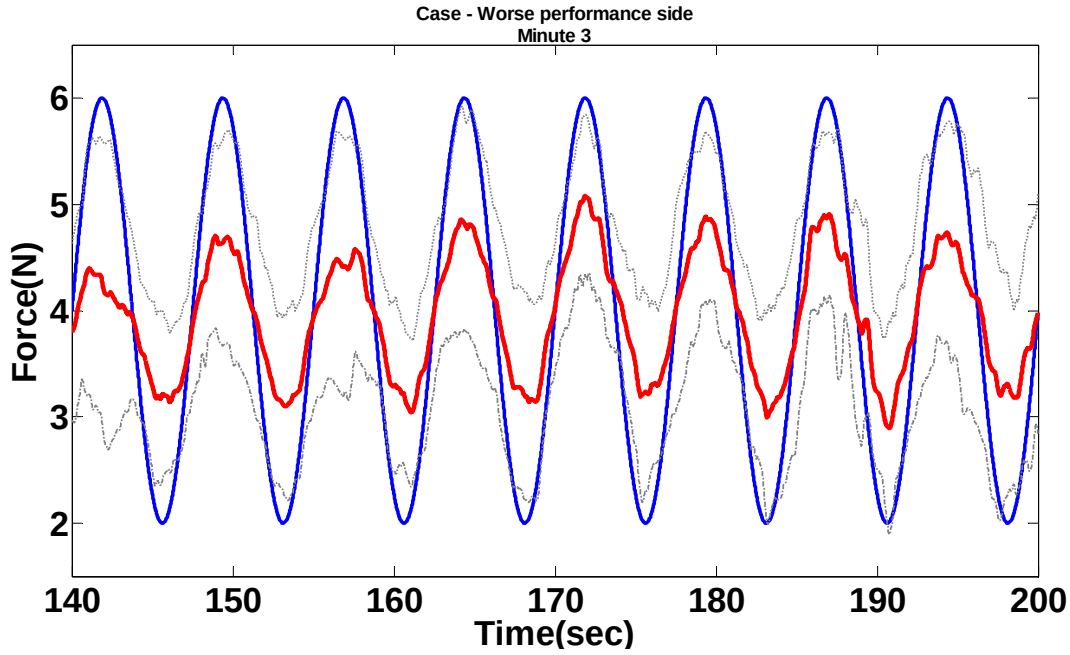

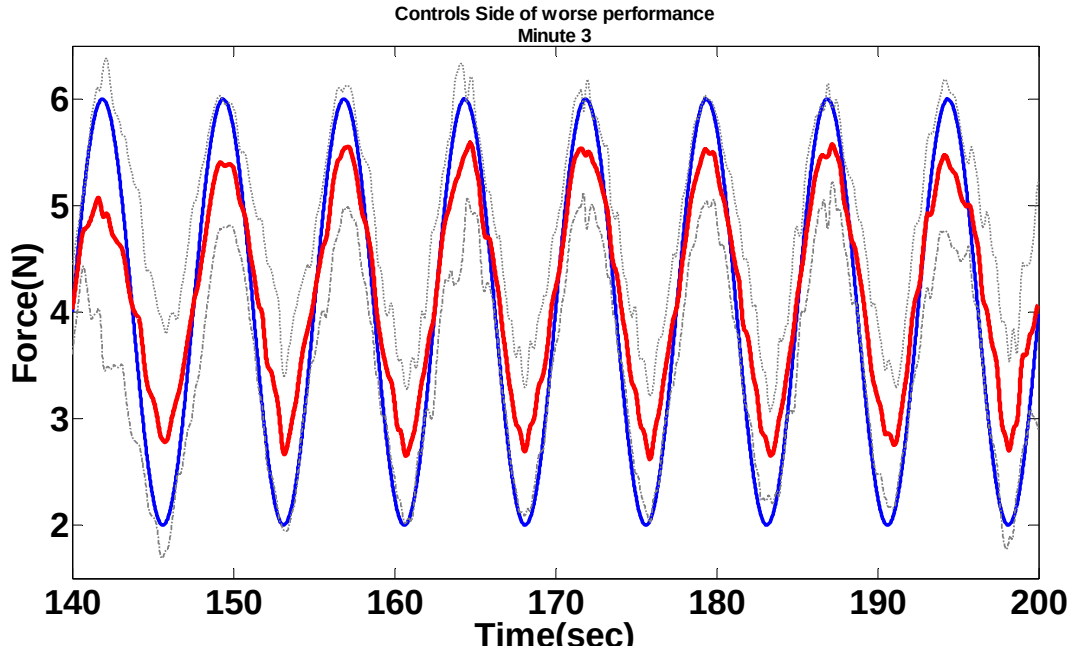

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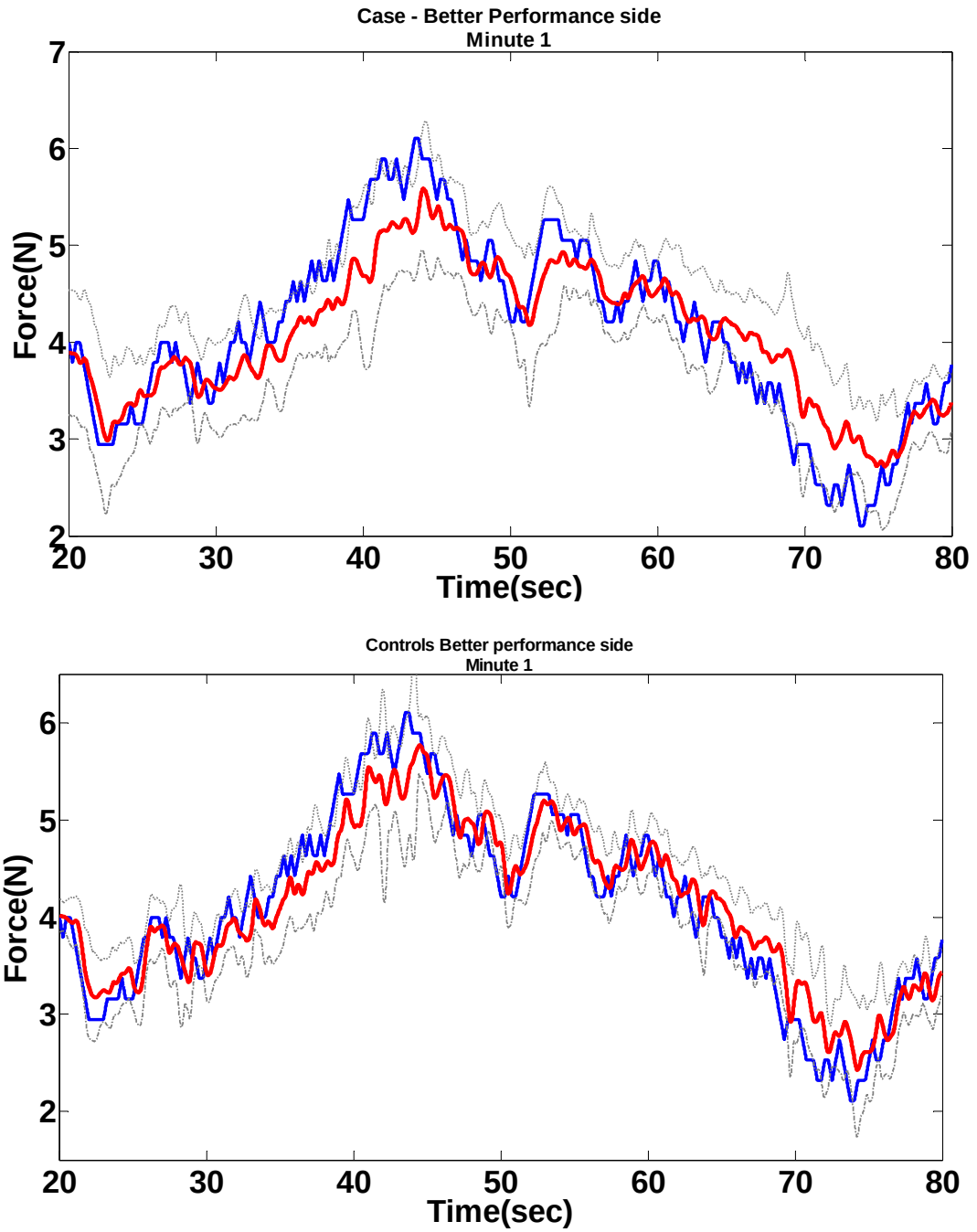

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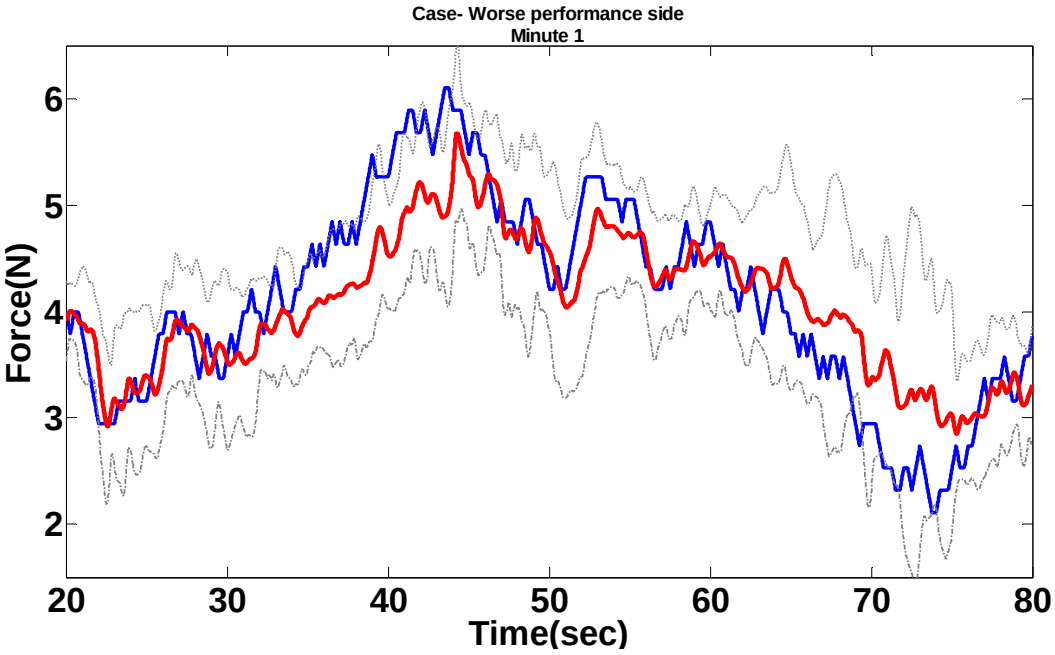

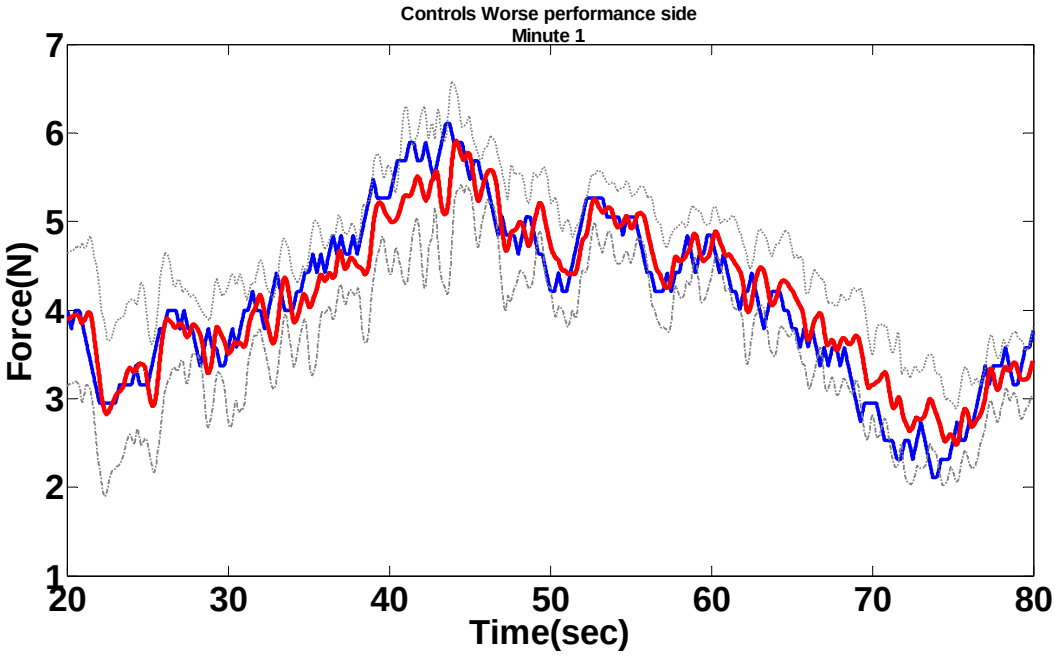

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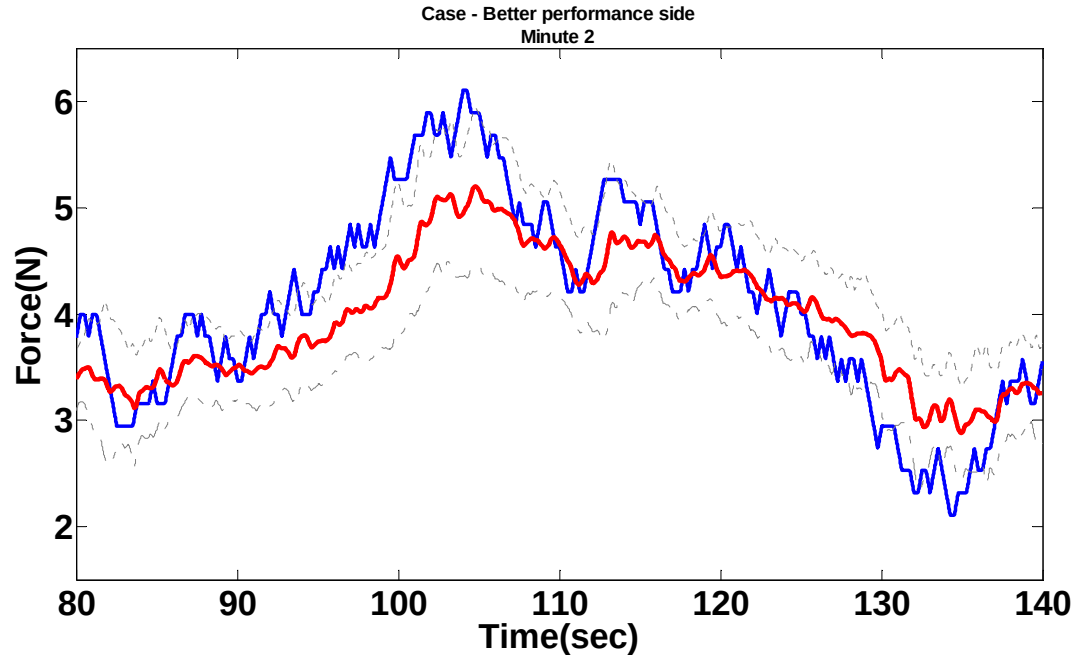

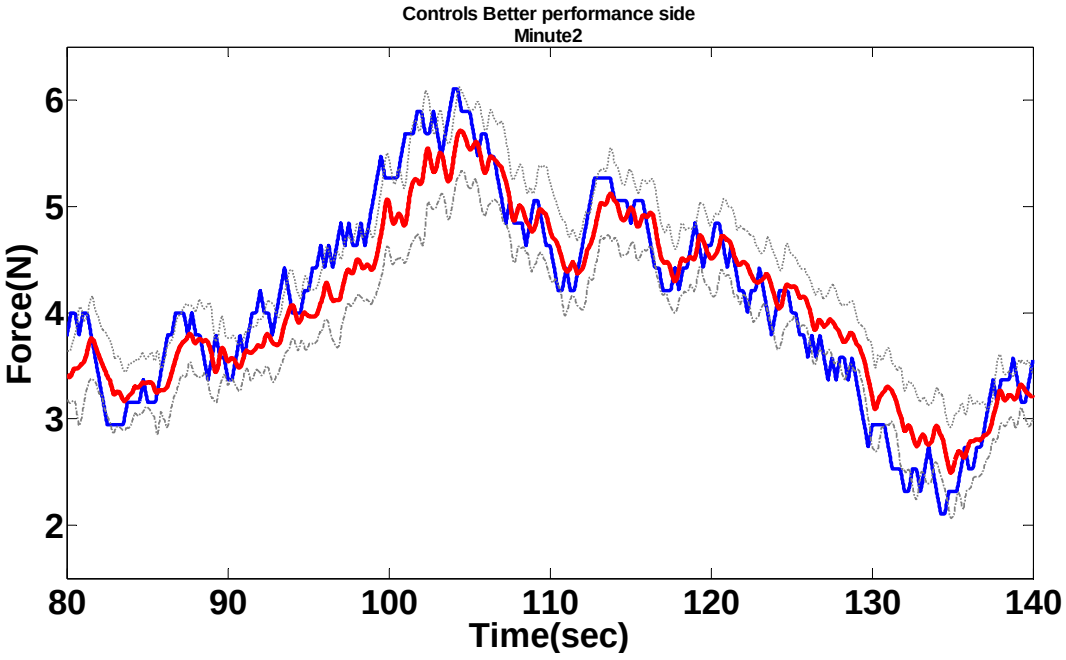

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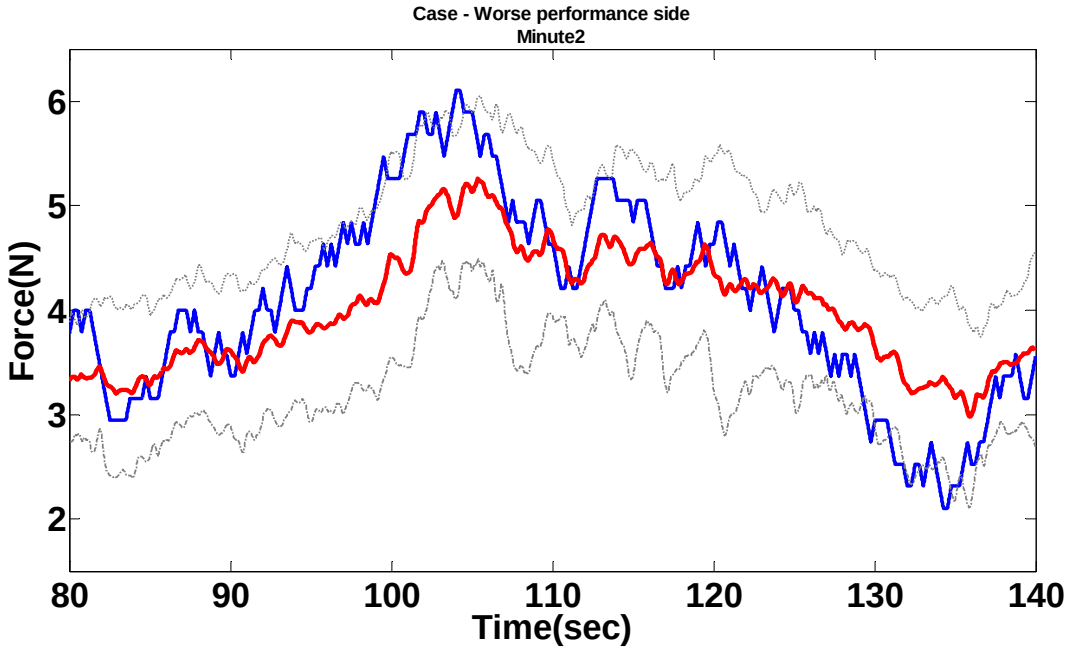

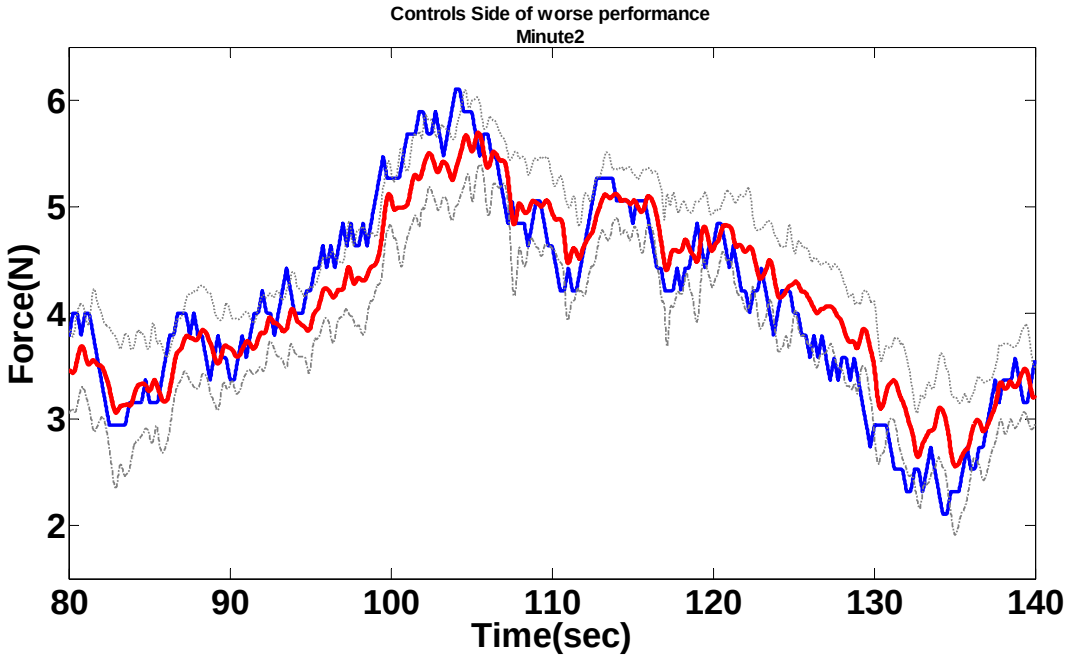

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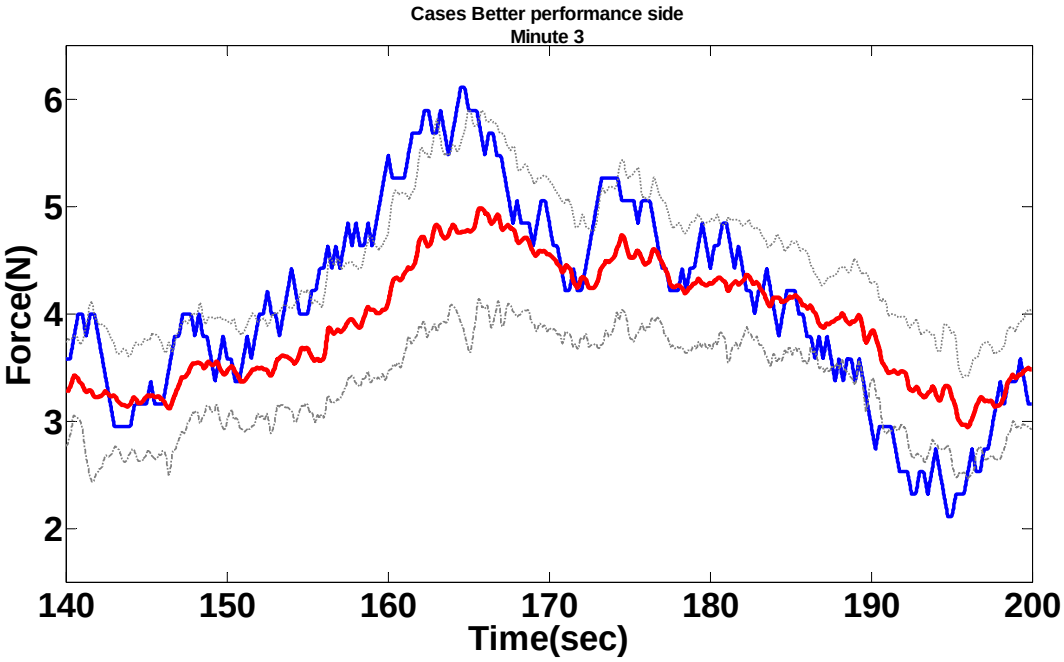

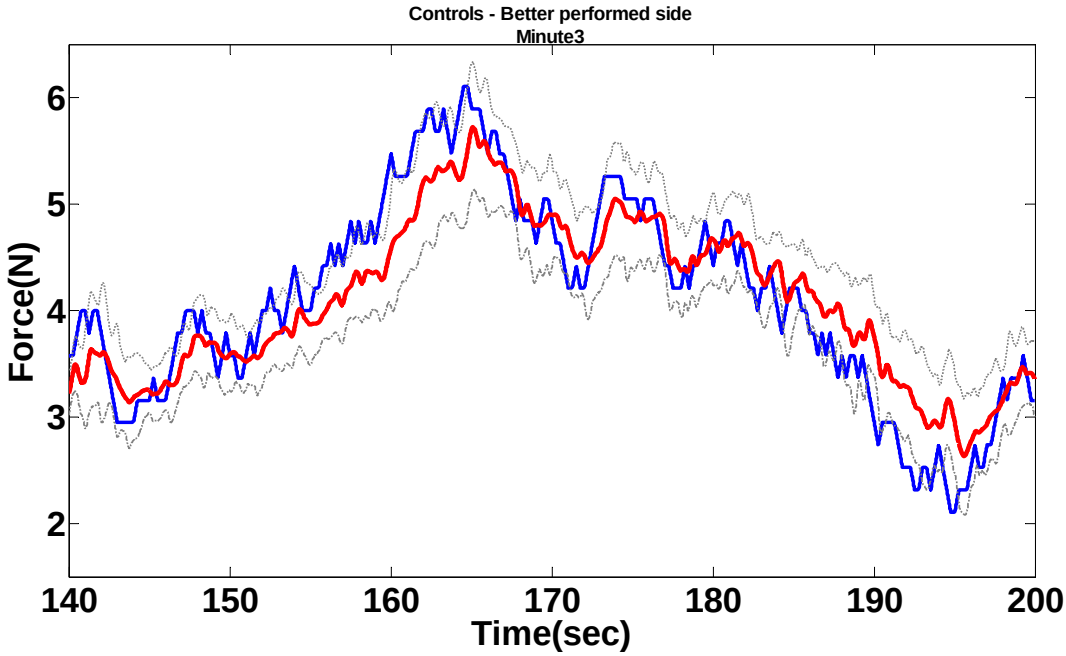

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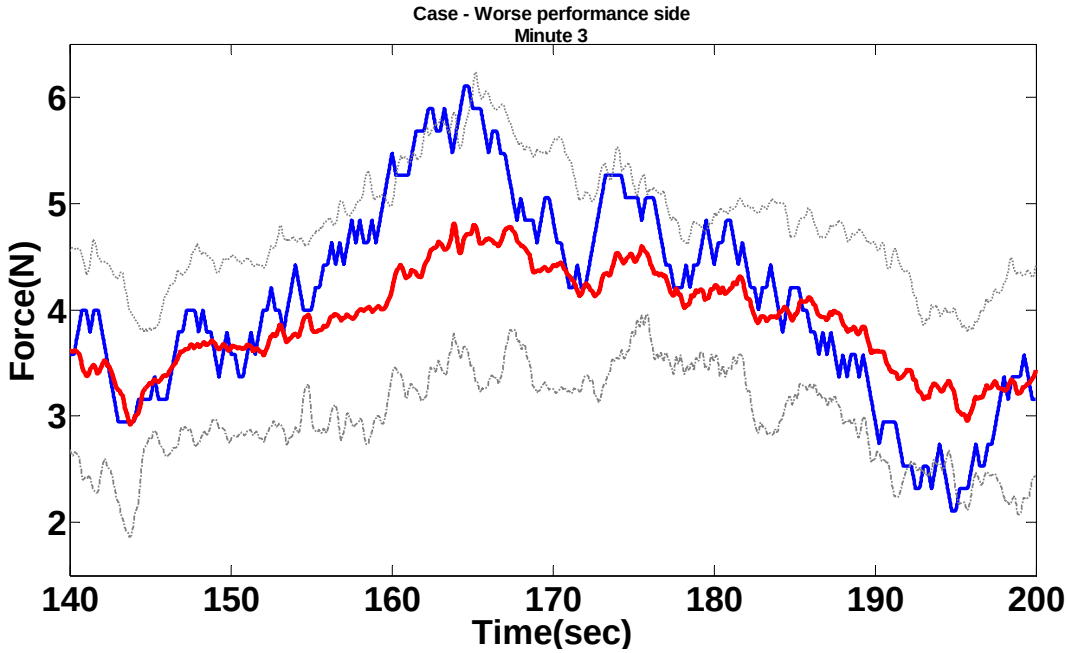

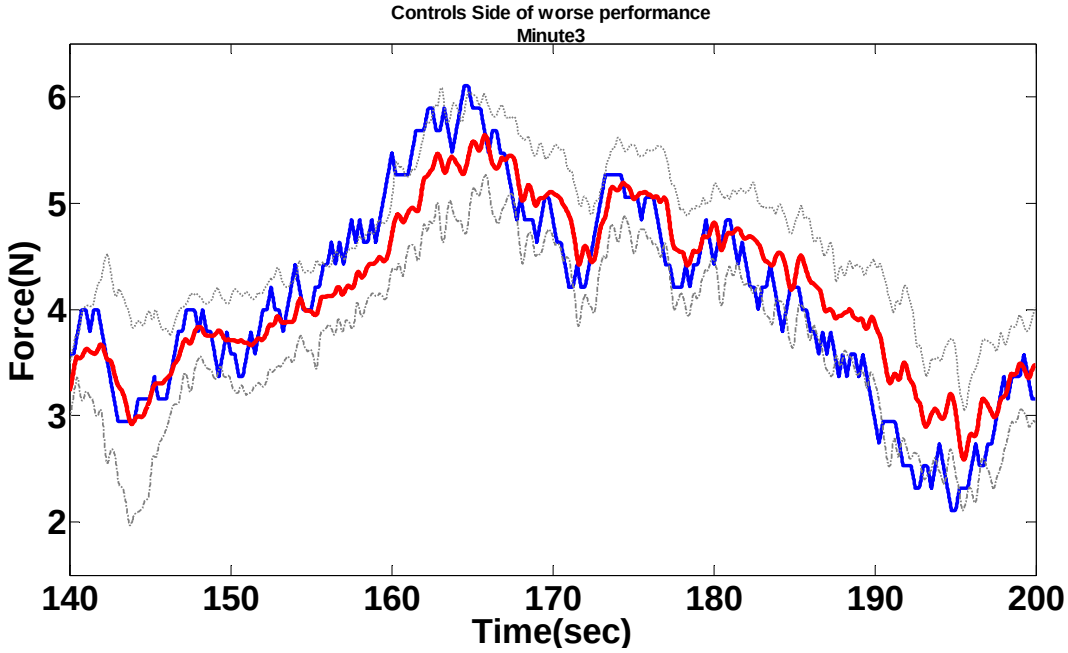

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