

Perioperative accelerometry for bradykinesia and tremor

Annemarie Smid



Perioperative accelerometry for bradykinesia and tremor

Annemarie Smid

Colophon

The studies in this thesis were conducted within the Health in Context Research Institute of the University Medical Center Groningen (UMCG) and under auspices of the research program Biology-Related, Artificial, and Interventional Neuroscience (BRAIN).

Publication of this thesis was financially supported by the University of Groningen, University Medical Center Groningen, the research school for Behavioral and Cognitive Neurosciences (BCN) and Nederlandse Vereniging voor Klinische Neurofysiologie (NVKNF).



rijksuniversiteit
 groningen

umcg:
Research Institute Health in Context



Printed by Ridderprint, ridderprint.nl

Layout and design by Ryanne Keja, persoonlijkproefschrift.nl

© 2026, Annemarie Smid, Groningen, The Netherlands

All rights reserved. No parts of this thesis may be reproduced or transmitted in any form or by any means without prior written permission of the author.



rijksuniversiteit
 groningen

Perioperative accelerometry for bradykinesia and tremor

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. ir. J.M.A. Scherpen
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 11 maart 2026 om 12:45 uur

door

Annemarie Smid

geboren op 26 juli 1995

Promotores

Prof. dr. J.M.C. van Dijk

Prof. dr. T. van Laar

Dr. G. Drost

Beoordelingscommissie

Prof. dr. ir. M.J.A.M. van Putten

Prof. dr. M.A.J. de Koning-Tijssen

Prof. dr. P.R. Schuurman

Paranimfen

Drs. A.S. Jansen

Drs. I.P.J. Kessels

Table of contents

Chapter 1.	Introduction and thesis outline	7
Chapter 2.	Objective clinical registration of tremor, bradykinesia, and rigidity during awake stereotactic neurosurgery: a scoping review	25
Chapter 3.	Supine MDS-UPDRS-III assessment: an explorative study	51
Chapter 4.	Perioperative quantification of MDS-UPDRS-III bradykinesia measurements in patients with Parkinson's Disease using accelerometry	65
Chapter 5.	Intraoperative quantification of MDS-UPDRS-III tremor measurements using 3D accelerometry: a pilot study	95
Chapter 6.	A novel accelerometry method to perioperatively quantify Essential Tremor based on Fahn-Tolosa-Marin criteria	115
Chapter 7.	The relevance of intraoperative clinical and accelerometric measurements for thalamotomy outcome	131
Chapter 8.	Perioperative quantification of MDS-UPDRS-III tremor measurements in patients with Parkinson's Disease using accelerometry	151
Chapter 9.	Summary and discussion	173
Appendix.	Nederlandse samenvatting (Dutch summary)	192
	Dankwoord (acknowledgements)	202
	Curriculum vitae	206
	List of publications	207
	Author contribution	208



Chapter 1

Introduction and
thesis outline

Introduction and thesis outline

Parkinson's Disease (PD) and Essential Tremor (ET) are the most common movement disorders, associated with bradykinesia and/or tremor in case of PD and with tremor as the dominant feature in ET [1–4]. PD is a progressive disorder that affects the central nervous system. Its cardinal motor symptom is bradykinesia, often combined with tremor and/or rigidity [4–7]. The predominant motor symptom in ET is tremor [8]. Both bradykinesia and tremor frequently occur in the upper extremities, although both can also be present in other parts of the body [7,8]. Clinically, several scales are used to quantify these symptoms, which take a considerable amount of time and show obvious intra- and interrater variability [9–17]. Although scoring criteria frequently feature quantitative thresholds, the results of these clinical scales may vary depending on the experience of the rater and the time for the measurement. As a potential solution, standardized objective measurement of these phenomena, applied at the outpatient clinic, the clinic, as well as intraoperatively, would create an important step towards more reliable outcome measures, decreased rater-dependence, and more uniform assessments. Furthermore, standardized objective measurement of these motor symptoms would allow for adequate comparisons of pre-, intra-, and postoperative states, and would improve the exchange of these data in clinical trials. Moreover, precise monitoring of motor symptoms during Deep Brain surgery contributes to optimal lead placement and a better prediction of postoperative motor improvement [18]. Therefore, this thesis focuses on the perioperative application of accelerometry to quantify bradykinesia and tremor of the hands.

Phenomenology of tremor and bradykinesia

Tremor is a rhythmic and oscillatory movement that occurs involuntary [8]. In PD, tremor is dominant in the 4–7 Hz frequency range and is generally observed unilaterally in the extremities [19,20]. Specifically in PD, the tremor is most prominent at rest, decreases in amplitude during voluntary movement of the affected body part, and increases during mental tasks or voluntary movement of other body parts [7,19]. A characteristic feature of a PD tremor is the so-called “pill-rolling” tremor of the thumb and index finger, as well as the re-emergence phenomenon [21]. In contrast, ET is characterized by upper body tremor, often bilaterally, with a stable tremor frequency in a range similar to that of PD tremor [20]. ET mainly occurs during certain postures and voluntary movement of the affected body part. Notably, also an intention tremor is present in ET patients, in which tremor amplitude increases towards the end of a goal-directed movement [22,23].

Bradykinesia, another hallmark of PD, is characterized by small amplitude, slowness, and hesitancy of voluntary movements, as well as a lack of overall movement [5,24]. The presence of bradykinesia is a key prerequisite for the diagnosis of PD, according to both the 1988 UK Brain Bank PD criteria [25] and the more sensitive 2015 MDS Clinical Diagnostic Criteria for Parkinson's Disease [7,26]. When performing repetitive movement tasks, bradykinetic patients exhibit progressive reduction of amplitude and speed during the task [24,25].

Clinical measurements of tremor and bradykinesia

Several disease specific measurement instruments are currently in use to clinically evaluate motor symptoms like tremor and bradykinesia, both inside and outside the surgical setting [24,27,28]. Examples are the internationally standardized Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) part III (MDS-UPDRS-III), the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM) and The ET Rating Assessment Scale (TETRAS) [24,27,28]. These three scales are the most commonly applied methods to clinically rate the severity of tremor and/or bradykinesia, and have been thoroughly standardized by panels of movement disorders experts. All are based on ordinal scores ranging from 0 to 4 points per item [10,29,30]. Each scale applies various scoring criteria and thresholds [24,27,28].

Despite international standardization by expert neurologists, the subjective assessment of symptom severity by clinicians introduces variability [17]. Results depend on the rater's experience and the timing of measurement, potentially leading to bias [9–16]. A low inter- and intra-reliability of the MDS-UPDRS was reported in the measurement of within-subject changes [9]. Similarly, a rather large intra-rater variation and considerable inter-rater disagreement was shown [12]. It was also shown that if patients are evaluated by two raters, their UPDRS ratings can differ up to 16 points [12]. Given that multiple caregivers with various expertise levels are involved in rating the patient in the pre-, intra-, and postoperative phase, it is inevitable that inter-rater variability occurs. Moreover, MDS-UPDRS-III is designed to be applied in the sitting position. However, to evaluate the clinical effect during stereotactic neurosurgery or to assess bedridden PD patients, the MDS-UPDRS-III is often used in a supine position. Research on the supine application of MDS-UPDRS-III and its influence on its variability is lacking. In summary, while rating scales provide valuable insights, their application requires careful consideration of potential biases and variability in clinical assessments [9–16,31,32].

Objective quantification of tremor and bradykinesia

To overcome the drawbacks mentioned above, an objective measurement technique that uniformly depicts movement information of tremor and bradykinesia might help to identify the incidence, severity, and fluctuations of motor symptoms over time. Moreover, flaws in the current scoring system can be identified and possibly corrected using objective input. The introduction of objective measures in these clinical assessments might reduce the current inter- and intra-rater variability. Given the time and effort that was put into internationally standardizing the previously mentioned scales, it would make sense to explore solutions that stay close to these standardized outcome measures.

Movement sensors allow the collection of such objective movement data, and fall under the umbrella of transducers, i.e. any sensor converting a physiological signal into an electrical signal [33]. Transducer-based measurements have proven to be an effective addition to clinical assessment in accurately evaluating tremor and bradykinetic symptoms [32,34–45]. Digital measurement tools like movement sensors have been

widely recognized as promising tools to improve remote monitoring of patients with movement disorders [46].

However, studies with intraoperative motor measurements are scarce and rarely focus on tracing the course of motor symptoms during surgery [44,45,47]. Moreover, an overview of the current options for intraoperative quantification of motor symptoms during stereotactic neurosurgery is lacking. At this moment, methods that are proven to be accurate in preclinical settings can be applied in a neurosurgical setting with hardly any adjustments.

Accelerometry recording and data analysis

Accelerometers are noninvasive transducers that in the past decade are proven accurate, cost-effective, and widely available [41,48]. An accelerometer measures linear movement-induced accelerations relative to the Earth's gravitational field [48]. Tri-axial accelerometry is most commonly used, in which the accelerations are measured along three perpendicular axes (X, Y and Z). The output of such devices is a 3D time series of accelerations expressed in gravitational units (g) in the frame of reference of the device, where one g-unit denotes the acceleration of Earth's gravity [41,48]. Commercially available accelerometers nowadays are lightweight, small, and water-resistant, and allow wireless recordings. The dynamic measurement range of accelerometers used for human movement analysis typically varies between 2 and 16 g-units and its resolution from 8-bit to 12-bit [48,49]. The sampling rate of the device may vary depending on the application, although generally a rate from 20 Hz up to 200 Hz is applied, which suffices for human movement analysis [48–51]. Previous studies showed that tremor and bradykinesia can be quantified using accelerometry [47,52–67]. As such, tremor can be detected using the accelerometers embedded in smartphones [50,68,69]. The novelty of this thesis lies in investigating the application of accelerometry to classify bradykinesia and tremor using algorithms based on the gold standard criteria.

Raw accelerometric data tends to be noisy. Therefore, several pre-processing steps are needed to obtain clinically useful information. The data is generally pre-processed to filter low frequency noise, the Earth's gravitation, and higher-order harmonics from the signal [49–51,70]. For example, a 0.25 Hz infinite impulse response filter can be used to remove drift from accelerometry data [51]. A zero-phase third order Butterworth bandpass filter with cutoff frequencies of 1 Hz and 20 Hz was applied by van Brummelen et al. before their acceleration analysis [50]. Also, acceleration data in g-units can be transformed to m/s^2 units by correcting for the gravitational acceleration ($1 \text{ g} = 9.81 \text{ m/s}^2$). To prepare data for bradykinesia analysis, low-pass filtering with a cut-off value of e.g. 3 Hz can be applied to remove possible tremor from the signal [71]. Similarly, high-pass filtering with a cut-off value of e.g. 3 Hz could be considered for tremor tasks where low-frequent movements of adjacent body parts are expected, for example during the finger-to-nose maneuver [47,72,73].

The techniques for analyzing accelerometry data vary depending on the motor symptom of interest. Given the extensive application of accelerometry for movement analysis, numerous examples exist on how to analyze these data. In previous research, the outcome

measures in tremor detection derived from accelerometric data vary from peak frequency [50] to acceleration magnitude [74]. For assessing bradykinesia, the opening velocity [75] and dwell time [76] captured during finger tapping tests have been used [44,51].

Accelerometry is mostly applied to analyze tremor, commonly using frequency analysis. The peak frequency or frequency variability is determined to distinguish between various tremor syndromes [20,77,78]. As tremor is generally a distinct sinusoidal movement, its dominant frequency can be approximated using the Fast Fourier transform (FFT), which is a method to represent a time-based signal in the frequency domain. Several studies have employed this data analysis technique. For example, an all-pole auto regressive model can be used to distinguish between pathological tremor and physiological tremor [51]. In this study, the frequency spectra, and Power Spectral Density (PSD) were estimated using the Burg method [79]. Luft et al. also used a PSD-based method to detect tremor based on accelerometry data [80]. The tremor amplitude in centimeters, as described in the MDS-UPDRS-III, can be calculated from the acceleration data by double integration [81]. The drift resulting from integration can be resolved by applying a high-pass filter. Trends that have been found in previous studies based on accelerometric data include the finding that tremor amplitude increases and tremor frequency decreases as the disease progresses [76,81,82]. A logarithmic relation was found between clinical tremor rating scale scores and tremor amplitude measured using accelerometry [35,71,76,82,83].

Considering its complicated presentation, bradykinesia tends to be more complex to be captured with accelerometry than tremor. Although an abundance of movement (hyperkinesia) like tremor is generally more straightforward to capture with movement sensors than a lack of physiological movement (hypokinesia), the field of quantifying bradykinesia using accelerometry is evolving [84–86]. As bradykinesia is more clearly observed during repetitive movement tasks, continuous movement data is usually captured while the subject performs repetitive tasks as quickly and with the largest amplitude as possible, like finger tapping [24]. Amplitude decrement can be calculated by comparing these continuous data to a certain reference value, either from the acceleration signal (g) or from integrated data (cm). Time values (s) or velocity (cm/s) can be used to determine deceleration during these tasks. Interruptions and arrests of the ongoing movement indicate lack of movement (i.e. acceleration) compared to a certain reference. Previous studies have used accelerometry for automated prediction of finger tapping scores [84,85] and estimation of the severity of bradykinesia fluctuations in PD [71,86]. Other groups have attempted to quantify bradykinesia during unscripted tasks and daily living activities [51,67,87–89]. Also, accelerometry was used to distinguish between on and off states based on mean velocity and movement percentage [89].

It is important to note that while accelerometry has been studied substantially for the quantification of tremor and (to a lesser extent) bradykinesia, previous studies have mainly focused on determining objective measures that solely correlate well with clinical outcome measures [127]. These were primarily relative outcome measures, and not absolute measures of e.g. tremor amplitude (in cm) as stated in the MDS-UPDRS-III and FTM. Studies on absolute agreement of accelerometric methods with clinical ratings is still lacking, mainly since direct comparison of continuous accelerometric measures to the discrete measures of e.g. the MDS-UPDRS is limited.

Perioperative motor quantification in neurosurgery

PD and ET currently lack curative options. Nevertheless, various therapies are available to reduce the symptoms related to bradykinesia and tremor. Among the available neurosurgical treatment options for motor symptom reduction are Deep Brain Stimulation (DBS) and Deep Brain Lesioning (thalamotomy, pallidotomy) [90–93]. Deep brain targets for neurosurgery include the subthalamic nucleus (STN), the ventral intermediate nucleus (VIM) of the thalamus, and the internal globus pallidus (GPi) [94–96]. The stereotactic planning of neurosurgical targets relies on preoperative MRI and perioperative CT imaging [93,96–104]. During DBS surgery, one or two stimulating electrodes are meticulously placed in the target, either unilaterally or bilaterally, aiming to electrically suppress the debilitating motor symptoms [96–99]. In thalamotomy (VIM) and pallidotomy (GPi), a thermal lesion (ablation) is inflicted by placing a probe in the VIM or GPi to reduce motor symptoms [94]. Accurate positioning of DBS electrodes and/or lesioning probe has shown to be key to treatment success [39,105–114]. With the use of frame-based, skull-mounted devices and merged MRI-CT imaging, an accuracy for electrode insertion of approximately 1 mm can be achieved [113,115–118], although a considerable publication bias on these data has been reported [105]. With accurate neuro-navigation techniques, DBS surgeries can be performed under general anesthesia [119–122]. DBS performed under general anesthesia was shown to be as safe and effective as under local anesthesia with intraoperative neuromonitoring [122]. However, stereotactic neurosurgery is still performed under local anesthesia in some tremor-dominant and complex patients, to allow for adjustment of the electrode or lesioning probe based on clinical and/or electrophysiological monitoring [18,94,123–127]. Since such positioning is partly based on the clinical perioperative findings of the neurologist, it is important to correctly measure these motor symptoms during neurosurgery in order to achieve maximal symptom reduction without side effects [18,94,127].

If the DBS procedure is performed under local anesthesia, an alleviation of motor symptoms can be observed during or immediately after placement of the DBS electrode [124,125]. This phenomenon is referred to as the microlesion or stun effect [123–125,127]. During awake thalamotomy or pallidotomy, this effect can also be observed intraoperatively upon placement of the lesioning probe [94]. Several studies describe how the intensity of the stun effect may be used as an indication of correct electrode positioning [123–126]. The magnitude of the micro-lesion effect as well as the clinical motor effect after lesioning or after actual stimulation via the electrode can be intraoperatively real-time monitored during awake procedures [101,128]. It is important to intraoperatively monitor motor symptoms and side effects to confirm optimal lead placement and predict postoperative motor improvement [18]. Objective methods to intraoperatively quantify symptom severity can help neurosurgeons to position the electrode inside the brain more accurately, contributing to the best possible clinical outcome [44,45,94,127]. The added value of objective motor measurements in the perioperative setting lies in uniform evaluation of therapy effect, despite multiple caretakers being involved, allowing analyses on improvement of DBS candidate selection [129–131], prediction of individual treatment effect [130,132], and intraoperative confirmation of optimal electrode positioning [18,123–

127,133]. Accelerometry seems to be especially suitable for this purpose. Therefore, the perioperative application of accelerometry to quantify tremor and bradykinesia is investigated in this thesis.

Problem statement

The perioperative identification of motor symptom incidence and severity is critical for evaluating stereotactic neurosurgery and to optimize DBS treatment. Previous research has highlighted the importance of intraoperative monitoring of motor symptoms and side effects supporting optimal lead placement, and predicting postoperative motor improvement.

Considering the potential biases and variability associated with standard clinical assessments of tremor and bradykinesia, and the semi-permanent nature of DBS, there is an unmet need for objective methods to uniformly quantify tremor and bradykinesia in the perioperative setting. Reliable and objective outcome measures are essential in both research and clinical settings. Accelerometry is thought to be an accurate method to yield objective outcome measures that can be used to optimize Deep Brain surgery candidate selection, predict postoperative symptom reduction, confirm optimal lead placement, and evaluate treatment effect.

Since perioperative studies on accelerometric motor measurements are lacking, especially in the intraoperative setting, it is unclear how tremor and bradykinesia can be objectively quantified perioperatively, and which reliabilities can be yielded. In addition, there is a knowledge gap on the translation of standardized clinical scales (e.g. MDS-UPDRS, FTM) to objective methods using accelerometry measuring tremor and bradykinesia. Translating these internationally standardized scales into objective measures allows for the identification of the flaws that lead to the current inter- and intra-rater variabilities of clinical scales. Identification of such flaws improves the gold standard, while objective input into clinical assessments allows for a more uniform assessment.

Therefore, this thesis is dedicated to investigating several aspects of the perioperative quantification of tremor and bradykinesia, including current options for intraoperative quantification of motor symptoms during stereotactic neurosurgery.

Thesis outline

This thesis aims to investigate the following hypotheses:

1. Objective measurement of bradykinesia and tremor using accelerometry is a useful method to quantify existing clinical motor scales in PD and ET.
2. The objective measurement of bradykinesia and tremor has added value in monitoring patients with PD and ET perioperatively.

In **Chapter 2**, we systematically review the objective measuring techniques applied during awake stereotactic neurosurgery to quantify tremor, bradykinesia, and rigidity. In **Chapter 3**, we study the validity of MDS-UPDRS-III assessment performed in the supine position, as measured by two independent clinical raters and accelerometry.

Subsequently, we investigate the perioperative application of accelerometry to quantify bradykinesia of the hands. In **Chapter 4**, we examined the translation of MDS-UPDRS-III bradykinesia tests to an objective accelerometry-based method, being measured in patients with PD undergoing neurosurgical treatment.

Thereafter, we focus on the perioperative application of accelerometry to quantify tremor. In **Chapter 5**, we study the potential value of 3D accelerometry to intraoperatively quantify MDS-UPDRS-III tremor measurements. In **Chapter 6**, we do the same, investigating the quantification of Fahn-Tolosa-Marin tremor tests using accelerometry in ET patients who underwent neurosurgery. In **Chapter 7**, we look at the value of intraoperative MDS-UPDRS-III assessment versus accelerometric tremor measurements to predict thalamotomy outcomes. **Chapter 8** focuses on the accelerometric quantification of MDS-UPDRS-III tremor scores in a larger cohort of patients with PD, in a perioperative setting.

Finally, **Chapter 9** entails a general discussion. We summarize and discuss the results presented in this thesis and elaborate on the future directions of quantifying bradykinesia and tremor.

References

- [1] Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis* 2018;8:S3–8. <https://doi.org/10.3233/JPD.181474>.
- [2] Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of Essential Tremor. *Movement Disorders* 2010;25:534–41. <https://doi.org/10.1002/mds.22838>.
- [3] Benito-León J, Bermejo-Pareja F, Morales J-M, Vega S, Molina J-A. Prevalence of Essential Tremor in Three Elderly Populations of Central Spain. *Movement Disorders* 2003;18:389–94. <https://doi.org/10.1002/mds.10376>.
- [4] Kalia L, Lang AE. Parkinson's Disease. *The Lancet* 2015;386:896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3).
- [5] Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's Disease. *Lancet Neurol* 2006;5:75–86. [https://doi.org/10.1016/S1474-4422\(05\)70285-4](https://doi.org/10.1016/S1474-4422(05)70285-4).
- [6] Hughes AJ, Daniel SE, Blankson S, Lees AJ. A Clinicopathologic Study of 100 Cases of Parkinson's Disease. *Arch Neurol* 1993;50:140–8. <https://doi.org/10.1001/archneur.1993.00540020018011>.
- [7] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's Disease. *Movement Disorders* 2015;30:1591–601. <https://doi.org/10.1002/mds.26424>.
- [8] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders* 2018;33:75–87. <https://doi.org/10.1002/mds.27121>.
- [9] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.
- [10] Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's Disease rating scale. *Arch Neurol* 2010;67:64–70.
- [11] Asakawa T, Fang H, Sugiyama K, Nozaki T, Kobayashi S, Hong Z, et al. Human behavioral assessments in current research of Parkinson's Disease. *Neurosci Biobehav Rev* 2016;68:741–72. <https://doi.org/10.1016/j.neubiorev.2016.06.036>.
- [12] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [13] Rovini E, Maremmani C, Cavallo F. How wearable sensors can support Parkinson's Disease diagnosis and treatment: A systematic review. *Front Neurosci* 2017;11. <https://doi.org/10.3389/fnins.2017.00555>.
- [14] Lu R, Xu Y, Li X, Fan Y, Zeng W, Tan Y, et al. Evaluation of Wearable Sensor Devices in Parkinson's Disease: A Review of Current Status and Future Prospects. *Parkinsons Dis* 2020;2020. <https://doi.org/10.1155/2020/4693019>.
- [15] Yang K, Xiong WX, Liu FT, Sun YM, Luo S, Ding ZT, et al. Objective and quantitative assessment of motor function in Parkinson's Disease-from the perspective of practical applications. *Ann Transl Med* 2016;4. <https://doi.org/10.21037/atm.2016.03.09>.
- [16] Ossig C, Antonini A, Buhmann C, Classen J, Csoti I, Falkenburger B, et al. Wearable sensor-based objective assessment of motor symptoms in Parkinson's Disease. *J Neural Transm* 2016;123:57–64. <https://doi.org/10.1007/s00702-015-1439-8>.

- [17] Krabbe P. The Measurement of Health and Health Status: Concepts, Methods and Applications from a Multidisciplinary Perspective. 1st ed. Academic Press; 2016.
- [18] Sammartino F, Rege R, Krishna V. Reliability of Intraoperative Testing During Deep Brain Stimulation Surgery. *Neuromodulation* 2020;23:525–9. <https://doi.org/10.1111/ner.13081>.
- [19] Van De Wardt J, Van Der Stouwe AMM, Dirkx M, Elting JWJ, Post B, Tijssen MAJ, et al. Systematic clinical approach for diagnosing upper limb tremor. *J Neurol Neurosurg Psychiatry* 2020;91:822–30. <https://doi.org/10.1136/jnnp-2019-322676>.
- [20] van der Stouwe AMM, Elting JW, van der Hoeven JH, van Laar T, Leenders KL, Maurits NM, et al. How typical are ‘typical’ tremor characteristics? Sensitivity and specificity of five tremor phenomena. *Parkinsonism Relat Disord* 2016;30:23–8. <https://doi.org/10.1016/j.parkreldis.2016.06.008>.
- [21] Jankovic J. Parkinson’s Disease: Clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79:368–76. <https://doi.org/10.1136/jnnp.2007.131045>.
- [22] Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential Tremor and cerebellar dysfunction: Clinical and kinematic analysis of intention tremor. *Brain* 2000;123:1568–80.
- [23] Louis ED, Frucht SJ, Rios E. Intention tremor in Essential Tremor: Prevalence and association with disease duration. *Movement Disorders* 2009;24:626–7. <https://doi.org/10.1002/mds.22423>.
- [24] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson’s Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [25] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson’s Disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4. <https://doi.org/10.1136/jnnp.55.3.181>.
- [26] Postuma RB, Poewe W, Litvan I, Lewis S, Lang AE, Halliday G, et al. Validation of the MDS clinical diagnostic criteria for Parkinson’s Disease. *Movement Disorders* 2018;33:1601–8. <https://doi.org/10.1002/mds.27362>.
- [27] Fahn S, Tolosa E, Marín C. Clinical Rating Scale for Tremor. *Parkinson’s Disease and Movement Disorders* 1988:225–34.
- [28] Elble R, Comella C, Fahn S, Hallett M, Jankovic J, Juncos JL, et al. Reliability of a new scale for Essential Tremor. *Movement Disorders* 2012;27:1567–9. <https://doi.org/10.1002/mds.25162>.
- [29] Ondo W, Hashem V, LeWitt PA, Pahwa R, Shih L, Tarsy D, et al. Comparison of the Fahn-Tolosa-Marin Clinical Rating Scale and the Essential Tremor Rating Assessment Scale. *Mov Disord Clin Pract* 2018;5:60–5. <https://doi.org/10.1002/mdc3.12560>.
- [30] Stacy MA, Elble RJ, Ondo WG, Wu SC, Hulihan J. Assessment of interrater and intrarater reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in Essential Tremor. *Movement Disorders* 2007;22:833–8. <https://doi.org/10.1002/mds.21412>.
- [31] Erro R, Fasano A, Barone P, Bhatia KP. Milestones in Tremor Research: 10 Years Later. *Mov Disord Clin Pract* 2022;9:429–35. <https://doi.org/10.1002/mdc3.13418>.
- [32] Lukšys D, Jonaitis G, Griškevičius J. Quantitative Analysis of Parkinsonian Tremor in a Clinical Setting Using Inertial Measurement Units. *Parkinsons Dis* 2018;2018. <https://doi.org/10.1155/2018/1683831>.
- [33] Haubenberger D, Abbruzzese G, Bain PG, Bajaj N, Benito-León J, Bhatia KP, et al. Transducer-based evaluation of tremor. *Movement Disorders* 2016;31:1327–36. <https://doi.org/10.1002/mds.26671>.
- [34] del Din S, Godfrey A, Mazzà C, Lord S, Rochester L. Free-living monitoring of Parkinson’s Disease: Lessons from the field. *Movement Disorders* 2016;31:1293–313. <https://doi.org/10.1002/mds.26718>.

- [35] Elble RJ, Hellriegel H, Raethjen J, Deuschl G. Assessment of Head Tremor with Accelerometers Versus Gyroscopic Transducers. *Mov Disord Clin Pract* 2017;4:205–11. <https://doi.org/10.1002/mdc3.12379>.
- [36] Wastensson G, Holmberg B, Johnels B, Barregard L. Quantitative Methods for Evaluating the Efficacy of Thalamic Deep Brain Stimulation in Patients with Essential Tremor. *Tremor and Other Hyperkinetic Movements* 2013;4. <https://doi.org/10.7916/D8VM4BoN>.
- [37] Elble RJ, Ondo W. Tremor rating scales and laboratory tools for assessing tremor. *J Neurol Sci* 2022;435. <https://doi.org/10.1016/j.jns.2022.120202>.
- [38] Rodríguez-Molinero A, Samà A, Pérez-López C, Rodríguez-Martín D, Alcaine S, Mestre B, et al. Analysis of correlation between an accelerometer-based algorithm for detecting Parkinsonian gait and UPDRS subscales. *Front Neurol* 2017;8. <https://doi.org/10.3389/fneur.2017.00431>.
- [39] Athawale TM, Johnson KA, Butson CR, Johnson CR. A statistical framework for quantification and visualisation of positional uncertainty in deep brain stimulation electrodes. *Comput Methods Biomech Biomed Eng Imaging Vis* 2019;7:438–49. <https://doi.org/10.1080/21681163.2018.1523750>.
- [40] Bobić V, Djurić-Jovičić M, Dragašević N, Popović MB, Kostić VS, Kvaščev G. An expert system for quantification of bradykinesia based on wearable inertial sensors. *Sensors (Switzerland)* 2019;19. <https://doi.org/10.3390/s1912644>.
- [41] Karas M, Bai J, Strączkiewicz M, Harezlak J, Glynn NW, Harris T, et al. Accelerometry Data in Health Research: Challenges and Opportunities: Review and Examples. *Stat Biosci* 2019;11:210–37. <https://doi.org/10.1007/s12561-018-9227-2>.
- [42] Mansur PHG, Cury LKP, Andrade AO, Pereira AA, Miotto GAA, Soares AB, et al. A Review on Techniques for Tremor Recording and Quantification. *Crit Rev Biomed Eng* 2007;35:343–62. <https://doi.org/10.1615/CritRevBiomedEng.v35.i5.10>.
- [43] García-Agundez A, Eickhoff C. Towards Objective Quantification of Hand Tremors and Bradykinesia Using Contactless Sensors: A Systematic Review. *Front Aging Neurosci* 2021;13. <https://doi.org/10.3389/fnagi.2021.716102>.
- [44] Shah A, Coste J, Lemaire JJ, Taub E, Schüpbach WMM, Pollo C, et al. Intraoperative acceleration measurements to quantify improvement in tremor during deep brain stimulation surgery. *Med Biol Eng Comput* 2017;55:845–58. <https://doi.org/10.1007/s11517-016-1559-9>.
- [45] Shah A, Coste J, Lemaire JJ, Schkommodau E, Taub E, Guzman R, et al. A novel assistive method for rigidity evaluation during deep brain stimulation surgery using acceleration sensors. *J Neurosurg* 2017;127:602–12. <https://doi.org/10.3171/2016.8.JNS152770>.
- [46] Erb MK, Karlin DR, Ho BK, Thomas KC, Parisi F, Vergara-Díaz GP, et al. mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's Disease. *NPJ Digit Med* 2020;3. <https://doi.org/10.1038/s41746-019-0214-x>.
- [47] Zajki-Zechmeister T, Kögl M, Kalsberger K, Frantal S, Homayoon N, Katschnig-Winter P, et al. Quantification of tremor severity with a mobile tremor pen. *Heliyon* 2020;6:e047. <https://doi.org/10.1016/j.heliyon.2020.e04702>.
- [48] Sievänen H, Kujala UM. Accelerometry - Simple, but challenging. *Scand J Med Sci Sports* 2017;27:574–8. <https://doi.org/10.1111/sms.12887>.
- [49] Salarian A, Russmann H, Vingerhoets FJG, Burkhard PR, Aminian K. Ambulatory monitoring of physical activities in patients with Parkinson's Disease. *IEEE Trans Biomed Eng* 2007;54:2296–9. <https://doi.org/10.1109/TBME.2007.896591>.
- [50] van Brummelen EMJ, Ziagkos D, de Boon WMI, Hart EP, Doll RJ, Huttunen T, et al. Quantification of tremor using consumer product accelerometry is feasible in patients with Essential Tremor and Parkinson's Disease: a comparative study. *J Clin Mov Disord* 2020;7. <https://doi.org/10.1186/s40734-020-00086-7>.

- [51] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [52] Dunnewold RJW, Hoff JI, van Pelt HCJ, Fredrikze PQ, Wagemans EAH, van Hilten BJJ. Ambulatory Quantitative Assessment of Body Position, Bradykinesia, and Hypokinesia in Parkinson's Disease. *Journal of Clinical Neurophysiology* 1998;15:235–42. <https://doi.org/10.1097/00004691-199805000-00007>.
- [53] Dunnewold RJW, Jacobi CE, van Hilten JJ. Quantitative assessment of bradykinesia in patients with Parkinson's Disease. *J Neurosci Methods* 1997;74:107–12.
- [54] Hoff JI, V/D Plas AA, Wagemans EAH, van Hilten JJ. Accelerometric Assessment of Levodopa-Induced Dyskinesias in Parkinson's Disease. *Movement Disorders* 2001;16:58–61.
- [55] Hoff JI, van der Meer V, van Hilten JJ. Accuracy of Objective Ambulatory Accelerometry in Detecting Motor Complications in Patients With Parkinson Disease. *Clin Neuropharmacol* 2004;27:53–7.
- [56] Rajaraman V, Jack D, Adamovich S v, Hening W, Sage J, Poizner H. A novel quantitative method for 3D measurement of Parkinsonian tremor. *Clinical Neurophysiology* 2000;111:338–43.
- [57] van Someren EJW. Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's Disease. *IEEE Transactions on Rehabilitation Engineering* 1997;5:394–8. <https://doi.org/10.1109/86.650297>.
- [58] Deuschl G, Lauk M, Timmer J. Tremor classification and tremor time series analysis. *Chaos* 1995;5:48–51. <https://doi.org/10.1063/1.166084>.
- [59] van Hilten JJ, Middelkoop HAM, Kerkhof GA, Roos RAC. A new approach in the assessment of motor activity in Parkinson's Disease. *J Neurol Neurosurg Psychiatry* 1991;54:976–9. <https://doi.org/10.1136/jnnp.54.11.976>.
- [60] Spyers-Ashby JM, Stokes MJ, Bain PG, Roberts SJ. Classification of normal and pathological tremors using a multidimensional electromagnetic system. *Med Eng Phys* 1999;21:713–23.
- [61] Battista L, Romaniello A. A wearable tool for continuous monitoring of movement disorders: clinical assessment and comparison with tremor scores. *Neurological Sciences* 2021;42:4241–8. <https://doi.org/10.1007/s10072-021-05120-6>.
- [62] Gauthier-Lafreniere E, Aljassar M, Rymar V, Milton J, Sadikot AF. A standardized accelerometry method for characterizing tremor: Application and validation in an ageing population with postural and action tremor. *Front Neuroinform* 2022;16. <https://doi.org/10.3389/fninf.2022.878279>.
- [63] Tsiouras MG, Tzallas AT, Rigas G, Tsouli S, Fotiadis DI, Konitsiotis S. An automated methodology for levodopa-induced dyskinesia: Assessment based on gyroscope and accelerometer signals. *Artif Intell Med* 2012;55:127–35. <https://doi.org/10.1016/j.artmed.2012.03.003>.
- [64] Thielgen T, Foerster F, Fuchs G, Hornig A, Fahrenberg J. Tremor in Parkinson's Disease: 24-hr monitoring with calibrated accelerometry. *Electromyogr Clin Neurophysiol* 2004;44:137–46.
- [65] Hoff JI, Wagemans EA, van Hilten BJ. Ambulatory Objective Assessment of Tremor in Parkinson's Disease. *Clin Neuropharmacol* 2001;24:280–3. <https://doi.org/10.1097/00002826-200109000-00004>.
- [66] Garcia Ruiz PJ, Sanchez Bernardos V. Evaluation of ActiTrac® (ambulatory activity monitor) in Parkinson's Disease. *J Neurol Sci* 2008;270:67–9. <https://doi.org/10.1016/j.jns.2008.02.002>.
- [67] Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's Disease. *J Parkinsons Dis* 2012;2:47–55. <https://doi.org/10.3233/JPD.2012.11071>.
- [68] Sajal MSR, Ehsan MT, Vaidyanathan R, Wang S, Aziz T, Mamun KA al. Telemonitoring Parkinson's Disease using machine learning by combining tremor and voice analysis. *Brain Inform* 2020;7:12. <https://doi.org/10.1186/s40708-020-00113-1>.

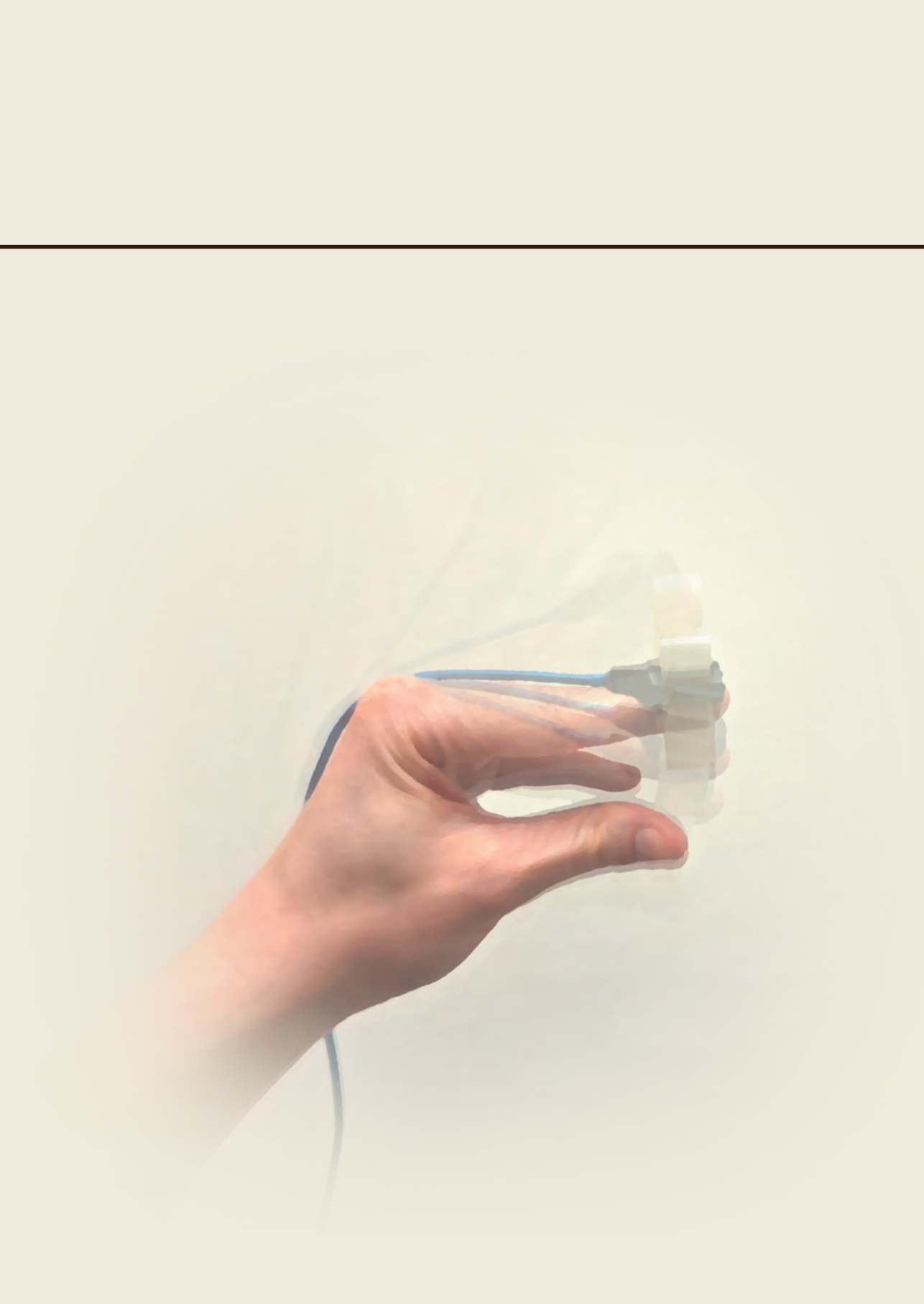
- [69] Daneault JF, Carignan B, Codère CÉ, Sadikot AF, Duval C. Using a smart phone as a standalone platform for detection and monitoring of pathological tremors. *Front Hum Neurosci* 2012;1:–31. <https://doi.org/10.3389/fnhum.2012.00357>.
- [70] Meigal AY, Rissanen SM, Tarvainen MP, Georgiadis SD, Karjalainen PA, Airaksinen O, et al. Linear and nonlinear tremor acceleration characteristics in patients with Parkinson's Disease. *Physiol Meas* 2012;33:395–412. <https://doi.org/10.1088/0967-3334/33/3/395>.
- [71] Patel S, Lorincz K, Hughes R, Huggins N, Growdon J, Standaert D, et al. Monitoring motor fluctuations in patients with parkinsons disease using wearable sensors. *IEEE Transactions on Information Technology in Biomedicine* 2009;13:864–73. <https://doi.org/10.1109/TITB.2009.2033471>.
- [72] Dai H, Zhang P, Lueth TC. Quantitative assessment of parkinsonian tremor based on an inertial measurement unit. *Sensors (Switzerland)* 2015;15:25055–71. <https://doi.org/10.3390/s151025055>.
- [73] Cai G, Lin Z, Dai H, Xia X, Xiong Y, Horng SJ, et al. Quantitative assessment of parkinsonian tremor based on a linear acceleration extraction algorithm. *Biomed Signal Process Control* 2018;42:53–62. <https://doi.org/10.1016/j.bspc.2018.01.008>.
- [74] Kostikis N, Hristu-Varsakelis D, Arnaoutoglou M, Kotsavasiloglou C. A smartphone-based tool for assessing parkinsonian hand tremor. *IEEE J Biomed Health Inform* 2015;19:1835–42. <https://doi.org/10.1109/JBHI.2015.2471093>.
- [75] Yokoe M, Okuno R, Hamasaki T, Kurachi Y, Akazawa K, Sakoda S. Opening velocity, a novel parameter, for finger tapping test in patients with Parkinson's Disease. *Parkinsonism Relat Disord* 2009;15:440–4. <https://doi.org/10.1016/j.parkreldis.2008.11.003>.
- [76] Maldonado-Naranjo A, Koop MM, Hogue O, Alberts J, MacHado A. Kinematic Metrics from a Wireless Stylus Quantify Tremor and Bradykinesia in Parkinson's Disease. *Parkinsons Dis* 2019;2019. <https://doi.org/10.1155/2019/6850478>.
- [77] Galperin I, Hillel I, Del Din S, Bekkers EMJ, Nieuwboer A, Abbruzzese G, et al. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's Disease. *Parkinsonism Relat Disord* 2019;62:85–90. <https://doi.org/10.1016/j.parkreldis.2019.01.022>.
- [78] Piña-Fuentes D, van Dijk JMC, Drost G, van Zijl JC, van Laar T, Tijssen MAJ, et al. Direct comparison of oscillatory activity in the motor system of Parkinson's Disease and dystonia: A review of the literature and meta-analysis. *Clinical Neurophysiology* 2019;130:917–24. <https://doi.org/10.1016/j.clinph.2019.02.015>.
- [79] Burg JP. Maximum entropy spectral analysis. Ph.D. dissertation. Stanford Univ. Stanford, CA, 1975.
- [80] Luft F, Sharifi S, Mugge W, Schouten AC, Bour LJ, van Rootselaar AF, et al. A power spectral density-based method to detect tremor and tremor intermittency in movement disorders. *Sensors (Switzerland)* 2019;19. <https://doi.org/10.3390/s19194301>.
- [81] Jeon H, Kim SK, Jeon B, Park KS. Distance estimation from acceleration for quantitative evaluation of Parkinson tremor. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2011*, p. 393–6. <https://doi.org/10.1109/IEMBS.2011.6090126>.
- [82] Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. *Brain* 2006;129:2660–6. <https://doi.org/10.1093/brain/awl190>.
- [83] Fisher JM, Hammerla NY, Rochester L, Andras P, Walker RW. Body-Worn Sensors in Parkinson's Disease: Evaluating Their Acceptability to Patients. *Telemedicine and E-Health* 2016;22:63–9. <https://doi.org/10.1089/tmj.2015.0026>.

- [84] Stamatakis J, Ambroise J, Crémers J, Sharei H, Delvaux V, Macq B, et al. Finger tapping clinimetric score prediction in Parkinson's Disease using low-cost accelerometers. *Comput Intell Neurosci* 2013;2013. <https://doi.org/10.1155/2013/717853>.
- [85] Habets JGV, Spooner RK, Mathiopoulou V, Feldmann LK, Busch JL, Roediger J, et al. A First Methodological Development and Validation of ReTap: An Open-Source UPDRS Finger Tapping Assessment Tool Based on Accelerometer-Data. *Sensors* 2023;23. <https://doi.org/10.3390/s23115238>.
- [86] Spooner RK, Banners BH, Schnitzler A, Florin E. Time-resolved quantification of fine hand movements as a proxy for evaluating bradykinesia-induced motor dysfunction. *Sci Rep* 2024;14. <https://doi.org/10.1038/s41598-024-55862-4>.
- [87] Hoff JJ, Van Der Meer V, Van Hilten JJ. Accuracy of Objective Ambulatory Accelerometry in Detecting Motor Complications in Patients With Parkinson Disease. *Clin Neuropharmacol* 2004;27:53–7.
- [88] Cancela J, Pansera M, Arredondo MT, Estrada JJ, Pastorino M, Pastor-Sanz L, et al. A comprehensive motor symptom monitoring and management system: The bradykinesia case. 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology, IEEE; 2010, p. 1008–11. <https://doi.org/10.1109/IEMBS.2010.5627775>.
- [89] Keijsers NLW, Horstink MWIM, Gielen SCAM. Ambulatory motor assessment in Parkinson's Disease. *Movement Disorders* 2006;21:34–44. <https://doi.org/10.1002/mds.20633>.
- [90] Kabra A, Sharma R, Kabra R, Baghel US. Emerging and Alternative Therapies For Parkinson Disease: An Updated Review. *Curr Pharm Des* 2018;24:2573–82. <https://doi.org/10.2174/1381612824666180820150150>.
- [91] Abosch A, Lozano A. Stereotactic neurosurgery for movement disorders. *Canadian Journal of Neurological Sciences* 2003;30. <https://doi.org/10.1017/s0317167100003279>.
- [92] Fejeran J, Salazar F, Alvarez CM, Jahangiri FR. Deep Brain Stimulation and Microelectrode Recording for the Treatment of Parkinson's Disease. *Cureus* 2022. <https://doi.org/10.7759/cureus.27887>.
- [93] Eskandar EN, Shinobu LA, Penney JB, Cosgrove GR, Counihan TJ. Stereotactic pallidotomy performed without using microelectrode guidance in patients with Parkinson's Disease: surgical technique and 2-year results. *J Neurosurg* 2000;92:375–83. <https://doi.org/10.3171/jns.2000.92.3.0375>.
- [94] Kremer NI, Pauwels RWJ, Pozzi NG, Lange F, Roothans J, Volkmann J, et al. Deep brain stimulation for tremor: Update on long-term outcomes, target considerations and future directions. *J Clin Med* 2021;10. <https://doi.org/10.3390/jcm10163468>.
- [95] Dallapiazza RF, Lee DJ, De Vloo P, Fomenko A, Hamani C, Hodaie M, et al. Outcomes from stereotactic surgery for Essential Tremor. *J Neurol Neurosurg Psychiatry* 2019;90:474–82. <https://doi.org/10.1136/jnnp-2018-318240>.
- [96] Chen KHS, Chen R. Invasive and Noninvasive Brain Stimulation in Parkinson's Disease: Clinical Effects and Future Perspectives. *Clin Pharmacol Ther* 2019;106:763–75. <https://doi.org/10.1002/cpt.1542>.
- [97] Hilker R, Voges J, Weber T, Kracht L, Roggendorf J, Baudrexel S, et al. STN-DBS activates the target area in Parkinson disease: An FDG-PET study. *Neurology* 2008;71:708–13.
- [98] Schor JS, Nelson AB. Multiple stimulation parameters influence efficacy of deep brain stimulation in parkinsonian mice. *Journal of Clinical Investigation* 2019;129:3833–8. <https://doi.org/10.1172/JCI122390>.
- [99] Chiken S, Nambu A. Mechanism of Deep Brain Stimulation: Inhibition, Excitation, or Disruption? *Neuroscientist* 2016;22:313–22. <https://doi.org/10.1177/1073858415581986>.
- [100] Fiegele T, Feuchtner G, Sohm F, Bauer R, Anton JV, Gotwald T, et al. Accuracy of stereotactic electrode placement in deep brain stimulation by intraoperative computed tomography. *Parkinsonism Relat Disord* 2008;14:595–9. <https://doi.org/10.1016/j.parkreldis.2008.01.008>.

- [101] Alterman RL, Kall BA, Cohen H, Kelly PJ. Stereotactic Ventrolateral Thalamotomy: is ventriculography necessary? *Neurosurgery* 1995;37:717–22. <https://doi.org/10.1227/00006123-199510000-00016>.
- [102] Sammartino F, Krishna V, King NKK, Lozano AM, Schwartz ML, Huang Y, et al. Tractography-Based Ventral Intermediate Nucleus Targeting: Novel Methodology and Intraoperative Validation. *Movement Disorders* 2016;31:1217–25. <https://doi.org/10.1002/mds.26633>.
- [103] King NKK, Krishna V, Sammartino F, Bari A, Reddy GD, Hodaie M, et al. Anatomic Targeting of the Optimal Location for Thalamic Deep Brain Stimulation in Patients with Essential Tremor. *World Neurosurg* 2017;107:168–74. <https://doi.org/10.1016/j.wneu.2017.07.136>.
- [104] King NKK, Krishna V, Basha D, Elias G, Sammartino F, Hodaie M, et al. Microelectrode recording findings within the tractography-defined ventral intermediate nucleus. *J Neurosurg* 2017;126:1669–75. <https://doi.org/10.3171/2016.3.JNS151992>.
- [105] Kremer NI, van Laar T, Lange SF, Statius Muller S, la Bastide-van Gemert S, Oterdoom DM, et al. STN-DBS electrode placement accuracy and motor improvement in Parkinson's Disease: systematic review and individual patient meta-analysis. *J Neurol Neurosurg Psychiatry* 2022;jnnp-2022-329192. <https://doi.org/10.1136/jnnp-2022-329192>.
- [106] Okun MS, Foote KD. Parkinson's Disease DBS: what, when, who and why? The time has come to tailor DBS targets. *Expert Rev Neurother* 2010;10:1847–57.
- [107] Okun MS, Tagliati M, Pourfar M, Fernandez HH, Rodriguez RL, Alterman RL, et al. Management of Referred Deep Brain Stimulation Failures A Retrospective Analysis From 2 Movement Disorders Centers. *Arch Neurol* 2005;62:1250–6.
- [108] Dembek TA, Roediger J, Horn A, Reker P, Oehrns C, Dafsari HS, et al. Probabilistic sweet spots predict motor outcome for deep brain stimulation in Parkinson disease. *Ann Neurol* 2019;86:527–38. <https://doi.org/10.1002/ana.25567>.
- [109] Saint-Cyr JA, Hoque T, Pereira LCM, Dostrovsky JO, Hutchison WD, Mikulis DJ, et al. Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. *J Neurosurg* 2002;97:1152–66.
- [110] Nguyen TAK, Nowacki A, Debove I, Petermann K, Tinkhauser G, Wiest R, et al. Directional stimulation of subthalamic nucleus sweet spot predicts clinical efficacy: Proof of concept. *Brain Stimul* 2019;12:1127–34. <https://doi.org/10.1016/j.brs.2019.05.001>.
- [111] Herzog J, Fietzek U, Hamel W, Morsnowski A, Steigerwald F, Schrader B, et al. Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's Disease. *Movement Disorders* 2004;19:1050–4. <https://doi.org/10.1002/mds.20056>.
- [112] Wodarg F, Herzog J, Reese R, Falk D, Pinsker MO, Steigerwald F, et al. Stimulation site within the MRI-defined STN predicts postoperative motor outcome. *Movement Disorders* 2012;27:874–9. <https://doi.org/10.1002/mds.25006>.
- [113] Verhagen R, Bour LJ, Odekerken VJJ, van den Munckhof P, Richard Schuurman P, de Bie RMA. Electrode location in a microelectrode recording-based model of the subthalamic nucleus can predict motor improvement after deep brain stimulation for Parkinson's Disease. *Brain Sci* 2019;9. <https://doi.org/10.3390/brainsci9030051>.
- [114] Sirica D, Hewitt AL, Tarolli CG, Weber MT, Zimmerman C, Santiago A, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. *Neurodegener Dis Manag* 2021;11:315–28. <https://doi.org/10.2217/nmt-2021-0002>.
- [115] Shamir RR, Joskowicz L, Spektor S, Shoshan Y. Target and trajectory clinical application accuracy in neuronavigation. *Neurosurgery* 2011;68:95–101. <https://doi.org/10.1227/NEU.0b013e31820828d9>.
- [116] Benabid AL, Pollak P, Hoffmann D, Gervason C, Hommel M, Perret JE, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 1991;337:403–6.

- [117] Holloway KL, Gaede SE, Starr PA, Rosenow JM, Ramakrishnan V, Jaimie Henderson AM. Frameless stereotaxy using bone fiducial markers for deep brain stimulation. *J Neurosurg* 2005;103:404–13.
- [118] Dallapiazza R, McKisic MS, Shah B, Elias WJ. Neuromodulation for Movement Disorders. *Neurosurg Clin N Am* 2014;25:47–58. <https://doi.org/10.1016/j.nec.2013.08.002>.
- [119] Holewijn RA, Verbaan D, Van Den Munckhof PM, Bot M, Geurtsen GJ, Dijk JM, et al. General Anesthesia vs Local Anesthesia in Microelectrode Recording-Guided Deep-Brain Stimulation for Parkinson Disease: The GALAXY Randomized Clinical Trial. *JAMA Neurol* 2021;78:1212–9. <https://doi.org/10.1001/jamaneurol.2021.2979>.
- [120] Ho AL, Ali R, Connolly ID, Henderson JM, Dhall R, Stein SC, et al. Awake versus asleep deep brain stimulation for Parkinson's Disease: a critical comparison and meta-analysis. *J Neurol Neurosurg Psychiatry* 2018;89:687–91. <https://doi.org/10.1136/jnnp-2016-314500>.
- [121] Liu Z, He S, Li L. General anesthesia versus local anesthesia for deep brain stimulation in Parkinson's Disease: A meta-analysis. *Stereotact Funct Neurosurg* 2020;97:381–90. <https://doi.org/10.1159/000505079>.
- [122] Chen T, Mirzadeh Z, Chapple KM, Lambert M, Evidente VGH, Moguel-Cobos G, et al. Intraoperative test stimulation versus stereotactic accuracy as a surgical end point: A comparison of Essential Tremor outcomes after ventral intermediate nucleus deep brain stimulation. *J Neurosurg* 2018;129:290–8. <https://doi.org/10.3171/2017.3.JNS162487>.
- [123] Cersosimo MG, Raina GB, Benarroch EE, Piedimonte F, Alemán GG, Micheli FE. Micro lesion effect of the globus pallidus internus and outcome with deep brain stimulation in patients with Parkinson's Disease and dystonia. *Movement Disorders* 2009;24:1488–93. <https://doi.org/10.1002/mds.22641>.
- [124] Erdogan S, Savas A, Aydin N, Akbostanci MC. Predictive factors for favorable outcome from subthalamic nucleus deep brain stimulation in Parkinson's Disease. *Turk Neurosurg* 2020;30:43–7. <https://doi.org/10.5137/1019-5149.JTN.25028-18.3>.
- [125] Lange SF, Kremer NI, van Laar T, Lange F, Steendam-Oldekamp TE, Oterdoom DLM, et al. The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation* 2021. <https://doi.org/10.1111/ner.13523>.
- [126] Pourfar M, Tang C, Lin T, Dhawan V, Kaplitt MG, Eidelberg DD. Assessing the microlesion effect of subthalamic deep brain stimulation surgery with FDG PET: Clinical article. *J Neurosurg* 2009;110:1278–82. <https://doi.org/10.3171/2008.12.JNS08991>.
- [127] Mahajan A, Bader A, Wang LL, Rekhtman A, Espay AJ, Dwivedi AK, et al. Thalamic Deep Brain Stimulation for tremor: The critical role of intraoperative testing. *Parkinsonism Relat Disord* 2020;73:45–9. <https://doi.org/10.1016/j.parkreldis.2020.03.022>.
- [128] Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *New England Journal of Medicine* 2016;375:730–9. <https://doi.org/10.1056/NEJMoa1600159>.
- [129] Lieber B, Taylor BES, Appelboom G, Mckhann G, Connolly ES. Motion Sensors to Assess and Monitor Medical and Surgical Management of Parkinson Disease. *World Neurosurg* 2015;84:561–6. <https://doi.org/10.1016/j.wneu.2015.03.024>.
- [130] Rügge D, Mahendran S, Stieglitz LH, Oertel MF, Gassert R, Lamberg O, et al. Tremor analysis with wearable sensors correlates with outcome after thalamic deep brain stimulation. *Clin Park Relat Disord* 2020;3. <https://doi.org/10.1016/j.prdoa.2020.100066>.
- [131] Khodakarami H, Farzanehfar P, Horne M. The use of data from the parkinson's kinetigraph to identify potential candidates for device assisted therapies. *Sensors (Switzerland)* 2019;19. <https://doi.org/10.3390/s19102241>.

- [132] Obwegeser AA, Uitti RJ, Witte RJ, Lucas JA, Turk MF, Wharen RE. Quantitative and Qualitative Outcome Measures after Thalamic Deep Brain Stimulation to Treat Disabling Tremors. *Neurosurgery* 2001;48:274–81.
- [133] Kremer NI, Oterdoom DLM, Absalom AR, ten Cate DW, van Dijk JMC, van Egmond ME, et al. Are we on the right track in DBS surgery for dystonic head tremor? Polymyography is a promising answer. *Parkinsonism Relat Disord* 2021;93:74–6. <https://doi.org/10.1016/j.parkreldis.2021.11.013>.



Chapter 2

Objective clinical registration of tremor, bradykinesia, and rigidity during awake stereotactic neurosurgery: a scoping review

Annemarie Smid

Zeus T. Dominguez-Vega

Teus van Laar

D. L. Marinus Oterdoom

Anthony R. Absalom

Martje E. van Egmond

Gea Drost

J. Marc C. van Dijk

Neurosurgical Review (2024)

doi: 10.1007/s10143-024-02312-4

Abstract

Background

Tremor, bradykinesia, and rigidity are incapacitating motor symptoms that can be suppressed with stereotactic neurosurgical treatment like Deep Brain Stimulation (DBS), and ablative surgery (e.g. thalamotomy, pallidotomy). Traditionally, clinicians rely on clinical rating scales for intraoperative evaluation of these motor symptoms during awake stereotactic neurosurgery. However, these clinical scales have a relatively high inter-rater variability and rely on experienced raters. Therefore, objective registration (e.g. using movement sensors) is a reasonable extension for intraoperative assessment of tremor, bradykinesia, and rigidity.

Objective

The main goal of this scoping review is to provide an overview of electronic motor measurements during awake stereotactic neurosurgery.

Methods

The protocol was based on the PRISMA extension for scoping reviews. After a systematic database search (PubMed, Embase, and Web of Science), articles were screened for relevance. Hundred-and-three articles were subject to detailed screening. Key clinical and technical information was extracted. The inclusion criteria encompassed use of electronic motor measurements during stereotactic neurosurgery performed under local anesthesia.

Results

Twenty-three articles were included. These studies had various objectives, including correlating sensor-based outcome measures to clinical scores, identifying optimal DBS electrode positions, and translating clinical assessments to objective assessments. The studies were highly heterogeneous in device choice, sensor location, measurement protocol, design, outcome measures, and data analysis.

Conclusion

This review shows that intraoperative quantification of motor symptoms is still limited by variable signal analysis techniques and lacking standardized measurement protocols. However, electronic motor measurements can complement visual evaluations and provide objective confirmation of correct placement of the DBS electrode and/or lesioning. On the long-term, this might benefit patient outcomes and provide reliable outcome measures in scientific research.

1. Introduction

Tremor, bradykinesia, and rigidity are debilitating motor symptoms that can be alleviated with stereotactic neurosurgical treatment [1,2]. Currently, intraoperative neurosurgical decisions are based, in part, on subjective and episodic evaluations of tremor, bradykinesia, and rigidity [3–13]. Objective registration is a reasonable extension for intraoperative assessment of these cardinal symptoms [6–11,14–20]. Unfortunately, motor symptoms remain difficult to measure objectively, due to the heterogeneity of the symptoms between patients. Currently, expert evaluation is often used as the gold standard in research aiming to validate objective methods. Studies performed outside the intraoperative setting showed that electronic measurements can improve clinical evaluation, resulting in for example a decrease in scoring error of up to 20% [21], increased reliability [12,22–24], and increased accuracy [7,24–27]. These results motivate further investigation of objective intraoperative registration of these motor symptoms. However, studies on intraoperative motor measurements are scarce and rarely focused on tracing the course of motor symptoms during surgery [6,19,28–30]. Also, there are inconsistencies in the methods and protocols that are described. As a result, objective and quantitative input is still lacking in the mainstream clinical decision-making for guiding and adjusting treatment. This paper aims to present a structured overview of current objective clinical registration of tremor, bradykinesia, and rigidity during awake stereotactic neurosurgery, to discuss the key findings in the current literature, and to identify trends that can be relevant for clinical practice.

1.1. Clinical background

Tremor, bradykinesia, and rigidity can occur in several movement disorders, like Parkinson's Disease (PD), Essential Tremor (ET), Dystonic Tremor (DT) and Holmes Tremor (HT). While the sole motor symptom in ET is tremor, patients with PD also suffer from bradykinesia and rigidity [31,32]. Tremor can also occur in dystonia, which is a movement disorder characterized by sustained or intermittent muscle contractions [33,34]. HT is a low frequency, more proximal tremor syndrome, frequently caused by an acquired lesion in the brainstem [31].

Open neurosurgical treatment options for motor symptom reduction consist of Deep Brain Stimulation (DBS) and radiofrequency (RF) needle ablation (e.g. thalamotomy and pallidotomy) [2]. Based on specific symptoms, potential targets include the subthalamic nucleus (STN), ventral intermediate nucleus (VIM), and globus pallidus internus (GPI) [1,33,35,36], among others. Incisionless approaches include application of Gamma Knife [37] or Magnetic Resonance Imaging (MRI)-guided focused ultrasound (MRgFUS) [30,38].

During procedures under local anesthesia, immediate alleviation of motor symptoms can usually be observed after placement of the DBS electrode, RF-lesioning probe or during the MRgFUS test lesion: the microlesion or stunning effect [1,34,39–41]. Several studies describe how the intensity of the stunning effect can be an indication of correct targeting [34,39–41]. The magnitude of the intraoperative effect on the symptoms can be

real-time monitored during awake procedures [38,42,43]. Sammartino et al. described the importance of intraoperative monitoring of motor symptoms and side effects for confirming optimal lead placement and predicting postoperative motor improvement [29].

Tremor, bradykinesia, and rigidity are often intraoperatively evaluated with disease-specific clinical rating scales, e.g., the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) [44] and the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM) [45]. As such, severity of symptoms is subjectively assessed by an expert [3–11,14,15] and its results depend on the rater's experience, which may result in significant bias [3–11,14]. For example, the results from Post et al. showed a rather large intra-rater variation and considerable inter-rater disagreement [4]. They also showed that if patients are evaluated by two different raters, the total UPDRS ratings can differ up to 16 points [4]. Different caregivers with different expertise levels are involved with rating the patient during the preoperative, intraoperative, and postoperative measurements, resulting in inter-rater variability. This lack in continuity in measurements might negatively affect patient outcomes [3–11,14].

1.2. Technical background

Wearable devices and video-based measurements allow for collection of data representing movement information of tremor, bradykinesia, and rigidity [46]. The use of such devices has been proven to aid experts in objectively quantifying symptoms during application of clinical protocols (e.g., MDS-UPDRS) [6,16–19]. This might reduce inter- and intra-rater variability and optimize clinical outcome. Nonetheless, devices have to fulfill various requirements in order to be suitable for human movement analysis, for example: small size, light weight, unobtrusive, reliable, and accurate [47]. Electromyography (EMG), accelerometers, gyroscopes, and optical devices that satisfy these requirements have already been validated for this purpose.

1.2.1. Tremor

The diagnosis of tremor is generally confirmed using EMG by measuring electrical activity of muscles [31,48–50]. Electrical signals of the measured muscle groups are amplified and filtered to remove noise and interference. Depending on the application, information can be analyzed using time-domain techniques for amplitude and duration analysis, or using frequency-domain techniques involving the frequency content of the signals [51]. This technique has good reliability when compared to clinical scales such as the MDS-UPDRS [52].

Accelerometry is also used to assess tremor, by measuring linear movement-induced accelerations relative to the gravitational field [47,53,54]. The acceleration signal is transformed using frequency analysis to discriminate tremor from other activities. Voluntary movement is generally concentrated at frequencies below 2 Hz, while most tremor subtypes have a dominant frequency of 3 Hz or greater [31,49]. Accelerometric data can be used to derive meaningful information about tremor, like frequency, amplitude, and constancy [6,28,46,47,53–55].

Gyroscopes are similarly suitable for tremor registration, especially for rotational PD tremor (“pill-rolling” tremor) [56]. Gyroscopes detect angular velocity of a rotating body by measuring the Coriolis force generated in a rotating reference frame [57,58]. These sensors measure the rate of rotation of an object around one, two, or three axes [58]. Similar to previous techniques, gyroscopic data is transformed to be analyzed in the frequency domain to obtain amplitude and dominant frequency as metrics to evaluate tremor presence, intensity, and frequency [59–61].

1.2.2. Bradykinesia

The most commonly used tasks to assess hand bradykinesia include finger tapping, opening/closing of the fist, and pronation/supination of the arm, as described in the MDS-UPDRS [44]. Quantification of slowness, hesitancy, and movement amplitude decrements can be measured with EMG [50,51,62], accelerometers [50,63], gyroscopes [56], and optical measurements [64–66]. Data from these devices is analyzed using various techniques like frequency analysis and velocity estimation, to quantify the severity of bradykinesia [23,56,62–67]. Strong associations between electronic measures and the clinical gold standard references (e.g., MDS-UPDRS) were reported for bradykinesia, indicating that the reliability of these techniques suffices clinical requirements [68]. Quantification of bradykinesia commonly employs a combination of sensors, in contrast to tremor being reliably quantified with a single sensor. A combination of accelerometers, gyroscopes, and magnetic sensors, known as Inertial Measurement Unit (IMU), is the most commonly used technology, reporting a moderate correlation or an acceptable receiver operating characteristic (ROC) compared to gold standard references [68].

1.2.3. Rigidity

Rigidity is generally evaluated with clinical tests (e.g., MDS-UPDRS) where slow passive flexion and extension of the joint of interest is performed by the examiner to feel the resistance of the passive movement (“cogwheel phenomenon”) [44,50]. Rigidity can usually be increased when a voluntary activation maneuver (e.g., fist opening/closing, or heel tapping) is performed by the contralateral limb [44,50]. The amount and pattern of muscle activity during the movement can be evaluated based on EMG analysis [24,50,69,70]. The outcome measures obtained using this technique include amount of resistance, uniformity of resistance, muscle activity amplitude, co-activation, pattern of muscle activity, and symmetry of muscle activity [24,50,69,70]. These metrics have shown to have good reliability (Intraclass Correlation Coefficient (ICC) 0.9) compared to clinical evaluation [24].

IMUs are also used to assess rigidity, by capturing e.g., the range of movement, angular velocity, linear acceleration, and orientation of body segments during movement [24,50,71,72]. Possible IMU outcome measures are joint angle, angular velocity, linear acceleration, jerk, and resistance to movement [24,50,71,72]. Good reliability (ICC 0.8) can be found compared to clinical evaluation [24].

2. Methods

2.1. Protocol

The protocol was based on PRISMA Extension for Scoping Reviews (PRISMA-ScR) [73].

2.2. Eligibility criteria

Peer-reviewed journal articles published in English were included. Eligible studies included electronic motor measurements in patients suffering from tremor, bradykinesia, and/or rigidity during awake stereotactic neurosurgery. Only human studies with an experimental or quasi-experimental design were included. Exclusion criteria were animal studies, (systematic) review articles, and conference abstracts. As this review focuses on electronic measurement of symptomatology, indirect measurement techniques, such as microelectrode recordings (MER), local field potentials (LFP), imaging, ultrasound, and intracerebral microvascular measurements, were not taken into account.

2.3. Search strategy

Key terms from relevant articles were extracted to build the search string, which was tested and refined accordingly. PubMed (MEDLINE, PubMed Central), Embase, and Web of Science were searched. No limit was applied for the publication date. The final search in all databases was performed on December 6, 2023. The result of each search was exported to Mendeley. As an example, the search string from PubMed is added to Appendix 1.

2.4. Source selection

Each title and abstract were screened by the first and second author for relevance. Any disagreements were resolved. Papers that passed the first screening underwent a full-text review and were categorized as either included or excluded.

3. Results

After screening and full-text review, 23 articles were included in the final review (Figure 1). The number of subjects and controls, clinical diagnoses, symptoms, and surgery specifications of the included studies are shown in Table 1. The results are summarized in Table 2–4 [74–96].

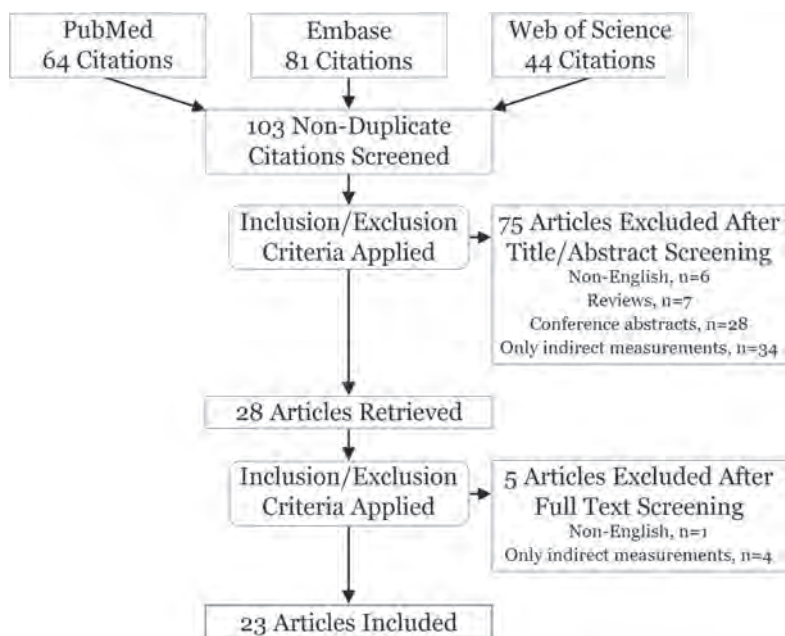


Figure 1. Search results and selection of articles.

Table 1. Overview of included studies

Authors, year [reference]	Participants					Symptoms			Surgery			Laterality		Targets		
	PD	ET	DT	HT	HC	Tre	Bra	Rig	DBS	Thal	Pal	Uni	Bi	STN	VIM	GPI
Landy et al., 2000 [74]	21					21		21			21	21				21
Koop et al., 2006 [75]	61				15		61		61			24	37	61		
Papapetropoulos et al., 2008 [76]	12				10	12	12		12			12		12		
Papapetropoulos et al., 2009 [77]	1					1			1			1			1	
Waldau et al., 2011 [78]	8				5		8		8			4	4	5	3	
Florin et al., 2012 [79]	14					8			14				14	14		
Kwon et al., 2014 [80]	8							8	8			2	6	8		
Hemm et al., 2016 [81]		5				5			5				5		5	
Florin et al., 2016 [82]		26				8			26				26	26		
Shah et al., 2017 [83]		15				15			15				15	7	8	

Table 1. Overview of included studies (*continued*)

Authors, year [reference]	Participants					Symptoms			Surgery			Laterality		Targets		
	PD	ET	DT	HT	HC	Tre	Bra	Rig	DBS	Thal	Pal	Uni	Bi	STN	VIM	GPI
Shah et al., 2017 [84]	9							9	9				9		9	
Milosevic et al., 2018 [85]	2	9				11			11			1	10		11	
Schaeffer et al., 2018 [86]	26	11				37		26	37			37			37	
Shah et al., 2020 [87]		5				5			5			1	4		5	
Wang et al., 2020 [88]	39					39			39			39		35		4
Lopes et al., 2020 [89]	59							59	59				59	59		
Wu et al., 2021 [90]	7						7		7				7	7		
Kremer et al., 2021 [91]			1			1			1				1		1	
Smid et al., 2022 [92]	28				26	28			22	6		6	22	22	6	
Yu et al., 2022 [93]	20				3		20		20				20	20		
Baek et al., 2023 [94]	9	9				18				18		18			18	
Smid et al., 2023 [95]	13	7		2		22				24		24			24	
Glowinsky et al., 2023 [96]		1				1			1				1		1	

Table 2. Overview of the intraoperative studies on objectively measuring tremor.

Device type	Location of the device	Outcome measure	References
Accelerometer	Held in the hand	Tremor amplitude (cm)	Papapetropoulos et al., 2008 (n=12) [76], Papapetropoulos et al., 2009 (n=1) [77]
		Center frequency (Hz)	
		SD of center frequency (frequency dispersion)	
		Harmonic index (HI)	
	Wrist	Standard deviation	Hemm et al., 2016 (n=5) [81], Shah et al., 2017 (n=15) [83], Shah et al., 2020 (n=5) [87]
		Signal energy	
		Amplitude of dominant frequency	
		Scalar sum of accelerations	
		Tremor reduction (%)	Milosevic et al., 2018 (n=11) [85]

Table 2. Overview of the intraoperative studies on objectively measuring tremor. (*continued*)

Device type	Location of the device	Outcome measure	References
Accelerometer	Hand dorsum	Acceleration (g)	Schaeffer et al., 2018 (n=37) [86]
		Average signal power (g ²)	
		Tremor frequency (Hz)	
	Index finger	Tremor frequency (Hz)	Smid et al., 2022 (n=28) [92], Smid et al., 2023 (n=22) [95]
		Tremor amplitude (cm)	
		Area-under-the-curve of power in 4–6 Hz range	Smid et al., 2022 (n=28) [92]
		Percentage of time that tremor was present (%)	
	Arm, forearm, and index finger	Joint angle reduction (%)	Back et al., 2023 (n=9) [94]
Gyroscope	Hand dorsum	Angular velocity (dps)	Schaeffer et al., 2018 (n=37) [86]
		Average signal power (dps ²)	
sEMG	Several muscle groups	EMG response	Landy et al., 2000 (n=21) [74]
	m. extensor digitorum communis m. flexor digitorum superficialis	Frequency (Hz)	Florin et al., 2012 (n=14) [79], Florin et al., 2016 (n=26) [82]
		Coherence (with LFP)	
	e. digitorum f. digitorum superficialis m. tibialis anterior m. gastrocnemius	Weighted Root Mean Square per second	Wang et al., 2020 (n=39) [88]
		Modified Mean Absolute Value	
		Waveform Length	
		Zero Crossings	
		Slope Sign Changes	
		Sample Entropy	
		Peak Frequency (Hz)	
		Peak Frequency Power	
	m. sternocleidomastoideus m. semispinalis cervicis	Median Amplitude Power	Kremer et al., 2021 (n=1) [91]
		Mean Amplitude Power	
	wrist flexor and extensor	Frequency Ratio	Glowinsky et al., 2023 (n=1) [96]
		EMG-burst activity (μV)	
		EMG-burst length (ms)	
		Frequency (Hz)	
		Neuronal/EMG coherence	
		Flexor-extensor cross-correlation	

Table 3. Overview of the intraoperative studies on objectively measuring bradykinesia.

Device type	Location of the device	Outcome measure	References
Gyroscope	Hand dorsum	Root mean square of angular velocity (deg/sec) Frequency (Hz)	Koop et al., 2006 (n=61) [75]
Optical device	In front of the patient	Velocity (units/s) Reaction time (ms)	Waldau et al., 2011 (n=8) [78]
	Around the patient	Distance (mm) between thumb and index finger	Wu et al., 2021 (n=7) [90], Yu et al., 2022 (n=20) [93]
		Distance (mm) fingertips and hand palm	
		Roll angle (°) of the hand palm	
		Frequency (Hz) Velocity (mm/s)	
Touch sensor	In front of the patient	Maximal frequency (Hz)	Papapetropoulos et al., 2008 (n=12) [76]

Table 4. Overview of the intraoperative studies on objectively measuring rigidity.

Device type	Location of the device	Outcome measure	References
Accelerometer	Hand dorsum	Acceleration (g) Average signal power (g ²)	Schaeffer et al., 2018 (n=37) [86]
	Wrist of the examiner	Standard deviation	
		Signal energy	Shah et al., 2017 (n=9) [84]
		Amplitude of dominant frequency	
		Inertia calculation	Kwon et al., 2014 (n=8) [80]
Torque sensor	Wrist of the examiner	Resistive torque integrated by angle (W) per cycle Resistive torque integrated by time (I) per cycle Mechanical impedance (Z)	
Potentiometer	Wrist of the examiner	Wrist angle (°)	
Gyroscope	Hand dorsum	Angular velocity (dps) Average signal power (dps ²)	Schaeffer et al., 2018 (n=37) [86]
	Hand palm	Angular velocity of the wrist (°/s)	Lopes et al., 2020 (n=59) [89]
sEMG	Several muscle groups	EMG response	Landy et al., 2000 (n=21) [74]

3.1. Demographics

Mean age and standard deviation of the included patients were only described in 14 of the included studies [74–77,79,80,82,88,90–93,95,96], and the disease duration in 10 studies [75–77,79,80,82,90,91,95,96]. For the studies that did mention these demographics, age ranged from 48 to 83 years, and the disease duration ranged from 3 to 35 years. Only one DT patient [91] and two HT patients [95] were described. Few studies included healthy participants (Table 1) [75,76,78,92,93].

3.2. Main research aims

The principal aim of most studies was to objectively quantify change in tremor, bradykinesia, or rigidity during stereotactic neurosurgery [74–77,80,83,84,86,87,89,90,92–95]. Few studies specifically aimed to validate their approaches on electronic measurement of tremor, bradykinesia, or rigidity intraoperatively [80,86,93]. Kremer et al. aimed to show how EMG can be used to quantify dystonic tremor reduction during VIM-DBS surgery [91]. The aim of Hemm et al. [81] and Shah et al. [87] was to optimize DBS electrode positioning. Other studies were focused to quantify stimulation effects [78,85,88,96]. Florin et al. aimed to intraoperatively identify causality patterns of tremor in two types of PD patients, by using surface EMG (sEMG) [79,82].

3.3. Clinical protocols

Most studies used tasks from the motor section of the MDS-UPDRS as their clinical intraoperative protocol [75,76,86,88–90,92,93,95]. Others did not use a standardized clinical scale intraoperatively [74,78,79,81,82,85,91,96]. Papapetropoulos et al. used FTM as a clinical protocol to intraoperatively assess tremor [77]. Baek et al. used postural tremor tasks, signature writing, Archimedes spiral, and point-to-point drawing to assess tremor intraoperatively [94]. Four studies used a modified MDS-UPDRS to rate tremor and rigidity [80,83,84,87]. Eleven out of 23 studies compared the electronic measurement data with a clinical scale, showing correlations ranging from -0.76 to 0.99 ($p < 0.001$) [12,75,80,83,86,88–90,92–94]. Several studies focused on creating an objective method for measuring clinical outcome measures with visually scored scales [75,76,86,90,92,93]. Smid et al. [92] aimed to translate a clinical scale to an objective scoring method, using internationally standardized MDS-UPDRS thresholds.

3.4. Technical aspects

3.4.1. Tremor

Of 16 included tremor-studies, 10 used accelerometry [76,77,81,83,85–87,92,94,95] and six used sEMG [74,79,82,88,91,96]. Only Shaeffer et al. [86] used both accelerometer and gyroscope data.

Frequency analysis was the most common technique to assess tremor, since 13 [74,76,77,79,81–83,85–88,92,95] out of 16 included studies used this to quantify tremor characteristics, mostly with the classical Fast Fourier Transform (FFT) [76,77,81,83,86–88]. Baek et al. did not mention their analysis technique [94]. Kremer et al. and Glowinsky et al. used raw sEMG data to investigate EMG burst activity by observation [91,96]. The periodogram [92,95] and coherence analysis [79,82] have also shown good performance.

Apart from frequency domain analysis, time domain analysis of the acceleration or angular velocity was also used to quantify tremor characteristics. Papapetropoulos et al. [76,77] and Smid et al. [92,95] used the acceleration signal to estimate the position and calculated the amplitude of tremor in centimeters. Hemm et al. [81] and Shah et al. [83,87] used the magnitude of the acceleration signal to estimate tremor intensity.

In all 16 included studies, different clinical tremor characteristics were considered as outcome measures of the electronic assessment. Eight studies objectively quantified tremor frequency [76,77,81,83,86–88,95], nine studies quantified amplitude [76,77,81,83,85,87,88,92,95], three quantified duration [85,88,92], two intensity [76,77], and eight irregularity [76,77,79,82,88,91,96]. All studies took the presence of tremor into account [74,76,77,79,81–83,85–88,92,95].

Most studies concluded that their quantitative approach might improve intraoperative monitoring or awake stereotactic targeting [74–78,80,81,83–95]. It differed per study why this was the conclusion. None of the included studies presented sufficient data to conclude that electronic measurements would improve monitoring or stereotactic neurosurgery. Only Shah et al. investigated whether the intraoperative neurosurgical decision would be different based on their measurements: 15 of the 26 decisions would have been different. They were not able to judge whether the expert-based or the accelerometry-based electrode position would have been the best clinical outcome [83,84]. Still, they did show the potential of tri-axial accelerometry complementing tremor assessment during neurosurgery [83,84]. Use of accelerometry to quantify change in tremor was reported to be superior with regard to traditional visual evaluation of tremor [76,77,81,83,85–87,92,94,95].

The added value of EMG for intraoperative tremor quantification was demonstrated in all six tremor EMG studies [74,79,82,88,91,96]. Wang et al. concluded that amplitude, motor unit firing rate, and changes in the regularity pattern could be used as quick intraoperative biomarkers to quantify and predict efficacy of DBS in PD patients with resting tremor [88]. Kremer et al. concluded that the easy-to-use objective technique of polymyography can facilitate optimization of DBS electrode placement [91].

3.4.2. Bradykinesia

Of the five included studies that measured bradykinesia, three studies used optical devices [78,90,93]. Papapetropoulos et al. [76] used a touch recording plate and Koop et al. [75] used a tri-axial gyroscope. Wu et al. [90] and Yu et al. [93] used a Leap Motion Controller (LMC) to assess bradykinetic movements, extracting information of the position and orientation of the hands during different tasks. Waldau et al. used an optical Virtual Reality (VR) glove to estimate the velocity of hand movements [78]. Common outcome measures were velocity estimation [75,78,90,93], reaction time [78], movement duration [78], position [90], orientation [90], rhythm [76], movement amplitude [90], and movement variability [93].

Koop et al. demonstrated a promising gyroscope-based method to quantify changes in upper extremity bradykinesia during different stages of DBS surgery [75]. Papapetropoulos et al. showed that maximal frequency FT as measured by the touch recording plate increased significantly in the stimulated hand after DBS electrode implantation [76]. Waldau et al. concluded that their VR glove may be useful as a quick intraoperative measurement to check correct electrode placement, complementing the clinician's and patient's subjective sense of improvement [78]. Wu et al. showed that intraoperative changes in bradykinesia can be evaluated with a noninvasive, objective, simple, and sensitive optical LMC device [90]. Yu et al. demonstrated how optical LMC measurements can be used during stereotactic neurosurgery to objectively assess bradykinesia, without interfering with voluntary movements [93]. The LMC was validated with a motion capture system, resulting in an average Pearson's correlation coefficient of 0.986 [93].

3.4.3. Rigidity

Similar to bradykinesia, intraoperative assessment of rigidity has received less attention compared to tremor, as only five studies were included in the review. There was little overlap in devices and analysis techniques, ranging from accelerometry [84], gyroscopes [89], sEMG [74], to IMUs [80,86].

Landy et al. showed that resting spontaneous EMG activity decreased if rigidity and/or tremor severity was reduced by lesioning. As such, sEMG may contribute to safe targeting in pallidotomy [74]. Kwon et al. showed that rigidity during DBS surgery can be quantified best by a biomechanical outcome measure called the viscous damping constant [80]. Shah et al. showed that 10 of 12 DBS placement choices would have been different if accelerometric data was considered by the neurosurgeon, showing the potential of accelerometry to assess rigidity during stereotactic neurosurgery [84]. Schaeffer et al. underlined that long-term work is necessary to assess whether motor quantification alters intraoperative decision-making, and how this influences patient outcomes [86]. Lopes et al. concluded that their device supports the intraoperative evaluation of the effectiveness of DBS surgery, and also foresee its application in pharmacological clinical trials [89].

4. Discussion

This scoping review clearly shows that there are many intraoperative possibilities to implement objective measurement techniques to guide DBS or ablation. Based on the reported literature, there is no consensus on protocols nor analysis techniques. Nevertheless, most studies show that objective measurements can very well complement expert evaluation, are easily applicable, and have the potential to improve targeting in stereotactic neurosurgery.

Comparison of the results is challenging, since the study designs and technical considerations were widely diverse. The described studies have varying cohorts (Table 1) and make use of various outcome measures (Table 2–4). Also, a wide variety of analysis techniques was applied in the included studies, making it difficult to conclude which approach was superior. None of the studies directly compared the clinical outcome of sensor-based stereotactic neurosurgeries with the clinical outcome of standard procedure. Consequently, none were able to show that electronic assessment was more sensitive or accurate than expert assessment, or outperformed clinical assessment in any other way. Also, it was not shown that electrode placement based on objective assessment was superior in clinical effect or surgical outcome to placement based on expert assessment.

Unfortunately, most of the described electronic motor measurements lack standardized protocols. There is currently no international consensus on clinical protocols for intraoperative monitoring during stereotactic neurosurgery for movement disorders. Also, solid proof or validation regarding which outcome measures are superior in quantifying the intraoperative effect of stereotactic neurosurgery is still lacking [97]. Journee et al. described conditions and limitations for performing intraoperative tremor, bradykinesia and rigidity measurements [50]. These aspects need to be considered when setting up a sensor-based approach for measuring motor symptoms in a clinical setting.

A possible reason that only one DT patient was included might be that stereotactic neurosurgery in dystonia patients is often performed under total anesthesia, which disallows intraoperative motor measurements. Also, the characteristics of DT are not as clearly defined as those in cases of parkinsonian and Essential Tremor, making it more difficult to quantify. Moreover, the interpretation of intraoperative assessments of DT is more challenging, since DT characteristics present higher variability compared to PD and ET [33,34].

The inclusion of only two HT patients is probably caused by the low prevalence of this tremor syndrome [98–100]. Also, the indication for DBS is not clear yet for this patient population [101]. Moreover, HT is more difficult to measure electronically due to low-frequent proximal muscle contractions, as opposed to distal tremor syndromes like PD and ET [31].

A possible reason for the low number of included studies for bradykinesia and rigidity is that these are more complex symptoms to measure than tremor. Sensor techniques that have been validated for the quantification of these symptoms are often too intricate and invasive for application in a neurosurgical setting [24,68].

It stood out that approaches in tremor-focused studies were more homogeneous than those for bradykinesia and rigidity. Though, studies on bradykinesia and rigidity

disclosed less information on their techniques than tremor-focused studies. As these are more complex symptoms to analyze, their full data analysis protocol might have been too expansive for publication. Another explanation might be the use of patented devices and software, limiting public knowledge on how signal processing and data analysis was done. The use of closed-source systems, along with high costs and complexities in appliance, may contribute to the lack of standardized, open-source protocols for quantifying motor symptoms during stereotactic neurosurgery [86].

It stood out there was fewer information available about the usefulness and efficacy of intraoperative electronic measurements of bradykinesia than for tremor. Commercially available systems were used in all five studies that were included for the bradykinesia section. Although this may have limited the data analyses techniques presented by the authors, there are several studies outside the neurosurgical setting available to show the usefulness and efficacy of these methods to assess bradykinesia [21,102].

Although the results of this review indicate that intraoperative clinical assessments might benefit from electronic motor measurements, some disadvantages are associated with these types of measurements (e.g., expenses, time investment, required technical knowledge). Additionally, objective measurements still need the interpretation of clinicians for clinical decision-making. Currently, it is not to be expected that objective methods for measuring motor symptoms will replace expert assessment. Nevertheless, these electronic methods can complement the current expert-approach, allowing objective input for clinical decision-making.

4.1. Future perspectives

In this scoping review, the spectrum of electronic techniques that can be applied to an intraoperative setting to measure tremor, bradykinesia and rigidity during awake stereotactic neurosurgery in Parkinson's Disease and Tremor patients was described. In order to definitely prove the added value of their use, a multicenter or global collaboration aiming to validate electronic outcome measures and standardize objective intraoperative protocols is proposed. The open-source publication of these protocols and data analysis techniques is key here. Also, randomized controlled trials, involving multiple expert movement disorders neurologists, are suggested to investigate the added sensitivity and accuracy of electronic measurements to improve clinical assessment. All of this aiming to come to a consensus on the intraoperative application of these electronic measurements.

Although data-driven approaches described in this review offer interesting data and many different parameters, their use is often accompanied with complex hardware and software [21,97]. For most techniques, sensor calibration and pre-processing of the data is intricate and time-consuming. So, technical expertise of these sensors and their data analysis is needed in order to come to data that is clinically useful. Since objective measurements result in complex quantitative data, their use calls for advanced data analysis to quickly evaluate large amounts of data, to identify classification patterns, and to present the data in a quickly interpretable manner. Machine learning algorithms and other mathematical procedures, such as principal component analysis, can be considered.

A number of techniques used intraoperatively can be used outside the operating room, for example at the outpatient clinic or at the patient's home. Electronic measurements can be applied preoperatively to aid prediction of surgery outcome and optimize selection of surgical candidates, as well as postoperatively to objectively monitor symptom severity at follow-up and to optimize DBS settings [103–108]. These are promising developments in the context of the uprise of closed-loop or adaptive DBS [109,110]. Also, there is great potential in applying sensor-based monitoring at home to support clinicians in optimally managing patients between hospital appointments [111,112]. Consistent use of accurate and objective methods to monitor motor symptoms throughout the caretaking process might contribute to the best possible clinical outcome. These quantitative measurements can complement clinical motor assessment in evaluating the efficacy of neurosurgical treatments [19].

5. Conclusion

This scoping review provides a comprehensive overview of the most common electronic methods for intraoperatively measuring tremor, bradykinesia, and rigidity, showing that there are many possibilities to implement objective measurement techniques in the intraoperative setting. On the other hand, a lack of standardization was identified in this field. Although most included studies provided reliable outcome measures that correlated well with clinical assessments, sensor-based assessment was not shown to be more sensitive or accurate than expert assessment. Also, it was not proven that electrode placement based on objective assessment was superior to placement based on clinical assessment. Nevertheless, it is clear that objective measurements can complement visual evaluation of motor symptoms and may provide an objective confirmation of the surgical result. On the long-term, this might benefit patient outcomes and provide reliable outcome measures in scientific research. For future research, it is suggested to develop standardized protocols with validated outcome measures that aid in predicting (long-term) neurosurgical outcome.

Appendix 1

Search string from PubMed

(“intraoperative*”[Title/Abstract] OR “intra-operative*”[Title/Abstract])
 AND
 (“quanti*”[Title/Abstract] OR “assess*”[Title/Abstract] OR “measur*”[Title/Abstract])
 AND
 (“Tremor”[Mesh] OR “Hypokinesia”[Mesh] OR “Muscle Rigidity”[Mesh] OR
 “tremor”[Title/Abstract] OR “bradykine*”[Title/Abstract] OR “rigid*”[Title/Abstract])
 AND
 (“Accelerometry”[Mesh] OR “Acceleration”[Mesh] OR “Myography”[Mesh] OR
 “reliab*”[Title/Abstract] OR “valid*”[Title/Abstract] OR “mechanic*”[Title/Abstract]
 OR “accelero*”[Title/Abstract] OR “velo*”[Title/Abstract] OR “EMG”[Title/Abstract] OR
 “gyroscop*”[Title/Abstract] OR “kinematic*”[Title/Abstract] OR “motion sensor*”[Title/
 Abstract])
 AND
 (“Deep Brain Stimulation”[Mesh] OR “DBS”[Title/Abstract] OR “neurosurg*”[Title/
 Abstract] OR “thalamotom*”[Title/Abstract] OR “pallidotom*”[Title/Abstract])
 NOT
 “animal”[Title/Abstract]

References

- [1] Kremer NI, Pauwels RWJ, Pozzi NG, Lange F, Roothans J, Volkmann J, et al. Deep brain stimulation for tremor: Update on long-term outcomes, target considerations and future directions. *J Clin Med* 2021;10. <https://doi.org/10.3390/jcm10163468>.
- [2] Abosch A, Lozano A. Stereotactic neurosurgery for movement disorders. *Canadian Journal of Neurological Sciences* 2003;30. <https://doi.org/10.1017/s0317167100003279>.
- [3] Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's Disease rating scale. *Arch Neurol* 2010;67:64–70.
- [4] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [5] Kremer NI, Smid A, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, et al. Supine MDS-UPDRS-III Assessment: An Explorative Study. *J Clin Med* 2023;12. <https://doi.org/10.3390/jcm12093108>.
- [6] Smid A, Elting JWJ, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative quantification of MDS-UPDRS tremor measurements using 3D accelerometry (abstract 394). *Movement Disorders* 2022;37:S206. <https://doi.org/10.1002/mds.29223>.
- [7] Rovini E, Maremmanni C, Cavallo F. How wearable sensors can support Parkinson's Disease diagnosis and treatment: A systematic review. *Front Neurosci* 2017;11. <https://doi.org/10.3389/fnins.2017.00555>.
- [8] Erro R, Fasano A, Barone P, Bhatia KP. Milestones in Tremor Research: 10 Years Later. *Mov Disord Clin Pract* 2022;9:429–35. <https://doi.org/10.1002/mdc3.13418>.
- [9] Ossig C, Antonini A, Buhmann C, Classen J, Csoti I, Falkenburger B, et al. Wearable sensor-based objective assessment of motor symptoms in Parkinson's Disease. *J Neural Transm* 2016;123:57–64. <https://doi.org/10.1007/s00702-015-1439-8>.
- [10] Asakawa T, Fang H, Sugiyama K, Nozaki T, Kobayashi S, Hong Z, et al. Human behavioral assessments in current research of Parkinson's Disease. *Neurosci Biobehav Rev* 2016;68:741–72. <https://doi.org/10.1016/j.neubiorev.2016.06.036>.
- [11] Lu R, Xu Y, Li X, Fan Y, Zeng W, Tan Y, et al. Evaluation of Wearable Sensor Devices in Parkinson's Disease: A Review of Current Status and Future Prospects. *Parkinsons Dis* 2020;2020. <https://doi.org/10.1155/2020/4693019>.
- [12] Smid A, Pauwels RWJ, Elting JWJ, Everlo CSJ, van Dijk JMC, Oterdoom DLM, et al. A Novel Accelerometry Method to Perioperatively Quantify Essential Tremor Based on Fahn-Tolosa-Marin Criteria. *J Clin Med* 2023 2023;12:4235. <https://doi.org/10.3390/jcm12134235>.
- [13] Smid A, Kremer NI, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, et al. [Abstract 659] Perioperative Use of the MDS-UPDRS Motor Section: Agreement Between Sitting and Supine Position. *Movement Disorders* 2023;38:S295–S295. <https://doi.org/10.1002/mds.29541>.
- [14] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.
- [15] Yang K, Xiong WX, Liu FT, Sun YM, Luo S, Ding ZT, et al. Objective and quantitative assessment of motor function in Parkinson's Disease-from the perspective of practical applications. *Ann Transl Med* 2016;4. <https://doi.org/10.21037/atm.2016.03.09>.
- [16] Lukšys D, Jonaitis G, Griškevičius J. Quantitative Analysis of Parkinsonian Tremor in a Clinical Setting Using Inertial Measurement Units. *Parkinsons Dis* 2018;2018. <https://doi.org/10.1155/2018/1683831>.

- [17] Elble RJ, Ondo W. Tremor rating scales and laboratory tools for assessing tremor. *J Neurol Sci* 2022;435. <https://doi.org/10.1016/j.jns.2022.120202>.
- [18] Bobić V, Djurić-Jovičić M, Dragašević N, Popović MB, Kostić VS, Kvašček G. An expert system for quantification of bradykinesia based on wearable inertial sensors. *Sensors (Switzerland)* 2019;19. <https://doi.org/10.3390/s19112644>.
- [19] Wastensson G, Holmberg B, Johnels B, Barregard L. Quantitative Methods for Evaluating the Efficacy of Thalamic Deep Brain Stimulation in Patients with Essential Tremor. *Tremor and Other Hyperkinetic Movements* 2013;4. <https://doi.org/10.7916/D8VM4BoN>.
- [20] Smid A, Oterdoom DLM, Pauwels RWJ, Tamasi K, Elting JWJ, Absalom AR, et al. [Abstract 1798] The added value of accelerometric monitoring during thalamotomy. *Movement Disorders* 2023;38:S793–4. <https://doi.org/10.1002/mds.29546>.
- [21] Martinez-Manzanera O, Roosma E, Beudel M, Borgemeester RWK, Van Laar T, Maurits NM. A Method for Automatic and Objective Scoring of Bradykinesia Using Orientation Sensors and Classification Algorithms. *IEEE Trans Biomed Eng* 2016;63:1016–24. <https://doi.org/10.1109/TBME.2015.2480242>.
- [22] Oyama G, Burq M, Hatano T, Marks WJ, Kapur R, Fernandez J, et al. Analytical and clinical validity of wearable, multi-sensor technology for assessment of motor function in patients with Parkinson's Disease in Japan. *Sci Rep* 2023;13. <https://doi.org/10.1038/s41598-023-29382-6>.
- [23] Maldonado-Naranjo A, Koop MM, Hogue O, Alberts J, MacHado A. Kinematic Metrics from a Wireless Stylus Quantify Tremor and Bradykinesia in Parkinson's Disease. *Parkinsons Dis* 2019;2019. <https://doi.org/10.1155/2019/6850478>.
- [24] Ferreira-sánchez MDR, Moreno-verdú M, Cano-de-la-cuerda R. Quantitative measurement of rigidity in parkinson's disease: A systematic review. *Sensors (Switzerland)* 2020;20. <https://doi.org/10.3390/s20030880>.
- [25] Maetzel W, Domingos J, Srulijes K, Ferreira JJ, Bloem BR. Quantitative wearable sensors for objective assessment of Parkinson's Disease. *Movement Disorders* 2013;28:1628–37. <https://doi.org/10.1002/mds.25628>.
- [26] Sica M, Tedesco S, Crowe C, Kenny L, Moore K, Timmons S, et al. Continuous home monitoring of Parkinson's Disease using inertial sensors: A systematic review. *PLoS One* 2021;16. <https://doi.org/10.1371/journal.pone.0246528>.
- [27] Antonini A, Reichmann H, Gentile G, Garon M, Tedesco C, Frank A, et al. Toward objective monitoring of Parkinson's Disease motor symptoms using a wearable device: wearability and performance evaluation of PDMonitor®. *Front Neurol* 2023;14. <https://doi.org/10.3389/fneur.2023.1080752>.
- [28] Zajki-Zechmeister T, Kögl M, Kalsberger K, Franthal S, Homayoon N, Katschnig-Winter P, et al. Quantification of tremor severity with a mobile tremor pen. *Heliyon* 2020;6:e047. <https://doi.org/10.1016/j.heliyon.2020.e04702>.
- [29] Sammartino F, Rege R, Krishna V. Reliability of Intraoperative Testing During Deep Brain Stimulation Surgery. *Neuromodulation* 2020;23:525–9. <https://doi.org/10.1111/ner.13081>.
- [30] Krishna V, Sammartino F, Agrawal P, Changizi BK, Bourekas E, Knopp M V, et al. Prospective Tractography-Based Targeting for Improved Safety of Focused Ultrasound Thalamotomy. *Neurosurgery* 2019;84:160–8. <https://doi.org/10.1093/neuros/nyy020>.
- [31] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders* 2018;33:75–87. <https://doi.org/10.1002/mds.27121>.
- [32] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's Disease. *Movement Disorders* 2015;30:1591–601. <https://doi.org/10.1002/mds.26424>.

- [33] Centen LM, Oterdoom DLM, Tijssen MAJ, Lesman-Leegte I, van Egmond ME, van Dijk JMC. Bilateral Pallidotomy for Dystonia: A Systematic Review. *Movement Disorders* 2021;36:547–57. <https://doi.org/10.1002/mds.28384>.
- [34] Cersosimo MG, Raina GB, Benarroch EE, Piedimonte F, Alemán GG, Micheli FE. Micro lesion effect of the globus pallidus internus and outcome with deep brain stimulation in patients with Parkinson's Disease and dystonia. *Movement Disorders* 2009;24:1488–93. <https://doi.org/10.1002/mds.22641>.
- [35] Dallapiazza RF, Lee DJ, De Vloo P, Fomenko A, Hamani C, Hodaie M, et al. Outcomes from stereotactic surgery for Essential Tremor. *J Neurol Neurosurg Psychiatry* 2019;90:474–82. <https://doi.org/10.1136/jnnp-2018-318240>.
- [36] Chen KHS, Chen R. Invasive and Noninvasive Brain Stimulation in Parkinson's Disease: Clinical Effects and Future Perspectives. *Clin Pharmacol Ther* 2019;106:763–75. <https://doi.org/10.1002/cpt.1542>.
- [37] Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with Essential Tremor. *Lancet Neurol* 2011;10:148–61.
- [38] Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *New England Journal of Medicine* 2016;375:730–9. <https://doi.org/10.1056/NEJMoa1600159>.
- [39] Lange SF, Kremer NI, van Laar T, Lange F, Steendam-Oldekamp TE, Oterdoom DLM, et al. The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation* 2021. <https://doi.org/10.1111/ner.13523>.
- [40] Erdogan S, Savas A, Aydin N, Akbostanci MC. Predictive factors for favorable outcome from subthalamic nucleus deep brain stimulation in Parkinson's Disease. *Turk Neurosurg* 2020;30:43–7. <https://doi.org/10.5137/1019-5149.JTN.25028-18.3>.
- [41] Pourfar M, Tang C, Lin T, Dhawan V, Kaplitt MG, Eidelberg DD. Assessing the microlesion effect of subthalamic deep brain stimulation surgery with FDG PET: Clinical article. *J Neurosurg* 2009;110:1278–82. <https://doi.org/10.3171/2008.12.JNS08991>.
- [42] Alterman RL, Kall BA, Cohen H, Kelly PJ. Stereotactic Ventrolateral Thalamotomy: is ventriculography necessary? *Neurosurgery* 1995;37:717–22. <https://doi.org/10.1227/00006123-199510000-00016>.
- [43] Mahajan A, Bader A, Wang LL, Rekhtman A, Espay AJ, Dwivedi AK, et al. Thalamic Deep Brain Stimulation for tremor: The critical role of intraoperative testing. *Parkinsonism Relat Disord* 2020;73:45–9. <https://doi.org/10.1016/j.parkreldis.2020.03.022>.
- [44] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [45] Fahn S, Tolosa E, Marín C. Clinical Rating Scale for Tremor. *Parkinson's Disease and Movement Disorders* 1988:225–34.
- [46] Haubenberger D, Abbruzzese G, Bain PG, Bajaj N, Benito-León J, Bhatia KP, et al. Transducer-based evaluation of tremor. *Movement Disorders* 2016;31:1327–36. <https://doi.org/10.1002/mds.26671>.
- [47] Elble RJ, McNames J. Using portable transducers to measure tremor severity. *Tremor and Other Hyperkinetic Movements* 2016;6. <https://doi.org/10.7916/D8DR2VCC>.
- [48] Jackson L, Klassen BT, Hassan A, Bower JH, Matsumoto JY, Coon EA, et al. Utility of tremor electrophysiology studies. *Clin Park Relat Disord* 2021;5. <https://doi.org/10.1016/j.prdoa.2021.100108>.

- [49] van der Stouwe AMM, Elting JW, van der Hoeven JH, van Laar T, Leenders KL, Maurits NM, et al. How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena. *Parkinsonism Relat Disord* 2016;30:23–8. <https://doi.org/10.1016/j.parkreldis.2016.06.008>.
- [50] Journee HL, Postma AA, Staal MJ. Intraoperative neurophysiological assessment of disabling symptoms in DBS surgery. *Neurophysiologie Clinique* 2007;37:467–75. <https://doi.org/10.1016/j.neucli.2007.10.006>.
- [51] Rissanen SM, Kankaanpää M, Tarvainen MP, Novak V, Novak P, Hu K, et al. Analysis of EMG and acceleration signals for quantifying the effects of deep brain stimulation in parkinsons disease. *IEEE Trans Biomed Eng* 2011;58:2545–53. <https://doi.org/10.1109/TBME.2011.2159380>.
- [52] A DFV, He T, Redoute J-M, Lee C, Yuce MR. Flexible Forearm Triboelectric Sensors for Parkinson's Disease Diagnosing and Monitoring. 2022 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), IEEE; 2022, p. 4909–12. <https://doi.org/10.1109/EMBC48229.2022.9871644>.
- [53] Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. *Brain* 2006;129:2660–6. <https://doi.org/10.1093/brain/awl190>.
- [54] Sievänen H, Kujala UM. Accelerometry - Simple, but challenging. *Scand J Med Sci Sports* 2017;27:574–8. <https://doi.org/10.1111/sms.12887>.
- [55] van Brummelen EMJ, Ziagkos D, de Boon WMI, Hart EP, Doll RJ, Huttunen T, et al. Quantification of tremor using consumer product accelerometry is feasible in patients with Essential Tremor and Parkinson's Disease: a comparative study. *J Clin Mov Disord* 2020;7. <https://doi.org/10.1186/s40734-020-00086-7>.
- [56] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [57] Aminian K, Najafi B. Capturing human motion using body-fixed sensors: outdoor measurement and clinical applications. *Comput Animat Virtual Worlds* 2004;15:79–94. <https://doi.org/10.1002/cav.2>.
- [58] Passaro VMN, Cuccovillo A, Vaiani L, de Carlo M, Campanella CE. Gyroscope technology and applications: A review in the industrial perspective. *Sensors (Switzerland)* 2017;17. <https://doi.org/10.3390/s17102284>.
- [59] Tsipouras MG, Tzallas AT, Rigas G, Tsouli S, Fotiadis DI, Konitsiotis S. An automated methodology for levodopa-induced dyskinesia: Assessment based on gyroscope and accelerometer signals. *Artif Intell Med* 2012;55:127–35. <https://doi.org/10.1016/j.artmed.2012.03.003>.
- [60] Rigas G, Tzallas AT, Tsipouras MG, Bougia P, Tripoliti EE, Baga D, et al. Assessment of Tremor Activity in the Parkinson's Disease Using a Set of Wearable Sensors. *IEEE Transactions on Information Technology in Biomedicine* 2012;16:478–87. <https://doi.org/10.1109/TITB.2011.2182616>.
- [61] Elble RJ, Hellriegel H, Raethjen J, Deuschl G. Assessment of Head Tremor with Accelerometers Versus Gyroscopic Transducers. *Mov Disord Clin Pract* 2017;4:205–11. <https://doi.org/10.1002/mdc3.12379>.
- [62] Milner-Brown HS, Fisher MA, Weiner WJ. Electrical properties of motor units in Parkinsonism and a possible relationship with bradykinesia. *J Neurol Neurosurg Psychiatry* 1979;42:35–41. <https://doi.org/10.1136/jnnp.42.1.35>.
- [63] Salarian A, Russmann H, Vingerhoets FJG, Burkhard PR, Aminian K. Ambulatory monitoring of physical activities in patients with Parkinson's Disease. *IEEE Trans Biomed Eng* 2007;54:2296–9. <https://doi.org/10.1109/TBME.2007.896591>.

- [64] Bank PJM, Marinus J, Meskers CGM, de Groot JH, van Hilten JJ. Optical Hand Tracking: A Novel Technique for the Assessment of Bradykinesia in Parkinson's Disease. *Mov Disord Clin Pract* 2017;4:875–83. <https://doi.org/10.1002/mdc3.12536>.
- [65] Kim MJ, Naydanova E, Hwang BY, Mills KA, Anderson WS, Salimpour Y. Quantification of Parkinson's Disease Motor Symptoms: A Wireless Motion Sensing Approach. 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), IEEE; 2020, p. 3658–61. <https://doi.org/10.1109/EMBC44109.2020.9175616>.
- [66] Weichert F, Bachmann D, Rudak B, Fisseler D. Analysis of the accuracy and robustness of the Leap Motion Controller. *Sensors (Switzerland)* 2013;13:6380–93. <https://doi.org/10.3390/s130506380>.
- [67] Yokoe M, Okuno R, Hamasaki T, Kurachi Y, Akazawa K, Sakoda S. Opening velocity, a novel parameter, for finger tapping test in patients with Parkinson's Disease. *Parkinsonism Relat Disord* 2009;15:440–4. <https://doi.org/10.1016/j.parkreldis.2008.11.003>.
- [68] Teshuva I, Hillel I, Gazit E, Giladi N, Mirelman A, Hausdorff JM. Using wearables to assess bradykinesia and rigidity in patients with Parkinson's Disease: a focused, narrative review of the literature. *J Neural Transm* 2019;126:699–710. <https://doi.org/10.1007/s00702-019-02017-9>.
- [69] Levin J, Krafczyk S, Valkovič P, Eggert T, Claassen J, Bötzel K. Objective measurement of muscle rigidity in Parkinsonian patients treated with subthalamic stimulation. *Movement Disorders* 2009;24:57–63. <https://doi.org/10.1002/mds.22291>.
- [70] Powell D, Joseph Threlkeld A, Fang X, Muthumani A, Xia R. Amplitude- and velocity-dependency of rigidity measured at the wrist in Parkinson's Disease. *Clinical Neurophysiology* 2012;123:764–73. <https://doi.org/10.1016/j.clinph.2011.08.004>.
- [71] Costa P, Rosas MJ, Vaz R, Cunha JP. Wrist rigidity assessment during Deep Brain Stimulation surgery. 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), IEEE; 2015, p. 3423–6. <https://doi.org/10.1109/EMBC.2015.7319128>.
- [72] Assis S, Costa P, Rosas MJ, Vaz R, Silva Cunha JP. An adaptive model approach for quantitative wrist rigidity evaluation during deep brain stimulation surgery. 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), IEEE; 2016, p. 5809–12. <https://doi.org/10.1109/EMBC.2016.7592048>.
- [73] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann Intern Med* 2018;169:467–73. <https://doi.org/10.7326/M18-0850>.
- [74] Landy HJ, Weiner WJ, Calancie B, Harris W, Shulman LM, Singer C, et al. Electromyography during Stereotactic Pallidotomy for Parkinson's Disease. *Stereotact Funct Neurosurg* 2000;74:21–9.
- [75] Koop MM, Andrzejewski A, Hill BC, Heit G, Bronte-Stewart HM. Improvement in a quantitative measure of bradykinesia after microelectrode recording in patients with Parkinson's Disease during deep brain stimulation surgery. *Movement Disorders* 2006;21:673–8. <https://doi.org/10.1002/mds.20796>.
- [76] Papapetropoulos S, Jagid JR, Sengun C, Singer C, Gallo B V. Objective monitoring of tremor and bradykinesia during DBS surgery for Parkinson disease. *Neurology* 2008;70:1244–9.
- [77] Papapetropoulos S, Gallo B V., Guevara A, Singer C, Mitsi G, Lyssikatos C, et al. Objective tremor registration during DBS surgery for Essential Tremor. *Clin Neurol Neurosurg* 2009;111:376–9. <https://doi.org/10.1016/j.clineuro.2008.10.017>.
- [78] Waldau B, Clayton DA, Gasperson LB, Turner DA. Analysis of the time course of the effect of subthalamic nucleus stimulation upon hand function in Parkinson's patients. *Stereotact Funct Neurosurg* 2011;89:48–55. <https://doi.org/10.1159/000323340>.

- [79] Florin E, Himmel M, Reck C, Maarouf M, Schnitzler A, Sturm V, et al. Subtype-specific statistical causalities in parkinsonian tremor. *Neuroscience* 2012;210:353–62. <https://doi.org/10.1016/j.neuroscience.2012.02.045>.
- [80] Kwon Y, Park SH, Kim JW, Ho Y, Jeon HM, Bang MJ, et al. Quantitative evaluation of parkinsonian rigidity during intra-operative deep brain stimulation. *Biomed Mater Eng* 2014;24:2273–81. <https://doi.org/10.3233/BME-141040>.
- [81] Hemm S, Pison D, Alonso F, Shah A, Coste J, Lemaire JJ, et al. Patient-specific electric field simulations and acceleration measurements for objective analysis of intraoperative stimulation tests in the thalamus. *Front Hum Neurosci* 2016;10. <https://doi.org/10.3389/fnhum.2016.00577>.
- [82] Florin E, Pfeifer J, Visser-Vandewalle V, Schnitzler A, Timmermann L. Parkinson subtype-specific Granger-causal coupling and coherence frequency in the subthalamic area. *Neuroscience* 2016;332:170–80. <https://doi.org/10.1016/j.neuroscience.2016.06.052>.
- [83] Shah A, Coste J, Lemaire JJ, Taub E, Schüpbach WMM, Pollo C, et al. Intraoperative acceleration measurements to quantify improvement in tremor during deep brain stimulation surgery. *Med Biol Eng Comput* 2017;55:845–58. <https://doi.org/10.1007/s11517-016-1559-9>.
- [84] Shah A, Coste J, Lemaire JJ, Schkommodau E, Taub E, Guzman R, et al. A novel assistive method for rigidity evaluation during deep brain stimulation surgery using acceleration sensors. *J Neurosurg* 2017;127:602–12. <https://doi.org/10.3171/2016.8.JNS152770>.
- [85] Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. *Brain* 2018;141:2142–55. <https://doi.org/10.1093/brain/awy139>.
- [86] Schaeffer EL, Liu DY, Guerin J, Ahn M, Lee S, Asaad WF. A low-cost solution for quantification of movement during DBS surgery. *J Neurosci Methods* 2018;303:136–45. <https://doi.org/10.1016/j.jneumeth.2018.03.013>.
- [87] Shah A, Vogel D, Alonso F, Lemaire JJ, Pison D, Coste J, et al. Stimulation maps: visualization of results of quantitative intraoperative testing for deep brain stimulation surgery. *Med Biol Eng Comput* 2020;58:771–84. <https://doi.org/10.1007/s11517-020-02130-y>.
- [88] Wang KL, Burns M, Xu D, Hu W, Fan SY, Han CL, et al. Electromyography Biomarkers for Quantifying the Intraoperative Efficacy of Deep Brain Stimulation in Parkinson's Patients With Resting Tremor. *Front Neurol* 2020;11. <https://doi.org/10.3389/fneur.2020.00142>.
- [89] Lopes EM, Vilas-Boas MDC, Dias D, Rosas MJ, Vaz R, Cunha JPS. IHAndU: A novel quantitative wrist rigidity evaluation device for deep brain stimulation surgery. *Sensors (Switzerland)* 2020;20. <https://doi.org/10.3390/s20020331>.
- [90] Wu J, Yu N, Yu Y, Li H, Wu F, Yang Y, et al. Intraoperative Quantitative Measurements for Bradykinesia Evaluation during Deep Brain Stimulation Surgery Using Leap Motion Controller: A Pilot Study. *Parkinsons Dis* 2021;2021. <https://doi.org/10.1155/2021/6639762>.
- [91] Kremer NI, Oterdoom DLM, Absalom AR, ten Cate DW, van Dijk JMC, van Egmond ME, et al. Are we on the right track in DBS surgery for dystonic head tremor? Polymyography is a promising answer. *Parkinsonism Relat Disord* 2021;93:74–6. <https://doi.org/10.1016/j.parkreldis.2021.11.013>.
- [92] Smid A, Elting JWJ, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative Quantification of MDS-UPDRS Tremor Measurements Using 3D Accelerometry: A Pilot Study. *J Clin Med* 2022;11:2275. <https://doi.org/10.3390/jcm11092275>.
- [93] Yu N, Yu Y, Lin J, Yang Y, Wu J, Liang S, et al. A non-contact system for intraoperative quantitative assessment of bradykinesia in deep brain stimulation surgery. *Comput Methods Programs Biomed* 2022;225. <https://doi.org/10.1016/j.cmpb.2022.107005>.

- [94] Baek H, Chen J, Lockwood D, Obusez E, Poturalski M, Nagel SJ, et al. Feasibility of Magnetic Resonance–Compatible Accelerometers to Monitor Tremor Fluctuations During Magnetic Resonance–Guided Focused Ultrasound Thalamotomy: Technical Note. *Operative Neurosurgery* 2023. <https://doi.org/10.1227/ons.0000000000000638>.
- [95] Smid A, Oterdoom DLM, Pauwels RWJ, Tamasi K, Elting JWJ, Absalom AR, et al. The Relevance of Intraoperative Clinical and Accelerometric Measurements for Thalamotomy Outcome. *J Clin Med* 2023;12:5887. <https://doi.org/10.3390/jcm12185887>.
- [96] Glowinsky S, Bergman H, Zarchi O, Fireman S, Reiner J, Tamir I. Electrophysiology-aided DBS targeting the ventral intermediate nucleus in an Essential Tremor patient with MRI-incompatible lead: A case report. *Physiol Rep* 2023;11:e15730. <https://doi.org/10.14814/phy2.15730>.
- [97] Kostikis N, Hristu-Varsakelis D, Arnaoutoglou M, Kotsavasiloglou C. A smartphone-based tool for assessing parkinsonian hand tremor. *IEEE J Biomed Health Inform* 2015;19:1835–42. <https://doi.org/10.1109/JBHI.2015.2471093>.
- [98] Raina GB, Cersosimo MG, Folgar SS, Giugni JC, Calandra C, Paviolo JP, et al. Holmes tremor Clinical description, lesion localization, and treatment in a series of 29 cases. *American Academy of Neurology* 2016;86:931–8.
- [99] Lehericy S, Grand ; S, Pollak ; P, Poupon ; F, Le Bas J-F, Limousin ; P, et al. Clinical characteristics and topography of lesions in movement disorders due to thalamic lesions. *Neurology* 2001;57:1055–66. <https://doi.org/10.1212/wnl.57.6.1055>.
- [100] Kim JS. Delayed onset mixed involuntary movements after thalamic stroke: clinical, radiological and pathophysiological findings. *Brain* 2001;124:299–309. <https://doi.org/10.1093/brain/124.2.299>.
- [101] Starr PA. Deep brain stimulation for other tremors, myoclonus, and chorea. *Handb Clin Neurol*, 2013, p. 209–15. <https://doi.org/10.1016/B978-0-444-53497-2.00016-4>.
- [102] Garcia-Agundez A, Eickhoff C. Towards Objective Quantification of Hand Tremors and Bradykinesia Using Contactless Sensors: A Systematic Review. *Front Aging Neurosci* 2021;13. <https://doi.org/10.3389/fnagi.2021.716102>.
- [103] Obwegeser AA, Uitti RJ, Witte RJ, Lucas JA, Turk MF, Wharen RE. Quantitative and Qualitative Outcome Measures after Thalamic Deep Brain Stimulation to Treat Disabling Tremors. *Neurosurgery* 2001;48:274–81.
- [104] Rügge D, Mahendran S, Stieglitz LH, Oertel MF, Gassert R, Lamercy O, et al. Tremor analysis with wearable sensors correlates with outcome after thalamic deep brain stimulation. *Clin Park Relat Disord* 2020;3. <https://doi.org/10.1016/j.prdoa.2020.100066>.
- [105] Khodakarami H, Farzanehfar P, Horne M. The use of data from the parkinson's kinetigraph to identify potential candidates for device assisted therapies. *Sensors (Switzerland)* 2019;19. <https://doi.org/10.3390/s19102241>.
- [106] Legros A, Diakonova N, Cif L, Hemm S, Vayssière N, Coubes P, et al. Accelerometric measurement of involuntary movements during pallidal deep brain stimulation of patients with generalized dystonia. *Brain Res Bull* 2004;64:363–9. <https://doi.org/10.1016/j.brainresbull.2004.09.002>.
- [107] Pulliam CL, Heldman DA, Orcutt TH, Mera TO, Giuffrida JP, Vitek JL. Motion sensor strategies for automated optimization of deep brain stimulation in Parkinson's Disease. *Parkinsonism Relat Disord* 2015;21:378–82. <https://doi.org/10.1016/j.parkreldis.2015.01.018>.
- [108] Lieber B, Taylor BES, Appelboom G, Mckhann G, Connolly ES. Motion Sensors to Assess and Monitor Medical and Surgical Management of Parkinson Disease. *World Neurosurg* 2015;84:561–6. <https://doi.org/10.1016/j.wneu.2015.03.024>.
- [109] Ferleger BI, Houston B, Thompson MC, Cooper SS, Sonnet KS, Ko AL, et al. Fully implanted adaptive deep brain stimulation in freely moving Essential Tremor patients. *J Neural Eng* 2020;17:056026. <https://doi.org/10.1088/1741-2552/abb416>.

- [110] Piña-Fuentes D, van Dijk JMC, van Zijl JC, Moes HR, van Laar T, Oterdoom DLM, et al. Acute effects of adaptive Deep Brain Stimulation in Parkinson's Disease. *Brain Stimul* 2020;13:1507–16. <https://doi.org/10.1016/j.brs.2020.07.016>.
- [111] Carroll C. Impact of Quantitative Assessment of Parkinson's Disease-Associated Symptoms Using Wearable Technology on Treatment Decisions. *J Parkinsons Dis* 2019;9:601.
- [112] Santiago A, Langston JW, Gandhi R, Dhall R, Brillman S, Rees L, et al. Qualitative evaluation of the personal kinetigraph TM movement recording system in a Parkinson's clinic. *J Parkinsons Dis* 2019;9:207–19. <https://doi.org/10.3233/JPD.181373>.



Chapter 3

Supine MDS-UPDRS- III assessment: an explorative study

Naomi I. Kremer*

Annemarie Smid*

Stèfan F. Lange

Iara Mateus Marçal

Katalin Tamasi

J. Marc C. van Dijk

Teus van Laar

Gea Drost

*Shared first authors

Journal of Clinical Medicine (2023)

doi: 10.3390/jcm12093108

Abstract

The Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) is designed to be applied in the sitting position. However, to evaluate the clinical effect during stereotactic neurosurgery or to assess bedridden patients with Parkinson's Disease (PD), the MDS-UPDRS-III is often used in a supine position. This explorative study evaluates the agreement of the MDS-UPDRS-III in the sitting and the supine positions. In 23 PD patients, the MDS-UPDRS-III was applied in both positions while accelerometric measurements were performed. Video recordings of the assessments were evaluated by two certified raters. Agreement between the sitting and supine MDS-UPDRS-III was studied using Cohen's kappa coefficient. Relationships between the MDS-UPDRS-III tremor scores and accelerometric amplitudes were calculated for both positions with linear regression. A fair to substantial agreement was found for MDS-UPDRS-III scores of individual items in the sitting and supine positions, while combining all tests resulted in a substantial agreement. The inter-rater reliability was fair to moderate for both positions. A logarithmic relationship between tremor scores and accelerometric amplitude was revealed for both the sitting and supine positions. Nevertheless, these data are insufficient to fully support the supine application of the MDS-UPDRS-III. Several recommendations are made to address the sensitivity of the scale to inter-rater variability. In conclusion, although an overall substantial agreement between sitting and supine MDS-UPDRS-III is confirmed, its application in the supine position is not endorsed for the whole range of its individual items. Caution is warranted in interpreting the supine MDS-UPDRS-III, pending additional research.

1. Introduction

The motor section (part III) of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) [1] is designed to be applied in the sitting position, but it is routinely used in the supine position to assess bedridden patients with Parkinson's Disease (PD), and to intraoperatively assess the clinical effect of stereotactic neurosurgery [2]. For example, deep brain stimulation (DBS) is a well-known and effective treatment for suppressing debilitating motor symptoms in patients suffering from PD [2]. Correct stereotactic electrode placement is essential for achieving successful treatment outcomes. The intraoperative improvement of motor symptoms during awake stereotactic neurosurgery indicates correct electrode placement [2]. Monitoring these motor symptoms intraoperatively allows for the optimization of electrode position and subsequently the treatment effect, underlining the importance of accurate intraoperative monitoring.

The MDS-UPDRS-III consists of 18 tests: (1) speech assessment, (2) facial expression, (3) rigidity, (4) finger tapping, (5) hand movements, (6) pronation-supination movements of the hands, (7) toe tapping, (8) leg agility, (9) arising from a chair, (10) gait, (11) freezing of gait, (12) postural stability, (13) posture, (14) global spontaneity of movement (body bradykinesia), (15) postural tremor of the hands, (16) kinetic tremor of the hands, (17) rest tremor amplitude, and (18) rest tremor constancy [1]. Test 3 is performed for the neck, right upper extremities (RUE), left upper extremities (LUE), right lower extremities (RLE), and left lower extremities (LLE). Tests 4–8 and 15–16 are performed on both the left and right side, and test 17 is performed for all extremities and the lip/jaw, resulting in 33 tasks in total [1].

During surgery, MDS-UPDRS-III testing is performed in the supine position, since patients are situated on the operating table with the head fixated in a stereotactic frame. Several studies have used the MDS-UPDRS-III in the supine position [2–6], even though the MDS-UPDRS-III was originally validated in the sitting position [7]. Therefore, the primary aim of this prospective study is to investigate the agreement between MDS-UPDRS-III assessments in sitting and supine position, in order to endorse the supine application of the MDS-UPDRS-III. In addition, this study aims to investigate the inter-rater reliability and the relation between the MDS-UPDRS-III and accelerometric measurements in the sitting versus supine positions.

2. Materials and methods

2.1. Participants

Adult PD patients were eligible if they were diagnosed by UK Brain Bank criteria [8] and were Hoehn and Yahr stage I–IV [9]. Exclusion criteria were any form of musculoskeletal system disorders, physical disabilities, and recent alcohol/drug abuse. Exemption from the act on research involving human subjects was granted by the local research ethical board. This study was conducted in compliance with the Helsinki Declaration for research on human beings. Written informed consent was obtained from each participant.

2.2. Materials

Two wired tri-axial accelerometers (MMA8452Q tri-Axis, Freescale Semiconductor, Inc., Austin, TX, USA) with a ± 2 g range and a 200 Hz sampling rate were used, as previously described by Smid et al. [3]. Accelerometry data were recorded with Lab-VIEW v. 2014 (National Instruments, Austin, TX, USA).

2.3. Measurements

Participants were invited to the outpatient clinic to undergo MDS-UPDRS-III assessments [1], which took on average 39 min (SD $\pm$ 16.9) to complete. Participants were instructed to use their usual Parkinsonian medication; time of last intake was noted. If applicable, the DBS device was turned off during the measurements. Of the 33 MDS-UPDRS-III tasks, items 1–8 and 14–18 were first performed in sitting position and subsequently items 1, 2, 4–6, and 14–18 in supine position. In the latter position, MDS-UPDRS-III item 3 could not be performed as there was no neurologist available to perform the rigidity assessment. Items 7 and 8 could not be performed in the supine position. MDS-UPDRS-III items 9–13 were performed once, as these were not possible in sitting or supine positions, in order to calculate the total MDS-UPDRS-III score. All tasks were recorded on video. Accelerometry data (with sensors on both index fingers) were recorded for upper extremity tremor (items 15 and 17), as described previously [3].

2.4. Video ratings

Two certified raters, blinded for patient characteristics, independently assessed MDS-UPDRS-III from video recordings. Recordings could be rewatched if necessary. To prevent bias, scoring of sitting and supine tasks of various participants was random.

2.5. Accelerometry analysis

Signal analysis was performed in MATLAB v. 2021a (MathWorks, Natick, MA, USA). Pre-processing of tri-axial acceleration data was performed as described by Smid et al. [3]. Accelerometric data measured during the upper extremity tremor tasks (items 15 and 17) were used to assess postural and rest tremor amplitude. The amplitude was calculated by determining the mean of all peaks in the twice-integrated absolute displacement vector, multiplied by two.

2.6. Statistical analysis

Statistical analysis was performed in IBM SPSS v. 28 (International Business Machines Corporation, New York, NY, USA).

2.6.1. Primary endpoint

Agreement between sitting and supine MDS-UPDRS-III scores was evaluated with Cohen's weighted kappa coefficient (κ). MDS-UPDRS-III items 1–2, 4–6, and 14–18 were used to calculate agreement between both positions. Item scores of both raters were averaged and rounded before calculating agreement. An agreement of $\kappa > 0.6$ between sitting versus supine was considered acceptable [10,11].

2.6.2. Secondary endpoints

For 28 of 33 MDS-UPDRS-III tasks, Cohen's weighted kappa coefficient (κ) was used to assess inter-rater reliability between the two MDS-UPDRS-III raters. The five rigidity tasks were excluded as these were only available in the sitting position.

Contrast coding of MDS-UPDRS-III tremor scores was defined to be orthogonal polynomial, of which the first contrast coefficient has a linear trend, to assess linearity between MDS-UPDRS tremor scores and the logarithm ($\log_{10}$) of the accelerometric tremor amplitude [3,12], assessed separately in sitting and supine positions. MDS-UPDRS tremor scores of the two raters were averaged and rounded per measurement.

3. Results

Twenty-three patients (four women; 61.5 ± 9.1 years) with PD were included. The average disease duration was 8.0 ± 5.4 years. The total MDS-UPDRS-III score was 37 ± 15 . The left hemibody was predominantly affected in 12 patients, while in 9 patients the right side was more affected. All measurements were performed with the patient in ON state. In 19 patients, the median interval (interquartile range) since last medication at the start of the measurements was 105 (140) min. In 13 patients, a DBS device was present. At the time of the assessment, these participants had been treated for 20.6 ± 14.4 months on average ($\pm$ SD).

3.1. MDS-UPDRS-III agreement in sitting and supine positions

Cohen's κ coefficient between sitting and supine MDS-UPDRS-III is shown in Table 1 and Figure 1. Aside from the outliers, a fair to substantial agreement was shown for the individual items, while combining all tests resulted in a substantial agreement for MDS-UPDRS-III scores in the sitting and supine positions [10,11]. Overall agreement (all tests combined) was beyond the acceptance level of 0.6 ($\kappa = 0.613$). However, the agreement between sitting and supine position was below the 0.6 threshold for several items (Table 1).

Cohen's κ results showed a perfect agreement for lip/jaw tremor and a near-perfect agreement for kinetic tremor of the right hand. A substantial agreement was shown for pronation/supination, body bradykinesia, and rest tremor of the left lower extremity, while a moderate agreement was shown for finger tapping of the left hand, hand movements,

postural tremor, kinetic tremor of the left hand, rest tremor of the left and right upper extremities, and constancy of rest tremor. A fair agreement was shown for speech, facial expression, finger tapping of the right hand, and lower extremity rest tremor [10,11].

Table 1. Cohen's kappa results: sitting versus supine (averaged rounded MDS-UPDRS scores).

MDS-UPDRS-III Test	Site	Cohen's κ	95% CI	<i>p</i>
3.1 Speech		0.300	-0.049, 0.649	0.073
3.2 Facial expression		0.369	0.099, 0.639	<0.001
3.4 Finger tapping	Left	0.407	0.131, 0.683	<0.001
	Right	0.325	0.031, 0.619	0.007
3.5 Hand movements	Left	0.561	0.281, 0.841	<0.001
	Right	0.566	0.282, 0.850	<0.001
3.6 Pronation/supination	Left	0.662	0.399, 0.925	<0.001
	Right	0.625	0.370, 0.880	<0.001
3.14 Body bradykinesia		0.674	0.417, 0.931	<0.001
3.15 Postural tremor	Left	0.441	0.174, 0.708	<0.001
	Right	0.467	0.218, 0.716	<0.001
3.16 Kinetic tremor	Left	0.432	0.122, 0.742	<0.001
	Right	0.810	0.616, 1.004	<0.001
3.17 Rest tremor amplitude	LUE	0.553	0.300, 0.806	<0.001
	RUE	0.525	0.278, 0.772	<0.001
	LLE	0.782	0.513, 1.051	<0.001
	RLE	0.350	0.038, 0.662	0.030
	Lip/jaw	1.000	1.000, 1.000	<0.001
3.18 Constancy of rest tremor		0.496	0.257, 0.735	<0.001
All tests combined		0.613	0.556, 0.670	<0.001

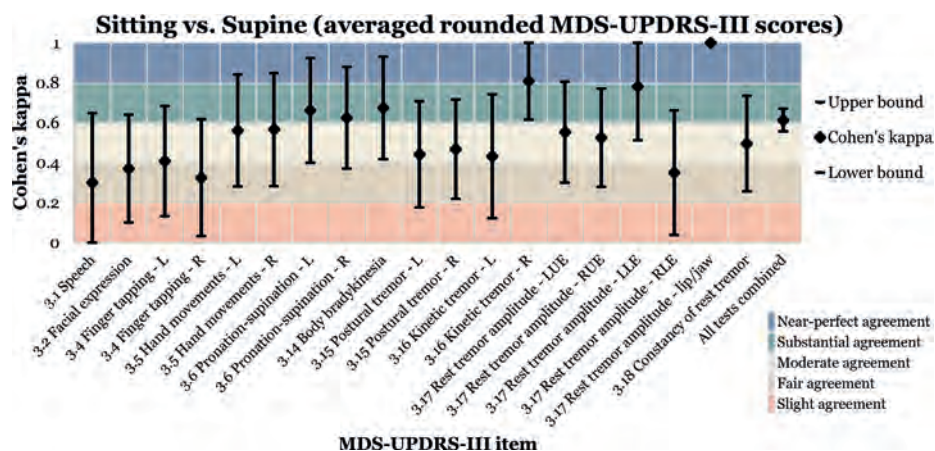


Figure 1. Cohen's kappa for sitting and supine MDS-UPDRS-III scores. L: Left side. R: Right side. LUE: Left upper extremities. RUE: Right upper extremities. LLE: Left lower extremities. RLE: Right lower extremities.

3.2. Secondary endpoints

3.2.1. Inter-rater reliability

The inter-rater reliability for sitting and supine MDS-UPDRS-III was calculated (see Tables 2 and 3). For the sitting position, the Cohen's κ coefficient ranged from -0.20 to 1.00 , and for the supine position, from -0.14 to 1.00 in. Aside from the outliers, the inter-rater reliability was fair to moderate in both positions [10,11].

Table 2. Cohen's kappa results: Inter-rater sitting position rater 1 versus rater 2.

MDS-UPDRS-III Test	Site	Cohen's κ	95% CI	<i>p</i>
3.1 Speech		-0.196	$-0.435, 0.043$	0.132
3.2 Facial expression		0.228	$-0.021, 0.477$	0.029
3.4 Finger tapping	Left	0.378	$0.119, 0.637$	<0.001
	Right	0.346	$0.091, 0.601$	0.002
3.5 Hand movements	Left	0.051	$-0.169, 0.271$	0.598
	Right	-0.040	$-0.297, 0.217$	0.744
3.6 Pronation-supination	Left	0.111	$-0.093, 0.315$	0.160
	Right	0.122	$-0.117, 0.361$	0.216
3.7 Toe tapping	Left	0.501	$0.242, 0.760$	<0.001
	Right	0.141	$-0.071, 0.353$	0.183
3.8 Leg agility	Left	0.351	$0.084, 0.618$	0.002
	Right	0.237	$-0.004, 0.478$	0.024
3.9 Arising from chair		0.704	$0.388, 1.020$	<0.001
3.10 Gait		0.473	$0.154, 0.792$	0.005
3.11 Freezing of gait		0.000	$0.000, 0.000$	<0.001
3.12 Postural stability		0.629	$0.384, 0.874$	<0.001
3.13 Posture		0.385	$0.124, 0.646$	<0.001
3.14 Body bradykinesia		0.075	$-0.168, 0.318$	0.462
3.15 Postural tremor	Left	0.550	$0.291, 0.809$	<0.001
	Right	0.786	$0.574, 0.998$	<0.001
3.16 Kinetic tremor	Left	0.398	$0.071, 0.725$	0.003
	Right	0.339	$0.092, 0.586$	0.009
3.17 Rest tremor amplitude	LUE	0.574	$0.343, 0.805$	<0.001
	RUE	0.742	$0.526, 0.958$	<0.001
	LLE	0.429	$0.100, 0.758$	0.005
	RLE	-0.045	$-0.112, 0.022$	0.766
	Lip/jaw	1.000	$1.000, 1.000$	<0.001
3.18 Constancy of rest tremor		0.468	$0.239, 0.697$	<0.001
All tests combined		0.431	$0.382, 0.480$	<0.001

Table 3. Cohen's kappa results: Inter-rater supine position rater 1 versus rater 2.

MDS-UPDRS-III Test	Site	Cohen's κ	95% CI	<i>p</i>
3.1 Speech		-0.135	-0.284, 0.014	0.104
3.2 Facial expression		0.140	-0.081, 0.361	0.140
3.4 Finger tapping	Left	0.371	0.102, 0.640	<0.001
	Right	0.303	0.031, 0.575	0.008
3.5 Hand movements	Left	0.061	-0.172, 0.294	0.547
	Right	0.168	-0.079, 0.415	0.138
3.6 Pronation-supination	Left	0.212	0.000, 0.424	0.011
	Right	-0.005	-0.164, 0.154	0.954
3.14 Body bradykinesia		0.250	-0.013, 0.513	0.033
3.15 Postural tremor	Left	0.512	0.242, 0.782	<0.001
	Right	0.717	0.462, 0.972	<0.001
3.16 Kinetic tremor	Left	0.129	-0.138, 0.396	0.198
	Right	0.457	0.218, 0.696	<0.001
3.17 Rest tremor amplitude	LUE	0.540	0.268, 0.812	<0.001
	RUE	0.509	0.256, 0.762	<0.001
	LLE	0.416	0.153, 0.679	0.003
	RLE	0.361	0.057, 0.665	0.013
	Lip/jaw	1.000	1.000, 1.000	<0.001
3.18 Constancy of rest tremor		0.604	0.392, 0.816	<0.001
All tests combined		0.385	0.326, 0.444	<0.001

3.2.2. The relationship between UPDRS scores and amplitude

In Figure 2, the accelerometric amplitude of resting and postural tremor tests in the sitting and supine positions are plotted against the given averaged MDS-UPDRS-III tremor scores. An accelerating increase in amplitude with increasing MDS-UPDRS-III score is noted in all subfigures. Hence, the log-transformed accelerometric tremor amplitudes of sitting and supine postural and rest tremor were regressed on the corresponding MDS-UPDRS-III tremor scores. There was strong evidence against the null hypothesis that the log-transformed amplitude was not linearly related to the MDS-UPDRS-III scores ($p < 0.001$) for both tremor tests, in both positions. The amplitude tended to increase as a logarithmic function of MDS-UPDRS-III scores ($R^2 > 0.712$) for all tests (Table 4).

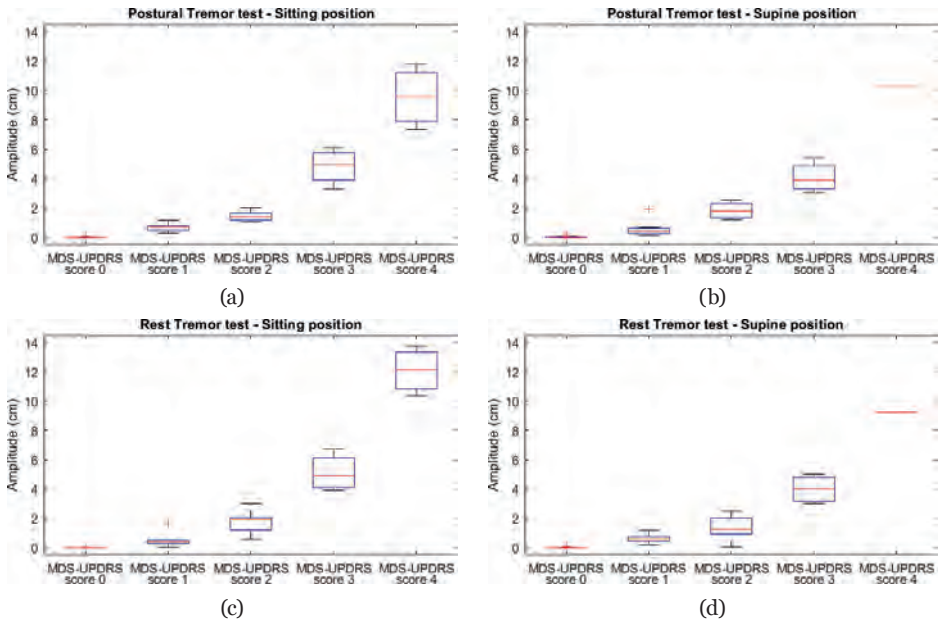


Figure 2. Boxplots of the tremor amplitude of the sitting postural (a), supine postural (b), sitting rest (c), and supine rest (d) tremor tests (per MDS-UPDRS score).

Table 4. Regression analysis results.

MDS-UPDRS-III Test	Position	R	R ² *	Coefficient **	95% CI	p
Postural tremor	Sitting	0.900	0.811	2.662	2.271, 3.052	<0.001
	Supine	0.862	0.743	2.873	2.360, 3.387	<0.001
Rest tremor	Sitting	0.905	0.818	3.604	3.088, 4.121	<0.001
	Supine	0.844	0.712	4.213	3.399, 5.027	<0.001

* Coefficient of determination; ** Contrast coefficient testing for linear trend.

4. Discussion

This study revealed a fair to substantial agreement for sitting and supine MDS-UPDRS-III scores. The inter-rater reliability was fair to moderate in both positions. The relationship between tremor amplitude and clinical tremor score in sitting position was shown to be similar to that in the supine position for both rest and postural tremors. Trends were consistent with the logarithmic relationship between tremor amplitude and clinical tremor score reported in previous studies [3,12].

In this explorative study, an acceptable overall agreement (all tests combined) between the sitting and supine position was found. However, several sub-items showed an agreement below the set acceptance level. Consequently, the supine use of the MDS-UPDRS-III is discouraged based on these data. Additional research is warranted and

perhaps an alternative version of the MDS-UPDRS-III should be designed, preferably by the expert panel of the MDS, for supine assessment of the items for which disagreement was shown in our study.

When assessing all MDS-UPDRS-III items separately, Cohen's κ coefficient between the scores in sitting and supine position had a wide range. This is explained by the small sample size. All MDS-UPDRS-III tests combined produced a substantial agreement with a relatively narrow 95% confidence interval. It was notable that there was no clear subgroup of items that consistently showed substantial agreement, or no agreement at all. In some patients the ratings for speech were higher in supine position than in sitting position. This could be due to gravitational force, which can influence speaking while reclining [13]. In the operative setting, decreased oral fluid intake and higher stress level may cause a dry mouth, worsening speech. The perfect agreement found for lip/jaw tremor (Tables 1–3) is explained by the fact that only 1 of the 23 participants had this symptom. Some of the lower agreements found between the sitting and supine position could also be accounted for by the relatively low inter-rater reliability found in this study, e.g., for the speech, hand movements and pronation/supination items. These findings are in line with those of previous studies, which have shown that the MDS-UPDRS-III within-patient reliability consists of a substantial amount of error variance, especially for the bradykinetic items [14–18]. The poor inter-rater reliability found for item 3.1 (Tables 2 and 3) could be explained by the speech criteria being open to interpretation, as it can differ between raters whether the words or sentences spoken by the patient are easy or poorly understood by the rater. This might result in different raters giving different ratings (e.g., with a difference of one point) to the same speech assessment. The disagreement found for item 3.11 (Table 2) occurred because none of the participants suffered from freezing, so the inter-rater reliability could not be properly calculated for that item.

4.1. Limitations

All measurements were initially performed in the sitting position and subsequently in the supine position. This might have introduced order effects, such as the influence of medication status and fatigue on the results, although measurements were performed in a short interval. Rigidity was not assessed in the supine position in this study due to logistic reasons. Additionally, facial expression could not be assessed properly during supine assessments, as the camera was positioned at the participant's feet, making it difficult to observe whether the lips were parted and explaining the lower agreement found for this item. Furthermore, the study uses a convenience sample—no formal calculation was performed as test variability could not be estimated.

4.2. Recommendations

In this study, it was shown that lower extremity tremor assessment can differ in supine versus sitting position. Since the legs are supported by the bed in supine position, this might have caused the amplitude of a lower extremity tremor to be suppressed. Moreover, since the legs are often positioned under blankets during surgery, their tremor

amplitude may be suppressed even more. Therefore, it is recommended to be aware of the position of the extremities during supine assessment of tremor.

Some MDS-UPDRS-III items (e.g., rigidity and tremor amplitude) are described in such a way that inter-rater variability is limited, as its criteria are less subject to interpretation. These items showed a higher inter-rater reliability in this study. Other items (e.g., the bradykinetic items) are more susceptible to inter-rater variability, since criteria as “slight”, “mild”, and “moderate” are open to interpretation. It can also differ per rater whether “slowing” of the movement during the task is rated, versus general “slowness” of movement during the whole task. Most importantly, the correct scoring of these items depends on the instructions given to the patient, which will influence how the task is performed. Criteria should be defined more clearly to minimize inter-rater variability.

4.3. Future perspectives

Although many studies already applied the MDS-UPDRS-III supinely [2–6], its use has not been validated in this position. In this explorative study, the agreement between MDS-UPDRS-III application in the sitting and supine positions was evaluated, and demonstrated that sitting and supine assessments may differ. However, in order to properly validate the supine application of the MDS-UPDRS-III, further research is indispensable. Additional experiments should be performed to determine the reproducibility of MDS-UPDRS-III items, in order to test variability between sitting and supine assessments to be assigned to the position in which measurements were performed. Rigidity assessments should be performed in the supine position to include the results of this item in the validation analysis. Additionally, order effects should be prevented by proper counterbalancing. The use of several video cameras from different angles could prevent difficulties with properly observing the participant. The sample size of future studies could be calculated based on the test variability of the current study. Therefore, a large-scale validation study is proposed, in which reproducibility analysis, order effects, and supine rigidity items are considered. As such, supine MDS-UPDRS-III application will be properly validated, or, in the case of unconvincing results, an alternative version of the MDS-UPDRS-III could be designed for supine use.

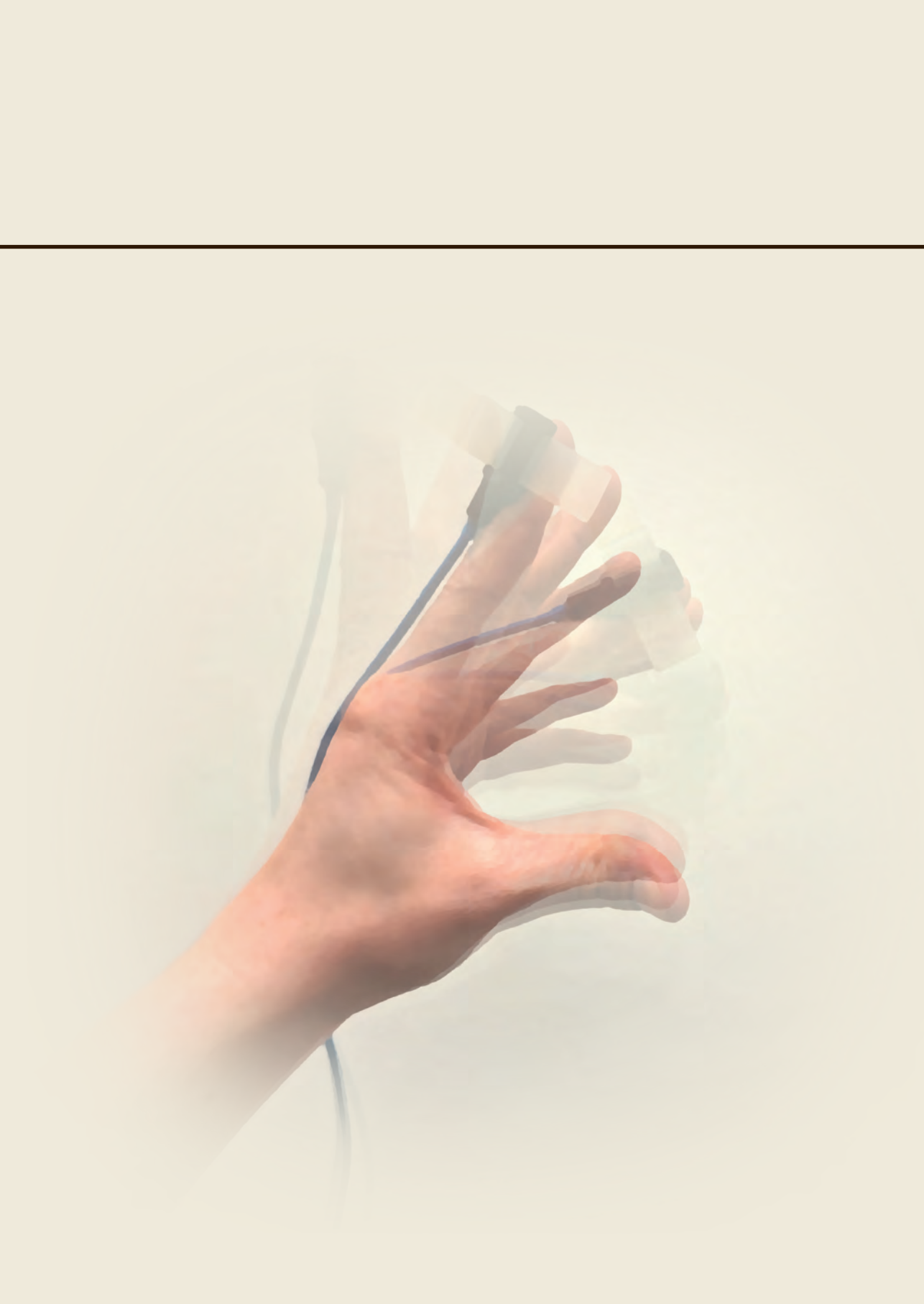
5. Conclusions

Although an overall substantial agreement between the MDS-UPDRS-III in the sitting and supine position is confirmed, its application in the supine position is not endorsed for the whole range of its individual items. In general, the MDS-UPDRS-III is found to be sensitive to inter-rater variability, for which recommendations are formulated. At present, in anticipation of additional research, caution is warranted in interpreting the supine MDS-UPDRS-III. In future studies, the test variability of the current study can be used to determine the sample size.

References

- [1] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [2] Lange SF, Kremer NI, van Laar T, Lange F, Steendam-Oldekamp TE, Oterdoom DLM, et al. The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation* 2021. <https://doi.org/10.1111/ner.13523>.
- [3] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative Quantification of MDS-UPDRS Tremor Measurements Using 3D Accelerometry: A Pilot Study. *J Clin Med* 2022;11:2275. <https://doi.org/10.3390/jcm11092275>.
- [4] Krauss P, Oertel MF, Baumann-Vogel H, Imbach L, Baumann CR, Sarnthein J, et al. Intraoperative Neurophysiologic Assessment in Deep Brain Stimulation Surgery and its Impact on Lead Placement. *J Neurol Surg A Cent Eur Neurosurg* 2021;82:018–26. <https://doi.org/10.1055/s-0040-1716329>.
- [5] Wu J, Yu N, Yu Y, Li H, Wu F, Yang Y, et al. Intraoperative Quantitative Measurements for Bradykinesia Evaluation during Deep Brain Stimulation Surgery Using Leap Motion Controller: A Pilot Study. *Parkinsons Dis* 2021;2021. <https://doi.org/10.1155/2021/6639762>.
- [6] Yu N, Yu Y, Lin J, Yang Y, Wu J, Liang S, et al. A non-contact system for intraoperative quantitative assessment of bradykinesia in deep brain stimulation surgery. *Comput Methods Programs Biomed* 2022;225. <https://doi.org/10.1016/j.cmpb.2022.107005>.
- [7] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders* 2008;23:2129–70. <https://doi.org/10.1002/mds.22340>.
- [8] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's Disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4. <https://doi.org/10.1136/jnnp.55.3.181>.
- [9] Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967;17:427–427. <https://doi.org/10.1212/WNL.17.5.427>.
- [10] McHugh M. Interrater reliability - the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276–82.
- [11] Ranganathan P, Pramesh C, Aggarwal R. Common pitfalls in statistical analysis: Measures of agreement. *Perspect Clin Res* 2017;8:187–91. https://doi.org/10.4103/picr.PICR_123_17.
- [12] Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. *Brain* 2006;129:2660–6. <https://doi.org/10.1093/brain/awl190>.
- [13] Shiller DM, Ostry DJ, Gribble PL. Effects of Gravitational Load on Jaw Movements in Speech. *The Journal of Neuroscience* 1999;19:9073–80. <https://doi.org/10.1523/JNEUROSCI.19-20-09073.1999>.
- [14] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [15] Yang K, Xiong WX, Liu FT, Sun YM, Luo S, Ding ZT, et al. Objective and quantitative assessment of motor function in Parkinson's Disease-from the perspective of practical applications. *Ann Transl Med* 2016;4. <https://doi.org/10.21037/atm.2016.03.09>.
- [16] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.

- [17] Rovini E, Maremmani C, Cavallo F. How wearable sensors can support Parkinson's Disease diagnosis and treatment: A systematic review. *Front Neurosci* 2017;11. <https://doi.org/10.3389/fnins.2017.00555>.
- [18] Lu R, Xu Y, Li X, Fan Y, Zeng W, Tan Y, et al. Evaluation of Wearable Sensor Devices in Parkinson's Disease: A Review of Current Status and Future Prospects. *Parkinsons Dis* 2020;2020. <https://doi.org/10.1155/2020/4693019>.



Chapter 4

Perioperative quantification of MDS-UPDRS-III bradykinesia measurements in patients with Parkinson's Disease using accelerometry

Annemarie Smid

Teus van Laar

Amber E. Pinkster

Jolien M. ten Kate

Naomi I. Kremer

D. L. Marinus Oterdoom

Katalin Tamasi

J. Marc C. van Dijk

Gea Drost

Journal of Clinical Neurophysiology (2025)

doi: 10.1016/j.clinph.2025.2111424

Abstract

Objective

The gold standard for assessing bradykinesia in Parkinson's Disease (PD) is the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS), although it is limited by inherent subjectivity and reliance on experienced raters. This study focused on translating the MDS-UPDRS upper limb bradykinesia assessments into an objective scoring method with 3D accelerometry.

Methods

In this study, 44 patients with PD and 44 healthy controls (matched on sex and age) were included. Two raters assessed MDS-UPDRS criteria for bradykinesia, while accelerometric measurements were conducted at the index fingers. Measurements were performed in an off-medication state. The 3D acceleration data produced quantitative measures, such as frequency and amplitude of hand movement. The algorithm for calculating accelerometric scores was based on MDS-UPDRS criteria with thresholds from healthy controls. Agreement between MDS-UPDRS bradykinesia scores and accelerometric scores was estimated with Cohen's kappa coefficient (κ).

Results

The accelerometric scores showed moderate agreement ($\kappa \geq 0.548$) with MDS-UPDRS ratings. The inter-rater agreement between the two MDS-UPDRS raters was moderate for all tests ($\kappa \geq 0.595$). Accelerometric test-retest reliability was good to excellent ($\text{ICC} \geq 0.764$, $p < 0.001$).

Conclusions

This study introduces an accelerometric algorithm to classify upper extremity bradykinesia according to MDS-UPDRS criteria, yielding high test-retest reliability.

Significance

Given its consistency, this method can potentially reduce MDS-UPDRS rater-dependency and improve objective monitoring of upper limb bradykinesia.

1. Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder accompanied by debilitating motor symptoms, with bradykinesia as the core feature [1,2]. Bradykinesia (slowness of movement) is defined as decline in amplitude or speed during continuous movement [1–3]. Considering its heterogenic and multifaceted presentation, accurate assessment of bradykinesia is key for correct diagnosis and treatment evaluation of PD. Several bradykinetic aspects can influence the assessment: decrease in movement amplitude, hesitations during the ongoing movement, and slowing of the ongoing movement.

Bradykinesia of the hands is most often assessed with the internationally standardized Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS). More specifically, MDS-UPDRS Motor Section (MDS-UPDRS-III) is used: finger tapping (item 3.4), hand movements (item 3.5), and pronation-supination (item 3.6) [4]. Number of hesitations of movement, level of slowing, and timing of amplitude decrements are evaluated [4]. Each item is rated with a single score 0–4, depending on the most bradykinetic expression. The lowest score corresponds to asymptomatic movement; higher scores indicate more severe bradykinesia [4]. Although a substantial number of MDS-UPDRS-III criteria have been defined, most criteria are not quantitative and thus sensitive to inter-rater variability [5–8]. Therefore, MDS-UPDRS-III assessment is limited by subjectivity and reliance on expert raters [8–10]. Especially the influence of tapping speed (and the associated instructions to perform the test with maximal amplitude and as quick as possible) on the decrement is an important source of variability in outcomes. If the task is not performed initially with maximal amplitude, proper assessment of amplitude decrement is not possible. Accurately assessing bradykinesia requires patients being given correct instructions, which is often linked to the rater's expertise, underlining the complexity of achieving standardization of bradykinesia assessment with currently available methods. Since caregivers with varying experience levels are involved in practice, a reliable and rater-independent method is warranted [6,7].

One way to overcome the shortcomings of visual ratings is use of objective motor-measurements, for example electronic motion-capture sensors. Correct signal analysis of objective data may provide quantitative, reliable outcomes to guide PD therapy. Unfortunately, such measures currently lack in standard clinical practice [10–12], due to price, size, and invasiveness of current systems [9]. Tri-axial accelerometers offer a solution given their accuracy, compactness, light weight, non-invasiveness, and relative inexpensiveness [5,10,13,14]. They record linear movement-induced accelerations as 3D timeseries in gravitational units (g) in the device's reference-frame [15,16]. Accelerometry allows quantification of relevant bradykinesia parameters (e.g., velocity, amplitude, rhythm) [17,18]. For example, movement rhythm is analyzed by approximating the dominant frequency using fast Fourier transformation (FFT) [10]. These measures can be applied to calculate objective scores based on MDS-UPDRS-III bradykinesia criteria.

Several studies have aimed to quantify bradykinesia, e.g. by predicting or estimating UPDRS-scores based on movement sensor data [19–22]. Stamatakis et al. used finger tapping accelerometry to predict UPDRS-scores using ordinal logistic regression [21]. Maldonado-Naranjo et al. investigated the relationship between MDS-UPDRS scores

and i.a. dwell time [23]. However, direct translation of upper extremity bradykinesia tests as described in MDS-UPDRS-III into objective accelerometric methodology has not yet been attempted. Considering the current dependance of PD treatment on subjective motor assessments, the need for reliable, rater-independent bradykinesia measurement is undeniable. Therefore, this study aims to translate upper extremity MDS-UPDRS-III bradykinesia scoring criteria into an objective rating with accelerometry data as input.

2. Materials and methods

This study was performed at the Parkinson Expertise Center of University Medical Center Groningen (UMCG).

2.1. Participants

PD patients assessed for Deep Brain Stimulation (DBS) surgery and age- and sex-matched Healthy Controls (HC) were included. PD patients were all diagnosed according to UK Brain Bank criteria [24] and were Hoehn Yahr stage I–V [25]. Exclusion criteria were diagnosis of any form of musculoskeletal system disorders or physical disabilities, recent alcohol/drugs abuse, and psychiatric disorders.

2.2. Materials

Two wired tri-axial accelerometers (MMA8452Q tri-Axis, Freescale Semiconductor, Inc., Austin, TX, USA) with $\pm 2g$ range and 200 Hz sampling rate were used [10]. The sensors were attached to the index fingers with adjustable straps (Figure 1).

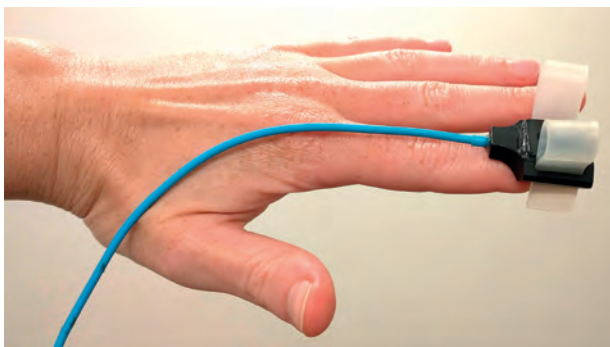


Figure 1. Accelerometer positioned at the left index fingertip.

Accelerometry data were recorded with LabVIEW v. 2017 (National Instruments, Austin, TX, USA), as described previously [10]. Signal analysis was performed in MATLAB v2023a (MathWorks, Natick, MA, USA). Statistical analysis was performed in IBM SPSS statistics v28 (International Business Machines Corporation, New York, NY,

USA). MDS-UPDRS-III items 3.4–3.6 were used for clinical assessment of participants [4]. MDS-UPDRS part II was used to assess motor aspects of daily living in the PD group [4].

2.3. Measurements

HC were measured to determine normal frequency, velocity, amplitude, and rhythm of finger tapping (FT), hand movement (HM), and pronation-supination (PS) tests. From these data, thresholds were calculated in relation to MDS-UPDRS-III upper extremity bradykinesia items. Accelerometers were placed at the distal phalanx of both index fingers. All measurements were conducted with the participant in sitting position. Tests lasted ten seconds each. MDS-UPDRS-III items 3.4–3.6 [4] were performed at both hands separately to assess FT, HM, and PS, while accelerometry data were simultaneously recorded. Patients were assessed before DBS surgery. All measurements were performed in an off-medication state, after a washout period of at least 12h. All tests were performed twice for each task, with an identical sequence (FT, HM, PS, FT, HM, PS), in order to determine test-retest reliability of the accelerometric approach. Bradykinesia severity was assessed for all measurements according to MDS-UPDRS-III by two experienced MDS-UPDRS certified raters (A. Smid, J.M. ten Kate), who were blinded to the scores of the other rater and to the accelerometric data.

2.4. Data pre-processing

Pre-processing was performed as described previously [10,13,14]. Calibrated raw acceleration data were converted from g-units to cm/s^2 . The norm of the acceleration vector in all three directions was calculated by taking the root mean square of the resultant signal of the three axes [23,26]. Non-causal second-order high-pass Butterworth filters (cut-off frequency 0.5 Hz) were used to remove low-frequency noise. Digital noise, possible tremor and higher-order harmonics were suppressed using non-causal second-order low-pass Butterworth filters (4 Hz) [10,23,26], resulting in filtered acceleration norm ($\vec{a}$).

2.5. Accelerometric outcome measures

In order to objectively quantify hand bradykinesia as described in MDS-UPDRS-III [4], all stated criteria should be objectified. Measures used in MDS-UPDRS-III bradykinesia items are (a) number of interruptions/arrests, (b) slowing, and (c) amplitude decrements. Thus, main accelerometric measures were (a) inactivity time, (b) mean increase in time per cycle, and (c) mean decrease in amplitude (Figure 2). Since timing of decrease in velocity and/or amplitude is important, individual Movement Cycles (MC) during the task were defined. For FT, a cycle was defined as one opening and closing of the index finger and thumb. For HM, a cycle was defined as one opening and closing of the hand. For PS, one cycle was defined as a single turn of the extended arm from palm up to palm down to palm up.

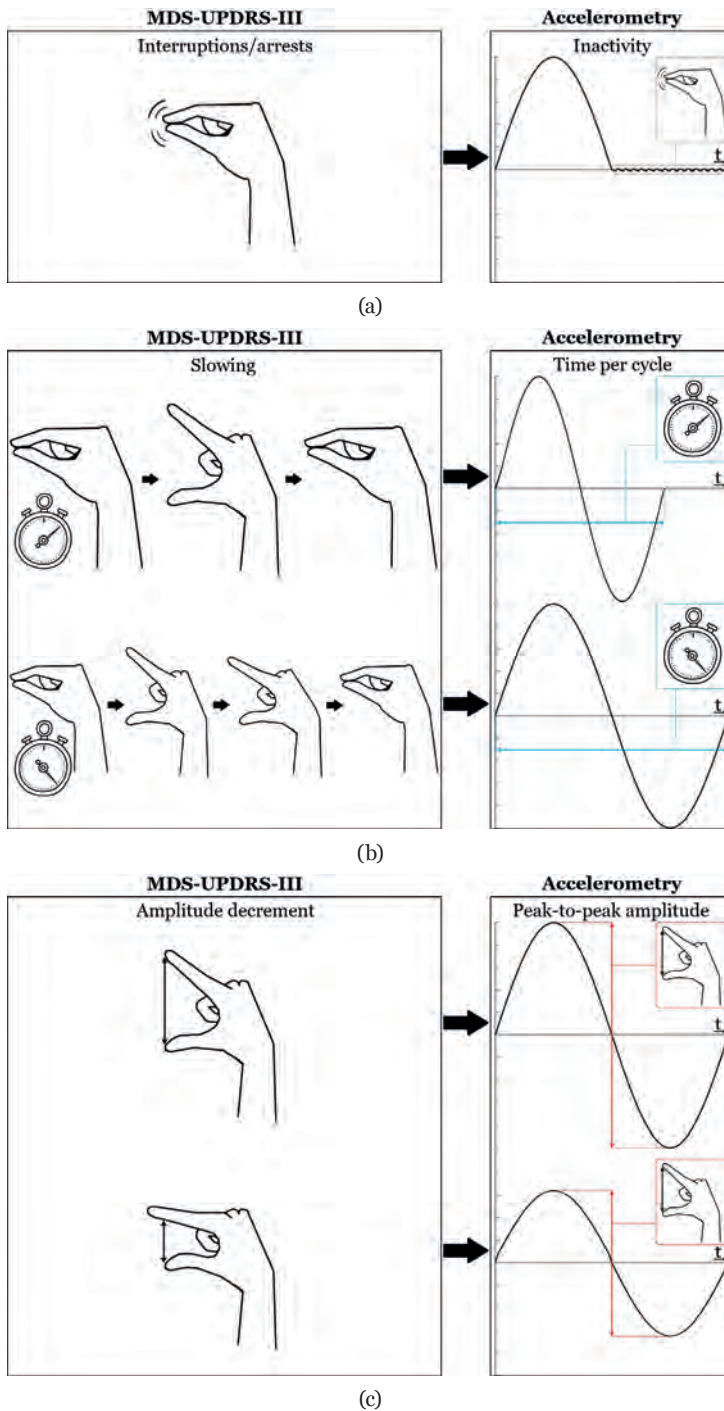


Figure 2. Schematic representation of the MDS-UPDRS-III measures translated to accelerometry measures for (a) interruptions/arrests, (b) velocity, and (c) amplitude, for FT.

2.5.1. Rhythm

The dominant frequency of the movement was estimated, in order to approximate the rhythm of the movement sequence. The FFT of $\vec{a}$ of each performed test was used to calculate dominant frequency (f_0) from the periodogram Power Spectral Density (PSD) estimate, using a Hann window [26] (Figure 3).

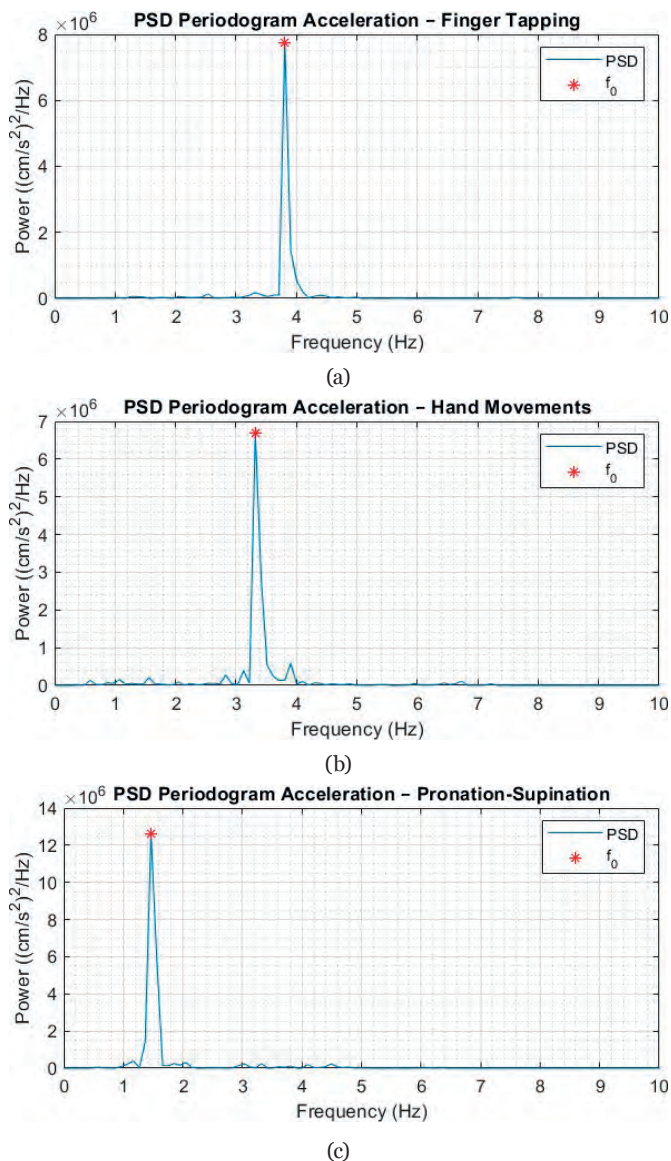


Figure 3. Example PSD periodogram for FT (a), HM (b) and PS (c), with dominant frequency f_0 marked by a red star (*).

2.5.2. Defining individual movement cycles

Segmentation of filtered acceleration norm $\vec{a}$ was performed for each performed test to evaluate bradykinesia characteristics for individual MC. Segmenting individual cycles was done by determining the point that $\vec{a}$ shifted from negative to positive. One cycle was defined as the data between two points where $\vec{a}$ shifted from negative to positive, capturing one period of the movement (Figure 4). Minimal distance between these two points was set at $1/(2 \times f_o)$ seconds, with a lower limit of 0.125 seconds (assuming a maximal movement frequency of 4 Hz). Only the first ten cycles were used for analysis, following MDS-UPDRS-III criteria [4].

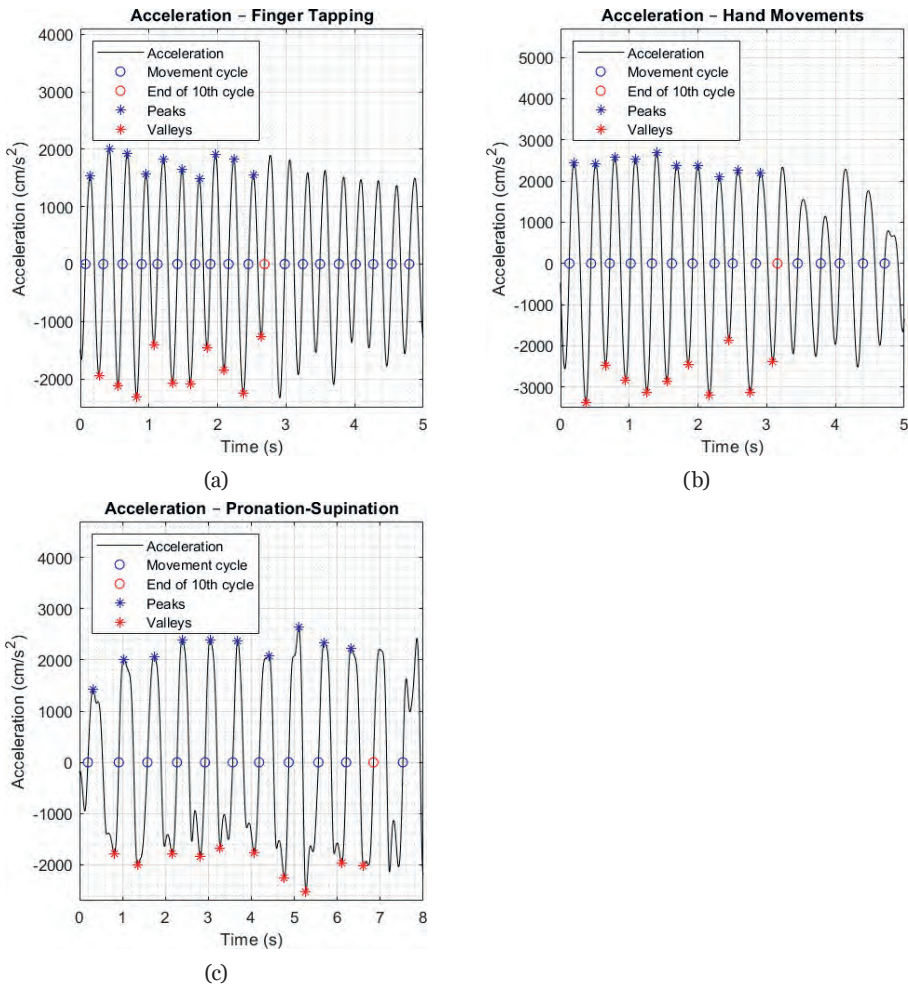


Figure 4. Example acceleration for FT (a), HM (b) and PS (c), given in black. Blue circles mark points where $\vec{a}$ shifted from negative to positive, marking beginning/ending of a movement cycle. Red circles mark the point when ten cycles were performed. The first ten peaks and valleys of $\vec{a}$ are marked by blue and red stars, respectively.

2.5.3. Interruptions/arrests

Interruptions/arrests (as mentioned in MDS-UPDRS) occur if the continuous movement sequence halts, resulting in hardly any movement (Figure 2a). In other words, an interruption was detected when acceleration falls below a certain threshold for a consecutive period exceeding a specific duration. The measure to determine presence of interruptions or arrests is called Inactivity Time (IT). IT was calculated from absolute acceleration ($\vec{a}_{abs}$), by computing the total amount of time the value of $\vec{a}_{abs}$ was below the threshold (p_{abs}), which was a certain percentage of the maximum $\vec{a}_{abs}$ for that measurement (Figure 5) [23].

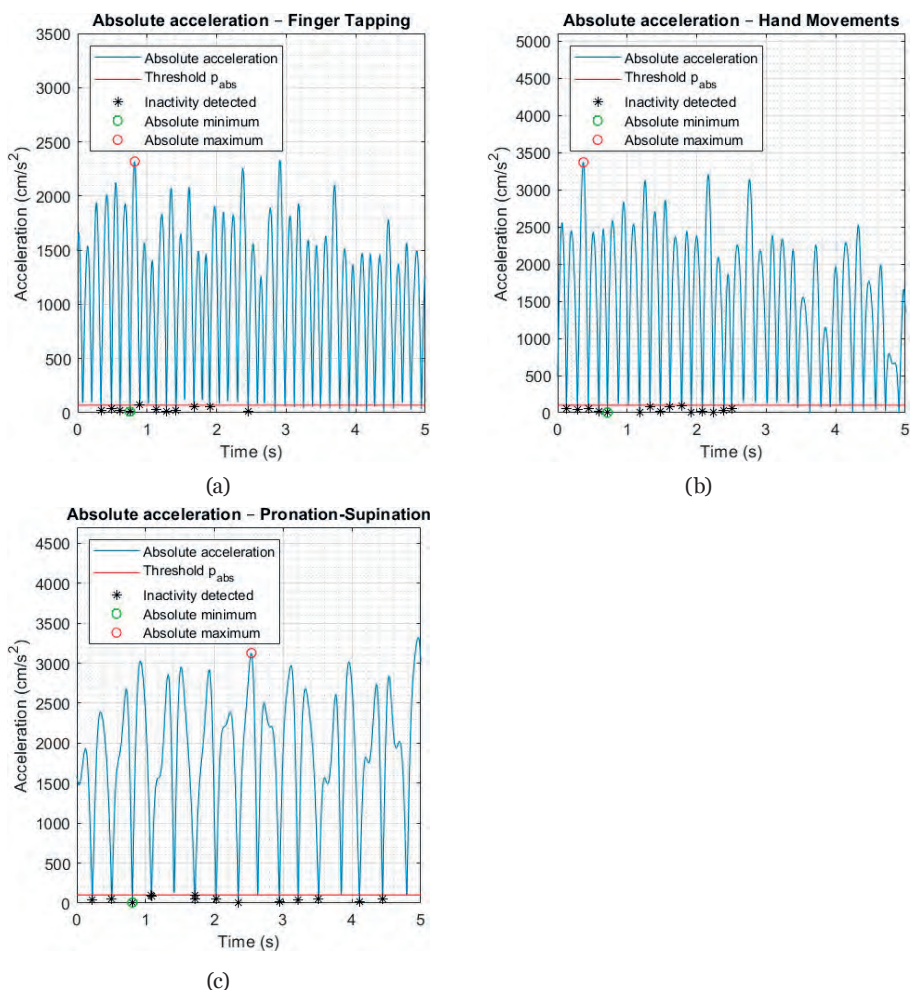


Figure 5. Example absolute acceleration for FT (a), HM (b) and PS (c). p_{abs} -threshold is given in red. Stars mark when inactivity was detected. Lowest and highest absolute acceleration values were marked by green and red circles, respectively.

2.5.4. Slowing

If slowing (Figure 2b) occurs during bradykinesia tests, the time per MC (T_c) increases. T_c was calculated by determining the length of the time interval of each defined MC (Figure 4). The T_c of the first cycle (T_{c_1}) was used as reference value, as MDS-UPDRS-III prescribes. Next, increase in T_c between T_{c_1} and the T_c of each consecutive MC was calculated (%) for the first ten cycles. Mean of these nine values was calculated per measurement (p_{T_c} (%)).

2.5.5. Amplitude decrements

The decrease in amplitude (Figure 2c) per MC compared to the first MC was calculated from $\tilde{a}$ (cm/s²). The amplitude (peak-to-peak distance) of each cycle was calculated by summing the $\tilde{a}$ -peak and $\tilde{a}$ -valley of the same cycle (blue and red stars in Figure 4). The amplitude of the first cycle (amp_1) was used as reference value, as MDS-UPDRS-III prescribes. Next, decrease in amplitude between amp_1 and the amplitude of each consecutive MC was calculated (%) for the first ten cycles. Mean of these nine values was calculated per measurement (p_{amp} (%)).

2.6. Accelerometric scores

The calculated accelerometric outcome measures were used as input for the scoring algorithm. The output of the algorithm is accelerometric (ACC) scores ranging from 0–4 per task, as MDS-UPDRS-III prescribes, as well as ACC sub-scores per criterion (interruptions/arrests, slowing, amplitude decrement). Quantitative thresholds based on MDS-UPDRS-III (e.g. number of interruptions) were used as cut-off values. The findings of section 2.6.1, 2.6.2, and 2.6.3 create the middle three branches of the algorithm (Figure 6). The highest score given to any of these three components was the final calculated accelerometric (ACC) score given to that test, as MDS-UPDRS-III prescribes. As such, MDS-UPDRS-based analysis of bradykinesia task performance, including a 0–4 score for each task, was provided in this study. All outcome measures were calculated for both hands for all corresponding tests.

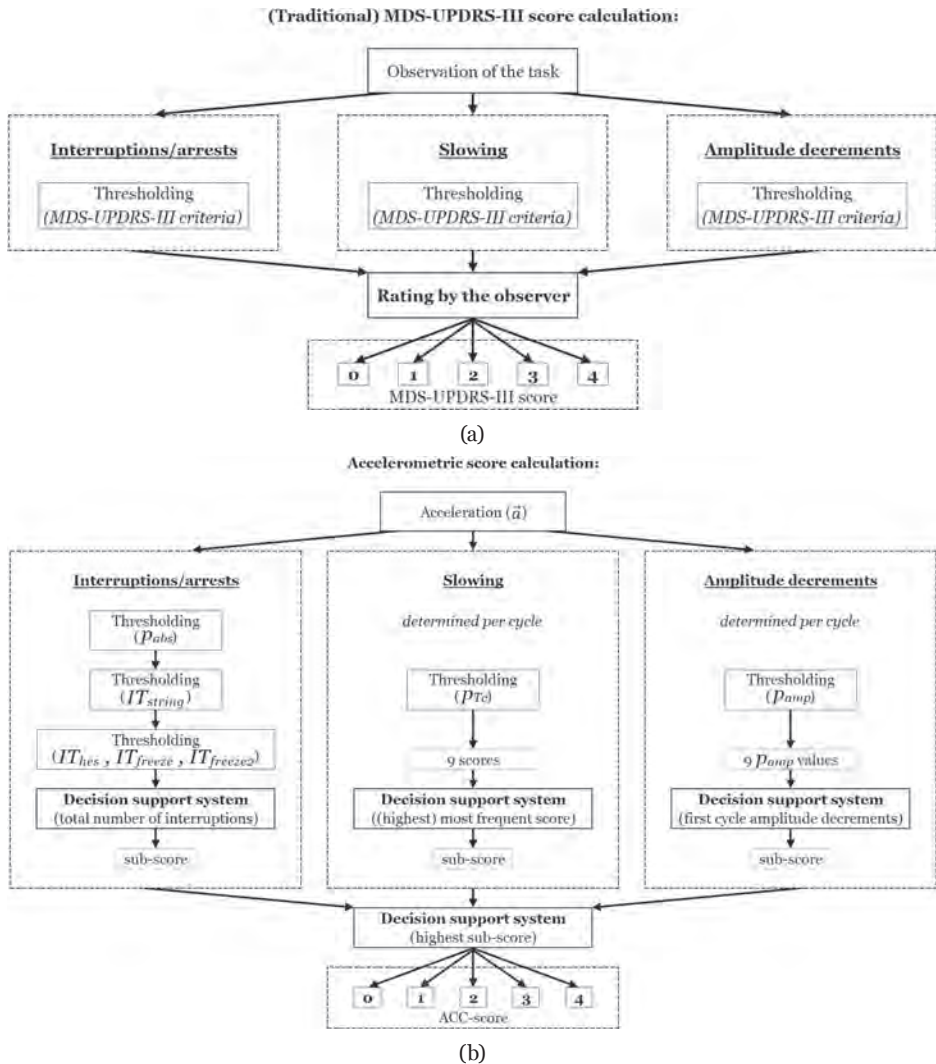


Figure 6. a) block diagram for standard MDS-UPDRS-III rating. b) Block diagram for accelerometric score calculation.

If MDS-UPDRS-III was not able to provide quantitative thresholds for particular measures, natural variations were calculated from the accelerometric HC data. These natural variations were used to establish thresholds able to distinguish asymptomatic (MDS-UPDRS-III score = 0) from symptomatic (MDS-UPDRS-III score ≥ 1) measurements. These thresholds are described in section 2.6.1–2.6.3 and summarized in Table 1.

Table 1. Overview of thresholds used for the accelerometric algorithm.

Threshold	Criterion	Explanation	Value
$1/(2 \times f_o)$	Defining individual movement cycles	Minimal difference between the start and end of a defined movement cycle.	$1/(2 \times f_o)$ seconds
p_{abs}	Interruptions/arrests	Percentage of the maximum $\vec{a}_{abs}$ of the first ten cycles.	3%
IT_{string}	Interruptions/arrests	Minimal number of seconds between two IT -samples to be included in the same IT -string.	0.1 seconds
IT_{hes}	Interruptions/arrests	Minimal number of IT -samples in an IT -string for being counted as a hesitation.	10 (equals 0.05 second)
IT_{freeze}	Interruptions/arrests	Minimal number of IT -samples in an IT -string for being counted as one freeze.	200 (equals 1 second)
$IT_{freeze2}$	Interruptions/arrests	Minimal number of IT -samples in an IT -string for being counted as two freezes.	500 (equals 2.5 seconds)
$p_{Tc(slight)}$	Slowing	Percentage of increase in Tc defined as “slight slowing”.	20%
$p_{Tc(mild)}$	Slowing	Percentage of increase in Tc defined as “mild slowing”.	40%
$p_{Tc(moderate)}$	Slowing	Percentage of increase in Tc defined as “moderate slowing”.	60%
$p_{Tc(severe)}$	Slowing	Percentage of increase in Tc defined as “severe slowing”.	80%
p_{amp}	Amplitude decrements	Percentage of maximal amplitude per cycle to detect amplitude decrement.	50%

Accelerometric HC data was analyzed to calculate natural variation and asymptomatic thresholds. Kolmogorov-Smirnov test of normality (one-sample K-S test) was used to determine whether data were normally distributed. According to the empirical rule, about 95% of data is within the population mean (μ) plus two times standard deviation (σ) for normally distributed data. So, threshold (t) was calculated according to:

$$t = \mu + 2\sigma \quad (\text{Eq. 1})$$

This rule was used to determine asymptomatic thresholds for inactivity time (IT_{hes} (s)), percentage of maximal acceleration (p_{abs} (%)), mean increase in Tc ($p_{Tc(slight)}$ (%)), and percentage of maximal amplitude (p_{amp} (%)).

2.6.1. Interruptions/arrests-scores

Interruptions and arrests in the first ten MC were detected by finding the IT -samples (all data points in $\vec{a}_{abs}$ that are below the p_{abs} -threshold) of that test (Figure 5).

The p_{abs} -threshold was calculated from HC data by calculating the maximum of $\vec{a}_{abs}$ ($\vec{a}_{max}$) and the minimum of $\vec{a}_{abs}$ ($\vec{a}_{min}$) of the first ten cycles (Figure 5). For each test, it was calculated what percentage $\vec{a}_{min}$ was of $\vec{a}_{max}$. Eq 1 was used to calculate the p_{abs} -threshold from these percentages, which resulted in a p_{abs} -threshold of 3% based on HC data.

Occurrence of a singular *IT*-sample (Figure 5) did not immediately result in the algorithm detecting an interruption. *IT*-samples had to be semi-consecutive, meaning that an *IT*-sample was at most 0.1 seconds (IT_{string}), apart from the next *IT*-sample. As such, *IT*-strings were calculated per measurement, where each string consisted of the *IT*-samples that were at most 0.1 seconds apart from each other. As soon as an *IT*-sample was more than 0.1 seconds removed from the next *IT*-sample, a new string was started. The length of each *IT*-string determined whether an interruption or arrest was detected.

Three thresholds were set for the length of the *IT*-string. The IT_{hes} -threshold was calculated by determining the total amount of *IT*-samples in each control test. This resulted in a IT_{hes} -threshold of ten data points. If an *IT*-string consisted of ten or more *IT*-samples, one interruption was counted. So, minimal duration of an interruption was 0.05 second. If an *IT*-string consisted of 200 (IT_{freeze}) or more data points, one arrest was counted. So, minimal “arrest” duration was 1.0 second. If an *IT*-string consisted of more than 500 (IT_{freeze}) *IT*-samples, two arrests were counted.

The scoring criteria for number of interruptions/arrests described in MDS-UPDRS-III were maintained for the accelerometric scoring. In addition, scores of 4 were given in case of >10 interruptions or >1 arrest.

2.6.2. Slowing-scores

Level of slowing during the first ten MC was determined based on p_{tc} -thresholds (Table 1). The first p_{tc} -threshold (to discriminate between score 0 and 1) was calculated based on the p_{tc} of HC data, according to Eq 1. This p_{tc} -threshold was calculated to be 20%.

To calculate a total score for slowing, separate analyses were done for each of the nine cycles following the reference cycle. If p_{tc} of that cycle was below 20%, it was counted as score 0 (“no problems”). If p_{tc} was above 20%, 40%, 60% or 80%, it was counted as score 1 (“slight slowing”), 2 (“mild slowing”), 3 (“moderate slowing”), or 4 (“severe slowing”), respectively. The thresholds of 40%, 60%, and 80% were estimates based on MDS-UPDRS-III descriptions and expert opinion. The most frequently occurring score of the nine individual scores determined the final slowing-score. If multiple scores occurred equally often, the highest of these most frequent scores was taken as the final slowing-score.

2.6.3. Amplitude-decrement-scores

The amplitude per MC was calculated as in section 2.5.5 (Figure 4). Amplitude (s_i) of the first MC was used as reference value, as MDS-UPDRS-III prescribes. The p_{amp} -threshold was calculated from HC data by computing decrease in amplitude compared to the reference in %. Mean difference in amplitude per cycle was calculated (% per test). With these percentages, the p_{amp} -threshold was calculated using Eq 1. A p_{amp} -threshold of 50% was calculated from HC. If the amplitude of a cycle decreased below 50% of s_i , that cycle was counted as an amplitude decrement. The cycle during which amplitude decremented first determined the score.

2.7. Statistical analysis

2.7.1. Primary endpoint

Level of agreement between accelerometric scores and averaged MDS-UPDRS-III scores of each test was evaluated by calculating concordance and Cohen's weighted kappa coefficient (κ) [27,28]. Mean absolute error (MAE) and root mean square error (RMSE) were calculated to determine the difference between accelerometric scores and averaged MDS-UPDRS-III scores.

2.7.2. Secondary endpoints

As first secondary endpoint, Cohen's weighted kappa coefficient (κ) was used to assess inter-rater reliability between the two MDS-UPDRS-III raters. Second, Spearman's correlation coefficient was used to assess correlation between accelerometric outcome measures (f_o , IT , p_{tr} , and p_{amp}) and MDS-UPDRS-III scores. Last, ICC (two-way mixed-effects model, single measurement, absolute agreement) of f_o , IT , p_{tr} , p_{amp} , and accelerometric scores was calculated for the repeated tests to determine test-retest reliability of the accelerometric approach [29]. The two-way mixed-effects model with a single measurement approach was chosen, as the selected measurements are the only measurements of interest, and the protocol was based on a single measurement rather than on the mean of multiple measurements [29].

3. Results

Forty-four PD patients (selected for DBS procedures) were included in this study (25 men, 19 women; age (mean $\pm$ SD): 62.6 ± 9.3 years). Forty-four matched HC were included in this study (25 men, 19 women; age (mean $\pm$ SD): 62.9 ± 8.9 years). In both the PD and HC group, 176 FT, 176 HM, and 176 PS-tests were performed (twice left-handed, and twice right-handed). All participants were right-handed. Median motor impairment in daily living in the PD group was an MDS-UPDRS part II score of 16 (range: 4–36) out of 52. Median total MDS-UPDRS-III score was 36 (range: 11–72) out of 132 in the PD group, and 0 (range: 0–0) in the HC group. Median MDS-UPDRS-III upper limb bradykinesia score was 10.5 (range: 3–23) out of 24 in the PD group, and 0 (range: 0–0) in the HC group. Median score of Montreal Cognitive Assessment (MOCA) in the PD group was 25 (range: 20–30) out of 30. The total daily levodopa equivalent dose (LED) is stated in Table 2.

Table 2. Demographics.

Variable	n (%) or mean ($\pm$ SD) or Not Applicable (N/A)	
	PD, n=44	HC, n=44
Gender (male)	25 (56.8%)	25 (56.8%)
Age (years)	62.6 ($\pm$ 9.3)	62.9 ($\pm$ 8.9)
Disease duration (years)	9.3 ($\pm$ 4.6)	N/A
LED (mg)	1783.0 ($\pm$ 720.9)	N/A
Hoehn Yahr stage (0–5)	2.5 ($\pm$ 0.8)	N/A
MOCA (0–30)	25.3 ($\pm$ 2.3)	N/A

3.1. Clinical MDS-UPDRS-III measurements

Cohen's weighted kappa coefficient between the two MDS-UPDRS-III raters showed moderate to substantial inter-rater reliability for all tests ($\kappa \geq 0.595$) [27]. For FT, κ was 0.622 (95% CI: 0.538, 0.706; $p < 0.001$). For HM, a κ of 0.595 (95% CI: 0.509, 0.681; $p < 0.001$) was found. For PS, κ was 0.617 (95% CI: 0.533, 0.701; $p < 0.001$). Finally, κ for all tests combined was 0.612 (95% CI: 0.563, 0.661; $p < 0.001$).

3.2. Accelerometric outcome measures

The main outcomes were f_o , IT , p_{Tc} , and p_{amp} . In Figure 7, these quantitative outcomes are plotted against averaged clinical ratings per test. An increase in IT , p_{Tc} , and p_{amp} with increasing MDS-UPDRS-III scores was observed for all tests. A decrease in f_o with increasing MDS-UPDRS-III scores was observed for all tests.

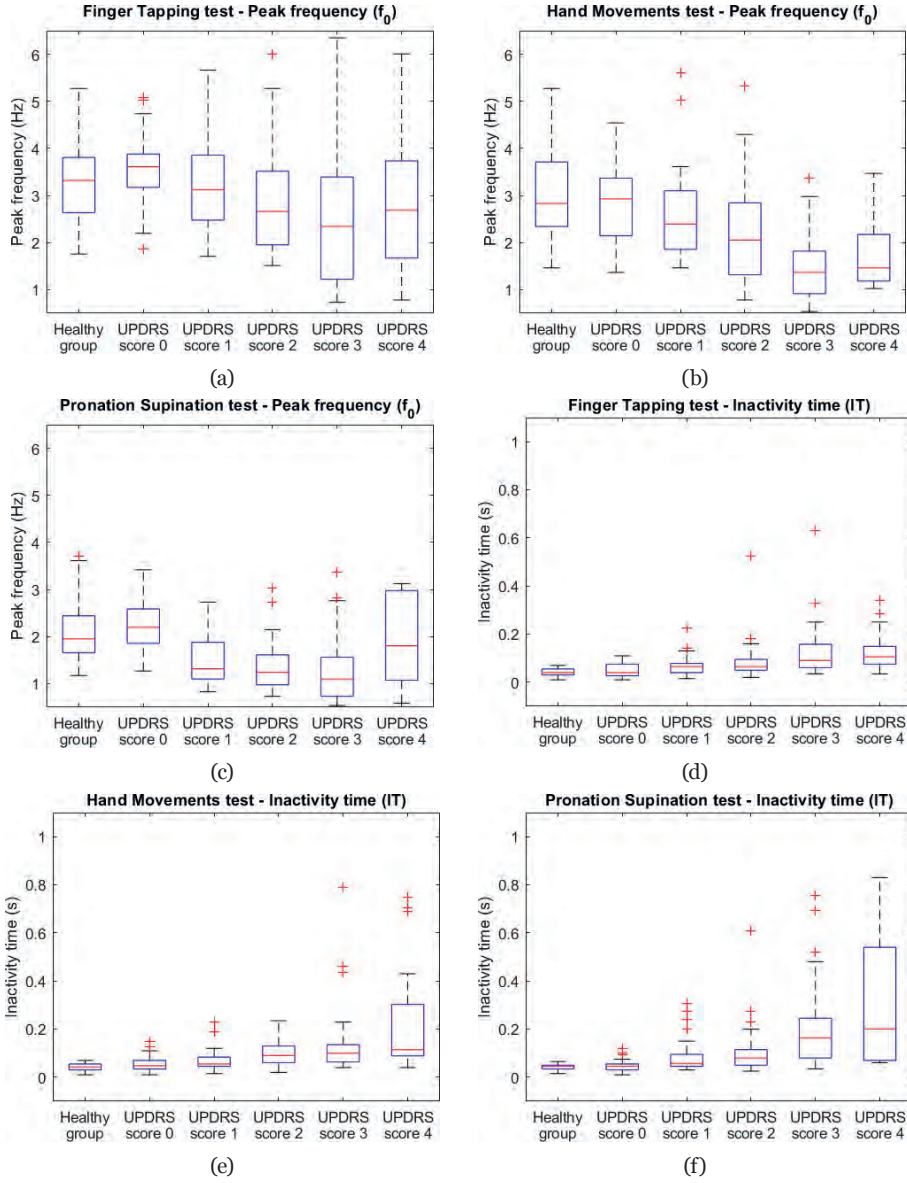


Figure 7. Boxplots of f_0 of FT (a), HM (b), and PS (c), and of IT of FT (d), HM (e), and PS (f) in HC and PD group, per MDS-UPDRS-III score. Outliers are marked with red crosses (+). For every boxplot, each group contains 176 samples.

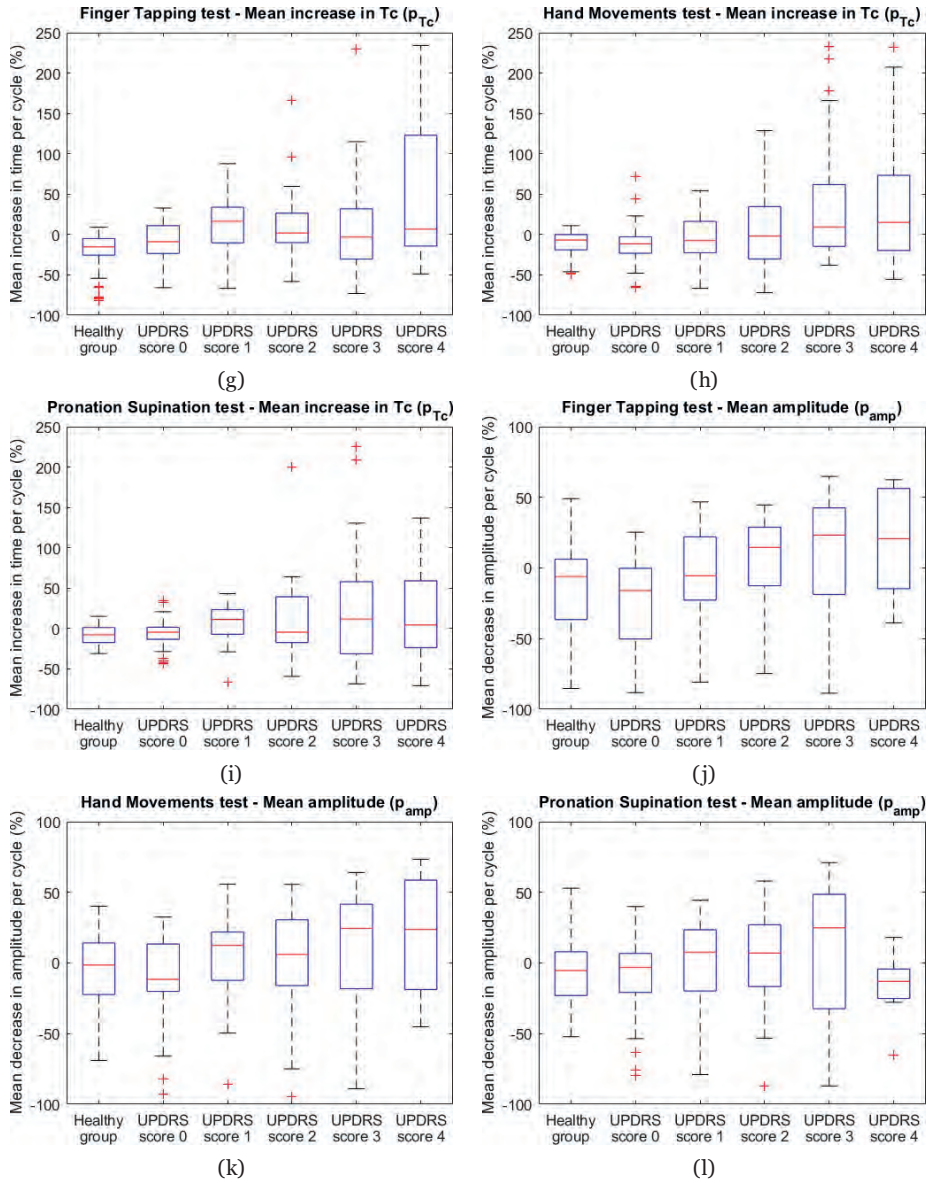


Figure 7. Boxplots of p_{Tc} of FT (g), HM (h), and PS (i), and of p_{amp} of FT (j), HM (k), and PS (l) in HC and PD group, per MDS-UPDRS-III score. Outliers are marked with red crosses (+). For every boxplot, each group contains 176 samples.

Correlations between accelerometric outcomes and MDS-UPDRS-III scores are given in Table 3. Weak to moderate negative correlations were found for f_o in all tasks ($p < 0.001$). Correlation between IT and MDS-UPDRS-III scores was moderate in all tests ($p < 0.001$). p_{amp} correlated moderately with MDS-UPDRS-III scores for FT ($p < 0.001$). Weak correlations were found in the remaining outcomes.

Table 3. Spearman's correlation between accelerometric outcome measures and MDS-UPDRS-III scores in the patient population.

MDS-UPDRS-III	Outcome measure	Spearman's ρ	R^2	95% CI	p
3.4 Finger tapping	f_o	-0.343	0.118	-0.470, -0.201	<0.001
	IT	0.468	0.219	0.340, 0.579	<0.001
	p_{Tc}	0.132	0.017	-0.021, 0.279	0.081
	p_{amp}	0.386	0.149	0.248, 0.508	<0.001
3.5 Hand movements	f_o	-0.506	0.256	-0.611, -0.384	<0.001
	IT	0.503	0.253	0.380, 0.609	<0.001
	p_{Tc}	0.264	0.070	0.116, 0.400	<0.001
	p_{amp}	0.258	0.067	0.110, 0.395	<0.001
3.6 Pronation-supination movements	f_o	-0.405	0.164	-0.524, -0.269	<0.001
	IT	0.622	0.387	0.509, 0.707	<0.001
	p_{Tc}	0.163	0.027	0.011, 0.308	0.030
	p_{amp}	0.155	0.024	0.003, 0.301	0.039

3.3. Accelerometric scores

No deviation from normality was detected by K-S tests for all HC data required for threshold calculation. Contingency tables of ACC-scores and averaged MDS-UPDRS-III scores in the PD group for all types of bradykinesia tests are given in heatmaps in Figure 8.

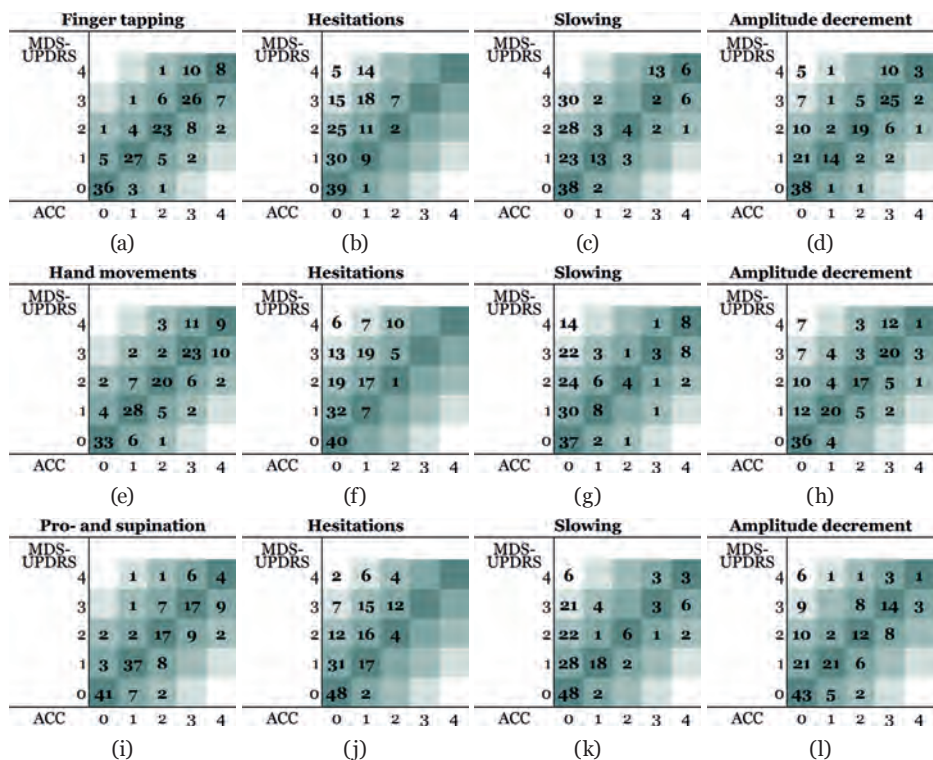


Figure 8. Contingency tables of averaged MDS-UPDRS-III scores and accelerometry (ACC) (sub-) scores of FT (a, b, c, d), HM (e, f, g, h), and PS (i, j, k, l) in the PD group. Clinical MDS-UPDRS-III scores are given on the y-axis, and ACC-scores are given on the x-axis. Matching scores are given in dark green, and outliers are given in the lightest shades.

Concordance and Cohen's κ -coefficient of agreement between ACC-scores and averaged MDS-UPDRS-III ratings per type of test, as well as mean error (MAE and RMSE) are given in Table 4. Concordance between MDS-UPDRS-III ratings and ACC-scores was substantial for all tests ($\geq 64.2\%$). Cohen's κ results showed moderate agreement for all tests [27,28]. On average, ACC-scores differed less than half a point from averaged MDS-UPDRS-III scores, as indicated by MAE.

Table 4. Agreement results.

MDS-UPDRS-III	Concordance	Cohen's κ	95% CI	RMSE	MAE
3.4 FT	68.2%	0.596	0.510, 0.682	0.674	0.364
3.5 HM	64.2%	0.548	0.460, 0.637	0.750	0.426
3.6 PS	65.9%	0.560	0.473, 0.646	0.723	0.398
All tests	66.1%	0.569	0.518, 0.620	0.716	0.396

3.4. Accelerometric reliability

In Table 5, test-retest reliability of the accelerometric method is given for f_o , IT , p_{Tc} , and p_{amp} , and accelerometric scores of the repeated tests. Reliability was excellent for both f_o and ACC-score of PS, and the remaining ICCs showed good test-retest reliability [29].

Table 5. Test-retest reliability of accelerometric approach (ICC: two-way mixed-effects model, single measurement, absolute agreement).

MDS-UPDRS-III	Outcome measure	ICC	95% CI	<i>p</i>
3.4 Finger tapping	f_o	0.844	0.825, 0.858	<0.001
	IT	0.777	0.655, 0.884	<0.001
	p_{Tc}	0.857	0.842, 0.868	<0.001
	p_{amp}	0.825	0.801, 0.844	<0.001
	ACC-score	0.865	0.823, 0.898	<0.001
3.5 Hand movements	f_o	0.895	0.861, 0.921	<0.001
	IT	0.764	0.695, 0.819	<0.001
	p_{Tc}	0.832	0.810, 0.849	<0.001
	p_{amp}	0.841	0.791, 0.879	<0.001
	ACC-score	0.833	0.781, 0.873	<0.001
3.6 Pronation-supination movements	f_o	0.908	0.878, 0.931	<0.001
	IT	0.852	0.835, 0.865	<0.001
	p_{Tc}	0.863	0.820, 0.897	<0.001
	p_{amp}	0.871	0.831, 0.903	<0.001
	ACC-score	0.904	0.845, 0.950	<0.001

4. Discussion

This study translated MDS-UPDRS-III hand bradykinesia assessments to an objective method with accelerometry. The relationship between clinical MDS-UPDRS-III scores and accelerometric data was studied, as well as agreement between clinical ratings and objective ACC-scores. An accelerometric scoring algorithm for MDS-UPDRS-III items 3.4–3.6 based on MDS-UPDRS-III criteria was proposed, incorporating the key bradykinesia characteristics: arrests, slowing and amplitude decrement.

Accelerometric measurements proved feasible for quantifying MDS-UPDRS-III hand bradykinesia tests, although the algorithm requires optimization for more reliable results. Discrepancies were observed between accelerometric outcomes and clinical scores, for example p_{Tc} not correlating with clinical scores. These discrepancies can be explained partially by the methodology for scoring MDS-UPDRS-III items, since high MDS-UPDRS-III scores do not automatically represent poor performance in all three components (interruptions/arrests, slowing, amplitude decrements). For example, while hesitations are often accompanied by a certain amount of slowing and amplitude decrement detected by the accelerometer, the severity of each of these three components will probably not be the same. The amount of hesitations might result in an MDS-UPDRS-

III score of 3, while the level of slowing and amplitude decrement might correspond with the criteria defined for MDS-UPDRS-III score 1 or 2. On the other hand, slowing might occur without any hesitation or amplitude decrement, possibly resulting in slowing-score 3, while hesitations and amplitude decrements were scored 0.

The study's main contribution is translating clinical MDS-UPDRS-III hand bradykinesia measurements to an objective scoring algorithm, with accelerometric data as input. HC were included to calculate natural variation of accelerometric measures, and to provide baseline thresholds for the objective scoring algorithm. The results provided by the algorithm are easy to interpret, as they are based on the same MDS-UPDRS-III criteria as PD caregivers are used to.

A key limitation is that no data was gathered on the separate components of each MDS-UPDRS-III bradykinesia rating according to clinical raters, preventing full evaluation of the algorithm's ability to isolate and measure specific motor deficits. It was not investigated which feature—hesitation, slowing, or amplitude decrement—contributed to the final score. Tasks with identical MDS-UPDRS-III scores were grouped to investigate the relationship between accelerometric outcomes and MDS-UPDRS-III scores. So, a patient with MDS-UPDRS-III score 2 might exhibit slowing without amplitude decrement, leading to low correlation between MDS-UPDRS-III score and amplitude decrement measure (p_{amp}), as the amplitude decrement here was sub-score 0. This means that current MDS-UPDRS-III scores are multi-interpretable, complicating the objectification of MDS-UPDRS-III assessments. As a result, assumptions had to be made for thresholds IT_{string} , IT_{hes} , IT_{freeze} , $IT_{freeze2}$ and p_{Te} . However, adjusting these thresholds yielded similar or worse correlations, indicating that the proposed thresholds might be close to optimal.

Other limitations include the lack of early-stage PD patients and on-medication assessments for the validation of this method. Also, the order of performing tasks was not randomized, which could have led to potential fatigue or learning effects. However, randomization of the tasks would have influenced the calculation of test-retest reliability, which has to be counterbalanced with the possible learning effects. Also, a single sensor position was chosen for all tasks (considering i.a. test-retest analysis), although the range of motion for PS might be larger at e.g. the hand palm or thumb. In future research, the application of multiple sensors might be considered to determine the optimal sensor position per task. Lastly, this study assumes that MDS-UPDRS-III scores are the real clinical truth. However, deviations caused by inter-rater variability have influenced the correlations and agreement between MDS-UPDRS-III and accelerometric outcome measures significantly. This suggests that the correlations would very likely improve if the MDS-UPDRS-III items would include the clinical sub-scores on hesitations, slowing and amplitude decrements.

4.1. Clinical MDS-UPDRS-III measurements

Inter-rater reliability of MDS-UPDRS-III scores was moderate to substantial in this study. Other studies have reported similar values, underlining the need to reduce rater-dependency of MDS-UPDRS-III measurements [6,8].

4.2. Accelerometric outcome measures

4.2.1. Interruptions/arrests

Although an increase in IT with increasing MDS-UPDRS-III scores can be observed in Figures 7d, 7e and 7f, these boxplots do not fully correspond with the expected outcome based on MDS-UPDRS-III criteria. IT stays below 1.0 second in all tasks. It is possible that the algorithm is too lenient in detecting hesitations, caused by suboptimal thresholds chosen for IT_{hes} , IT_{freeze} , and/or $IT_{freeze2}$. If this is the case, thresholds for detecting hesitations should be adjusted in the algorithm, preferably based on clinical MDS-UPDRS-III sub-scores for interruptions/arrests. Another explanation could be that hardly any hesitation and no freezes occurred in the PD group, resulting in no freezes being detected by the algorithm. The smaller range of hesitations in MDS-UPDRS-III score group 4 in Figure 7d might be due to MDS-UPDRS-III scoring based on another criterion, i.e., slowing or amplitude decrement.

4.2.2. Slowing

In Figures 7g, 7h, and 7i, the boxplots of p_{tc} -values overlap for most UPDRS groups in all tasks. This could be explained by Figure 7 showing mean p_{tc} -values of each test, and not the nine separate p_{tc} values of each test. Multiple p_{tc} -values were negative, meaning that participants moved faster with each cycle. This might be explained by a hesitant first MC. Another explanation could be that participants did not continue moving with the largest possible amplitude, leading to shorter cycles over time.

4.2.3. Amplitude decrements

The boxplots in Figures 7j, 7k and 7l overlap for most score groups in all tasks, which could be explained by Figure 7 showing mean p_{amp} values of each test, and not the moment that amplitude decrement occurs, being part of the MDS-UPDRS-III criterion. These boxplots also show that in some tests amplitude increased after the first MC, since all groups show some negative p_{amp} values. This could be explained by the first cycle not being a reliable reference, as the task might start hesitantly, resulting in relatively small amplitude of the first MC. Assuming the first MC has smaller (submaximal) amplitude, and subsequent cycles are normal, amplitude decrement later on in the sequence might not be detected by the algorithm. This would result in ACC-scores misrepresenting the actual motor performance. Alternatively, the median amplitude or the maximal amplitude of the first ten MC could be used for calculating amplitude decrement, although these are not the literal rating instructions of the MDS-UPDRS-III. This underlines the importance of uniform instructions to the participant and the participants' adherence thereto, and correct timing of the accelerometric measurement.

4.3. Accelerometric scores

It was noted from Table 4 and Figures 8a, 8e and 8i that agreement between MDS-UPDRS-III and ACC-scores was only moderate in all tests [27,28]. Some studies have already shown that recorded accelerometric data and visual evaluations do not correlate very well, especially because minor changes in movement are hard to estimate visually [18,30].

4.3.1. Interruptions/arrests-scores

Figures 8b, 8f and 8j show that the algorithm provides the same ACC sub-score for hesitations in MDS-UPDRS-III 0 group in 97.7% of cases, demonstrating its ability to correctly detect absence of interruptions. On the other hand, the algorithm consistently provided lower ACC sub-scores than the corresponding MDS-UPDRS-III scores that were given for that task in the higher MDS-UPDRS-III groups. As no accelerometric sub-scores 2, 3 and 4 were given for the interruptions/arrests criterion, and no clinical sub-scores were available, it cannot be checked whether the algorithm was correct for these scores.

4.3.2. Slowing-scores

A broad range of ACC sub-scores per MDS-UPDRS-III group is seen in Figures 8c, 8g and 8k. Success rate of the algorithm for MDS-UPDRS-III score 0 is 94.6%. For MDS-UPDRS-III scores 1–4, provided ACC sub-scores often did not correspond with clinical ratings. Whether this was due to suboptimal chosen p_{tc} -thresholds, or absence of slowing in (most of) these cases, remains unclear.

4.3.3. Amplitude-decrement-scores

Most final ACC-scores resulted from the ACC sub-score for amplitude decrements. Total success rate for amplitude decrements was 53.8% in all tests combined. Still, a broad range of ACC sub-scores per MDS-UPDRS-III group can be seen in Figures 8d, 8h and 8l. Again, absence of clinical MDS-UPDRS-III sub-scores disallows proper analysis of sub-score heatmaps. Consequently, it cannot be determined from Figure 8 whether the algorithm correctly scored amplitude decrements. Since signal noise could have influenced the results (for e.g. amplitude decrement), smoothing filters could be considered in future research to reduce possible noise in parameter estimation.

4.4. Accelerometric reliability

Reliability of the proposed accelerometric approach was good to excellent for all outcome measures and the final ACC-scores. Similar reliabilities were found in other studies [13]. It stood out that the accelerometric method achieved higher test-retest reliabilities than the inter-rater reliability for MDS-UPDRS-III in this study, underlining its potential for more objective monitoring of hand bradykinesia.

4.5. Future perspectives

Instead of comparing final MDS-UPDRS-III scores to ACC (sub-)scores, it is recommended to clinically score each criterion of MDS-UPDRS-III on the related sub-scores for interruptions/arrests, slowing, and amplitude decrements for each performed task. Future research should pay more attention to these separate components. For instance, the modified Bradykinesia Rating Scale (mBRS) [31] could be employed by clinical raters to separately score speed, amplitude, and rhythm, allowing more granular comparison with objective metrics in future research. The current overall scoring of these items does not allow for accurate comparisons with accelerometric outcomes, or any objective method. The addition of MDS-UPDRS-III sub-scores would allow for optimization of thresholds for each criterion in the accelerometric algorithm. For example, this would allow determination of average length of a hesitation and average length of a freeze. Also, thresholds for slight, mild, moderate, and severe slowing could be optimized based on clinical MDS-UPDRS-III sub-scores. This is essential for creating an algorithm that detects all bradykinetic features accurately and equally, not overlooking significant fluctuations in specific features.

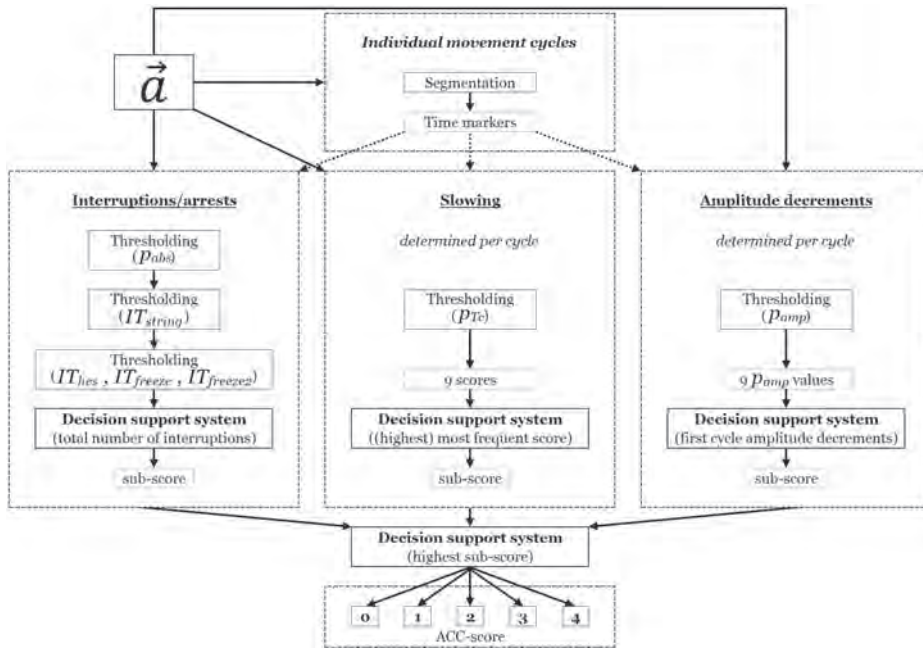
The thresholds proposed in this study were based on asymptomatic outcome measures derived from healthy participants, which might not account for the observed variability in bradykinesia, especially in early PD. Figure 8 suggests good performance of the HC-based thresholds (e.g. discrimination between slowing-score 0 and 1). So, at least for slowing this seems to correspond well to clinically relevant changes in the patient population. However, this correspondence is more difficult to determine for the other components. Therefore, to better align the proposed algorithm with real-world situations, validation against several levels of PD severity is recommended. Also, on-medication assessments should be included in the future to evaluate the influence of e.g. medication-induced dyskinesias on accelerometric results. This will improve the sensitivity and specificity of the algorithm in distinguishing subtle bradykinetic changes, especially when clinical sub-scores are available. The threshold selection process could have been strengthened by ROC-based analysis comparing objective features against expert-labeled sub-scores, which unfortunately are not part of the MDS-UPDRS-III scores on bradykinesia, as used in this study.

Considering its compactness and relatively low data load, the proposed technique allows for implementation in wearable devices combined with telemedicine, resulting in more assessment options for remote clinical check-ups and improving the insight on disease progression for physicians and patients. Previous work investigating PD monitoring in free-living conditions showed significant correlations between the results of bradykinesia detecting algorithms and clinical assessments [32–35]. Sica et al. showed that accelerometers allow continuous data collection and can potentially facilitate PD monitoring, providing relevant information about the patient’s motor status [36]. Remote PD monitoring could also allow analyses on prediction of therapy response, optimizing medication dosages, and fine-tuning DBS settings, especially when this technique is deemed feasible for unsupervised use in home settings. This could not only help optimize PD therapies, but also improve patient self-management.

5. Conclusion

In conclusion, this study shows that MDS-UPDRS-III upper limb bradykinesia tests can be translated to objective accelerometric measurements, although further research is needed to optimize the algorithm, for which recommendations were made. Moderate agreement was found between MDS-UPDRS-III ratings and accelerometry scores in advanced PD patients, offering performances comparable to human raters. However, accelerometric test-retest reliability was good to excellent. Therefore, this accelerometric technology has the potential to reduce rater-dependency of MDS-UPDRS-III upper extremity measurements, providing objective monitoring of bradykinesia, being the core feature of PD.

Appendix 1



Appendix Figure 1. Block diagram for accelerometric score calculation.

References

- [1] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's Disease. *Movement Disorders* 2015;30:1591–601. <https://doi.org/10.1002/mds.26424>.
- [2] Kalia L, Lang AE. Parkinson's Disease. *The Lancet* 2015;386:896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3).
- [3] Jankovic J. Parkinson's Disease: Clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79:368–76. <https://doi.org/10.1136/jnnp.2007.131045>.
- [4] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [5] Kremer NI, Smid A, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, et al. Supine MDS-UPDRS-III Assessment: An Explorative Study. *J Clin Med* 2023;12. <https://doi.org/10.3390/jcm12093108>.
- [6] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.
- [7] Lukšys D, Jonaitis G, Griškevičius J. Quantitative Analysis of Parkinsonian Tremor in a Clinical Setting Using Inertial Measurement Units. *Parkinsons Dis* 2018;2018. <https://doi.org/10.1155/2018/1683831>.
- [8] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [9] Bobić V, Djurić-Jovičić M, Dragašević N, Popović MB, Kostić VS, Kvaščev G. An expert system for quantification of bradykinesia based on wearable inertial sensors. *Sensors (Switzerland)* 2019;19. <https://doi.org/10.3390/s19112644>.
- [10] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative Quantification of MDS-UPDRS Tremor Measurements Using 3D Accelerometry: A Pilot Study. *J Clin Med* 2022;11:2275. <https://doi.org/10.3390/jcm11092275>.
- [11] Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's Disease obtained using mobile health technologies. *Movement Disorders* 2019;34:657–63. <https://doi.org/10.1002/mds.27671>.
- [12] Hobert MA, Maetzler W, Aminian K, Chiari L. Technical and clinical view on ambulatory assessment in Parkinson's Disease. *Acta Neurol Scand* 2014;130:139–47. <https://doi.org/10.1111/ane.12248>.
- [13] Smid A, Pauwels RWJ, Elting JWW, Everlo CSJ, van Dijk JMC, Oterdoom DLM, et al. A Novel Accelerometry Method to Perioperatively Quantify Essential Tremor Based on Fahn-Tolosa-Marin Criteria. *J Clin Med* 2023;12:4235. <https://doi.org/10.3390/jcm12134235>.
- [14] Smid A, Oterdoom DLM, Pauwels RWJ, Tamasi K, Elting JWW, Absalom AR, et al. The Relevance of Intraoperative Clinical and Accelerometric Measurements for Thalamotomy Outcome. *J Clin Med* 2023;12:5887. <https://doi.org/10.3390/jcm12185887>.
- [15] Sievänen H, Kujala UM. Accelerometry - Simple, but challenging. *Scand J Med Sci Sports* 2017;27:574–8. <https://doi.org/10.1111/sms.12887>.
- [16] Karas M, Bai J, Strączkiewicz M, Harezlak J, Glynn NW, Harris T, et al. Accelerometry Data in Health Research: Challenges and Opportunities: Review and Examples. *Stat Biosci* 2019;11:210–37. <https://doi.org/10.1007/s12561-018-9227-2>.

- [17] Dunnewold RJW, Hoff JI, van Pelt HCJ, Fredrikze PQ, Wagemans EAH, van Hilten BJJ. Ambulatory Quantitative Assessment of Body Position, Bradykinesia, and Hypokinesia in Parkinson's Disease. *Journal of Clinical Neurophysiology* 1998;15:235–42. <https://doi.org/10.1097/00004691-199805000-00007>.
- [18] Yokoe M, Okuno R, Hamasaki T, Kurachi Y, Akazawa K, Sakoda S. Opening velocity, a novel parameter, for finger tapping test in patients with Parkinson's Disease. *Parkinsonism Relat Disord* 2009;15:440–4. <https://doi.org/10.1016/j.parkreldis.2008.11.003>.
- [19] Lin Z, Dai H, Xiong Y, Xia X, Horng S-J. Quantification assessment of bradykinesia in Parkinson's Disease based on a wearable device. 2017 39th IEEE Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Jeju Island, Korea: 2017, p. 803–6.
- [20] Sano Y, Kandori A, Shima K, Yamaguchi Y, Tsuji T, Noda M, et al. Quantifying Parkinson's Disease finger-tapping severity by extracting and synthesizing finger motion properties. *Med Biol Eng Comput* 2016;54:953–65. <https://doi.org/10.1007/s11517-016-1467-z>.
- [21] Stamatakis J, Ambrose J, Crémers J, Sharei H, Delvaux V, Macq B, et al. Finger tapping clinimetric score prediction in Parkinson's Disease using low-cost accelerometers. *Comput Intell Neurosci* 2013;2013. <https://doi.org/10.1155/2013/717853>.
- [22] Smid A, Dominguez-Vega ZT, van Laar T, Oterdoom DLM, Absalom AR, van Egmond ME, et al. Objective clinical registration of tremor, bradykinesia, and rigidity during awake stereotactic neurosurgery: a scoping review. *Neurosurg Rev* 2024;47. <https://doi.org/10.1007/s10143-024-02312-4>.
- [23] Maldonado-Naranjo A, Koop MM, Hogue O, Alberts J, MacHado A. Kinematic Metrics from a Wireless Stylus Quantify Tremor and Bradykinesia in Parkinson's Disease. *Parkinsons Dis* 2019;2019. <https://doi.org/10.1155/2019/6850478>.
- [24] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's Disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4. <https://doi.org/10.1136/jnnp.55.3.181>.
- [25] Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967;17:427–427. <https://doi.org/10.1212/WNL.17.5.427>.
- [26] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [27] McHugh M. Interrater reliability - the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276–82.
- [28] Ranganathan P, Pramesh C, Aggarwal R. Common pitfalls in statistical analysis: Measures of agreement. *Perspect Clin Res* 2017;8:187–91. https://doi.org/10.4103/picr.PICR_123_17.
- [29] Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016;15:155–63. <https://doi.org/10.1016/j.jcm.2016.02.012>.
- [30] Shah A, Coste J, Lemaire JJ, Schkommodau E, Taub E, Guzman R, et al. A novel assistive method for rigidity evaluation during deep brain stimulation surgery using acceleration sensors. *J Neurosurg* 2017;127:602–12. <https://doi.org/10.3171/2016.8.JNS152770>.
- [31] Kishore A, Espay AJ, Marras C, Al-Khairalla T, Arenovic T, Asante A, et al. Modified Bradykinesia Rating Scale (mBRS). *Movement Disorders* 2014. <https://www.movementdisorders.org/MDS/MDS-Rating-Scales/Modified-Bradykinesia-Rating-Scale-MBRS-.htm>.
- [32] Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's Disease. *J Parkinsons Dis* 2012;2:47–55. <https://doi.org/10.3233/JPD.2012-11071>.

- [33] Rodríguez-Molinero A, Pérez-López C, Samá A, De Mingo E, Rodríguez-Martín D, Hernández-Vara J, et al. A kinematic sensor and algorithm to detect motor fluctuations in Parkinson disease: Validation study under real conditions of use. *JMIR Rehabil Assist Technol* 2018;20. <https://doi.org/10.2196/rehab.8335>.
- [34] Pérez-López C, Samà A, Rodríguez-Martín D, Català A, Cabestany J, de Mingo E, et al. Monitoring Motor Fluctuations in Parkinson's Disease Using a Waist-Worn Inertial Sensor. *Advances in Computational Intelligence*, 2015, p. 461–74. https://doi.org/10.1007/978-3-319-19258-1_38.
- [35] Pastorino M, Cancela J, Arredondo MT, Pansera M, Pastor-Sanz L, Villagra F, et al. Assessment of bradykinesia in Parkinson's Disease patients through a multi-parametric system. 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, IEEE; 2011, p. 1810–3. <https://doi.org/10.1109/IEMBS.2011.6090516>.
- [36] Sica M, Tedesco S, Crowe C, Kenny L, Moore K, Timmons S, et al. Continuous home monitoring of Parkinson's Disease using inertial sensors: A systematic review. *PLoS One* 2021;16. <https://doi.org/10.1371/journal.pone.0246528>.



Chapter 5

Intraoperative quantification of MDS-UPDRS-III tremor measurements using 3D accelerometry: a pilot study

Annemarie Smid

Jan Willem J. Elting

J. Marc C. van Dijk

Bert Otten

D. L. Marinus Oterdoom

Katalin Tamasi

Tjitske Heida

Teus van Laar

Gea Drost

Journal of Clinical Medicine (2022)

doi: 10.3390/jcm11092275

Abstract

The most frequently used method for evaluating tremor in Parkinson's Disease (PD) is currently the internationally standardized Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS). However, the MDS-UPDRS is associated with limitations, such as its inherent subjectivity and reliance on experienced raters. Objective motor measurements using accelerometry may overcome the shortcomings of visually scored scales. Therefore, the current study focuses on translating the MDS-UPDRS tremor tests into an objective scoring method using 3D accelerometry. An algorithm to measure and classify tremor according to MDS-UPDRS criteria is proposed. For this study, 28 PD patients undergoing neurosurgical treatment and 26 healthy control subjects were included. Both groups underwent MDS-UPDRS tests to rate tremor severity, while accelerometric measurements were performed at the index fingers. All measurements were performed in an off-medication state. Quantitative measures were calculated from the 3D acceleration data, such as tremor amplitude and area-under-the-curve of power in the 4–6 Hz range. Agreement between MDS-UPDRS tremor scores and objective accelerometric scores was investigated. The trends were consistent with the logarithmic relationship between tremor amplitude and MDS-UPDRS score reported in previous studies. The accelerometric scores showed a substantial concordance (>69.6%) with the MDS-UPDRS ratings. However, accelerometric kinetic tremor measures poorly associated with the given MDS-UPDRS scores ($R^2 < 0.3$), mainly due to the noise between 4 and 6 Hz found in the healthy controls. This study shows that MDS-UPDRS tremor tests can be translated to objective accelerometric measurements. However, discrepancies were found between accelerometric kinetic tremor measures and MDS-UPDRS ratings. This technology has the potential to reduce rater dependency of MDS-UPDRS measurements and allow more objective intraoperative monitoring of tremor.

1. Introduction

Parkinson's Disease (PD) is the fastest growing neurodegenerative disorder globally and is accompanied by debilitating motor symptoms, such as tremor [1–4]. A Parkinsonian tremor is generally observed in the extremities and is dominant in the 4 Hz to 6 Hz frequency range [4–7]. Considering the heterogenic presentation of PD and the broad range of possible and ever-evolving therapies, accurate assessment of tremor is key for the correct treatment of PD [6,8].

The most frequently used and best validated method for evaluating PD symptoms is the internationally standardized Movement Disorder Society Unified PD Rating Scale part III (MDS-UPDRS-III) [2,9–12]. Tremor at the hands is assessed using a total of three tremor tests: the postural tremor test, the kinetic tremor test (finger-to-nose maneuver), and the rest tremor test. During these tests, the amplitude (in centimeters) of tremor is assessed by eye. The constancy of rest tremor is assessed as the (estimated) percentage of time that rest tremor is present during the measurement. As the MDS-UPDRS-III is currently the best validated tool available for scoring tremor, the MDS-UPDRS-III is used to evaluate disease progression and therapy effect on tremor symptoms [9,10,13].

An established therapy in advanced PD patients is Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN). During this neurosurgical treatment, leads are surgically implanted in the STN to electrically suppress motor symptoms [14,15]. Another neurosurgical option for treating tremor symptoms is a thalamotomy, where a unilateral ablation is made in the thalamus [16]. During awake thalamotomy and STN-DBS surgery, MDS-UPDRS-III measurements are performed to examine the clinical effect of stimulation and to optimize the lead position [17,18].

Unfortunately, the MDS-UPDRS is associated with limitations, such as its inherent subjectivity and reliance on experienced raters [19–22]. Thus, PD treatment decisions, e.g., permanent lead position in neurosurgery, currently depend, in part, on subjective motor assessments. Several caretakers with different levels of expertise in the MDS-UPDRS are involved with the patient throughout the caretaking process, underlining the need for a reliable and rater-independent measurement method [19,20,22].

Objective motor measurements might overcome the shortcomings, such as substantial inter- and intra-rater variability, of visually scored scales. However, objective measures to evaluate the clinical effect of PD therapies on motor symptoms are currently lacking in clinical practice, including the intraoperative setting, as most research is performed in laboratories [22–25].

Research on quantifying tremor in PD patients has been performed mainly with the use of transducers [13,26–30]. Tri-axial accelerometry is a subcategory of transducers that in the past decade has proven to be accurate, cost-effective, and widely available [19,20,31,32]. Accelerometers are particularly well suited for the assessment of tremor, as most relevant parameters can be calculated from the measured acceleration signal [19,31,32]. Moreover, these non-invasive sensors can easily be integrated into standard clinical tests [32].

The main outcome measures analyzed from accelerometric data are the dominant frequency and the amplitude of the tremor [17,29,33]. As tremor is generally a distinct sinusoidal movement, its dominant frequency can be approximated using the fast

Fourier transform [33]. The frequency spectra and power spectral density (PSD) can be estimated using the Burg method, by fitting an autoregressive model to the signal through minimizing the forward and backward prediction errors [34]. These accelerometric outcome measures might be applicable to calculate objective scores based on the tremor criteria stated in the MDS-UPDRS-III.

As the clinical care for patients with PD currently depends on subjective evaluations of tremor, there is a need for a reliable and rater-independent measurement method for monitoring these symptoms in PD. Therefore, this study focuses on translating the MDS-UPDRS-III tremor tests to an objective method to rate tremor severity using accelerometry. This study also aims to show that these measurements can be performed in an intraoperative setting, allowing direct objective input for clinical decision-making. As a first step in the process of creating a more reliable and rater-independent method, the agreement between accelerometry-based tremor amplitude scores and MDS-UPDRS-III scores are examined in this pilot study. This technology could reduce rater dependency of MDS-UPDRS-III measurements and allow more objective intraoperative monitoring of tremor.

2. Materials and methods

This pilot study was performed at the neurosurgical department of the University Medical Center Groningen (UMCG). Exemption from the act on research involving human subjects was granted by the local medical ethics review committee (METc UMC Groningen). This study was conducted in compliance with the Helsinki Declaration for research on human beings.

2.1. Subjects

Patients with PD undergoing unilateral thalamotomy or bilateral STN-DBS surgery and healthy controls were included. The participants were screened by the researcher (A.S.) and were given oral information and a participant information letter. Written informed consent was obtained for each participant. All participants were adults, and able and willing to adhere to the study. All patient participants were diagnosed with PD according to UK Brain Bank criteria [35]. None of the healthy controls had a current diagnosis of PD or any neurological disease. Exclusion criteria were diagnosis of any form of musculoskeletal system disorders or physical disabilities, recent alcohol or drugs abuse, and psychosis or current depression. None of the participants were treated with tremor-inducing drugs during the study.

2.2. Materials

Two wired tri-axial accelerometers (MMA8452Q tri-Axis, Freescale Semiconductor, Inc., Austin, TX, USA) with a range of ± 2 g and a sampling rate of 200 Hz were used. The accelerometers were secured in in-house developed, non-conductive plastic cases

and were attached to the index fingers with adjustable silicon straps (see Figure 1). The choice for plastic cases and silicon straps was made so that the sensors could be cleaned easily. Wired sensors were used to minimize interference with other equipment in the operating room.



Figure 1. Accelerometer positioned at the base of the right index finger.

The accelerometers were connected to a Windows 7 laptop via a USB port. Accelerometry data were recorded using a measurement program built in-house in LabVIEW v. 2017 (National Instruments, Austin, TX, USA). Signal analysis was performed in MATLAB v. 2021a (MathWorks, Natick, MA, USA) and statistical analysis was performed in IBM SPSS statistics v. 25 (International Business Machines Corporation, New York, NY, USA). MDS-UPDRS-III items 3.15–3.18 were used for the clinical assessment of the participants [12].

2.3. Measurements

Healthy participants were measured to determine the natural variation of noise in the 4–6 Hz frequency range and to calculate thresholds from the accelerometric data. Patients were measured while undergoing a neurosurgical procedure. All measurements were performed in an off-medication state, after a washout period of at least 12h.

The sensors were placed at the base of the index finger of each hand during all measurements. All accelerometry measurements were performed in a supine position while the participant was awake. Accelerometry data were recorded (A.S.) while a PD expert neurologist (T.v.L.) scored the motor skill tests for both hands according to the MDS-UPDRS-III criteria. MDS-UPDRS-III tests 3.15–3.18 [12] were performed to assess postural, kinetic, and rest tremor amplitude, and constancy of rest tremor (CRT), respectively. Tests lasted ten seconds each.

In the patient population, the set of tests described above were performed before and after lead insertion. These intraoperative tests were part of the standard clinical care given at the UMCG and did, therefore, not prolong the surgeries.

2.4. Data pre-processing

Raw acceleration data were converted from g-units to cm/s^2 . The norm of the acceleration vector in all three directions was used for all analyses, by taking the root mean square of the resultant signal of the three axes [13,29]. A non-causal second-order high-pass Butterworth filter with a cutoff frequency of 0.5 Hz was used to remove low-frequency noise and gravitational acceleration effects. To suppress digital noise and higher-order harmonics, a non-causal second-order low-pass Butterworth filter of 20 Hz was applied. These filter settings were chosen with the underlying aim to not alter outcome measures or calculations, following recommendations from previous research [13,17,29].

The approximate cumulative numerical integral of the filtered acceleration vector was computed via the trapezoidal method over a time of ten seconds (2000 samples) to calculate the velocity (cm/s) per test. The calculated velocity vector was centered in order to correct for the constant that is added to the vector due to integration. Next, the corrected velocity was integrated numerically to the displacement (cm) of the sensor per test via the same integration method as described above. The displacement vector was filtered using a non-causal second-order high-pass Butterworth filter with a cutoff frequency of 1.2 Hz to suppress low-frequency trends caused by integration. For the kinetic tremor tests, a cut-off frequency of 3 Hz was maintained for this high-pass filter, to suppress the amplitude of low frequent arm movements that occurred during this type of test.

2.5. Accelerometry measures

To assess postural, kinetic, and rest tremor, the area under the curve (AUC) of tremor power within the 4–6 Hz tremor frequency band, and the amplitude were calculated from the accelerometry data. The periodogram PSD estimate was calculated to find the power of the acceleration norm (cm/s^2) [29]. Next, the AUC of the power in the 4 Hz and 6 Hz frequency band ($\text{PAUC}_{\text{tremor}}: (\text{cm/s}^2)^2$) was calculated from this periodogram via trapezoidal numerical integration. For the assessment of constancy of tremor, the $\text{PAUC}_{\text{tremor}}$ was calculated for each second of the rest tremor test, resulting in ten values of $\text{PAUC}_{\text{tremor}}$ per test. The percentage of time that tremor was present ($T_{\text{tremor}}: \%$) was calculated by summing the number of seconds where the $\text{PAUC}_{\text{tremor}}$ was above the CRT threshold calculated from the healthy group (see Section 2.6). The amplitude of the performed test was calculated by determining the mean of all peaks in the absolute displacement vector, and multiplying this mean by two.

2.6. Objective MDS-UPDRS-III scores

Following the calculation of accelerometric outcome measures, objective scores were calculated from the accelerometric data based on the criteria stated in the MDS-UPDRS-III. The descriptive evaluations of the MDS-UPDRS-III items 3.15–3.18 were applied for determining the score of the acceleration measurements via a scoring algorithm written in MATLAB.

First, thresholds were calculated to distinguish healthy and asymptomatic measurements (MDS-UPDRS-III score 0) from symptomatic measurements (MDS-UPDRS-III score ≥ 1). As the only criteria given for an MDS-UPDRS-III score of 0 was “no tremor”, $PAUC_{tremor}$ of each test was calculated from the accelerometric data of the healthy control group to determine the natural variation of noise between 4 and 6 Hz. These natural variations were used to determine thresholds that distinguish measurements of MDS-UPDRS-III score 0 from those of MDS-UPDRS-III score ≥ 1 . The Kolmogorov–Smirnov test of normality (one-sample K-S test) was used to determine whether the data were normally distributed. In normally distributed data, about 95% of the values are expected to fall within two standard deviations from the population mean. This rule was used to determine the thresholds for $PAUC_{tremor}$ of all tremor tests of the healthy controls.

2.6.1. Postural, kinetic and rest tremor amplitude

If the $PAUC_{tremor}$ of the test was below the calculated threshold, a score of 0 (“no tremor”) was given. Otherwise, a score of 1 or higher was given, based on the amplitude that was measured during that test. The same amplitude limits used in the MDS-UPDRS-III item 3.15 were applied for determining the score of the postural tremor tests measured using accelerometry, as described in Table 1. The same method was used for the kinetic and rest tremor tests. Table 1 shows the limits from the MDS-UPDRS-III items 3.16 and 3.17.

Table 1. Description of MDS-UPDRS-III scoring criteria [12].

Score	Scoring Criteria MDS-UPDRS-III Items 3.15–17	Score	Scoring Criteria MDS-UPDRS-III Item 3.18
0	No tremor	0	No tremor
1	≤ 1 cm in maximal amplitude	1	Tremor is present $\leq 25\%$ of the time
2	> 1 cm but < 3 cm in maximal amplitude	2	Tremor is present 26–50% of the time
3	3–10 cm in maximal amplitude	3	Tremor is present 51–75% of the time
4	> 10 cm in maximal amplitude	4	Tremor is present $> 75\%$ of the time

2.6.2. Constancy of rest tremor

If the $PAUC_{tremor}$ of the test was below the threshold of the rest tremor test (MDS-UPDRS-III item 3.17), a CRT-score of 0 (“no tremor”) was given. Otherwise, the CRT-score was based on the calculated $PAUC_{tremor}$ per second. This variable was calculated for all healthy measurements to determine the CRT threshold. Next, it was determined if tremor was present during each second of the test in the patient population. A tremor was detected if $PAUC_{tremor}$ per second was above the CRT threshold. Each second that tremor was present was summed up, resulting in a total number of seconds that tremor was present (T_{tremor}). This value was used to calculate the percentage of the total time that tremor was present. The limits from the MDS-UPDRS-III item 3.18 were used, as described in Table 1.

2.7. Statistical analysis

The association between the clinically scored MDS-UPDRS-III scores and accelerometric outcome measures was analyzed using linear regression. Contrast coding of the MDS-UPDRS-III scores was defined to be orthogonal polynomial, of which the first contrast coefficient is linear trend, to assess whether there was a linear relationship between MDS-UPDRS-III scores and the logarithm ($\log_{10}$) of the accelerometry outcome measures, as found in previous studies [31,36]. Concordance and Cohen's weighted kappa coefficient (κ) were calculated to measure the agreement between MDS-UPDRS-III and accelerometry scores [37,38]. The root mean square error (RMSE) and the mean absolute error (MAE) were computed to determine how far the accelerometry scores deviated from the clinically scored MDS-UPDRS-III ratings.

3. Results

Twenty-eight patients with PD undergoing thalamotomy or STN-DBS procedures were included in this study (16 men, 12 women; age (mean $\pm$ SD): 63 ± 6.9 years). For the healthy group, 26 healthy participants were included in this study (14 men, 12 women; age (mean $\pm$ SD): 63 ± 7.3 years). In the healthy group, 156 measurements were performed. Intraoperatively, 197 measurements were performed in 28 patients. No complications occurred during the performed neurosurgical procedures.

3.1. Accelerometry measures

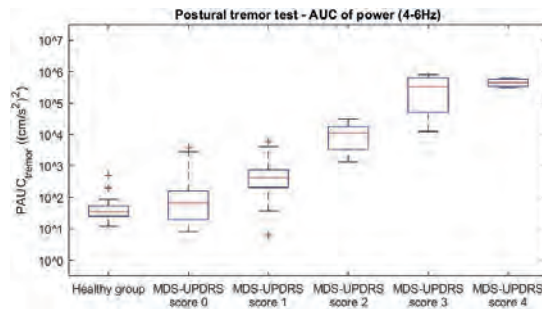
The main outcome measures were the $PAUC_{tremor}$ and amplitude of the postural, kinetic, and rest tremor tests, and $PAUC_{tremor}$ per second and T_{tremor} of the constancy of rest tremor tests. All of these parameters were log-transformed for the regression analysis, except for T_{tremor} , as this outcome measure contained values of zero. The log-transformed accelerometric measures and T_{tremor} were regressed on the MDS-UPDRS-III scores. There was strong evidence against the null hypothesis that the log-transformed outcome measures were not linearly related to the MDS-UPDRS-III scores ($p < 0.001$) for postural tremor, rest tremor, and constancy of rest tremor, see Table 2. $PAUC_{tremor}$ and $PAUC_{tremor}$ per second tended to increase as a logarithmic function of MDS-UPDRS scores ($R^2 > 0.735$) for these tests, respectively. Conversely, no strong evidence was found against the null hypothesis that the log-transformed kinetic tremor outcome measures were not linearly related to the MDS-UPDRS-III scores.

Table 2. Regression analysis results.

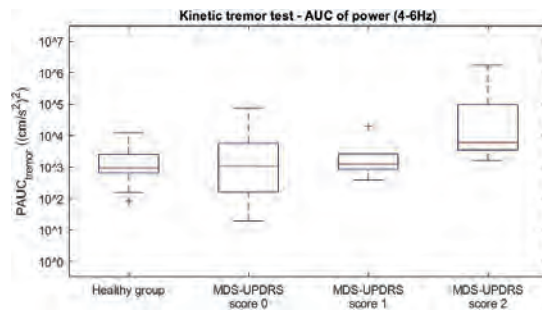
MDS-UPDRS-III Test	Outcome Measure	R	R ²	Coefficient **	95% CI	p
3.15 Postural tremor	Log(PAUC _{tremor})	0.869	0.755	3.171	2.737, 3.605	<0.001
	Log(Amplitude)	0.805	0.648	1.312	1.079, 1.544	<0.001
3.16 Kinetic tremor	Log(PAUC _{tremor})	0.379	0.144	1.749	0.584, 2.914	0.004
	Log(Amplitude)	0.513	0.264	1.030	0.560, 1.499	<0.001
3.17 Rest tremor amplitude	Log(PAUC _{tremor})	0.904	0.818	4.256	3.769, 3.769	<0.001
	Log(Amplitude)	0.912	0.832	2.032	1.811, 2.253	<0.001
3.18 Rest tremor constancy	Log(PAUC _{tremor} /s)	0.857	0.735	2.322	1.985, 2.660	<0.001
	T _{tremor}	0.974	0.949	7.180	6.779, 7.581	<0.001

* Coefficient of determination; ** Contrast coefficient testing for linear trend.

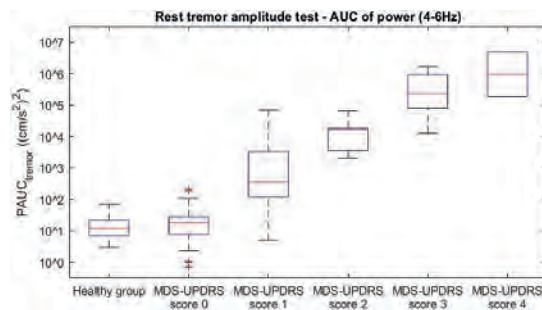
In Figures 2 and 3, the quantitative outcome measures of each tremor test are plotted against the given MDS-UPDRS-III scores. An increase in both PAUC_{tremor} and amplitude with increasing MDS-UPDRS-III score can be seen for the postural tremor (Figures 2a and 3a) and rest tremor amplitude (Figures 2c and 3c) tests. This is also the case for the PAUC_{tremor} per second of the constancy of rest tremor tests (Figure 2d). These relationships seem to be logarithmic. For kinetic tremor, 73% of PAUC_{tremor} and 73% of amplitude values of the MDS-UPDRS-III groups fell within the range of the healthy group (Figures 2b and 3b).



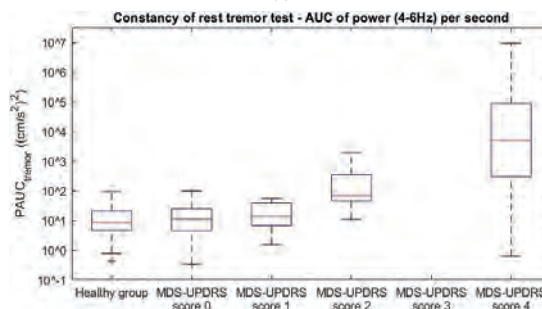
(a)



(b)



(c)



(d)

Figure 2. Boxplots of the $PAUC_{tremor}$ between 4–6 Hz of the postural (a), kinetic (b), and rest tremor (c) tests in the healthy group and the patient population (per MDS-UPDRS-III score). The $PAUC_{tremor}$ between 4–6 Hz per second of the rest tremor test in all groups is given in boxplot (d).

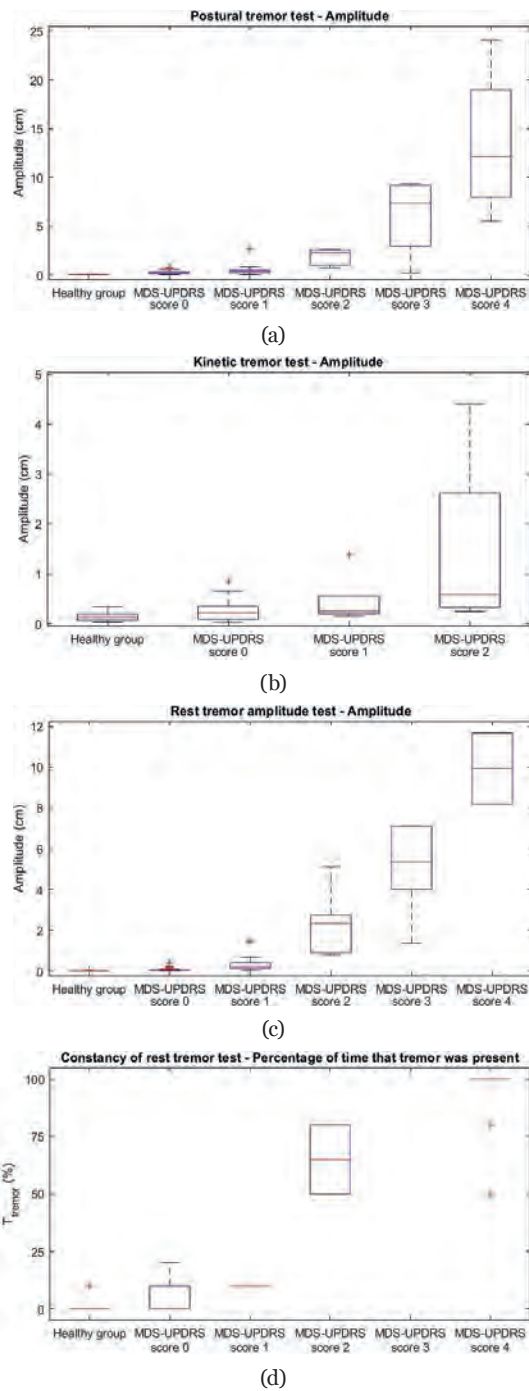


Figure 3. Boxplots of the total amplitude of the postural (a), kinetic (b), and rest tremor (c) tests, and of the T_{tremor} of the constancy of rest tremor test (d) in the healthy group and the patient population (per MDS-UPDRS-III score).

3.2. Objective MDS-UPDRS-III scores

The results of the one-sample K-S test showed that all required data of the healthy group were normally distributed for the threshold determination. A $PAUC_{tremor}$ threshold of $271 (cm/s^2)^2$ was calculated from the healthy population for the postural tremor tests. This threshold was calculated to be $6237 (cm/s^2)^2$ and $55 (cm/s^2)^2$ for the kinetic and rest tremor test, respectively. For the constancy of rest tremor test, a $PAUC_{tremor}$ per second threshold of $54 (cm/s^2)^2$ was calculated from the healthy population. The contingency tables of the MDS-UPDRS-III scores and the accelerometry scores (ACC) in the patient population for all tremor tests are given in heatmaps in Figure 4.

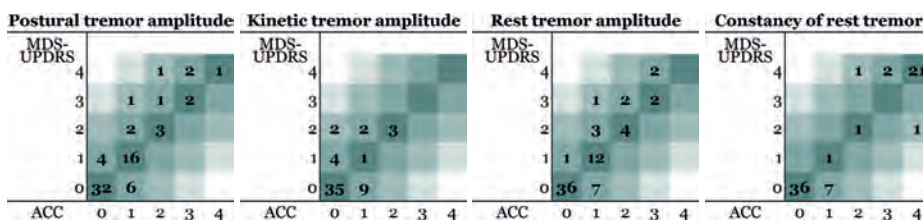


Figure 4. Contingency tables of the given MDS-UPDRS-III scores and calculated accelerometry (ACC) scores of the tremor tests in the patient population.

Concordance and Cohen's κ coefficient between the MDS-UPDRS-III and ACC-scores per type of test, and the average error (RMSE and MAE) are given in Table 3. Concordance between the MDS-UPDRS-III scores and the objective scores was strong for all four tremor tests. Cohen's κ results showed a substantial agreement for rest tremor amplitude and constancy, and postural tremor and a fair agreement for kinetic tremor tests [37,38]. As indicated by the MAE, accelerometry scores deviated on average less than half a point from the MDS-UPDRS-III scores.

Table 3. Agreement results.

MDS-UPDRS-III Test	Concordance	Cohen's κ	95% CI	RMSE	MAE
3.15 Postural tremor	76.1%	0.614	0.563, 0.665	0.569	0.268
3.16 Kinetic tremor	69.6%	0.239	0.137, 0.341	0.641	0.339
3.17 Rest tremor amplitude	77.1%	0.620	0.597, 0.643	0.521	0.243
3.18 Rest tremor constancy	84.3%	0.726	0.628, 0.824	0.493	0.186

4. Discussion

In this pilot study, MDS-UPDRS-III tremor assessments were translated to an objective method using accelerometry measurements. The relationship between clinical MDS-UPDRS-III scores and the quantitative measures calculated from accelerometry data was investigated, as well as the agreement between clinically scored MDS-UPDRS-III ratings and objective scores calculated from accelerometric data. A quantitative scoring algorithm for MDS-UPDRS-III tests 3.15–3.18 based on accelerometry measurements was proposed.

This study showed that accelerometric measurements are a feasible option for quantifying the MDS-UPDRS-III tremor tests. The trends were consistent with the logarithmic relationship between tremor amplitude and MDS-UPDRS-III score reported in previous studies [13,31,36]. This study also showed discrepancies between accelerometric outcome measures and clinically scored MDS-UPDRS-III ratings, mainly in the kinetic tremor tests.

4.1. Contributions

The main contribution of this study is translating MDS-UPDRS-III tremor measurements to an objective scoring algorithm based on accelerometry. Healthy controls were included in this research to calculate natural variation of $PAUC_{tremor}$ between 4 and 6 Hz, and to provide baseline thresholds for the objective scoring algorithm. As PD treatment decisions during awake thalamotomy and STN-DBS surgery, e.g., permanent lead position, currently depend, in part, on subjective MDS-UPDRS-III tremor assessments, this study focused on neurosurgical PD patients. In this study, the quantification of tremor measurements was investigated in the intraoperative setting, providing direct objective input for clinical decision-making during neurosurgery. The results provided by the algorithm are clinically meaningful and easy to interpret, as they are based on the same MDS-UPDRS-III criteria PD caregivers are used to working with.

4.2. Accelerometry measures

The results of the intraoperative use of our accelerometry-based scoring algorithm were presented. The $PAUC_{tremor}$ and amplitude outcomes of the tremor measurements in both the healthy and the patient group were consistent with previous research, namely a logarithmic relationship with the given MDS-UPDRS-III tremor scores [13,31,36].

Another main finding was the relatively large variation in $PAUC_{tremor}$ during the kinetic tremor tests in the healthy group. This led to a large overlap between this outcome measure of patients with PD and healthy subjects (Figure 2c). The power in the frequency band of 4–6 Hz is possibly influenced by the higher harmonics of the intentional kinetic arm movement made during these tests. Furthermore, when participants move their arm too fast, the frequency of the arm movement can overlap with that of the tremor frequency band, resulting in a higher measured amplitude and $PAUC_{tremor}$ between 4 Hz and 6 Hz.

Overall, it stood out that relatively few patients were included that scored 2, 3, or 4 on the MDS-UPDRS-III scale. This was most likely caused by the clinical effect of the surgery, as only the measurements performed before lead placement received high MDS-UPDRS-III scores. More than half of all tests were performed after lead insertion, and were influenced by the microlesion effect, resulting in lower MDS-UPDRS-III scores for post insertion measurements [18].

In this study, the constancy of rest tremor was calculated over the time that the rest tremor test was performed. As a next step, rest tremor constancy should be assessed during the whole examination.

4.3. Objective MDS-UPDRS-III scores

Strong concordance was found between the clinically scored MDS-UPDRS-III ratings and accelerometry-based scores, whereas Cohen's κ was considerably lower. This could be explained by the large number of scores of zero (meaning no tremor was observed) in this study population. The effect of the outliers in this dataset can be seen in the high value of RMSE, indicating an error of 0.5 to 0.7 point between MDS-UPDRS-III and accelerometric scores. From Figure 4 one could argue that the accelerometric approach underestimates the amplitude of tremor, or that the clinical assessment overestimates it. Some studies have already shown that recorded accelerometric data and visual evaluations according to clinical scales do not correlate very well, mainly because minor changes in tremor are hard to assess by eye [17]. This is especially the case when the amplitude at baseline is small; whereas accelerometers can detect these small changes [17]. An explanation for the imperfect agreement with clinical assessments found in other studies might be that objective measurements outperform clinical scales at the level of the individual patient [23]. After all, movement sensors are able to capture subtle changes in PD symptoms as the disease progresses that cannot be captured using discrete scoring schemes, such as the MDS-UPDRS-III [39].

The large differences between the three calculated $\text{PAUC}_{\text{tremor}}$ thresholds (Section 3.2) can be explained by the hand positions during tremor tests. Due to muscle tension that emerges when stretching the arms out in front of the body, the threshold of the $\text{PAUC}_{\text{tremor}}$ is higher for postural tremor than for rest tremor, during which there is low muscle tension present in healthy persons. The kinetic tremor threshold is even higher due to increased muscle tension and arm movement. The large variation in $\text{PAUC}_{\text{tremor}}$ in kinetic tremor tests possibly led to a threshold that could not sufficiently distinguish between healthy and symptomatic measurements.

Lastly, the discrepancies between Figures 3 and 4 can be explained by how the scoring algorithm first analyses whether the $\text{PAUC}_{\text{tremor}}$ between 4 and 6 Hz of a test is above the threshold. If this is not the case, a score of 0 ("no tremor") is given. Although the total amplitude or T_{tremor} for that test might have been substantial, these values were not taken into account for the scoring if the $\text{PAUC}_{\text{tremor}}$ was below the threshold. This approach was chosen, as the total amplitude could also be caused by movements outside the 4–6 Hz frequency range.

4.4. Inconsistencies

One of the largest limitations in this research was insufficient measurements in patients with PD that scored above 2 on the MDS-UPDRS-III scale. This led to an underrepresentation of more severely affected PD patients.

Secondly, although the scoring neurologist (T.v.L.) in this study is a PD expert, there was only one rater. To increase the reliability of the MDS-UPDRS-III ratings, the scores of several experienced neurologists rating the same patient should be included in future research. This will also allow for the comparison of the MDS-UPDRS-III inter-rater variability and that of the accelerometry scoring algorithm.

MDS-UPDRS-III tests do not call for the use of instrumental aids, such as rulers, but instead rely on the naked eye. This might have caused discrepancies between the outcomes of the accelerometric measurements and the clinically scored MDS-UPDRS-III ratings. Previous studies have shown that the distances measured using objective techniques often do not agree with the distances that were visually estimated by the MDS-UPDRS-III rater [31,40].

In contrast to the PD group, the healthy group was not assessed in an intraoperative setting. This might have affected the calculated thresholds, and, therefore, possibly influenced the results of the algorithm in the PD group. The environmental effects and stress that patients undergoing surgery may experience were not simulated for the healthy controls, which might have influenced the occurrence of tremor in the healthy group. In this study, the $PAUC_{tremor}$ values of healthy persons were used to correct for activity in the 4–6 Hz frequency band that is present when a person does not suffer from any range of Parkinsonian tremor. Still, it cannot be assumed that all power in the 4–6 Hz frequency range is caused by tremor. Objective criteria for assessing whether a spectral peak is present are essential for determining if the observed movement is tremor [7,29,36]. A dominant spectral peak between 4 Hz and 6 Hz that could be identified upon visual or automatic inspection of the periodogram should also result in a substantially higher value of $PAUC_{tremor}$. This will be investigated further in our ongoing research.

Considering the large natural variation found in this pilot study, it is recommended to perform future studies with more healthy participants that are age-matched to the patient population. It is also recommended to include more participants with PD, especially patients that score higher than a score of 1 according to the MDS-UPDRS-III tremor criteria.

4.5. Future perspectives

Research on techniques for PD motor quantification and defining objective outcome measures is currently on the rise [23]. It is expected that, over time, the use of objective measurement tools will be preferred by physicians as an addition to the internationally standardized clinical scales that are currently used to assess the course of PD symptoms [41]. As stated by Elble and Ondo, transducers, such as accelerometers, can complement clinical assessment to quantify tremor severity [42]. The clinical importance of this objective method lies in the reduction of inter- and intra-rater variability, allowing

clinicians to rate patients more uniformly. This will be further investigated in our ongoing research following this pilot study, where the variability and reproducibility of both the MDS-UPDRS tests and the accelerometry-based method are examined and compared. Reduced inter- and intra-rater variability in monitoring tremor will contribute to tracking the disease progression and treatment effect more precisely. To aid clinicians in optimizing patient outcomes, it is critical to present these complex quantitative data in a quickly interpretable manner, for example using scores according to the MDS-UPDRS-III. The proposed technique might also form a solution to the clinical problem that physicians are faced with when visually scoring dystonic and Essential Tremor. The frequency range and settings used in current scoring algorithm could be customized to standardized dystonic and Essential Tremor rating scale criteria with few adjustments [7,43,44].

Another promising line of research involves machine learning methods, such as neural networks or support vector machine classification of PD and healthy subjects based on accelerometry measures. Besides efficiently handling vast amounts of high-dimensional data, machine learning methods hold promise not just in early disease detection and (differential) diagnosis, but also in estimating tremor severity [30,31,39,45,46].

Future steps to take in the development of the techniques proposed in this article are data collection in “free-living” conditions, relevant to the patient’s functioning, and using this data for generating individualized feedback to clinicians, caregivers, and patients [23]. This will aid in tailoring treatments to the individual patient and increasing patient self-management.

5. Conclusions

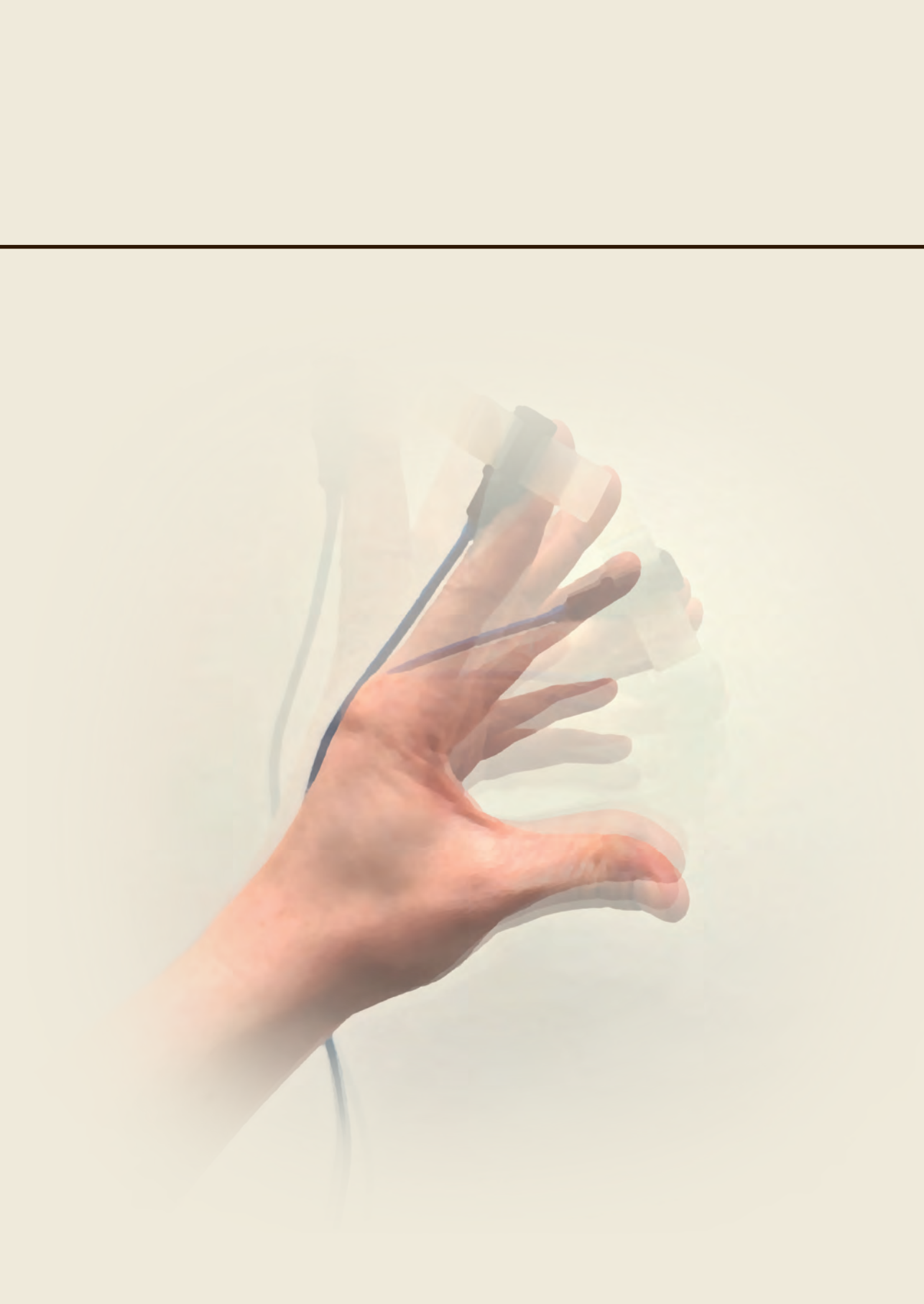
This study showed that the MDS-UPDRS-III tremor tests can be quantified using accelerometric measurements. Substantial agreement was found between the clinically scored MDS-UPDRS-III ratings and accelerometry-based scores. The postural tremor, rest tremor, and constancy of rest tremor data were consistent with a logarithmic relationship reported in previous studies. Discrepancies were found between objective outcome measures and the MDS-UPDRS-III ratings of the kinetic tremor test, mainly due to the natural variation found in the healthy group. Future research should focus on investigating the variability and reproducibility of MDS-UPDRS-III measures and accelerometric outcome measures, especially for kinetic tremor. This technology could reduce rater dependency of MDS-UPDRS-III measurements and allow more objective intraoperative monitoring of tremor.

References

- [1] Tysnes OB, Storstein A. Epidemiology of Parkinson's Disease. *J Neural Transm* 2017;124:901–5. <https://doi.org/10.1007/s00702-017-1686-y>.
- [2] Galperin I, Hillel I, Del Din S, Bekkers EMJ, Nieuwboer A, Abbruzzese G, et al. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's Disease. *Parkinsonism Relat Disord* 2019;62:85–90. <https://doi.org/10.1016/j.parkreldis.2019.01.022>.
- [3] Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis* 2018;8:S3–8. <https://doi.org/10.3233/JPD.181474>.
- [4] Jankovic J. Parkinson's Disease: Clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79:368–76. <https://doi.org/10.1136/jnnp.2007.131045>.
- [5] Vaillancourt DE, Newell KM. The dynamics of resting and postural tremor in Parkinson's Disease. *Clinical Neurophysiology* 2000;111:2046–56.
- [6] Kalia L, Lang AE. Parkinson's Disease. *The Lancet* 2015;386:896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3).
- [7] van der Stouwe AMM, Elting JW, van der Hoeven JH, van Laar T, Leenders KL, Maurits NM, et al. How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena. *Parkinsonism Relat Disord* 2016;30:23–8. <https://doi.org/10.1016/j.parkreldis.2016.06.008>.
- [8] Erb MK, Karlin DR, Ho BK, Thomas KC, Parisi F, Vergara-Diaz GP, et al. mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's Disease. *NPJ Digit Med* 2020;3. <https://doi.org/10.1038/s41746-019-0214-x>.
- [9] Journee HL, Postma AA, Staal MJ. Intraoperative neurophysiological assessment of disabling symptoms in DBS surgery. *Neurophysiologie Clinique* 2007;37:467–75. <https://doi.org/10.1016/j.neucli.2007.10.006>.
- [10] Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's Disease rating scale. *Arch Neurol* 2010;67:64–70.
- [11] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [12] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. Movement Disorders Society - Unified Parkinson Disease Rating Scale. 2008. www.movementdisorders.org (accessed February 1, 2022).
- [13] Maldonado-Naranjo A, Koop MM, Hogue O, Alberts J, MacHado A. Kinematic Metrics from a Wireless Stylus Quantify Tremor and Bradykinesia in Parkinson's Disease. *Parkinsons Dis* 2019;2019. <https://doi.org/10.1155/2019/6850478>.
- [14] Chen KHS, Chen R. Invasive and Noninvasive Brain Stimulation in Parkinson's Disease: Clinical Effects and Future Perspectives. *Clin Pharmacol Ther* 2019;106:763–75. <https://doi.org/10.1002/cpt.1542>.
- [15] Hemm S, Wårdell K. Stereotactic implantation of deep brain stimulation electrodes: A review of technical systems, methods and emerging tools. *Med Biol Eng Comput* 2010;48:611–24. <https://doi.org/10.1007/s11517-010-0633-y>.
- [16] Bruce BB, Foote KD, Rosenbek J, Sapienza C, Romrell J, Crucian G, et al. Aphasia and thalamotomy: Important issues. *Stereotact Funct Neurosurg* 2004;82:186–90. <https://doi.org/10.1159/000082207>.
- [17] Shah A, Coste J, Lemaire JJ, Taub E, Schüpbach WMM, Pollo C, et al. Intraoperative acceleration measurements to quantify improvement in tremor during deep brain stimulation surgery. *Med Biol Eng Comput* 2017;55:845–58. <https://doi.org/10.1007/s11517-016-1559-9>.

- [18] Lange SF, Kremer NI, van Laar T, Lange F, Steendam-Oldekamp TE, Oterdoom DLM, et al. The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation* 2021. <https://doi.org/10.1111/ner.13523>.
- [19] Lukšys D, Jonaitis G, Griškevičius J. Quantitative Analysis of Parkinsonian Tremor in a Clinical Setting Using Inertial Measurement Units. *Parkinsons Dis* 2018;2018. <https://doi.org/10.1155/2018/1683831>.
- [20] Rodríguez-Molinero A, Samà A, Pérez-López C, Rodríguez-Martín D, Alcaine S, Mestre B, et al. Analysis of correlation between an accelerometer-based algorithm for Detecting Parkinsonian gait and UPDRS subscales. *Front Neurol* 2017;8:1–6. <https://doi.org/10.3389/fneur.2017.00431>.
- [21] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [22] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.
- [23] Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's Disease obtained using mobile health technologies. *Movement Disorders* 2019;34:657–63. <https://doi.org/10.1002/mds.27671>.
- [24] Farzanehfar P, Woodrow H, Braybrook M, McGregor S, Evans A, Nicklason F, et al. Objective measurement in routine care of people with Parkinson's Disease improves outcomes. *NPJ Parkinsons Dis* 2018;4:1–8. <https://doi.org/10.1038/s41531-018-0046-4>.
- [25] Hobert MA, Maetzler W, Aminian K, Chiari L. Technical and clinical view on ambulatory assessment in Parkinson's Disease. *Acta Neurol Scand* 2014;130:139–47. <https://doi.org/10.1111/ane.12248>.
- [26] Teshuva I, Hillel I, Gazit E, Giladi N, Mirelman A, Hausdorff JM. Using wearables to assess bradykinesia and rigidity in patients with Parkinson's Disease: a focused, narrative review of the literature. *J Neural Transm* 2019;126:699–710. <https://doi.org/10.1007/s00702-019-02017-9>.
- [27] Oung QW, Muthusamy H, Lee HL, Basah SN, Yaacob S, Sarillee M, et al. Technologies for assessment of motor disorders in Parkinson's Disease: A review. *Sensors (Switzerland)* 2015;15:21710–45. <https://doi.org/10.3390/s150921710>.
- [28] Ossig C, Antonini A, Buhmann C, Classen J, Csoti I, Falkenburger B, et al. Wearable sensor-based objective assessment of motor symptoms in Parkinson's Disease. *J Neural Transm* 2016;123:57–64. <https://doi.org/10.1007/s00702-015-1439-8>.
- [29] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [30] Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's Disease: Challenges and opportunities. *Movement Disorders* 2016;31:1272–82. <https://doi.org/10.1002/mds.26642>.
- [31] Jeon H, Lee W, Park H, Lee HJ, Kim SK, Kim HB, et al. High-accuracy automatic classification of Parkinsonian tremor severity using machine learning method. *Physiol Meas* 2017;38:1980–99. <https://doi.org/10.1088/1361-6579/aa8e1f>.
- [32] Lieber B, Taylor BES, Appelboom G, Mckhann G, Connolly ES. Motion Sensors to Assess and Monitor Medical and Surgical Management of Parkinson Disease. *World Neurosurg* 2015;84:561–6. <https://doi.org/10.1016/j.wneu.2015.03.024>.

- [33] Rigas G, Tzallas AT, Tsiouras MG, Bougia P, Tripoliti EE, Baga D, et al. Assessment of Tremor Activity in the Parkinson's Disease Using a Set of Wearable Sensors. *IEEE Transactions on Information Technology in Biomedicine* 2012;16:478–87. <https://doi.org/10.1109/TITB.2011.2182616>.
- [34] Burg JP. Maximum entropy spectral analysis. Ph.D. dissertation. Stanford Univ. Stanford, CA, 1975.
- [35] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's Disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4. <https://doi.org/10.1136/jnnp.55.3.181>.
- [36] Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. *Brain* 2006;129:2660–6. <https://doi.org/10.1093/brain/awl190>.
- [37] McHugh M. Interrater reliability - the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276–82.
- [38] Ranganathan P, Pramesh C, Aggarwal R. Common pitfalls in statistical analysis: Measures of agreement. *Perspect Clin Res* 2017;8:187–91. https://doi.org/10.4103/picr.PICR_123_17.
- [39] Heldman DA, Espay AJ, LeWitt PA, Giuffrida JP. Clinician versus machine: Reliability and responsiveness of motor endpoints in Parkinson's Disease. *Parkinsonism Relat Disord* 2014;20:590–5. <https://doi.org/10.1016/j.parkreldis.2014.02.022>.
- [40] Jeon H, Kim SK, Jeon B, Park KS. Distance estimation from acceleration for quantitative evaluation of Parkinson tremor. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2011*, p. 393–6. <https://doi.org/10.1109/IEMBS.2011.6090126>.
- [41] Mahadevan N, Demanuele C, Zhang H, Volfson D, Ho B, Erb MK, et al. Development of digital biomarkers for resting tremor and bradykinesia using a wrist-worn wearable device. *NPJ Digit Med* 2020;3. <https://doi.org/10.1038/s41746-019-0217-7>.
- [42] Elble RJ, Ondo W. Tremor rating scales and laboratory tools for assessing tremor. *J Neurol Sci* 2022;435. <https://doi.org/10.1016/j.jns.2022.120202>.
- [43] Fahn S, Tolosa E, Marín C. Clinical Rating Scale for Tremor. *Parkinson's Disease and Movement Disorders* 1988:225–34.
- [44] Zajki-Zechmeister T, Kögl M, Kalsberger K, Frantal S, Homayoon N, Katschnig-Winter P, et al. Quantification of tremor severity with a mobile tremor pen. *Heliyon* 2020;6:e047. <https://doi.org/10.1016/j.heliyon.2020.e04702>.
- [45] Moon S, Song H-J, Sharma VD, Lyons KE, Pahwa R, Akinwuntan AE, et al. Classification of Parkinson's Disease and Essential Tremor based on balance and gait characteristics from wearable motion sensors via machine learning techniques: a data-driven approach. *J Neuroeng Rehabil* 2020;17:125. <https://doi.org/10.1186/s12984-020-00756-5>.
- [46] Hssayeni MD, Jimenez-Shahed J, Burack MA, Ghoraani B. Wearable Sensors for Estimation of Parkinsonian Tremor Severity during Free Body Movements. *Sensors* 2019;19:4215. <https://doi.org/10.3390/s19194215>.



Chapter 6

A novel accelerometry method to perioperatively quantify Essential Tremor based on Fahn-Tolosa- Marin criteria

Annemarie Smid

Rik W. J. Pauwels

Jan Willem J. Elting

Cheryl S. J. Everlo

Marc C. van Dijk

D. L. Marinus Oterdoom

Teus van Laar

Katalin Tamasi

A. M. Madelein van der Stouwe

Gea Drost

Journal of Clinical Medicine (2023)

doi: 10.3390/jcm12134235

Abstract

Disease status, progression and treatment effect of Essential Tremor (ET) patients are currently assessed with clinical scores, like the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM). Use of objective and rater-independent monitoring of tremor may improve clinical care for patients with ET. Therefore, the focus of this study is to develop an objective accelerometry-based method to quantify ET, based on FTM-criteria. Thirteen patients with ET and 13 matched healthy participants underwent FTM-tests to rate tremor severity, paired with tri-axial accelerometric measurements at the index fingers. Analogue FTM assessments were performed by four independent raters based on video recordings. Quantitative measures were derived from the accelerometric data, e.g. area under the curve of power in the 4–8 Hz range (AUCP) and maximal tremor amplitude. As such, accelerometric tremor scores were computed, using thresholds based on healthy measurements and FTM-criteria. Agreement between accelerometric and clinical FTM-scores was analyzed with Cohen's kappa coefficient. It was assessed whether there was a relationship between mean FTM-scores and the natural logarithm ($\ln$) of the accelerometric outcome measures using linear regression. The agreement between accelerometric and FTM-scores was substantial for resting and intention tremor tests ($\geq 72.7\%$). However, the agreement between accelerometric postural tremor data and clinical FTM-ratings ($\kappa=0.459$) was low, although their logarithmic ($\ln$) relationship was substantial ($R^2 \geq 0.724$). Accelerometric test-retest reliability was good to excellent ($\text{ICC} \geq 0.753$). This pilot study shows that tremor can be quantified with accelerometry, using healthy thresholds and FTM-criteria. The test-retest reliability of the accelerometric tremor scoring-algorithm indicates that our low-cost accelerometry-based approach is a promising one. The proposed easy-to-use technology could diminish rater-dependency of FTM-scores and enable physicians to monitor ET patients more objectively in clinical, intraoperative and home settings.

1. Introduction

Essential Tremor (ET) is a common movement disorder, with typically a stable tremor frequency between 4 Hz and 8 Hz [1–3]. In clinical practice, qualitative rating of tremor is used to guide therapy. On one hand, patient-rated scales like the Quality of Life in Essential Tremor Questionnaire (QUEST) and Visual Analog Scale (VAS) are used to assess quality of life and patient satisfaction [4–7]. On the other hand, tremor rating scales like the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM) are also used by clinicians to assess disease severity, progression and treatment effect [8,9]. During awake stereotactic neurosurgery aiming to alleviate tremor, the FTM-scale is used to score tremor severity. Although the FTM is not a purely objective [10] scale, with assessments that may vary between raters, its results are directly applied in patient management [11,12]. As such, there is a clear need for measurements that allow precise and objective monitoring of ET, providing reliable outcomes [13,14].

Nowadays, hospitals are equipped with transducers to perform quantitative tremor measurements, but these can be complex, costly, and time-consuming. Prior studies have shown that transducer-based methods can complement clinical and intraoperative assessments [15–18]. Still, regular and rater-independent assessment of tremor often lacks in clinical practice [13].

A promising and inexpensive technique to objectively quantify tremor is tri-axial accelerometry (purchase costs 10US\$~30US\$). Outcome measures such as peak frequency and tremor amplitude can be calculated from accelerometric data, which could be used to translate clinical scales, such as the FTM, to a rater-independent method [18–20].

Previous research has mainly focused on determining objective measures that correlate well with clinical outcome measures, instead of attempting to literally translate a rating scale to a sensor-based method [12,13,15,21,22]. Therefore, using standardized FTM-criteria, our new approach is to develop an objective accelerometry-based scoring-algorithm. Since most of the FTM-criteria focus on the tremor amplitude in centimeters, the same amplitude thresholds are applied to our novel accelerometry-based scoring-algorithm. The use of scoring thresholds based on accelerometric measurements in healthy volunteers will aid in differentiating physiological tremor from symptomatic measurements [18]. This way, we will develop a novel transducer-based method to contribute to the clinical assessment of tremor [16].

The focus of this study is to translate FTM (part A) into an objective accelerometry-based tremor rating algorithm. In this pilot study, the agreement between accelerometric and clinical FTM-scores is evaluated. The proposed technology could diminish rater-dependency of FTM tremor measurements and enable physicians to monitor patients with ET more objectively.

2. Materials and methods

This research project was performed in a tertiary referral center for movement disorders. The study was granted exemption from requiring ethics approval by the local

medical ethics review committee, as the protocol was not deemed clinical research with human subjects as meant in the Dutch Act on Medical Research Involving Human Subjects. The study was conducted in compliance with the Helsinki Declaration for human research. The same materials as previously described by Smid et al. were used [18].

2.1. Study participants

Between September 2020 and December 2021, patients with ET visiting the neurosurgical outpatient clinic (as part of the standard workup for stereotactic surgery) were included and matched with healthy participants (HP) for gender and age. All participants were adult and provided written informed consent for participation. ET patients had undergone a video-assisted surface-EMG accelerometric tremor registration to confirm the diagnosis [2]. None of the HP had a current diagnosis of ET or any neurological disease.

2.2. Clinical FTM measurements

All tremor measurements were performed at the outpatient clinic. The participant was sitting in a chair with armrests during all measurements. Tremor severity was assessed using a total of three FTM-tests: postural (wing-beating), intention (finger-to-nose) and at rest (arms on the armrest, hands free from the armrest). These tests were performed once for each hand.

Video recordings of the hands were made during the patient measurements, to assess tremor severity according to the FTM-scale by four experienced raters (A.S., R.W.J.P., C.S.J.E. and A.M.M.v.d.S.). The raters were blinded for the accelerometric data.

2.3. Accelerometry measurements

Accelerometric data were recorded at the same time the clinical FTM tremor tests were performed for both hands. The sensors were placed at the proximal phalanx of both index fingers (Figure 1).

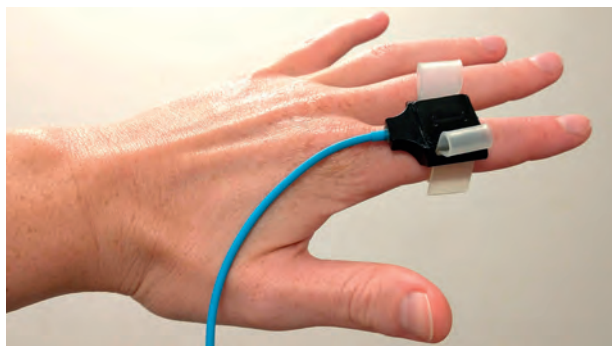


Figure 1. Accelerometer positioned at the left index finger.

Accelerometry measurements in healthy participants were performed to determine the natural variation of noise in the 4–8 Hz frequency range and to calculate thresholds of the accelerometric data for the scoring-algorithm. Accelerometric data were recorded for ten seconds per test. Both hands performed the instructed posture (resting and postural) simultaneously, resulting in two (repeated) recordings per hand for each test. The intention tremor test was performed separately for each hand, so only data from the ipsilateral sensor were recorded during that test.

2.4. Accelerometric outcome measures

Data pre-processing was performed as described by Smid et al. [18]. Raw acceleration data were converted from g-units to cm/s^2 . The root mean square of the resultant vector of the three axes was calculated in order to determine the acceleration norm [18]. To remove low-frequency noise, a non-causal second-order 0.5 Hz high-pass Butterworth filter was applied. A non-causal second-order 20 Hz low-pass Butterworth filter was used to suppress digital noise and higher-order harmonics [18,22]. To calculate the velocity (cm/s) per test, the approximate cumulative numerical integral of the filtered acceleration vector was computed over a time of ten seconds (2000 samples) via the trapezoidal method. The mean of the calculated velocity was subtracted from this vector to correct for the constant added during the integration step. Next, the corrected velocity was integrated numerically to the amplitude (cm). The amplitude vector was filtered using a non-causal second-order 1 Hz high-pass Butterworth filter to suppress the drift caused by integration. For the intention tremor tests, a cut-off frequency of 3 Hz was maintained here, to suppress the amplitude of low frequent arm movements [22].

To assess resting, postural and intention tremor, two main outcome measures were calculated from the accelerometry data per respective test: (1) the area under the curve (AUC) of power within the 4–8 Hz tremor frequency band, and (2) the maximal amplitude.

From the periodogram power spectral density (PSD) estimate, the AUC of the power in the 4–8 Hz frequency band (AUCP: $(\text{cm/s}^2)^2$) was calculated via trapezoidal numerical integration (Figure 2) [18,22].

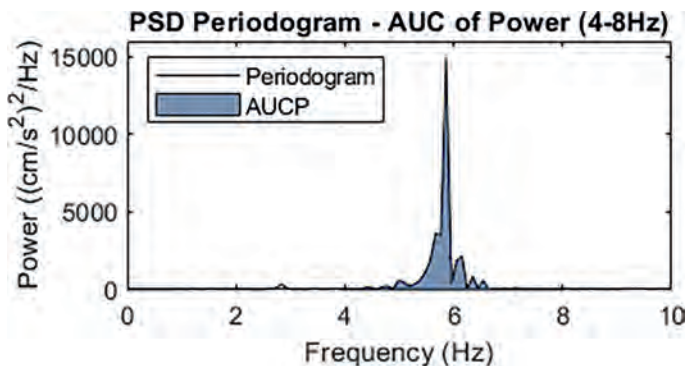


Figure 2. Example PSD periodogram, with the AUCP (4–8 Hz) given in blue.

The maximal amplitude of the performed test was calculated by multiplying the maximum value of the absolute amplitude vector by two, since tremor is a sinusoid-like movement with equably negative and positive peaks.

2.5. Accelerometry-based scores

Objective scores were calculated from the accelerometric data, based on the standardized scoring criteria stated in the FTM-scale (part A) [8]. The descriptive evaluations of the FTM were applied to calculate an accelerometry-based score via a custom scoring-algorithm written in MATLAB. Like the FTM, the output of the scoring-algorithm was a tremor score ranging from 0 to 4.

First, AUCP thresholds were calculated to differentiate healthy or asymptomatic measurements (FTM-score 0) from symptomatic measurements (FTM-score ≥ 1). As the only criteria given for an FTM-score of 0 is “none”, AUCP of each test was calculated from the accelerometric HP data to determine the natural variation of noise between 4–8 Hz. These natural variations were used to determine thresholds that distinguish measurements of FTM-score 0 from those of FTM-score ≥ 1 . The Kolmogorov-Smirnov test of normality (one-sample K-S test) was used to determine whether the data were normally distributed. The thresholds for AUCP of the three different tremor conditions were defined as more than two standard deviations above the mean of the HP tremor tests.

Next, amplitude thresholds were calculated to distinguish between slight (FTM-score 1) and more severe (FTM-score ≥ 2) tremor. Maximal amplitude of each test was calculated from the accelerometric HP data. Again, the thresholds were defined as more than two standard deviations above the mean amplitude of the HP tremor tests. These amplitude thresholds were calculated separately for the resting, postural and intention tremor tests.

If the AUCP of the test was below the calculated threshold, an accelerometric (ACC) score of 0 was given (Figure 3). Otherwise, a score of 1 or higher was given, based on the maximal amplitude measured during that test. If the maximal amplitude of the test was below the calculated amplitude threshold, a score of 1 was given. For the higher scores, the same amplitude limits described in the FTM-scale were applied to calculate accelerometric scores (Figure 3).

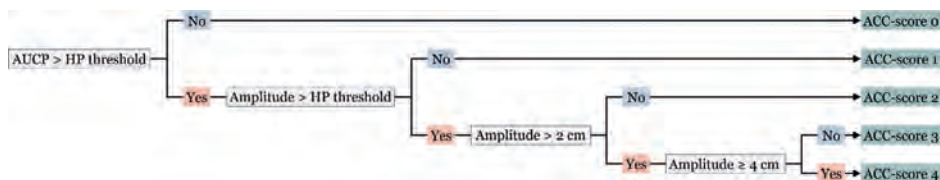


Figure 3. Flowchart of the accelerometry-based scoring-algorithm, based on HP thresholds calculated from healthy participant (HP) and standardized FTM scoring criteria. Following the flowchart, the “No” pathways are given in blue and the “Yes” pathways are given in orange.

2.6. Statistical analysis

The ICC (two-way random effects model, mean of k raters, absolute agreement) of the four different raters was calculated to determine the inter-rater variability of the clinical FTM assessment [23]. The two-way random effects model, mean of k raters approach was chosen here, as the inter-rater variability results are to be generalized to any raters who possess the same characteristics as the selected raters, and there was more than one rater.

Linear regression was used to analyze the relationship between the video-rated FTM-scores and the two accelerometry outcome measures. For each test, the FTM-scores provided by the four raters were averaged. The averaged FTM-scores were used as the predictor and the outcome was the accelerometric outcome measure. Elble et al. described how the Weber-Fechner law of psychophysics postulates a logarithmic relationship between tremor ratings and tremor amplitude [24]. Therefore, it was assessed whether there was a linear relationship between mean FTM-scores and the natural logarithm (ln) of the accelerometric outcome measures, as found in previous studies [15,17,18,24]. To this end, contrast coding of the mean FTM-ratings was defined to be orthogonal polynomial, of which the first contrast coefficient is linear trend [18].

Concordance and Cohen's weighted kappa coefficient (κ) were calculated to measure the agreement between the mean FTM-score and accelerometric score of each test [25,26]. The root mean square error (RMSE) and the mean absolute error (MAE) were computed to indicate how much the accelerometric scores differed from the mean FTM-scores.

Lastly, the ICC (two-way mixed effects model, single measurement, absolute agreement) of AUCP, maximal amplitude and accelerometric scores was calculated for the repeated resting and postural tremor tests in order to determine the test-retest reliability of the accelerometric approach [23]. The two-way mixed effects model, single measurement approach was chosen here, as the selected measurements are the only measurements of interest, and the protocol was based on a single measurement and not on the mean of multiple measurements [23].

3. Results

Thirteen patients with ET (9 men, 4 women; age (mean $\pm$ SD): 73 $\pm$ 5 years) and 13 healthy participants (9 men, 4 women; age (mean $\pm$ SD): 73 $\pm$ 8 years) were included in this study. In the patient population, 44 resting, 44 postural and 44 intention tremor tests were performed. A total of 78 measurements were performed in the healthy group. Median tremor severity in the patient population was an FTM (part A) score of 10 (range: 2–19) out of 24.

3.1. Clinical FTM measurements

The ICC-index between the four FTM-raters showed a good to excellent inter-rater reliability for all tremor tests (ICC $\geq$ 0.893) [23]. The ICC for the resting tremor test was 0.935 (95% CI: 0.855, 0.970; $p < 0.001$). For the postural tremor test, an ICC of 0.953 (95%

CI: 0.918, 0.975; $p < 0.001$) was found. The ICC for the intention tremor test was 0.893 (95% CI: 0.813, 0.944; $p < 0.001$). Lastly, the ICC for all tremor tests combined was 0.959 (95% CI: 0.941, 0.972; $p < 0.001$).

3.2. Accelerometric outcome measures

The main outcome measures were the AUCP and maximal amplitude of the resting, postural, and intention tremor tests. In Figure 4, the quantitative outcome measures of each tremor test are plotted against the averaged clinical FTM-ratings. An increase in both AUCP and amplitude with increasing FTM-score can be seen for all tremor tests. These relationships tend to be logarithmic.

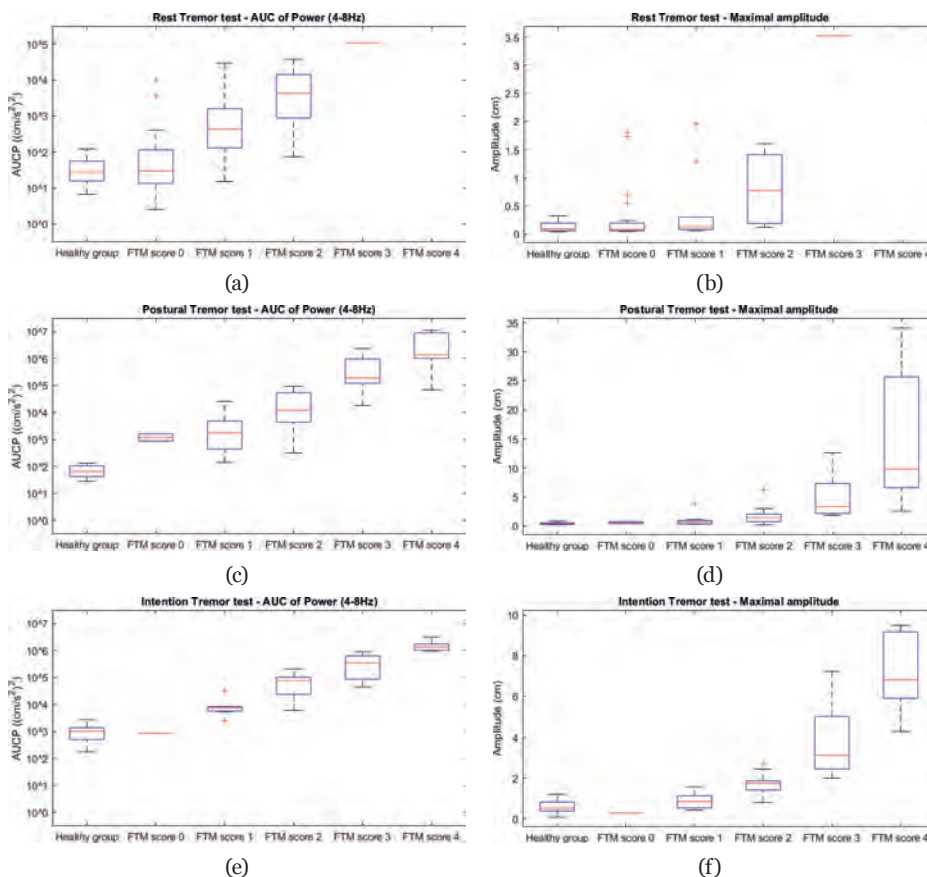


Figure 4. Boxplots of the AUCP between 4 Hz and 8 Hz of the resting (a), postural (c), and intention (e) tremor tests, and of the amplitude of the resting (b), postural (d), and intention (f) tremor tests in the healthy group and the patient population (per FTM-score).

The main outcome measures were the AUCP and maximal amplitude of the resting, postural, and intention tremor tests. These accelerometric measures were natural log (ln) transformed and regressed on the averaged FTM-scores. There was strong evidence against the null hypothesis that the ln-transformed outcome measures were not linearly related to the mean FTM-ratings ($p < 0.001$) for all tremor tests (Table 1). In short, there was evidence for a logarithmic (ln) relationship between these variables.

AUCP tended to increase as a logarithmic function of FTM-scores ($R^2 \geq 0.714$) for the postural and intention tests. This relationship was less strong for the resting tremor tests ($R^2 = 0.642$).

The accelerometric amplitude also tended to increase as a logarithmic function of FTM-scores ($R^2 \geq 0.729$) for the postural and intention tests. Again, this relationship was less strong for the resting tremor tests ($R^2 = 0.408$).

Table 1. Regression analysis results.

FTM-test	Outcome Measure	R	R^2 *	Coefficient**	95% CI	p
Resting tremor	Ln(AUCP)	0.801	0.642	8.042	5.716, 10.368	<0.001
	Ln(Amplitude)	0.639	0.408	2.887	1.541, 4.233	<0.001
Postural tremor	Ln(AUCP)	0.851	0.724	7.765	2.908, 9.622	<0.001
	Ln(Amplitude)	0.857	0.735	2.784	1.779, 3.790	<0.001
Intention tremor	Ln(AUCP)	0.845	0.714	5.884	4.444, 7.325	<0.001
	Ln(Amplitude)	0.854	0.729	2.463	1.882, 3.044	<0.001

* Coefficient of determination; ** Contrast coefficient testing for linear trend.

3.3. Accelerometry-based scores

No deviation from normality was detected by K-S tests for all HP data required for the threshold calculation. The AUCP threshold was used to differentiate FTM-scores 0 from FTM-scores ≥ 1 . An AUCP threshold of $123 \text{ (cm/s}^2\text{)}^2$ was calculated from the healthy population for the resting tremor test. This threshold was calculated to be $141 \text{ (cm/s}^2\text{)}^2$ and $2552 \text{ (cm/s}^2\text{)}^2$ for the postural and intention tremor test, respectively. The amplitude thresholds were used to differentiate FTM-scores 1 from FTM-scores ≥ 2 . The amplitude thresholds were calculated to be 0.32 cm, 0.78 cm and 1.24 cm for the resting, postural and intention tremor test, respectively. The contingency tables of the averaged FTM-scores and the ACC-scores in the patient population for all tremor tests are given in heatmaps in Figure 5.

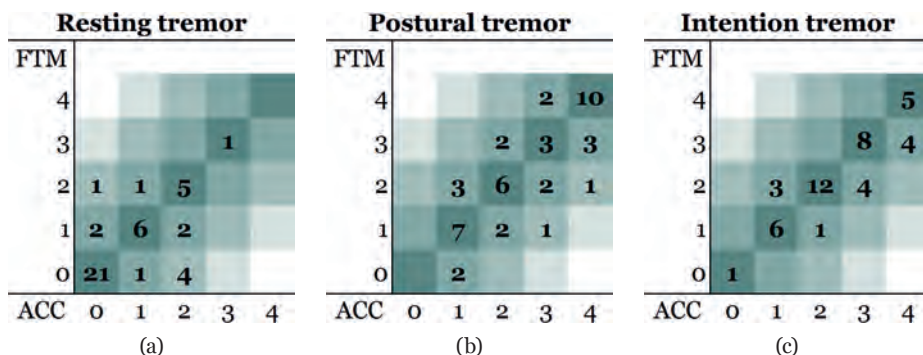


Figure 5. Contingency tables of the mean FTM-scores and calculated accelerometry (ACC) scores of the resting (a), postural (b) and intention (c) tremor tests in the patient population.

Concordance and Cohen's κ coefficient of agreement between the averaged FTM-scores and the ACC-scores per type of test, and the mean error (RMSE and MAE) are given in Table 2. Concordance between the FTM-scores and the objective scores was strong for resting and intention tremor tests ($\geq 72.7\%$). Cohen's κ results showed a moderate agreement for resting and postural tremor and a substantial agreement for intention tremor tests [25,26]. On average, the accelerometric scores differed less than half a point from the mean FTM-ratings, as indicated by the MAE.

Table 2. Agreement results.

FTM-test	Concordance	Cohen's κ	95% CI	RMSE	MAE
Resting tremor	75.0%	0.581	0.470, 0.692	0.77	0.36
Postural tremor	59.1%	0.459	0.334, 0.584	0.74	0.45
Intention tremor	72.7%	0.632	0.516, 0.748	0.52	0.27

In table 3, the test-retest reliability of the accelerometer-based method is given for the AUCP and amplitude outcome measures, and the calculated accelerometry scores of the repeated resting and postural tremor test. Reliability was excellent for the AUCP and amplitude of the postural tremor test, and the remaining ICCs showed a good test-retest reliability [23].

Table 3. Test-retest reliability of accelerometric approach (ICC: two-way mixed-effects-model, single measurement, absolute agreement).

FTM-test	Outcome Measure	ICC	95% CI	<i>p</i>
Resting tremor	AUCP	0.887	0.793, 0.938	<0.001
	Amplitude	0.772	0.583, 0.875	<0.001
	ACC-score	0.753	0.512, 0.856	<0.001
Postural tremor	AUCP	0.954	0.915, 0.975	<0.001
	Amplitude	0.936	0.875, 0.966	<0.001
	ACC-score	0.890	0.799, 0.940	<0.001

4. Discussion

This pilot study focused on translating FTM tremor evaluations to objective accelerometry measurements. A scoring-algorithm written in MATLAB to quantify tremor using tri-axial accelerometry measurements, based on FTM-criteria and HP thresholds was proposed. This study showed that tri-axial accelerometry is a promising technology for translating FTM-tests. The association between tremor amplitude and FTM-score were consistent with the logarithmic (ln) relationship shown in previous research [15,17,24].

The main contribution of this study is translating FTM measurements to an objective method, allowing clinicians to rate patients more uniformly. Although the inter-rater reliabilities found in this study were high, the validity of the FTM depends on the experience of the rater, underlining the need for an objective method [9,11–13,18].

Patients from the stereotactic surgery trajectory were selected in order to ensure the inclusion of high FTM tremor severity scores. Four experienced FTM-raters were employed in order to provide reliable input for the comparison between clinical FTM-scores and ACC-scores. The FTM inter-rater variabilities found in this research were similar to the reliabilities of the FTM (part A) reported in previous studies [9,27].

The complex data gathering in our objective approach is presented in a way that is easy to interpret by physicians, as the ACC-scores are based on the FTM-criteria used in clinical practice. This research contributes to creating quantitative outcome measures in ET research and enabling physicians and other personnel to monitor patients with ET more objectively. Considering the few materials needed to perform the proposed accelerometric measurements, this technique is also suitable for monitoring tremor during awake neurosurgical procedures (e.g. Deep Brain Stimulation surgery, MRI guided Focused Ultrasound and radioactive Gamma knife thalamotomy) [18,28–31]. As a future perspective, sensor-based measurement methods like the one described in this article may allow patients to perform smartphone-assisted measurements at home, increasing patient self-management.

The trends between the clinical FTM-scores and the AUCP, and between the clinical FTM-scores and the maximal amplitude of the three different tremor measurements were in line with the findings of other studies [15,17,18,24]. This relationship was strongest for postural and intention tremor tests. Unsurprisingly, it was less strong for the resting tremor tests, considering the low number of resting tremor measurements with an FTM-score above 2. This is to be expected in patients with a diagnosis of ET, as it is a phenotype that by definition is dominated by action tremor. This made the linear regression analysis more susceptible to the effects of outliers.

The unweighted agreement between accelerometric scores and FTM-ratings was strong for resting and intention tremor tests ($\geq 72.7\%$) [25]. However, a low agreement (59.1%) between accelerometric postural tremor data and clinical FTM-ratings was found, although the linear relationship between ln-transformed accelerometric postural tremor amplitude and clinical FTM-ratings was substantial ($R^2 \geq 0.724$). These discrepancies could be explained by objective measurements capturing small changes in amplitude that are difficult to evaluate visually. Continuous data is by definition capable of finer

grained distinctions than the discrete ordinal scale employed by the FTM, which is an advantage in monitoring disease progression [13,28]. However, the discrepancies could also be explained by the visual rating capturing aspects of the tremor that could not be measured at the position of the placed accelerometer, e.g. isolated tremor in the thumb.

The accelerometric test-retest reliability was good to excellent ($ICC \geq 0.753$) [23]. In both resting tremor and postural tremor test, the test-retest reliability was highest for AUCP outcome measure ($ICC \geq 0.887$). This is explained by the large scale of AUCP values, in contrast to the 5-point scale of accelerometric scores. The test-retest reliability was lowest for the accelerometric score outcome in both resting and postural tremor. This is explained by AUCP and/or amplitude values being close to the calculated threshold, which makes the scoring-algorithm sensitive for providing different scores to similar performances.

There are a number of limitations to this study. First, this study is a pilot study (proof of concept) with a relatively small sample size. In future research, this approach should be tested in a larger population in order to properly validate the proposed accelerometry-based approach. Future studies should also include out-of-sample validations in unseen data to avoid overfitting of the approach. Also, to determine the test-retest reliability, there was only data available of the resting and postural tremor tests. So, the reliability of the accelerometric approach was not assessed for the intention tremor tests. Also, the test-retest reliability was calculated based on two consecutive tests. It would be desirable to use three or more repetitions, preferably separated in time. As the test-retest reliability in clinicians was not investigated, a direct comparison between reliability of the accelerometric approach and the FTM assessment was not possible.

In this study, the FTM-scale was used as the gold standard for assessing ET severity. As this method relies on measurement by eye, this could explain the imperfect agreement found between accelerometric scores and clinical FTM-ratings. Previous studies showed that visually estimated distances often do not agree with the distances measured objectively [21,24,32,33]. On the other hand, it is argued that the with-in-subject random variability of tremor from moment to moment makes it hard to lower the test-retest reliability of clinical assessments using transducers [16].

Third, the proximal phalanx of the index finger was chosen to measure hand tremor. If clinical raters primarily observe tremor in the more distal region of the index finger, or in a different part of the hand altogether, this will cause discrepancies in the agreement between the FTM and the accelerometric approach. Also, the amplitude of tremor can differ between proximal and distal positions of the hand [1,2,34]. Therefore, it is important to carefully consider possible sensor positions in future research.

Last, when clinicians rate according to the FTM, it is considered whether the tremor is intermittent: mild to moderate tremor may be intermittent (FTM-scores 1 and 2). The tremor intermittency was not incorporated in the accelerometric scoring-algorithm. Together with possible difference in observed tremor amplitude, these aspects might complicate the comparison between sensor-based and clinical assessments. These issues have to be taken into account when further validating this technique, with the goal to monitor tremor more objectively, both in the clinic and in the home setting.

5. Conclusions

This pilot study showed that tremor can be accelerometrically quantified based on healthy thresholds and clinical FTM-criteria. Agreement between clinical FTM-scores and accelerometric scores was substantial. The logarithmic relationship between accelerometric data and FTM-ratings was in line with previous findings. The reported test-retest reliability of the ACC tremor scoring-algorithm indicates that our accelerometry-based approach is a promising one. The proposed technology could be developed further in order to diminish rater-dependency of FTM tremor measurements and enable physicians to monitor patients with ET more objectively, both in various clinical settings, such as intraoperative monitoring, and in the home environment.

References

- [1] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders* 2018;33:75–87. <https://doi.org/10.1002/mds.27121>.
- [2] van der Stouwe AMM, Elting JW, van der Hoeven JH, van Laar T, Leenders KL, Maurits NM, et al. How typical are ‘typical’ tremor characteristics? Sensitivity and specificity of five tremor phenomena. *Parkinsonism Relat Disord* 2016;30:23–8. <https://doi.org/10.1016/j.parkreldis.2016.06.008>.
- [3] Kremer NI, Pauwels RWJ, Pozzi NG, Lange F, Roothans J, Volkmann J, et al. Deep brain stimulation for tremor: Update on long-term outcomes, target considerations and future directions. *J Clin Med* 2021;10. <https://doi.org/10.3390/jcm10163468>.
- [4] Kovács M, Makkos A, Janszky J, Kovács N. Independent validation of the Quality of Life in Essential Tremor Questionnaire (QUEST). *Ideggyogy Sz* 2017;70:193–202. <https://doi.org/10.18071/isz.70.0193>.
- [5] Demiryurek BE. Botulinum Toxin Monotherapy for the Treatment of Essential Tremor: Life Quality Effect. *Clin Neuropharmacol* 2021;44:1–4. <https://doi.org/10.1097/WNF.0000000000000428>.
- [6] Børretzen MN, Bjerknes S, Sæhle T, Skjelland M, Skogseid IM, Toft M, et al. Long-term follow-up of thalamic deep brain stimulation for Essential Tremor - patient satisfaction and mortality. *BMC Neurol* 2014;14. <https://doi.org/10.1186/1471-2377-14-120>.
- [7] Zhang K, Bhatia S, Oh MY, Cohen D, Angle C, Whiting D. Long-term results of thalamic deep brain stimulation for Essential Tremor: Clinical article. *J Neurosurg* 2010;112:1271–6. <https://doi.org/10.3171/2009.10.JNS09371>.
- [8] Fahn S, Tolosa E, Marín C. Clinical Rating Scale for Tremor. *Parkinson's Disease and Movement Disorders* 1988:225–34.
- [9] Stacy MA, Elble RJ, Ondo WG, Wu SC, Hulihan J. Assessment of interrater and intrarater reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in Essential Tremor. *Movement Disorders* 2007;22:833–8. <https://doi.org/10.1002/mds.21412>.
- [10] Krabbe P. *The Measurement of Health and Health Status: Concepts, Methods and Applications from a Multidisciplinary Perspective*. 1st ed. Academic Press; 2016.
- [11] Elble R, Bain P, João Forjaz M, Haubenberger D, Testa C, Goetz CG, et al. Task force report: Scales for screening and evaluating tremor: Critique and recommendations. *Movement Disorders* 2013;28:1793–800. <https://doi.org/10.1002/mds.25648>.
- [12] McGurrian P, McNames J, Wu T, Hallett M, Haubenberger D. Quantifying Tremor in Essential Tremor Using Inertial Sensors—Validation of an Algorithm. *IEEE J Transl Eng Health Med* 2021;9:1–10. <https://doi.org/10.1109/JTEHM.2020.3032924>.
- [13] Zajki-Zechmeister T, Kögl M, Kalsberger K, Franthal S, Homayoon N, Katschnig-Winter P, et al. Quantification of tremor severity with a mobile tremor pen. *Heliyon* 2020;6:e047. <https://doi.org/10.1016/j.heliyon.2020.e04702>.
- [14] Haubenberger D, Abbruzzese G, Bain PG, Bajaj N, Benito-León J, Bhatia KP, et al. Transducer-based evaluation of tremor. *Movement Disorders* 2016;31:1327–36. <https://doi.org/10.1002/mds.26671>.
- [15] Elble RJ, Hellriegel H, Raethjen J, Deuschl G. Assessment of Head Tremor with Accelerometers Versus Gyroscopic Transducers. *Mov Disord Clin Pract* 2017;4:205–11. <https://doi.org/10.1002/mdc3.12379>.
- [16] Elble RJ, Ondo W. Tremor rating scales and laboratory tools for assessing tremor. *J Neurol Sci* 2022;435. <https://doi.org/10.1016/j.jns.2022.120202>.

- [17] Wastensson G, Holmberg B, Johnels B, Barregard L. Quantitative Methods for Evaluating the Efficacy of Thalamic Deep Brain Stimulation in Patients with Essential Tremor and Other Hyperkinetic Movements 2013;4. <https://doi.org/10.7916/D8VM4BoN>.
- [18] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative Quantification of MDS-UPDRS Tremor Measurements Using 3D Accelerometry: A Pilot Study. *J Clin Med* 2022;11:2275. <https://doi.org/10.3390/jcm11092275>.
- [19] Karas M, Bai J, Strączkiewicz M, Harezlak J, Glynn NW, Harris T, et al. Accelerometry Data in Health Research: Challenges and Opportunities: Review and Examples. *Stat Biosci* 2019;11:210–37. <https://doi.org/10.1007/s12561-018-9227-2>.
- [20] Sievänen H, Kujala UM. Accelerometry—Simple, but challenging. *Scand J Med Sci Sports* 2017;27:574–8. <https://doi.org/10.1111/sms.12887>.
- [21] Jeon H, Kim SK, Jeon B, Park KS. Distance estimation from acceleration for quantitative evaluation of Parkinson tremor. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2011*, p. 393–6. <https://doi.org/10.1109/IEMBS.2011.6090126>.
- [22] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [23] Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016;15:155–63. <https://doi.org/10.1016/j.jcm.2016.02.012>.
- [24] Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. *Brain* 2006;129:2660–6. <https://doi.org/10.1093/brain/awl190>.
- [25] McHugh M. Interrater reliability - the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276–82.
- [26] Ranganathan P, Pramesh C, Aggarwal R. Common pitfalls in statistical analysis: Measures of agreement. *Perspect Clin Res* 2017;8:187–91. https://doi.org/10.4103/picr.PICR_123_17.
- [27] Hooper J, Taylor R, Pentland B, Whittle IR. Rater Reliability of Fahn's Tremor Rating Scale in Patients With Multiple Sclerosis. *Arch Phys Med Rehabil* 1998;79:1076–9. [https://doi.org/10.1016/S0003-9993\(98\)90174-5](https://doi.org/10.1016/S0003-9993(98)90174-5).
- [28] Shah A, Coste J, Lemaire JJ, Taub E, Schüpbach WMM, Pollo C, et al. Intraoperative acceleration measurements to quantify improvement in tremor during deep brain stimulation surgery. *Med Biol Eng Comput* 2017;55:845–58. <https://doi.org/10.1007/s11517-016-1559-9>.
- [29] Papapetropoulos S, Gallo B V., Guevara A, Singer C, Mitsi G, Lyssikatos C, et al. Objective tremor registration during DBS surgery for Essential Tremor. *Clin Neurol Neurosurg* 2009;111:376–9. <https://doi.org/10.1016/j.clineuro.2008.10.017>.
- [30] Journee HL, Postma AA, Staal MJ. Intraoperative neurophysiological assessment of disabling symptoms in DBS surgery. *Neurophysiologie Clinique* 2007;37:467–75. <https://doi.org/10.1016/j.neucli.2007.10.006>.
- [31] Kremer NI, Smid A, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, et al. Supine MDS-UPDRS-III Assessment: An Explorative Study. *J Clin Med* 2023;12. <https://doi.org/10.3390/jcm12093108>.
- [32] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative quantification of MDS-UPDRS tremor measurements using 3D accelerometry. *Movement Disorders* 2022;37:S206. <https://doi.org/10.1002/mds.29223>.
- [33] Jeon H, Lee W, Park H, Lee HJ, Kim SK, Kim HB, et al. Automatic classification of tremor severity in Parkinson's Disease using an wearable device. *Sensors (Switzerland)* 2017;17. <https://doi.org/10.3390/s17092067>.
- [34] Chan PY, Ripin ZM, Halim SA, Arifin WN, Yahya AS, Eow GB, et al. Motion characteristics of subclinical tremors in Parkinson's Disease and normal subjects. *Sci Rep* 2022;12. <https://doi.org/10.1038/s41598-022-07957-z>.



Chapter 7

The relevance of intraoperative clinical and accelerometric measurements for thalamotomy outcome

Annemarie Smid

D. L. Marinus Oterdoom

Rik W. J. Pauwels

Katalin Tamasi

Jan Willem J. Elting

Anthony R. Absalom

Teus van Laar

J. Marc C. van Dijk

Gea Drost

Journal of Clinical Medicine (2023)

doi: 10.3390/jcm12185887

Abstract

Thalamotomy alleviates medication-refractory tremor in patients with movement disorders such as Parkinson's Disease (PD), Essential Tremor (ET) and Holmes tremor (HT). However, limited data is available on tremor intensity during different thalamotomy stages. Also, the predictive value of intraoperative tremor status for treatment outcome remains unclear. Therefore, we aimed to quantify tremor status during thalamotomy, and postoperatively. Data were gathered between January 2020 and June 2023 during consecutive unilateral thalamotomy procedures in patients with PD (n=13), ET (n=8) and HT (n=3). Movement Disorder Society Unified PD Rating Scale part III (MDS-UPDRS-III) scores and tri-axial accelerometry data were obtained during rest, postural, and intention tremor tests. Measurements were performed intraoperatively (1) before lesioning-probe insertion, (2) directly after lesioning-probe insertion, (3) during coagulation, (4) directly after coagulation, and (5) 4–6 months post-surgery. Accelerometric data were recorded continuously during the coagulation process. Outcome measures included MDS-UPDRS-III tremor scores and accelerometric parameters (peak frequency, tremor amplitude, and area under the curve of power (AUCP)). Tremor intensity was assessed for the insertion effect (1-2), during coagulation (3), post-coagulation effect (1-4), and postoperative effect (1-5). Following insertion and coagulation, tremor intensity improved significantly compared to baseline ($p<0.001$). The insertion effect clearly correlated with the postoperative effect ($\rho=0.863$, $p<0.001$). Both tremor amplitude and AUCP declined gradually during coagulation. Peak frequency did not change significantly intraoperatively. In conclusion, the study data show that both the intraoperative insertion effect and the post-coagulation effect are good predictors for thalamotomy outcome.

1. Introduction

The most common movement disorders with disabling tremor are Parkinson's Disease (PD), Essential Tremor (ET) and Holmes Tremor (HT) [1,2]. Tremor in PD is generally observed in the extremities at rest (4–7 Hz) [3–6]. ET is a monosymptomatic disease, predominated by bilateral action tremor (4–7 Hz) [2,6,7]. Patients with HT suffer from rest, postural, and intention tremor due to low-frequency proximal and distal muscle contraction (<5 Hz) [2,8].

If disabling tremor cannot be suppressed with medication, then a thalamotomy, involving radiofrequency (RF) ablation of the thalamic ventral intermediate nucleus (VIM), is an effective treatment option [9–21]. Thalamotomies are generally performed unilaterally, since bilateral procedures have increased risk of speech and balance impairments [22,23]. Surgery is generally performed under local anesthesia in awake conditions, in order to judge the intraoperative tremor improvement and to minimize side effects. The ever-changing environment in which newer methods of lesioning or ablating the VIM are performed, such as Magnetic Resonance Guided Focused Ultrasound (MRgFUS) [24,25] and Gamma Knife thalamotomy [26], also poses a challenge for the intraoperative monitoring of tremor. Although there are few thalamotomy-related reports on the relevance of intraoperative tremor measurements, the effects measured intraoperatively are hypothesized to predict thalamotomy outcome.

After insertion of a RF-lesioning probe in the target area and before heating or stimulation of the tip, immediate tremor alleviation can be observed during surgery: the insertion effect or microlesion effect [27]. In this article, the term 'insertion effect' (IE) is maintained. It is postulated that occurrence of the IE indicates accurate placement of the RF-lesioning probe within the VIM, underlining the need to adequately monitor tremor intensity intraoperatively [27,28]. As soon as a permanent lesion is inflicted, tremor suppression is immediately observed [21]. This is called the 'post-coagulation effect' (PCE).

There are several methods to monitor tremor intensity [27–29]. Clinical scales (e.g., Movement Disorder Society Unified PD Rating Scale part III [MDS-UPDRS-III]) are often used to assess surgical results [30,31]. However, although the MDS-UPDRS-III is a standardized scoring system, results can vary based on the experience of the rater [31–35]. Sensor-based measurements, like tri-axial accelerometry, allow for objective and continuous quantification of tremor intensity [34,36,37]. Several studies have demonstrated that accelerometry can complement clinical assessment during neurosurgery, aiding clinicians in uniformly assessing tremor [38–41].

Although studies have focused on clinical results and side effects of thalamotomy, there is little data available on the neurophysiological aspects [21,22,42]. Also, there is no consensus on how the IE and PCE relate to the postoperative effect (PE) of unilateral thalamotomy. Therefore, this study focuses on accelerometry measurements during all surgical stages of RF-thalamotomy, including tremor severity in the postoperative phase. The novelty of this work lies in the quantification of tremor intensity during all surgical stages of thalamotomy, based on clinical assessment and accelerometry. The aim of this study is to quantify the clinical changes in tremor during the different stages of thalamotomy using both the MDS-UPDRS-III and tri-axial accelerometry. Secondly,

we aim to investigate the relationship between intraoperative findings and clinical outcome. Lastly, our aim is to investigate the correlation between clinical assessments and accelerometric outcome measures.

2. Materials and methods

This observational study was conducted at the neurosurgical department of the University Medical Center Groningen (UMCG), The Netherlands. The local medical ethics review committee judged that the study does not fall within the remit of the Dutch ‘Research involving human subjects Act’. The study was performed in compliance with the Helsinki Declaration for research on human beings. All participants provided written informed consent for the use of their data.

2.1. Study participants

Data were gathered between January 2020 and June 2023 from consecutive patients with an indication for unilateral RF-thalamotomy. In patients with PD, diagnosis was established according to the UK Brain Bank criteria [43]. For those with ET and HT, the diagnosis was made by movement disorders neurologists, confirmed with a video-assisted surface-EMG accelerometric tremor registration [6]. The treatment plan was discussed and established in a multidisciplinary meeting before inclusion of the study for all participants.

2.2. Surgical procedure

Participants were withheld tremor-suppressing medication for at least 12 hours prior to the thalamotomy. Anesthesia administration, frame placement, and target identification were performed as described by Lange and Kremer et al. [28]. In short, the VIM was accessed by penetrating the brain using a bipolar RF probe (TCB013 RF TC Brain Electrode 2x2mm, Inomed Medizintechnik GmbH, Emmendingen, Germany) via a cranial burr hole. Prior to inserting the bipolar RF electrode, baseline tremor intensity of the contralateral arm (relative to the hemisphere being treated) was evaluated (see section 2.4). Directly after insertion of the electrode in the target, the same evaluations were performed to assess the IE. When an acceptable position was found, the electrode tip was heated to 90°C for 60 seconds by an Inomed Neuro N50 lesion generator. Directly after coagulation, the tremor evaluations were performed once more. Until improvement in tremor was deemed satisfactory, the electrode was repositioned, and the subsequent steps were repeated.

2.3. Materials

A tri-axial accelerometer (MMA8452Q tri-Axis, Freescale Semiconductor, Inc.) with a sampling rate of 200 Hz and range of $\pm 2g$ was used. The sensor was secured in a

custom-built non-conductive plastic case, and attached to the proximal phalanx of the contralateral index finger (relative to the treated hemisphere) with an adjustable silicon strap (Figure 1) [38].

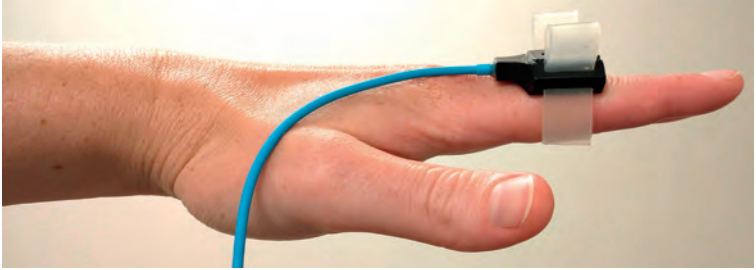


Figure 1. Accelerometer positioned at the left index finger.

Accelerometric data were recorded in LabVIEW v. 2017 (National Instruments, Texas, USA) [38]. Signal analysis was performed in MATLAB v. 2022b (MathWorks, Massachusetts, USA). Statistical analysis was performed in IBM SPSS statistics v. 26 (International Business Machines Corporation, New York, USA). MDS-UPDRS-III items 3.15–3.17 were used for assessment of participants [44].

2.4. Measurements

All measurements were performed with the participant awake and in supine position [38]. Tremor severity was assessed with three tremor tests: postural (arm stretched out), intention (finger-to-nose maneuver) and at rest. Accelerometric data were recorded during these tremor tests, while a movement disorders neurologist simultaneously assessed MDS-UPDRS-III scores.

Measurements were performed: (1) before lesioning probe insertion, (2) after lesioning probe insertion, (3) during coagulation, (4) after coagulation, and (5) at 4–6 months follow-up (Figure 2). The three tremor tests were performed at step 1, 2, 4 and 5. Step 1 to 4 were repeated until improvement in tremor was deemed satisfactory. Accelerometric data were recorded continuously during coagulation (Figure 2).

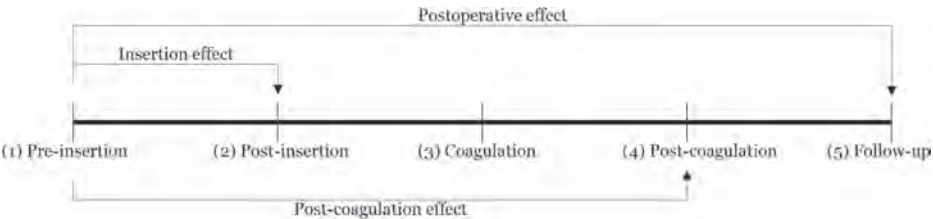


Figure 2. Tremor severity was measured at five time points to assess the IE, the PCE and the PE: 1) pre-insertion and 2) post-insertion of the lesioning probe, 3) during coagulation, 4) directly after coagulation during surgery, and 5) 4–6 months follow-up.

For each outcome measure, the sum of the values of the three tremor tests at that measurement moment was used for analysis. The three different effects that were calculated for each type of summed outcome measure (SOM) were defined as follows. The insertion effect (IE) was defined as the SOM just prior to insertion of the lesioning probe (1) minus the SOM immediately post-insertion (2). The post-coagulation effect (PCE) was defined as the pre-insertion SOM (1) minus the SOM directly after coagulation (4). The postoperative effect (PE) was defined as the pre-insertion SOM (1) minus the SOM at follow-up (5), see Figure 2.

It is hypothesized that both IE and PCE correlate with PE, for both MDS-UPDRS-III and accelerometric SOM. Secondary, it is hypothesized that MDS-UPDRS-III tremor scores correlate with accelerometric outcome measures.

2.5. Accelerometric measures

Accelerometric data pre-processing was performed as described previously [38]. To assess postural, intention, and rest tremor, three outcome measures were calculated from the accelerometry data per respective test: (1) dominant frequency; (2) maximal amplitude; (3) area under the curve of power within the tremor frequency band (AUCP) [38]. The tremor frequency band was defined as 4–7 Hz for PD and ET, and 2–5 Hz for HT, based on the frequencies found during preoperative recordings.

To determine the power of the acceleration norm (cm/s^2), the periodogram power spectral density (PSD) estimate was calculated [45]. Via trapezoidal numerical integration, the AUCP in the 2–5 Hz and 4–7 Hz frequency band was calculated from this periodogram. The dominant or peak frequency was defined as the frequency with the highest power value. For the calculation of the mean tremor amplitude, the mean of all peaks in the absolute amplitude vector were determined. This mean was multiplied by two in order to calculate the mean tremor amplitude [38].

2.6. Statistical analysis

The main outcome measures used for the statistical analyses were MDS-UPDRS-III tremor sum-score, summed amplitude, and summed AUCP. Based on visual inspection of the histograms of the outcome variables, nonparametric tests were used for all analyses. The alpha level was determined to be 5%. Wilcoxon signed-rank test was used to analyze the IE, PCE and PE (Figure 2). Spearman's rank correlation coefficient (Spearman's ρ) was used to calculate the strength of association between the IE and PE, and between the PCE and PE. Spearman's ρ was also applied to calculate the correlation between the MDS-UPDRS-III scores and accelerometric amplitude, and between the MDS-UPDRS-III scores and AUCP of each tremor test.

3. Results

A group of 22 patients (15 men, 7 women; age 69.9 ± 11.3 years) were included. Data were gathered from 13 surgeries in 13 patients with PD, eight surgeries in seven patients with ET (one re-operation after 11 months) and three surgeries in two patients with HT (one re-operation after 14 months). In 17 out of 24 procedures, a single coagulation attempt was sufficient for a satisfactory effect on tremor severity (Table 1).

Table 1. Demographics.

Demographic	Total population	PD	ET	HT
Gender (percentage)	Male: 15 (68.2%) Female: 7 (31.8%)	Male: 9 (69.2%) Female: 4 (30.8%)	Male: 4 (57.1%) Female: 3 (42.9%)	Male: 2 (100.0%) Female: 0 (0.0%)
Mean (SD) age (years)	69.9 (11.3)	70.8 (8.4)	76.0 (5.2)	49.0 (10.4)
Mean (SD) disease duration (years)	8.4 (5.0)	7.9 (4.1)	11.4 (6.4)	4.4 (0.7)
Mean (SD) follow-up (months)	5.4 (1.1)	5.5 (0.9)	4.9 (1.1)	6.4 (1.2)
Treated hemisphere (percentage)	Right: 10 (45.5%) Left: 12 (54.5%)	Right: 5 (38.5%) Left: 8 (61.5%)	Right: 3 (42.9%) Left: 4 (57.1%)	Right: 2 (100.0%) Left: 0 (0.0%)
Number of coagulation attempts (SD)	1.4 (0.7)	1.1 (0.3)	1.6 (0.9)	2.3 (0.6)

3.1. Quantification of changes during thalamotomy stages

Post-insertion MDS-UPDRS-III tremor sum-scores were significantly lower when compared to pre-insertion: 5 (1–11) vs. 2 (0–8) [$p < 0.001$]. The pre-insertion MDS-UPDRS-III sum-scores were significantly higher than the post-coagulation sum-scores, from 5 (1–11) to 0 (0–6) [$p < 0.001$]. A significant decrease was found in the postoperative MDS-UPDRS-III sum-scores compared to the pre-insertion sum-scores, from 5 (1–11) to 0 (0–6) [$p < 0.001$] (Figure 3a).

The summed tremor amplitude at pre-insertion was significantly higher when compared to post-insertion: 5 (0–61) cm vs. 1 (0–58) cm [$p < 0.001$]. The pre-insertion summed amplitude was also significantly higher than at post-coagulation, from 5 (0–61) cm to 0 (0–30) cm [$p < 0.001$]. A significant decrease was found in the postoperative summed amplitude compared to pre-insertion, from 5 (0–61) cm to 1 (0–9) cm [$p < 0.001$] (Figure 3b).

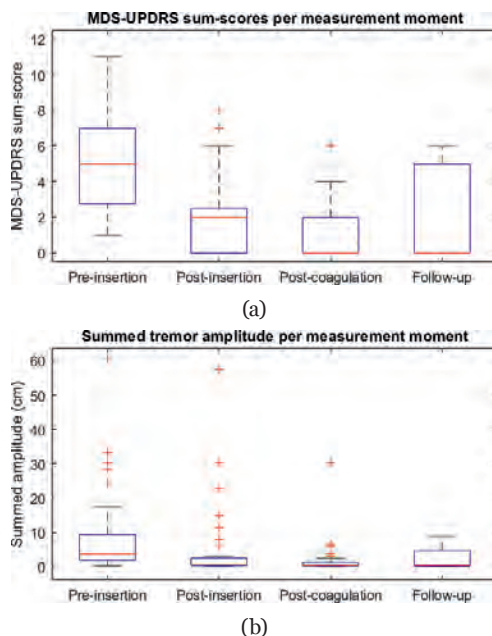


Figure 3. Boxplots with median and interquartile range for (a) MDS-UPDRS-III tremor sum-scores and (b) summed tremor amplitude, at pre-insertion, post-insertion, post-coagulation and follow-up for all participants.

The MDS-UPDRS-III tremor sum-score data per measurement moment of Figure 3a are given separately for each patient group in figure 4a.

For the PD group, post-insertion MDS-UPDRS-III sum-scores were significantly lower when compared to pre-insertion: 6 (1–10) vs. 0 (0–2) [$p < 0.001$]. The pre-insertion MDS-UPDRS-III sum-scores of the PD group were significantly higher than the post-coagulation sum-scores, from 6 (1–10) to 0 (0–1) [$p < 0.001$]. A significant decrease was found in the postoperative MDS-UPDRS-III sum-scores compared to the pre-insertion sum-scores of the PD group, from 6 (1–10) to 0 (0–3) [$p < 0.001$] (Figure 4a).

In the ET group, MDS-UPDRS-III sum-scores significantly decreased from 3 (2–11) pre-insertion to 2 (0–7) post-insertion [$p = 0.018$]. The pre-insertion MDS-UPDRS-III sum-scores of the ET group were also significantly higher than the post-coagulation sum-scores, from 3 (2–11) to 0 (0–4) [$p = 0.003$]. The pre-insertion summed amplitude of the ET group decreased from 3 (2–11) to 0 (0–6) postoperatively, although this decrease was not significant [$p = 0.387$] (Figure 4a).

The post-insertion MDS-UPDRS-III sum-scores of the HT group were lower than at pre-insertion: 6 (2–11) vs. 6 (2–8) [$p = 0.109$]. The pre-insertion MDS-UPDRS-III sum-scores decreased significantly from 6 (2–11) to 4 (0–6) [$p = 0.024$] post-coagulation. The decrease in MDS-UPDRS-III sum-scores at pre-insertion from 6 (2–11) to 5 (5–6) [$p = 0.288$] postoperatively was not significant (Figure 4a).

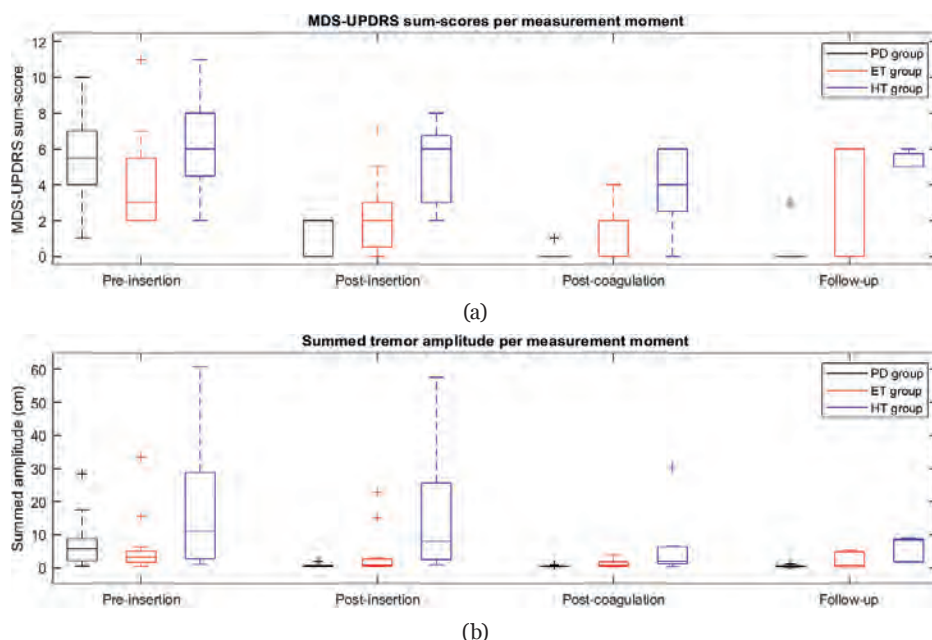


Figure 4. Boxplots with median and interquartile range for (a) MDS-UPDRS-III tremor sum-scores and (b) summed tremor amplitude at pre-insertion, post-insertion, post-coagulation and follow-up for each group (PD group in black, ET group in red, HT group in blue).

In Figure 4b, the summed tremor amplitude data per measurement moment of Figure 3b are given separately for each patient group.

The summed tremor amplitude of the PD group at pre-insertion was significantly higher when compared to post-insertion: 6 (0–28) cm vs. 0 (0–2) cm [$p < 0.001$]. The pre-insertion summed amplitude was also significantly higher than at post-coagulation, from 6 (0–28) cm to 0 (0–1) cm [$p < 0.001$]. A significant decrease was found in the postoperative summed amplitude compared to pre-insertion, from 6 (0–28) cm to 0 (0–1) cm [$p < 0.001$] (Figure 4b).

In the ET group, the summed amplitude significantly decreased from 3 (0–33) cm pre-insertion to 1 (0–23) cm post-insertion [$p = 0.002$]. The pre-insertion summed amplitude of the ET group was also significantly higher than the post-coagulation amplitude, from 3 (0–33) cm to 1 (0–4) cm [$p = 0.002$]. The pre-insertion summed amplitude of the ET group decreased from 3 (0–33) cm to 1 (0–5) cm postoperatively, although this decrease was not significant [$p = 0.209$] (Figure 4b).

The summed tremor amplitude of the HT group at pre-insertion was higher than at post-insertion: 11 (1–61) cm vs. 8 (1–58) cm [$p = 0.075$]. The post-coagulation summed amplitude of the HT group was significantly lower than that at pre-insertion: 11 (1–61) cm vs. 2 (0–30) cm [$p = 0.018$]. The decrease in summed amplitude from 11 (1–61) cm at pre-insertion to 8 (2–9) cm postoperative was not significant [$p = 0.237$] (Figure 4b).

3.1.1. During coagulation

Tremor amplitude and AUCP declined gradually during coagulation in all patients (Figure 5). The amplitudes at $t=10s$ were significantly higher compared to $t=60s$, from 2 (0–13) cm to 0 (0–6) cm [$p<0.001$]. AUCP at $t=60s$ decreased significantly compared to AUCP at $t=10s$, from 5182 (cm/s^2)² (55–484986) to 173 (cm/s^2)² (10–30474) [$p<0.001$]. Peak frequency did not change significantly during the coagulation process, from 3 (1–6) Hz to 3 (1–7) Hz [$p>0.05$].

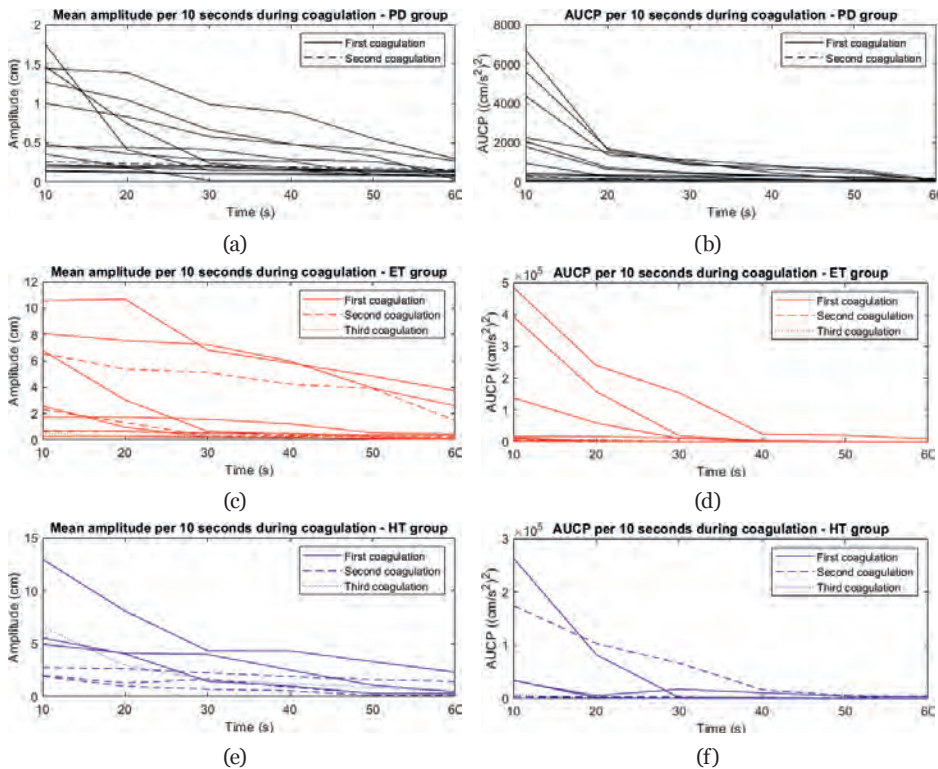


Figure 5. The mean amplitude per 10 seconds (a, c, e) and AUCP per 10 seconds (b, d, f) during the 60-second coagulation process, given for the PD group (a, b), ET group (c, d) and HT group (e, f).

For the PD group, the amplitudes at $t=10s$ were significantly higher compared to $t=60s$, from 1 (0–2) cm to 0 (0–0) cm [$p<0.001$]. AUCP at $t=60s$ decreased significantly compared to AUCP at $t=10s$ in the PD group, from 705 (cm/s^2)² (55–6719) to 51 (cm/s^2)² (10–173) [$p<0.001$].

The amplitudes in the ET group at $t=10s$ were significantly higher compared to $t=60s$, from 2 (0–11) cm to 0 (0–4) cm [$p<0.001$]. AUCP of the ET group at $t=60s$ decreased significantly compared to AUCP at $t=10s$, from 11382 (cm/s^2)² (329–484986) to 295 (cm/s^2)² (101–9513) [$p<0.001$].

For the HT group, the amplitudes at $t=10s$ were significantly higher compared to $t=60s$, from 5 (2–13) cm to 0 (0–2) cm [$p<0.001$]. AUCP at $t=60s$ decreased significantly compared to AUCP at $t=10s$ in the HT group, from 33360 (cm/s²)² (867–263567) to 772 (cm/s²)² (172–5301) [$p<0.001$].

3.2. Relation between intraoperative findings and outcome

The IE was found to be significantly associated with PE for all outcome measures [Spearman's $\rho>0.690$; $p<0.001$] (Table 2). This was also the case for correlation between the PCE and PE [Spearman's $\rho>0.918$; $p<0.001$] (Table 3). The MDS-UPDRS-III tremor sum-scores and summed amplitude of the IE and PE were plotted per patient group and number of the coagulation attempts in Figure 6. The MDS-UPDRS-III sum-scores and summed amplitude of the PCE and PE per patient group and number of the coagulation attempts are shown in Figure 7.

Table 2. Spearman's correlation between Insertion Effect and Postoperative Effect.

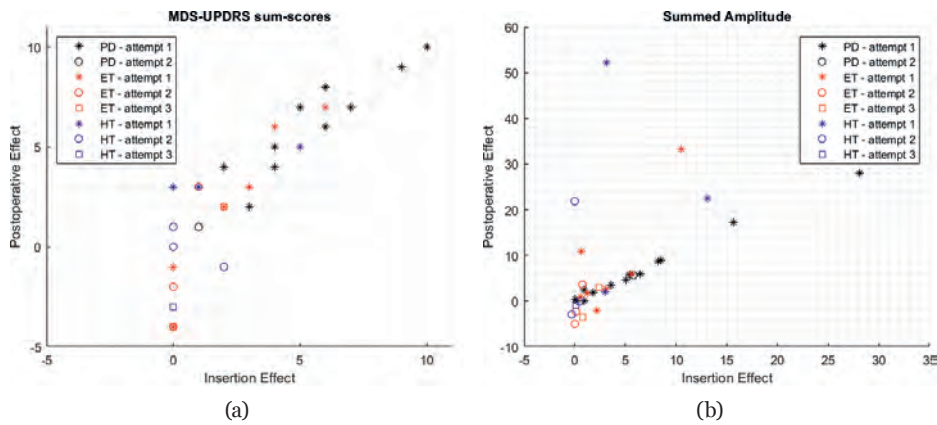
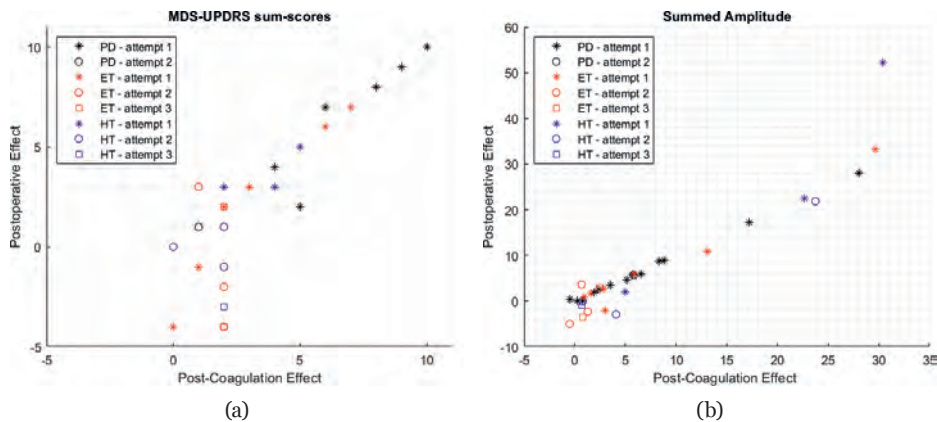
Coagulation attempt	Outcome measure	Spearman's ρ	R ²	95% CI	<i>p</i>
Only first attempts	MDS-UPDRS-III sum-scores	0.863	0.745	0.693, 0.942	<0.001
	Summed AUCP	0.975	0.951	0.940, 0.990	<0.001
	Summed Amplitude	0.690	0.476	0.377, 0.861	<0.001
Only final attempts	MDS-UPDRS-III sum-scores	0.967	0.934	0.920, 0.986	<0.001
	Summed AUCP	0.898	0.807	0.766, 0.957	<0.001
	Summed Amplitude	0.783	0.612	0.538, 0.906	<0.001

Table 3. Spearman's correlation between Post-Coagulation Effect and Postoperative Effect.

Coagulation attempt	Outcome measure	Spearman's ρ	R ²	95% CI	<i>p</i>
Only first attempts	MDS-UPDRS-III sum-scores	0.950	0.903	0.882, 0.980	<0.001
	Summed AUCP	0.936	0.876	0.849, 0.973	<0.001
	Summed Amplitude	0.982	0.965	0.957, 0.993	<0.001
Only final attempts	MDS-UPDRS-III sum-scores	0.934	0.873	0.846, 0.973	<0.001
	Summed AUCP	0.955	0.911	0.892, 0.981	<0.001
	Summed Amplitude	0.918	0.843	0.809, 0.966	<0.001

Table 4. Spearman's correlation between the MDS-UPDRS-III scores and the accelerometric outcome measures for each type of tremor test.

Outcome measure	Tremor condition	Spearman's ρ	R^2	95% CI	p
Mean amplitude	Rest tremor	0.706	0.498	0.605, 0.784	<0.001
	Postural tremor	0.867	0.751	0.815, 0.905	<0.001
	Intention tremor	0.811	0.657	0.740, 0.863	<0.001
	All combined	0.815	0.664	0.775, 0.848	<0.001
AUCP	Rest tremor	0.714	0.510	0.616, 0.791	<0.001
	Postural tremor	0.903	0.815	0.864, 0.931	<0.001
	Intention tremor	0.731	0.535	0.638, 0.804	<0.001
	All combined	0.812	0.659	0.772, 0.845	<0.001

**Figure 6.** The correlation between Insertion Effect and Postoperative Effect for the MDS-UPDRS-III tremor sum-scores (a) and summed tremor amplitude (b), given for each group (PD group in black, ET group in red, HT group in blue).**Figure 7.** The correlation between Post-Coagulation Effect and Postoperative Effect for the MDS-UPDRS-III tremor sum-scores (a) and summed tremor amplitude (b), given for each group (PD group in black, ET group in red, HT group in blue).

3.3. Correlation between clinical and accelerometric measures

The MDS-UPDRS-III tremor scores of the individual tremor tests correlated significantly with accelerometric amplitude [Spearman's $\rho > 0.706$; $p < 0.001$]. These results were also significant for the correlation between MDS-UPDRS-III scores and AUCP for the individual tremor tests [Spearman's $\rho > 0.714$; $p < 0.001$] (Table 4).

4. Discussion

In this study, accelerometric and clinical tremor assessments were performed during various stages of unilateral RF-thalamotomy in patients with PD, ET and HT. Postoperative tremor intensity after unilateral thalamotomy was also studied. The aim of this research was to quantify changes in tremor intensity during surgery, and to evaluate the relationship between intraoperative findings and clinical outcome.

This study shows that tri-axial accelerometry can objectively quantify intraoperative treatment effects during RF-thalamotomy. Tri-axial accelerometry showed that tremor amplitude and AUCP declined gradually during the coagulation process and that peak frequency did not change significantly during the surgical procedure. Also, IE and PCE significantly correlated with the PE at follow-up, as shown by both MDS-UPDRS-III ratings and accelerometric assessment. The main contribution of this study is that accelerometric measurements can provide standardized and objective input for clinical decision-making during thalamotomy. Moreover, accelerometry can be performed real-time during the coagulation process to show the change in tremor intensity.

Both tremor amplitude and AUCP declined gradually during the coagulation process, but peak frequency did not change significantly. These findings suggest that the activity of the fundamental tremor generator changes with lesioning, and probably not the generator itself. Previously, Earhart et al. reported that tremor frequency did not change with changes in Deep Brain Stimulation (DBS) of the VIM [46]. Other studies have shown that neuronal firing is inhibited during VIM-DBS [47,48], which might explain why tremor amplitude and not tremor frequency is reduced.

The IE and PCE evaluated in this study were consistent with previously reported findings [10–12,27,28,38,39,49]. It is generally thought that IE can predict outcome of stereotactic surgery [27,28,50,51]. The results of this study suggest that a strong IE predicts successful tremor suppression postoperatively. Concurrently, these data indicate that the absence of both the IE and PCE predicts no change in tremor intensity after surgery. Therefore, these results suggest that the IE and PCE should be taken into account during intraoperative clinical decision-making for replacement of the lesioning probe.

The high correlation between the IE and the PE in this study can be explained by the use of accelerometry-based outcome measures. For example, a Spearman's ρ up to 0.975 was found in the AUCP outcome measure. Accelerometric measurements allow for continuous outcome measures, in contrast to discrete ordinal scales like the MDS-UPDRS-III. Another explanation for differences in correlation between IE and PE might be that earlier research was performed in patients undergoing DBS [27,28,50,51].

The strength of the correlations between IE and PE, and between PCE and PE differed amongst the three patient groups and the number of coagulation attempt, as can be seen in Figures 6 and 7. The relationship between IE and PE, and between PCE and PE seemed to be stronger for the PD group, compared to the ET group and HT group, as can be seen in Figures 6 and 7. No conclusions can be based on these findings as the study was not designed or powered to investigate these differences, and the small sizes of the subgroups precluded further testing of the statistical significance of these differences.

The results of this study suggest that RF-thalamotomy is an effective treatment in patients with unilateral tremor. At the same time, the medical field is evolving with alternative procedures like MRgFUS [24,25] and Gamma Knife thalamotomy [26]. These new interventions require an operative setting (e.g., MRI-scanner, radioactive environment) that does not allow real-time intraoperative clinical assessment by a neurologist. Accelerometry offers a solution, providing reliable and objective measures for clinical decision-making during surgery [38,39,52]. This is supported by Baek et al., who found that accelerometry can be used for determining the location and number of MRgFUS targets to achieve optimal tremor reduction [53].

Apart from the fact that accelerometry provides rater-independent measurements, standardized accelerometric measures can settle the current uncertainty on the outcome of tremor treatment. Other benefits of this technique are that it is widely available and inexpensive (purchase costs 10US\$~30US\$), and analysis is easy and straightforward [37,38,52,54]. Also, this low-power technology does not involve disposable parts and has an estimated lifespan of at least ten years, making it a sustainable measurement method [55,56].

4.1. Limitations

Due to the surgical setting with restricted freedom of movement for the patient, it was not possible to perform a full MDS-UPDRS-III assessment. Instead, only tremor items that the treatment aimed to improve were used for the measurements. Also, the results of the intraoperative measurements could have been influenced by stress, fatigue, or sedative medication effects during the surgery.

Second, all consecutive patients undergoing thalamotomy between January 2020 and June 2023 were included, even patients in whom multiple lesions were made. This might have caused discrepancies in our results, as the IE of the first attempt may have influenced the effect of the subsequent attempt. For this reason, outcomes of the first and final attempt have been reported separately. This provides insight into how both results relate to the clinical outcome.

5. Conclusions

This study shows that tremor amplitude and AUCP both declined gradually during the coagulation process and that peak frequency did not change significantly during the procedures. It was also shown that both the insertion effect and the post-coagulation effect are good predictors for thalamotomy outcome. The MDS-UPDRS-III scores of the individual tremor tests correlated significantly with the accelerometric outcome measures. Accelerometric monitoring of tremor allows the objective quantification of these intraoperative parameters, reducing the dependency on experienced raters for reliable clinical assessments.

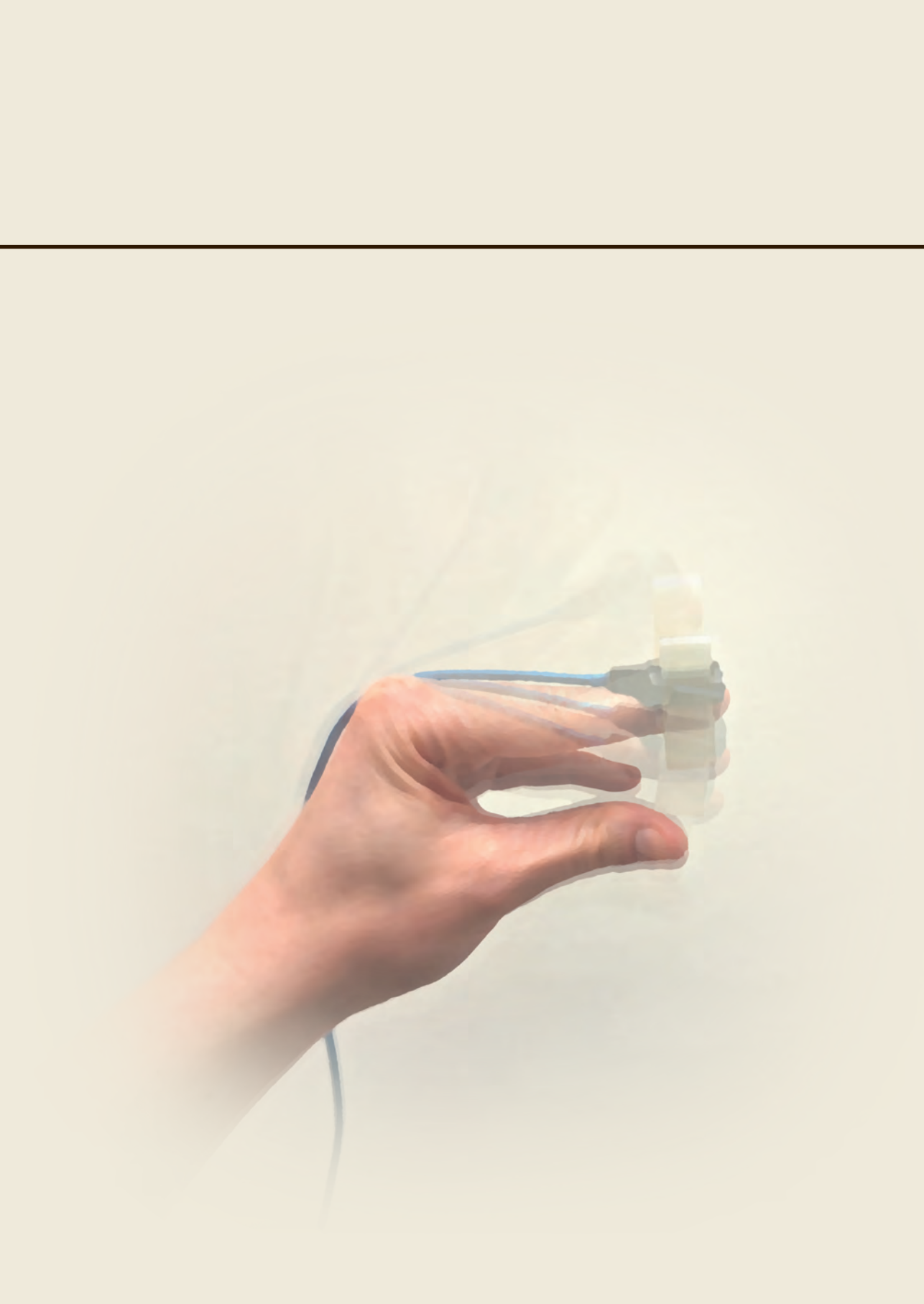
References

- [1] Jankovic J, Fahn S. Physiologic and Pathologic Tremors - Diagnosis, mechanism, and management. *Ann Intern Med* 1980;93:460–5. <https://doi.org/10.7326/0003-4819-93-3-460>.
- [2] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders* 2018;33:75–87. <https://doi.org/10.1002/mds.27121>.
- [3] Jankovic J. Parkinson's Disease: Clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79:368–76. <https://doi.org/10.1136/jnnp.2007.131045>.
- [4] Vaillancourt DE, Newell KM. The dynamics of resting and postural tremor in Parkinson's Disease. *Clinical Neurophysiology* 2000;111:2046–56.
- [5] Kalia L, Lang AE. Parkinson's Disease. *The Lancet* 2015;386:896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3).
- [6] van der Stouwe AMM, Elting JW, van der Hoeven JH, van Laar T, Leenders KL, Maurits NM, et al. How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena. *Parkinsonism Relat Disord* 2016;30:23–8. <https://doi.org/10.1016/j.parkreldis.2016.06.008>.
- [7] van de Wardt J, van der Stouwe AMM, Dirks M, Elting JWJ, Post B, Tijssen MAJ, et al. Systematic clinical approach for diagnosing upper limb tremor. *J Neurol Neurosurg Psychiatry* 2020;91:822–30. <https://doi.org/10.1136/jnnp-2019-322676>.
- [8] Kim MC, Son BCW, Miyagi Y, Kang JK. Vim thalamotomy for Holmes' tremor secondary to midbrain tumour. *J Neurol Neurosurg Psychiatry* 2002;73:453–5. <https://doi.org/10.1136/jnnp.73.4.453>.
- [9] Pauwels RWJ, Oterdoom DLM, Drost G, van Laar T, van Dijk JMC. Long-Term Patient-Reported Outcome of Radiofrequency Thalamotomy for Tremor. *Stereotact Funct Neurosurg* 2020;98:187–92. <https://doi.org/10.1159/000506999>.
- [10] Jankovic J, Cardoso F, Grossman RG, Hamilton WJ. Outcome after Stereotactic Thalamotomy for Parkinsonian, Essential, and Other Types of Tremor. *Neurosurgery* 1995;37:680–7. <https://doi.org/10.1227/00006123-199510000-00011>.
- [11] Fox MW, Ahlskog JE, Kelly PJ. Stereotactic ventrolateralis thalamotomy for medically refractory tremor in post-levodopa era Parkinson's Disease patients. *J Neurosurg* 1991;75:723–30. <https://doi.org/10.3171/jns.1991.75.5.723>.
- [12] Akbostanci MC, Slavin KV, Burchiel KJ. Stereotactic Ventral Intermedial Thalamotomy for the Treatment of Essential Tremor: Results of a Series of 37 Patients. *Stereotact Funct Neurosurg* 1999;72:174–7. <https://doi.org/10.1159/000029722>.
- [13] Hassler R, Riechert T. Indikationen und lokalisationsmethode der gezielten hiernoperationen. *Nervenarzt* 1954;25:441–7.
- [14] Tripathi M, Mehta S, Singla R, Ahuja CK, Tandalya N, Tuleasca C, et al. Vim stereotactic radiosurgical thalamotomy for drug-resistant idiopathic Holmes tremor: a case report. *Acta Neurochir (Wien)* 2021;163:1867–71. <https://doi.org/10.1007/s00701-020-04489-1>.
- [15] Hopfner F, Deuschl G. Managing Essential Tremor. *Neurotherapeutics* 2020;17:1603–21. <https://doi.org/10.1007/s13311-020-00899-2>.
- [16] Ferreira JJ, Mestre TA, Lyons KE, Benito-León J, Tan EK, Abbruzzese G, et al. MDS evidence-based review of treatments for Essential Tremor. *Movement Disorders* 2019;34:950–8. <https://doi.org/10.1002/mds.27700>.
- [17] Martínez-Moreno NE, Sahgal A, De Salles A, Hayashi M, Levivier M, Ma L, et al. Stereotactic radiosurgery for tremor: Systematic review. *J Neurosurg* 2019;130:589–600. <https://doi.org/10.3171/2017.8.JNS17749>.

- [18] Espay AJ, Mandybur GT, Revilla FJ. Surgical Treatment of Movement Disorders. *Clin Geriatr Med* 2006;22:813–25. <https://doi.org/10.1016/j.cger.2006.06.002>.
- [19] Shahzadi S, Tasker RR, Lozano A. Thalamotomy for Essential and Cerebellar Tremor. *Stereotact Funct Neurosurg* 1995;65:11–7. <https://doi.org/10.1159/000098890>.
- [20] Schuurman PR, Bosch DA, Bossuyt PMM, Bonsel GJ, van Someren EJW, de Bie RMA, et al. A Comparison of Continuous Thalamic Stimulation and Thalamotomy for Suppression of Severe Tremor. *New England Journal of Medicine* 2000;342:461–8. <https://doi.org/10.1056/NEJM200002173420703>.
- [21] Dallapiazza RF, Lee DJ, De Vloo P, Fomenko A, Hamani C, Hodaie M, et al. Outcomes from stereotactic surgery for Essential Tremor. *J Neurol Neurosurg Psychiatry* 2019;90:474–82. <https://doi.org/10.1136/jnnp-2018-318240>.
- [22] Bruce BB, Foote KD, Rosenbek J, Sapienza C, Romrell J, Crucian G, et al. Aphasia and thalamotomy: Important issues. *Stereotact Funct Neurosurg* 2004;82:186–90. <https://doi.org/10.1159/000082207>.
- [23] Alshaikh J, Fishman PS. Revisiting bilateral thalamotomy for tremor. *Clin Neurol Neurosurg* 2017;158:103–7.
- [24] Pooja NA, Pahuja SK, Veer K. Significance of MRI Guided Focused Ultrasound Thalamotomy for Parkinson's Disease: A Review. *Current Medical Imaging Formerly Current Medical Imaging Reviews* 2021;17:714–9. <https://doi.org/10.2174/1573405616666201223142505>.
- [25] Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *New England Journal of Medicine* 2016;375:730–9. <https://doi.org/10.1056/NEJMoa1600159>.
- [26] Ohye C, Shibasaki T, Sato S. Gamma knife thalamotomy for movement disorders: evaluation of the thalamic lesion and clinical results. *J Neurosurg* 2005;102:234–40. https://doi.org/10.3171/jns.2005.102.s_supplement.0234.
- [27] Tykocki T, Nauman P, Koziara H, Mandat T. Microlesion Effect as a Predictor of the Effectiveness of Subthalamic Deep Brain Stimulation for Parkinson's Disease. *Stereotact Funct Neurosurg* 2013;91:12–7. <https://doi.org/10.1159/000342161>.
- [28] Lange SF, Kremer NI, van Laar T, Lange F, Steendam-Oldekamp TE, Oterdoom DLM, et al. The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation: Technology at the Neural Interface* 2021;ner.13523. <https://doi.org/10.1111/ner.13523>.
- [29] Cersosimo MG, Raina GB, Benarroch EE, Piedimonte F, Alemán GG, Micheli FE. Micro lesion effect of the globus pallidus internus and outcome with deep brain stimulation in patients with Parkinson's Disease and dystonia. *Movement Disorders* 2009;24:1488–93. <https://doi.org/10.1002/mds.22641>.
- [30] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders* 2008;23:2129–70. <https://doi.org/10.1002/mds.22340>.
- [31] Kremer NI, Smid A, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, et al. Supine MDS-UPDRS-III Assessment: An Explorative Study. *J Clin Med* 2023;12. <https://doi.org/10.3390/jcm12093108>.
- [32] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [33] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.

- [34] Lukšys D, Jonaitis G, Griškevičius J. Quantitative Analysis of Parkinsonian Tremor in a Clinical Setting Using Inertial Measurement Units. *Parkinsons Dis* 2018;2018. <https://doi.org/10.1155/2018/1683831>.
- [35] Rodríguez-Molinero A, Samà A, Pérez-López C, Rodríguez-Martín D, Alcaine S, Mestre B, et al. Analysis of correlation between an accelerometer-based algorithm for Detecting Parkinsonian gait and UPDRS subscales. *Front Neurol* 2017;8:1–6. <https://doi.org/10.3389/fneur.2017.00431>.
- [36] Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's Disease: Challenges and opportunities. *Movement Disorders* 2016;31:1272–82. <https://doi.org/10.1002/mds.26642>.
- [37] Lieber B, Taylor BES, Appelboom G, Mckhann G, Connolly ES. Motion Sensors to Assess and Monitor Medical and Surgical Management of Parkinson Disease. *World Neurosurg* 2015;84:561–6. <https://doi.org/10.1016/j.wneu.2015.03.024>.
- [38] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative Quantification of MDS-UPDRS Tremor Measurements Using 3D Accelerometry: A Pilot Study. *J Clin Med* 2022;11:2275. <https://doi.org/10.3390/jcm11092275>.
- [39] Shah A, Coste J, Lemaire JJ, Taub E, Schüpbach WMM, Pollo C, et al. Intraoperative acceleration measurements to quantify improvement in tremor during deep brain stimulation surgery. *Med Biol Eng Comput* 2017;55:845–58. <https://doi.org/10.1007/s11517-016-1559-9>.
- [40] Papapetropoulos S, Gallo B V., Guevara A, Singer C, Mitsi G, Lyssikatos C, et al. Objective tremor registration during DBS surgery for Essential Tremor. *Clin Neurol Neurosurg* 2009;111:376–9. <https://doi.org/10.1016/j.clineuro.2008.10.017>.
- [41] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative quantification of MDS-UPDRS tremor measurements using 3D accelerometry (abstract 394). *Movement Disorders* 2022;37:S206. <https://doi.org/10.1002/mds.29223>.
- [42] Iacono RP, Henderson JM, Lonser RR. Combined stereotactic thalamotomy and posteroventral pallidotomy for Parkinson's Disease. *J Image Guid Surg* 1995;1:133–40. [https://doi.org/10.1002/\(SICI\)1522-712X\(1995\)1:3<133::AID-IGS2>3.0.CO;2-B](https://doi.org/10.1002/(SICI)1522-712X(1995)1:3<133::AID-IGS2>3.0.CO;2-B).
- [43] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's Disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4. <https://doi.org/10.1136/jnnp.55.3.181>.
- [44] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [45] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [46] Earhart GM, Hong M, Tabbal SD, Perlmuter JS. Effects of Thalamic Stimulation Frequency on Intention and Postural Tremor. *Exp Neurol* 2007;208:257–63.
- [47] Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. *Brain* 2018;141:2142–55. <https://doi.org/10.1093/brain/awy139>.
- [48] Elble RJ. Mechanisms of deep brain stimulation for Essential Tremor. *Brain* 2014;137:4–6. <https://doi.org/10.1093/brain/awt347>.
- [49] Nagaseki Y, Shibazaki T, Hirai T, Kawashima Y, Wada H, Ohye C. Long-term follow-up results of selective VIM-thalamotomy. *J Neurosurg* 1986;65:296–302.
- [50] Maltête D, Derrey S, Chastan N, Debono B, Gérardin E, Fréger P, et al. Microsubthalamotomy: An immediate predictor of long-term subthalamic stimulation efficacy in Parkinson disease. *Movement Disorders* 2008;23:1047–50. <https://doi.org/10.1002/mds.22054>.

- [51] Mann JM, Foote KD, Garvan CW, Fernandez HH, Jacobson IV CE, Rodriguez RL, et al. Brain penetration effects of microelectrodes and DBS leads in STN or GPI. *J Neurol Neurosurg Psychiatry* 2009;80:794–7. <https://doi.org/10.1136/jnnp.2008.159558>.
- [52] Smid A, Pauwels RWJ, Elting JWJ, Everlo CSJ, van Dijk JMC, Oterdoom DLM, et al. A Novel Accelerometry Method to Perioperatively Quantify Essential Tremor Based on Fahn-Tolosa-Marin Criteria. *J Clin Med* 2023 2023;12:4235. <https://doi.org/10.3390/jcm12134235>.
- [53] Baek H, Chen J, Lockwood D, Obusez E, Poturalski M, Nagel SJ, et al. Feasibility of Magnetic Resonance–Compatible Accelerometers to Monitor Tremor Fluctuations During Magnetic Resonance–Guided Focused Ultrasound Thalamotomy: Technical Note. *Operative Neurosurgery* 2023. <https://doi.org/10.1227/ons.0000000000000638>.
- [54] Sievänen H, Kujala UM. Accelerometry—Simple, but challenging. *Scand J Med Sci Sports* 2017;27:574–8. <https://doi.org/10.1111/sms.12887>.
- [55] Băzu M, Gălăţeanu L, Ilian V, Loicq J, Habraken S, Collette J-P. Quantitative Accelerated Life Testing of MEMS Accelerometers. *Sensors* 2007;7:2846–59. <https://doi.org/10.3390/s7112846>.
- [56] Semiconductor F. Data Sheet: Technical Data Xtrinsic MMA8452Q 3-Axis, 12-bit/8-bit Digital Accelerometer. 2010.



Chapter 8

Perioperative quantification of MDS-UPDRS-III tremor measurements in patients with Parkinson's Disease using accelerometry

Annemarie Smid

Jan Willem J. Elting

Teus van Laar

Jolien M. ten Kate

D. L. Marinus Oterdoom

Katalin Tamasi

J. Marc C. van Dijk

Gea Drost

Submitted

Abstract

Background

Tremor in patients with Parkinson's Disease (PD) is usually evaluated using the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS). Limitations of the MDS-UPDRS include subjectivity and rater-dependency, which may be overcome by accelerometry.

Aim

This study focused on relating the MDS-UPDRS hand tremor scores to an objective scoring method with 3D accelerometry. An accelerometric algorithm to measure and classify tremor of the hands according to MDS-UPDRS criteria is proposed.

Methods: Sixty-four patients with PD and 64 healthy controls (matched on sex and age) were included. Two raters assessed MDS-UPDRS criteria for tremor, while accelerometry was performed at the index finger. Measurements were executed in an off-medication state, after a washout period of at least 12h. The 3D acceleration data included amplitude and area-under-the-curve of power in the 4–7 Hz range. Agreement between MDS-UPDRS and accelerometric scores was analyzed with Cohen's kappa coefficient (κ).

Results

The trends between tremor amplitude and MDS-UPDRS score were consistent with the logarithmic relationship reported in previous studies. Overall, the accelerometric scores showed a substantial agreement ($>80.2\%$, $\kappa \geq 0.732$) with the tremor amplitude according to MDS-UPDRS ratings. Accelerometric constancy of rest tremor (CRT) measures correlated less with MDS-UPDRS scores ($R^2 < 0.469$, $p < 0.001$) than the other tasks, which could be explained by CRT being calculated only for the time window where RT was performed. Accelerometric test-retest reliability was good to excellent ($ICC \geq 0.789$, $p < 0.001$).

Conclusions

MDS-UPDRS tremor tests can be reliably translated to objective accelerometric measurements. However, discrepancies were found between accelerometric CRT-measures and MDS-UPDRS ratings. Accelerometry could complement visual evaluations of tremor, aiming to reduce rater-variability of MDS-UPDRS measurements and allow for more objective monitoring of tremor in the clinical setting.

1. Introduction

Tremor is a potentially disabling motor symptom of Parkinson's Disease (PD) [1–5]. It is characterized by involuntary, rhythmic and oscillatory movement [1]. In PD, tremor is dominant in the 4–7 Hz frequency range and is generally observed unilaterally in the extremities [6–8]. PD tremor is most prominent at rest, decreases in amplitude during voluntary movement of the affected body part, and increases during mental tasks or when voluntarily moving other body parts [5,6]. Accurate tremor evaluations can significantly benefit PD management, considering the diverse manifestations of PD and continuously evolving treatment options.

PD tremor of the hands is most often assessed using the Movement Disorder Society Unified PD Rating Scale part III (MDS-UPDRS-III): postural tremor (3.15), kinetic tremor (3.16), rest tremor (3.17), and constancy of rest tremor (3.18) [9]. Tremor severity is rated based on the observed maximal amplitude (3.15–3.17) and presence (3.18) of tremor during the examination period [9].

Although a substantial number of criteria is defined for the rating, not all criteria are quantitative [10–15]. Therefore, it might be difficult to estimate the amplitude in centimeters or to detect minor changes in tremor by eye [14–18]. Consequently, these visual evaluations are prone to vary across raters [10–15]. Throughout the clinical caretaking process, multiple caregivers with varying levels of experience with the MDS-UPDRS-III are involved, highlighting the necessity for consistent evaluation tools [10–12].

The addition of movement sensors during tremor assessment may overcome the shortcomings of visual evaluations. Proper data analysis may result in reliable quantitative outcome measures to guide PD therapy. Unfortunately, few systems have made their way from the laboratory setting to the outpatient clinic, possibly due to their cost, size or invasiveness [17,19–21].

Tri-axial accelerometers are precise, noninvasive and relatively low-cost movement sensors that measure linear accelerations relative to the Earth's gravitational field [15,17,22–24]. Their output is a 3D timeseries of accelerations expressed in gravitational units (g) in the frame of reference of the sensor [25,26]. Accelerometers allow quantification of parameters that are relevant for assessing tremor (e.g., amplitude, frequency) [27,28]. These accelerometric measures could be applied to calculate objective tremor scores based on MDS-UPDRS-III criteria [17,18,22].

Previous studies have mainly focused on quantifying tremor by merely predicting or estimating UPDRS-scores using movement sensor data, without literal translation of MDS-UPDRS-III scoring criteria to accelerometric measures [16,29–32]. For example, Schifino et al. used acceleration power spectral density (PSD) to detect tremors in PD and correlated these data with MDS-UPDRS-III scores [33]. Still, direct translation of the upper extremity MDS-UPDRS-III tremor items to an objective accelerometric method has not yet been described. Therefore, this study directly relates the upper extremity MDS-UPDRS-III tremor ratings to an objective method measuring tremor severity using accelerometry in a clinical setting.

2. Methods

This prospective study was performed at the Parkinson Expertise Center (Punt voor Parkinson) of the University Medical Center Groningen (UMCG), the Netherlands. Exemption from the act on research involving human subjects was granted by the local medical ethics review committee (METc UMC Groningen). This study was conducted in full compliance with the Helsinki Declaration for research on human beings.

2.1. Participants

Between July 2021 and July 2023, consecutive patients with PD in the trajectory for Deep Brain Stimulation (DBS) surgery, and age- and sex-matched healthy controls (HC) were included. Screening of the participants was performed by the primary researcher (A.S.). All participants received oral information and a participant information letter. Written informed consent was obtained from each participant. All PD patients were diagnosed according to UK Brain Bank criteria [34] and were Hoehn and Yahr stage I–V [35]. None of the HC had a current diagnosis of PD or any neurological disease. Exclusion criteria were musculoskeletal system disorders or physical disabilities, recent alcohol/drugs abuse, and psychosis or current depression. None of the participants were treated with tremor-inducing drugs during the study.

2.2. Materials

Two wired tri-axial accelerometers (MMA8452Q tri-Axis, Freescale Semiconductor, Inc., Austin, TX, USA) with a range of $\pm 2g$ and a sampling rate of 200 Hz were used [17,22,23]. The accelerometers were secured in in-house developed, non-conductive plastic cases [17,22,23]. The sensors were attached to the index fingers with adjustable silicon straps (see Figure 1).

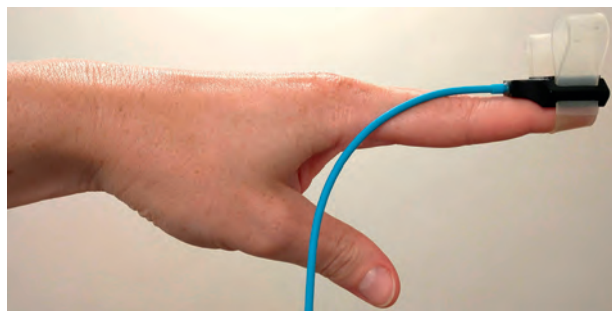


Figure 1. Accelerometer positioned at the tip of the left index finger.

Accelerometry data were recorded with LabVIEW v. 2017 (National Instruments, Austin, TX, USA), as described previously by Smid et al. [17,22,23]. Signal analysis was performed in MATLAB v. 2023a (MathWorks, Natick, MA, USA) and statistical

analysis was performed in IBM SPSS statistics v. 28 (International Business Machines Corporation, New York, NY, USA). The assessment of the participants included MDS-UPDRS-III items 3.15–3.18 [9]. MDS-UPDRS part II was used to evaluate the motor aspects of experiences of daily living in the PD group [9].

2.3. Measurements

Healthy controls (HC) were included to determine the natural variation of the 4–7 Hz frequency range of postural tremor (PT), kinetic tremor (KT), rest tremor (RT) and constancy of rest tremor (CRT) tests. Also, HC data were used to calculate thresholds from the accelerometric data that were not quantitatively described in MDS-UPDRS-III 3.15–3.18. All measurements were conducted in an off-medication state, with a washout period of at least 12h. If applicable, DBS devices were turned off during the measurements (at least 12h) before testing. The accelerometers were placed at the distal phalanx of the index finger of each hand during all measurements. All accelerometry measurements were performed with the participant in a sitting position. Tests lasted ten seconds each. MDS-UPDRS-III tasks 3.15–3.17 [9] were performed at both hands separately to assess PT, KT, RT, and CRT, respectively, while accelerometric data were recorded simultaneously. All tests were performed twice for each task, in order to determine the accelerometric test-retest reliability. Tremor severity was assessed by two MDS-UPDRS-III raters who were blinded to the accelerometric data.

2.4. Data pre-processing

Pre-processing was performed in part as described previously [17,22,23]. Calibrated raw acceleration data (g) were converted to cm/s^2 . The norm of the acceleration vector in all three directions was calculated from the root mean square of the resultant signal of the three axes [36,37]. Non-causal second-order high-pass (0.5 Hz) and low-pass (20 Hz) Butterworth filters were used to remove digital noise and higher-order harmonics [17,36,37], resulting in the filtered acceleration norm ($\vec{a}$).

Velocity (cm/s) was calculated from $\vec{a}$ by computing the approximate cumulative numerical integral of $\vec{a}$ over a ten-second period (2000 samples) using the trapezoidal method. In order to correct for the constant that is added to the vector due to integration, this vector was centered to compute the corrected velocity ($\vec{v}$).

Displacement (cm) was calculated from $\vec{v}$ via the same numerical integration method as described above. This vector was filtered using a non-causal second-order high-pass 1.2 Hz Butterworth filter to suppress low-frequency trends caused by integration, producing displacement vector $\vec{s}$. For KT, this high-pass filter applied a cut-off frequency of 3 Hz to suppress the amplitude of low frequent arm movements [17,37].

2.5. Accelerometric outcome measures

Two main outcome measures were calculated to assess RT, PT, and KT: 1) the area under the curve of power within the 4–7 Hz [22] tremor frequency band (AUCP) and 2)

the maximal amplitude ($\vec{s}_{max}$). The AUCP ($(\text{cm/s}^2)^2$) was calculated from the periodogram PSD estimate via trapezoidal numerical integration (Figure 2a). The $\vec{s}_{max}$ (peak-to-peak distance) of each performed task was calculated by determining all peaks in the absolute displacement ($\vec{s}_{abs}$ (cm)), given in black stars (*) in Figure 2b. The mean of all computed $\vec{s}_{abs}$ peaks was multiplied by factor 2 to produce $\vec{s}_{max}$.

To assess CRT, the AUCP was calculated for each second of RT, resulting in ten AUCP/s values per test. The Percentage of Time that Tremor was Present (PTTP) was calculated from the number of seconds that AUCP was above the CRT-threshold calculated from the healthy group (Section 2.6).

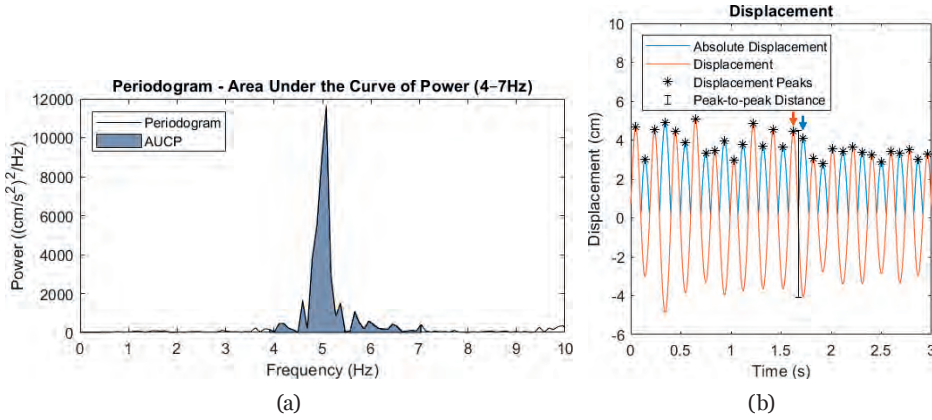


Figure 2. Example PSD periodogram for determination of AUCP (4–7 Hz), given in blue (a) and schematic determination of maximal amplitude based on all displacement peaks of the test. A red and blue arrow mark two displacement peaks. Peak-to-peak distance is given in black lines.

2.6. Accelerometric scores

The calculated accelerometric outcome measures (AUCP, $\vec{s}_{max}$, and PTTP) are used as input for the scoring algorithm. The output of the algorithm is accelerometric (ACC) scores ranging from 0–4 per task, as MDS-UPDRS-III prescribes. The quantitative thresholds (in cm and %) provided by the MDS-UPDRS-III were used as cut-off values in the algorithm (Table 1). Other necessary thresholds were derived from accelerometric data of the HC (Table 2), according to the empirical rule [17,22,38]. This rule states that, for normally distributed data, about 95% of the data within the population is within the population mean (μ) plus two times the population standard deviation (σ). So, the threshold (t) is calculated according to:

$$t = \mu + 2\sigma \quad (\text{Eq. 1})$$

This rule was used to determine the asymptomatic thresholds for the AUCP, and thresholds for AUCP per second to determine PTTP (Table 2). The distribution of the data was determined using Kolmogorov-Smirnov test of normality (one sample K-S test).

Table 1. Description of MDS-UPDRS-III 3.15–3.18 scoring criteria [9].

Score	Severity	MDS-UPDRS-III 3.15–3.17	MDS-UPDRS-III 3.18
0	Normal	No tremor.	No tremor.
1	Slight	Tremor is present but less than 1 cm in amplitude.	Tremor at rest is present $\leq 25\%$ of the entire examination period.
2	Mild	Tremor is at least 1 but less than 3 cm in amplitude.	Tremor at rest is present 26–50% of the entire examination period.
3	Moderate	Tremor is at least 3 but less than 10 cm in amplitude.	Tremor at rest is present 51–75% of the entire examination period.
4	Severe	Tremor is at least 10 cm in amplitude.	Tremor at rest is present $> 75\%$ of the entire examination period.

Table 2. Overview of thresholds based on HC data used for the accelerometric algorithm.

Threshold	Task	Explanation	Value
PT-threshold	PT	Minimal value of AUCP for a PT-test to be scored ≥ 1 .	$396^* \text{ (cm/s}^2\text{)}^2$
KT-threshold	KT	Minimal value of AUCP for a KT-test to be scored ≥ 1 .	$4441^* \text{ (cm/s}^2\text{)}^2$
RT-threshold	RT, CRT	Minimal value of AUCP for an RT or CRT-test to be scored ≥ 1 .	$152^* \text{ (cm/s}^2\text{)}^2$
CRT-threshold	CRT	Minimal value of AUCP per second for that second to be labelled as “tremor present”.	$70^* \text{ (cm/s}^2\text{)}^2$

* See Section 3.2.

The first step of the algorithm for all tasks is to determine whether tremor is present [17,22]. Since the MDS-UPDRS-III solely states the criterium for score 0 is “no tremor”, the AUCP of each test was calculated from the accelerometric data of the HC group to determine the natural variation of noise between 4–7 Hz. Since healthy persons can exhibit activity in the 4–7 Hz frequency range (e.g. due to physiological tremor), AUCP-thresholding can aid in preventing physiological movements being rated as Parkinsonian tremor. An AUCP-threshold was calculated for each task (PT, KT, RT) using HC data and the empirical rule (Table 2). In the PD group, an ACC-score of 0 (“no tremor”) was given by the algorithm if the AUCP was below the calculated PT-, KT-, or RT-threshold (resp.). Otherwise, a score of 1 or higher was given, based on the amplitude ($\vec{s}_{max}$) that was measured during that test. No thresholds for $\vec{s}_{max}$ were calculated based on HC data, since these quantitative thresholds were provided in MDS-UPDRS-III.

For item 3.18, a CRT-score of 0 (“no tremor”) was given if the AUCP of the test was below the RT-threshold. Otherwise, the ACC-score for CRT was based on the calculated PTPP. The CRT-threshold was calculated from HC data based on the ten values of AUCP per second. In the PD group, a tremor was detected if AUCP per second was above the CRT-threshold. Each second that tremor was present was summed up and used to calculate the PTPP (%). The quantitative thresholds described in MDS-UPDRS-III were applied in %.

As a result, an MDS-UPDRS-based analysis of tremor, including an ACC-score (0–4) for each task, is provided (Figure 3). All outcome measures were calculated for both the right- and the left-hand sensor for all corresponding tests.

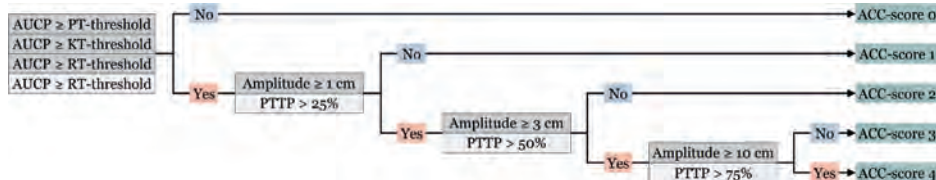


Figure 3. Flowchart for accelerometric score calculation, based on thresholds calculated from healthy controls and standardized MDS-UPDRS-III criteria. The pathways for PT, KT and RT are given in dark grey, while CRT is given in light grey. “No” pathways are given in blue. “Yes” pathways are given in orange.

2.7. Statistical analysis

2.7.1. Primary endpoint

For each test performed, the MDS-UPDRS-III scores provided by two raters were averaged. The level of agreement between the mean MDS-UPDRS-III score and accelerometric score of each test was evaluated by computing concordance and Cohen’s weighted kappa coefficient (κ) [39,40]. As co-primary endpoint, the mean absolute error (MAE) and the root mean square error (RMSE) were calculated to determine the level of deviation of accelerometric scores from the MDS-UPDRS-III scores.

2.7.2. Secondary endpoints

As first secondary endpoint, the inter-rater reliability between the two MDS-UPDRS-III raters was analyzed using Cohen’s weighted kappa coefficient (κ).

Second, the association between accelerometric outcome measures and mean MDS-UPDRS-III scores was studied with linear regression. The mean MDS-UPDRS-III scores were used as the predictor. Contrast coding of MDS-UPDRS-III scores was defined to be orthogonal polynomial, of which the first contrast coefficient is linear trend. Consequently, analyses were performed on whether there was a linear relationship between MDS-UPDRS-III scores and the natural logarithm ($\ln$) of the accelerometry outcome measures, as previously described [17,22,41,42].

Third, the correlation between accelerometric outcome measures (AUCP, $\vec{s}_{max}$, PTPP) and mean MDS-UPDRS-III scores was evaluated using Spearman’s correlation coefficient (ρ).

Last, the test-retest reliability of the accelerometric approach was assessed based on the ICC (two-way mixed effects model, single measurement, absolute agreement) of the AUCP, $\vec{s}_{max}$, PTPP and accelerometric scores for the repeated tasks [22,38,43].

3. Results

Sixty-four PD patients were included in this study (32 men, 32 women; age (mean $\pm$ SD): 61.8 ± 8.6 years) versus 64 HCs (32 men, 32 women; age (mean $\pm$ SD): 60.9 ± 8.9 years). Median motor impairment of PD patients was an MDS-UPDRS-II rating of 15 (range: 3–36) out of 52. In 23 patients, a DBS device was present. At the time of the assessment, these participants had been treated for 10.1 ± 4.3 months on average ($\pm$ SD). In all PD patients and HC, 256 PT-, 256 KT-, and 256 RT-tests were performed (twice left-handed, and twice right-handed).

3.1. Clinical MDS-UPDRS-III ratings

Cohen's κ coefficient showed moderate to substantial inter-rater reliability of the two MDS-UPDRS-III raters for all tests ($\kappa \geq 0.444$) [39]. κ was 0.560 (95% CI: 0.468, 0.652; $p < 0.001$) for PT. κ was 0.444 (95% CI: 0.350, 0.538; $p < 0.001$) for KT. κ was 0.558 (95% CI: 0.478, 0.638; $p < 0.001$) for RT. κ was 0.489 (95% CI: 0.379, 0.599; $p < 0.001$) for CRT. Lastly, κ was 0.512 (95% CI: 0.435, 0.589; $p < 0.001$) for all tasks combined.

3.2. Accelerometric outcome measures

The main accelerometric outcomes were AUCP, $\vec{s}_{max}$, PTP, which were plotted against the averaged MDS-UPDRS-III ratings per task in Figure 4. With increasing MDS-UPDRS-III scores, an increase in AUCP and tremor amplitude can be observed for all tremor amplitude tasks. AUCP per second and PTP also increased with increasing MDS-UPDRS-III scores for CRT. Figure 4g shows a prominent number of outliers for AUCP per second.

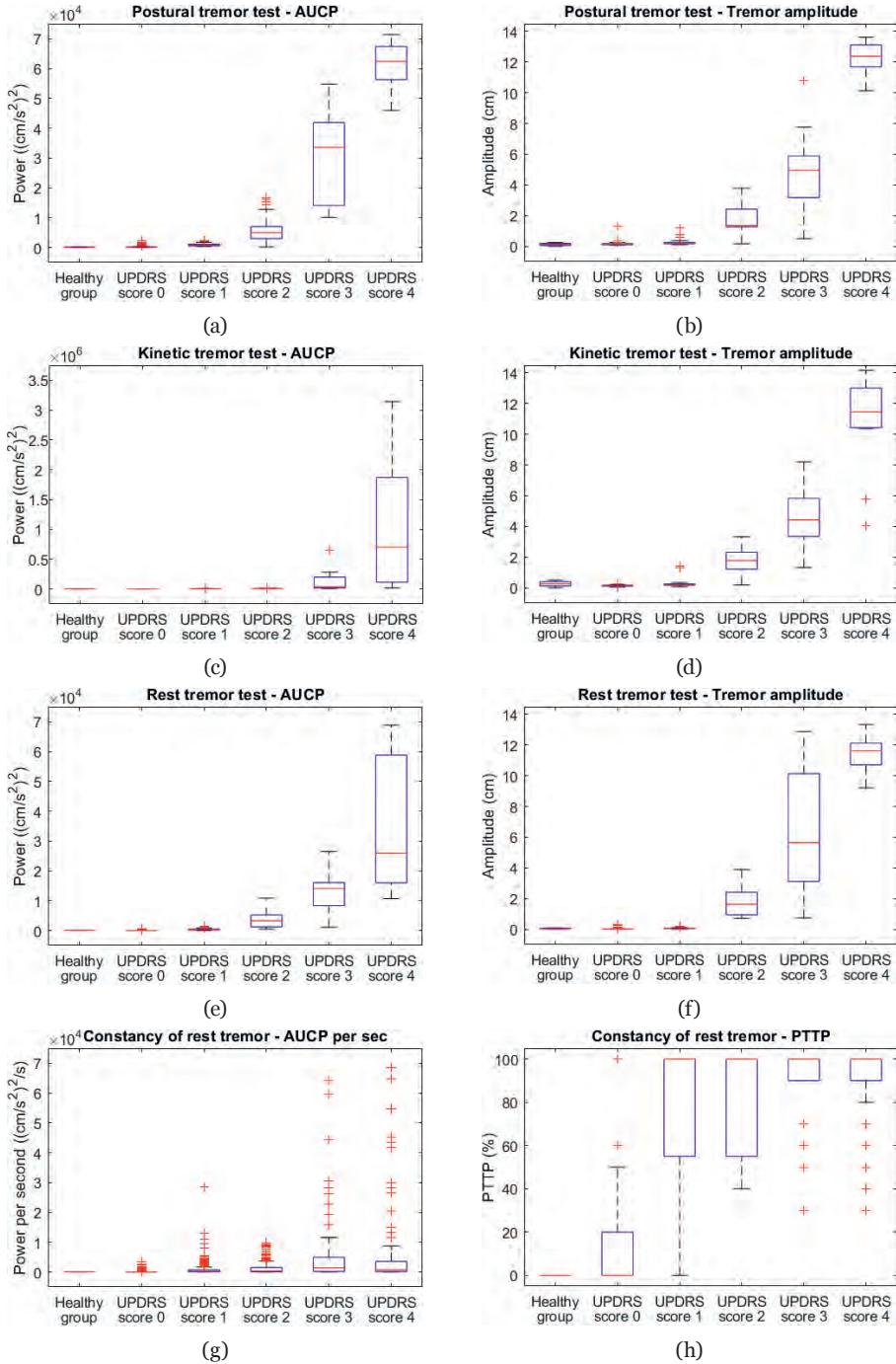


Figure 4. Boxplots of the AUCP of PT (a), KT (c), and RT (e), and of the $\vec{s}_{\max}$ of PT (b), KT (d), and RT (f), and of the AUCP per second of CRT (g), and of the PTPP of CRT (h) in the HC and the patient group, per MDS-UPDRS-III score. Outliers are marked with red crosses (+).

All accelerometric outcomes were natural log (ln) transformed for regression analysis, except for PTPP, as this outcome measure contained values of zero. The ln-transformed measures and PTPP were regressed on the mean MDS-UPDRS-III scores. There was strong evidence against the null hypothesis that the log-transformed outcome measures were not linearly related to the MDS-UPDRS-III scores ($p < 0.001$) for all tasks, see Table 3. AUCP and AUCP per second tended to increase as an ln-function of MDS-UPDRS-III ($R^2 > 0.518$).

Table 3. Regression analysis results.

Task	Measure	R	R ² *	Coefficient**	95% CI	p
PT	ln(AUCP)	0.833	0.693	9.343	8.571, 10.114	<0.001
	ln($\vec{s}_{max}$)	0.778	0.606	3.140	2.826, 3.454	<0.001
KT	ln(AUCP)	0.773	0.598	5.376	4.829, 5.923	<0.001
	ln($\vec{s}_{max}$)	0.739	0.546	2.213	1.962, 2.463	<0.001
RT	ln(AUCP)	0.871	0.759	11.855	11.025, 12.685	<0.001
	ln($\vec{s}_{max}$)	0.839	0.705	5.443	5.006, 5.880	<0.001
CRT	ln(AUCP/s)	0.720	0.518	4.228	3.473, 4.984	<0.001
	PTTP	0.766	0.587	5.733	5.137, 6.330	<0.001

* Coefficient of determination; ** Contrast coefficient testing for linear trend.

Table 4 shows the correlations between accelerometric outcome measures (AUCP, $\vec{s}_{max}$, PTPP) and MDS-UPDRS-III scores. A good correlation was found for $\vec{s}_{max}$ in all tasks ($p < 0.001$). All correlations between AUCP and MDS-UPDRS-III scores were good ($p < 0.001$). The remaining measures showed moderate correlation with MDS-UPDRS-III scores ($p < 0.001$) [43].

Table 4. Spearman's correlation between accelerometric outcome measures and MDS-UPDRS-III scores in the patient population.

Task	Measure	Spearman's ρ	R ²	95% CI	p
PT	AUCP	0.810	0.656	0.762, 0.850	<0.001
	$\vec{s}_{max}$	0.786	0.618	0.713, 0.848	<0.001
KT	AUCP	0.830	0.689	0.765, 0.884	<0.001
	$\vec{s}_{max}$	0.759	0.576	0.681, 0.825	<0.001
RT	AUCP	0.845	0.714	0.805, 0.878	<0.001
	$\vec{s}_{max}$	0.802	0.643	0.751, 0.843	<0.001
CRT	AUCP/s	0.685	0.469	0.611, 0.747	<0.001
	PTTP	0.715	0.511	0.647, 0.772	<0.001

3.3. Accelerometric scores

All HC data required for threshold calculation were normally distributed according to K-S test results ($p < 0.001$). Table 2 shows the values of thresholds calculated from HC data. The contingency tables of mean MDS-UPDRS-III scores and ACC-scores in the patient population are given in heatmaps in Figure 5 for all tasks.

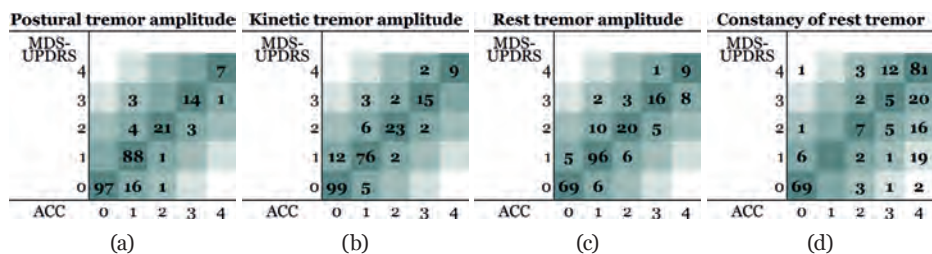


Figure 5. Contingency tables of the mean MDS-UPDRS-III (UPDRS) scores and calculated accelerometry (ACC) scores of the PT (a), KT (b), RT (c) and CRT (d) in the patient group. The clinical UPDRS scores are given on the y-axis, and the ACC-scores calculated by the algorithm are given on the x-axis. Matching scores are given in the dark green diagonal, neighboring scores are given in light green, and discrepant pairs are given in the lightest shades.

Table 5 shows concordance and Cohen's κ coefficient of agreement between the mean MDS-UPDRS-III ratings and the accelerometric scores per task, as well as the mean error (MAE and RMSE). Concordance between the MDS-UPDRS-III ratings and the ACC-scores was substantial for all tasks ($\geq 63.3\%$). Cohen's κ results showed a moderate to substantial agreement for all tasks [39,40,43]. The MAE (range 0.129–0.188) indicates that the ACC-scores differed less than a quarter point from the mean MDS-UPDRS-III ratings on average for PT, KT and RT.

Table 5. Agreement between MDS-UPDRS-III and ACC-scores for MDS-UPDRS-III items 3.15–3.18.

Task	Concordance	Cohen's κ	95% CI	p	RMSE	MAE
3.15 PT	88.7%	0.830	0.773, 0.887	<0.001	0.400	0.129
3.16 KT	86.7%	0.805	0.744, 0.866	<0.001	0.410	0.145
3.17 RT	82.0%	0.744	0.679, 0.809	<0.001	0.451	0.188
3.18 CRT	63.3%	0.468	0.394, 0.542	<0.001	1.204	0.652
All tasks	80.2%	0.732	0.701, 0.763	<0.001	0.704	0.278

3.4. Accelerometric reliability

In Table 6, the test-retest reliability of both the MDS-UPDRS and the accelerometric method is given for the accelerometric outcome measures and the calculated ACC-scores of the repeated tasks. Accelerometric reliability was excellent for both the $\vec{s}_{max}$ and ACC-score of RT, and the remaining ICCs showed good test-retest reliability. The clinical approach (MDS-UPDRS-III score) showed moderate to good test-retest reliability (ICC) [43].

Table 6. Test-retest reliability (ICC: two-way mixed effects model, single measurement, absolute agreement).

MDS-UPDRS-III task	Outcome measure	ICC	95% CI	<i>p</i>
3.15 Postural tremor of the hands	AUCP	0.800	0.729, 0.871	<0.001
	$\vec{s}_{max}$	0.815	0.745, 0.867	<0.001
	ACC-score	0.815	0.744, 0.867	<0.001
	MDS-UPDRS score	0.696	0.578, 0.814	<0.001
3.16 Kinetic tremor of the hands	AUCP	0.789	0.694, 0.879	<0.001
	$\vec{s}_{max}$	0.889	0.844, 0.921	<0.001
	ACC-score	0.866	0.813, 0.904	<0.001
	MDS-UPDRS score	0.766	0.719, 0.813	<0.001
3.17 Rest tremor amplitude of the hands	AUCP	0.870	0.819, 0.907	<0.001
	$\vec{s}_{max}$	0.928	0.898, 0.949	<0.001
	ACC-score	0.920	0.887, 0.943	<0.001
	MDS-UPDRS score	0.829	0.741, 0.917	<0.001
3.18 Constancy of rest tremor of the hands	AUCP/s	0.869	0.818, 0.907	<0.001
	PTTP	0.868	0.811, 0.907	<0.001
	ACC-score	0.869	0.817, 0.907	<0.001
	MDS-UPDRS score	0.664	0.593, 0.735	<0.001
Tasks 3.15-3.17 combined	AUCP	0.891	0.849, 0.927	<0.001
	$\vec{s}_{max}$	0.909	0.888, 0.927	<0.001
	ACC-score	0.917	0.901, 0.931	<0.001
	MDS-UPDRS score	0.831	0.778, 0.884	<0.001
All tasks combined	ACC-score	0.899	0.879, 0.916	<0.001
	MDS-UPDRS score	0.736	0.687, 0.785	<0.001

4. Discussion

This study describes the relation of MDS-UPDRS-III hand tremor assessments to an objective accelerometric method based on the MDS-UPDRS-III using thresholds calculated from healthy participant data. This study proposes a quantitative scoring algorithm for MDS-UPDRS-III tests 3.15–3.18 using accelerometry. The agreement between clinically scored MDS-UPDRS-III ratings and objective scores calculated from accelerometric data was studied, showing that MDS-UPDRS-III hand tremor tests can be accurately quantified with accelerometry, although the algorithm still needs to be optimized in order to provide better agreement. Trends were consistent with the logarithmic relationship between tremor amplitude and MDS-UPDRS-III scores described in previous studies, for both amplitude and AUCP as measured by the accelerometer [15,17,22,42,44,45]. However, this study also showed discrepancies between accelerometric CRT-measures and clinically scored MDS-UPDRS-III ratings, particularly in the agreement between ACC- and clinical scores.

The primary contribution of this study is relating MDS-UPDRS-III hand tremor measurements to an objective scoring algorithm using accelerometry in a clinical setting,

using the gold standard as a basis. In addition, HC were included to determine the natural variation of the accelerometric outcome measures and to provide the thresholds needed for the algorithm that were not stated in the MDS-UPDRS-III. The HC group was matched for age and sex with the PD group, and two certified MDS-UPDRS raters assessed all participants in order to correct for the effects of inter-rater variability. The ACC-scores generated by the algorithm are straightforward to understand, as they are based on the same MDS-UPDRS-III criteria that PD caregivers are already familiar with.

The main limitation of this study is that the gold standard used in this study is flawed to a certain extent. Even though the MDS-UPDRS-III is the most standardized and most used method for measuring upper extremity Parkinsonian tremor, amplitudes are difficult to assess visually. Two experienced raters were employed for this study, and still inter-rater reliability was not perfect, which is in line with previous studies [15–17,27]. This implies that rating the same patient at the same moment in the same condition will result in different assessments per rater, which complicates using the MDS-UPDRS-III as the gold standard.

4.1. Clinical MDS-UPDRS-III ratings

This study shows a moderate to substantial inter-rater reliability of the MDS-UPDRS-III ratings. Comparable values have been observed in other studies, highlighting the importance of a more uniform approach to perform MDS-UPDRS-III assessments [10,13,17,28].

4.2. Accelerometric outcome measures

Figure 4 and Table 3 illustrate that the trends between tremor amplitude and MDS-UPDRS-III scores were consistent with the logarithmic relationship reported in previous studies [15,17,22,42,44,45]. Overall, good correlations were found between accelerometric outcome measures and MDS-UPDRS-III scores, indicating that the algorithm comes to similar conclusions as the MDS-UPDRS-III raters. However, the accelerometric constancy of rest tremor (CRT) measures showed only moderate correlation with MDS-UPDRS scores ($R^2 < 0.469$, $p < 0.001$), likely due to the calculation of CRT in the 10-second time window when RT was performed, instead of continuously during the whole examination. The choice to only use accelerometric data that was certainly performed in the RT position to calculate CRT was made to ensure correct calculation of CRT-scores based on accelerometric data captured in a controlled setting. However, this might have led to a discrepancy between the input for the MDS-UPDRS-III scores and the input for the accelerometer. To improve the real-life application of the accelerometric algorithm, its agreement with MDS-UPDRS-III results should be compared to ACC-results based on continuous data in RT position as input for the algorithm. An explanation for the outliers shown in Figure 4g is the grouping of continuous accelerometric data (AUCP per second) according to ordinal MDS-UPDRS-III, where all ten values per test are grouped under a single rating. For example, MDS-UPDRS-III CRT-score 1 indicates that tremor is absent 51–75% of the time, meaning that at least 25% of accelerometric values of that test

are above the threshold, probably resulting in outliers. With increasing tremor severity and constancy, AUCP per second values tend to increase as well. Although investigating CRT over a longer period of time might not directly solve this issue, it will allow a more granular analysis of the time that tremor was present.

4.3. Accelerometric scores

Table 5 and Figure 5 show substantial agreement between MDS-UPDRS-III ratings and ACC-scores for PT, KT, and RT [39,40]. The lower agreement between MDS-UPDRS-III and ACC-scores for CRT can be explained by the provided MDS-UPDRS-III scores being mainly dichotomous, as there was a high density of CRT-scores 0 and 4, inherent to CRT-ratings. The MDS-UPDRS-III CRT-score automatically defaults to 0 when no rest tremor is observed, either by the raters or the algorithm. In this dataset, there were several instances where the mean MDS-UPDRS-III score was 1–3 and the ACC-score was 4 for CRT. This could be explained by the accelerometer detecting minor tremors not visible for the naked eye. Previous studies have noted that suboptimal correlations between accelerometry and clinical evaluations can arise from subtle movement changes being challenging to estimate visually [17,22,27,46].

Also, the threshold of $70 \text{ (cm/s}^2\text{)}^2$ for determining CRT might be suboptimal, despite being based on data of healthy subjects. Considering the ceiling effect that is displayed in Figure 5d, it would be reasonable to investigate higher CRT-thresholds in future research.

Figure 5a shows an overestimation of MDS-UPDRS-III PT-score 0 being rated as score 1 by the accelerometer. This phenomenon is less strong for KT. This might be explained by KT-date undergoing 3 Hz high-pass filtering to suppress the amplitude of low frequent arm movements, while this cut-off was set at 1.2 Hz for PT. High-pass filtering with e.g. 2 Hz cut-off might suppress movements caused by muscle contraction while holding the arms in position during the PT task.

4.4. Accelerometric reliability

The test-retest reliability of the accelerometric method was good to excellent for all outcome measures and ACC-scores, underlining its potential to allow objective monitoring of hand tremor. Comparable levels of reliability have been reported in previous studies [22,38]. Overall, it stood out that MDS-UPDRS-III test-retest reliability was consistently lower than accelerometric reliability for all tasks.

4.5. Future perspectives

The field of quantifying PD motor skills using movement sensors is evolving [47,48]. The notion that inter- and intra-rater variability of the MDS-UPDRS should be reduced, and assessments should be performed uniformly, is shared among PD experts worldwide [19,49,50]. Minimizing variability in tremor assessment will enhance the accuracy of evaluating disease progression and treatment effects. The algorithm proposed in this paper could also address a clinical challenge faced by physicians when visually scoring

other tremor syndromes (e.g. Essential Tremor). With relatively minor adjustments, the frequency range and parameters used in the current scoring algorithm could be tailored to align with standardized rating scale criteria for other tremor types, e.g. the Fahn-Tolosa-Marín Clinical Rating Scale for Tremor and The ET Rating Assessment Scale [51,52].

To support clinicians in improving patient outcomes, it is essential to present these complex quantitative data in a format that is easy to interpret. Addressing big data problems will become increasingly manageable with the rise of machine learning and artificial intelligence. Examples include neural networks and support vector machines, which allow effective management of large volumes of multidimensional data [41,47,53–56]. However, the internal workings of these tools might not be transparent due to black box algorithms. Therefore, the method proposed in this manuscript is a form of non-black box programming, where each analysis step and threshold to produce the output is known. This way, there is transparency on how the algorithm arrives at its outcome measures, and the output can be validated. Future research should focus on optimizing the accelerometric thresholds of the proposed algorithm. Further investigating the variability of MDS-UPDRS-III measures and accelerometric outcome measures is recommended to optimize this technique.

Future development of the method presented in this paper should also focus on quantifying the clinical evaluation of PD therapies, and continuous data collection in real-life environments that reflect the patient's daily functioning. These data could be used to generate personalized feedback for clinicians, caregivers, and patients, which will support individualized treatment approaches and enhance self-management of the patient.

5. Conclusion

This study showed that the MDS-UPDRS-III tremor tests can be quantified using accelerometry with high reliability, providing clinically meaningful outcomes. The accelerometric data were consistent with the logarithmic relationship reported in previous studies. Agreement between the clinically scored MDS-UPDRS-III ratings and accelerometric scores was substantial. Discrepancies in the constancy of rest tremor were found, for which recommendations were formulated. The proposed method has the potential to reduce rater dependency of MDS-UPDRS-III measurements and to allow for more uniform assessment of hand tremor in PD.

References

- [1] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders* 2018;33:75–87. <https://doi.org/10.1002/mds.27121>.
- [2] Tysnes OB, Storstein A. Epidemiology of Parkinson's Disease. *J Neural Transm* 2017;124:901–5. <https://doi.org/10.1007/s00702-017-1686-y>.
- [3] Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis* 2018;8:S3–8. <https://doi.org/10.3233/JPD.181474>.
- [4] Kalia L, Lang AE. Parkinson's Disease. *The Lancet* 2015;386:896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3).
- [5] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's Disease. *Movement Disorders* 2015;30:1591–601. <https://doi.org/10.1002/mds.26424>.
- [6] van de Wardt J, van der Stouwe AMM, Dirkx M, Elting JWW, Post B, Tijssen MAJ, et al. Systematic clinical approach for diagnosing upper limb tremor. *J Neurol Neurosurg Psychiatry* 2020;91:822–30. <https://doi.org/10.1136/jnnp-2019-322676>.
- [7] van der Stouwe AMM, Elting JW, van der Hoeven JH, van Laar T, Leenders KL, Maurits NM, et al. How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena. *Parkinsonism Relat Disord* 2016;30:23–8. <https://doi.org/10.1016/j.parkreldis.2016.06.008>.
- [8] Lee RE, Chan PY. Explainable artificial intelligence for searching frequency characteristics in Parkinson's Disease tremor. *Sci Rep* 2023;13. <https://doi.org/10.1038/s41598-023-45802-z>.
- [9] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [10] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.
- [11] Lukšys D, Jonaitis G, Griškevičius J. Quantitative Analysis of Parkinsonian Tremor in a Clinical Setting Using Inertial Measurement Units. *Parkinsons Dis* 2018;2018. <https://doi.org/10.1155/2018/1683831>.
- [12] Rodríguez-Molinero A, Samà A, Pérez-López C, Rodríguez-Martín D, Alcaine S, Mestre B, et al. Analysis of correlation between an accelerometer-based algorithm for detecting Parkinsonian gait and UPDRS subscales. *Front Neurol* 2017;8. <https://doi.org/10.3389/fneur.2017.00431>.
- [13] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [14] Smid A, Kremer NI, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, et al. [Abstract 659] Perioperative Use of the MDS-UPDRS Motor Section: Agreement Between Sitting and Supine Position. *Movement Disorders* 2023;38:S295–S295. <https://doi.org/10.1002/mds.29541>.
- [15] Kremer NI, Smid A, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, et al. Supine MDS-UPDRS-III Assessment: An Explorative Study. *J Clin Med* 2023;12. <https://doi.org/10.3390/jcm12093108>.
- [16] Shah A, Coste J, Lemaire JJ, Taub E, Schüpbach WMM, Pollo C, et al. Intraoperative acceleration measurements to quantify improvement in tremor during deep brain stimulation surgery. *Med Biol Eng Comput* 2017;55:845–58. <https://doi.org/10.1007/s11517-016-1559-9>.

- [17] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative Quantification of MDS-UPDRS Tremor Measurements Using 3D Accelerometry: A Pilot Study. *J Clin Med* 2022;11:2275. <https://doi.org/10.3390/jcm11092275>.
- [18] Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, et al. Intraoperative quantification of MDS-UPDRS tremor measurements using 3D accelerometry (abstract 394). *Movement Disorders* 2022;37:S206. <https://doi.org/10.1002/mds.29223>.
- [19] Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's Disease obtained using mobile health technologies. *Movement Disorders* 2019;34:657–63. <https://doi.org/10.1002/mds.27671>.
- [20] Farzanehfar P, Woodrow H, Braybrook M, McGregor S, Evans A, Nicklason F, et al. Objective measurement in routine care of people with Parkinson's Disease improves outcomes. *NPJ Parkinsons Dis* 2018;4:1–8. <https://doi.org/10.1038/s41531-018-0046-4>.
- [21] Hobert MA, Maetzler W, Aminian K, Chiari L. Technical and clinical view on ambulatory assessment in Parkinson's Disease. *Acta Neurol Scand* 2014;130:139–47. <https://doi.org/10.1111/ane.12248>.
- [22] Smid A, Pauwels RWJ, Elting JWW, Everlo CSJ, van Dijk JMC, Oterdoom DLM, et al. A Novel Accelerometry Method to Perioperatively Quantify Essential Tremor Based on Fahn-Tolosa-Marin Criteria. *J Clin Med* 2023 2023;12:4235. <https://doi.org/10.3390/jcm12134235>.
- [23] Smid A, Oterdoom DLM, Pauwels RWJ, Tamasi K, Elting JWW, Absalom AR, et al. The Relevance of Intraoperative Clinical and Accelerometric Measurements for Thalamotomy Outcome. *J Clin Med* 2023;12:5887. <https://doi.org/10.3390/jcm12185887>.
- [24] Smid A, Oterdoom M, Pauwels R, Tamasi K, Elting JW, Absalom A, et al. [Abstract 1798] The added value of accelerometric monitoring during thalamotomy. *Movement Disorders* 2023;38:S793–4. <https://doi.org/10.1002/mds.29546>.
- [25] Sievänen H, Kujala UM. Accelerometry - Simple, but challenging. *Scand J Med Sci Sports* 2017;27:574–8. <https://doi.org/10.1111/sms.12887>.
- [26] Karas M, Bai J, Strączkiewicz M, Harezlak J, Glynn NW, Harris T, et al. Accelerometry Data in Health Research: Challenges and Opportunities: Review and Examples. *Stat Biosci* 2019;11:210–37. <https://doi.org/10.1007/s12561-018-9227-2>.
- [27] Yokoe M, Okuno R, Hamasaki T, Kurachi Y, Akazawa K, Sakoda S. Opening velocity, a novel parameter, for finger tapping test in patients with Parkinson's Disease. *Parkinsonism Relat Disord* 2009;15:440–4. <https://doi.org/10.1016/j.parkreldis.2008.11.003>.
- [28] Smid A, Dominguez-Vega ZT, van Laar T, Oterdoom DLM, Absalom AR, van Egmond ME, et al. Objective clinical registration of tremor, bradykinesia, and rigidity during awake stereotactic neurosurgery: a scoping review. *Neurosurg Rev* 2024;47. <https://doi.org/10.1007/s10143-024-02312-4>.
- [29] Rigas G, Gatsios D, Fotiadis DI, Chondrogiorgi M, Tsironis C, Konitsiotis S, et al. Tremor UPDRS estimation in home environment. 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), IEEE; 2016, p. 3642–5. <https://doi.org/10.1109/EMBC.2016.7591517>.
- [30] Jeon H, Kim SK, Jeon B, Park KS. Distance estimation from acceleration for quantitative evaluation of Parkinson tremor. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2011*, p. 393–6. <https://doi.org/10.1109/IEMBS.2011.6090126>.
- [31] Thielgen T, Foerster F, Fuchs G, Hornig A, Fahrenberg J. Tremor in Parkinson's Disease: 24-hr monitoring with calibrated accelerometry. *Electromyogr Clin Neurophysiol* 2004;44:137–46.
- [32] Schaeffer EL, Liu DY, Guerin J, Ahn M, Lee S, Asaad WF. A low-cost solution for quantification of movement during DBS surgery. *J Neurosci Methods* 2018;303:136–45. <https://doi.org/10.1016/j.jneumeth.2018.03.013>.

- [33] Schifino GP, da Cunha MJ, Marchese RR, Mabília V, Vian LHA, Pereira F dos S, et al. Smart Watch Sensors for Tremor Assessment in Parkinson's Disease—Algorithm Development and Measurement Properties Analysis. *Sensors* 2025;25. <https://doi.org/10.3390/s25144313>.
- [34] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's Disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4. <https://doi.org/10.1136/jnnp.55.3.181>.
- [35] Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967;17:427–427. <https://doi.org/10.1212/WNL.17.5.427>.
- [36] Maldonado-Naranjo A, Koop MM, Hogue O, Alberts J, MacHado A. Kinematic Metrics from a Wireless Stylus Quantify Tremor and Bradykinesia in Parkinson's Disease. *Parkinsons Dis* 2019;2019. <https://doi.org/10.1155/2019/6850478>.
- [37] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [38] Smid A, van Laar T, Pinkster AE, ten Kate JM, Kremer NI, Oterdoom DLM, et al. Perioperative quantification of clinical bradykinesia measurements in patients with Parkinson's Disease using accelerometry. *Clinical Neurophysiology* 2025;211:1424. <https://doi.org/10.1016/j.clinph.2025.2111424>.
- [39] McHugh M. Interrater reliability - the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276–82.
- [40] Ranganathan P, Pramesh C, Aggarwal R. Common pitfalls in statistical analysis: Measures of agreement. *Perspect Clin Res* 2017;8:187–91. https://doi.org/10.4103/picr.PICR_123_17.
- [41] Jeon H, Lee W, Park H, Lee HJ, Kim SK, Kim HB, et al. High-accuracy automatic classification of Parkinsonian tremor severity using machine learning method. *Physiol Meas* 2017;38:1980–99. <https://doi.org/10.1088/1361-6579/aa8e1f>.
- [42] Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. *Brain* 2006;129:2660–6. <https://doi.org/10.1093/brain/awl190>.
- [43] Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016;15:155–63. <https://doi.org/10.1016/j.jcm.2016.02.012>.
- [44] Wastensson G, Holmberg B, Johnels B, Barregard L. Quantitative Methods for Evaluating the Efficacy of Thalamic Deep Brain Stimulation in Patients with Essential Tremor. *Tremor and Other Hyperkinetic Movements* 2013;4. <https://doi.org/10.7916/D8VM4BoN>.
- [45] Elble RJ, Hellriegel H, Raethjen J, Deuschl G. Assessment of Head Tremor with Accelerometers Versus Gyroscopic Transducers. *Mov Disord Clin Pract* 2017;4:205–11. <https://doi.org/10.1002/mdc3.12379>.
- [46] Shah A, Coste J, Lemaire JJ, Schkommodau E, Taub E, Guzman R, et al. A novel assistive method for rigidity evaluation during deep brain stimulation surgery using acceleration sensors. *J Neurosurg* 2017;127:602–12. <https://doi.org/10.3171/2016.8.JNS152770>.
- [47] Evers LJW, Raykov YP, Heskes TM, Krijthe JH, Bloem BR, Little MA. Passive Monitoring of Parkinson Tremor in Daily Life: A Prototypical Network Approach. *Sensors* 2025;25. <https://doi.org/10.3390/s25020366>.
- [48] Keba M, Bachmann M, Lass J, Rätsep T. Assessing Parkinson's Rest Tremor from the Wrist with Accelerometry and Gyroscope Signals in Patients with Deep Brain Stimulation: An Observational Study. *J Clin Med* 2025;14. <https://doi.org/10.3390/jcm14062073>.
- [49] Elble RJ, Ondo W. Tremor rating scales and laboratory tools for assessing tremor. *J Neurol Sci* 2022;435. <https://doi.org/10.1016/j.jns.2022.120202>.
- [50] Mahadevan N, Demanuele C, Zhang H, Volfson D, Ho B, Erb MK, et al. Development of digital biomarkers for resting tremor and bradykinesia using a wrist-worn wearable device. *NPJ Digit Med* 2020;3. <https://doi.org/10.1038/s41746-019-0217-7>.

- [51] Elble R, Comella C, Fahn S, Hallett M, Jankovic J, Juncos JL, et al. Reliability of a new scale for Essential Tremor. *Movement Disorders* 2012;27:1567–9. <https://doi.org/10.1002/mds.25162>.
- [52] Fahn S, Tolosa E, Marín C. Clinical Rating Scale for Tremor. *Parkinson's Disease and Movement Disorders* 1988:225–34.
- [53] Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's Disease: Challenges and opportunities. *Movement Disorders* 2016;31:1272–82. <https://doi.org/10.1002/mds.26642>.
- [54] Heldman DA, Espay AJ, LeWitt PA, Giuffrida JP. Clinician versus machine: Reliability and responsiveness of motor endpoints in Parkinson's Disease. *Parkinsonism Relat Disord* 2014;20:590–5. <https://doi.org/10.1016/j.parkreldis.2014.02.022>.
- [55] Liu S, Yuan H, Liu J, Lin H, Yang C, Cai X. Comprehensive analysis of resting tremor based on acceleration signals of patients with Parkinson's Disease. *Technology and Health Care* 2022;30:895–907. <https://doi.org/10.3233/THC-213205>.
- [56] Channa A, Cramariuc O, Memon M, Popescu N, Mammone N, Ruggeri G. Parkinson's Disease resting tremor severity classification using machine learning with resampling techniques. *Front Neurosci* 2022. <https://doi.org/10.3389/fnins.2022.955464>.



Chapter 9

Summary and
discussion

Summary

Bradykinesia and tremor are common motor symptoms associated with Parkinson's Disease (PD) and Essential Tremor (ET). Bradykinesia is a prerequisite for diagnosis of PD, and tremor is the dominant symptom in ET [1–4]. The focus of this thesis is on the accelerometric quantification of bradykinesia and tremor of the upper extremities in PD and ET. Criteria from existing, well-validated, and internationally accepted clinical rating scales were objectively quantified using accelerometry, aiming to improve consistency and reliability in perioperative assessments.

Chapter 1 discusses the characteristics of tremor and bradykinesia and their neurosurgical options. Accurate perioperative assessment of both bradykinesia and tremor is essential for accomplishing optimal symptom suppression [5]. Contemporary clinical motor assessments are hampered by inter-rater variability, underlining the demand for an objective tool to perioperatively assess bradykinesia and tremor [6–9]. Accelerometry holds the promise of accurate and cost-effective quantification of bradykinesia and tremor, which allows for more consistent outcome measures and potentially may improve patients outcomes [10,11].

Traditionally, clinicians rely on clinical rating scales for evaluation of these motor symptoms during awake stereotactic neurosurgery. However, these scales have a high inter-rater variability and rely on experienced raters. Therefore, objective registration using movement sensors is a promising extension for intraoperative assessment of motor symptoms. Hence, **chapter 2** provides a structured overview of objective electronic measurements of motor symptoms during awake stereotactic neurosurgery. Intraoperative quantification of motor symptoms is still limited by variable signal analysis techniques and lacking standardized measurement protocols. Nevertheless, electronic motor measurements can complement visual evaluations and thus provide objective confirmation of accurate placement of the DBS electrode and/or lesion.

Currently, the most commonly used clinical scale to assess Parkinsonian motor symptoms is the internationally standardized Movement Disorder Society Unified PD Rating Scale part III (MDS-UPDRS-III). MDS-UPDRS-III is designed and validated for the sitting position. However, MDS-UPDRS-III is applied in a supine position in the operating theatre. Therefore, in **chapter 3**, the agreement between MDS-UPDRS-III scores in the sitting and supine positions was studied. Clinical evaluation by two independent MDS-UPDRS raters and accelerometric measurements were performed in both positions. The agreement between individual MDS-UPDRS-III items in the sitting and supine positions varied from fair to substantial. The inter-rater reliability was fair to moderate for both positions. Although overall substantial agreement between sitting and supine MDS-UPDRS-III was confirmed, its application in the supine position is not endorsed for the whole range of individual items, especially for resting tremor and finger tapping. Several recommendations are made to address the sensitivity of the MDS-UPDRS-III to inter-rater variability. Caution is warranted in interpreting the supine MDS-UPDRS-III, pending additional research.

Despite its drawbacks, MDS-UPDRS-III remains the gold standard for assessing tremor and bradykinesia in PD. During perioperative motor evaluations aiming to

optimize the clinical outcome of stereotactic neurosurgery, objective measurements using accelerometry may overcome the shortcomings of visually scored scales. Therefore, **chapter 4** focused on transforming MDS-UPDRS-III upper limb bradykinesia assessments into an objective scoring method, using 3D accelerometry in a perioperative setting to produce an algorithm for calculating accelerometric bradykinesia scores. This algorithm was based on MDS-UPDRS-III criteria with thresholds calculated from healthy controls. Given its consistency, this method can reduce MDS-UPDRS-III rater-dependency and improve objective monitoring of upper limb bradykinesia. Given the heterogeneous features of upper limb bradykinesia, this chapter underlines the complexity of quantifying bradykinesia with MDS-UPDRS-III.

Since MDS-UPDRS-III is less suitable for intraoperative tremor evaluation, the aim of **chapter 5** was to transform intraoperative MDS-UPDRS-III tremor tests into an objective algorithm with 3D accelerometry. Thresholds were derived from healthy controls. The area-under-the-curve of power in the 4–6 Hz frequency range was revealed as a new accelerometric outcome measure to detect the presence of Parkinsonian tremor. This outcome measure showed a substantial concordance between accelerometric scores and MDS-UPDRS-III ratings. Discrepancies were found in the results of the kinetic tremor test, mainly due to the noise between 4 and 6 Hz found in healthy controls, for which recommendations were formulated. This chapter took the first step in translating MDS-UPDRS-III tremor tests to an objective accelerometric method, aiming to reduce rater-dependency and allow for more consistent intraoperative monitoring of tremor.

Nowadays, the disease status, progression, and treatment effects of ET are assessed with clinical scores, such as the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM). Since the use of rater-independent monitoring of tremor may improve clinical care and may reduce variability in perioperative evaluations, **chapter 6** focused on the development of an objective accelerometry-based method to quantify ET, based on FTM-criteria. Four independent raters performed FTM assessments, while quantitative measures were derived from accelerometric data (e.g., the area under the curve of power in the 4–8 Hz frequency band and maximal tremor amplitude). This chapter shows that tremors can be quantified with accelerometry in a perioperative setting, using FTM-criteria and thresholds based on healthy controls. The test-retest reliability of the accelerometric tremor scoring algorithm indicated that our low-cost accelerometry-based approach is a promising one. The proposed easy-to-use technology can diminish FTM-rater dependency and enable physicians to consistently monitor ET patients.

Thalamotomy is well-known to alleviate medication-refractory tremor, e.g. in patients with movement disorders such as PD, ET, and Holmes tremor (HT). However, limited data is available on the course of tremor intensity during thalamotomy. Also, the predictive value of the intraoperative tremor status for postoperative treatment outcomes remains unclear. Therefore, in **chapter 7**, MDS-UPDRS-III scores and tri-axial accelerometry data were obtained during rest, postural, and intention tremor tests intraoperatively. Measurements were performed in PD, ET and HT patients: (1) before lesioning-probe insertion, (2) directly after lesioning-probe insertion, (3) during coagulation, (4) directly after coagulation, and (5) 4–6 months post-surgery. Continuous accelerometric data were recorded during the coagulation process. Tremor intensity was evaluated for the insertion

effect (1–2), during coagulation (3), post-coagulation effect (1–4), and postoperative effect (1–5). This chapter showed that both the intraoperative insertion effect and the post-coagulation effect are good predictors for longer-term thalamotomy outcome, underlining the value of quantitative intraoperative measurements.

Chapter 8 describes the development of the previously described accelerometric algorithm to measure and classify tremor of the hands, according to MDS-UPDRS-III criteria. The MDS-UPDRS-III hand tremor scores of 64 PD patients were related to our objective scoring method with 3D accelerometry. Two raters assessed MDS-UPDRS-III criteria for tremor severity, while accelerometry was performed at the index finger. The accelerometric area-under-the-curve of power in the 4–7 Hz range was applied to determine tremor presence, using thresholds based on data from healthy controls. The trends between tremor amplitude and MDS-UPDRS score were consistent with the logarithmic relationship reported in previous studies. Overall, the accelerometric scores showed a substantial agreement ($>80.2\%$, $\kappa \geq 0.732$) with the tremor amplitude according to MDS-UPDRS-III ratings. Discrepancies were found between accelerometric constancy of rest tremor (CRT) measures and MDS-UPDRS-III ratings, which are explained by CRT being calculated only for the time window that rest tremor test was measured. Considering the good to excellent accelerometric test-retest reliability in this study, chapter 8 demonstrates that MDS-UPDRS-III tremor measurements can be reliably translated to objective accelerometric scores. As such, accelerometry can complement visual evaluations of tremor, aiming to reduce rater-variability and allow for objective monitoring.

Discussion and future perspectives

Hypotheses and main outcomes

The aim of this thesis was to investigate the perioperative application of accelerometry, in order to objectively quantify bradykinesia and tremor.

First, it was hypothesized that measurement of bradykinesia and tremor using accelerometry would be a useful method to objectively quantify existing clinical motor scales in PD and ET. Although moderate agreement was found between standard clinical assessments for hand bradykinesia and accelerometric scores, the correlation between MDS-UPDRS-III and accelerometric outcome measures overall was weak (**chapter 4**). This can be explained partially by the set-up of the MDS-UPDRS-III item on bradykinesia, using a composite score of three components that play a role in bradykinesia (slowing, hesitations, amplitude decrement), while each accelerometric outcome measure was based on just a single component. The heterogeneous presentation of bradykinesia and the fact that the composite score is determined by the most affected component, can explain the poor correlations found in this study. Therefore, research in this field should shift the focus to investigating each component of bradykinesia, to allow comparison with objective metrics. Without clinical sub-scores of the separate components of bradykinesia, further optimization of this accelerometric approach is expected to falter.

The study which tried to quantify PD tremor showed an overall substantial agreement between the MDS-UPDRS-III and accelerometric scores (**chapter 5** and **8**). The data showed a moderate to good correlation between MDS-UPDRS-III and accelerometric outcome measures, although some discrepancies were found in the results of the kinetic tremor tests (**chapter 5**) and the constancy of the resting tremor tests (**chapter 8**). Resting tremor and postural tremor can be reliably quantified using accelerometry with the proposed algorithm. Optimizations in filter settings and thresholding, and validation against several levels of PD severity is recommended to improve the algorithm in future research.

The agreement between FTM and accelerometric scores was substantial for resting and intention tremor tests in the ET population (**chapter 6**). The agreement between accelerometric postural tremor scores and FTM-ratings ($\kappa=0.459$) was low, although their logarithmic relationship was substantial ($R^2 \geq 0.724$). Recommendations include validating the accelerometric algorithm in a larger cohort of ET patients and to reconsider the sensor positions in future research. In this study, the proximal phalanx of the index finger was chosen to measure hand tremor. If clinical raters primarily observe tremor in the more distal region of the index finger, or in a different part of the hand altogether, this will cause discrepancies in the agreement between the FTM and the accelerometric approach. Moreover, tremor amplitude will differ between proximal and distal positions of the hand. Also, tremor intermittency should be incorporated during further optimization of the algorithm, since intermittency is part of the composite score for tremor severity as defined in the FTM-scale.

Second, it was hypothesized that the objective measurement of bradykinesia and tremor would have added value in monitoring patients with PD and ET peri- and intraoperatively. This thesis indeed shows that the benefit of using accelerometry peri- and intraoperatively in patients with PD and ET mainly consists of a more uniform rating, which is a big advantage, because many different raters are involved in the overall neurosurgical trajectory, creating a lot of interindividual variance. PD patients showed a good to excellent test-retest reliability for both tremor (**chapter 5** and **8**) and bradykinesia (**chapter 4**). This range of accelerometric reliability was also found for ET (**chapter 6**). So, algorithms using accelerometric data are able to provide ratings rather similar to FTM and MDS-UPDRS-III assessments of tremor and bradykinesia. These algorithms are also suitable to produce continuous outcome measures on frequency, amplitude, velocity, and power, within certain frequency bands. Therefore, future research should test these measures to optimize DBS candidate selection, to guide optimal lead placement, and to evaluate the overall treatment effects.

The effect of DBS surgery, measured by accelerometry as well as clinical assessments, was not taken into account in this thesis, although these data are available from our center.

The relevance of perioperative motor quantification

The accelerometric method described in **chapter 5** and **7** can be applied in an intraoperative setting. Application of the same sensors at the outpatient clinic is a relatively small step, as shown in **chapter 3, 4, 6** and **8**. Monitoring and measuring

treatment effects is particularly crucial when resources and personnel are scarce. Motion sensors can be applied preoperatively to optimize the selection of surgical candidates, as well as postoperatively to objectively monitor symptom improvement at follow-up [12]. These studies underline the added value of quantifying bradykinesia and tremor in different stages of the perioperative setting.

From a physiological perspective, it would be nice to get more insight in the specific mechanisms and effects of DBS, for instance on individual components of tremor (amplitude, frequency, or constancy) and on bradykinesia (speed, amplitude, or hesitation). Previous data showed already how motion sensors can aid in optimizing DBS settings [13]. This will be even more promising with the implementation of “closed loop” or adaptive DBS [14,15] allowing for the development of solid biomarkers [16–19]. Motion sensors that provide input for aDBS [19,20] allow for stimulation on demand, may aid in personalized DBS settings and can save battery life [15,17].

Furthermore, there is great potential in applying sensor-based monitoring at home, to support clinicians in the optimal management of their patients in between outpatient clinic appointments [21,22]. As shown in this thesis, and confirmed by others, these quantitative measurements can complement clinical motor assessments in determining symptom severity and evaluating the efficacy of neurosurgical treatment [23].

The accuracy of current neuronavigation techniques allows DBS to be performed under general anesthesia in the majority of cases, with good results, which has limited the role of perioperative monitoring on tremor and bradykinesia [24–27]. However, from the perspective of patient comfort and surgical workflow, stereotactic neurosurgery performed under general anesthesia has considerable advantages [28]. The current practice shows that some procedures are still performed under local anesthesia, for instance in tremor-dominant and complex patients, to allow for adjustment of the electrode position, based on the magnitude of the micro-lesion effect, the side-effects and the motor effect [5,29–35]. Radiofrequency (RF) thalamotomy is also often performed awake with intraoperative monitoring. Even though RF lesioning is performed since the 1950s, it remains a relevant and cost-effective treatment option for patients suffering from tremor [36–38].

For target confirmation, intraoperative monitoring is especially relevant in surgery targeting the VIM, as the size and relative hypocellularity of this structure make it less discernible from the adjacent thalamic nuclei on MRI [30,39]. The immediate suppression of tremor with high frequent (>100 Hz) stimulation of the VIM allows for quick target confirmation and can simplify DBS programming by identifying the relevant contacts [28,30].

Accelerometry is also a feasible method to detect changes in tremor during MR-guided focused ultrasound (MRgFUS) [40]. After each sonication, real-time accelerometric recordings offered objective quantification of changes in tremor, consistent with the clinical assessment. Recent techniques in intraoperative monitoring use intraoperative local field recording or MER to optimize targeting, which may limit the value of accelerometry, as studied in this thesis [41]. Boëx et al. showed that β -oscillations computed from local field potentials (LFP) are useful to confirm STN location and to predict motor improvement [42]. On the other hand, the use of MER is associated with a

slightly higher rate of severe complications (e.g. hematoma and mortality) [43]. Shah et al. described how “stimulation maps” using MER and electric field simulation data can assist in identifying optimal DBS lead placement [44].

Although DBS is increasingly being performed under general anesthesia [45], it is expected that awake neurosurgery and intraoperative motor measurements remain effective strategies for optimal symptom reduction for PD and ET patients, especially in complex situations where the reliability offered by IONM is essential in achieving optimal lead positioning.

Accelerometric data analysis

A number of assumptions and choices were made to realize the accelerometric algorithms described in **chapter 4–6** and **8**. The thresholds used in these algorithms can be optimized by using data from patients with a wide range of symptom severity, as described in **chapter 4** and **5**. Choices made in the pre-processing stage also played a role in reaching optimal thresholds, for example by fine-tuning filter settings. The lower limit for the high-pass filter in **chapter 5, 6** and **8** was based on the type of exercise, like suppressing signals with frequencies below 3 Hz for kinetic tremor tests to remove low-frequent arm movements inherent to this exercise. In **chapter 4**, associated tremor was suppressed using a 4 Hz low-pass filter during bradykinesia assessments, although this might have suppressed relevant high-frequent tapping movements as well. Also, the frequency range applied to determine tremor power varied per chapter, from 4–6 Hz (**chapter 5**) and 4–8 Hz (**chapter 6**) to 4–7 Hz (**chapter 8**). Other groups have applied various other thresholds, all with promising results. Linden et al. used a wider frequency range (3–12 Hz) for the calculation of tremor power [46]. Shah et al. found a dominant tremor frequency in the range of 3–6 Hz in their ET and PD population [47]. These considerations, combined with the options for threshold adjustment, filter settings, and parameter selection may lead to a variety of algorithms as described in this thesis. Given the many options to fine-tune such algorithms, there is need for an effective way to check all possibilities and to come to an optimal version. Optimization and broad validation of the proposed algorithms are a prerequisite for application without clinical supervision, for example to monitor the course of motor symptoms at home, in order to give the patient feedback about their therapy.

The data-driven approach described in the previous section allows for collection of interesting data and parameters, which can offer valuable information for movement disorder diagnosis, progression, and treatment evaluation. On the other hand, the practical application of these approaches is often accompanied by complex hardware and software [48,49]. Most of these techniques rely on precise sensor calibration. Moreover, data pre-processing can be intricate and time-consuming. Therefore, in-house technical expertise of modalities and data analysis is essential in achieving clinically useful information. Since objective measurements result in complex quantitative data, advanced data analysis is required to rapidly evaluate large amounts of data and to make the data interpretable for clinicians. A large part of such techniques is covered by machine learning algorithms, but other mathematical procedures, like principal component analysis, can

also be considered. Examples of machine learning algorithms range from relatively simple linear and logistic models to complex deep neural networks. These techniques could also be employed to facilitate the fine tuning of algorithm thresholds, as described in the first paragraph of this section.

Previous work described several techniques, ranging from machine learning to non-black-box analysis, to classify symptoms or to find relevant parameters to explain abnormal motor performance. The algorithms in this thesis are the result of non-black-box programming, in which each modification of the data is programmed separately. In other research groups, deep learning techniques were employed to estimate motor symptom presence and severity in PD from accelerometry at the wrist [50]. Häring et al. successfully validated a machine learning approach based on accelerometry at the hands to differentiate ET from PD [51]. Bradykinetic gait severity was quantified by Samà et al. using tri-axial accelerometry at the waist and a machine learning method based on a support vector machines classifier [52]. Habets et al. proposed an open-source tool for the automated prediction of finger tapping scores based on machine learning classification models and accelerometry at the index fingers [53]. The systematic review from Fu et al. concludes that machine learning is a conducive method to classify motor performance of the hands, and that future research focused on processing collected smartphone data are especially interesting [54]. Still, these techniques call for further investigations, since accuracies vary per movement disorder [55]. High accuracies were achieved for PD, but machine learning achieved moderate to poor accuracy for ET and dystonic tremor, underscoring the difficulty of using artificial intelligence to classify specific tremor syndromes due to lack of specificity in clinical and neuropathological features [55].

Future perspectives

In this thesis, accelerometry was shown to be a feasible method to quantify tremor and bradykinesia severity in PD and ET. The studies described in **chapter 3–5** and **8** exclusively included patients with PD, while **chapter 2, 6, and 7** described the application of objective motor measurements in ET patients. Future research may focus on the role of accelerometry in severity assessment of dystonic tremor, Holmes tremor, and cerebellar tremor [56]. For example, Jabarkheel et al. already applied accelerometers to ascertain tremor characteristics in focal and segmental dystonia patients [57]. As for bradykinesia, chapter 4 underlines that the quantification of bradykinesia requires the separation of all three components (slowing, hesitations, amplitude decrement) in future research, since composite scores prevent precise analysis between clinical ratings and objective outcome measures.

It is recommended to further develop the accelerometric method proposed in this thesis to improve severity assessments. However, this technology can also be applied as a diagnostic tool [51,58], and for treatment evaluation [46,59–62]. Barrantes et al. used accelerometry to distinguish healthy volunteers, ET patients, and PD patients, aiding in establishing a correct diagnosis in patients with tremor of undecided origin [63].

This thesis did not explicitly show that the inter- and/or intra-rater variability of FTM or MDS-UPDRS-III decreases with the use of accelerometry. To strengthen the argument that accelerometry can aid in reducing scoring variability and rater dependency, I would recommend to perform a randomized controlled trial on the influence of accelerometry on clinical assessments for both tremor and bradykinesia. Also, the test-retest reliability (ICC) of clinical versus accelerometric scores should be formally compared, using bootstrapping [64].

Apart from accelerometry, also other transducers could be good candidates for the purposes described in this thesis. For example, gyroscopes can measure angular velocity within the frame of reference of the device, and magnetometers can record the course of the motion sensor relative to Earth's magnetic field [65]. To quantify motor symptoms, previous studies have employed a combination of accelerometers, gyroscopes, and/or magnetometers, often called an inertial measurement unit (IMU). For example, Tsipouras et al. used a combination of gyroscopes and accelerometers to distinguish between the ON and OFF state in PD patients [66]. Keba et al. showed that various accelerometric and gyroscope signal features perform well in characterizing rest tremor at the wrist in PD [67]. Finally, the rotating motion of the typical Parkinsonian “pill-rolling” tremor of the hands can be captured using a gyroscope.

Overall, an accurate and objective sensor, like an accelerometer, can measure the presence, severity, and fluctuations of motor symptoms like tremor and bradykinesia more precisely than the naked eye. However, it is difficult to determine which approach yields better results with the currently available resources. Given that the practical use of the current formal gold standards (like MDS-UPDRS-III or FTM) would be limited (e.g. due to a limited number of trained staff), what would be the significance of a substantial agreement between accelerometric outcome measures and these clinical scales in that case? Martínez-García-Peña et al. underlined the challenge of objectively evaluating movement disorders, since clinical assessments often rely on the experience of the rater, which complicates validation of objective methods [68]. A new gold standard might be developed in future research by employing new technologies, like 3D video analysis using trajectory reconstruction. Accelerometry can be integrated into video analysis, allowing tailoring to case complexity [68]. As video may suffer from loss of fine detail during rapid movements, the combination of video analysis with accelerometry would benefit from the mutual strengths [68]. Mason et al. used a combination of video analysis and accelerometry to quantify motor improvement in a dystonia patient during DBS-VIM surgery [69]. An important prerequisite for combining modalities is consistent data across all modalities. The downsides of multi-model approaches are complicated data collection and increased development complexity compared to single-modality systems [68]. Still, the application of other modalities, or a combination thereof, remains promising to create a “new gold standard”, and to achieve goals such as classification of tremor and bradykinesia, without clinical supervision, and to monitor symptoms at home.

As pointed out in **chapter 2**, most sensor-based approaches described in previous research lack standardized protocols [48]. International consensus on clinical or IONM protocols (including signal analysis techniques) during stereotactic neurosurgery is lacking. Moreover, outcome measures to quantify treatment effects of stereotactic

neurosurgery vary per study, awaiting solid validation in the perioperative setting. Conditions and limitations of executing motor measurements during IONM were previously described by Journée et al. [70]. To improve patient comfort, measurements should last 10 seconds at most, require minimal patient effort, using very few and small transducers. It is important to simplify measurement characteristics from body-worn sensors, while maintaining performance in symptom detection [71]. Careful consideration of sensor position is recommended, to allow measurement of the optimal range of motion (**chapter 6**). These aspects are essential for setting up a sensor-based approach in the perioperative setting. Standardized protocols with validated outcome measures have to be developed, that aid in predicting (long-term) outcomes.

Chapter 3 has shown that MDS-UPDRS-III is subject to inter-rater variability, for which recommendations were formulated. Certain MDS-UPDRS-III items (e.g., finger tapping) were found to be more susceptible to inter-rater variability, possibly due to criteria formulated as “slight”, “mild”, and “moderate”, which leaves interpretation open to the rater. Moreover, terms like “slowing” of the movement during the task can also be interpreted by the rater as general “slowness of movement” during the whole task. In practice, it depends on the rater how these criteria are applied. Therefore, international consensus is recommended, and MDS-UPDRS-III criteria and instructions should be sharpened to minimize inter-rater variability, and to allow optimization of bradykinesia and tremor assessments. For the time-being, clinical scales (e.g., MDS-UPDRS-III and FTM) are the best available standardized methods for assessing tremor and bradykinesia. Although clinical outcome measures might be difficult to reproduce, they most accurately reflect the actual clinical reality.

Translation of the clinical reality to an objective measurement method remains challenging. In **chapter 4**, accelerometric features that related to MDS-UPDRS-III bradykinesia criteria were selected. However, these features were often not the precise parameters described in the MDS-UPDRS-III, neither were they the exact MDS-UPDRS-III rating instructions followed in the algorithm. Further validation of these features is needed to ensure the use of reliable outcome measures in research and clinical settings. The current MDS-UPDRS-III bradykinesia scores are composite scores, reducing three different components (slowing, hesitations, and amplitude decrement) to a single score, instead of using sub-scores to show how a patient performs per component separately. This complicates comparison between MDS-UPDRS-III bradykinesia scores and objective outcome measures. Extracting features from objective measurement methods that correspond well to the clinical scoring of bradykinesia requires a more delicate assessment of bradykinesia than the MDS-UPDRS-III currently can offer. For future research, a viable option would be employing the modified Bradykinesia Rating Scale (mBRS) [72], which separately scores velocity, rhythm, and amplitude, allowing for a more granular comparison with objective metrics.

It is important to note that even though measurement methods described in this thesis present objective measures, their use will still be prone to subjectivity, since decision making is based on the interpretation of (objective) measures by the clinician. Therefore, it is not expected that objective methods to measure motor symptoms will replace clinical assessment. Nevertheless, the proposed methods can complement the current approach,

allowing objective input to be gathered for clinical decision making. This may improve the application of existing clinical scales by providing objective feedback on the outcome measures that are being scored, reducing variability among raters and allowing more uniform ratings of motor performance, despite several caretakers being involved with the patient.

Conclusions

This dissertation shows that the principle of quantifying existing clinical motor scales in PD and ET, using a specific accelerometric algorithm to objectively measure bradykinesia and tremor, is feasible. Overall, moderate to substantial agreement was found between the clinical ratings and accelerometric scores, showing that accelerometry offers performances comparable with human raters. However, this algorithm should be finetuned to yield more reliable results, and should be validated on a wider set of clinical (sub-)scores.

Second, this thesis shows that the objective measurement of bradykinesia and tremor has added value in monitoring patients with PD and ET peri- and intraoperatively. Test-retest reliability of the proposed accelerometric methods in perioperative settings ranged from good to excellent, indicating that our objective approach certainly has added value. Future research should determine the exact influence of accelerometry on clinical assessments for both tremor and bradykinesia.

References

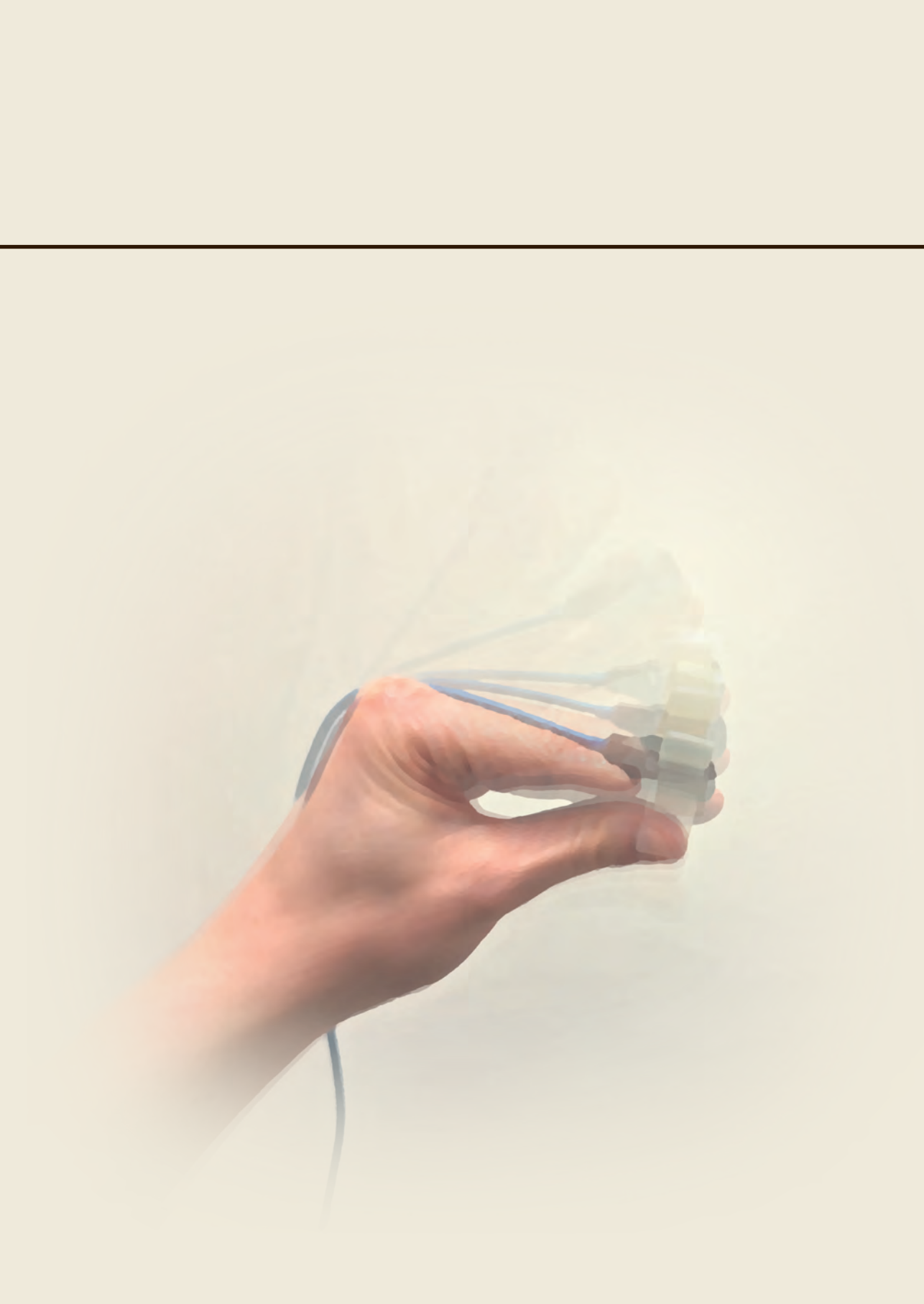
- [1] Kalia L, Lang AE. Parkinson's Disease. *The Lancet* 2015;386:896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3).
- [2] Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of Essential Tremor. *Movement Disorders* 2010;25:534–41. <https://doi.org/10.1002/mds.22838>.
- [3] Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's Disease. *Lancet Neurol* 2006;5:75–86. [https://doi.org/10.1016/S1474-4422\(05\)70285-4](https://doi.org/10.1016/S1474-4422(05)70285-4).
- [4] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's Disease. *Movement Disorders* 2015;30:1591–601. <https://doi.org/10.1002/mds.26424>.
- [5] Sammartino F, Rege R, Krishna V. Reliability of Intraoperative Testing During Deep Brain Stimulation Surgery. *Neuromodulation* 2020;23:525–9. <https://doi.org/10.1111/ner.13081>.
- [6] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [7] Krabbe P. *The Measurement of Health and Health Status: Concepts, Methods and Applications from a Multidisciplinary Perspective*. 1st ed. Academic Press; 2016.
- [8] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.
- [9] Erb MK, Karlin DR, Ho BK, Thomas KC, Parisi F, Vergara-Diaz GP, et al. mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's Disease. *NPJ Digit Med* 2020;3. <https://doi.org/10.1038/s41746-019-0214-x>.
- [10] Rovini E, Maremmani C, Cavallo F. How wearable sensors can support Parkinson's Disease diagnosis and treatment: A systematic review. *Front Neurosci* 2017;11. <https://doi.org/10.3389/fnins.2017.00555>.
- [11] Karas M, Bai J, Strączkiewicz M, Harezlak J, Glynn NW, Harris T, et al. Accelerometry Data in Health Research: Challenges and Opportunities: Review and Examples. *Stat Biosci* 2019;11:210–37. <https://doi.org/10.1007/s12561-018-9227-2>.
- [12] Lieber B, Taylor BES, Appelboom G, Mckhann G, Connolly ES. Motion Sensors to Assess and Monitor Medical and Surgical Management of Parkinson Disease. *World Neurosurg* 2015;84:561–6. <https://doi.org/10.1016/j.wneu.2015.03.024>.
- [13] Pulliam CL, Heldman DA, Orcutt TH, Mera TO, Giuffrida JP, Vitek JL. Motion sensor strategies for automated optimization of deep brain stimulation in Parkinson's Disease. *Parkinsonism Relat Disord* 2015;21:378–82. <https://doi.org/10.1016/j.parkreldis.2015.01.018>.
- [14] Ferleger BI, Houston B, Thompson MC, Cooper SS, Sonnet KS, Ko AL, et al. Fully implanted adaptive deep brain stimulation in freely moving Essential Tremor patients. *J Neural Eng* 2020;17:056026. <https://doi.org/10.1088/1741-2552/abb416>.
- [15] Piña-Fuentes D, van Dijk JMC, van Zijl JC, Moes HR, van Laar T, Oterdoom DLM, et al. Acute effects of adaptive Deep Brain Stimulation in Parkinson's Disease. *Brain Stimul* 2020;13:1507–16. <https://doi.org/10.1016/j.brs.2020.07.016>.
- [16] Stam MJ, van Wijk BCM, Buijink AWG, Piña-Fuentes D, de Bie RMA, Schuurman R, et al. Long-term consistency of aperiodic and periodic physiomarkers in subthalamic local field potentials in Parkinson's Disease. *NPJ Parkinsons Dis* 2025;11. <https://doi.org/10.1038/s41531-025-01053-5>.

- [17] Habets JGV, Heijmans M, Kuijf ML, Janssen MLF, Temel Y, Kubben PL. An update on adaptive deep brain stimulation in Parkinson's Disease. *Movement Disorders* 2018;33:1834–43. <https://doi.org/10.1002/mds.115>.
- [18] Mitchell KT, Starr PA. Smart neuromodulation in movement disorders, 2020, p. 153–61. <https://doi.org/10.1016/B978-0-444-63934-9.00012-3>.
- [19] Rojas E, Schmidt SL, Chowdhury A, Pajic M, Turner DA, Won DS. A comparison of an implanted accelerometer with a wearable accelerometer for closed-loop DBS. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, vol. 2022- July, Institute of Electrical and Electronics Engineers Inc.; 2022, p. 3439–42. <https://doi.org/10.1109/EMBC48229.2022.9871232>.
- [20] di Biase L, Tinkhauser G, Martin Moraud E, Caminiti ML, Pecoraro PM, Di Lazzaro V. Adaptive, personalized closed-loop therapy for Parkinson's Disease: biochemical, neurophysiological, and wearable sensing systems. *Expert Rev Neurother* 2021;21:1371–88. <https://doi.org/10.1080/14737175.2021.2000392>.
- [21] Carroll C. Impact of Quantitative Assessment of Parkinson's Disease-Associated Symptoms Using Wearable Technology on Treatment Decisions. *J Parkinsons Dis* 2019;9:601.
- [22] Santiago A, Langston JW, Gandhi R, Dhall R, Brillman S, Rees L, et al. Qualitative evaluation of the personal kinetigraph TM movement recording system in a Parkinson's clinic. *J Parkinsons Dis* 2019;9:207–19. <https://doi.org/10.3233/JPD181373>.
- [23] Wastensson G, Holmberg B, Johnels B, Barregard L. Quantitative Methods for Evaluating the Efficacy of Thalamic Deep Brain Stimulation in Patients with Essential Tremor. *Tremor and Other Hyperkinetic Movements* 2013;4. <https://doi.org/10.7916/D8VM4BoN>.
- [24] Holeywijn RA, Verbaan D, Van Den Munckhof PM, Bot M, Geurtsen GJ, Dijk JM, et al. General Anesthesia vs Local Anesthesia in Microelectrode Recording-Guided Deep-Brain Stimulation for Parkinson Disease: The GALAXY Randomized Clinical Trial. *JAMA Neurol* 2021;78:1212–9. <https://doi.org/10.1001/jamaneurol.2021.2979>.
- [25] Ho AL, Ali R, Connolly ID, Henderson JM, Dhall R, Stein SC, et al. Awake versus asleep deep brain stimulation for Parkinson's Disease: a critical comparison and meta-analysis. *J Neurol Neurosurg Psychiatry* 2018;89:687–91. <https://doi.org/10.1136/jnnp-2016-314500>.
- [26] Liu Z, He S, Li L. General anesthesia versus local anesthesia for deep brain stimulation in Parkinson's Disease: A meta-analysis. *Stereotact Funct Neurosurg* 2020;97:381–90. <https://doi.org/10.1159/000505079>.
- [27] Chen T, Mirzadeh Z, Chapple KM, Lambert M, Evidente VGH, Moguel-Cobos G, et al. Intraoperative test stimulation versus stereotactic accuracy as a surgical end point: A comparison of Essential Tremor outcomes after ventral intermediate nucleus deep brain stimulation. *J Neurosurg* 2018;129:290–8. <https://doi.org/10.3171/2017.3.JNS162487>.
- [28] van den Munckhof P, Bot M, Schuurman PR. Targeting of the Subthalamic Nucleus in Patients with Parkinson's Disease Undergoing Deep Brain Stimulation Surgery. *Neurol Ther* 2021;10:61–73. <https://doi.org/10.1007/s40120-021-00233-8>.
- [29] Kremer NI, Pauwels RWJ, Pozzi NG, Lange F, Roothans J, Volkmann J, et al. Deep brain stimulation for tremor: Update on long-term outcomes, target considerations and future directions. *J Clin Med* 2021;10. <https://doi.org/10.3390/jcm10163468>.
- [30] Dallapiazza R, McKisic MS, Shah B, Elias WJ. Neuromodulation for Movement Disorders. *Neurosurg Clin N Am* 2014;25:47–58. <https://doi.org/10.1016/j.nec.2013.08.002>.
- [31] Lange SF, Kremer NI, van Laar T, Lange F, Steendam-Oldenkamp TE, Oterdoom DLM, et al. The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation* 2021. <https://doi.org/10.1111/ner.13523>.

- [32] Erdogan S, Savas A, Aydin N, Akbostanci MC. Predictive factors for favorable outcome from subthalamic nucleus deep brain stimulation in Parkinson's Disease. *Turk Neurosurg* 2020;30:43–7. <https://doi.org/10.5137/1019-5149.JTN.25028-18.3>.
- [33] Cersosimo MG, Raina GB, Benarroch EE, Piedimonte F, Alemán GG, Micheli FE. Micro lesion effect of the globus pallidus internus and outcome with deep brain stimulation in patients with Parkinson's Disease and dystonia. *Movement Disorders* 2009;24:1488–93. <https://doi.org/10.1002/mds.22641>.
- [34] Mahajan A, Bader A, Wang LL, Rekhtman A, Espay AJ, Dwivedi AK, et al. Thalamic Deep Brain Stimulation for tremor: The critical role of intraoperative testing. *Parkinsonism Relat Disord* 2020;73:45–9. <https://doi.org/10.1016/j.parkreldis.2020.03.022>.
- [35] Pourfar M, Tang C, Lin T, Dhawan V, Kaplitt MG, Eidelberg DD. Assessing the microlesion effect of subthalamic deep brain stimulation surgery with FDG PET: Clinical article. *J Neurosurg* 2009;110:1278–82. <https://doi.org/10.3171/2008.12.JNS08991>.
- [36] Dallapiazza RF, Lee DJ, De Vloo P, Fomenko A, Hamani C, Hodaie M, et al. Outcomes from stereotactic surgery for Essential Tremor. *J Neurol Neurosurg Psychiatry* 2019;90:474–82. <https://doi.org/10.1136/jnnp-2018-318240>.
- [37] Sweet WH, Mark VH, Hamlin H. Radiofrequency Lesions in the Central Nervous System of Man and Cat. *J Neurosurg* 1960;17:213–25. <https://doi.org/10.3171/jns.1960.17.2.0213>.
- [38] Martínez-Moreno NE, Sahgal A, De Salles A, Hayashi M, Levivier M, Ma L, et al. Stereotactic radiosurgery for tremor: Systematic review. *J Neurosurg* 2019;130:589–600. <https://doi.org/10.3171/2017.8.JNS17749>.
- [39] Hirai T, Ohye C, Nagaseki Y, Matsumura M. Cytometric analysis of the thalamic ventralis intermedius nucleus in humans. *J Neurophysiol* 1989;61:478–87. <https://doi.org/10.1152/jn.1989.61.3.478>.
- [40] Gauthier-Lafreniere E, Aljassar M, Rymar V, Milton J, Sadikot AF. A standardized accelerometry method for characterizing tremor: Application and validation in an ageing population with postural and action tremor. *Front Neuroinform* 2022;16. <https://doi.org/10.3389/fninf.2022.878279>.
- [41] Holdefer RN, Cohen BA, Greene KA. Intraoperative local field recording for deep brain stimulation in Parkinson's Disease and Essential Tremor. *Movement Disorders* 2010;25:2067–75. <https://doi.org/10.1002/mds.23232>.
- [42] Boëx C, Tyrand R, Horvath J, Fleury V, Sadri S, Corniola M, et al. What Is the Best Electrophysiologic Marker of the Outcome of Subthalamic Nucleus Stimulation in Parkinson Disease? *World Neurosurg* 2018;120:e1217–24. <https://doi.org/10.1016/j.wneu.2018.09.047>.
- [43] Hariz MI, Fodstad H. Do Microelectrode Techniques Increase Accuracy or Decrease Risks in Pallidotomy and Deep Brain Stimulation? *Stereotact Funct Neurosurg* 1999;72:157–69. <https://doi.org/10.1159/000029720>.
- [44] Shah A, Vogel D, Alonso F, Lemaire JJ, Pison D, Coste J, et al. Stimulation maps: visualization of results of quantitative intraoperative testing for deep brain stimulation surgery. *Med Biol Eng Comput* 2020;58:771–84. <https://doi.org/10.1007/s11517-020-02130-y>.
- [45] Zhou Y, Fu S, Du L, Yang Z, Cai Y. General anesthesia versus local anesthesia for deep brain stimulation targeting of STN in Parkinson's Disease: A systematic review and meta-analysis. *Medicine (United States)* 2024;103:E37955. <https://doi.org/10.1097/MD.00000000000037955>.
- [46] van der Linden C, Berger T, Brandt GA, Strelow JN, Jergas H, Baldermann JC, et al. Accelerometric Classification of Resting and Postural Tremor Amplitude. *Sensors (Basel)* 2023;23. <https://doi.org/10.3390/s23208621>.
- [47] Shah A, Coste J, Lemaire JJ, Taub E, Schüpbach WMM, Pollo C, et al. Intraoperative acceleration measurements to quantify improvement in tremor during deep brain stimulation surgery. *Med Biol Eng Comput* 2017;55:845–58. <https://doi.org/10.1007/s11517-016-1559-9>.

- [48] Kostikis N, Hristu-Varsakelis D, Arnaoutoglou M, Kotsavasiloglou C. A smartphone-based tool for assessing parkinsonian hand tremor. *IEEE J Biomed Health Inform* 2015;19:1835–42. <https://doi.org/10.1109/JBHI.2015.2471093>.
- [49] Martinez-Manzanera O, Roosma E, Beudel M, Borgemeester RWK, van Laar T, Maurits NM. A Method for Automatic and Objective Scoring of Bradykinesia Using Orientation Sensors and Classification Algorithms. *IEEE Trans Biomed Eng* 2016;63:1016–24. <https://doi.org/10.1109/TBME.2015.2480242>.
- [50] Donié C, Das N, Endo S, Hirche S. Estimating motor symptom presence and severity in Parkinson's Disease from wrist accelerometer time series using ROCKET and InceptionTime. *Sci Rep* 2025;15. <https://doi.org/10.1038/s41598-025-04263-2>.
- [51] Häring V, Selzam V, Martin-Rodriguez JF, Schwingenschuh P, Tamás G, Köhler L, et al. Phenotypical Differentiation of Tremor Using Time Series Feature Extraction and Machine Learning. *Movement Disorders* 2025. <https://doi.org/10.1002/mds.70032>.
- [52] Samà A, Pérez-López C, Rodríguez-Martín D, Català A, Moreno-Aróstegui JM, Cabestany J, et al. Estimating bradykinesia severity in Parkinson's Disease by analysing gait through a waist-worn sensor. *Comput Biol Med* 2017;84:114–23. <https://doi.org/10.1016/j.combiomed.2017.03.020>.
- [53] Habets JGV, Spooner RK, Mathiopoloulou V, Feldmann LK, Busch JL, Roediger J, et al. A First Methodological Development and Validation of ReTap: An Open-Source UPDRS Finger Tapping Assessment Tool Based on Accelerometer-Data. *Sensors* 2023;23. <https://doi.org/10.3390/s23115238>.
- [54] Fu Y, Zhang Y, Ye B, Babineau J, Zhao Y, Gao Z, et al. Smartphone-Based Hand Function Assessment: Systematic Review. *J Med Internet Res* 2024;26. <https://doi.org/10.2196/51564>.
- [55] Balachandrar A, Algarni M, Oliveira L, Marsili L, Merola A, Sturchio A, et al. Are smartphones and machine learning enough to diagnose tremor? *J Neurol* 2022;269:6104–15. <https://doi.org/10.1007/s00415-022-11293-7>.
- [56] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders* 2018;33:75–87. <https://doi.org/10.1002/mds.27121>.
- [57] Jabarkheel Z, Wagle Shukla A. Clinical and physiological characteristics of tremor in a large cohort of focal and segmental dystonia. *Dystonia* 2024;3. <https://doi.org/10.3389/dyst.2024.12551>.
- [58] Ghassemi NH, Marxreiter F, Pasluosta CF, Kugler P, Schlachetzki J, Schramm A, et al. Combined accelerometer and EMG analysis to differentiate Essential Tremor from Parkinson's Disease. 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), IEEE; 2016, p. 672–5. <https://doi.org/10.1109/EMBC.2016.7590791>.
- [59] Teskey WJE, Elhabiby M, El-Sheimy N. Inertial sensing to determine movement disorder motion present before and after treatment. *Sensors* 2012;12:3512–27. <https://doi.org/10.3390/s120303512>.
- [60] Wilkes BJ, Wagle Shukla A, Casamento-Moran A, Hess CW, Christou EA, Okun MS, et al. Effects of ventral intermediate nucleus deep brain stimulation across multiple effectors in Essential Tremor. *Clinical Neurophysiology* 2020;131:167–76. <https://doi.org/10.1016/j.clinph.2019.10.019>.
- [61] Ushe M, Mink JW, Revilla FJ, Wernle A, Schneider Gibson P, McGee-Minnich L, et al. Effect of stimulation frequency on tremor suppression in Essential Tremor. *Movement Disorders* 2004;19:1163–8. <https://doi.org/10.1002/mds.20231>.
- [62] Spooner RK, Bagners BH, Schnitzler A, Florin E. Time-resolved quantification of fine hand movements as a proxy for evaluating bradykinesia-induced motor dysfunction. *Sci Rep* 2024;14. <https://doi.org/10.1038/s41598-024-55862-4>.

- [63] Barrantes S, Sánchez Egea AJ, González Rojas HA, Martí MJ, Compta Y, Valdeoriola F, et al. Differential diagnosis between Parkinson's Disease and Essential Tremor using the smartphone's accelerometer. *PLoS One* 2017;12. <https://doi.org/10.1371/journal.pone.0183843>.
- [64] Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. Chapman and Hall/CRC; 1994. <https://doi.org/10.1201/9780429246593>.
- [65] Elble RJ, Ondo W. Tremor rating scales and laboratory tools for assessing tremor. *J Neurol Sci* 2022;435. <https://doi.org/10.1016/j.jns.2022.120202>.
- [66] Tsipouras MG, Tzallas AT, Rigas G, Tsouli S, Fotiadis DI, Konitsiotis S. An automated methodology for levodopa-induced dyskinesia: Assessment based on gyroscope and accelerometer signals. *Artif Intell Med* 2012;55:127–35. <https://doi.org/10.1016/j.artmed.2012.03.003>.
- [67] Keba M, Bachmann M, Lass J, Rätsep T. Assessing Parkinson's Rest Tremor from the Wrist with Accelerometry and Gyroscope Signals in Patients with Deep Brain Stimulation: An Observational Study. *J Clin Med* 2025;14. <https://doi.org/10.3390/jcm14062073>.
- [68] Martínez-García-Peña R, Koens LH, Azzopardi G, Tijssen MAJ. Video-Based Data-Driven Models for Diagnosing Movement Disorders: Review and Future Directions. *Movement Disorders* 2025. <https://doi.org/10.1002/mds.30327>.
- [69] Mason XL, Cross KA, Arac A, Bordelon Y, Wu AD. Vim-Thalamic Deep Brain Stimulation for Cervical Dystonia and Upper-Limb Tremor: Quantification by Markerless-3D Kinematics and Accelerometry. *Tremor and Other Hyperkinetic Movements* 2022;12. <https://doi.org/10.5334/tohm.673>.
- [70] Journee HL, Postma AA, Staal MJ. Intraoperative neurophysiological assessment of disabling symptoms in DBS surgery. *Neurophysiologie Clinique* 2007;37:467–75. <https://doi.org/10.1016/j.neucli.2007.10.006>.
- [71] Shawen N, O'Brien MK, Venkatesan S, Lonini L, Simuni T, Hamilton JL, et al. Role of data measurement characteristics in the accurate detection of Parkinson's Disease symptoms using wearable sensors. *J Neuroeng Rehabil* 2020;17. <https://doi.org/10.1186/s12984-020-00684-4>.
- [72] Kishore A, Espay AJ, Marras C, Al-Khairalla T, Arenovic T, Asante A, et al. Modified Bradykinesia Rating Scale (mBRS). *Movement Disorders* 2014. <https://www.movementdisorders.org/MDS/MDS-Rating-Scales/Modified-Bradykinesia-Rating-Scale-MBRS-.htm>.



Appendix

Nederlandse samenvatting

Dankwoord

Curriculum vitae

List of publications

Author contribution

Nederlandse samenvatting

Perioperatieve accelerometrie voor bradykinesie en tremor

Bradykinesie en tremor zijn veelvoorkomende bewegingssymptomen die geassocieerd worden met de ziekte van Parkinson (ZvP) en Essentiële Tremor (ET). Bradykinesie wordt gekarakteriseerd door een afnemende amplitude van repetitieve stereotype bewegingen, traagheid van vrijwillige bewegingen en gebrek aan algemene motorische activiteit [1–4]. De aanwezigheid van bradykinesie is een voorwaarde voor het stellen van de diagnose ZvP [1,3,4]. Tremor, een ritmische en oscillerende onvrijwillige beweging, vormt het voornaamste symptoom bij ET tijdens het innemen van een positie of bij het naderen van een doelwit [2–5]. Momenteel worden meerdere beoordelingsschalen gebruikt om bewegingssymptomen zoals tremor en bradykinesie te evalueren bij de ZvP en ET, zowel binnen als buiten de chirurgische context [6,7]. Deze klinische beoordelingen van tremor en bradykinesie door klinici zijn echter subjectief en blijven, ondanks internationale standaardisatie door deskundige neurologen, gevoelig voor variabiliteit [8]. De resultaten zijn namelijk afhankelijk van de ervaring van de beoordelaar en het tijdstip van de meting, wat tot bias kan leiden [9–13]. Hoewel de beoordelingsschalen waardevolle inzichten verschaffen, vereist de toepassing een zorgvuldige overweging van potentiële vertekeningen en variabiliteit in klinische beoordelingen [9–15].

Aangezien er momenteel geen curatieve behandelopties zijn voor de ZvP en ET, is de behandeling gericht op het verminderen van bewegingssymptomen zoals bradykinesie en tremor. Diepe Brein Stimulatie (DBS) en letselchirurgie (bijv. thalamotomie) behoren tot de neurochirurgische opties hiervoor [16–19]. Tijdens een DBS-operatie worden één of twee elektroden uiterst nauwkeurig in het doelgebied in de hersenen geplaatst, unilateraal of bilateraal, om zo middels lokale stimulatie de invaliderende bewegingssymptomen te onderdrukken [20–23]. Tijdens thalamotomie wordt een thermische laesie (ablatie) aangebracht door een elektrode in de thalamus te positioneren ter reductie van de bewegingssymptomen [24]. Nauwkeurige plaatsing van de DBS-electroden en/of de laesie blijkt cruciaal voor het behandelingsucces [25–33]. Omdat een dergelijke positionering deels is gebaseerd op de perioperatieve bevindingen door de neuroloog, is het van essentieel belang dat de bewegingssymptomen tijdens de operatie correct en consistent worden gemeten om zo maximale symptoomreductie zonder bijwerkingen te realiseren [24,34,35]. Objectieve metingen met bewegingssensoren kunnen hieraan bijdragen, bijvoorbeeld met behulp van accelerometrie [36,37]. Accelerometers zijn non-invasieve sensoren die lineaire versnellingen meten relatief aan het gravitatieveld van de Aarde, veelal tri-axiaal langs drie loodrechte assen (X-Y-Z) [37]. De specificaties, eigenschappen en kosteneffectiviteit van commercieel beschikbare accelerometers maken deze bewegingssensoren uiterst geschikt voor het detecteren van tremor en bradykinesie, zoals reeds in eerder onderzoek is aangetoond [38–51]. Er is echter nog geen onderzoek verricht naar het vertalen van de klinische metingen naar een objectieve meetmethode.

Dit proefschrift richt zich op het perioperatief toepassen van accelerometrie voor het objectief kwantificeren van bradykinesie en tremor van de handen bij ZvP en ET. Bestaande, gevalideerde en internationaal geaccepteerde klinische beoordelingsschalen

zijn objectief gekwantificeerd met accelerometrie, met als doel de consistentie en betrouwbaarheid van beoordelingen te verbeteren.

Hoofdstuk 1 beschrijft de kenmerken van tremor en bradykinesie en hun neurochirurgische behandelopties. Een nauwkeurige perioperatieve beoordeling van zowel bradykinesie als tremor is essentieel om optimale symptoomonderdrukking te bereiken [34]. Klinische beoordelingen worden gehinderd door variabiliteit tussen beoordelaars, wat de noodzaak voor een objectieve methode voor de perioperatieve evaluatie van bradykinesie en tremor benadrukt [8,9,11,52]. Accelerometrie biedt de mogelijkheid om bradykinesie en tremor nauwkeurig en kosteneffectief te kwantificeren, waardoor metingen consistent worden en patiëntuitkomsten potentieel verbeteren [12,36].

Clinici gebruiken doorgaans voornamelijk subjectieve beoordelingsschalen voor de evaluatie van bewegingssymptomen tijdens wakkere stereotactische neurochirurgie. Deze schalen vertonen echter een hoge variabiliteit tussen beoordelaars en zijn afhankelijk van hun expertise. Daarom vormt objectieve registratie met behulp van bewegingssensoren een veelbelovende uitbreiding voor de beoordeling van bewegingssymptomen.

Hoofdstuk 2 biedt een gestructureerd overzicht van objectieve metingen van tremor en bradykinesie tijdens een stereotactische hersenoperatie. Het intra-operatief kwantificeren van bewegingssymptomen wordt nog steeds beperkt door uiteenlopende signaalanalysetechnieken en het ontbreken van gestandaardiseerde meetprotocollen. Desalniettemin kunnen elektronische metingen de visuele evaluaties aanvullen en zo een objectieve bevestiging bieden van de nauwkeurige plaatsing van de DBS-electrode en/of laesie.

Momenteel is de internationaal gestandaardiseerde “Movement Disorder Society Unified Parkinson’s Disease Rating Scale” deel III (MDS-UPDRS-III) de meest gebruikte klinische schaal voor het beoordelen van bewegingssymptomen bij patiënten met ZvP. De MDS-UPDRS-III is ontworpen en gevalideerd voor de situatie waarin de patiënt zich in de zittende positie bevindt. In de operatiekamer wordt de schaal echter toegepast met de patiënt in rugligging. Daarom beschrijft **hoofdstuk 3** het onderzoek naar de overeenstemming tussen MDS-UPDRS-III scores in een zittende en liggende positie. In beide posities werden zowel klinische evaluaties door twee onafhankelijke MDS-UPDRS beoordelaars als accelerometrie-metingen uitgevoerd. De overeenstemming tussen afzonderlijke MDS-UPDRS-III onderdelen in de zittende en liggende positie varieerde van matig tot aanzienlijk. Ook de betrouwbaarheid tussen beoordelaars was in beide posities matig tot redelijk. Alhoewel er gemiddeld genomen een substantiële overeenstemming tussen zittende en liggende MDS-UPDRS-III werd gevonden, wordt toepassing van MDS-UPDRS-III in rugligging niet aanbevolen voor het volledige spectrum van individuele items, in het bijzonder niet voor rusttremor en vinger-tikken. Er worden verschillende aanbevelingen gedaan om de gevoeligheid van de MDS-UPDRS-III voor variabiliteit tussen beoordelaars te verminderen. Al met al is voorzichtigheid geboden bij de interpretatie van de MDS-UPDRS-III in rugligging, in afwachting van aanvullend onderzoek.

De MDS-UPDRS-III blijft ondanks zijn beperkingen de gouden standaard voor het beoordelen van tremor en bradykinesie bij ZvP. Zo ook tijdens perioperatieve evaluaties

van bewegingssymptomen, die zijn gericht op het optimaliseren van de klinische uitkomst van stereotactische neurochirurgie. Objectieve metingen met behulp van accelerometrie zouden mogelijk de tekortkomingen van deze evaluaties met klinische schalen kunnen compenseren. **Hoofdstuk 4** richt zich daarom op het vertalen van de MDS-UPDRS-III score van bradykinesie van de handen naar een objectieve meetmethode, door gebruik te maken van 3D-accelerometrie in een perioperatieve setting. Zo werd een algoritme ontwikkeld voor het berekenen van bradykinesie-scores met behulp van accelerometrie. Dit algoritme was gebaseerd op MDS-UPDRS-III criteria, met drempelwaarden berekend uit de data van gezonde controles. Deze consistente methode kan de afhankelijkheid van beoordelaars bij MDS-UPDRS-III verminderen en de objectieve monitoring van bradykinesie van de handen verbeteren. Gezien de heterogene kenmerken van bradykinesie benadrukt dit hoofdstuk de complexiteit van het kwantificeren van bradykinesie met de MDS-UPDRS-III. Voor toekomstig onderzoek wordt aangeraden om de drie verschillende componenten van bradykinesie (vertraging, aarzeling in de bewegingen en amplitudevermindering) separaat te beoordelen, in plaats van ze alle drie te reduceren tot één samengestelde klinische score, zoals in de huidige MDS-UPDRS-III beschreven staat.

Aangezien de MDS-UPDRS-III minder geschikt is voor intra-operatieve evaluatie van tremor, is het doel van **hoofdstuk 5** om intra-operatieve MDS-UPDRS-III tremortesten te vertalen naar een objectief algoritme met behulp van 3D-accelerometrie. Drempelwaarden werden afgeleid van gezonde controles. Het oppervlak onder de curve van de vermogensspectra in het frequentiebereik van 4–6 Hz werd geïdentificeerd als een nieuwe uitkomstmaat voor het detecteren van de aanwezigheid van tremor bij patiënten met ZvP. Deze uitkomstmaat vertoonde een substantiële overeenstemming tussen accelerometrie-scores en MDS-UPDRS-III beoordelingen. Er werden discrepanties gevonden in de resultaten van de kinetische tremortest, vooral veroorzaakt door ruis in het bereik van 4–6 Hz data van gezonde controles, waarvoor aanbevelingen zijn geformuleerd. Dit hoofdstuk zet de eerste stap in het vertalen van MDS-UPDRS-III tremortesten naar een objectieve accelerometrie-methode, met als doel de afhankelijkheid van beoordelaars te verminderen en een meer consistente intra-operatieve monitoring van tremor mogelijk te maken.

Tegenwoordig worden de ziektestatus, progressie en behandelingseffecten van ET beoordeeld met klinische scores, zoals de “Fahn-Tolosa-Marin Clinical Rating Scale for Tremor” (FTM). Aangezien het gebruik van beoordelaar-onafhankelijke monitoring van tremor de klinische zorg kan verbeteren en de variabiliteit in perioperatieve evaluaties kan verminderen, richt **hoofdstuk 6** zich op de ontwikkeling van een objectieve accelerometrie-methode om ET te kwantificeren, gebaseerd op FTM-criteria. Vier onafhankelijke beoordelaars voerden FTM-beoordelingen uit, terwijl tegelijkertijd kwantitatieve maten werden afgeleid uit accelerometrie-data (bijvoorbeeld het oppervlak onder de curve van het vermogen in de frequentieband van 4–8 Hz, en de maximale tremoramplitude). Dit hoofdstuk toont aan dat tremor in een perioperatieve setting gekwantificeerd kan worden met accelerometrie, gebruikmakend van FTM-criteria en drempelwaarden gebaseerd op gezonde controles. De betrouwbaarheid van herhaaldelijke testen van het tremorscore-algoritme wijst erop dat deze kosteneffectieve,

op accelerometrie gebaseerde benadering veelbelovend is. De voorgestelde, gebruiksvriendelijke technologie kan de beoordelaarsafhankelijkheid verminderen en zorgverleners in staat stellen patiënten met ET consistent te monitoren.

Thalamotomie is een ingreep om medicatieresistente tremor te verbeteren, bijvoorbeeld bij patiënten met ZvP, ET en Holmes tremor (HT). Er zijn echter slechts beperkte data beschikbaar over het verloop van de tremorintensiteit tijdens thalamotomie. Ook blijft de voorspellende waarde van de intra-operatieve tremorstatus voor postoperatieve behandeluitkomsten onduidelijk. Daarom beschrijft **hoofdstuk 7** het onderzoek waarin MDS-UPDRS-III scores en accelerometrie-data werden verzameld tijdens intra-operatieve rust-, houdings- en intentietremortesten. Metingen werden uitgevoerd bij ZvP-, ET- en HT-patiënten: (1) vóór het inbrengen van de laesie-electrode, (2) direct na het inbrengen van de laesie-electrode, (3) tijdens coagulatie, (4) direct na coagulatie, en (5) 4–6 maanden na de operatie. Tijdens het coagulatieproces werden continue accelerometrie-data geregistreerd. Tremorintensiteit werd geëvalueerd voor het insertie-effect (1–2), tijdens coagulatie (3), het post-coagulatie-effect (1–4), en het postoperatieve effect (1–5). Dit hoofdstuk laat zien dat zowel het intra-operatieve insertie-effect als het post-coagulatie-effect goede voorspellers zijn voor de lange-termijn uitkomst van thalamotomie, waarmee de toegevoegde waarde van objectieve kwantitatieve intra-operatieve metingen wordt benadrukt.

Hoofdstuk 8 beschrijft de ontwikkeling van het eerder beschreven tremorscore-algoritme om handtremor te meten met accelerometrie en te classificeren volgens de MDS-UPDRS-III criteria. De MDS-UPDRS-III tremorscores van 64 patiënten met ZvP werden vergeleken met de objectieve scoringsmethode met 3D-accelerometrie. Twee beoordelaars evalueerden de tremoreerst o.b.v. MDS-UPDRS-III, terwijl accelerometrie werd gemeten aan de wijsvinger. Het oppervlak onder de curve van het vermogen in het frequentiebereik van 4–7 Hz werd toegepast om de aanwezigheid van tremor te bepalen, gebruikmakend van drempelwaarden gebaseerd op data van gezonde controles. De trends tussen tremoramplitude en MDS-UPDRS-III score waren consistent met de logaritmische relatie die in eerdere onderzoeken werd gerapporteerd. Al met al vertoonden de accelerometrie-scores een substantiële overeenstemming ($>80,2\%$, $\kappa \geq 0,732$) met de tremoramplitude volgens de MDS-UPDRS-III beoordelingen. Er werden discrepanties gevonden tussen accelerometrie-metingen van de consistentie van rusttremor (CRT) en MDS-UPDRS-III, wat kan worden verklaard doordat CRT uitsluitend werd berekend voor het tijdsvenster waarin de rusttremor taak werd uitgevoerd. Gezien de goede tot uitstekende betrouwbaarheid van herhaalde accelerometrie in dit onderzoek, is hiermee aangetoond dat MDS-UPDRS-III tremormetingen betrouwbaar kunnen worden vertaald naar objectieve accelerometrie-scores. Accelerometrie kan derhalve klinische beoordelingen van tremor complementeren, met als doel de variabiliteit tussen beoordelaars te verminderen en objectieve monitoring mogelijk te maken.

Conclusie

Dit proefschrift toont aan dat het haalbaar is om middels accelerometrie gestandaardiseerde klinische beoordelingen van bradykinesie en tremor bij ZvP en ET te objectiveren en te kwantificeren. Er werd een matige tot substantiële overeenstemming gevonden tussen de klinische beoordelingen en de accelerometrie-scores, wat aantoont dat accelerometrie data levert die vergelijkbaar zijn met die van klinische beoordelaars. Het accelerometrie-algoritme dient echter verder verfijnd te worden om de betrouwbaarheid van deze resultaten te verbeteren, en dient gevalideerd te worden binnen een bredere set van klinische (sub-)scores. Daarnaast laat dit proefschrift zien dat de objectieve meting van bradykinesie en tremor een duidelijke meerwaarde heeft bij het monitoren van patiënten met ZvP en ET, zowel voor, tijdens als na de operatie. De betrouwbaarheid van de voorgestelde accelerometrie-methoden in de perioperatieve omgeving varieerde van goed tot uitstekend, wat aangeeft dat deze objectieve benadering zeker toegevoegde waarde heeft. Toekomstig onderzoek dient de precieze rol van accelerometrie bij het beoordelen zowel tremor als bradykinesie in de klinische setting nader vast te stellen.

Referenties

- [1] Kalia L, Lang AE. Parkinson's Disease. *The Lancet* 2015;386:896–912. [https://doi.org/10.1016/S0140-6736\(14\)61393-3](https://doi.org/10.1016/S0140-6736(14)61393-3).
- [2] Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of Essential Tremor. *Movement Disorders* 2010;25:534–41. <https://doi.org/10.1002/mds.22838>.
- [3] Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's Disease. *Lancet Neurol* 2006;5:75–86. [https://doi.org/10.1016/S1474-4422\(05\)70285-4](https://doi.org/10.1016/S1474-4422(05)70285-4).
- [4] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's Disease. *Movement Disorders* 2015;30:1591–601. <https://doi.org/10.1002/mds.26424>.
- [5] Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders* 2018;33:75–87. <https://doi.org/10.1002/mds.27121>.
- [6] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. *MDS_UPDRS_Updated_August2019* 2019;1–34. www.movementdisorders.org (accessed September 26, 2022).
- [7] Fahn S, Tolosa E, Marin C. Clinical Rating Scale for Tremor. *Parkinson's Disease and Movement Disorders* 1988;225–34.
- [8] Krabbe P. *The Measurement of Health and Health Status: Concepts, Methods and Applications from a Multidisciplinary Perspective*. 1st ed. Academic Press; 2016.
- [9] Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's Disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* 2019;34:1480–7. <https://doi.org/10.1002/mds.27790>.
- [10] Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's Disease rating scale. *Arch Neurol* 2010;67:64–70.
- [11] Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement Disorders* 2005;20:1577–84. <https://doi.org/10.1002/mds.20640>.
- [12] Rovini E, Maremmani C, Cavallo F. How wearable sensors can support Parkinson's Disease diagnosis and treatment: A systematic review. *Front Neurosci* 2017;11. <https://doi.org/10.3389/fnins.2017.00555>.
- [13] Ossig C, Antonini A, Buhmann C, Classen J, Csoti I, Falkenburger B, et al. Wearable sensor-based objective assessment of motor symptoms in Parkinson's Disease. *J Neural Transm* 2016;123:57–64. <https://doi.org/10.1007/s00702-015-1439-8>.
- [14] Erro R, Fasano A, Barone P, Bhatia KP. Milestones in Tremor Research: 10 Years Later. *Mov Disord Clin Pract* 2022;9:429–35. <https://doi.org/10.1002/mdc3.13418>.
- [15] Lukšys D, Jonaitis G, Griškevičius J. Quantitative Analysis of Parkinsonian Tremor in a Clinical Setting Using Inertial Measurement Units. *Parkinsons Dis* 2018;2018. <https://doi.org/10.1155/2018/1683831>.
- [16] Kabra A, Sharma R, Kabra R, Baghel US. Emerging and Alternative Therapies For Parkinson Disease: An Updated Review. *Curr Pharm Des* 2018;24:2573–82. <https://doi.org/10.2174/1381612824666180820150150>.
- [17] Abosch A, Lozano A. Stereotactic neurosurgery for movement disorders. *Canadian Journal of Neurological Sciences* 2003;30. <https://doi.org/10.1017/s0317167100003279>.

- [18] Fejeran J, Salazar F, Alvarez CM, Jahangiri FR. Deep Brain Stimulation and Microelectrode Recording for the Treatment of Parkinson's Disease. *Cureus* 2022. <https://doi.org/10.7759/cureus.27887>.
- [19] Eskandar EN, Shinobu LA, Penney JB, Cosgrove GR, Counihan TJ. Stereotactic pallidotomy performed without using microelectrode guidance in patients with Parkinson's Disease: surgical technique and 2-year results. *J Neurosurg* 2000;92:375–83. <https://doi.org/10.3171/jns.2000.92.3.0375>.
- [20] Hilker R, Voges J, Weber T, Kracht L, Roggendorf J, Baudrexel S, et al. STN-DBS activates the target area in Parkinson disease: An FDG-PET study. *Neurology* 2008;71:708–13.
- [21] Schor JS, Nelson AB. Multiple stimulation parameters influence efficacy of deep brain stimulation in parkinsonian mice. *Journal of Clinical Investigation* 2019;129:3833–8. <https://doi.org/10.1172/JCI122390>.
- [22] Chiken S, Nambu A. Mechanism of Deep Brain Stimulation: Inhibition, Excitation, or Disruption? *Neuroscientist* 2016;22:313–22. <https://doi.org/10.1177/1073858415581986>.
- [23] Chen KHS, Chen R. Invasive and Noninvasive Brain Stimulation in Parkinson's Disease: Clinical Effects and Future Perspectives. *Clin Pharmacol Ther* 2019;106:763–75. <https://doi.org/10.1002/cpt.1542>.
- [24] Kremer NI, Pauwels RWJ, Pozzi NG, Lange F, Roothans J, Volkmann J, et al. Deep brain stimulation for tremor: Update on long-term outcomes, target considerations and future directions. *J Clin Med* 2021;10. <https://doi.org/10.3390/jcm10163468>.
- [25] Athawale TM, Johnson KA, Butson CR, Johnson CR. A statistical framework for quantification and visualisation of positional uncertainty in deep brain stimulation electrodes. *Comput Methods Biomech Biomed Eng Imaging Vis* 2019;7:438–49. <https://doi.org/10.1080/21681163.2018.1523750>.
- [26] Kremer NI, van Laar T, Lange SF, Statius Muller S, la Bastide-van Gemert S, Oterdoom DM, et al. STN-DBS electrode placement accuracy and motor improvement in Parkinson's Disease: systematic review and individual patient meta-analysis. *J Neurol Neurosurg Psychiatry* 2022;jnnp-2022-329192. <https://doi.org/10.1136/jnnp-2022-329192>.
- [27] Lange SF, Kremer NI, van Laar T, Lange F, Steendam-Oldekamp TE, Oterdoom DLM, et al. The Intraoperative Microlesion Effect Positively Correlates With the Short-Term Clinical Effect of Deep Brain Stimulation in Parkinson's Disease. *Neuromodulation: Technology at the Neural Interface* 2021;ner.13523. <https://doi.org/10.1111/ner.13523>.
- [28] Okun MS, Tagliati M, Pourfar M, Fernandez HH, Rodriguez RL, Alterman RL, et al. Management of Referred Deep Brain Stimulation Failures A Retrospective Analysis From 2 Movement Disorders Centers. *Arch Neurol* 2005;62:1250–5.
- [29] Dembek TA, Roediger J, Horn A, Reker P, Oehr C, Dafsari HS, et al. Probabilistic sweet spots predict motor outcome for deep brain stimulation in Parkinson disease. *Ann Neurol* 2019;86:527–38. <https://doi.org/10.1002/ana.25567>.
- [30] Nguyen TAK, Nowacki A, Debove I, Petermann K, Tinkhauser G, Wiest R, et al. Directional stimulation of subthalamic nucleus sweet spot predicts clinical efficacy: Proof of concept. *Brain Stimul* 2019;12:1127–34. <https://doi.org/10.1016/j.brs.2019.05.001>.
- [31] Herzog J, Fietzek U, Hamel W, Morsnowski A, Steigerwald F, Schrader B, et al. Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's Disease. *Movement Disorders* 2004;19:1050–4. <https://doi.org/10.1002/mds.20056>.
- [32] Verhagen R, Bour LJ, Odekerken VJJ, Van Den Munckhof P, Richard Schuurman P, De Bie RMA. Electrode location in a microelectrode recording-based model of the subthalamic nucleus can predict motor improvement after deep brain stimulation for Parkinson's Disease. *Brain Sci* 2019;9. <https://doi.org/10.3390/brainsci9030051>.

- [33] Sirica D, Hewitt AL, Tarolli CG, Weber MT, Zimmerman C, Santiago A, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. *Neurodegener Dis Manag* 2021;11:315–28. <https://doi.org/10.2217/nmt-2021-0002>.
- [34] Sammartino F, Rege R, Krishna V. Reliability of Intraoperative Testing During Deep Brain Stimulation Surgery. *Neuromodulation* 2020;23:525–9. <https://doi.org/10.1111/ner.13081>.
- [35] Mahajan A, Bader A, Wang LL, Rekhtman A, Espay AJ, Dwivedi AK, et al. Thalamic Deep Brain Stimulation for tremor: The critical role of intraoperative testing. *Parkinsonism Relat Disord* 2020;73:45–9. <https://doi.org/10.1016/j.parkreldis.2020.03.022>.
- [36] Karas M, Bai J, Strączkiewicz M, Harezlak J, Glynn NW, Harris T, et al. Accelerometry Data in Health Research: Challenges and Opportunities: Review and Examples. *Stat Biosci* 2019;11:210–37. <https://doi.org/10.1007/s12561-018-9227-2>.
- [37] Sievänen H, Kujala UM. Accelerometry—Simple, but challenging. *Scand J Med Sci Sports* 2017;27:574–8. <https://doi.org/10.1111/sms.12887>.
- [38] Zajki-Zechmeister T, Kögl M, Kalsberger K, Franthal S, Homayoon N, Katschnig-Winter P, et al. Quantification of tremor severity with a mobile tremor pen. *Heliyon* 2020;6:e047. <https://doi.org/10.1016/j.heliyon.2020.e04702>.
- [39] Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJG, Aminian K. Quantification of tremor and bradykinesia in Parkinson's Disease using a novel ambulatory monitoring system. *IEEE Trans Biomed Eng* 2007;54:313–22. <https://doi.org/10.1109/TBME.2006.886670>.
- [40] Salarian A, Russmann H, Vingerhoets FJG, Burkhard PR, Aminian K. Ambulatory monitoring of physical activities in patients with Parkinson's Disease. *IEEE Trans Biomed Eng* 2007;54:2296–9. <https://doi.org/10.1109/TBME.2007.896591>.
- [41] van Brummelen EMJ, Ziagos D, de Boon WMI, Hart EP, Doll RJ, Huttunen T, et al. Quantification of tremor using consumer product accelerometry is feasible in patients with Essential Tremor and Parkinson's Disease: a comparative study. *J Clin Mov Disord* 2020;7. <https://doi.org/10.1186/s40734-020-00086-7>.
- [42] Dunnewold RJW, Hoff JJ, van Pelt HCJ, Fredrikze PQ, Wagemans EAH, van Hilten BJJ. Ambulatory Quantitative Assessment of Body Position, Bradykinesia, and Hypokinesia in Parkinson's Disease. *Journal of Clinical Neurophysiology* 1998;15:235–42. <https://doi.org/10.1097/00004691-199805000-00007>.
- [43] Dunnewold RJW, Jacobi CE, Van Hilten JJ. Quantitative assessment of bradykinesia in patients with Parkinson's Disease. *J Neurosci Methods* 1997;74:107–12.
- [44] Rajaraman V, Jack D, Adamovich S V, Hening W, Sage J, Poizner H. A novel quantitative method for 3D measurement of Parkinsonian tremor. *Clinical Neurophysiology* 2000;111:338–43.
- [45] Deuschl G, Lauk M, Timmer J. Tremor classification and tremor time series analysis. *Chaos* 1995;5:48–51. <https://doi.org/10.1063/1.166084>.
- [46] Van Hilten JJ, Middelkoop HAM, Kerkhof GA, Roos RAC. A new approach in the assessment of motor activity in Parkinson's Disease. *J Neurol Neurosurg Psychiatry* 1991;54:976–9. <https://doi.org/10.1136/jnnp.54.11.976>.
- [47] Spyers-Ashby JM, Stokes MJ, Bain PG, Roberts SJ. Classification of normal and pathological tremors using a multidimensional electromagnetic system. *Med Eng Phys* 1999;21:713–23.
- [48] Battista L, Romaniello A. A wearable tool for continuous monitoring of movement disorders: clinical assessment and comparison with tremor scores. *Neurological Sciences* 2021;42:4241–8. <https://doi.org/10.1007/s10072-021-05120-6>.
- [49] Gauthier-Lafreniere E, Aljassar M, Rymar V, Milton J, Sadikot AF. A standardized accelerometry method for characterizing tremor: Application and validation in an ageing population with postural and action tremor. *Front Neuroinform* 2022;16. <https://doi.org/10.3389/fninf.2022.878279>.

- [50] Thielgen T, Foerster F, Fuchs G, Hornig A, Fahrenberg J. Tremor in Parkinson's Disease: 24-hr monitoring with calibrated accelerometry. *Electromyogr Clin Neurophysiol* 2004;44:137–46.
- [51] Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's Disease. *J Parkinsons Dis* 2012;2:47–55. <https://doi.org/10.3233/JPD.2012-11071>.
- [52] Erb MK, Karlin DR, Ho BK, Thomas KC, Parisi F, Vergara-Diaz GP, et al. mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's Disease. *NPJ Digit Med* 2020;3. <https://doi.org/10.1038/s41746-019-0214-x>.

Dankwoord

Dit proefschrift vormt het einde van een intensief en leerzaam hoofdstuk uit mijn leven. Deze thesis had niet tot stand kunnen komen zonder de inspiratie en steun van velen. Bij deze wil ik graag iedereen bedanken die zowel direct als indirect heeft bijgedragen aan de totstandkoming van dit proefschrift.

Allereerst wil ik graag mijn dank betuigen aan alle patiënten en vrijwilligers die hebben deelgenomen aan de onderzoeken. Ik heb enorme waardering voor jullie bereidheid om bij te dragen aan wetenschappelijk onderzoek. Dit werk was niet mogelijk geweest zonder jullie deelname.

Prof. dr. J.M.C. van Dijk, beste Marc, bedankt voor jouw vertrouwen in mij. Je hebt je vanaf het begin van mijn carrière bij het UMCG ingezet voor mijn toekomst, en dat waardeer ik enorm. Ik kon je laagdrempelig opzoeken voor advies of om even bij te praten. Dankzij jouw snelle feedback werden onze manuscripten in vlot tempo beter en beter. Ik heb veel van je geleerd, en ik ben dankbaar voor de vrijheid die je me hebt gegeven om me te ontwikkelen als onderzoeker en als zorgverlener. Bedankt voor het creëren van kansen en jouw volharding in het zoeken naar oplossingen. Ik blik met plezier terug op dit leerzame PhD-traject en onze samenwerking, nogmaals ontzettend bedankt voor jouw inzet en vertrouwen.

Prof. dr. T. van Laar, beste Teus, bedankt voor je steun en begeleiding tijdens de afgelopen jaren. Jouw vakinhoudelijke kennis over de ziekte van Parkinson was zeer waardevol voor de totstandkoming van dit proefschrift. Bedankt voor de goede discussies en jouw adviezen. Ik ben dankbaar voor de mooie onderzoeken die we hebben kunnen uitvoeren in Punt voor Parkinson, en de ruimte die je me gaf om me te ontplooien in de kliniek. Bedankt voor de fijne samenwerking en jouw vertrouwen in mij.

Dr. G. Drost, beste Gea, bedankt dat je mijn potentie zag en onvermoeibaar voor mijn carrière in het UMCG hebt gestreden. Onze samenwerking van de laatste jaren heeft me veel geleerd, en ik kijk er met plezier op terug. De herinnering aan hoe we in 2019 begonnen met de eerste stappen richting dit proefschrift, brengt een glimlach op mijn gezicht. De warmte waarmee je met collega's samenwerkt, en hoe je met anderen meebeweegt om gezamenlijke doelen te bereiken, is inspirerend. Ik bewonder jouw doorzettingsvermogen, zorgvuldigheid en zorgzaamheid. Je hebt een fantastisch team om je heen gebouwd bij de KNF, en een ontzettend leuke en talentvolle groep promovendi samengebracht. Bedankt voor de levenslessen, de gezelligheid, en jouw mentorschap. Ik heb ervan genoten om met je samen te werken en hoop nog veel van je te leren bij de KNF. Ontzettend bedankt voor alle tijd die je in mijn opleiding hebt gestoken.

Dank aan de leden van leescommissie, prof. dr. ir. M.J.A.M. van Putten, prof. dr. M.A.J. Koning-Tijssen, en prof. dr. P.R. Schuurman, voor uw tijd en moeite om dit proefschrift te beoordelen.

Ik wil graag alle medeauteurs bedanken voor hun inzet en samenwerking: Zeus Dominguez-Vega, Marinus Oterdoom, Anthony Absalom, Martje van Egmond, Naomi Kremer, Stèfan Lange, Iara Mateus Marçal, Katalin Tamasi, Amber Pinkster, Jolien ten Kate, Jan Willem Elting, Bert Otten, Ciska Heida, Rik Pauwels, Cheryl Everlo, en Madelein van der Stouwe.

Beste **Paulus** en **Wim**, bedankt voor jullie bijdrage als patiënt-onderzoekers. Ik hecht veel waarde aan jullie perspectief op deze onderzoekslijn en wil jullie bedanken voor onze brainstormsessies om het studieprotocol te optimaliseren. Bedankt voor jullie vrouwen in mij.

Jolien, enorm bedankt voor alles wat je me geleerd hebt over het afnemen van de MDS-UPDRS, het programmeren van diepe hersenstimulatoren, en de praktische zaken die bij het DBS-zorgpad komen kijken. We hebben een hele periode nauw samengewerkt, waarbij ik wekelijks tijdens jouw spreekuur en de dagbehandelingen aansloot om mijn metingen uit te voeren. Ik heb veel bewondering voor hoe zorgvuldig jij de DBS-zorg coördineert, altijd met oog voor de patiënt als persoon, en rekening houdend met de rest van de DBS-collega's. Ik heb met plezier jouw taken overgenomen toen je op wereldreis ging en toen je met zwangerschapsverlof was. Dank voor je behulpzaamheid en jouw inzet voor dit proefschrift.

Zeus, Naomi en **Rik**, bedankt voor jullie enthousiasme en vastberadenheid. Ik vond onze samenwerking erg fijn, en ik hoop dat we in de toekomst weer samen aan projecten kunnen werken.

Jan Willem, bedankt voor jouw onvermoeibare inzet voor het optimaliseren van het meetprogramma voor accelerometrie in LabVIEW. Dit proefschrift was niet hetzelfde geweest zonder jouw inspanningen. Ik heb veel geleerd van onze discussies en jouw goede suggesties, daarvoor wil ik je graag bedanken.

Fiete, bedankt voor je hulp tijdens de intra-operatieve metingen en jouw opbeurende humor. Ik hoop nog veel van je te mogen leren bij de KNF. Ook dank aan alle KNF-laboranten.

Alle OK-assistenten die betrokken zijn bij functionele neurochirurgische ingrepen, bedankt voor jullie geduld en hulp tijdens de intra-operatieve metingen. **Sijeesh, Engelina, Silvana, Angélique** en **Niels**, bedankt voor de gezelligheid tijdens de DBS-cursus in Ierland, ik hoop dat we in de toekomst nog meer kunnen samenwerken. Ook dank aan de OK-planning van de neurochirurgie.

Marinus, bedankt voor het mede mogelijk maken van de intra-operatieve metingen en alles wat je me geleerd hebt over stereotactische neurochirurgie. Ik hoop dat we onze fijne samenwerking in de toekomst kunnen voortzetten, om zo de DBS-zorg verder te optimaliseren.

Katalin, enorm bedankt voor al je hulp bij de statistische analyses. Ik hecht veel waarde aan onze goede discussies en jouw waardevolle inzichten en suggesties, dank daarvoor.

Mijn PhD collega's, **Bianca, Sebastiaan, Naomi, Lilian, Marieke, Nadia, Svea, Lina** en **Nick**, bedankt voor jullie hulp en de gezellige lunches, PhD-borrels en pizza-avonden. Ik waardeer het enorm dat jullie altijd bereid waren om mij te helpen wanneer dat nodig was. Met jullie enthousiasme en veerkracht hebben jullie mij gemotiveerd tijdens dit PhD-project. Bedankt dat jullie zulke fijne collega's waren, dit promotietraject was niet hetzelfde geweest zonder jullie.

Ik wil graag alle onderzoekers en neurologen van de hyperkinetische onderzoeksgroep (waaronder **Liesanne, Wieke, Inge, Saar, Sjoukje, Elina, Anne, Danique, Madelein, Cheryll, Sterre, Lisette, Sarah, Jelle, Elze, Lenny, Olof, Alma,**

Mariya, Rafael, Izebel en Ellen) bedanken voor de gezelligheid tijdens congressen en de inspiratie die ik bij jullie heb mogen opdoen. Ook dank daarvoor aan de Parkinson-onderzoekers van de neurologie.

Ronald, bedankt voor al je hulp bij het regelen van IT-zaken en je altijd aanstekelijke vrolijkheid.

Diane, bedankt voor je hulp bij de documentatie van mijn studies. Ik waardeer erg hoe benaderbaar je bent en hoe goed je met me mee hebt gedacht, bedankt daarvoor.

Alida, Emma, Janette, Nadine en Yvonne, bedankt voor het vinden van oplossingen voor de onmogelijke taak om regelmatig meetings in te plannen met het gehele promotieteam. Ik stel jullie geduld en onze gezellige praatjes tussendoor erg op prijs. Ook dank daarvoor aan **Manon, Mieke en Sharon**.

Susan, bedankt voor de goede gesprekken, het meedenken over mijn toekomst en het creëren van mogelijkheden binnen een systeem dat (nog) niet helemaal ingericht lijkt te zijn voor mijn beroepsgroep. Ik waardeer het erg dat jouw deur altijd open staat, bedankt daarvoor.

Marina, bedankt voor de kansen die je voor mij hebt gevormd zodat ik me kan ontwikkelen binnen de neurologie. Ik ben je ontzettend dankbaar voor wat ik allemaal van je heb mogen leren. Heel erg bedankt voor je steun en goede adviezen.

Lianne, bedankt voor je veerkracht en vertrouwen. We hebben de afgelopen jaren heel wat meegemaakt samen. Ik stel het erg op prijs hoe lief en behulpzaam je bent, en altijd bereid om even bij te praten, daarvoor ben ik je erg dankbaar.

Sanne, Wieke en Liesanne, bedankt voor jullie steun in verdrietige tijden. Ik heb veel geluk met zulke lieve collega's zoals jullie. Bedankt voor de troost die we bij elkaar kunnen vinden. Ik hoop dat we nog erg lang mogen samenwerken en dat ik nog veel van jullie kan leren.

Dank aan **Martje**. Het blijkt maar weer dat er geen absolute morele weegschaal is die al het goede wat je hebt gedaan mee laten wegen in hoe het leven loopt. Het leek allemaal zo vanzelfsprekend toen we nog samenwerkten. Het lachen, het praten, het samen vooruit. Mede dankzij jouw oplossingen was geen conflict of probleem te groot, we kwamen er altijd uit. Ik zal alles wat je me geleerd hebt over DBS, bewegingsstoornissen, en de omgang met patiënten altijd koesteren. Ik ben zo ontzettend dankbaar dat ik met je heb mogen samenwerken, dat ik heb kunnen groeien dankzij jou. De warmte die jij uitstraalde zet mij ertoe om simpelweg beter te zijn; een betere zorgverlener, een betere collega, een beter mens. Je blijft me blijven inspireren om net zo goed te zijn voor anderen als dat jij altijd was.

Het voltooien van dit promotietraject was niet mogelijk geweest zonder de steun van mijn lieve (schoon)familie en vrienden.

Angelique, Jamyro, Lidia, Lilian, Lisette, Marleen en Regina, ik ben zo ontzettend dankbaar voor de hechte vriendengroep die wij samen vormen. De helft van ons kent elkaar al sinds groep 2, en door de jaren heen groeiden we uit tot deze gezellige groep grapjassen. Ondanks dat we ieder onze eigen weg gingen na de middelbare school, vonden we elkaar altijd weer terug in Beilen en omstreken. Iedere keer dat we samen zijn, is het net als vanouds. Bedankt dat ik mijn hart bij jullie kon luchten op momenten dat

het even tegenzat en dat jullie mij telkens weer kunnen laten lachen. Jullie hebben altijd een speciaal plekje in mijn hart.

Femmy, bedankt voor je vriendschap door dik en dun. Al sinds klas 4 heb je me een luisterend oor geboden wanneer ik het nodig had, het klikte meteen tussen ons. Ik was zo blij dat jij ook in Enschede bent gaan studeren, en ik ben dankbaar voor alle mooie momenten die we samen gedeeld hebben. Jouw intelligentie en doorzettingsvermogen inspireren mij om beter te zijn. Bedankt voor alle therapeutische baksessies, theebransjes en je grenzeloze vertrouwen in mij.

Mijn paranimfen **Anne-Jet** en **Ilona**, dankjulliewel voor de steun die jullie mij geboden hebben door de jaren heen. Ik ben zo dankbaar voor jullie vriendschap, al vanaf de eerste week dat we begonnen met de bachelor Technische Geneeskunde. Jullie zijn echt goud waard. Ik ben zo blij dat ik op jullie kan rekenen, en dat ik helemaal mezelf kan zijn bij jullie. Bedankt voor jullie humor, vertrouwen en toewijding.

Wytze en **Engelien**, bedankt dat jullie zulke lieve en zorgzame schoonouders voor mij zijn. Ik heb me vanaf het begin helemaal thuis gevoeld bij jullie in Friesland. Doordat jullie en de **pakes** en **beppes** mij met open armen hebben ontvangen, voel ik me echt onderdeel van de familie. Bedankt dat jullie mij onvoorwaardelijk steunen.

Opja Jan, bedankt dat je me van jongst af aan hebt gestimuleerd om altijd mijn best te doen. Ik zal je wijsheden en je humor nooit vergeten. Bedankt voor jouw vertrouwen in mij.

Albert-Jan, lieve appie, ik ben zo blij met jou als mijn kleine broertje, ook al toren je inmiddels ver boven mij uit. Ik heb jarenlang gewenst dat je weer een kleuter was, toen was je nog schattig. Maar naarmate we volwassen werden, zijn we steeds hechter geworden, en ik waardeer de band die we nu hebben enorm. Bedankt voor de goede gesprekken, je kookkunsten en alle berenknuffels.

Lieve **papa en mama**, duizendmaal dank voor dit mooie leven en alle kansen die ik heb gekregen dankzij jullie. Ik ben zo ontzettend dankbaar dat ik altijd op jullie kan rekenen. Jullie hebben me geleerd dat ik met hard werken en vastberadenheid alles kan bereiken waar ik mijn zinnen op zet. Bedankt dat jullie in mij geloven, en mij aanmoedigen om mijn doelen te behalen. Jullie weten me te kalmeren als er paniek dreigt, en krijgen mij altijd weer aan het lachen, hoe wanhopig ik me ook voel. Bedankt voor jullie eeuwige steun en onvoorwaardelijke liefde en vertrouwen.

Allerliefste **Wilmer**, bedankt dat jij altijd voor mij klaar staat. Je bent al meer dan tien jaar mijn steun en toeverlaat. Alles is leuker als jij bij me bent. Bedankt voor je geduld, je humor, en je zorgzaamheid. Ik ben enorm dankbaar dat we elkaar hebben gevonden en kijk ernaar uit om de rest van mijn leven met jou mee te maken. Je haalt het beste in mij naar boven. Bedankt voor alle avonturen die we samen hebben beleefd, en de vele avonturen die ons ongetwijfeld te wachten staan. Ik hou van jou.

Curriculum vitae

Annemarie Smid, daughter of Frank and Marga Smid, was born on July 26th, 1995 in Borne, the Netherlands. She grew up in Beilen, and went to primary school G.A. de Ridder and middle school Dr. Nassau College in Beilen, the Netherlands. After finishing pre-university education at Quintus (Dr. Nassau College, Assen, the Netherlands) in 2013, she started her study in Technical Medicine at the University of Twente (UT) in Enschede, the Netherlands. While living on the UT campus, Annemarie was captivated by the vibrant student life of Enschede and she was soon charmed into participating in several extracurricular activities. She joined several committees at student associations AEGEE-Enschede, S.K.V. Vakgericht and study association S.V. Paradoks. Annemarie became president of student korfbal association Vakgericht in 2014, and after this part-time board year she was asked to take place in the advisory board from 2015 to 2018. In 2016, she obtained her bachelor's degree in Technical Medicine and was accepted for the Technical Medicine master. From 2016–2017, Annemarie was secretary of the Kick-In Committee 2017 of the UT Student Union, spending one full-time year on the organization of the nine-day long introduction period of the university. Before starting her medical clerkships, she joined the intercontinental study tour 'Kaizen' to Japan in 2018, organized by S.V. Paradoks.



During her third M2 internship (neurosurgery, UMCG) in 2019, Annemarie became sure of her interest in Deep Brain Stimulation (DBS) therapy. She worked on a new protocol for accelerometric tremor measurements during DBS surgery in patients with Parkinson's Disease. During her M3 internship at the UMCG, she wrote her thesis on the quantification of MDS-UPDRS motor measurements in patients with Parkinson's Disease during neurosurgical procedures (chapter 5) and she wrote research proposals. She received a grant from the Parkinson Vereniging (patient association) to perform research on objective measurements of tremor and bradykinesia in Parkinson's Disease patients. In 2020, Annemarie was accepted for the GSMS PhD Open Rounds of the University of Groningen, just before obtaining her master's degree in December 2020. She officially started her full-time PhD trajectory in February 2021. From October 2022, Annemarie combined her PhD work with a part-time position at the DBS-OCD team of the UMCG psychiatry department (UCP). In July 2023, she started part-time as Technical Physician as part of the DBS Dystonia team at the neurology department of the UMCG. Annemarie also took on the postoperative aftercare of tremor patients with DBS during the second half of 2023. In March 2024, she became data manager of the NEMO research group at the Movement Disorders expertise center Groningen. Annemarie joined the DBS team at Punt voor Parkinson (Groningen, the Netherlands) as Technical Physician from November 2024 to March 2025. Since then, she has combined her neurology, UCP and NEMO work with finalizing her PhD thesis. Annemarie strives to further specialize in DBS treatments, and ultimately aims to become a Technical Medical Specialist.

List of publications

Smid A, Elting JWW, van Dijk JMC, Otten B, Oterdoom DLM, Tamasi K, Heida T, van Laar T, Drost G. Intraoperative Quantification of MDS-UPDRS Tremor Measurements Using 3D Accelerometry: A Pilot Study. *J Clin Med.* 2022 Apr 19;11(9):2275. doi: 10.3390/jcm11092275. PMID: 35566401; PMCID: PMC9104023.

Kremer NI, **Smid A**, Lange SF, Mateus Marçal I, Tamasi K, van Dijk JMC, van Laar T, Drost G. Supine MDS-UPDRS-III Assessment: An Explorative Study. *J Clin Med.* 2023 Apr 25;12(9):3108. doi: 10.3390/jcm12093108. PMID: 37176549; PMCID: PMC10179103.

Smid A, Pauwels RWJ, Elting JWW, Everlo CSJ, van Dijk JMC, Oterdoom DLM, van Laar T, Tamasi K, van der Stouwe AMM, Drost G. A Novel Accelerometry Method to Perioperatively Quantify Essential Tremor Based on Fahn-Tolosa-Marin Criteria. *J Clin Med.* 2023 Jun 23;12(13):4235. doi: 10.3390/jcm12134235. PMID: 37445270; PMCID: PMC10342906.

Smid A, Oterdoom DLM, Pauwels RWJ, Tamasi K, Elting JWW, Absalom AR, van Laar T, van Dijk JMC, Drost G. The Relevance of Intraoperative Clinical and Accelerometric Measurements for Thalamotomy Outcome. *J Clin Med.* 2023 Sep 10;12(18):5887. doi: 10.3390/jcm12185887. PMID: 37762828; PMCID: PMC10532071.

Smid A, Dominguez-Vega ZT, van Laar T, Oterdoom DLM, Absalom AR, van Egmond ME, Drost G, van Dijk JMC. Objective clinical registration of tremor, bradykinesia, and rigidity during awake stereotactic neurosurgery: a scoping review. *Neurosurg Rev.* 2024 Feb 14;47(1):81. doi: 10.1007/s10143-024-02312-4. PMID: 38355824; PMCID: PMC10866747.

Smid A, van Laar T, Pinkster AE, Ten Kate JM, Kremer NI, Oterdoom DLM, Tamasi K, van Dijk JMC, Drost G. Perioperative quantification of clinical bradykinesia measurements in patients with Parkinson's disease using accelerometry. *Clin Neurophysiol.* 2026 Jan;181:2111424. doi: 10.1016/j.clinph.2025.2111424. Epub 2025 Nov 7. PMID: 41242065.

Author contribution

The contributions of the PhD candidate, Annemarie Smid, to this thesis are detailed below for each chapter, using the Contributor Role Taxonomy (CRediT). Contributions are listed according to role definitions as established by the CRediT system.

Chapter 1: Introduction and thesis outline

Conceptualization: Conceived the idea for this research and formulated research aims in collaboration with the supervisory team.

Investigation: Performed evidence collection and literature research.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from the supervisory team.

Chapter 2: Objective clinical registration of tremor, bradykinesia, and rigidity during awake stereotactic neurosurgery: a scoping review

Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.

Methodology: Designed scoping review methodology.

Investigation: Conducted literature research.

Data Curation: Managed the collected data, and annotated collected data.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from co-authors and the supervisory team.

Visualization: Created figures and tables to present the data.

Chapter 3: Supine MDS-UPDRS-III assessment: an explorative study

Conceptualization: Conceived the research questions regarding accelerometry in collaboration with the co-authors.

Software: Programmed the MATLAB algorithm to pre-process and classify accelerometric data.

Formal analysis: Processed acc data in MATLAB. Conducted statistical analyses using SPSS.

Investigation: Performed clinical assessments of included patients.

Data curation: Managed accelerometric data and clinical MDS-UPDRS-III ratings.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from co-authors and the supervisory team.

Visualization: Created figures and tables to present the data.

Chapter 4: Perioperative quantification of MDS-UPDRS-III bradykinesia measurements in patients with Parkinson's Disease using accelerometry

Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.

Methodology: Developed the measurement protocol to quantify bradykinesia using MDS-UPDRS-III and accelerometry.

Software: Programmed the MATLAB algorithm to pre-process and classify accelerometric data.

Formal analysis: Processed accelerometric data in MATLAB. Conducted statistical analyses using SPSS.

Investigation: Performed participant recruitment (patients and healthy volunteers), accelerometric measurements, and clinical assessments of included patients.

Data curation: Managed participant data, ensured de-identification and secure storage.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from co-authors and the supervisory team.

Visualization: Created figures and tables to present the data.

Project administration: Coordinated participant inclusion, planning, measurements execution.

Chapter 5: Intraoperative quantification of MDS-UPDRS-III tremor measurements using 3D accelerometry: a pilot study

Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.

Methodology: Developed the measurement protocol to intraoperatively quantify tremor using MDS-UPDRS-III and accelerometry.

Software: Programmed the MATLAB algorithm to pre-process and classify accelerometric tremor data.

Formal analysis: Processed accelerometric data in MATLAB. Conducted statistical analyses using SPSS.

Investigation: Performed participant recruitment (patients and healthy volunteers) and accelerometric measurements.

Data curation: Managed participant data, ensured de-identification and secure storage.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from co-authors and the supervisory team.

Visualization: Created figures and tables to present the data.

Project administration: Coordinated participant inclusion, planning and execution of measurements.

Chapter 6: A novel accelerometry method to perioperatively quantify Essential Tremor based on Fahn-Tolosa-Marin criteria

Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.

Methodology: Developed the measurement protocol to quantify tremor using FTM and accelerometry.

Software: Programmed MATLAB algorithm to pre-process and classify accelerometric ET data.

Formal analysis: Processed accelerometric data in MATLAB. Conducted statistical analyses using SPSS.

Investigation: Performed participant recruitment (patients and healthy volunteers), accelerometric measurements, and clinical assessments of included patients.

Data curation: Managed participant data, ensured de-identification and secure storage.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from co-authors and the supervisory team.

Visualization: Created figures and tables to present the data.

Project administration: Coordinated participant inclusion, planning and execution of measurements.

Chapter 7: The relevance of intraoperative clinical and accelerometric measurements for thalamotomy outcome

Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.

Methodology: Developed the measurement protocol to intraoperatively quantify tremor using MDS-UPDRS-III and accelerometry during all stages of thalamotomy.

Software: Programmed the MATLAB algorithm to pre-process and classify accelerometric tremor data (disease-specific).

Formal analysis: Processed accelerometric data in MATLAB. Conducted statistical analyses using SPSS.

Investigation: Performed participant recruitment (patients and healthy volunteers) and accelerometric measurements.

Data curation: Managed participant data, ensured de-identification and secure storage.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from co-authors and the supervisory team.

Visualization: Created figures and tables to present the data.

Project administration: Coordinated participant inclusion, planning and execution of measurements.

Chapter 8: Perioperative quantification of MDS-UPDRS-III tremor measurements in patients with Parkinson's Disease using accelerometry

Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.

Methodology: Developed the measurement protocol to quantify tremor using MDS-UPDRS-III and accelerometry.

Software: Programmed the MATLAB algorithm to pre-process and classify accelerometric tremor data.

Formal analysis: Processed accelerometric data in MATLAB. Conducted statistical analyses using SPSS.

Investigation: Performed participant recruitment (patients and healthy volunteers), accelerometric measurements, and clinical assessments of included patients.

Data curation: Managed participant data, ensured de-identification and secure storage.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from co-authors and the supervisory team.

Visualization: Created figures and tables to present the data.

Project administration: Coordinated participant inclusion, planning and execution of measurements.

A

Chapter 9: Summary and discussion

Conceptualization: Conceived the idea for this research and formulated research aims in collaboration with the supervisory team.

Investigation: Performed evidence collection and literature research.

Writing—original draft preparation: Wrote the initial draft of this chapter. Revised content following feedback from the supervisory team.

General contributions (applicable to entire thesis)

Software: Optimized the LabVIEW program for acquisition of accelerometric data.

Funding acquisition: Wrote the initial draft of the grant application related to objectively measuring motor symptoms using accelerometry and revised the application following feedback from the supervisory team.

Writing – review & editing: Performed final review and editing of all thesis chapters based on committee feedback.

