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Master thesis

Quantification of parkinsonian tremor, bradykinesia and rigidity using the PowerGlove in combination with a force sensor

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ABSTRACT

Introduction: The quantification of Parkinson's disease motor symptoms is highly subjective using the clinical score for severity (UPDRS). A system that is able to objectively quantificate the hand motor symptoms could improve the diagnosis and therapy of Parkinson's disease.

Objective: The aim of this study to evaluate whether the PowerGlove system in combination with a force sensor is a valid and reliable system in measuring different degrees of severity in hand motor symptoms in patients with Parkinson's disease.

Methods: The severity of the Parkinson's symptoms were measured with the complete UPDRS in the off- and on-medication state by rater B. In the off-medication state, the PowerGlove measurements took place three times, instructed twice by rater A and once by rater B, in which the patient performed tremor, bradykinesia and rigidity tasks. In the on-medication state the measurement was once performed and was instructed by rater A. Quantitative parameters included are peak power and total power in the tremor band, root mean square (RMS) of the acceleration, RMS of the angular velocity and maximal tremor amplitude for quantification of tremor. For bradykinesia, the RMS of the acceleration and the RMS of the angular velocity were analysed as well and the amplitude of movement, movement time and number of stops were studied. For rigidity, the torque at 30 and 60 degrees extension, maximal range of motion, impedance, stiffness and viscous damping constant were studied.

Results: Significant differences between the off- and on-medication state were found for the RMS of the angular velocity for all bradykinesia tasks, as well as for the RMS of the acceleration and standard deviation of the movement time for the pro-and supination task and the movement time for the closing task. For the rigidity task, significant difference between off- and on-medication state were found for the torque, range of motion, impedance and viscous damping constant. Furthermore, significant relations were found between the all tremor parameters and the UPDRS scores for resting tremor.

High reliability was found for the RMS of the acceleration and for the RMS of the angular velocity for the tremor tasks and for the RMS of the angular velocity for the bradykinesia tasks. For Rigidity, high intra-rater reliability was found for the torque, range of motion, impedance and viscous damping constant. All tremor parameters showed high intra-rater reliability in measuring resting tremor.

Conclusion: Results of this study suggest that quantification of the hand motor symptoms of Parkinson's disease is possible with the use of the PowerGlove system in combination with a force sensor. Further research is needed to evaluate the use of the PowerGlove system in measuring tremor.

PREFACE

The master thesis is the final part of the Biomedical Engineering master's program in which an individual scientific research is performed. This report presents the study towards a quantitative method to measure tremor, bradykinesia and rigidity in Parkinson's disease patients. In this study, several parameters were investigated that were possibly able to quantitatively measure the Parkinson's disease motor symptoms. Besides, the PowerGlove software is extended and improved to measure the right hand and calculate wrist angles and finger segment positions.

I am grateful to all people that were involved in this study. In particular, I would like to thank my supervisors ir. K.J. van Dijk and dr. ir. J.C. van den Noort for always being willing to help me when confronted with problems. This study was not possible without their help. I want to thank dr. ir. H.G. Kortier for explaining and helping with the PowerGlove software. I also want to thank dr. ir. T. Heida, prof. dr. ir. P.H. Veltink and ir. R. Verhagen for their useful feedback and dr. ir. A.C. Schouten as well. Last but not least, I would like to thank my parents and friends for their moral support.

Michelle Vos

Enschede, August 30, 2015

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CHAPTER 1

INTRODUCTION

1.1 Parkinson's disease

In 1817, James Parkinson was the first to describe Parkinson's disease (PD) [6]. PD is a common neurodegenerative disorder with an estimated prevalence of 0 - 3% of the population in industrialized countries and about 1% in people over 60 years of age [7] [8].

PD arises due to a loss of dompaminergic neurons in the substantia nigra pars compacta (SNc) [9] and a characteristic feature is the presence of Lewy bodies [10]. The Lewy body is a neuronal inclusion and it consists of a structurally altered neurofilament. These appear when there is excessive loss of neurons [11]. Loss of dopaminergic neurons have an effect on the basal ganglia-thalamocortical motor circuit. The basal ganglia are directly connected to the cortex via different parallel loops and deal with the control of movement, behaviour, cognition, reward and emotions. The globus pallidus pars interna (GPi) and the substantia nigra pars reticulata (SNr) are the major output nuclei and form a connection to the cortex via the thalamus. Signals from the cerebral cortex are processed through the basal ganglia-thalamocortical motor circuit and return to the cortex via a feedback pathway. Output from the motor circuit is directed through the internal segment of the GPi and the SNr. This output is inhibitory and suppresses movement. Loss of dopaminergic neurons causes pathological activity patterns in this circuit resulting in the symptoms of PD [12]. See Figure 1.1 for an overview of the basal ganglia - thalamocortical motor circuit.

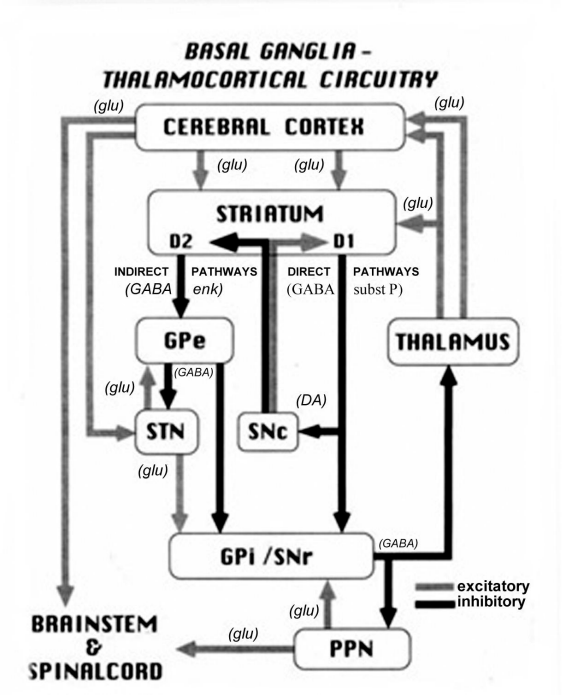


Figure 1.1: *Schematic representation of the basal ganglia - thalamocortical motor circuit and its neurotransmitters [1].*

There are four characteristic motor symptoms of PD: tremor at rest, rigidity, akinesia or bradykinesia and postural instability. A changed handwriting with micrographia and reduced facial expression are early features of PD. Other symptoms may be a flexed posture, freezing (motor blocks), loss of arm swing on one side, loss of smell or a persisting glabellar tap reflex. However, the above mentioned symptoms may not all be present in one patient [9, 13]. Bradykinesia, slowness of movement, is the most characteristic symptom. PD patients may therefore show slowness in daily activities, slow reaction times and may have difficulties in fine motor control [13]. Tremor can easily be seen in PD patients and is the most common symptom. Of PD patients, 75% will eventually get resting tremor [14]. There are two types of tremor: resting tremor when no muscles are activated and action tremor when a muscle is contracted. A distinction for action tremor can be made between postural (when counteracting gravity), kinetic (during voluntary movement) and isometric (when the muscle is contracted without movement of the segment) tremor. Kinetic tremor can be subdivided in intentional (when there is a goal) and task-specific (during specific movements) tremor. In PD, the amplitude of the tremor decreases during movement. Although PD patients have tremor in rest it is also possible that posture tremor is present or a mixture of these types is present [15]. Resting tremor is a rhythmic movement at a frequency between 4 and 6 Hz but this can vary between patients. It usually involves the distal part of an extremity. Tremor of the hand is often described as a pronation-supination movement [13]. The symptom rigidity is a state of continuous firm, tense muscles with marked resistance to passive movement, usually with the cogwheel phenomenon when tremor is present. Rigidity can occur in the wrist or ankles as well as

in the neck, shoulders or hips. Reinforcing manoeuvres, like contralateral activation, increase rigidity and help with detecting mild rigidity [13].

1.1.1 UPDRS (item 20-25)

The clinical features of PD are measured using different rating scales of which the Unified Parkinson's Disease Rating Scale (UPDRS) is the most accepted and used one [16]. This scale has four components and a total of 50 questions in which velocity, amplitude and rhythm of movements are rated. Each item has five rating options (0-4). Where 0 means no symptoms and 4 means severe symptoms [17].

Resting tremor (item 20) is rated by its persistence and amplitude. The persistence is judged at the end of the examination. In this way, it can be estimated more reliably based on several minutes. It is rated by how much the tremor is present during the examination. For the amplitude, the maximal amplitude observed at any moment during the observation is scored. The tremor is examined for the four limbs, lips and jaw. To rate posture tremor (item 21), the hands have to be stretched forward with hand palms down and the maximal amplitude is rated of the present tremor. This test takes 10 seconds. Kinetic tremor (item 21) is tested by letting the patient move his finger between his nose and the finger of the investigator. Kinetic tremor can be present during the whole movement or at the end of the movement when the target is approached. For each test, the maximal tremor amplitude is used to score tremor and both hands are judged separately.

Bradykinesia is tested by letting the patient perform finger tapping, open and closing of the hand and pro- and supination movements of the hand. To rate finger tapping (item 23), the patient needs to perform 10 finger taps as fast and with a largest amplitude as possible. During open and closing of the hand (item 24), the patient has to make a firm fist and open the hand showing the palm of the hand to the investigator and repeat this as fast as possible. Ten repetitions need to be performed as well. For pro- and supination movements (item 24), the patient has to stretch his arm forward with his hand palm facing downwards and turn the hand in a way that the hand palm is facing up and repeat this 10 times. The velocity, amplitude, hesitations, pauses and decrease in amplitude are taken into account to score bradykinesia. Both hands are rated separately for each test.

The rigidity (item 22) is determined by passively moving the limbs and neck of the patient. The patient has to relax while the examiner performs this test. In case no rigidity is observed, the patient has to perform an activation movement, like finger tapping or hand opening and closing, in the contralateral limb and while the examiner passively move the limb.

In appendix A, an overview of the UPDRS (item 20-25) scoring is given.

1.1.2 Treatment

Treatment of PD initially starts with administration of levodopa but eventually every patient develops dyskinesia due to this medication, which is called levodopa induced dyskinesia. In this case, deep brain stimulation (DBS) can reduce the symptoms of PD. Besides, DBS is used because of unpredictable fluctuations in response to levodopa before levodopa induced dyskinesia is developed. The device used in DBS consists of an implemented pulse generator which is connected to the lead that contains the stimulation electrodes [18]. DBS involves an electrical current causing an electrical field which decreases the mean firing rate of the neurons in the GPi or the subthalamic nucleus (STN). Stimulation of the STN is most frequently applied in case of advanced PD [12, 19]. MRI data of the brain is used to determine the location for the electrode placement. The surgery is performed while the patient is awake and during the surgery, the implantation is tested to see the effect of stimulation at that position. After the surgery, the stimulation settings have to be defined and adjustments are made by visual observation of the benefits and adverse effects in response to the stimuli [18].

1.2 Problem definition and relevance

Assessment of the clinical conditions of PD has to be done in hospital setting and by an experienced observer. Unfortunately, the assessment of symptoms with the UPDRS is highly dependent on the experience of the physician and varies between different physicians. The inter-rater variability of bradykinesia, tremor and rigidity is inconsistent [16, 20], the clinical scale has limited resolution for small changes in severity of the symptoms [21] and long term fluctuations can not be assessed with the UPDRS [22]. For

therapeutic purposes it is desired to have an objective assessment of the motor state and fluctuations to apply the correct medication dosage, to find the best place for DBS stimulation and control stimulation parameters. Automatic and objective assessment of the symptoms is therefore useful to control therapeutic parameters and thereby improving interventions. Furthermore, by quantification of the effect of dopaminergic medication on the symptoms, the effect of DBS can be predicted.

1.3 State of the art

Because of the clinical importance and the reliability of the rating scales, several studies already tried to objectively measure PD symptoms. This section gives an overview of these studies.

1.3.1 Tremor

It has been shown that, with the use of accelerometer data, tremor types can distinguished from each other and accelerometer data can be used to register movement intensity and duration [23]. Several studies showed the use of accelerometers in diagnosing tremor [20, 24–27]. Roy et al. showed that tremor can as well be detected with accelerometers in combination with surface electromyography (sEMG) [28]. Bonato et al. showed that the root mean square (RMS) of the accelerometer data corresponds to on- and off-medication states of the patients [29]. However, not all studies showed the same results. In the study of Scanlon et al. [30], the RMS of the accelerometer signal did not differ between on- and off-medication states. When correlated to the UPDRS, the RMS of the angular velocity strongly correlated in the study of Salarian et al. [31].

Peak power of the angular velocity signal and of the accelerometer signal were significant different between essential tremor patients and healthy subjects as is shown by Sprdlik et al. [26]. Heldman et al. [32] investigated the use of accelerometers and gyroscopes in quantification of tremor using the peak power as well and showed that the peak powers of both gyroscope data and accelerometer data correlated with the clinical score. Mostile et al. [33] also found a strong correlation between the peak power of both the gyroscope and accelerometer data and the clinical rating scale for posture tremor and moderate correlations for kinetic tremor.

Deneault et al. [34] tried to quantify tremor making use of the accelerometer in smart phones. The tremor amplitude, tremor regularity, power distribution (sum of the power between 3 and 7 Hz, divided by the total power), median power frequency (frequency where 50% of the power lies below it and 50% above), power dispersion (the width of the frequency band containing 68% of total power) and harmonic index (ratio considering a rectangle bounded on the sides by the frequency band (0 to 20 Hz) and vertically from 0 to the height of the highest peak. The harmonic index is the proportion of the area of this rectangle lying above the power spectrum itself.) all correlated with the UPDRS and showed a good inter-rater reliability. In the study of Peirleoni et al. [35], in which an accelerometer is used, the median frequency was also correlated with the UPDRS.

1.3.2 Bradykinesia

Salarian et al. [31] computed the RMS of the gyroscope data and the average range of movements (angle) when performing activities of daily living. These parameters were both significantly different in on- and off-medication state. However, only the RMS of the gyroscope data was correlated with the UPDRS.

Jun et al. [21] calculated the RMS of the velocity, RMS of the angle, peak power and total power from the gyroscope data. All were significantly correlated with the UPDRS. Koop et al. [36] investigated the RMS velocity of angular movements as well and it also correlated with the UPDRS.

The standard deviation (SD) of a single finger tap interval, average of finger tap velocities and average of finger tap amplitudes were calculated from accelerometer data by Okuno et al. [37]. The SD of the finger tapping interval was higher and more irregular with higher UPDRS scores and the amplitude and velocity of the finger taps decreased with higher UPDRS scores [37]. According the Niazmand et al. [20], the average and SD of the movement time are both higher in patients with bradykinesia. In contrast, tap rate (the number of tappings in 30 seconds) and movement time was not correlated with the UPDRS as shown in the study of Dunnewold et al. [38].

1.3.3 Rigidity

In the study of Endo et al. [39], a novel system containing two force sensors, a gyroscope and EMG surface electrode was used to quantify rigidity. Parameters that were studied are the stiffness (in flexion and extension), the sum of the difference of bias (summation of flexion torque values at 30, 60, and 90 degrees) and EMG index for biceps brachii and triceps brachii muscles (ratio of integrated value of rectified and smoothed surface EMG between stretched and collapsed muscle). All parameters correlated with the UPDRS. The sum of the difference of bias and the EMG index for biceps brachii had the best correlations. Xia et al. [40] found a correlation between rigidity and EMG ratio (the normalized EMG activity of stretched muscles divided by the normalized EMG activity of shortened muscles) as well.

Prochazka et al. [41] used a hand-held force measuring device to measure stiffness and viscosity around the elbow joint in PD patients and calculated the impedance using these two parameters. Forces were manually imposed and systematic differences between raters were present. Despite this, the mean impedance was similar for different raters and there was a close correlation with the UPDRS. Tabbal et al. [42] used the impedance as well to measure elbow rigidity and also found a correlation with the UPDRS.

In the study of Lorentzen et al. [43], the ankle stiffness was computed using force sensors and a gyroscope positioned at the foot. The ankle stiffness was significantly larger in spinal cord injured and multiple sclerosis patients and showed high intra- and inter-rater reliability for the spinal cord injured patients.

Kwon et al. [44] developed a portable system to measure torque when movement is manually imposed to the wrist and used the stiffness, viscous damping constant, mechanical work (resistive torque integrated by angle), mechanical impulse (resistive torque integrated by time) and mechanical impedance. The viscous damping constant, stiffness and mechanical impulse were all able to discriminate between baseline DBS setting and optimal DBS setting. Also, when comparing to the UPDRS, the mechanical impulse showed moderate correlation and the viscous damping constant showed good performance in representing the reduction in clinical score. The impedance was poor in differentiating between baseline and optimal DBS setting as well as in showing a correlation in changes in the clinical score. The mechanical work was moderate at both differentiating between on- and off-state and showing a correlation with the UPDRS.

The viscous damping constant, stiffness, work and impulse were also investigated by Park et al. [45] using the same measurement set-up as Kwon et al. [44]. The viscous damping constant and stiffness were the most reliable and were correlated with the UPDRS score. The mechanical work score during extension was also reliable and correlated with the UPDRS.

Fung et al. [46] evaluated the use of the mechanical impulse and mechanical work to objectively measure rigidity. Mechanical impulse scores were significantly higher in PD patients than in controls but this was not the case for mechanical work scores. However, with the effect of activation (moving the contralateral arm between two markers), the mechanical impulse and mechanical work scores were both significantly different between controls and PD patients.

Quantitative features of wrist rigidity were evaluated by examining the mechanical impulse, mechanical work and stiffness bij Xia et al. [47]. A servomotor was used to impose flexion and extension to the wrist. The mechanical work score was significantly higher in off- than in on-medication state and the stiffness also differed significantly.

Sepheri et al. [48] investigated the relation between the slope of the torque-angle data, hysteresis (the area between flexion and extension torque-angle curves), range of motion and normalized hysteresis (hysteresis divided by range of motion). Mean values were significantly different between patients and controls. The highest correlations were found between the UPDRS and the normalized hysteresis and the lowest correlations between the UPDRS and the range of motion.

Niazmand et al. [20] used the force exerted to the wrist during passive flexion of the elbow, to quantify rigidity but no significant correlations between the force and severity of rigidity were found.

Myometry (quantitative method of muscle contraction) is used by Marusiak et al. [49] to distinguish changes in resting muscle stiffness between medication states in PD patients. In this study, EMG is included as well. Myometry and EMG measurements both showed excellent reproducibility. In on-medication state, the resting muscle stiffness and electrical activity was significantly lower than in off-medication state.

1.4 PowerGlove

The PowerGlove system (see Figure 1.2) is a measurement system to reconstruct hand and finger movements. It contains 3D inertial sensors (gyroscopes and accelerometers) which are placed on all dorsal segments of the hand and fingers. It also contains magnetometers on the hand segments and on the distal part of the fingers.

A 3D accelerometer measures the acceleration along three axes and consists of a mass-spring-damper system. Using Newton's second law, $force = mass \times acceleration$ (in which the force consists of the force needed to accelerate the mass and the gravitational force and the acceleration consists of the inertial acceleration and the gravitational acceleration), the acceleration can be calculated [50]. The action of gravity as well as movements can be assessed [51]. Accelerometers can be used to determine the orientation of a body segment [52], acceleration and inclination of a segment [53] and frequency of movements [54].

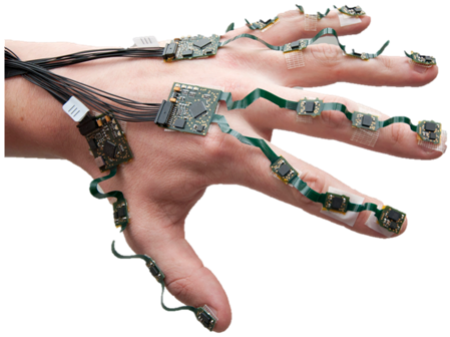


Figure 1.2: *The PowerGlove system [2]*

Rate gyroscopes are angular velocity sensors and thus measure the angular rate of rotation. It is based on the Coriolis force which is a force in a rotating reference frame [50]. Gyroscopes provide information about joint angle [55], angular velocity of a rotational movement [56] and angular displacement [57].

Accelerometers and gyroscopes can be combined for more reliable results. Accelerometers are less precise during movements and the position derived form the accelerometer signal is dependent on the length of the segment of interest. On the other hand, gyroscopes get more biased over time [58].

Magnetometers are used to measure the local earth magnetic field vector and provides information about the orientation as well [59].

The PowerGlove software (based on Matlab) uses anatomical constraints between segments to minimize errors in relative orientation and a Kalman filter is used to estimate optimal orientation [2]. This system thus provides raw accelerometer (100 Hz), gyroscope (200 Hz) and magnetometer data (100 Hz) as well as segment and joint orientation, fingertip positions and the relative and absolute hand positions in real time [2]. This system has been validated against an optical marker system. The difference between these two systems ranges between 2 and 14 degrees and the largest errors occurred in movements with high velocities [60].

1.4.1 Calibration procedures

The signals are measured within the sensor coordinate frame. By performing a sensor to segment calibration the orientation of the sensor with respect to the segment can be found. For the left hand, the coordinate system is defined by the x-axis pointing radial, the y-axis pointing distal to the MCP joint of the middle finger and the z-axis pointing dorsal to the back of the hand (Figure 1.3). This results in positive angles for extension, abduction and pronation as in the International Society of Biomechanics (ISB) recommendations [61].

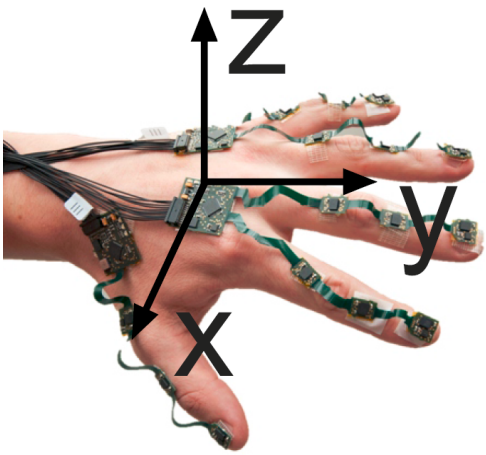


Figure 1.3: *Coordinate frame of the left hand*

The adduction-abduction (z-)axis is supposed to be in the opposite direction of the gravitational acceleration and is found by placing the hand horizontal with the palmar side down. The z-axis is determined using the accelerometer output: $e_z^{Seg} = \frac{g}{|g|}$ in which e_z^{Seg} is the z-axis of the segment and g is the gravitational acceleration. By performing flexion and extension of the metacarpal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) (see Figure 1.4 for an anatomical overview of the finger

joints) joints around the x-axis, the x-axis can be found using gyroscope output: $e_x^{Seg} = \frac{\omega}{|\omega|}$ with the x-axis of the segment e_x^{Seg} and the angular velocity ω. The y-axis can then be calculated by the cross-product of the x- and z-axis. Subsequently, the sensor to segment orientation is given by: $R = [e_x^{Seg} \quad (e_z^{Seg} \times e_x^{Seg}) \quad e_z^{Seg}]$. The orientation of the hand sensor can be obtained by performing an eight shaped movement with the hands placed together. The angular velocity measured with the gyroscopes of all the different hand segments are assumed to be identical and therefore the coordinate frame of the hand sensors can be equalized to the coordinate frame of the finger segments [2, 59].

Besides the sensor calibration, a magnetic calibration procedure has to be performed. The magnetometers are disturbed by ferromagnetic metals and electronic equipment that generate magnetic fields [59]. Therefore, the magnetic field of the environment has to be measured and has to be taken into account.

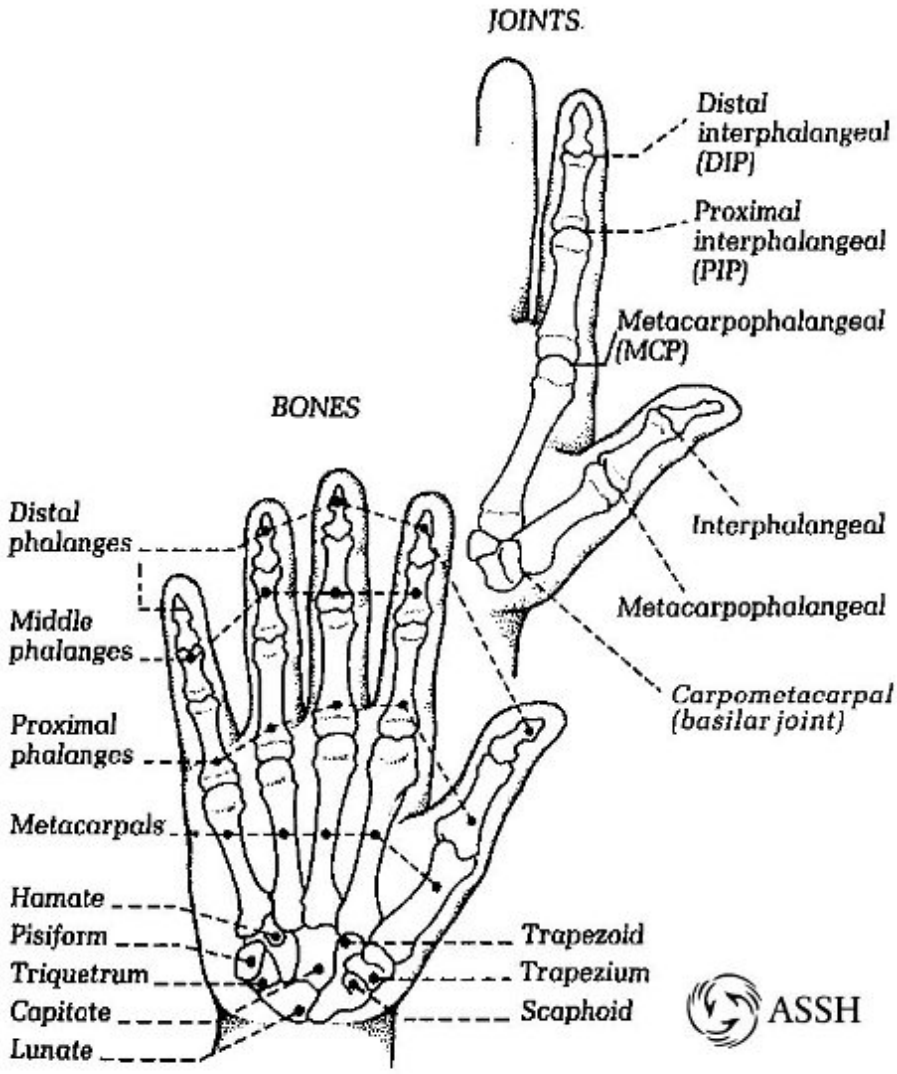


Figure 1.4: *Anatomy of the bones and joints in the hand [3]*

1.4.2 Rotation matrices and quaternions

Quaternions are used in the PowerGlove software to represent orientations and rotations of the hand and finger segments. In this section, a short overview of the theory used in the software about rotations matrices and quaternions is given.

Any rotation can be given as a composition of rotations about three axes. In case the rotation is about the z-axis the resulting equation is: $\begin{bmatrix} x_2 \\ y_2 \\ z_2 \end{bmatrix} = \begin{bmatrix} cos\theta & sin\theta & 0 \\ -sin\theta & cos\theta & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x_1 \\ y_1 \\ z_1 \end{bmatrix}$. The equation can be written in

a simpler form $\mathbf{r}_2 = A\mathbf{r}_1$ where A is called the rotation matrix which take $\mathbf{r}_1$ into $\mathbf{r}_2$. In 3D, the rotation is not well defined and the axis, about which the rotation occurs, needs to be specified.

The angle of rotation about a coordinate axis is called Euler angle. A sequence of such rotations is an Euler angle sequence. Euler angles represent orientations as a series of three independent rotations around its axes. But the disadvantage of Euler angles is that the angles must be used in the given order. Quaternions are used to represent orientations and rotations of an object in three dimensions as well. An advantage of quaternions is that the order of rotations around the different axes is not of importance and it is more compact since it contains only four numbers instead of nine.

A quaternion is defined as $q = q_0 + \mathbf{q} = q_0 + \mathbf{i}q_1 + \mathbf{j}q_2 + \mathbf{k}q_3$. q_0 is called the scalar part of the quaternion and is the angle of rotation while **q** is the vector part of the quaternion and is the axis about which the rotation occurs. q_0, q_1, q_2, q_3 are real numbers or scalars and are called the components of the quaternion and **i**, **j** and **k** are the standard orthonormal unit vectors (**i** $= (1,0,0)$, **j** $= (0,1,0)$ and **k** $= (0,0,1)$).

If a rotation is defined by the matrix $A = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$ then its fixed axis of rotation is $v = \mathbf{i}(a_{23} - a_{32}) + \mathbf{j}(a_{31} - a_{13}) + \mathbf{k}(a_{12} - a_{21})$.

If a rotation matrix M is given $M = \begin{bmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{bmatrix}$ the corresponding quaternion is:

$$q_0 = \left(\frac{1}{2}\right)\sqrt{m_{11} + m_{22} + m_{33} + 1} \tag{1.1a}$$

$$q_1 = (m_{32} - m_{23})/4q_0 \tag{1.1b}$$

$$q_2 = (m_{13} - m_{31})/4q_0 \tag{1.1c}$$

$$q_3 = (m_{21} - m_{12})/4q_0 \tag{1.1d}$$

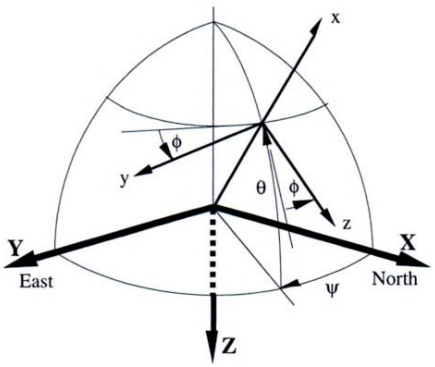


Figure 1.5: *Heading, elevation and bank angles [4]*

From this quaternion the Euler angles can be calculated:

$$tan\psi = \frac{2q_1q_2 + 2q_0q_3}{2q_0^2 + 2q_1^2 - 1} \tag{1.2a}$$

$$sin\theta = -2q_1q_3 - 2q_0q_2 \tag{1.2b}$$

$$tan\phi = \frac{2q_2q_3 + 2q_0q_1}{2q_0^2 + 2q_3^2 - 1} \tag{1.2c}$$

These three euler angle rotations relate the body coordinate frame to the local reference coordinate frame. ψ is the heading angle and a rotation about the z-axis, θ is the elevation angle and rotation about the new y-axis and ϕ is the bank angle and rotation about the new x-axis as illustrated in Figure 1.5.

The transition quaternion t takes the quaternion p into quaternion q:

$$t = pq^* \tag{1.3}$$

where q^* is the complex conjugate of a quaternion:

$$q^* = q_0 - \mathbf{q} = q_0 - \mathbf{i}q_1 - \mathbf{j}q_2 - \mathbf{k}q_3 \tag{1.4}$$

and the product of two quaternions is [4]:

$$pq = \begin{bmatrix} p_0 & -p_1 & -p_2 & -p_3 \\ p_1 & p_0 & -p_3 & p_2 \\ p_2 & p_3 & p_0 & -p_1 \\ p_3 & -p_2 & p_1 & p_0 \end{bmatrix} \begin{bmatrix} q_0 \\ q_1 \\ q_2 \\ q_3 \end{bmatrix} \tag{1.5}$$

1.5 Research questions

Given the problem definition, there is need for a system that has a lower inter-rater variability and higher the resolution compared to the UPDRS and is able to assess long term fluctuations. The PowerGlove system in combination with a force sensor will be used in this study to quantify the hand motor symptoms (tremor, bradykinesia and rigidity) in PD patients. The following research questions are defined:

- Is the PowerGlove system in combination with a force sensor valid to measure rigidity, bradykinesia and tremor in PD? To be useful, the PowerGlove system has to be able to measure at least a difference severity of the symptoms. Therefore, the difference between the off- and on-medication state will be analysed. The relation with the UPDRS is investigated as well.
- Is the PowerGlove system reliable to measure rigidity, bradykinesia and tremor? What is the intra-rater and inter-rater reliability and agreement?

To achieve this, the PowerGlove software has to be further developed to measure the wrist angles, obtain reliable positions of the different finger segments and make it possible to measure the right hand.

CHAPTER 2

METHODS

2.1 PowerGlove

The system, as described in section 1.4, is extended with a 3D gyroscope, a 3D accelerometer and a 3D magnetometer on the lower arm in order to measure wrist angles. A 3D force sensor (F/T-sensor, ATI mini45, ATI Industrial Automation USA) as shown in Figure 2.1, is added to measure the force which the examiner applies to the hand during the rigidity measurements. The sensor strip on the ring and little finger is omitted since these fingers would give minimal additional information. Several additions are made as well in the PowerGlove software as are described below.

Figure 2.1: *Force sensor (ATI mini45)*

2.1.1 PowerGlove software

Calibration lower arm sensor

For calibration of the sensor on the lower arm, the hand and lower arm have to be placed flat on the table during the calibration procedure. With the accelerometer data, the z-axis can be found because this axis is in the opposite direction of the gravitational acceleration (see section 1.4.1). By making the assumption that the x-axis of wrist is in the xy-plane of the global reference system and by setting the x-axis equal to (1,0,0), the y-axis can be determined which is the cross product of the x- and z-axis. The rotation matrix obtained can be converted into a quaternion using Equation (1.1).

Wrist angle calculation

The transition quaternion between the hand and the lower arm is the product of the complex conjugate of the quaternion of the arm and the quaternion of the lower arm (see Equations (1.3), (1.4) and (1.5)). The Euler angles (sequence zyx) are then calculated using Equation (1.2) to calculate the angle of the wrist [4].

Segment lengths

In the original software, standard segment lengths were used based on a general hand model [2]. These segment lengths were defined in a matrix in which the length of every finger segment of each finger is defined in three dimensions. Segment lengths are used in the calculation of fingertip positions in the hand model algorithm of the PowerGlove and to optimize this, the segment lengths of the patient will be entered into the software. Before the measurement, the lengths of every hand and finger segment is measured in the y-direction. The lengths in the other directions are calculated by using the ratios of the standard segment lengths (see Table 2.1 and Table 2.2 for the segment lengths and Figure 1.4 for the bones of the hand).

Table 2.1: *Segment lengths of the thumb of the left hand*

Finger	Version	Direction	Segment lengths			
			scophoid and trapezium	metacarpals	proximal phalanx	distal phalanx
Thumb	default	x	0.0250	0	0	0
		y	0.0100	0.0550	0.0400	0.0340
		z	-0.0300	0	0	0
	patient specific	x	$\frac{2.5e-2}{5.5e-2}$*length metacarpals	0	0	0
		y	$\frac{1e-2}{5.5e-2}$*length metacarpals	length metacarpals	length proximal phalanx	length distal phalanx
		z	$\frac{-3e-2}{5.5e-2}$*length metacarpals	0	0	0

Table 2.2: *Segment lengths of the index finger and middle finger of the left hand*

Finger	Version	Direction	Segment lengths			
			metacarpals	proximal phalanx	middle phalanx	distal phalanx
Index	default	x	0.0320	0	0	0
		y	0.0900	0.0530	0.0280	0.0250
		z	-0.0080	0	0	0
	patient specific	x	$\frac{3.2e-2}{9e-2}$*length metacarpals	0	0	0
		y	length metacarpals	length proximal phalanx	length middle phalanx	length distal phalanx
		z	$\frac{-0.8e-2}{9e-2}$*length metacarpals	0	0	0
Middle	default	x	0.0060	0	0	0
		y	0.0920	0.0560	0.0360	0.0270
		z	-0.0050	0	0	0
	patient specific	x	$\frac{0.6e-2}{9.2e-2}$*length metacarpals	0	0	0
		y	length metacarpals	length proximal phalanx	length middle phalanx	length distal phalanx
		z	$\frac{-0.5e-2}{9.2e-2}$*length metacarpals	0	0	0

Right hand analysis

The coordinate system of the right hand differs from the left hand. For the right hand, the coordinate frame is: the x-axis pointing in the ulnar direction, the y-axis pointing proximally to the elbow and the z-axis pointing to the palmar side of the hand (see Figure 2.2).

First, to measure the right hand, the sensors need to be turned over to fit over the right hand. The unit-length direction vectors of the x-axis, j_1 and j_2 are only dependent of the sensor's mounting orientation [62]. For the right hand, j_1 and j_2 are pointing in the opposite direction compared to the left hand because the sensors were turned over, resulting in a x-axis in radial direction. The x-axis is converted to pointing in the ulnar direction by changing the sign of the unit-length direction vectors j_1 and j_2. The direction of the z-axis is for the right hand in the same direction as the gravitational acceleration. The z-axis is therefore calculated by $e_z^{Seg} = \frac{-g}{|-g|}$. The y-axis is then the cross product of the x- and z-axis.

The coordinate frame of the hand sensors can be aligned to the coordinate frame of the finger sensors in the same manner as for the left hand (see section 1.4.1). The matrix R, in which the sensor to segment orientation is given, becomes $R = [-e_x^{Seg} \quad -e_y^{Seg} \quad -e_z^{Seg}]$ resulting in angles in accordance with the ISB recommendations [61].

The arm sensor is calibrated using only accelerometer data. The z-axis, pointing to the palmar side, is calculated using $e_z^{Seg} = \frac{-g}{|-g|}$. The x- and y-axis are then calculated as described earlier in this section.

The segment lengths are also adjusted so that the positions of the finger segments correspond to those of the left hand. The lengths in the x-, y- and z-direction are all in the opposite direction compared to the segment lengths of the left hand given in Table 2.1 and in Table 2.2.

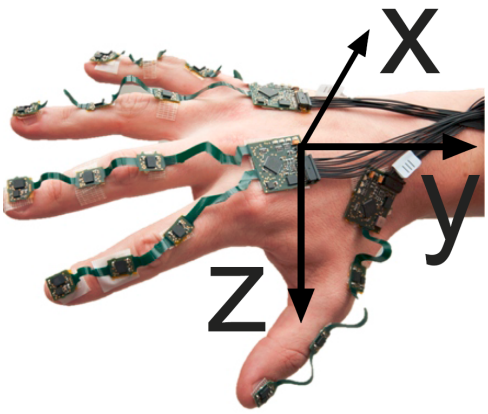


Figure 2.2: *Coordinate frame of the right hand*

2.2 Study design

The measurements took place at the Academical Medical Centre (AMC) in Amsterdam. The measurement protocol was approved by the medical research ethics committee. Patients who were screened for DBS were approached to participate in this study. At the first day they arrived at the hospital and stopped using their PD medication. At this day examiner A informed the patient about the study. In the evening, the patient was asked whether he/she wanted to be included and informed consent was given. Then the width of hand palm, the length of every finger segment of the thumb, index and middle finger, the size of the hand from wrist to top of the middle finger and the distance between the centre of the force sensor and the wrist were measured.

At the second day the standard screening took place in which the symptoms of the patient were rated with the UPDRS by examiner B in off- and on-medication state. The PowerGlove measurements took place before or after the complete UPDRS test (this was randomized). For the PowerGlove measurements, patients were situated in a chair and the sensors were attached to the most affected hand using tape and Velcro tape. Then, the calibration movements were performed. These movements are:

- The hand and wrist are placed on a flat surface.
- The thumb is placed on a flat surface.
- Flexion of the DIP joint of the thumb.
- Flexion of the fingers in the MCP joint with fingers stretched.
- Flexion of all finger joints (MCP, PIP and DIP).
- The hands are put together and moved in an eight-shaped movement.
- Pro- and supination movement of the hand. (The pro- and supination movement can be used to optimise the calibration of the arm sensor so that the software could calculate the angle around the z-axis as well. This is not implemented yet.)

In between these movements the hand and wrist were placed on a flat surface. During the calibration, the arm of the patient rests on the arm support of the chair and the hand and arm are placed flat using the arm support. The measurement set-up can be seen in Figure 2.3.

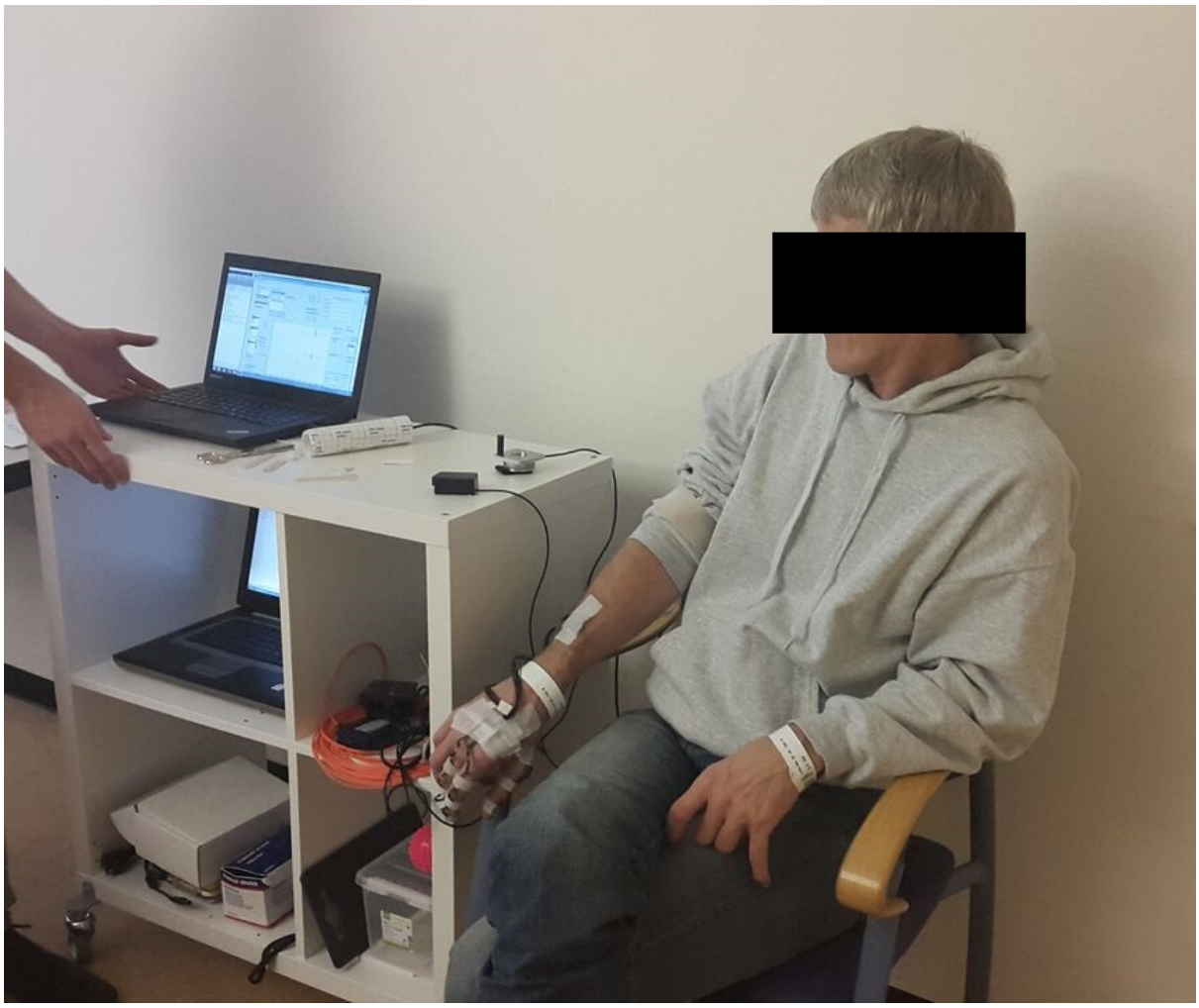


Figure 2.3: *Measurement set-up*

The calibration procedure was followed by the PowerGlove measurement. During the measurement, the patient performed several hand movement tasks (items 20-25 of the UPDRS) which included:

- a relaxing task (resting tremor);
- a mental task (resting tremor);
- holding their hands below their chin (posture tremor);
- moving the tip of the index finger between their nose and the finger of the examiner (kinetic tremor);
- finger tapping (bradykinesia);
- pro- and supination of the hand (bradykinesia);
- hand open- and closing (bradykinesia);
- extension of the wrist (rigidity);
- extension of the wrist with contralateral activation (rigidity).

Extension of the wrist was passively done with the help of the examiner and the examiner applied the force sensor during this task while the lower arm was held in a constant position. Trigger pulses were given between all tasks to synchronize the time lines of the PowerGlove signals and force signals and to discriminate between the different tasks during the analysis. The measurement was repeated three times to study the intra- and inter-rater reliability. Rater A instructed the patient twice (referred to as measurement A1 and A2) and rater B once (measurement B1). The order of this was randomized. After the measurement, the calibration movements were repeated in case a sensor was moved during the measurement.

Thereafter, the patient takes a fast-acting variant of their morning dose of levodopa and one hour after medication is taken, the on-measurements or on-medication screening (UPDRS) started (the order was randomized as well). First, the calibration procedure was performed then the PowerGlove measurement was done once and was instructed by rater A (measurement on) [5].

An overview of the time schedule is given in Figure 2.4.

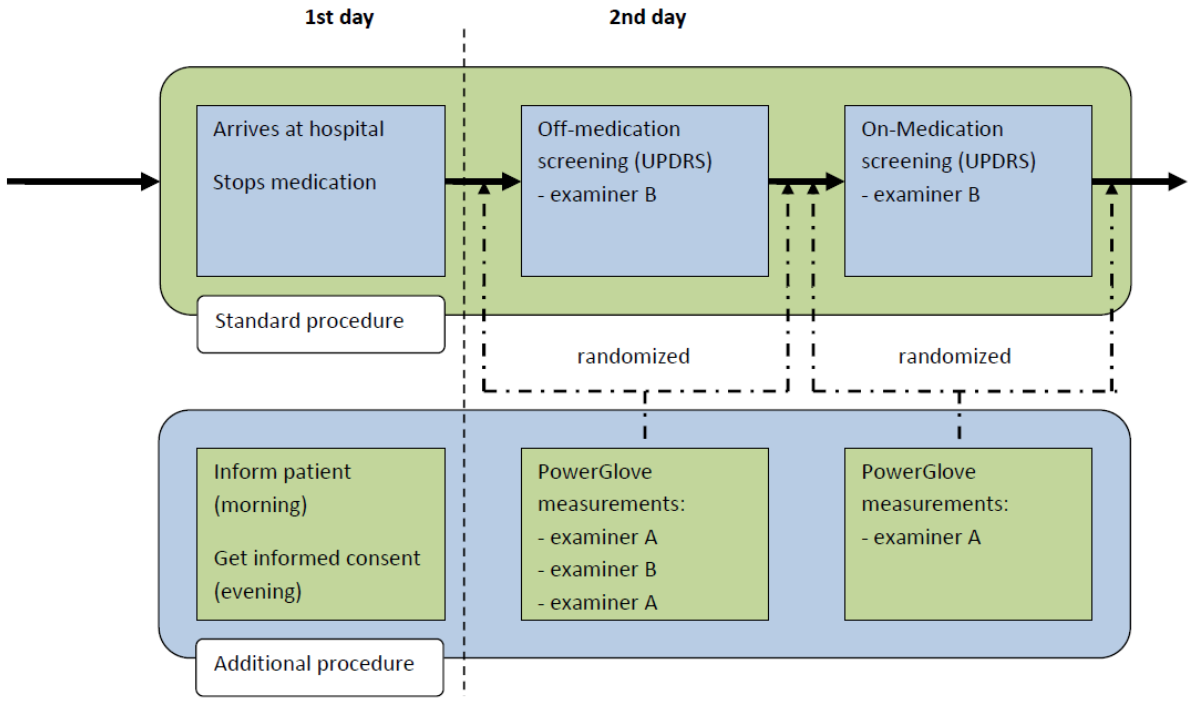


Figure 2.4: *Flow chart of the standard screening procedure and the PowerGlove measurements [5]*

2.2.1 Study population

Patients who are possible candidates for DBS stimulation were approached for this study. These patients have PD symptoms for more than five years, have on/off fluctuations with or without levodopa induced dyskinesias, have a good response to PD medication and their symptoms disturb them in their daily activities [5].

In order to be included, a subject must meet all of the following inclusion criteria:

- The subject is selected to undergo the preoperative screening for PD DBS.
- The subject is able to communicate adequately in Dutch or English.
- The subject is between the age of 18 and 80.

A potential subject who meets any of the following criteria was excluded:

- Medical (or other) history other than PD which restricts hand movement (e.g. complicated wrist fractures or severe arthritis).
- Inability to correctly place the PowerGlove on the subject's hand or to correctly perform calibration.

A total of 22 patients were included. Clinical details of the included patients are given in table 2.3.

2.3 Data analysis

Data is analysed using MatLab R2013b (The Mathworks inc. Massachusetts, USA). Data is analysed offline to calculate joint angles and positions of the finger segments as well as wrist joint moments. A manual for the offline analysis can be found in appendix B. Analysis and calculations made for the parameters used for quantification are described in the following subsection.

Table 2.3: *Patient characteristics*

Patient	Age	Gender	Disease duration (years)	Dominant hand	Most affected hand	Measured hand	Off-measurement before/after UPDRS	On-measurement before/after UPDRS	Order of off-measurements*	Levodopa dose (mg)
1	67	M	16	R	R	L/R	A	A	2	350
2	56	M	7	R	L	L/R	A	B	3	375
3	72	M	13	R	L	L	B	B	3	300
4	69	M	17	R	L	L	B	A	3	300
5	withdrawn									
6	67	M	23	R	R	R	A	B	1	225
7	70	F	10	R	R	R	B	B	2	450
8	45	M	10	R	R	R	A	A	1	200
9	55	M	8	R	R	R	B	A	3	300
10	withdrawn									
11	70	F	7	R	L	L	A	B	1	150
12	60	M	19	R	L	L	A	A	2	300
13	64	M	6	R	L	L	B	B	3	300
14	68	M	6	R	L	R	B	A	3	150
15	58	M	14	R	L	L	A	A	1	250
16	67	M	14	R	R	R	A	A	2	350
17	72	M	14	R	R	R	A	B	1	350
18	55	M	19	L	L	L	B	-	2	-
19	56	M	14	R	L	L	B	A	3	350
20	67	F	16	R	R	R	B	A	3	325
21	59	M	15	R	L	L	B	A	1	200
22	55	M	11	R	L	L	A	B	2	200
23	67	M	11	R	R	R	B	B	2	168
24	65	M	15	R	R	R	B	A	3	336

*1, BAA; 2, ABA; 3, AAB

2.3.1 Task distinction

To distinguish between different tasks, trigger pulses were given during the measurements. A trigger pulse disturbs the magnetic field and when given close to the magnetometer this disturbance can be seen in the magnetometer signal. By visual inspection of the shape of the magnetometer signal and the pulses and by knowing the order in which the tasks occurred, the tasks can be distinguished from each other. In Figure 2.5, the data obtained with the magnetometer on the hand segment (sensorstrip of the index and middle finger) is visualized. The three signals represent the magnetic field in three different directions. The numbers and lines indicate the time intervals of each task (1: relaxing task, 2: mental task, 3: posture tremor, 4: kinetic tremor, 5: finger tapping task, 6: pro- and supination task, 7: closing task, 8: wrist extension and 9: wrist extension with contralateral activation).

The PowerGlove data was synchronized with the data of the force sensor for the rigidity tasks. The triggers were found by finding the maximal values in the data. Each trigger pulse contains three peaks of which the third peak is slightly higher than the other two and this peak was therefore used to synchronise the signals. In the magnetometer signal, the third peak is manually selected. After synchronization of the signals, the rigidity tasks are distinguished from each other by visually detecting wrist extension using the wrist angles. The time in between the tasks is used to discriminate between the two rigidity tasks.

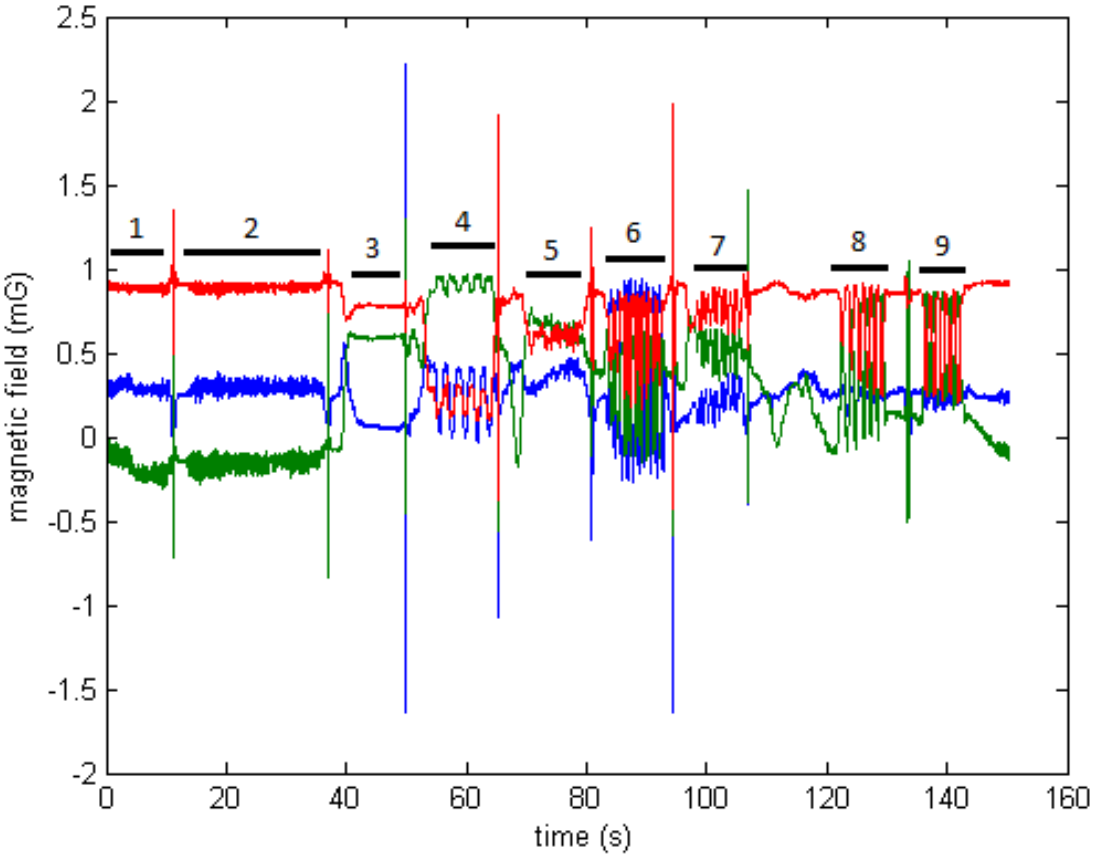


Figure 2.5: *Magnetometer signal of the hand segment of the index finger during a complete measurement with the lines and numbers representing the time intervals of 1: relaxing task, 2: mental task, 3: posture tremor, 4: kinetic tremor, 5: finger tapping task, 6: pro- and supination task, 7: closing task, 8: wrist extension and 9: wrist extension with contralateral activation.*

2.3.2 Tremor

According to the literature, good results were found using the RMS of the accelerometer signal, RMS of the angular velocity, peak power of the accelerometer data as well as for the gyroscope data and the tremor amplitude (see Section 1.3). The amplitude and the persistence is rated in the UPDRS as well. Since the peak in the power spectral density (see Figure 3.1) is broader for posture and kinetic tremor, the power in the tremor band is analysed as well.

The following five parameters are calculated for each of the four tremor tasks:

1. peak power in the tremor band;
2. power in the tremor band;
3. RMS of the acceleration;
4. RMS of the angular velocity;
5. maximal tremor amplitude.

It is hypothesized that these parameters will all have a higher value when tremor is more severe.

These parameters are obtained as follows. First, the accelerometer, gyroscope and position data are filtered using a high pass second order butterworth filter (3 Hz) to remove the gravitational acceleration, artefacts and voluntary movements of the data [32, 34].

1-2. The power is obtained by using Welch' method (a Hamming window resulting in eight sections of the data with 50% overlap between segments). The power of the acceleration signal in three dimensions of the distal part of the index signal has the highest power and will be used since tremor was most present in this sensor. Resting tremor has a frequency of 4-7 Hz and posture and kinetic a frequency of 7-12 Hz. The maximal power is therefore determined by finding the local maximum between 4 to 7 Hz for resting tremor and between 7-12 Hz for posture and kinetic tremor [63]. The power of the tremor band is calculated by integration (step widths of 0.1 Hz) of the power in the frequency band ranging from 4 to 7 Hz for resting tremor and 7-12 Hz for posture and kinetic tremor.

3-4. For the RMS of the acceleration and for the RMS of the angular velocity, the data of the fingertip of the index finger is used as well. The signal is squared, the mean and root are calculated for the x-, y- and z-direction. The mean of the RMS values in all directions is calculated since the direction in which tremor occurs differed between patients and between tasks.

5. The position of the finger tip with respect to the hand is calculated by combining the positions with respect to the hand in all three directions. The difference vector between the two most outlying positions during the tremor task and its magnitude, which is the maximal amplitude (in meters), is calculated.

2.3.3 Bradykinesia

Good results were found in literature for bradykinesia when the RMS of the angular velocity, range of movement, RMS of the angle, the SD of the finger tap intervals, average finger tap amplitudes, velocity of the finger taps and movement time were used for quantification of the severity of bradykinesia (see Section 1.3). For the UPDRS scoring, the amplitude, the number of interruptions and velocity of movement are taken into account.

Therefore, the following parameters are investigated:

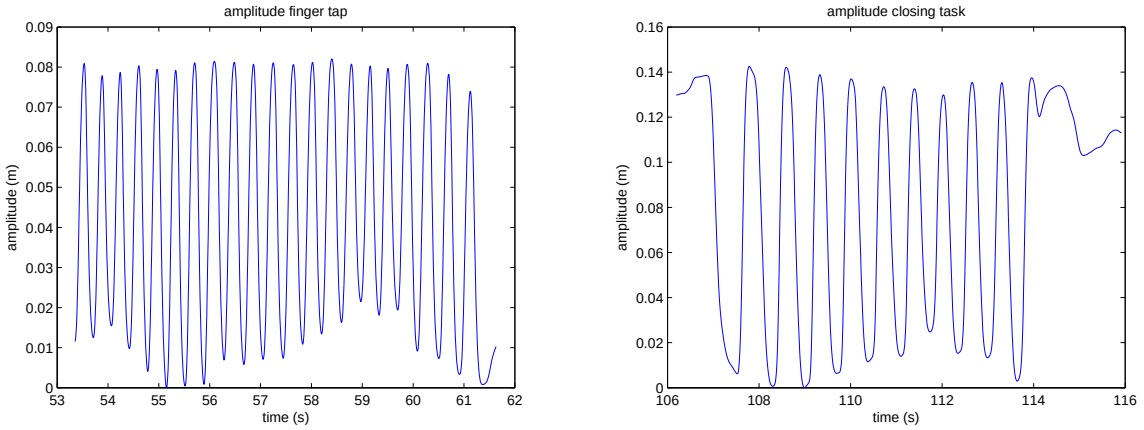
1. RMS of the acceleration (finger tapping task, pro-/supination task and closing task);
2. RMS of the angular velocity (finger tapping task, pro-/supination task and closing task);
3. amplitude of the tip of the index finger (finger tapping task and closing task);
4. movement time and SD (finger tapping task, pro-/supination task and closing task);
5. number of stops (finger tapping task, pro-/supination task and closing task).

It is hypothesised that the RMS of the acceleration, RMS of the angular velocity and amplitude of the movements will decrease with higher scores for severity of bradykinesia while the movement time, SD of the movement time and number of stops increase with higher scores for severity of bradykinesia.

These parameters are obtained as follows. First, the measured signals are filtered using a low pass second order butterworth filter (4 Hz) to remove tremor and high frequency noise [31].

1-2. The RMS of the acceleration and of the angular velocity are calculated as described in subsection 2.3.2. The gravitational acceleration is removed from the accelerometer signal by subtracting the mean of the accelerometer signal. For the finger tapping and closing tasks the sensor of the distal part of the index finger is used while for the pro- and supination task the hand sensor is used.

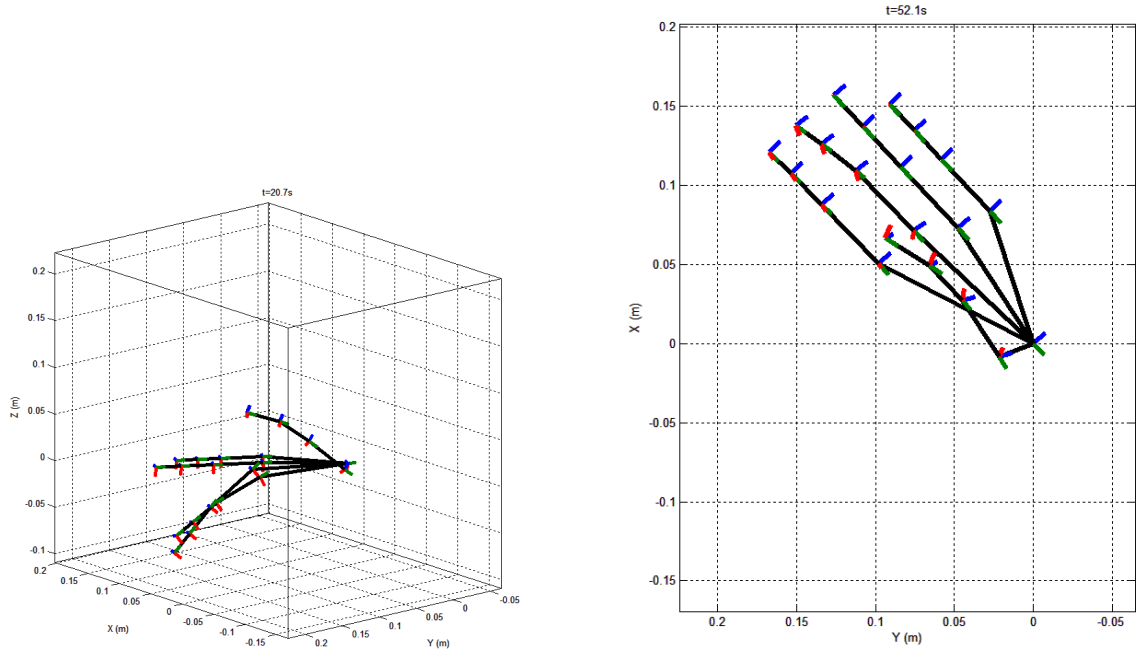
3. The amplitude of the index finger is only used for the finger tapping task and closing task. The position of the finger tip is calculated by combining the positions in all three directions. The difference vector between the two most outlying positions is calculated and its magnitude which is the maximal amplitude (in meters) as well. Then the mean of all the amplitudes is calculated (see Figure 2.6). The mean amplitude is corrected for the finger length when inter-subject comparisons are made. The thumb was excluded during finger tapping because the contribution of the thumb is minimal and the calibration of the thumb is difficult resulting in an offset as can be seen in Figure 2.7 and therefore the position of the thumb was not always reliable.



(a) finger tapping amplitude

(b) amplitude tip of the index finger during closing task

Figure 2.6: *Amplitudes*



(a) side view

(b) top view

Figure 2.7: *Offset in joint angle in the CM joint of the thumb.*

4. The movement time is the time it takes to perform one finger tap, one open- and closing of the hand or one pro- and supination movement. In all tasks, the position data of the tip of the index finger with respect to the hand is used. The peaks are detected with peak-to-peak separations greater than 0.2 seconds. The time between each peak and the mean of all these individual movement times are calculated as well as the SD (see Figure 2.8).

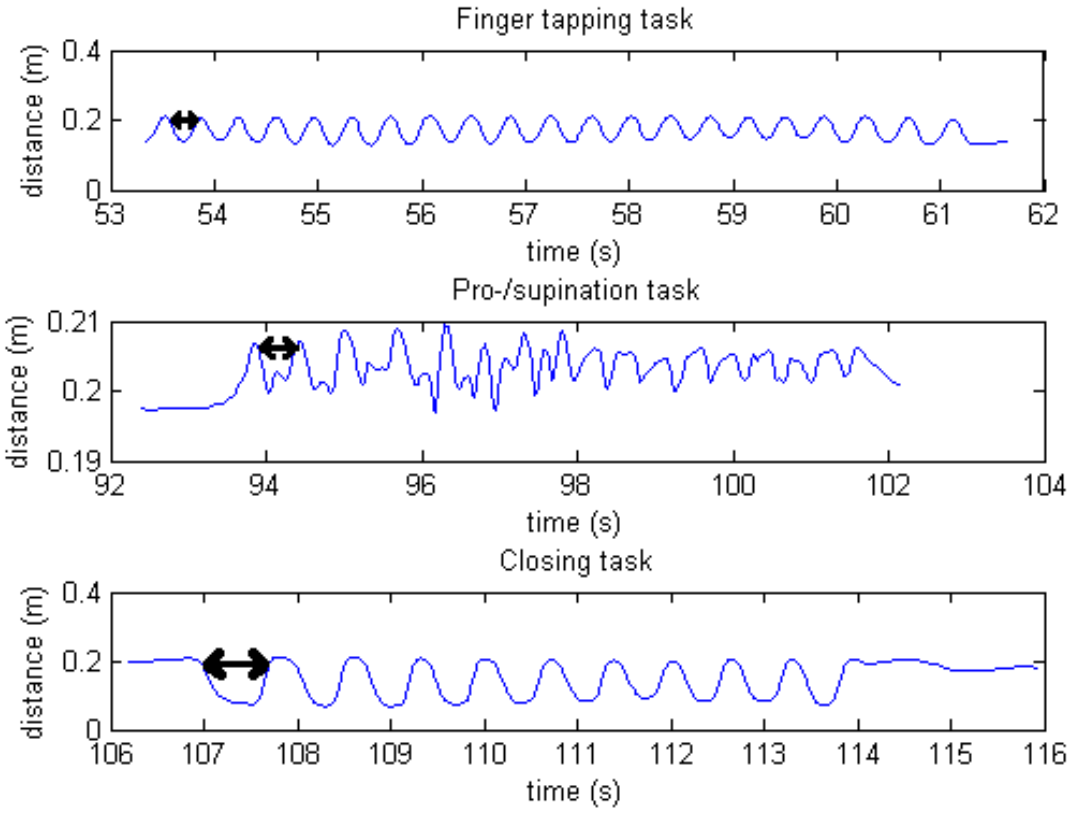


Figure 2.8: *Distance of the tip of the index finger with respect to the hand. Arrows indicating one movement time.*

5. A stop is when the rhythm of the movement is interrupted. A stop is detected when the movement time of one finger tap, one open- and closing or one pro-/supination is larger than 150% of the average movement time measured for that task during that trial. All stops during each task are summed.

2.3.4 Rigidity

For rigidity, the impedance, stiffness and viscous damping constant had good results according to the literature (see Section 1.3). In the UPDRS scoring, the range of motion and the resistance to passive movement are taken into account.

Therefore, the following parameters are used to quantify rigidity:

1. torque at 30 and 60 degrees wrist extension;
2. maximal range of motion;
3. impedance;
4. stiffness;
5. viscous damping constant.

It is hypothesised that the torque, range of motion, impedance, stiffness and viscous damping constant increase with severity of rigidity and the range of motion decrease with severity of rigidity.

These parameters are obtained as follows. Force data is synchronised to the data measured with the PowerGlove using the pulses given between each task and the force data is downsampled to 100 Hz.

1. The torque is calculated using the force which is directly obtained from the data measured with the force sensor. The force measured in the z-direction is used since only the extension of the hand is of interest. The torque is then calculated using $T = F \cdot d$ in which T is the torque, F the force and d

is the distance between the wrist and the centre of the force sensor which was measured before the measurement. The intervals in which extension takes place are manually selected using data of the wrist angle. The range of motion reaches its maximum at the third extension as can be seen in Figure 2.9. The first two extensions will therefore be discarded in the analysis. The torque which was applied to the wrist at the moment the wrist angle reached 30 and 60 degrees is used. The mean of the torque at 30 and 60 degrees of the third to last extension is then calculated.

2. For the maximal range of motion, the maximal extension angle which occurred at any moment during the task is used.

3. The impedance to passive extension is calculated using the following formula: $Z = \frac{Fd}{\theta}$ in which Z is the impedance, F the force exerted on the hand, d the distance between the wrist and the force sensor and θ the angular displacement [42]. The average of the third to last extension will be used as well.

4-5. The wrist can be described by the following equation of motion: $T = Kx + Bv + C$ in which T is the torque, K the stiffness, x the displacement, B the viscous damping constant, v the angular velocity and C a constant offset torque [43]. This represents a simple spring-damper system with constant elasticity, offset and viscosity. Least-square estimation is used to find the best fitting parameters K, B and C. Since the frequency is low, the acceleration is minimal and the inertial component is omitted. For this estimation, the average of the third to last extension will be used as well.

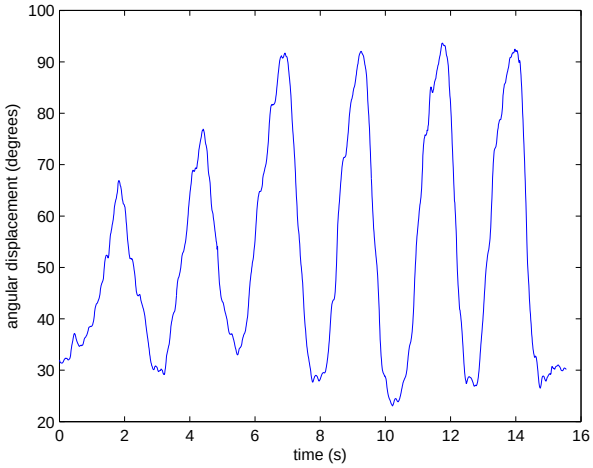


Figure 2.9: *Angular displacement during extension of the wrist without contralateral activation. From the third extension on the angle stabilises.*

2.4 Statistical analysis

Statistical analyses were performed using MatLab R2013b (The Mathworks inc. Massachusetts, USA). The Anderson-Darling test was applied to test if a normal distribution adequately described the set of data. A p-value of less than 0.05 was considered to indicate statistical significance. All reported p-values are two-sided.

The validity of the measurement set-up is studied by using the UPDRS score as a gold standard. Different conditions of the patient are studied by whether the PowerGlove can distinguish between off- and on-medication state and using a change in UPDRS score as a reference. The relation between the UPDRS scores and the results of the PowerGlove measurements will be studied as well. The reliability of the system was studied by analysing the inter- and intra-rater reliability in the off-medication state.

2.4.1 Off-On difference

The resulted parameters in the off-medication state (first measurement of rater A) were compared to the results of the on-medication state. Two groups were analysed. One group in which patients were included who had a difference in UPDRS score between the on- and off-measurement and a second group in which patients did not have a difference in UPDRS scores in order to test whether the PowerGlove system is able to detect small improvements due to medication where the UPDRS failed to detect small changes. Besides, for kinetic tremor it was studied whether kinetic tremor could be detected during the bradykinesia tasks, in which kinetic tremor could be present, as well. Wilcoxon signed-rank test was used, since the data was not normally distributed, for pairwise comparisons with a 95% confidence interval (CI) to assess whether their population mean ranks differ.

2.4.2 Relation to UPDRS

To find a relationship between UPDRS scores and the parameters, the first off-measurement of rater A were taken into account. Spearman's correlation coefficients with 95% CI were calculated to assess the

degree of a non-linear relationship between variables. For resting tremor both UPDRS scores (tremor amplitude and persistence) were analysed.

Mann-Whitney U test (or Wilcoxon rank-sum test) was used, since the data was not normally distributed, to test whether individual UPDRS scores could be distinguish from each other. A 95% CI to assess whether the population mean ranks differ between subgroups of UPDRS scores was used. The p-value is corrected for the multiple comparisons by the Bonferroni correction: a p-value less than 0.05/i, with i the number of comparisons, was considered significant.

2.4.3 Reliability and agreement

The inter- and intra-rater reliability and agreement are studied by evaluating the intraclass correlation coefficient (ICC) and the standard error of measurement (SEM). The ICC relates the measurement error to the variability between subjects [64]. A two-way anova is used. The expression for the variance ratio is: $\rho = \sigma_T^2/(\sigma_T^2 + \sigma_J^2 + \sigma_I^2 + \sigma_E^2)$ with σ_T^2 the variance between patients, σ_I^2 the variance in interaction between rater and patient, σ_J^2 the variance between raters and σ_E^2 variance in error. This is estimated by: $ICC(2,1) = \dfrac{BMS - EMS}{BMS + (k-1)EMS + k(JMS - EMS)/n}$, with the between target mean squares (BMS), the residual sum of squares (EMS), the between judges sum of squares (JMS), the number of raters (k) and the number of patients (n). An ICC value higher than 0.7 is generally considered as good [65, 66].

The SEM is a parameter for agreement between raters. It can be calculated by $SEM = \sigma\sqrt{1 - ICC}$ and using the pooled SD of the measurements for σ. However, the pooled SD does not include systematic errors. Therefore, ICC(3,1) is used to calculate the SEM. For ICC(3,1), the variance ratio is $\rho = \dfrac{\sigma_T^2 - \sigma_I^2/(k-1)}{\sigma_T^2 + \sigma_I^2 + \sigma_E^2}$. This is estimated by $ICC(3,1) = \dfrac{BMS - EMS}{BMS + (k-1)EMS}$ [65, 66].

The intra-rater reliability and agreement will calculated using data of the A1 and A2 measurement and the inter-rater reliability and agreement will be calculated by using data of the A1 and B1 measurement.

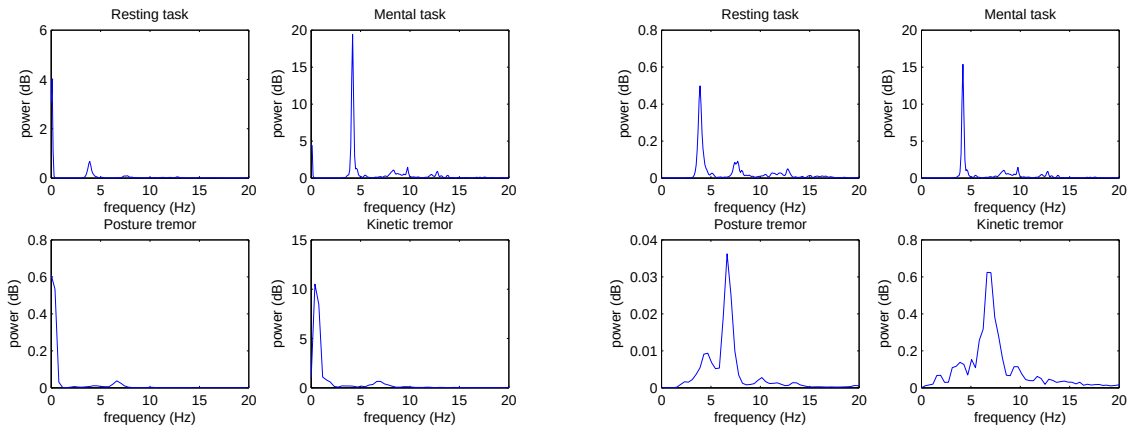
CHAPTER 3

RESULTS

3.1 Off-on difference

3.1.1 Tremor

A typical example of the power spectral density of a patient with resting (UPDRS score for amplitude is 3, UPDRS score for persistence is 4), posture (UPDRS score is 3) and kinetic (UPDRS score is 2) tremor is presented in Figure 3.1. In Figure 3.1(a), the power spectral density of the raw accelerometer data is given. In Figure 3.1(b), the power spectral density of the accelerometer data is given when the data was filtered with a the high pass filter (3 Hz) to remove artefacts and voluntary movements as described in Section 2.3.2. For the mental task, the power of the peak is decreased from approximately 20 dB to approximately 15 dB after filtering. It can also be seen that for kinetic tremor, the peak is broader and thus multiple frequencies are present.



(a) Raw data

(b) Filtered data

Figure 3.1: *Power spectral density of the raw and filtered (high-pass, 3 Hz) accelerometer data of the accelerometer placed on the tip of the index finger. The UPDRS scores for resting tremor are 3 for the tremor amplitude and 4 for the tremor persistence. For posture tremor, the UPDRS score is 3 and the UPDRS score is 2 for kinetic tremor.*

A total of 10 patients had a difference in UPDRS score between the off- and on-medication state for resting tremor. For posture tremor, nine patients had a difference in UPDRS score between the off- and on-medication state and for kinetic tremor six patients. For the tremor tasks, no significant differences between the off- and on-measurement were found (see Table 3.1). The mean differences between the off- and on-measurements (on minus off) and SDs are given in Table 3.1 as well. For the relaxing task, mental task and posture tremor the mean difference is negative for each parameter indicating a decrease in parameter values in on- compared to the off-medication state and thus less tremor after medication use. For kinetic tremor, the values increase in the on-state for each parameter except for the peak power. For all tremor tasks, the percentage difference of the peak power and power band is higher than 85% and of the RMS of the acceleration and angular velocity higher than 50% for the relax task, mental and posture tremor but still not significant.

Table 3.1: *Comparison of the parameter values in the off- and on-medication state and the mean differences and SDs between off- and on-medication state for each task and parameter. Patients with a difference in UPDRS score between the off- and on-measurement were included. The number of patients included, n, are given for each test. P-values below 0.05 are printed in bold.*

		Peak power (dB)	Power band (dB)	RMS acceleration (m/s^2)	RMS angular velocity (rad/s)	Tremor amplitude (m)
Relaxing task (n=10)	p-value	0.56	0.63	0.63	0.63	0.92
	difference ± SD	-1.6 (-88%) ±5.3	-13 (-90%) ±45	-0.58 (-54%) ±2.2	-0.12 (-59%) ±0.40	$-2.9*10^{-3}$ (-35%) ±0.012
Mental task (n=10)	p-value	0.28	0.28	1	0.28	0.49
	difference ±SD	-7.2 (-90%) ±16	-45 (-92%) ±111	-1.2 (-65%) ±3.2	-0.27 (-70%) ±0.62	$-6.8*10^{-3}$ (-51%) ±0.016
Posture tremor (n=9)	p-value	0.91	0.82	0.65	0.73	0.25
	difference ±SD	-0.67 (-96%) ±2.0	-7.6 (-92%) ±22	-1.3 (-76%) ±4.2	-0.15 (-66%) ±0.48	$-4.4*10^{-3}$ (-47%) ±0.023
Kinetic tremor (n=6)	p-value	0.44	0.69	0.31	0.42	0.089
	difference ±SD	-0.18 (-8.1%) ±1.1	17 (35%) ±51	0.64 (25%) ±1.11	0.14 (23%) ±0.39	0.014 (70%) ±0.016

In Figure 3.2, the values of the off- and on-measurements are visualised of the mental task. For two patients with a difference in UPDRS score of 3 for resting tremor between off- and on-medication state, it can be clearly seen that the parameter values decrease in the on-measurement. Figures containing data of the relaxing task, posture tremor and kinetic tremor can be found in Figure C.1,C.3 and C.4 respectively in Appendix C.1.1.

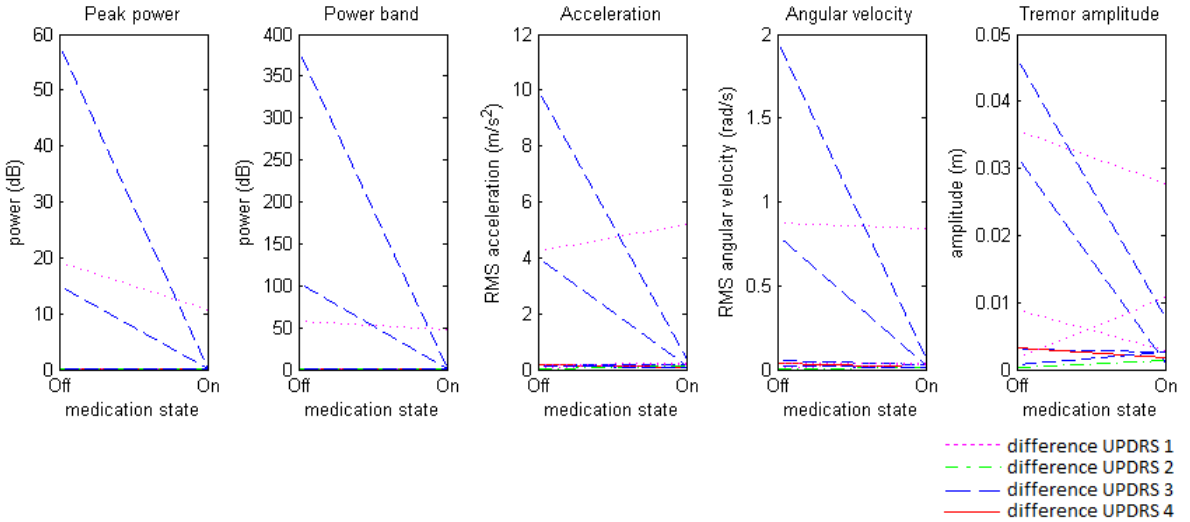


Figure 3.2: *Parameter values of the off- and on-measurement for the mental task. The difference UPDRS gives the difference in UPDRS score for resting tremor between the off- and on-measurement.*

In Table 3.2, the p-values and mean differences and SDs of the comparison between the off- and on-measurement are given for kinetic tremor during the bradykinesia tasks. Six patients with a difference in UPDRS score for kinetic tremor between off- and on-medication state were included. The difference is always positive, meaning an increase of the parameter values in the on-measurement compared to off-measurement, except for the peak power during the finger tapping task. For the closing task, all parameter values were significant different in the on-medication state from the off-medication state. The

tremor amplitude was significantly different in the on-state compared to the off-state for the finger tapping and pro- and supination task as well. But for all these parameters, the parameter values increased in the on-state which means there would be more kinetic tremor in the on-medication state.

Table 3.2: *Comparison of the parameter values in the off- and on-medication state and the mean differences and SDs between off- and on-medication state for the bradykinesia tasks. Six patients with a difference in UPDRS score between off- and on-measurement for kinetic tremor were included. P-values below 0.05 are printed in bold.*

	Task		Peak power (dB)	Power band (dB)	RMS acceleration (m/s^2)	RMS angular velocity (rad/s)	Tremor amplitude (m)
Bradykinesia (n=6)	Finger tapping task	p-value	0.28	0.23	0.084	0.065	**0.027**
		difference ±SD	15 (278%) ±46	208 (191%) ±625	3.0 (34%) ±4.0	0.91 (40%) ±1.2	0.010 (23%) ±0.011
	Pro- and supination task	p-value	0.63	0.23	0.23	0.70	**0.014**
		difference ±SD	-1.1 (-9.2%) ±15	42 (20%) ±313	2.3 (35%) ±5.6	0.077 (4.8%) ±1.1	0.042 (73%) ±0.045
	Closing task	p-value	**$2.0*10^{-3}$**	**$3.9*10^{-3}$**	**0.020**	**0.027**	**0.014**
		difference ±SD	3.5 (170%) ±3.0	83 (159%) ±86	3.2 (52%) ±3.1	0.95 (53%) ±1.01	0.013 (33%) ±0.011

Twelve patients had no difference in UPDRS score between off- and on-medication state for resting tremor. For posture tremor and kinetic tremor, 13 patients and 16 patients respectively had no difference in UPDRS score between the off- and on-measurement. In Table 3.3, the p-values and mean differences and SDs of the comparison between the off- and on-measurement are given when no difference is detected with UPDRS scoring. The differences were only negative for the RMS of the acceleration and the tremor amplitude for the relaxing task and for the peak power, power in the tremor band, RMS of the acceleration and the RMS of the angular velocity for the posture tremor which indicates a decrease in tremor after medication use but the corresponding p-values were all higher than 0.05 and thus not significant. Significant results were found for the RMS of the acceleration and angular velocity and for the tremor amplitude in the mental task and kinetic tremor. The power in the tremor band of the mental task was significantly different in the on-state as well. However, the parameter values increase after medication use.

Table 3.3: *Comparison of the parameter values in the off- and on-medication state and the mean differences and SDs between off- and on-medication state for each task and parameter. Patients with no difference in UPDRS score between off- and on-measurement were included. The number of patients included, n, are given for each task. P-values below 0.05 are printed in bold.*

		Peak power (dB)	Power band (dB)	RMS acceleration (m/s^2)	RMS angular velocity (rad/s)	Tremor amplitude (m)
Relaxing task (n=12)	p-value	0.47	0.62	0.62	0.85	0.23
	difference ±SD	$4.3*10^{-3}$ (186%) ±0.02	0.079 (259%) ±0.33	-0.032 (-18%) ±0.25	$4.3*10^{-3}$ (12%) ±0.041	$-0.71*10^{-3}$ (-17%) $\pm 5.6*10^{-3}$
Mental task (n=12)	p-value	0.11	**0.043**	**0.027**	**0.016**	**0.077**
	difference ±SD	0.041 (103%) ±0.13	0.39 (103%) ±1.22	0.18 (233%) ±.26	0.081 (709%) ±0.16	$6.0*10^{-3}$ (361%) ±0.012
Posture tremor (n=13)	p-value	0.41	0.68	0.17	0.58	0.64
	difference ±SD	-0.013 (-57%) ±0.042	-0.20 (-49%) ±0.70	-0.11 (-32%) ±0.24	$-8.4*10^{-3}$ (-17%) ±0.039	$0.55*10^{-3}$ (27%) $\pm 3.5*10^{-3}$
Kinetic tremor (n=16)	p-value	0.21	0.063	**$7.2*10^{-3}$**	**$6.1*10^{-3}$**	**$4.4*10^{-4}$**
	difference ±SD	0.65 (95%) ±1.79	15.48 (93%) ±33	0.83 (53%) ±1.15	0.18 (51%) ±0.20	0.012 (73%) ±0.078
	sd	1.79	33.35	1.15	0.20	0.078

3.1.2 Bradykinesia

A total of 16 patients had a difference in UPDRS score between off- and on-medication state for the finger tapping task. For the RMS of the angular velocity, the off-on difference was significant. The mean difference is positive indicating less bradykinesia after medication use for the finger tapping task. No significant differences were found for the other parameters. For the pro- and supination task, 19 patients had a difference in UPDRS score. The p-values for the RMS of the acceleration and the RMS of the angular velocity are 0.0153 and 0.0019 respectively and for the SD of the movement time 0.027 and thus significant. The mean difference for the RMS of the acceleration and angular velocity are positive meaning that pro- and supination movements were faster in the on-medication state. The decrease in the SD of the movement time indicates that the rhythm of movement was more constant in the on-state. For the closing task, 16 patients had a difference in UPDRS score. Significant off-on differences were found for the RMS of the angular velocity and for the movement time. The mean difference for the RMS of the angular velocity is positive suggesting an increase in value in the on-measurement. For the movement time, the difference between off- and on-state is negative for each task meaning a decrease in movement time after medication use. Both results showed that the closing task could be faster performed in the on-medication state. In Table 3.4, all p-values are given as well as all mean differences and SDs for the parameters during each task.

Table 3.4: *Comparison of the parameter values between the off- and on-medication state and the mean differences and SDs between off- and on-medication state for each task and parameter. Patients with a difference in UPDRS score between off- and on-measurement were included. The number of patients included, n, are given for each task. P-values below 0.05 are printed in bold.*

		RMS acceleration (m/s^2)	RMS angular velocity (rad/s)	amplitude (m)	movement time (s)	SD movement time (s)	number of stops
Finger tapping task (n=16)	p-value	0.098	**0.018**	0.088	0.070	0.41	0.25
	difference ±SD	0.66 (14%) ±2.1	0.76 (24%) ±1.14	0.018 (39%) ±0.045	-0.10 (20%) ±0.24	-0.029 (-20%) ±0.19	-0.19 (-75%) ±0.40
Pro-/supination task (n=19)	p-value	**0.015**	**$1.9*10^{-3}$**	-	0.059	**0.027**	1
	difference ±SD	3.1 (56%) ±5.05	2.0 (55%) ±2.4	-	-0.088 (-19%) ±0.22	-0.088 (-27%) ±0.28	0
Closing task (n=16)	p-value	0.056	**$5.4*10^{-3}$**	0.49	**$9.7*10^{-3}$**	0.079	1
	difference ±SD	1.3 (27%) ±2.9	1.7 (40%) ±2.1	$6.1*10^{-3}$ (5.6%) ±0.034	-0.15 (-20%) ±0.19	-0.072 (-36%) ±0.15	0.063 (-) ±0.25

In Figure 3.3, the parameter values of the off- and on-measurement are visualised. Figures containing data of the finger tapping and closing task can be found Figures C.5 and C.9 in Appendix C.1.2.

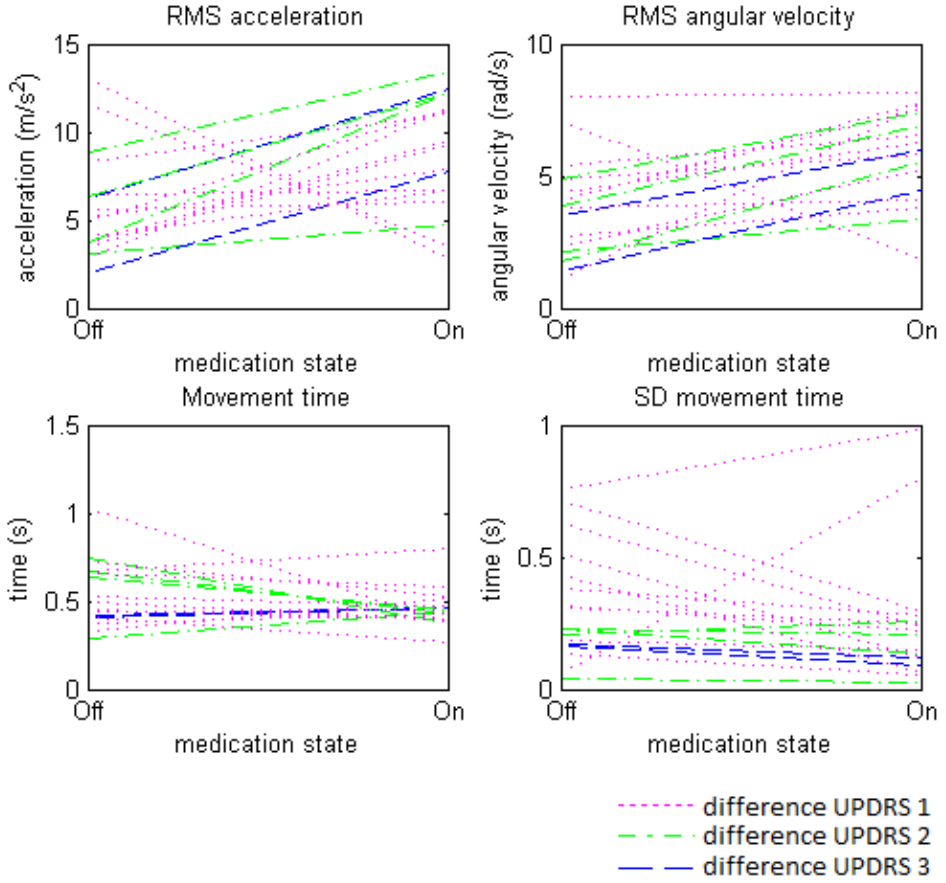


Figure 3.3: *Parameter values of the off- and on-measurement for the pro- and supination task. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement.*

For the finger tapping task, six patients did not have a difference in UPDRS score. For the pro- and supination task, two patients were included and for the closing task five patients. With this limited number of patients, no significant results were found. In Table C.1 in Appendix C.1.2, the results of the comparisons between off- and on-medication state for the bradykinesia parameters are given when there was no difference in UPDRS score between the off- and on-measurement.

In Figure 3.4, the parameter values of the finger tapping task in the off- and on-state are visualized for patients with no difference in UPDRS score. In 4 of the 6 patients, an increase in RMS of the acceleration, RMS of the angular velocity and decrease in movement time after medication use is seen which indicates faster movements in the on-medication state. Figures containing data of the pro- and supination task and the closing task can be found in Figures C.8 and C.9 respectively in Appendix C.1.2.

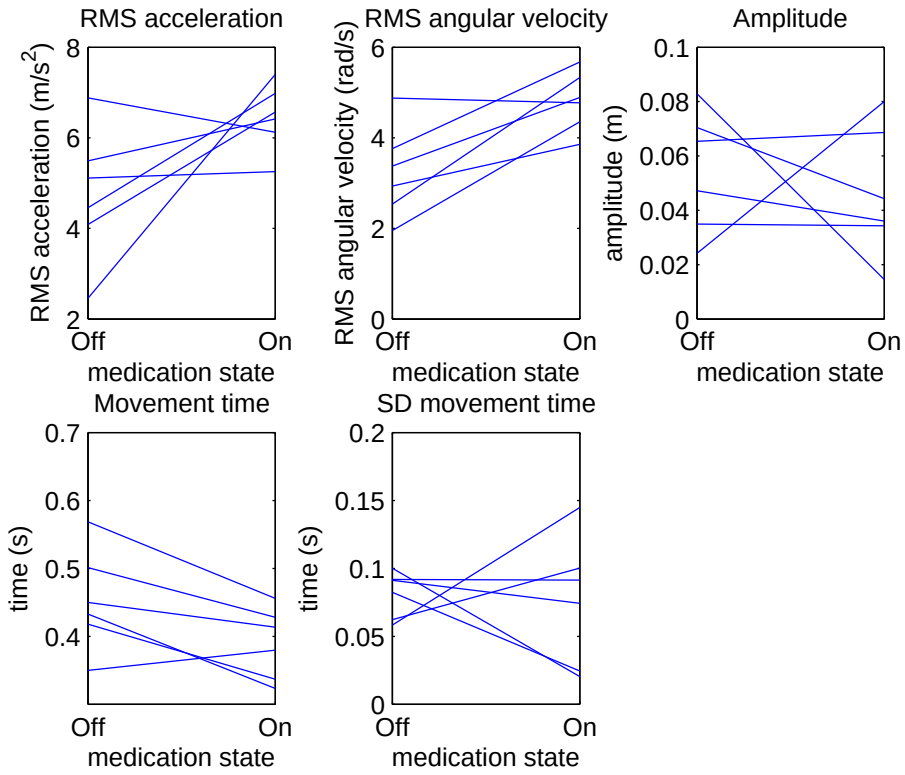


Figure 3.4: *Parameter values of the on- and off-measurement for the finger tapping task when there was no difference in UPDRS score.*

3.1.3 Rigidity

A total of 13 patients had a difference in UPDRS score for rigidity between the off- and on-medication state. For the first task (without contralateral activation), significant results were found for the torque at 60 degrees, the range of motion and viscous damping constant. However, for the second task with contralateral activation all p-values, except for the stiffness, were significant. In Table 3.5 all p-values are given as well as the mean differences and SDs. The parameter values decrease in the on-state for the torque, impedance, stiffness and viscous damping constant in both tasks. This means less torque was needed to extend the wrist, less resistance was present, the wrist was less stiff and less damping was present in the on-medication state. For the range of motion, the value increases in the on-measurement and thus the range of motion was larger with medication.

Table 3.5: *Comparison of the parameter values in the off- and on-medication state and the mean differences and SDs between off- and on-medication state for each task and parameter. Thirteen patients with a difference in UPDRS score between off- and on-measurement were included. P-values below 0.05 are printed in bold.*

		Torque (Nm)		Range of motion (deg)	Impedance (Nm/deg)	Stiffness (Nm/rad)	Viscous damping constant (Nm/rad/s)
		60	30				
Wrist extension	p-value	**$6.1*10^{-3}$**	0.11	**$6.1*10^{-3}$**	0.080	0.76	**$8.1*10^{-3}$**
	difference ±SD	-0.61 (-40%) ±0.83	-0.26 (-36%) ±0.53	15 (19%) ±18	$-9.7*10^{-3}$ (-37%) ±0.016	-0.37 (-298%) ±0.97	$-8.9*10^{-3}$ (-33%) ±0.011
Wrist extension with contralateral activation	p-value	**$6.1*10^{-3}$**	**$8.1*10^{-3}$**	**$8.1*10^{-3}$**	**0.022**	0.24	**$3.4*10^{-3}$**
	difference ±SD	-0.87 (-46%) ±0.87	-0.50 (-56%) ±0.55	17 (22%) ±18	-0.016 (-50%) ±0.022	-0.62 (-214%) ±1.9	$-9.4*10^{-3}$ (-30%) ±0.013

In Figure 3.5, the parameter values of the off- and on-measurement for the wrist extension with contralateral activation are visualised. In Figure C.13 in Appendix C.1.3, the visualisation of the parameter values of the off- and on-measurement of the wrist extension without contralateral activation can be found.

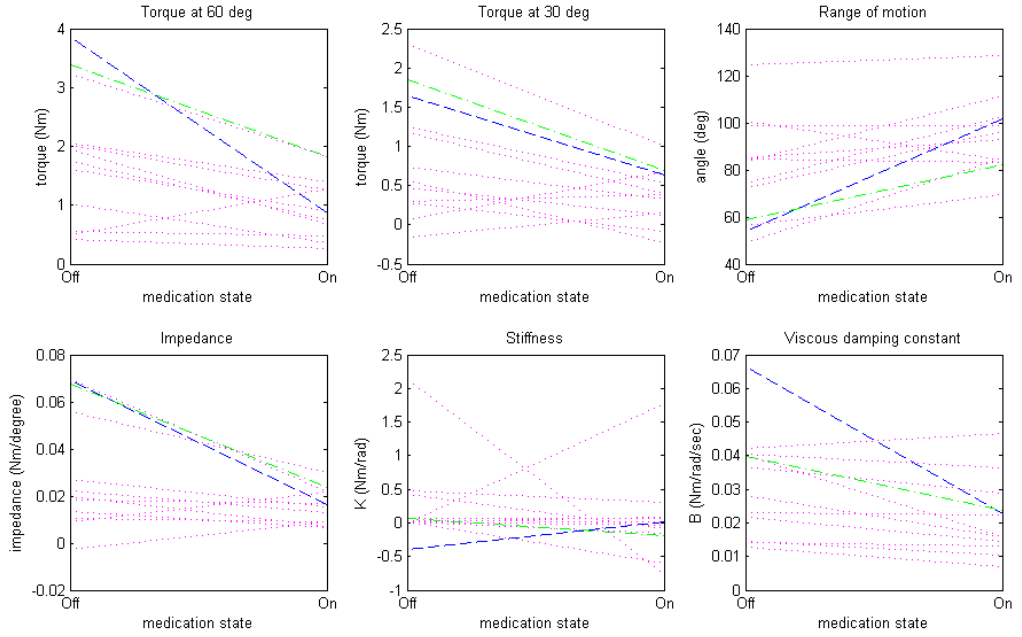


Figure 3.5: *Parameter values of the off- and on-measurement for the wrist extension with contralateral activation. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement.*

For rigidity, four patients had no difference in UPDRS score. No significant results were found when off- and on-measurement were compared. In Table C.2 in Appendix C.1.3, the obtained results are given.

In Figure 3.6, the parameter values in off- and on-state are visualized for patients with no difference in UPDRS score for the rigidity task with contralateral activation. In all patients, a decrease in torque, stiffness and viscous damping constant is seen. There was thus less torque needed to extend the wrist, less resistance was present and less damping was present as well. An increase in range of motion and impedance is seen after medication use. The figure containing data of the rigidity task without contralateral activation can be found in Figure C.12.

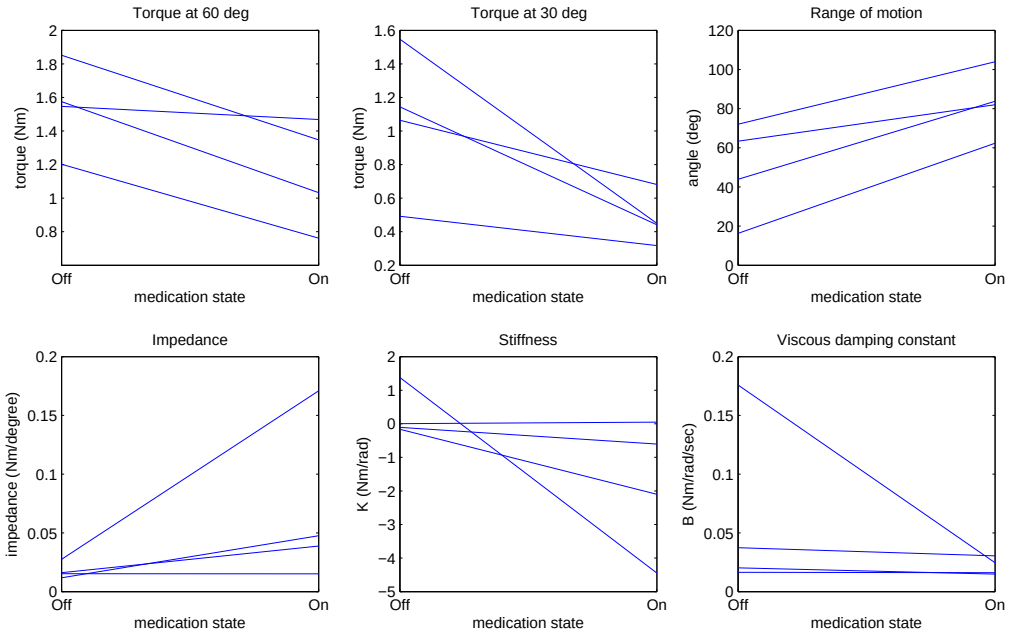


Figure 3.6: *Off- and on-parameter values for the rigidity task with contralateral activation when there was no difference detecting with the UPDRS.*

3.2 Relation with UPDRS

3.2.1 Tremor

Tremor amplitude

To investigate the relation between the tremor parameters and the UPDRS score for tremor amplitude, the UPDRS scores in the off-medication state of 21 patients with corresponding measurement values were included to find a correlation with the UPDRS. The Spearman's correlation coefficients and their p-values can be found in Table 3.6 for tremor. All relations are positive and the values of the parameters thus increase with a higher UPDRS score. The peak power and the power in the tremor band both correlated significantly with the UPDRS scores for all tasks. Besides, all parameter values for the mental task correlated with the UPDRS scores as well. For the mental task, the results can be seen in Figure C.15. Furthermore, the RMS of the angular velocity for posture and kinetic tremor and the RMS of the acceleration for the kinetic tremor correlated with the UPDRS.

See Figure C.15, C.17 and C.18 for a visual representation of the relation between the tremor parameters and the UPDRS scores for the relaxing task, posture tremor and kinetic tremor in Appendix C.2.

Table 3.6: *The correlation coefficients between the tremor parameters and UPDRS scores. Twenty-one patients were included. P-values below 0.05 are printed in bold.*

		Peak power	Power band	RMS acceleration	RMS angular velocity	Tremor amplitude
Relaxing task	r	0.48	0.43	0.35	0.41	0.051
	p-value	**0.025**	**0.049**	0.12	0.064	0.83
Mental task	r	0.60	0.61	0.73	0.70	0.55
	p-value	$\mathbf{3.2{*}10^{-3}}$	$\mathbf{2.3{*}10^{-3}}$	$\mathbf{1.6{*}10^{-4}}$	$\mathbf{4.1{*}10^{-4}}$	$\mathbf{9.7{*}10^{-3}}$
Posture tremor	r	0.43	0.43	0.36	0.47	0.33
	p-value	**0.045**	**0.043**	0.11	**0.031**	0.14
Kinetic tremor	r	0.63	0.67	0.49	0.54	0.17
	p-value	$\mathbf{2.0{*}10^{-3}}$	$\mathbf{5.7{*}10^{-4}}$	**0.023**	**0.011**	0.45

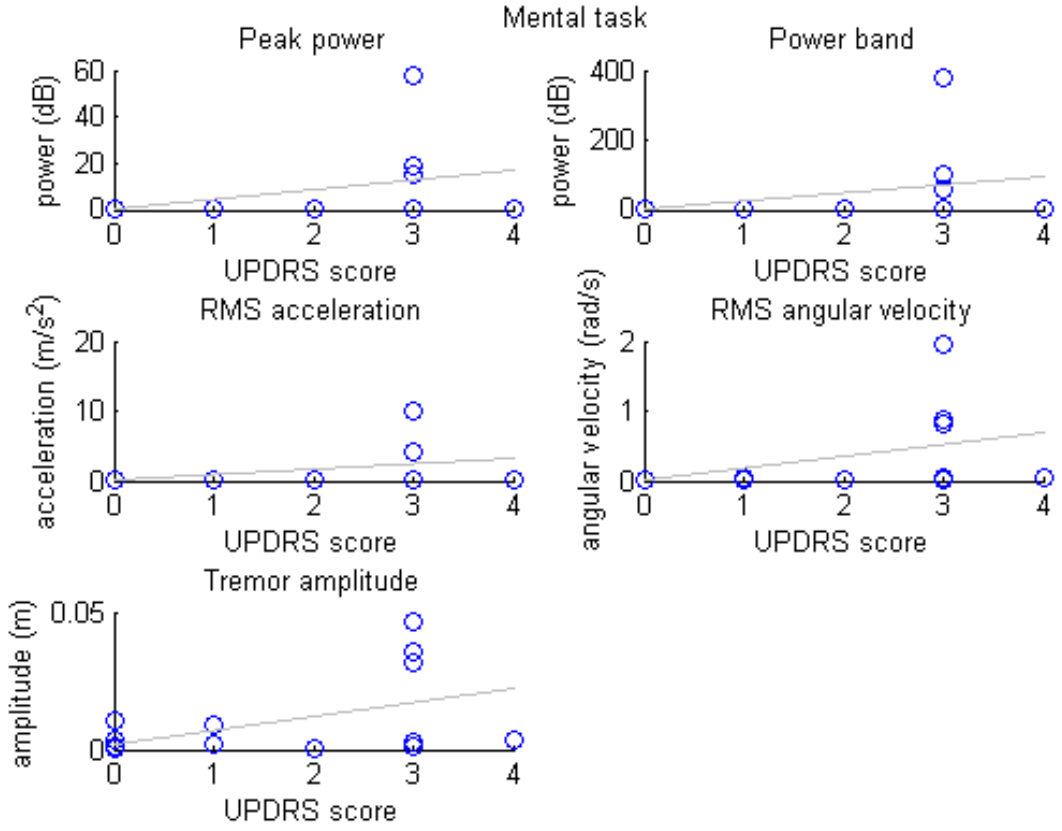


Figure 3.7: *Scatter plot with least-squares line of the obtained results for the mental task and the UPDRS scores for the tremor amplitude. Twenty-one patients were included.*

The differences between individual UPDRS scores are studied as well. The p-values are given in Table 3.7. For the mental task, the peak powers of the 0 and 1 UPDRS scores are significantly different from each other. For kinetic tremor, the RMS of the angular velocity was significantly different between the UPDRS scores 0 and 1.

Table 3.7: *Comparison of the individual UPDRS scores. The number of patients included, n, are given for each group of UPDRS score. P-values below 0.05/i, with i the number of comparisons, are printed in bold.*

	UPDRS groups	Peak power	Power band	RMS acceleration	RMS angular velocity	Tremor amplitude
Relaxing task	0(n=12)-1(n=3)	0.84	0.84	0.36	0.63	0.95
	1(n=3)-2(n=1)	1	1	1	1	0.5
	2(n=1)-3(n=5)	0.33	0.33	0.33	0.33	0.33
	3(n=5)-4(n=1)	0.67	0.67	0.33	0.33	0.33
Mental task	0(n=12)-1(n=3)	**$8.8*10^{-3}$**	0.048	0.29	0.048	0.14
	1(n=3)-2(n=1)	0.5	0.5	0.5	0.5	0.5
	2(n=1)-3(n=5)	0.33	0.33	0.33	0.33	0.33
	3(n=5)-4(n=1)	0.67	1	0.67	0.67	1
Posture tremor	0(n=12)-1(n=6)	0.62	0.89	0.96	0.75	0.96
	1(n=6)-2(n=1)	0.29	0.29	0.29	0.29	0.29
	2(n=1)-3(n=3)	1	1	1	1	1
Kinetic tremor	0(n=14)-1(n=4)	0.13	0.08	0.079	**0.018**	0.16
	1(n=4)-2(n=4)	0.69	0.69	0.49	0.69	0.34

Tremor persistence

In Table 3.8, the Spearman's correlation coefficients and their p-values are given when tremor persistence is used as the UPDRS score for resting tremor. For the relaxing task, only a correlation between the RMS of the angular velocity and UPDRS was found. During the mental task, all parameters were significantly correlated with the UPDRS scores for tremor persistence. All relations are positive.

Table 3.8: *The correlation coefficients between the tremor parameters for rest tremor and UPDRS scores for tremor persistence. Twenty-one patients were included. P-values below 0.05 are printed in bold.*

		Peak power	Power band	RMS acceleration	RMS angular velocity
Relaxing task	r	0.37	0.29	0.36	0.48
	p-value	0.086	0.18	0.098	**0.024**
Mental task	r	0.73	0.68	0.56	0.73
	p-value	**$1.1*10^{-4}$**	**$4.3*10^{-4}$**	**0.0071**	**$1.1* 10^{-4}$**

3.2.2 Bradykinesia

A total of 21 UPDRS scores with corresponding measurement values are included to study the correlation between the bradykinesia values and the UPDRS. The Spearman's correlation coefficients and their p-values can be found in Table 3.9.

For the finger tapping task, the no significant correlations were found. The relations between the parameters and the UPDRS scores are negative for the RMS of the acceleration, RMS of the angular velocity and amplitude which mean that a higher value corresponds with a lower score on the UPDRS. For the movement time, SD of the movement time and number of stops, this relation is positive.

For the pro- and supination task, the correlation between the RMS of the acceleration and the UPDRS was significant. All relations were negative and thus a higher value of the parameter corresponds with a lower score on the UPDRS. This is also visualised in Figure 3.8.

For the closing task, no significant correlations were found. The relations between the parameters and the UPDRS scores are negative for the RMS of the acceleration, the RMS of the angular velocity and the amplitude and positive for the movement time and SD of the movement time.

Table 3.9: *The correlation coefficients of the bradykinesia parameters and UPDRS scores. Twenty-one patients were included. P-values below 0.05 are printed in bold.*

		RMS acceleration	RMS angular velocity	amplitude	movement time	SD movement time	number of stops
Finger tapping task	r	-0.29	-0.40	-0.31	0.13	0.42	0.34
	p-value	0.19	0.071	0.18	0.58	0.055	0.13
Pro-/supination task	r	-0.55	-0.38	-	-0.12	-0.11	-
	p-value	**0.010**	0.087	-	0.62	0.63	-
Closing task	r	-0.16	-0.42	-0.041	0.23	0.13	-
	p-value	0.48	0.060	0.86	0.32	0.56	-

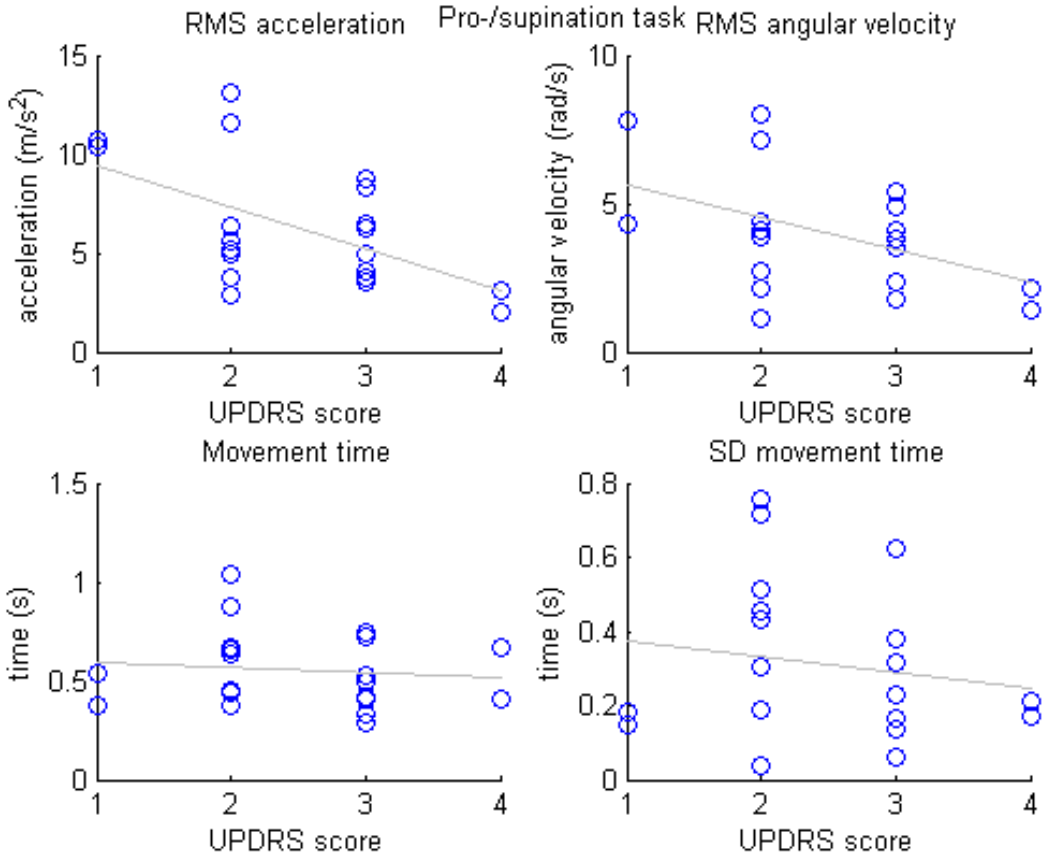


Figure 3.8: *Scatter plot with least-squares line of the obtained results for the pro- and supination task and their UPDRS score. Twenty-one patients were included.*

For a visual representation of the relation between the bradykinesia parameters and the UPDRS scores for the finger tapping and closing task, see Figures C.19 and C.21 in Appendix C.2.

The difference between individual UPDRS scores are analysed as well. For the finger tapping task, a significant difference was found between UPDRS scores 1 and 2 for the SD of the movement time. For the pro- and supination task, a significant difference between UPDRS scores 3 and 4 was found for the RMS of the acceleration. In Table 3.10 are all p-values given.

Table 3.10: *Comparison of the individual UPDRS scores. The number of patients included, n, are given for each group of UPDRS score. P-values below 0.05/i, with i the number of comparisons, are printed in bold.*

	UPDRS groups	RMS acceleration	RMS angular velocity	amplitude	movement time	SD movement time	number of stops
Finger tapping task	1(n=10)-2(n=6)	0.15	0.15	0.26	0.042	**$2.5*10^{-4}$**	0.25
	2(n=6)-3(n=6)	0.48	1	0.31	0.24	0.39	1
Pro-/supination task	1(n=1)-2(n=9)	0.33	0.33	-	0.22	0.32	1
	2(n=9)-3(n=8)	0.89	0.96	-	0.14	0.37	1
	3(n=8)-4(n=3)	**0.012**	0.024	-	0.076	0.78	1
Closing task	0(n=1)-1(n=9)	1	0.80	0.20	0.60	0.40	1
	1(n=9)-2(n=8)	0.74	0.16	0.37	0.96	0.67	1
	2(n=8)-3(n=4)	0.93	0.28	0.46	0.15	0.28	1

3.2.3 Rigidity

Nineteen patients were included to study the relation between the UPDRS and the rigidity parameters. The Spearman's correlation coefficients and their p-values can be found in Table 3.11.

No significant correlations between the parameters and the UPDRS scores were found for both rigidity tasks. For the first task, without contralateral activation, the relation between the UPDRS scores and the torque, range of motion, impedance, and viscous damping constant are positive and negative for the stiffness. For the wrist extension with contralateral activation, the relation between the UPDRS scores and the torque, impedance, stiffness and viscous damping constant are positive and negative for the range of motion. This means more torque is needed, more resistance is present, more stiffness is present, more damping is present and the range of motion is smaller with a higher UPDRS score. These results are shown in Figure 3.9.

Table 3.11: *The correlation coefficients between the rigidity parameters and UPDRS scores. Nineteen patients were included. P-values below 0.05 are printed in bold.*

		Torque		Range of motion	Impedance	Stiffness	Viscous damping constant
		60	30				
Wrist extension	r	0.37	0.15	0.053	0.032	-0.11	0.17
	p-value	0.11	0.54	0.83	0.89	0.66	0.48
Wrist extension with contralateral activation	r	0.39	0.27	-0.012	0.19	0.13	0.40
	p-value	0.097	0.27	0.96	0.45	0.76	0.59

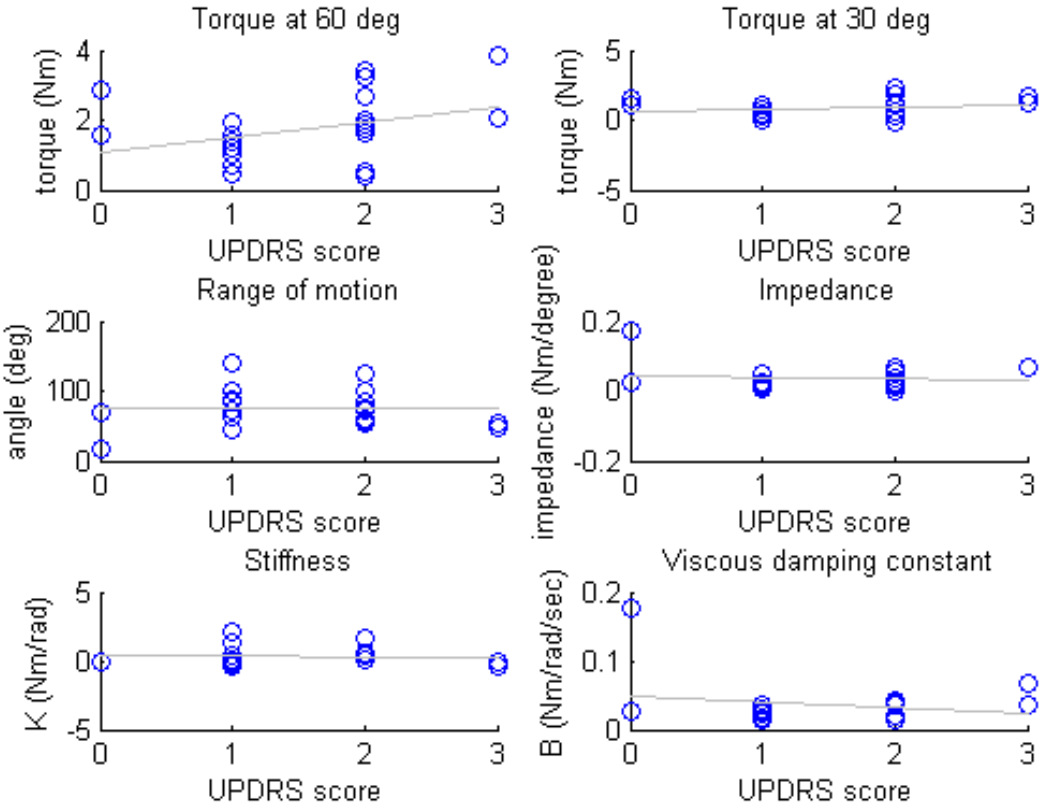


Figure 3.9: *Scatter plot with least-squares line of the obtained results for the rigidity task with contralateral activation and their UPDRS score. Nineteen patients were included.*

See Figure C.22 in Appendix C.2 for a visual representation of the relation between the rigidity parameters and the UPDRS scores for the wrist extension without contralateral activation.

The difference between individual UPDRS scores are studies as well. In Table 3.12 are all p-values given. No significant results were found.

Table 3.12: *Comparison of the individual UPDRS scores. The number of patients, n, are given for each group. P-values below 0.05/i, with i the number of comparisons are printed in bold.*

	UPDRS groups	Torque		Range of motion	Impedance	Stiffness	Viscous damping constant
		60	30				
Wrist extension	0(n=1)-1(n=5)	0.33	0.33	0.33	0.33	0.67	0.33
	1(n=5)-2(n=9)	0.52	0.52	0.90	0.70	0.042	0.61
	2(n=9)-3(n=2)	0.15	0.33	0.15	0.32	0.44	0.22
Wrist extension with contralateral activation	0(n=1)-1(n=5)	1	0.33	0.33	0.33	0.67	0.33
	1(n=5)-2(n=9)	0.52	0.79	0.61	0.70	1	0.70
	2(n=9)-3(n=2)	0.15	0.33	0.036	0.036	0.073	0.33

3.3 Reliability and agreement

3.3.1 Tremor

For tremor, 21 patients were included to test the reliability and agreement. The ICCs and SEM values are given in Table 3.13.

The ICCs for the intra-rater reliability are higher than 0.7 for each parameter of the relaxing and mental task. The ICCs for the intra-rater reliability of the posture and kinetic tremor are similar: ICCs of the RMS of the acceleration, RMS of the angular velocity and the tremor amplitude are higher than 0.7.

For the inter-rater reliability, the ICCs of the RMS of the acceleration and angular velocity are higher than 0.7 for all tasks. Furthermore, the ICC of the tremor amplitude is higher than 0.7 for the mental task as well as the ICC of the peak power and power in the tremor band.

The highest SEM value (9.0 dB) for the peak power was found for the intra-rater measurements of the mental task. For the power in the tremor band this was 63.2 dB for the intra-rater measurements of posture tremor. For the RMS of the acceleration and the RMS of the angular velocity, the highest SEM values are 1.0 m/s^2 and 0.3 rad/s respectively and were found for the intra-rater measurements of the mental task. The highest SEM value (0.01 m) for the tremor amplitude was found for the inter-rater measurements of the relaxing task.

Table 3.13: *Intra- and inter-rater reliability and agreement for the tremor parameters. Twenty-one patients were included. ICC higher than 0.7 are printed bold.*

			Peak power (dB)	Power band (dB)	RMS acceleration (m/s^2)	RMS angular velocity (rad/s)	Tremor amplitude (m)
Relaxing task	Intra	ICC	**0.90**	**0.88**	**0.84**	**0.86**	**0.80**
		SEM	1.4	13.5	0.8	0.1	$5.2*10^{-3}$
	Inter	ICC	0.46	0.53	**0.89**	**0.98**	0.38
		SEM	2.0	16.0	0.4	0.03	0.010
Mental task	Intra	ICC	**0.71**	**0.89**	**0.84**	**0.76**	**0.90**
		SEM	9.0	29.8	1.0	0.3	$4.8*10^{-3}$
	Inter	ICC	0.49	0.68	**0.97**	**0.97**	**0.90**
		SEM	6.9	35.8	0.4	0.08	$4.0*10^{-3}$
Posture tremor	Intra	ICC	0.05	0.07	**0.94**	**0.75**	**0.94**
		SEM	7.5	63.2	0.6	0.2	$3.4*10^{-3}$
	Inter	ICC	0.14	0.18	**0.96**	**0.84**	**0.98**
		SEM	2.8	29.3	0.5	0.12	0.002
Kinetic tremor	Intra	ICC	0.69	0.59	**0.77**	**0.76**	**0.75**
		SEM	0.8	20.1	0.5	0.1	$3.4*10^{-3}$
	Inter	ICC	**0.78**	**0.71**	**0.73**	**0.78**	0.69
		SEM	0.7	17.2	0.6	0.12	$4.0*10^{-3}$

3.3.2 Bradykinesia

For bradykinesia, 21 patients were included to test the reliability and agreement. The ICCs and SEM values are given in Table 3.14.

The ICCs within (intra) and between (inter) raters were all higher than 0.7 for the RMS of the angular velocity and the amplitude for all bradykinesia tasks. For the finger tapping and pro- and supination tasks, ICCs of the RMS of the accleration for both inter- and intra-rater were higher than 0.7. For the movement time, the ICCs were higher than 0.7 for the intra-rater reliability for the pro- and supination and closing task and for the inter-rater reliability for the finger tapping task.

The SEM values were consistently higher for the intra-rater measurements with respect to the inter-rater measurements for the finger tapping task. For the closing task, the SEM values were consistently higher for the inter-rater measurements with respect to the intra-rater measurements. The highest SEM value for the RMS of the acceleration is 0.91 m/s^2 for the inter-rater measurements of the pro- and supination task. For the RMS of the angular velocity and the movement time, the highest SEM values are 0.75 rad/s and 0.12 s respectively for the inter-rater measurements of the closing task. The highest SEM value for the amplitude was 0.012 m for both the intra- and inter-rater measurements of the closing task.

Table 3.14: *Intra- and inter-rater reliability and agreement for the bradykinesia parameters. Twenty-one patients were included.*

			RMS acceleration (m/s^2)	RMS angular velocity (rad/s)	amplitude (m)	movement time (s)	SD movement time (s)	number of stops
Finger tapping	Intra	ICC	**0.85**	**0.87**	**0.82**	0.56	0.10	-0.21
		SEM	0.57	0.38	0.010	0.11	0.16	0.42
	Inter	ICC	**0.90**	**0.92**	**0.72**	**0.84**	0.34	0.15
		SEM	0.52	0.31	0.01	0.08	0.12	0.35
Pro-/supination	Intra	ICC	**0.92**	**0.96**	-	**0.77**	0.39	-
		SEM	0.88	0.39	-	0.10	0.19	-
	Inter	ICC	**0.91**	**0.91**	-	0.67	0.57	-
		SEM	0.91	0.54	-	0.10	0.11	-
Closing task	Intra	ICC	0.60	**0.85**	**0.78**	**0.75**	0.51	-
		SEM	1.11	0.64	0.012	0.10	0.10	-
	Inter	ICC	0.70	**0.79**	**0.72**	0.64	0.27	-
		SEM	0.71	0.75	0.012	0.12	0.10	-

3.3.3 Rigidity

For rigidity, 17 patients were included to test the reliability and agreement. The ICCs and SEM values are given in Table 3.15.

The ICCs were higher than 0.7 for the torque at 60 degrees extension, range of motion, impedance and viscous damping constant for the intra-rater measurements of both tasks. For the first task without contralateral activation, the ICC of the intra-rater measurements is higher than 0.7 as well for the torque at 30 degrees extension. For the inter-rater measurements, all ICCs were lower than 0.7.

The SEM values were all higher for the inter-rater measurements with respect to the intra-rater measurements. The highest SEM values were 15.91 deg and 0.0093 Nm/rad/s for the range of motion and the viscous damping constant respectively for the first rigidity task without contralateral activation and 0.90 Nm, 0.024 Nm/deg and 0.64 Nm/rad for the torque, impedance and stiffness respectively and were measured during the extension task with contralateral activation.

Table 3.15: *Intra- and inter-rater reliability and agreement for the bradykinesia parameters. Seventeen patients were included.*

			Torque (Nm)		Range of motion (deg)	Impedance (Nm/deg)	Stiffness (Nm/rad)	Viscous damping constant (Nm/rad/s)
			60	30				
Wrist extension	Intra	ICC	**0.84**	**0.74**	**0.90**	**0.83**	0.47	**0.73**
		SEM	0.34	0.30	6.8	$7.4*10^{-3}$	0.38	$6.3*10^{-3}$
	Inter	ICC	-0.04	-0.17	0.42	-0.05	-0.74	0.15
		SEM	0.76	0.52	16	0.018	0.56	$9.3*10^{-3}$
Wrist extension with contralateral activation	Intra	ICC	**0.83**	0.66	**0.87**	**0.87**	-0.068	**0.83**
		SEM	0.39	0.39	8.0	$7.8*10^{-3}$	0.55	$6.1*10^{-3}$
	Inter	ICC	0.17	0.019	0.51	0.047	-0.47	0.18
		SEM	0.90	0.68	14	0.024	0.64	$8.8*10^{-3}$

CHAPTER 4

DISCUSSION

In this study, the PowerGlove in combination with a force sensor was used for quantification of tremor, bradykinesia and rigidity in PD patients. This study represents the first step toward a system that can accurately quantify PD motor symptoms.

4.1 Tremor

For the PowerGlove system to be useful in DBS surgery, it must at least be able to reflect a reduction in UPDRS score. Differences between off- and on-medication state could not be measured for tremor. Scanlon et al. [30] included 16 PD patients and 8 controls and found no significant differences between off- and on-state as well. Sprdlik et al. [26] included 28 essential tremor patients and 25 controls and found significant differences between those groups. In this study, only 10 patients with resting tremor, nine patients with posture tremor and six patients with kinetic tremor were included and not all of these patients (visually) showed tremor during the measurements. The non-significant results may be due to the small group of patients who presented tremor during the measurement. The mean differences between the off- and on-measurement of the peak power and power of the tremor band were higher than 85% and of the RMS of the acceleration and angular velocity higher than 50%. However, this was not significant. This could be due to the high SDs of the differences (see table 3.1).

The differences in parameter values between off- and on-medication state were all negative except for kinetic tremor, meaning all parameters had a higher mean value in the off-state. This suggest that tremor was less present in the on-medication state but this was not significant. Values of individual patients can be seen in Figure 3.2 and this shows that when the UPDRS score decrease with a value of 3, the parameter values also decrease. This indicates that the PowerGlove could possibly be able to measure the effect of medication on resting tremor. Posture and kinetic tremor do not respond to levodopa. Differences in off- and on-medication state are therefore not expected which is in accordance with the obtained results.

Significant results were found for kinetic tremor during the bradykinesia tasks. For the closing task all parameters were significantly different in the on-state compared to the off-state. However, the mean difference suggest that tremor was more present in the on-state. This is probably the movement of the task which was not completely filtered out of the data. It is also possible that levodopa induced dyskinesia was present and was not completely filtered out of the data as well.

Small distinctions in tremor severity between off- and on-state could not be assessed with the PowerGlove when there was no difference in UPDRS score between the off- and on-state. It is likely that many patients who did not have a difference in UPDRS, did not have tremor at all.

When related to the tremor amplitude score of the UPDRS, correlations were found for the peak power and power in the tremor band for the relaxing task. With a mental task, correlations were found for all parameters. For the relaxing task, only the RMS of the angular velocity correlated with UPDRS score of the tremor persistence. With a mental task, all parameters correlated with the tremor persistence. When the patient is distracted with a mental task, the tremor increases [67] and it is therefore expected that stronger correlations will be found with a mental task and this is shown in the results as well.

For posture tremor, correlations between the UPDRS and the RMS of the angular velocity, peak power and power in the tremor band were found. For kinetic tremor, correlations between the UPDRS and the RMS of the angular velocity, RMS of the acceleration, peak power and power in the tremor band were found. This is in accordance with the results Mostile et al. [33] and Heldman et al. [32] obtained.

In contrast to the off-on differences, where no significant results were found, significant correlations were found between the parameters and the UPDRS. A total of 21 patients were included in this test. Twelve patients were included with an UPDRS score of 0 for resting tremor, 13 patients with a UPDRS score of 0 for posture tremor and 16 patients with an UPDRS score of 0 for kinetic tremor. Relations

were significant because when the UPDRS score is 0, tremor was not measured with the PowerGlove as well. The results also showed that an UPDRS score of 0 is significantly different from an UPDRS of 1 for the peak power in the mental task and for the RMS of the angular velocity of the kinetic tremor. These findings indicate that with the use of these parameters, the PowerGlove might be able to detect tremor.

The reliability for intra- and inter-rater measurements were both high for the RMS of the acceleration and the RMS of the angular velocity. The SEM values showed similar agreement. This means that the reliability of these parameters is not dependent of the rater.

The lowest ICCs were observed for the peak power and power in the tremor band for the intra-rater measurement of posture tremor. This could be caused by the large measurement errors as can be concluded from the SEM values (7.5 dB and 63.2 dB for the peak power and power in the tremor band respectively) which are large compared to the on/off difference that is desired to be measured. Besides, the ICCs for the intra-rater measurements were high ($>$0.7) for the peak power and power in the tremor band for the relaxing task and mental task but low ($<$0.7) for the inter-rater measurements. However, SEM values of both intra- and inter-rater measurements are low compared to the off/on differences as can be seen in Figure 3.2. It can therefore be concluded that the low ICCs are caused by the small variability between subjects. The same conclusion can be made for the tremor amplitude where the ICC of the inter-rater measurements is low but the SEM values are low compared to the on/off difference as well.

4.2 Bradykinesia

For bradykinesia, the RMS of the angular velocity in off-medication state during the finger tapping task, pro- and supination task and the closing task was significantly different from on medication state. This also applies for the RMS of the acceleration and the SD of the movement time during the pro- and supination task and the movement time during the pro- and supination and closing task. The values of the RMS of the acceleration and angular velocity and amplitudes increased in the on-state and the movement time and SD decreased. This is as expected since this all indicates that medication reduced bradykinesia.

When the UPDRS was not able to detect changes, no significant differences were found with the PowerGlove either. However, the mean value of the RMS of the acceleration and angular velocity increased in the on-state compared to the off-state and the movement time decreased. In Figure 3.4 is seen that in 4 of the 6 individual values of the RMS of the acceleration and angular velocity increased in the on-state compared to the off-state and the movement time decreased. This may indicate that the PowerGlove might have a better resolution.

Correlations with the UPDRS were found for the RMS of acceleration for the pro- and supination task. This is in accordance with the results of Salarian et al. [31] who showed that the RMS of the angular velocity is correlated with the UPDRS but the average range of motion is not.

The number of stops was not a very useful parameter. Since this parameter is also used in the UPDRS scoring it is important to take this parameter into account when using the PowerGlove system. Only a few stops were detected during the measurements and therefore no reliable results were found. The boundary was defined by inspection of the data of a patient which contained a clear stop. However, this boundary may be too strict to detect the stops. It is also possible that the patients did not show as much stops during the measurements as they would during activities of daily living (like handwriting, eating, dressing and self-care).

The number repetitions was different for every measurement trial and for every patient. For bradykinesia, the change in amplitude over the time course is an indication of the severity of bradykinesia. More repetitions therefore results in overestimation of the bradykinesia severity whereas less repetitions results in underestimation of the severity.

The ICCs showed good reliability for both the intra- and inter-rater measurement for the RMS of the angular velocity and amplitude. The intra- and inter-rater reliability for the RMS of the acceleration was good for both the finger tapping and pro- and supination task but not for the closing task. The SEM values are low for the closing task compared to the smallest on/off difference thus the low ICCs are the result of small variations between subjects. The inter-rater reliability of the movement time was low for the pro- and supination task and closing task and the intra-rater reliability was low for the movement time for the finger tapping task. The SEM values are all small compared to the on/off differences as can be seen in Figure 3.3. The low ICC is thus caused by small inter-subject differences.

4.3 Rigidity

For the rigidity, significant differences between the off- and on-measurement were found for the torque at 60 degrees extension, range of motion and viscous damping constant between medication states. When the wrist was extended with contralateral activation, significant differences were found for the torque at 60 and 30 degrees extension, range of motion, impedance and viscous damping constant. The reinforcing manoeuvre (contralateral activation) thus facilitated detection of rigidity with these parameters.

When correlated with the UPDRS, none of the parameters correlated significantly with the UPDRS. The torque, range of motion, impedance and viscous damping constant were able to detect on-off differences but failed to show a correlation with the UPDRS. This could be because these parameters could vary highly between patients. However, inter-subject variations can be detected and therefore they could be useful parameters when applied during DBS to find the best electrode position, best DBS settings or predict the effect of DBS.

Small significant differences in severity of rigidity between off- and on-state could not be assessed with the PowerGlove when there was no difference in UPDRS score. However, the torque, impedance and viscous damping constant all decreased in the on-state compared to the off-state and the range of motion increased (see Figure 3.6). This may indicate that the PowerGlove is potentially be able to detect small variations in severity.

The ICCs were high ($>$0.7) for the intra-rater measurements of the torque at 60 degrees extension, range of motion, impedance and viscous damping constant for both tasks. Without contralateral activation, the ICC for the intra-rater measurement is high for the torque at 30 degrees as well. The ICCs for the inter-rater measurements are low ($<$0.7) and the SEM values are consistently higher than the SEM values of the inter-rater measurements. Only for the rigidity tasks, an action of the rater was needed. A clear difference could be visually observed in posture of the raters and the way raters performed the rigidity measurements. This could explain the low inter-rater reliability of the rigidity parameters. Instructing the raters how to use the force sensor and to consistently perform the measurements could improve the inter-rater reliability.

Some ICCs were negative. This is the result of small inter-subject variations compared to intra-subject variations. The ICCs should be within the interval [0, 1]. These negative ICCs are thus not reliable.

In this study, a significant difference between the off- and on-medication state was found for the impedance. This corresponds with the literature where the impedance gave good results [41, 42, 45]. In contrast with results for the stiffness, Lorentzen et al. [43] did find a significant difference for the stiffness between off- and on-state. However, no correlation between the stiffness and the UPDRS was found by Kwon et al. [44]. Also in this study, no significant correlation was found between the stiffness and UPDRS. Viscous damping [45], and impedance [41, 43] are the most reliable parameters from literature which agrees with the results obtained in this study. Rigidity is sensitive to the velocity with which the wrist is extended. It is believed to be related to enhanced long-loop (long-latency) reflexes. The viscous damping constant may reflect the velocity-dependency of long-loop reflexes [44] which could also explain why good results are obtained with this parameter.

The stiffness [45] was also reliable in literature. However, in this study the stiffness was not reliable and no significant differences and correlations were found as well. A difference in velocity of the wrist extension results in a different stiffness. When the rater performs the movement faster the contribution of the viscous stiffness will be larger [41]. The wrist was extended at a low frequency and therefore the inertial component was not taken into account because this will not have significant influence on the stiffness. However, when higher velocities are applied, the inertial component will influence the stiffness in a way that a lower stiffness and damping are computed. Taken the inertial component into account or using slower movements may result in more correct values for the stiffness. Components of the impedance are the stiffness, effective mass and damping [68]. Addition of the inertia or slower movements could therefore result in better results for the impedance as well.

Sepheri et al. [48] found no correlation with the range of motion and the UPDRS. Results obtained in this study showed as well that the range of motion does not correlate with the UPDRS but inter-subject variations could actually be measured. The range of motion is probably very patient specific and therefore not correlated with the UPDRS.

Niazmand et al. [20] found no correlation with the force and the UPDRS. The torque is the force times the moment arm and results showed that this is a good parameter to show on-off differences. This parameter can thus be used to assess inter-subject differences as well.

4.4 System and software

Joint angles and position of finger segments calculated with the PowerGlove software are reliable on the calibration of the sensors. Slight offsets in joint angles could be introduced when the arm and/or hand were not placed perfectly flat. Patients could also have difficulties in stretching all finger joints due to stiffness of these joints resulting in offsets. Besides this, the hand is placed flat multiple times during the calibration measurement. Selecting different time points at which this occurs result in slightly different angles. The same occurs in the other calibration tasks where the time interval needs to be selected. Time points and intervals were therefore chosen by selecting time points and intervals resulting in reasonable values of joint angle.

Sensors can be displaced during the measurement. When this was observed during the measurement, the calibration was repeated but it could be possible that a sensor was slightly moved but that is was not noticed by the rater.

The positions of fingertips are calculated using orientation and length of the segments of the finger. An offset in joint angle can pass through an error in position of the fingertip.

The software makes use of a hand model in which segment lengths in the x- and z-direction are estimated. If the patient has hands with different ratios between the x-, y-, and z-direction, the position of the segments are not completely correct.

The offset in joint angle was frequently seen in the carpometacarpal joint (see Figure 1.4) of the thumb which is visualised in Figure 2.7. This is a saddle joint with two degrees of freedom enabling flexion/extension and adduction/abduction [69]. This joint is difficult to calibrate adequately because of its degrees of freedom. The finger tapping amplitude is therefore based on only the amplitude of the index finger. Significant differences in severity of bradykinesia could be obtained by addition of the amplitude of the thumb.

There was no consistency between measurements in terms of time intervals and repetitions of tasks. When using a constant time interval and amount of repetitions for each task it would be more reliable to compare within and between subjects. For the tremor persistence it would be necessary to have a longer measurement of the resting tremor. The time interval selected for tremor contained the whole interval. When tremor was not continuously present, tremor severity could be estimated lower than the actual value. Since not all tremor patients showed tremor during the measurements it was not possible to select a time interval containing tremor. To be consistent and to increase the chance of detecting tremor which was not visually present, the whole interval was selected for all patients.

Before calculation of the tremor parameters, the used signals are filtered with a high pass filter (3 Hz). In Figure 3.1(b), the PSD of the raw and the filtered accelerometer data is given. It can be seen that for the mental task the peak power decreases after filtering. This could have influenced the results for the resting tremor. However, in the on-state patients could suffer from levodopa induced dyskinesia which has a frequency of 1-3 Hz [70]. By using a lower cut-off value for the filter, the levopoda induced dyskinesia could influence the parameter values of the on-measurement.

The frequency band used for the peak power and power in the tremor band for posture and kinetic tremor is 7 to 12 Hz. This frequency band also contains physiological tremor which ranges from 8 to 12 Hz [71]. This can not be filtered out of the data without losing signal of interest. Physiological tremor can thus have influenced the results. Kinetic tremor can be subdivided in task-specific tremor and intentional tremor (when the finger approached the nose or finger of the rater) as described in Section 1.1. In this study only task-specific tremor is analysed. It could be possible that when analysing the signal when the finger of the patient approaches the nose or the finger of the rater, better results for kinetic tremor are obtained.

Accelerometers measures the inertial acceleration as well as the gravitational acceleration. Rotation of the segment with the accelerometer produces a time-varying gravitational signal that contaminates the inertial acceleration. This also occurs during tremor and this gravitational artifact cannot be removed by the high-pass filter. The gravitational artifact will thus affect the accelerometer signal at all frequencies of rotational motion [72]. Using the gyroscope data for the peak power and the power in the frequency band could possibly give better results.

For the peak power and power in the tremor band, different frequency windows are used for resting tremor and posture and kinetic tremor. For the other parameters (RMS of the acceleration, RMS of the angular velocity and tremor amplitude), this distinction was not made. It could be possible that during the task for a specific tremor type another tremor type was measured. It is therefore useful to study the effect of using different filters for resting tremor and posture and kinetic tremor in measuring tremor.

Some patients could not perform all bradykinesia tasks well. Especially the pro- and supination task was difficult for some patients. When a patient can not perform a task, it will be scored with a UPDRS score of 4 (see Appendix A). In this study, it could not be assessed whether the patient could perform the task. However, in case the patient was not able to, the RMS of the acceleration and angular velocity and amplitudes will have a low value and the movement time would be large which would be quantified as severe. However, for the physician it could be important to know whether a task could be performed.

In Figure 2.8, the position signal of the index finger with respect to the hand is given which is used to calculate the movement time. As can be seen, the average movement time of the pro- and supination task is more difficult to obtain since the peaks are broader and differ in height. In the software, the data point with the highest value will be detected which is different for every peak when they are broader. Errors in the measured movement time could arise due to this.

In this study, 1 force sensor is used and only extension of the wrist was taken into account. Rigidity is more pronounced in extension than in flexion [40, 47]. Considering this and our results, 1 force sensor is enough to find off/on differences for rigidity.

The force sensor is manually applied to the hand by the rater. Consequently, the moment arm differs between measurements and raters and can be different from the moment arm measured before the measurement. Deviations in the torque and in impedance, stiffness and viscous damping constant which are derived from the torque, can arise.

During passive wrist extension, it was sometimes difficult for patients to remain fully passive. Abnormal reactions to shortening of muscles occur in PD. When a muscle is passively shortened, this muscle is activated. This shortening reaction contributes to the torque as it act agonistically with the passive movement. Another reflex, the stretch reflex which responds to slow stretch, is also exaggerated in PD and can also contribute to the torque as it acts antagonistically with the passive movement [40]. Distinctions between reflex and passive stiffness can be made by using EMG [43].

In the calculation of the wrist angle, the assumption is made that the z-axis of the wrist is in the xy-plane of the global reference frame (see Section 2.1.1). This resulted in logical wrist flexion and extension angles. The disadvantage of this method is that no reliable rotations around the z-axis can be calculated. The major force is applied in the z-direction but small forces were also applied in the x- and y-direction. Taken these forces into account as well as endo- and exorotation and pro- and supination may detect smaller variations in severity of ridigity.

In general, the parameters were not significantly correlated with the UPDRS. This may be caused by large inter-subject differences. To be useful in the clinical setting, it is most important to measure the intra-subject differences with the PowerGlove.

The main advantage of the PowerGlove comparing to other systems is that it measures the joint angles of the fingers as well as the wrist. This makes it possible to measure tremor, bradykinesia and rigidity when a force sensor is used as well. A disadvantage is that tremor and rigidity can only be measured at the hand and wrist while tremor can also occur in the legs and rigidity in the neck. This can not be measured with the PowerGlove system. Another disadvantage is that attachment for the sensors to the hand of the patient and measuring the segment length is time consuming. Designing a glove would extremely improve the user friendliness of the system.

The inter- and intra-reliability is studied in the off-medication state. In the off-medication state the symptoms are more present and more variability in the severity of the symptoms is present than in the on-medication state. Because of the large inter-subject differences, the ICCs can result in high reliability even when the system variability due to measurement error is high. In the on-medication state the symptoms are more subtle. Further research to the validity and reliability in the on-medication state is needed to investigate ability of the PowerGlove system in measuring small differences in severity of the symptoms.

CHAPTER 5

CONCLUSION & RECOMMENDATIONS

5.1 Conclusion

In conclusion, the PowerGlove system in combination with a force sensor can be used to measure bradykinesia and rigidity in PD patients. For bradykinesia, the RMS of the angular velocity could detect on/off differences and had a high intra- and inter-rater reliability. For rigidity, the torque at 60 degrees extension, the range of motion and the viscous damping constant could detect on/off differences and these parameters had a high intra-rater reliability.

The results showed that using only the sensor on the hand and lower arm (with both containing a 3D acceleromter, 3D gyroscope and 3D magnetometer) in combination with a force sensor is sufficient in measuring on/off differences in rigidity when measurements are performed by the same rater. For the RMS of the angular velocity, the gyroscope on the tip if the index finger is used and this showed to be sufficient to reliably measure the on/off differences in bradykinesia.

Further research in measuring tremor using the PowerGlove is needed to determine the use of the PowerGlove system in measuring tremor.

5.2 Recommendations

Improvements as described in the discussion should make it possible to improve the analysis and the results obtained in this study. Below an overview of the recommendations is given, ordered by symptom. Furthermore, recommendations for the PowerGlove system are given as well.

5.2.1 Tremor

- More patients suffering from tremor should be included to have sufficient statistical power.
- Longer time intervals for the relaxing and mental tasks are necessary to obtain reliable results for the tremor persistence.
- A tremor detecting method should enable to analyse only the time intervals containing tremor so that the tremor is not underestimated.

5.2.2 Bradykinesia

- A constant amount of repetitions is needed to quantify the severity of bradykinesia.
- The detection of stops have to be improved to accurately detect the stops that occur during the measurement.
- The calibration of the thumb needs to be improved to calculate the carpometacarpal joint angle.
- The contribution of the thumb to the finger tapping amplitude should be added to detect significant differences in finger tapping amplitude.
- A method to detect whether a task could be performed should be implemented.
- The calculation of the movement time during the pro- and supination task should be improved.

5.2.3 Rigidity

- Instructions on how to perform the rigidity measurements should be given to the raters to improve the inter-rater reliability. The raters should have similar velocity and range of movement.
- Exact placement of the force sensor to the hand is desired to have the same moment arm in each measurement trail.
- The interial component should be included to obtain more accurate results for the stiffness and viscous damping constant.

5.2.4 System

- The PowerGlove system should be implemented in a glove to improve the user-friendlyness of the system in the clinical setting.
- The calibration of the sensor on the lower arm needs to be extended so that the y-axis can be determined by the pro- and supination movement of the lower arm and the rotation about the z-axis can be calculated.

APPENDIX A

UPDRS

Table A.1: *Description of the UPDRS scoring, part 1.*

	0	1	2	3	4
Amplitude resting tremor (UPDRS item 20)	no tremor	tremor is present with an amplitude smaller than 1 cm	tremor with an amplitude of at least 1 cm but smaller than 3 cm	tremor with an amplitude of at least 3 cm but smaller than 10 cm	tremor with an amplitude of at least 10 cm
Persistence resting tremor (UPDRS item 20)	no tremor	tremor present during less than 25% of the measurement	tremor present during less than 26-50% of the measurement	tremor present during less than 51-75% of the measurement	tremor present during more than 75% of the measurement
Posture Tremor (UPDRS item 21)	no tremor	tremor is present with an amplitude smaller than 1 cm	tremor with an amplitude of at least 1 cm but smaller than 3 cm	tremor with an amplitude of at least 3 cm but smaller than 10 cm	tremor with an amplitude of at least 10 cm
Kinetic tremor (UPDRS item 21)	no tremor	tremor is present with an amplitude smaller than 1 cm	tremor with an amplitude of at least 1 cm but smaller than 3 cm	tremor with an amplitude of at least 3 cm but smaller than 10 cm	tremor with an amplitude of at least 10 cm
Rigidity (UPDRS item 22)	no rigidity	rigidity only with contralateral activation	rigidity observed without contralateral activation but range of motion is achieved	rigidity observed without contralateral activation but range of motion is achieved with effort	rigidity observed without contralateral activation but range of motion is not achieved

Table A.2: *Description of the UPDRS scoring, part 2.*

	0	1	2	3	4
Finger tapping (UPDRS item 23)	no problems	the rhythm is one or two times interrupted or there is a minimal delay or the amplitude decreases at the end	the rhythm is three or five times interrupted or there is a slight delay or the amplitude decreases halfway of the test	the rhythm is more than five times interrupted or there is a moderate delay or at least one longer interruption or the amplitude decreases after the first finger tap	the test can not be performed
Hand opening and closing (UPDRS item 24)	no problems	the rhythm is one or two times interrupted or there is a minimal delay or the amplitude decreases at the end	the rhythm is three or five times interrupted or there is a slight delay or the amplitude decreases halfway of the test	the rhythm is more than five times interrupted or there is a moderate delay or at least one longer interruption or the amplitude decreases after the first finger tap	the test can not be performed
Pro- and supination (UPDRS item 25)	no problems	the rhythm is one or two times interrupted or there is a minimal delay or the amplitude decreases at the end	the rhythm is three or five times interrupted or there is a slight delay or the amplitude decreases halfway of the test	the rhythm is more than five times interrupted or there is a moderate delay or at least one longer interruption or the amplitude decreases after the first finger tap	the test can not be performed

APPENDIX B

MANUAL

1. Open offlineAnalysisMichelle
2. Type in the name of the measurement you want to analyse as filestr and run the current cell
3. newSegmentCalibration = 1; and run current cell
4. Select a file with movements for segment calibration
5. Select the following time intervals:
   - Thumb: Indicate proximal back pointing upwards. Use the left mouse button to pick the point in the accelerometer signal when the thumb is flat. Use right mouse button to continue.
   - Indicate proximal (thumb medial) rotation around x-axis. Use left mouse button indicate the range where rotation of the thumb occurs. Use right mouse button to continue.
   - Index: Indicate proximal back pointing upwards. Use left mouse button to select the point in the accelerometer signal when the index finger is flat. Use right mouse button to continue.
   - Indicate proximal (thumb medial) rotation around x-axis. Use left mouse button indicate the range where rotation of the joints of the index finger occurs. Use right mouse button to continue.
   - Give global rotation. Use left mouse button indicate the range of the global rotation. Use right mouse button to continue.
   - Save segment calibration
   - Enter the name of the segment calibration file in segmentCalFile = ”;
6. newSegmentCalibration = 0;
7. applyMagMapping = 1; and run current cell
   - Select a file with movements for magnetic calibration
   - Select the undisturbed part of the magnetic measurement
   - Load existing sensor calibration file
   - Save sensor calibration file
   - Enter the name of the sensor calibration file in sensorCalFile = ”;
8. applyMagMapping = 0;
9. In case of measurement of the right hand: applyRight = 1;
10. Use applySegmentLength = 1; to enter the segment lengths of the subject (in meters). Each segment is referred to as the anatomical name of the corresponding bone. When the segment lengths are already available use applySegmentLength = 0; and load the segment lengths.
11. Adjust filtersettings if desired
12. Run entire script

APPENDIX C

RESULTS

C.1 Off/on difference

C.1.1 Tremor

Relaxing task

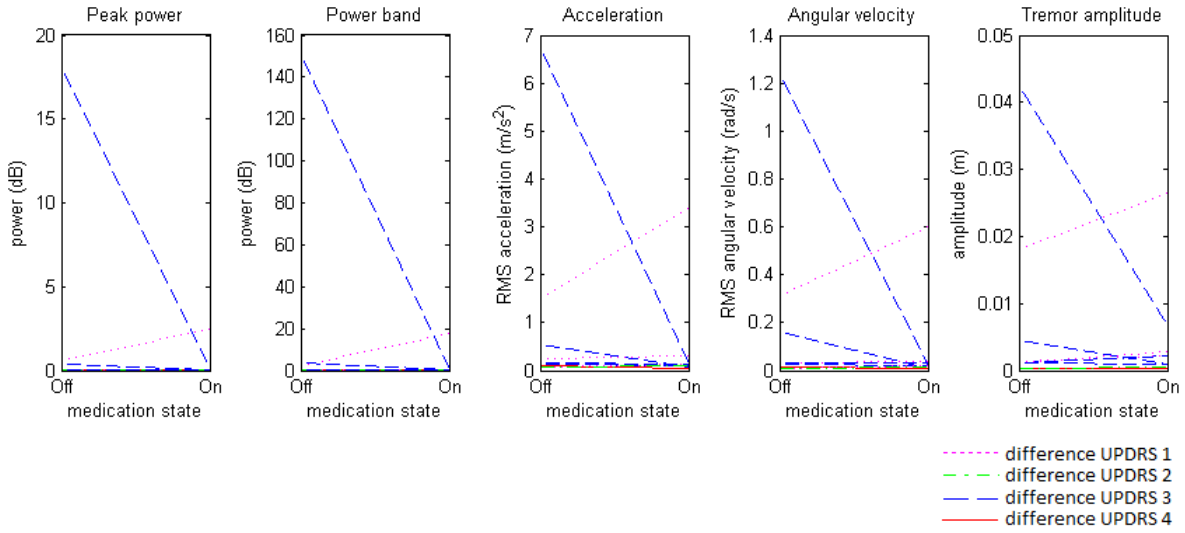


Figure C.1: *Parameter values of the off- and on-measurement for the relaxing task. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Ten patients were included.*

Mental task

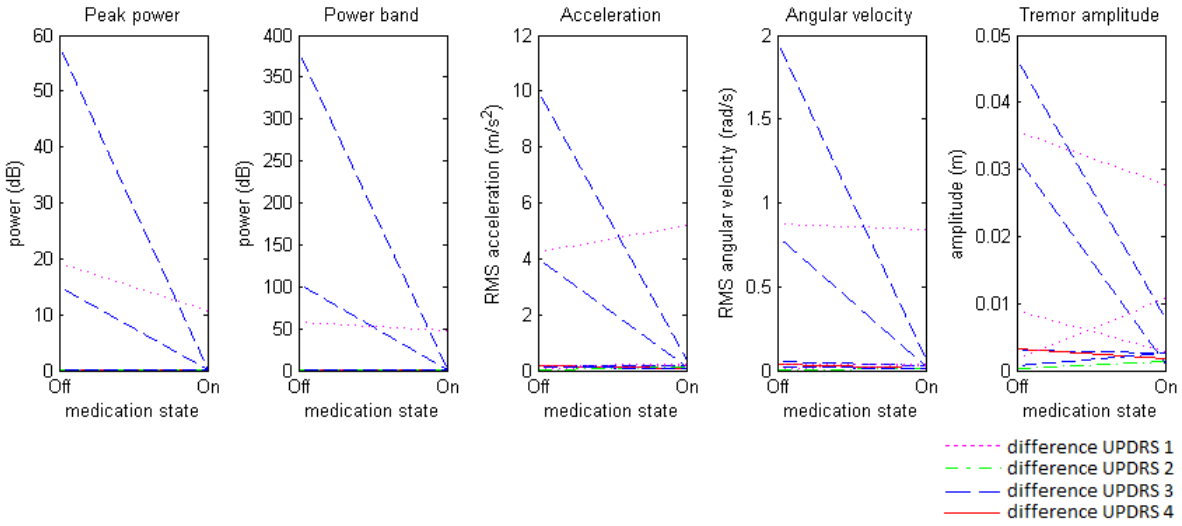


Figure C.2: *Parameter values of the off- and on-measurement for the mental task. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Ten patients were included.*

Posture tremor

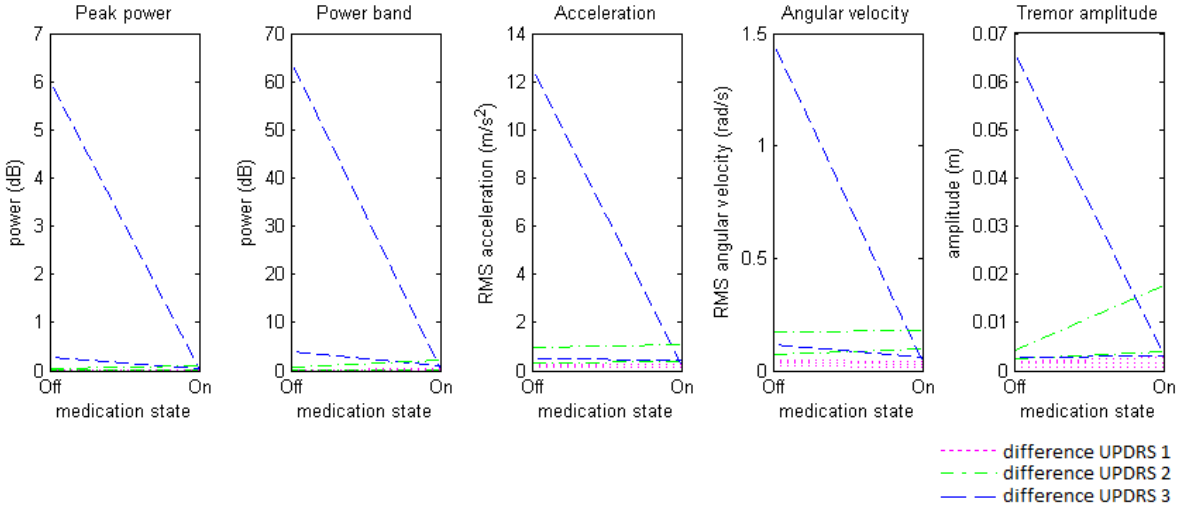


Figure C.3: *Parameter values of the off- and on-measurement for posture tremor. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Nine patients were included.*

Kinetic tremor

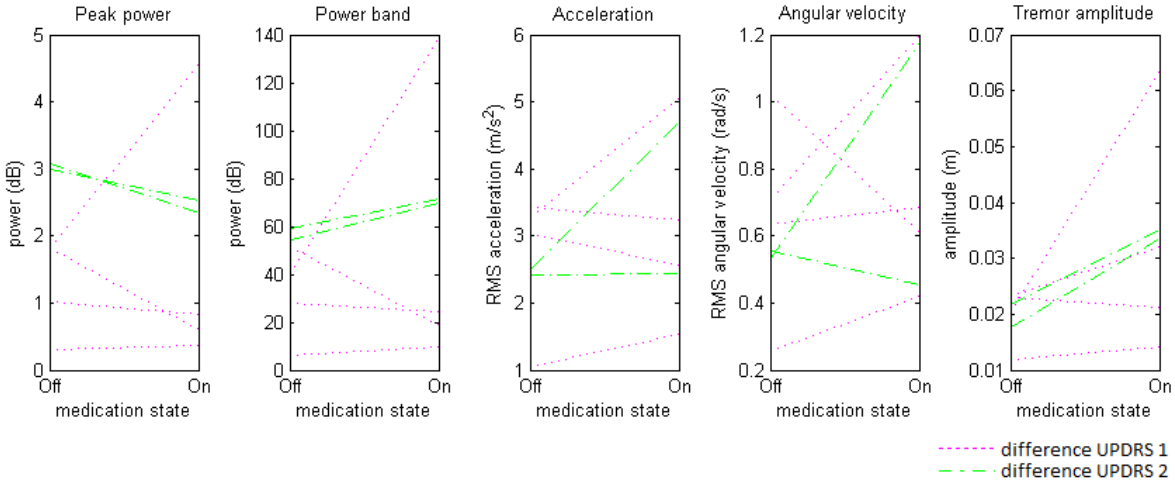


Figure C.4: *Parameter values of the off- and on-measurement for kinetic tremor. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Six patients were included.*

C.1.2 Bradykinesia

Table C.1: *Comparison of the parameter values in the off- and on-medication state and the mean difference and SD between on- and off-medication state for each task and parameter. Patients with no difference in UPDRS score between on- and off-measurement are included. The number of patients included, n, are given for each task. P-values below 0.05 are printed in bold.*

		RMS acceleration (m/s^2)	RMS angular velocity (rad/s)	amplitude (m)	movement time (s)	SD movement time (s)	number of stops
Finger tapping task (n=6)	p-value	0.094	0.063	0.56	0.063	0.84	1
	difference $\pm$SD	1.7 (36%) $\pm$2.0	1.6 (49%) $\pm$1.05	-0.0079 (-15%) $\pm$0.041	-0.064 (-14%) $\pm$0.054	-0.0051 (-6.3%) $\pm$0.061	0
Pro-/supination task (n=2)	p-value	0.50	0.50	-	1	0.50	1
	difference $\pm$SD	2.0 (19%) $\pm$2.1	0.68 (11%) $\pm$0.75	-	-0.026 (-5.8%) $\pm$0.087	-0.053 (-32%) $\pm$0.055	0
Closing task (n=5)	p-value	0.063	0.063	0.31	0.44	0.44	1
	difference $\pm$SD	0.96 (21%) $\pm$0.88	1.4 (31%) $\pm$1.1	0.0099 (9.0%) $\pm$0.020	-0.066 (11%) $\pm$0.15	-0.10 (-57%) $\pm$0.18	0

Finger tapping

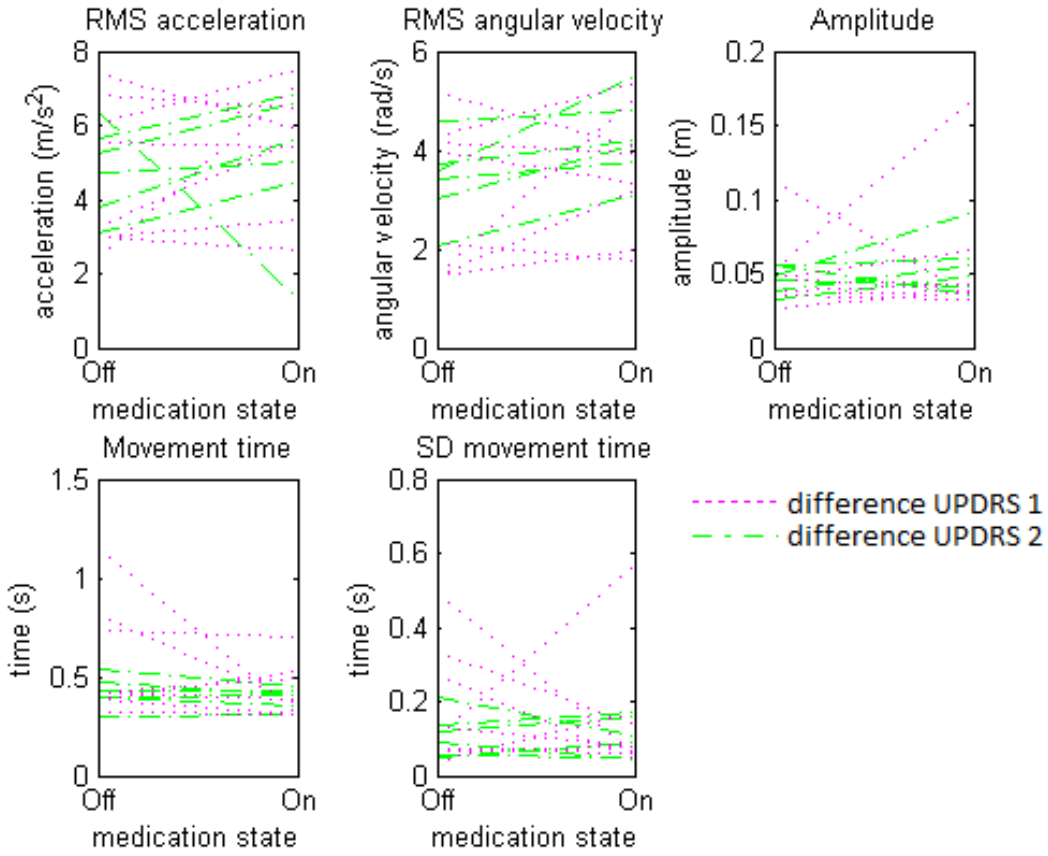


Figure C.5: *Parameter values of the off- and on-measurement for the finger tapping task. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Sixteen patients were included.*

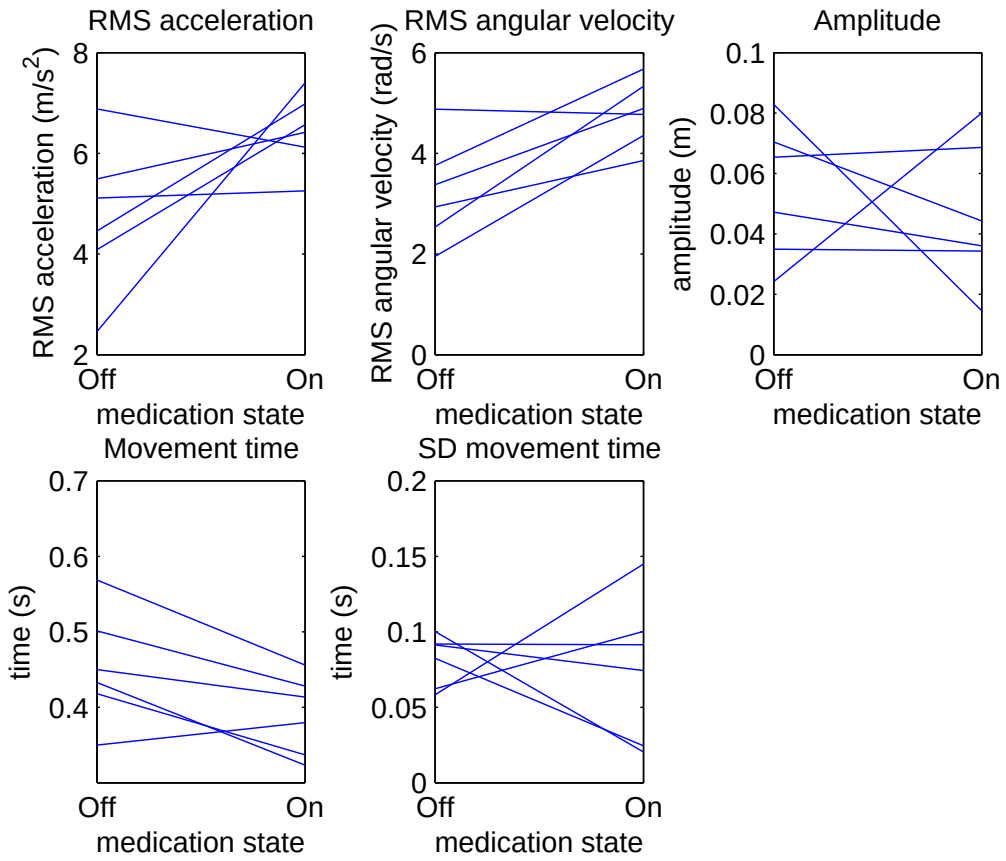


Figure C.6: *Off and on parameter values for the finger tapping task when there was no difference in UPDRS score. Six patients were included.*

Pro- and supination

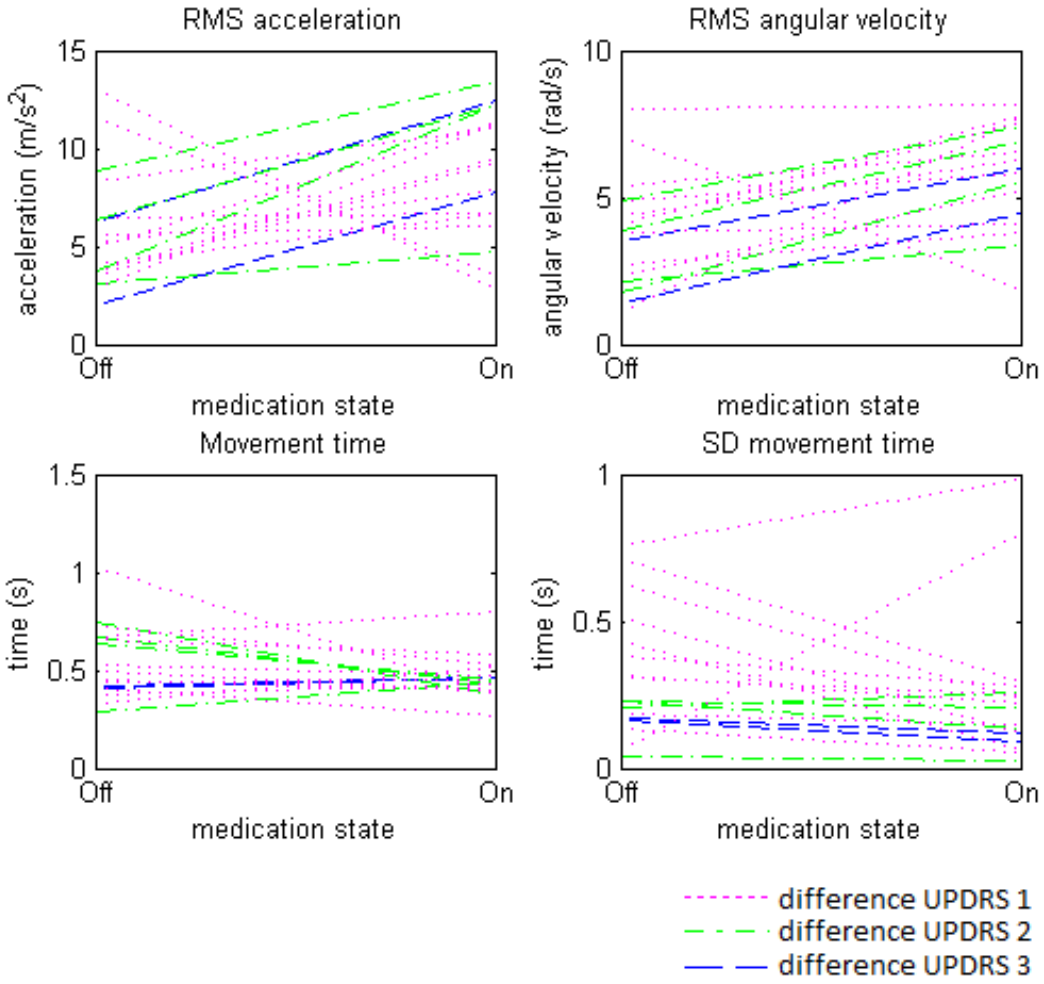


Figure C.7: *Parameter values of the off- and on-measurement for the pro- and supination task. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Nineteen patients were included.*

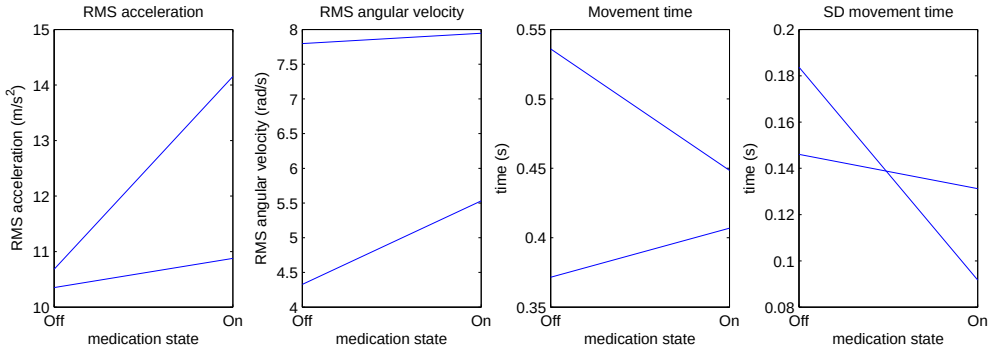


Figure C.8: *Off- and on-parameter values for the pro- and supination task when there was no difference in UPDRS score. Two patients were included.*

Closing task

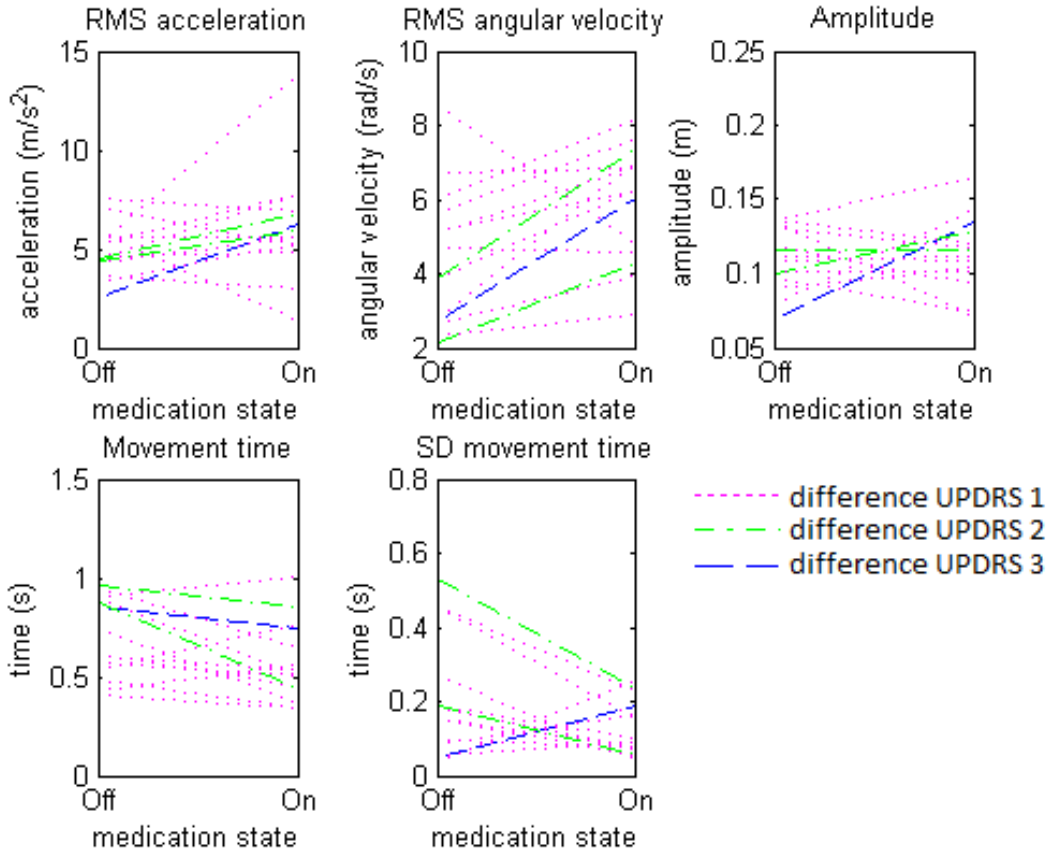


Figure C.9: *Parameter values of the off- and on-measurement for the closing task. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Sixteen patients were included.*

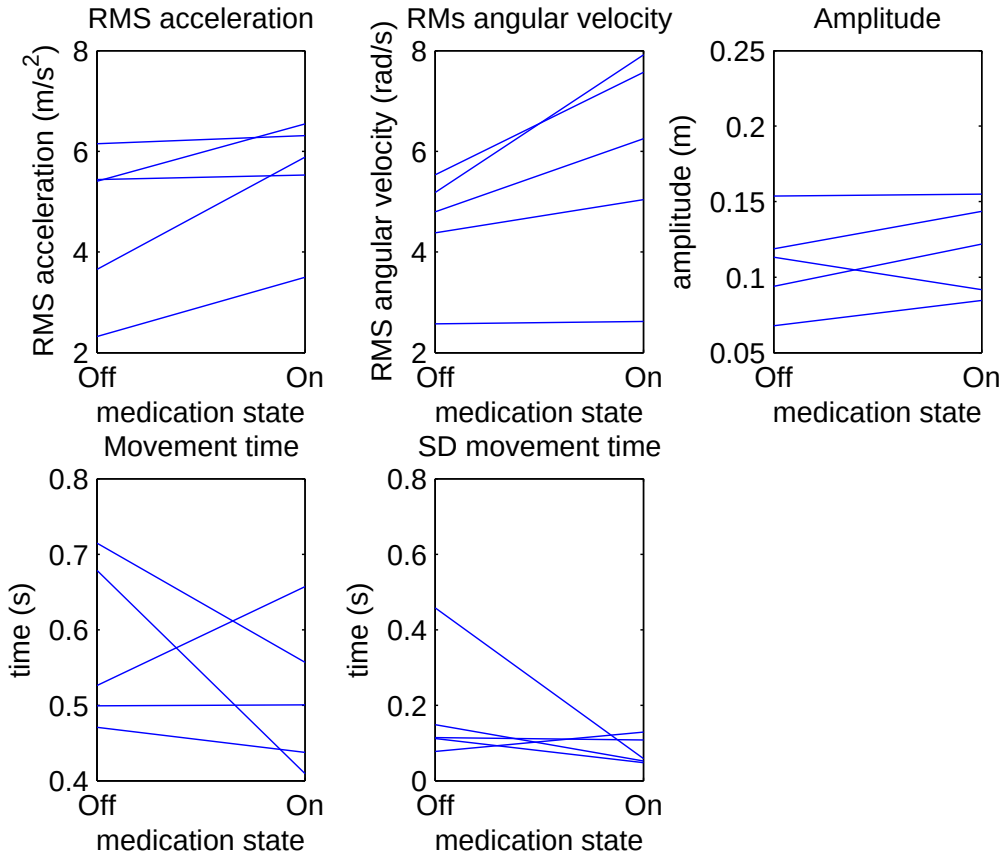


Figure C.10: *Off and on parameter values for the closing task when there was no difference in UPDRS score. Five patients were included.*

C.1.3 Rigidity

Table C.2: *Comparison of the parameter values in the off- and on-medication state and the mean differences and SDs between off- and on-medication state for each task and parameter. Four patients with no difference in UPDRS score between off- and on-measurement were included. P-values below 0.05 are printed in bold.*

		Torque (Nm)		Range of motion (deg)	Impedance (Nm/deg)	Stiffness (Nm/rad)	Viscous damping constant (Nm/rad/s)
		60	30				
Wrist extension	p-value	0.13	0.25	0.13	0.25	0.88	0.38
	difference ±SD	-0.58 (-38%) ±0.33	-0.59 (-60%) ±0.66	29 (58%) ±18	-0.052 (-79%) ±0.086	0.34 (293%) ±0.79	-0.031 (-66%) ±0.059
Wrist extension with contralateral activation	p-value	0.13	1	0.88	0.13	0.38	0.63
	difference ±SD	-0.18 (-11%) ±0.24	0.0069 (0.73%) ±1.3	0.20 (0.43%) ±75.76	-0.057 (-90%) ±0.061	-0.54 (-102%) ±1.01	-0.039 (-61%) ±0.076

Wrist extension

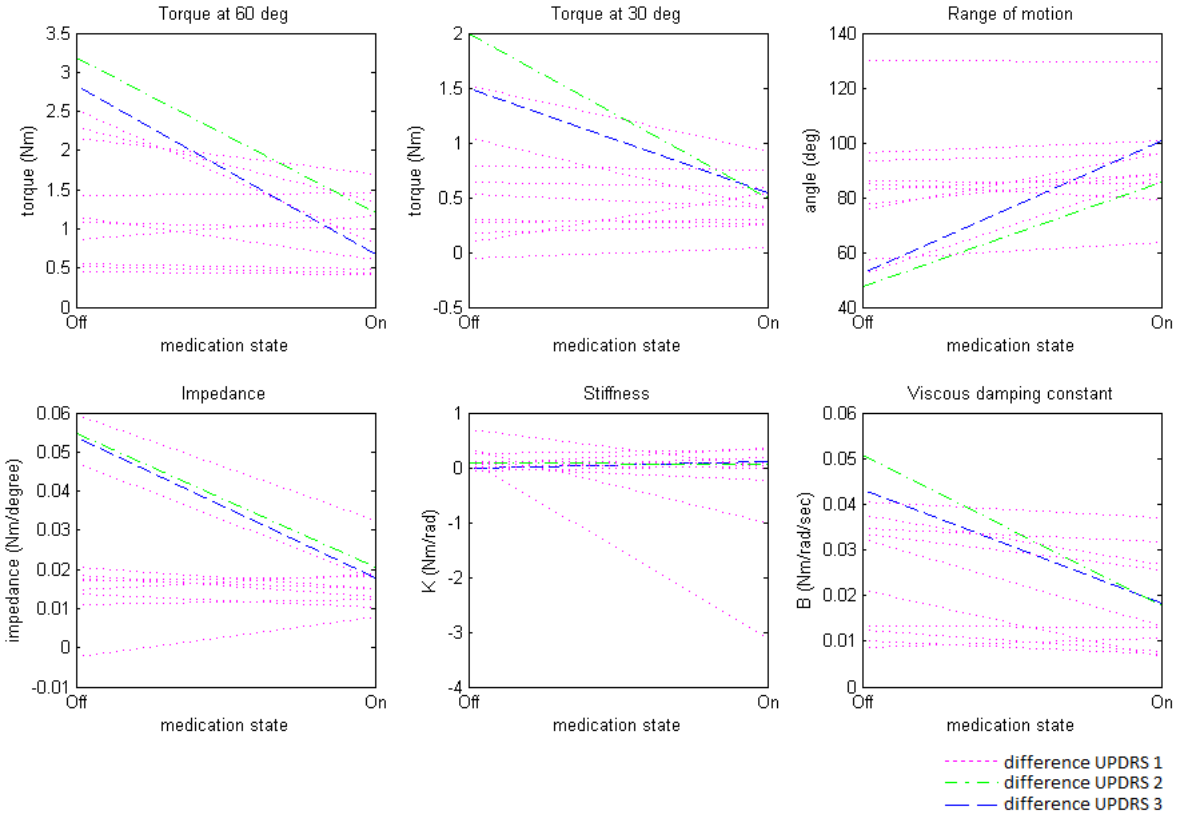


Figure C.11: *Parameter values of the off- and on-measurement for the rigidity task without contralateral extension. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement. Thirteen patients were included.*

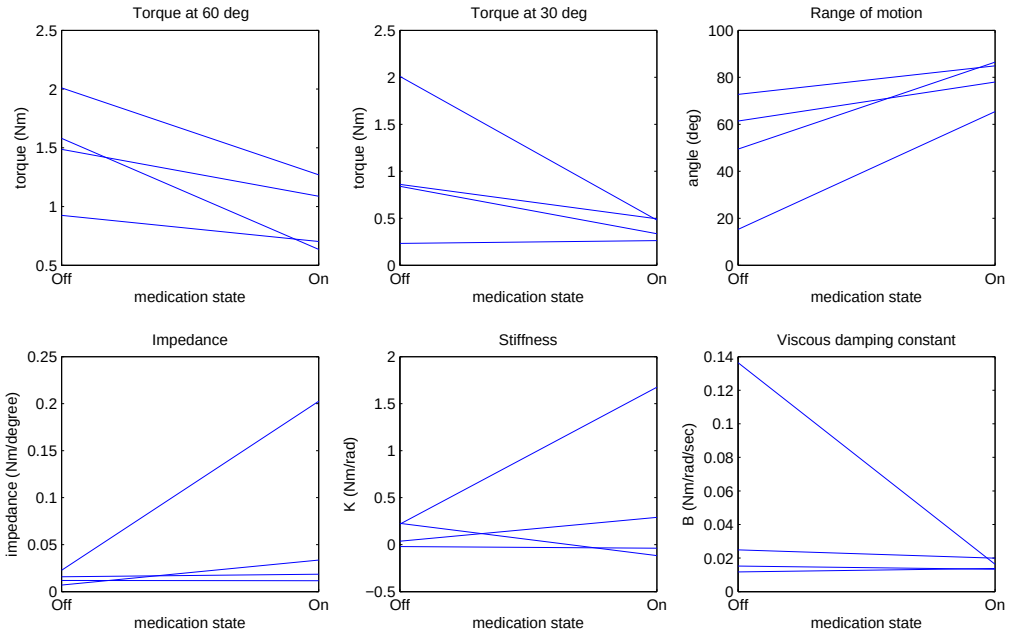


Figure C.12: *Off- and on-parameter values for the rigidity task when there was no difference in UPDRS score. Four patients were included.*

Wrist extension with contralateral activation

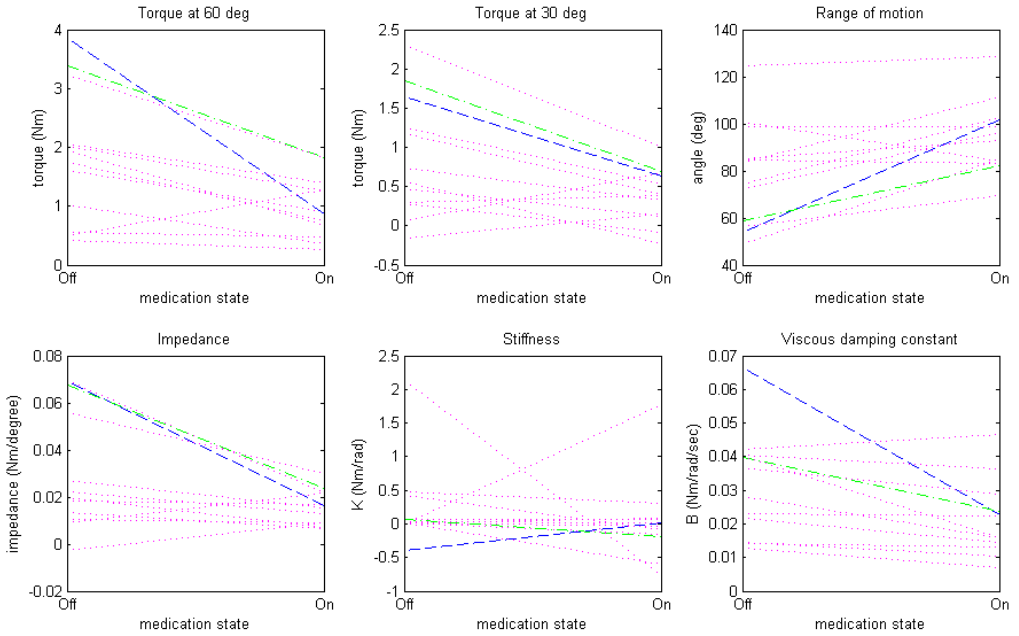


Figure C.13: *Parameter values of the off- and on-measurement for the rigidity task with contralateral extension. The UPDRS difference gives the difference in UPDRS score between the off- and on-measurement.*

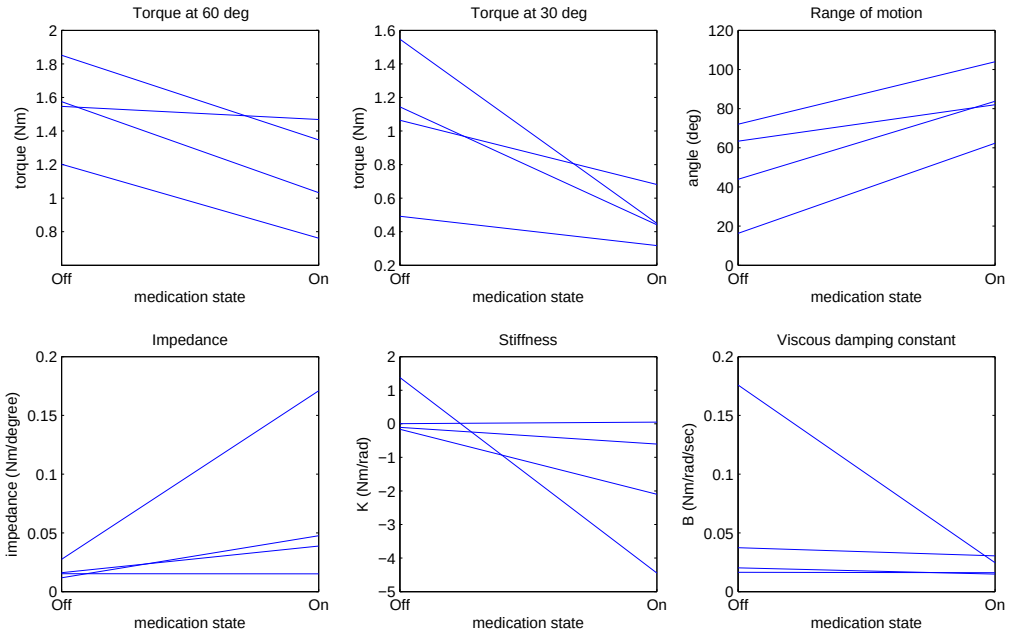


Figure C.14: *Off- and on-parameter values for the rigidity task with contralateral activation when there was no difference in UPDRS score. Four patients were included.*

C.2 Relation with UPDRS

C.2.1 Tremor

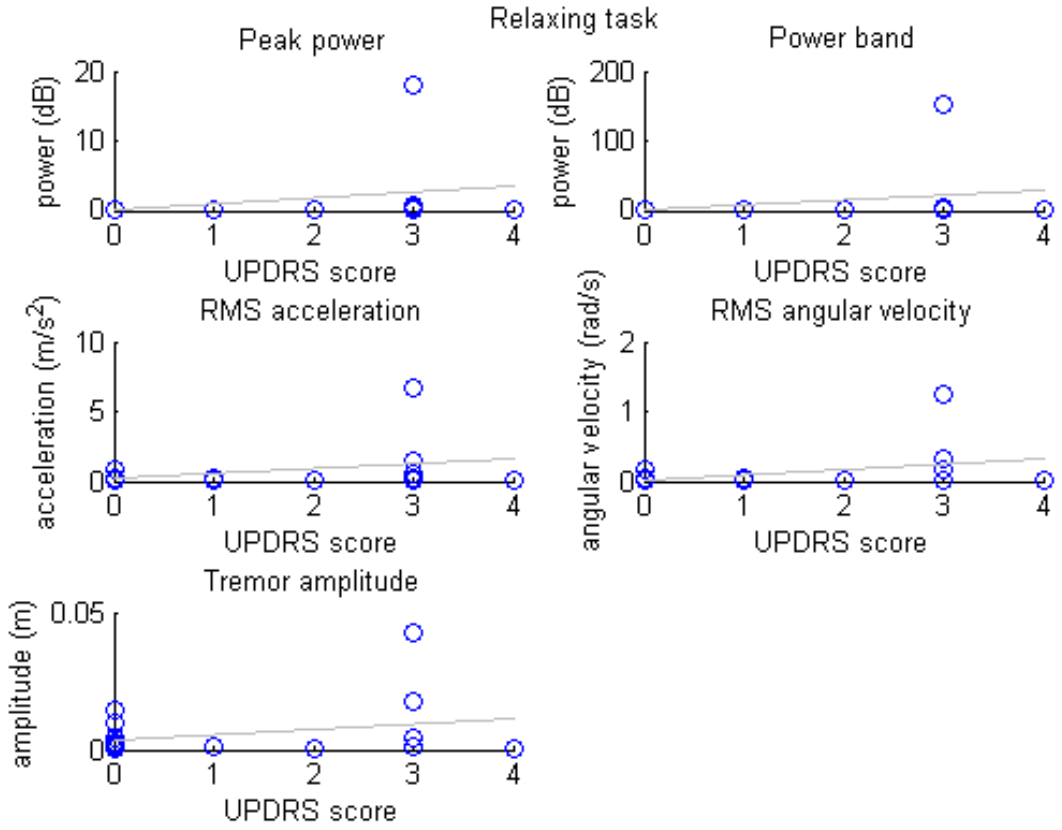


Figure C.15: *Obtained results of peak power, power band, acceleration, angular velocity and tremor amplitude and their relationship with the UPDRS scores for the relaxing task.*

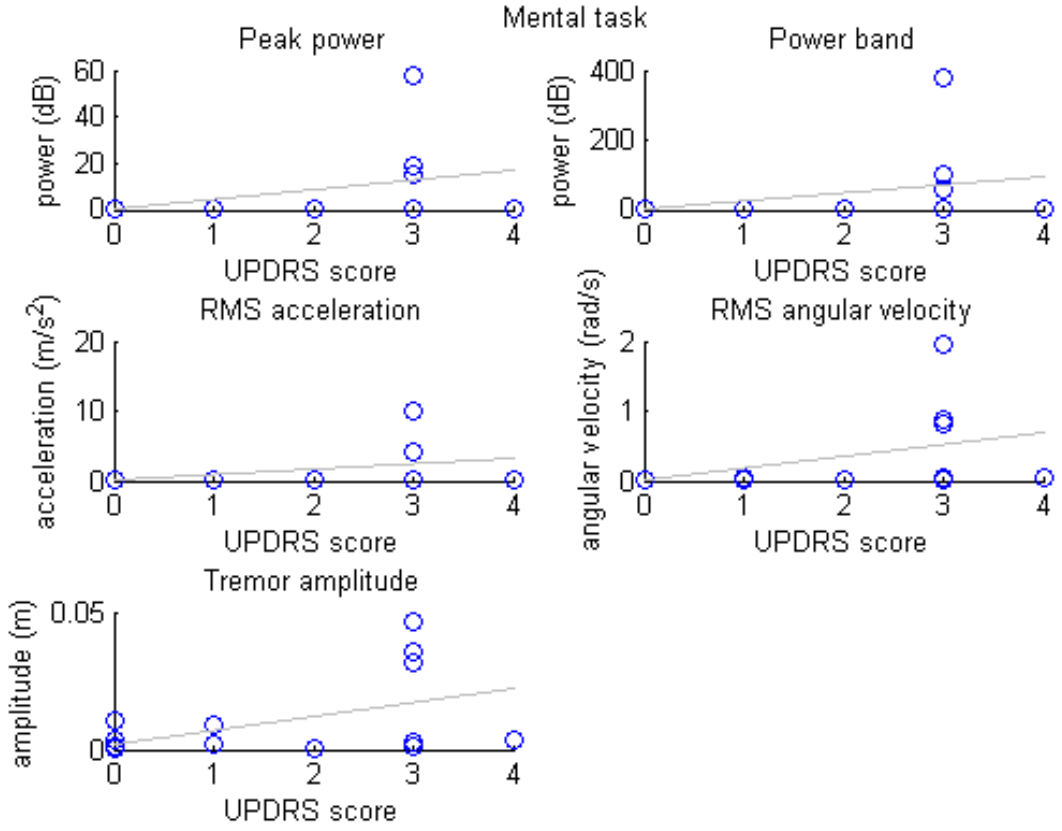


Figure C.16: *Obtained results of peak power, power band, acceleration, angular velocity and tremor amplitude and their relationship with the UPDRS scores for the mental task*

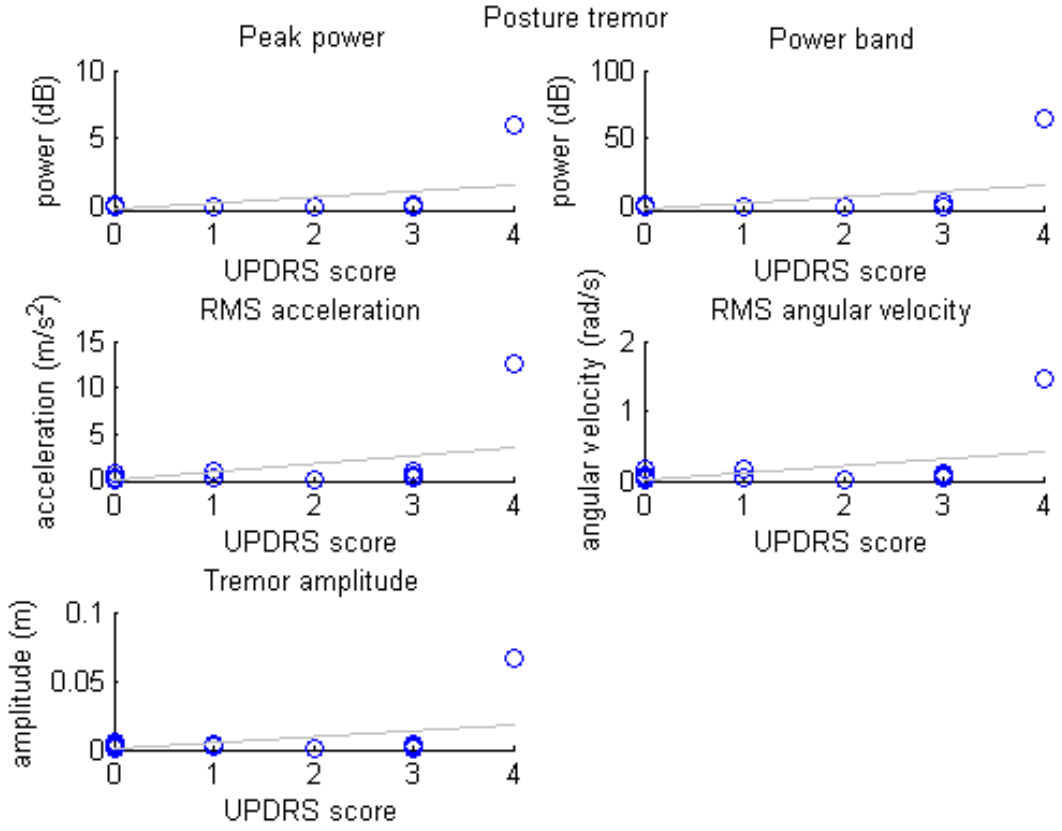


Figure C.17: *Obtained results of peak power, power band, acceleration, angular velocity and tremor amplitude and their relationship with the UPDRS scores for posture tremor.*

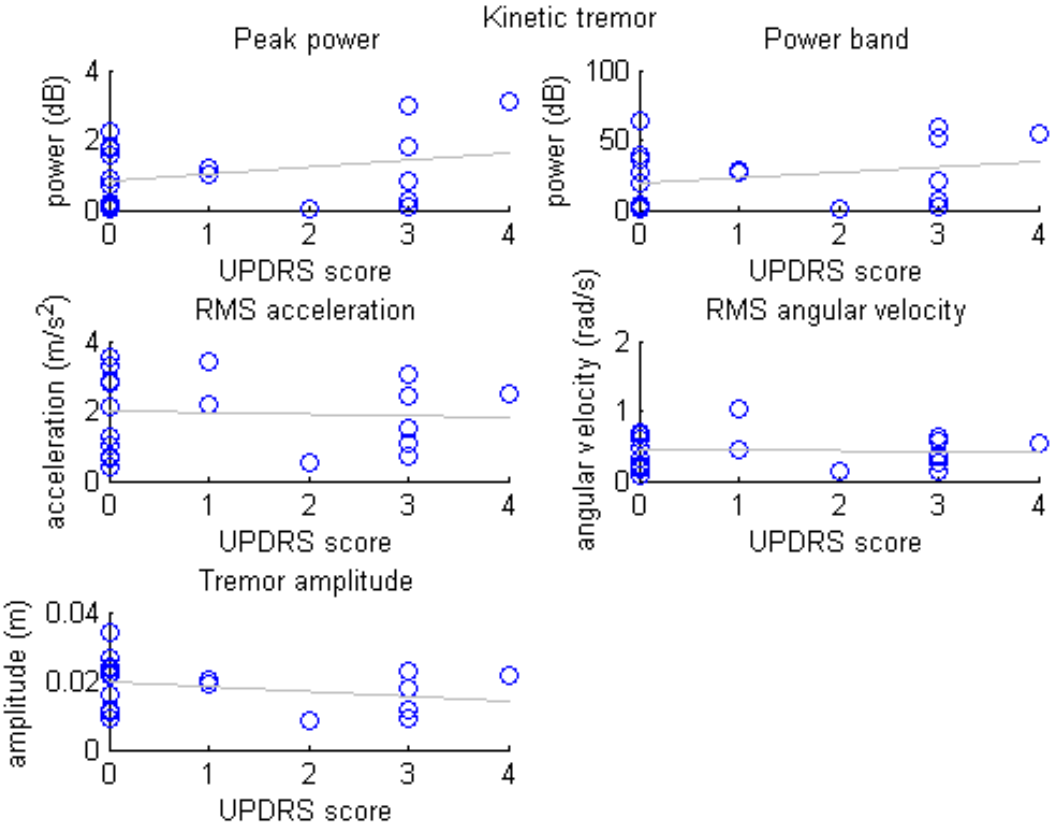


Figure C.18: *Obtained results of peak power, power band, acceleration, angular velocity and tremor amplitude and their relationship with the UPDRS scores for kinetic tremor.*

C.2.2 Bradykinesia

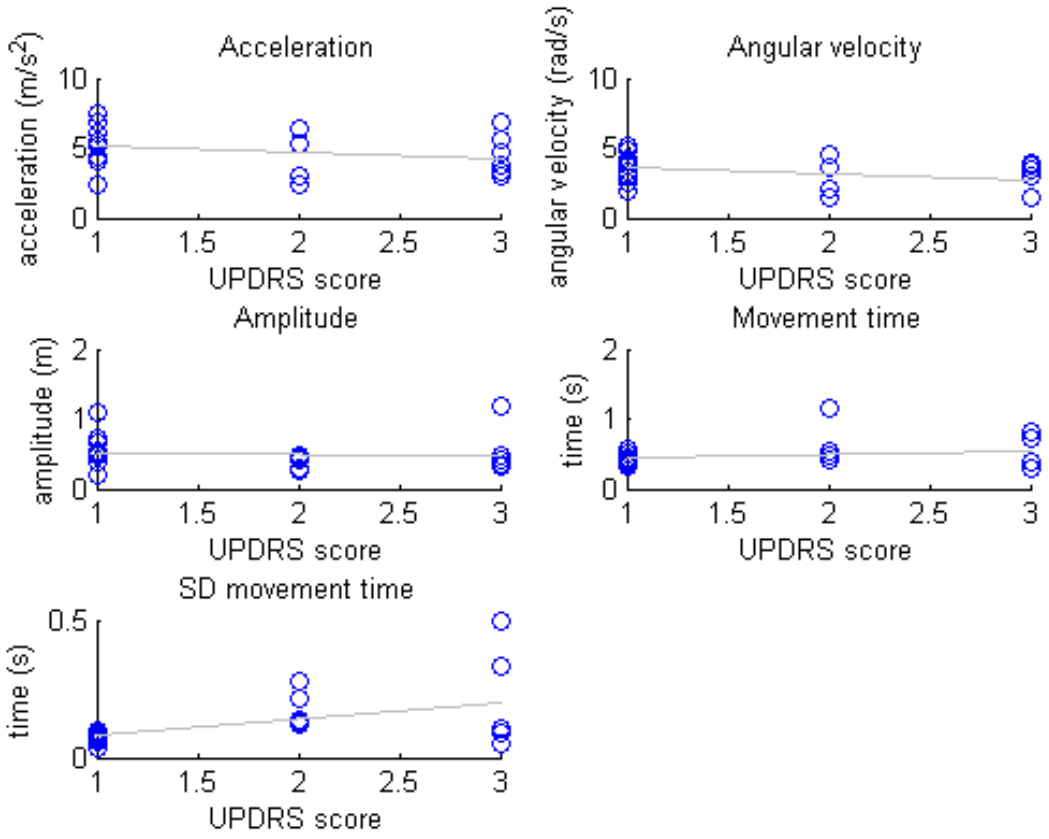


Figure C.19: *Obtained results of acceleration, angular velocity, amplitude and movement time and their relationship with the UPDRS scores for the finger tapping task.*

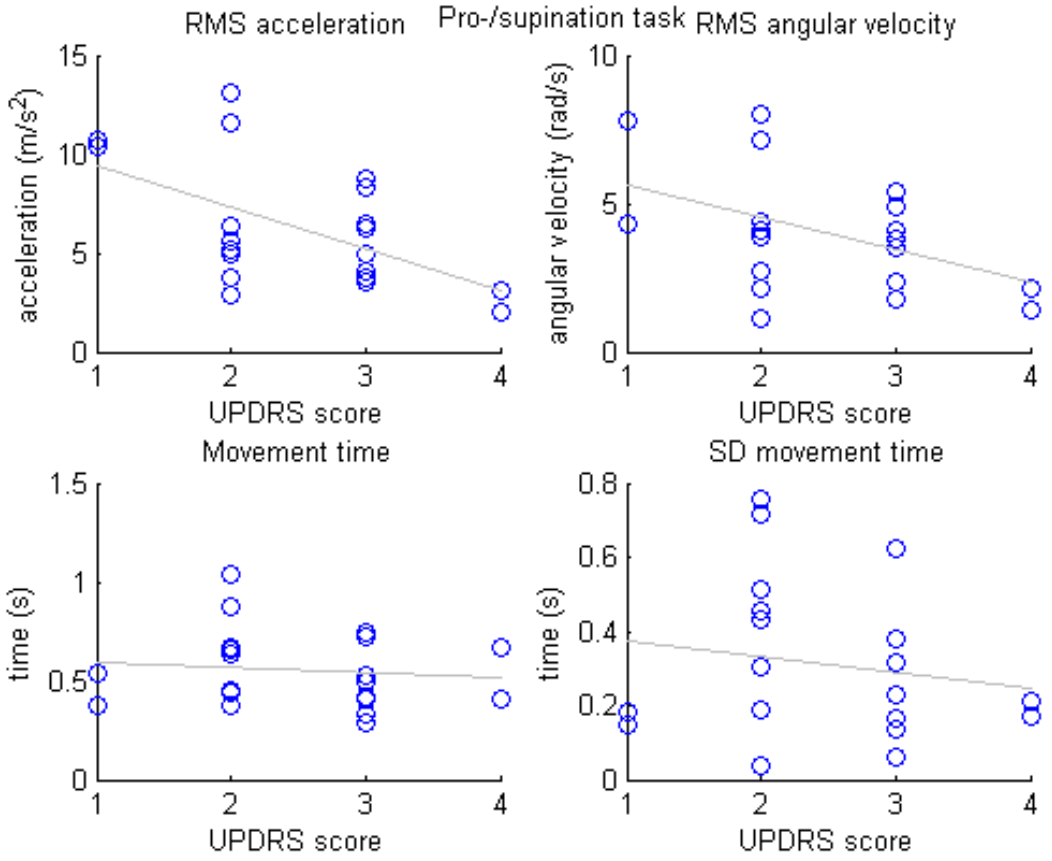


Figure C.20: *Obtained results of acceleration, angular velocity and movement time and their relationship with the UPDRS scores for the pro- and supination task.*

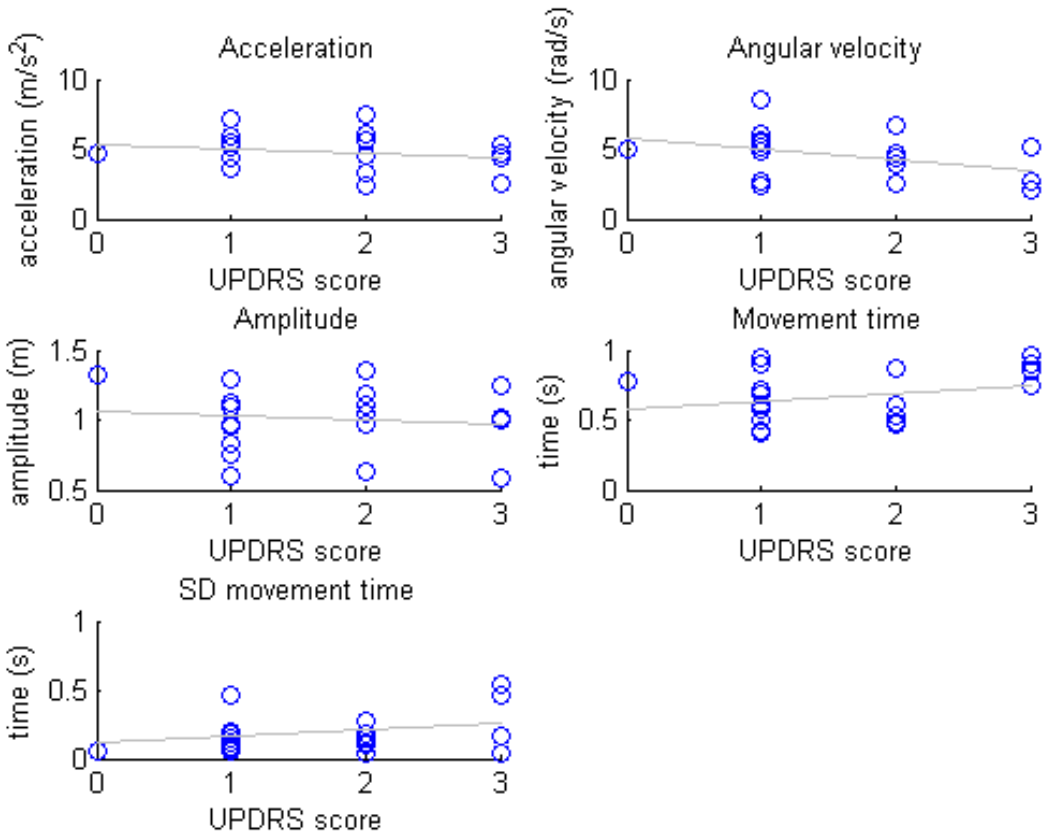


Figure C.21: *Obtained results of acceleration, angular velocity, amplitude and movement time and their relationship with the UPDRS scores for the closing task.*

C.2.3 Rigidity

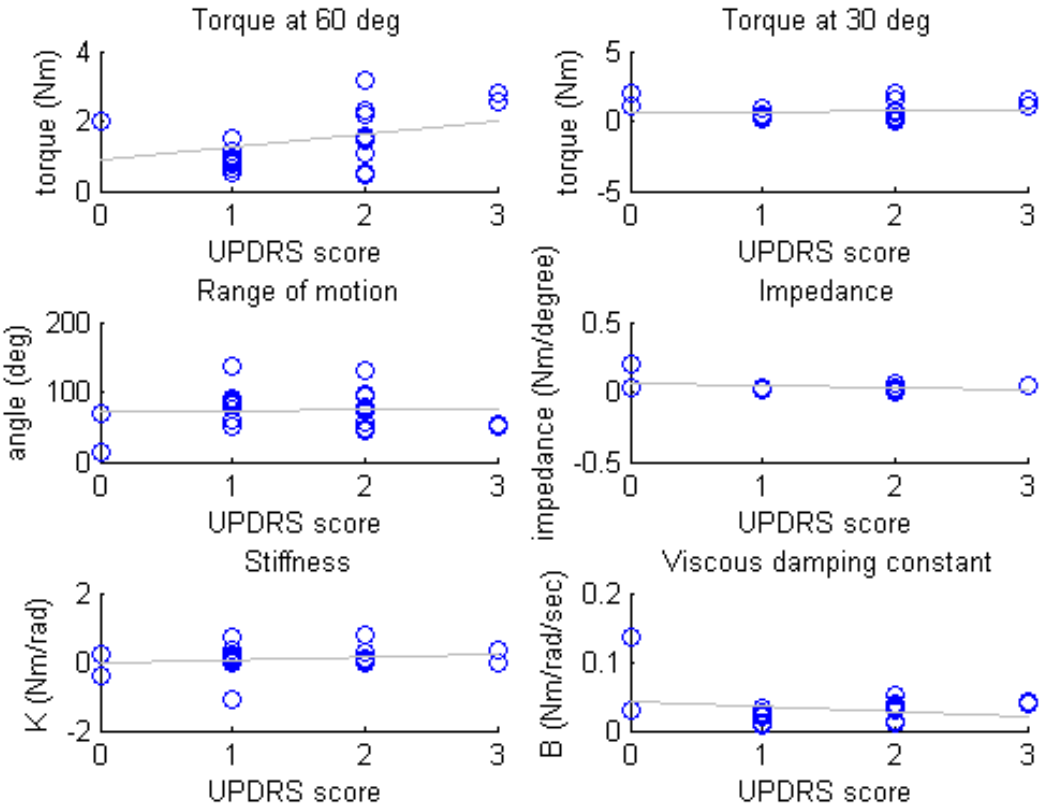


Figure C.22: *Obtained results of torque, range of motion, impedance, stiffness and viscous damping constant and their relationship with the UPDRS scores for the rigidity task without contralateral activation.*

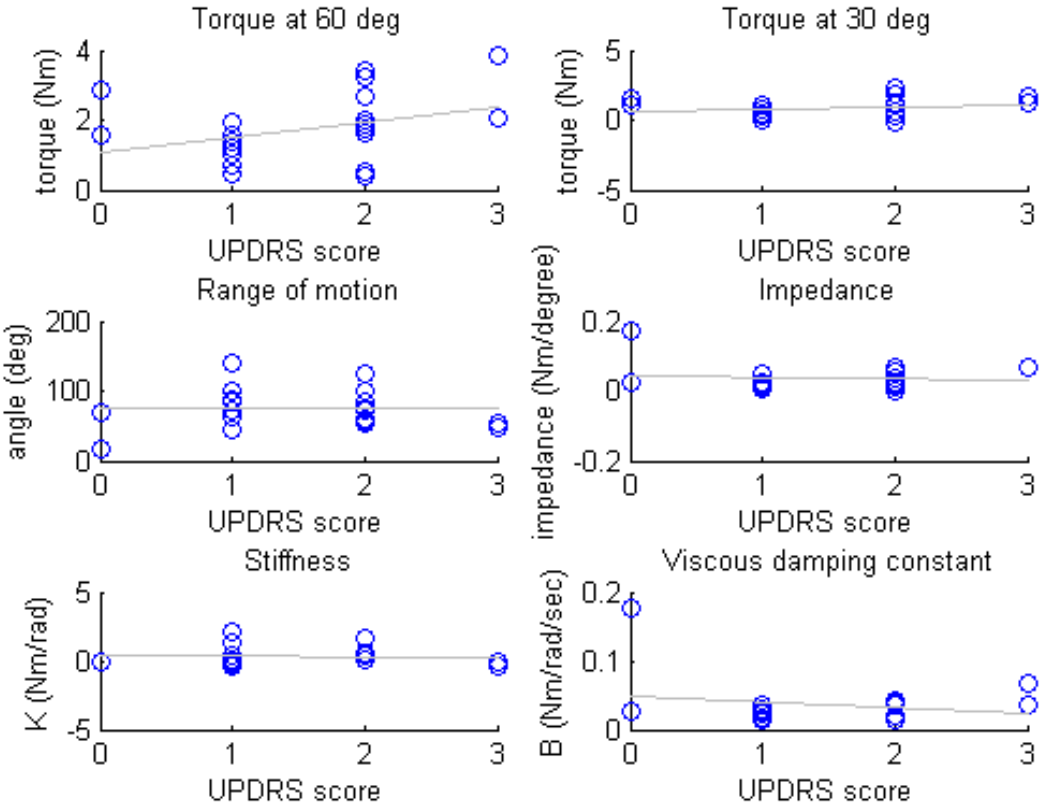


Figure C.23: *Obtained results of torque, range of motion, impedance, stiffness and viscous damping constant and their relationship with the UPDRS scores for the rigidity task with contralateral activation.*

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