Parkinsonian rigidity

Jacobi-Postma, Alida Annechien

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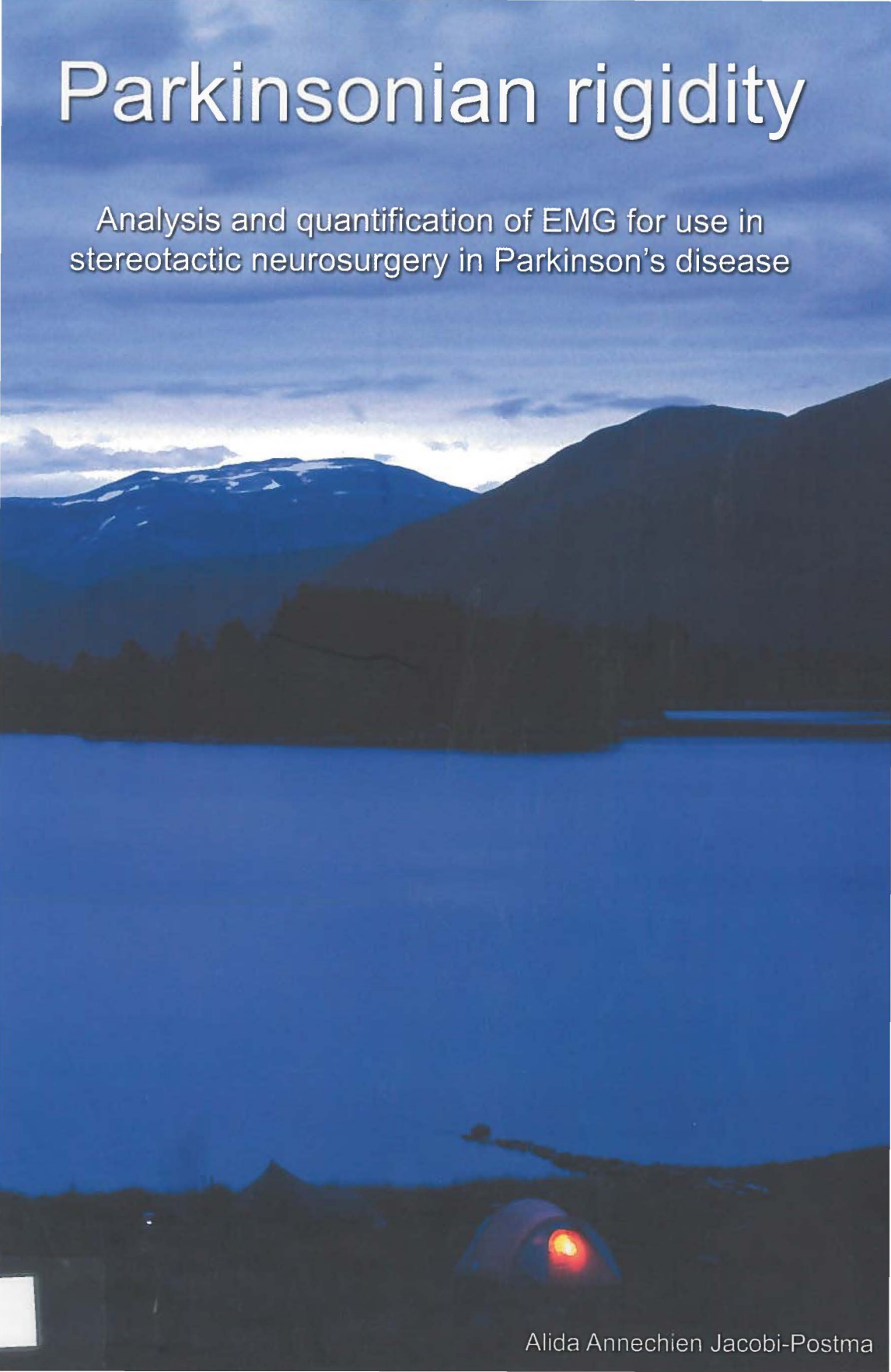
Analysis and quantification of EMG for use in stereotactic neurosurgery in Parkinson's disease



Alida Annechien Jacobi-Postma

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Analysis and quantification of EMG for use in stereotactic neurosurgery in Parkinson's disease

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Stellingen behorende bij het proefschrift

Parkinsonian rigidity

Analysis and quantification of EMG for use in stereotactic neurosurgery in Parkinson's disease

1. EMG bevat veel informatie betreffende parkinsonrigiditeit, maar is onbewerkt niet geschikt als objectieve maat ~ *dit proefschrift.*

2. Het tandradfenomeen is een consistente, maar onregelmatige bevinding ~ *dit proefschrift.*

3. De toevoeging in de definitie van de UPDRS om het tandradfenomeen uit te sluiten negeert een van de belangrijkste kenmerken van rigiditeit bij de ziekte van Parkinson ~ *dit proefschrift.*

4. Wie de negatieve BAL kaatst... kan rigiditeit verwachten ~ *dit proefschrift.*

5. Principiële kenmerken van conventionele filtermethoden leggen grote beperkingen op voor analyse van het tandradfenomeen bij parkinsonrigiditeit. Second order moment filtering biedt daarentegen een krachtig alternatief dat primair geschikt is voor detectie en analyse van tandradbursten in EMG's ~ *dit proefschrift.*

6. De flexoren in de onderarm spelen een grotere rol bij de rigiditeitveranderingen dan de extensor spieren ~ *dit proefschrift.*

7. Anatomische en neurofysiologische methoden zullen blijvend gecombineerd moeten worden voor optimale plaatsing van de elektroden gebruikt bij diepe brein stimulatie (DBS).

8. De kwaliteit van de vraag bepaalt de kwaliteit van het antwoord. Binnen de radiodiagnostiek wordt de kracht van de kwaliteit van de vraag ondergewaardeerd.

9. De marktwerking in de gezondheidszorg binnen de muren van de academische instelling gaat ten koste van topspecialistische kennis en zorg.

10. De radiologie wordt steeds lichter.

11. Meer diffusie leidt tot minder confusie.

12. "Imagination is more important than knowledge. For knowledge is limited to all we now know and understand, while imagination embraces the entire world, and all there ever will be to know and understand." ~ *Albert Einstein.*

Linda Jacobi-Postma, 23 november 2009

CMB.

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Parkinsonian rigidity

Analysis and quantification of EMG for use in stereotactic neurosurgery in Parkinson's disease

Proefschrift

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Voor

Foppe

Gerianne

Rixt

Willem-Thijs

Contents

Abbreviations

PD	Parkinson's Disease
UPDRS	Unified Parkinson's Disease Rating Scale
CLA	Contralateral activation
DBS	Deep Brain Stimulation
STN	Subthalamic nucleus
NRGC	Nucleus Reticularis Giganto Cellularis
GPi	Globus Pallidus internus
GPe	Globus Pallidus externus
SN	Substantia nigra
EMG	Electromyography
SNR	Signal-to-noise ratio
FWR	Full wave rectified
FT	Fourier Transform
STFT	Short Time Fourier Transform
DWT	Discrete Wavelet Transform
WT	Wavelet Transform
TF	Threshold Factor
BAL	Balance Coefficient
MBAF	Mean Burst Amplitude Function
SOMF	Second Order Moment Function
Len	Lengthening phase
Sh	Shortening phase
Ext	Extensor
Flex	Flexor

Chapter 1

Introduction and scope of the thesis

For reasons of legibility and comprehension, the text has been written as a chapter. Parts of this chapter are published in:

Journée HL, Postma AA, Staal MJ. Intraoperative neurophysiological assessment of disabling symptoms in DBS surgery.
Neurophysiol.Clin. 2007;37:467-75.

Aim of the thesis

The aim of this thesis was to investigate a method for quantification of parkinsonian rigidity, suitable for use in an intra-operative setting. Rigidity is a form of muscle hypertonia and is characterized by an increase in stiffness during passive movement excursion of a limb segment [1-3].
The concept and underlying pathophysiology of parkinsonian rigidity were studied. Electromyography (EMG) was used to search for the presence of the components of rigidity, namely the lead pipe phenomenon and the cogwheel phenomenon. Signal analysis was carried out to separate these components, and new methods of signal analysis were developed to deal with interference of tremor and active co-operation of the patient (negative rigidity). The correlation between the components of the EMG and the clinical rigidity score were assessed.

Description of Parkinson's disease

'Parkinson's Disease' (PD) as first described in 1817 by James Parkinson, was characte-rized by resting tremor, flexed posture, festinating gait and lessened muscular power [4]. Today's description of the disease includes a large range of symptoms such as tremor, bradykinesia, rigidity and an altered walking pattern. Alterations in the autonomic nervous system and mental functions can be present as well.
Dyskinesia, dystonia and on-off fluctuations can be the result of medication, in particular of dopaminergic drugs. In the off-state, the symptoms are dominated by bradykinesia, freezing, dystonia and rigidity. In the on-state, these symptoms largely disappear, but dyskinesias and excessive involuntary movements can be present. Tremor can occur in both states. The resting tremor in PD occurs with a frequency of about 4-5 Hz. The frequency is different in action tremor and postural tremor, which can be present in PD as well [5].

Therapeutical options: the role of neurosurgical interventions

Surgical treatment for PD has been attempted since the early 20th century, when Leriche performed bilateral rhizotomy. Early interventions concerned the corticospinal system and were directed at nerve roots, spinal cord, brainstem and cortex [6]. These were abandoned because of the unwanted associated loss of voluntary movement. Clinicopathological studies in various movement disorders and the accumulating information on the neuroanatomic circuitry of subcortical structures led to the concept that the pathological substrate for movement disorders lay in the extra pyramidal motor system [6]. In 1939 Meyers removed two-thirds of the head of the caudate nucleus by a transventricular approach, thereby abolishing tremor without resulting paralysis. Thereafter surgical lesions to other extrapyramidal structures were carried out, but mortality was high with the transventricular approach [7;8]. Imaging of intracranial structures by

ventriculography with air or positive contrast agents led to the re-introduction of stereotactic atlases and stereotactic instruments by Spiegel and Wycis in 1947; this permitted more accurate target location and therefore was associated with fewer side effects. The anterodorsal segment of the pallidum as target was gradually moved to the posteroventral pallidum by Leksell [9]. In the late 1950s most neurosurgeons abandoned pallidotomy in favor of lesions of the ventrolateral thalamus, which gave a dramatic improvement of tremor and had less side effects.

With the introduction of L-dopa in 1969 stereotactic neuroablative surgery in PD became virtually extinct. L-dopa could reduce rigidity and control tremor [10], moreover, there was also palliation of bradykinesia with this drug. Balance problems and dementia were not influenced by L-dopa. After a few years, several problems related to L-dopa treatment became apparent. Patholo-gical adaptation to the medication in a progressive disorder was one of the unwanted effects. Higher doses were required and severe peak-dose dyskinesia and wearing off were added to the already broad spectrum of symptoms.

Neurosurgical therapy regained interest due to these long term problems, and was stimulated as well by further development and improvement in neurosurgery and neuroimaging methods, and insight in neurobiology of targets.

Thalamotomy in the group of patients with end-stage disease was usually ineffective; the problem was no longer tremor but bradykinesia, on-off fluctuations, dyskinesia and rigidity. Leksell's posteroventral pallidotomy was re-introduced by Laitinen [9;11], who was soon followed by other groups. Pallidotomy showed mainly improvement of contralateral dyskinesia and bilateral procedures were restricted due to side effects. Deep brain stimulation (DBS) in the ventral intermediate nucleus of the thalamus was introduced by Benabid as therapy for PD in tremor dominant disease in 1987. The advantages of DBS over ablative surgery are the relative safety of bilateral procedures in contrast to lesioning procedures, possibility of adjustment of parameters and reversibility of some of the potential unwanted effects [12]. DBS of the thalamus produced relief of contralateral tremor, but not of other parkinsonian symptoms, and thus interest shifted towards the pallidum and the subthalamic nucleus (STN) as target areas.

Today, patients with pathological adaptation to medication are possible candidates for neurosurgical operations.

In such an operation, an electrode is introduced into the brain to coagulate or stimulate a part of the basal ganglia circuitry. At present the thalamus, the pallidum and the STN are the preferred targets for intervention [12;13]. Procedures directed at the thalamus are especially effective in patients with predominant tremor [14;15]. In the thalamus both DBS and coagulation are possible. In the pallidum, coagulation as well as DBS is possible when on-off fluctuations with dyskinesia are the most disabling symptoms. Coagulation, however, is preferably not performed bilaterally because of possible serious unwanted effects [13;16;17]. In recent years DBS of the STN is preferred to pallidum intervention [13;18]. The target

symptoms are tremor, dyskinesia, rigidity and dystonia. A neuroprotective role was ascribed to the STN, but to date not substantiated [19-21]. DBS of the STN can be performed bilaterally in one session; in this way bilateral improvement of the symptoms can be obtained.

The prevalence of PD in literature varies widely, because of differences in diagnostic criteria and in age distribution within the study popula-tions. The prevalence in Europe varies between 100-320 per 100.000 [22-24]. These numbers rise with increasing age [22], leading to a prevalence in the Netherlands between 25.000 and 50.000 persons. Of these only about 68 per year have undergone neurosurgical intervention in the past years.

Neuromonitoring in surgery for Parkinson's disease

Monitoring of parkinsonian symptoms during surgery is essential for optimal positioning of electrodes for DBS or coagulation. In our centre most operations take place under local anesthesia and with stereotactic techniques. During operation the effect of electrode positioning on adjacent structures, the result of a micro lesion, the test lesion, and if relevant the effect of the coagulation on the targeted symptoms, are evaluated.

The symptoms are assessed by neurological examination and intra-operative neuromonitoring [25].

In all procedures the effect of low-frequency stimulation to detect interference with internal capsule fibers is checked by accelerometry.

In thalamotomy or DBS of the thalamus, tremor is the predominant targeted symptom and recordings with accelerometers measuring amplitude and accelera-tion of the tremor provide objective quantification of the symptoms.

In pallidotomy or DBS of the pallidum, one of the targeted symptoms is dyskinesia. However, during the procedure, the patient is in the off-state, where dyskinesia is not present. The only symptoms present for quantification are rigidity and bradykinesia. Finger tapping and diadochokinesia tests are used as indicators of bradykinesia. These are quantified by recording frequency and amplitude of these movements. These tests depend on cooperation of the patient during the session. When a patient tires, test results may alter dramatically, despite improvement in bradykinesia.

In DBS STN the targeted symptoms are dyskinesia and dystonia, and to a lesser extent rigidity and bradykinesia. The dyskinesia is again not present in the off-state and no neuromonitoring test is presently available for quantification of dystonia. Bradykinesia is quantified as mentioned above.

Since rigidity is the most noticeable symptom in pallidotomy, DBS of the pallidum and of the STN, while the other symptoms cannot be reliably quantified, rigidity is most useful for monitoring. This underlines the urgent need for intra-operative neurophysiological monitoring of rigidity as an important clinical outcome

measure when performing interventions in parkinsonian patients. The difficulty of measuring rigidity during surgical intervention is the specific topic of this thesis.
For rigidity, still no accepted method for quantification is available. In daily neurological practice, and at present during operation, rigidity is clinically rated according to the Unified Parkinson's Disease Rating Scale (UPDRS), a 5-point rigidity scale. The inter-rater reliability of this test is good for high rigidity scores, but inconsistent for mild rigidity. An objective scoring of rigidity is strongly preferred because of its implication in the above mentioned decision making.

Rigidity as indicator of surgical effectivity

Several authors have attempted to quantify rigidity, but no method for quantification of rigidity has been incorporated in standard peri-operative and preoperative assessment of rigidity in PD so far. Rigidity is still assessed clinically. Some of the authors used large cumbersome devices or measured reflexes and muscle activity in parkinsonian rigidity [26-31].
The intra-operative setting of rigidity measurements is subject to a number of conditions, which differ from laboratory experiments. This setting stresses the need for a small device that can be connected to the present intra-operative monitoring system. It has to be fast and the demands for patient cooperation have to be low because of the lengthy operative procedure. There should be a good correlation of the objective score and the clinical rigidity (today's 'gold' standard). Although we know that the inter- and intra-rater reliability in assessing clinical rigidity can vary among observers, no better gold standard is available.
The advantages of quantification, over clinical testing, should be the capability of detecting gradual changes, and better reproducibility.
We propose that EMG is suitable to objectify rigidity, since an increase in muscle contraction is registered as an increase in firing pattern of alpha motor neurons and recruitment of motor units. The EMG thus should provide information concerning rigidity. An increase in EMG activity in patients with parkinsonian rigidity is however described with varying correlations [26;27]. More recently, some authors used unprocessed EMG data as indicator of rigidity [31-34]. EMG signals carry information about cycle-related EMG activity of rigidity during passive flexion and extension of the limb including the cogwheel phenomenon, which is visible as a burst pattern [26;27].
The success of objective measurement and quantification of rigidity with an optimal correlation with the UPDRS depends in our opinion on well selected choices of techniques for signal analysis of EMG data. In the UPDRS scoring of rigidity, the cogwheel phenomenon is excluded to prevent its influence on the score: "Judged on passive movements of major joints with the patient relaxed in sitting position; the cogwheeling to be ignored" [35]. A method for rigidity quantification should preferably comply with this definition.

The objectives of this thesis

The aim of this thesis was to investigate a method for quantification of parkinsonian rigidity, suitable for use in an intra-operative setting, by

1. description of the concept of parkinsonian rigidity and the underlying pathophysiology of parkinsonian rigidity.
2. description of the methods used for quantifying rigidity and investigation of their applicability for intra-operative use.
3. assessment of the EMG's capability for studying parkinsonian rigidity: the lead pipe phenomenon and the cogwheel phenomenon.
4. identification of a method of signal analysis, which can separate the background activity of the EMG from the irregular bursts of the cogwheel phenomenon: time variant wavelet transform.
5. development of new methods of signal analysis to overcome interference of tremor and negative rigidity: the introduction of balance coefficient and second order moment filtering (SOMF) and assessment of its applicability in quantification of parkinsonian rigidity.
6. assessment of the correlation between the extracted parts of the EMG and the clinical rigidity score according to the UPDRS.

Outline of this thesis

Chapter 2 describes current pathophysiological concepts of parkinsonian rigidity.
Chapter 3 describes the material and methods as applied in the different studies.
Chapter 4 contains a literature review and discussion on methods for clinical scoring of rigidity and quantification, followed by a pilot study to investigate the applicability of EMG signals in quantification of rigidity.
Chapter 5 deals with time variant wavelet filtering (WT) as a tool to detect, separate and quantify cogwheel bursts from background EMG of the tonic component of rigidity. The results of WT-analysis on EMG data in a patient group operated for PD and the features for assessment of parkinsonian rigidity are discussed. The consequences of two newly identified important interfering problems for automatic quantification, tremor and negative rigidity, are considered, lastly.
Chapter 6 introduces a new analysis technique based on a so-called balance coefficient. This coefficient has two features: 1) it is intended to automatically detect and identify the presence of negative rigidity and tremor that may corrupt rigidity measurements and 2) it can be used to quantify rigidity. After describing the concept of the balance coefficient, the results of its application in a group of

patients undergoing deep brain stimulation of the subthalamic nucleus for PD, are discussed.
Chapter 7 deals with the introduction and application of a second order moment function as an alternative method to overcome the interfering problems of negative rigidity and tremor as dealt with in chapter 5 and 6.
Chapter 8 discusses the results and the impact in daily practice of the studies presented in this thesis.
Chapter 9 summarizes the findings.

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Chapter 2

Parkinsonian rigidity – characteristics and pathophysiology Review of literature

A.A. Postma, H.L. Journée, M.J. Staal, K.L. Leenders. Parkinsonian rigidity – characteristics and pathophysiology. Review of literature.
Submitted

Abstract

Introduction

Rigidity in parkinsonian patients is characterized by an increase in stiffness during passive movement of a limb. This chapter gives a review of the theories concerning the pathophysiology of parkinsonian rigidity, which has only partially been unravelled. Theories range from alterations at muscle level to alterations at brain level.

Methods

Published data was reviewed for characteristics of parkinsonian rigidity and for pathophysiological theories of parkinsonian rigidity.

Results

Rigidity in Parkinson's disease (PD) consists basically of a lead pipe phenomenon, sometimes interrupted by a cogwheel phenomenon.

The cogwheel phenomenon, interruptions of tonic resistance in parkinsonian rigidity, is believed to represent action tremor, because of the similarity in frequency (7-14 Hz), despite the presence of the characteristic resting tremor of PD (4-9 Hz).

The constant component of rigidity, which is the lead pipe phenomenon, could arise from physiological modification of muscle or joint properties, or from modification of neural mechanisms at brain or spinal cord level.

For a long time a major role was ascribed to the long loop reflex (LLR). Today the theory of Delwaide concerning autogenic inhibition can explain the major part of the electrophysiological findings in parkinsonian rigidity.

In parkinsonian rigidity the reticulospinal tract descends from the nucleus reticularis giganto cellularis (NRGC) with less activity, and influences Ia- and Ib-interneurons. Reduced facilitation of Ib and facilitation of Ia interneurons lead to reduced inhibition (Ib) and facilitation (Ia) of α-motor neurons and is proposed as the final mechanism at spinal level for rigidity.

In PD, alterations in the basal ganglia circuitry, due to a dopamine deficit in the substantia nigra, is a well-accepted model. The basal ganglia circuitry projects to the tegmentum and reticular formation and could, via the NRGC, influence the Ia and Ib interneurons indirectly. Modifications of muscles and LLR are explained in this model as compensatory mechanisms.

Conclusion

The pathophysiology of parkinsonian rigidity is still not fully understood. Alterations at different levels finally exert abnormal firing patterns at the lower motor unit.

Introduction

'Parkinson's Disease' (PD) as first described in 1817 by James Parkinson, is characterized by 'resting tremor, flexed posture, festinating gait and lessened muscular power' [1]. Today's description of the disease includes a large spectrum of symptoms like tremor, bradykinesia, rigidity and altered gait. Alterations in the autonomic nervous system and cognitive and affective changes can be present as well.
Parkinsonian rigidity is one of the disabling cardinal symptoms of PD. Despite its clinical importance, objective quantification of parkinsonian rigidity is not available. There are several hypotheses about parkinsonian rigidity ranging from modification of muscles to modifications of different neural mechanisms.
This chapter reviews the characteristics of parkinsonian rigidity and summarizes the pathophysiology theories presented so far. A suggestion for future objective measurement of rigidity is given.

Methods

A review was performed of publications in MEDLINE.
The MEDLINE database was searched for all available publications on rigidity in Parkinson's Disease. Search terms were 'rigidity', 'pathophysiology' and 'Parkinson's disease'.
Titles and abstracts were screened for possible inclusion in the review and the references were screened for additional publications.

Definition and clinical manifestations of parkinsonian rigidity

Rigidity is a form of muscle hypertonia and is characterized by an increase in stiffness during passive movement of a limb segment [2-4]. The examiner scores the perceived resistance according to a 5-point clinical rating scale, ranging from clinically absent to severe rigidity, when the range of motion is achieved with difficulty [5].
In parkinsonian patients the stiffness is irrespective of the direction of the mobilization [6]. This stiffness is experienced during the whole movement, in contrast to spasticity for instance, which has an uneven distribution [7]. The clinically observed intensity remains the same whether extensor or flexor muscles are stretched and regardless of the angle over which the joint is moved [3;7;8]. More recent publications suggest a larger role for flexor muscles in rigidity [9;10]. Rigidity may be generalized and be present in limb muscles as well as in axial muscles. For example, rigidity may be present in orofacial, respiratory and paravertebral

muscles. Parkinsonian rigidity can be more pronounced in the larger proximal muscles [11;12], probably due to greater muscle mass [6].
Some controversy exists whether rigidity depends on the velocity of muscle movement. According to some authors, the stiffness is modified by the speed of the imposed displacement, albeit less obvious than in spasticity. It may sometimes be most pronounced upon slow movements [3;13] or, on the contrary, sometimes be enhanced in faster movements [14]. Terävänen stated that the ideal speed of passive movement for optimal detection of parkinsonian rigidity is between 140-190 °/s [14].
When a limb is stretched in parkinsonian rigidity, the limb will remain in the same position when released and shows no tendency to return to its previous position, in contrast to spasticity [7].
When an examiner applies large excursions, he may perceive rigidity as a continuous resisting force, the so-called lead-pipe phenomenon, or as a fast repetitive interrupted resistance. This latter is called cogwheel phenomenon.
The frequency of this cogwheel phenomenon is at 7-14 Hz. This is at a higher rate than the characteristic resting tremor of PD (4-9 Hz). It is therefore supposed that these interruptions should have the same origin as the postural tremor [15-17], and thus has a different pathophysiological mechanism from the resting tremor, which is thought to originate from a central oscillator [4;18].
Another characteristic of parkinsonian rigidity is the reinforcement of resistance by contralateral activation. Rigidity is increased in mirror movements or contralateral activation, so called Froment maneuver. Stress and anxiety may also reinforce muscle rigidity [3;19]. This increase is more pronounced in proximal muscles compared to distal muscles [3]. The reinforcement of contralateral activation is even more pronounced when the subject is standing instead of sitting [3;20]. Spontaneous fluctuations of rigidity occur from hour to hour and day to day, even from minute to minute [19].
Rigidity is not solely a characteristic of PD. Rigidity can also be found in other diseases of the basal ganglia.
Rigidity in the context of this thesis is rigidity as seen in parkinsonian patients. Such rigidity is characterized by increased stiffness, experienced during a passive movement of a limb segment and should present the clinical characteristics indicated above [3;6].

Pathophysiology of parkinsonian rigidity

Despite the availability of many clinical and neurophysiological data the pathophysiology of parkinsonian rigidity is still not fully understood. Several hypotheses have been developed.
The constant rigidity could either arise from physiological modification of muscle or joint properties, or from modification of neural mechanisms [3;4;21].

A. Modification of muscle properties

Alterations of muscle properties could originate from altered elastic stiffness of the muscle and joint capsule or from transformation of the contractile apparatus. Altered mechanical properties of the muscle were emphasized by Dietz and Watts [22-24]. Changes in muscle of parkinsonian patients were seen in pathological studies, showing a tendency towards hypertrophy of type I fibres and sometimes towards type II fibres in the muscle [25]. Contractile properties of the muscle, however, are normal in parkinsonian patients [26]. Rapid fluctuations in muscle tone, as is seen in on-off fluctuations, cannot be explained by altered muscle properties [3;27-29].

These muscle changes mentioned above are probably the consequence of the modified pattern of motor unit activation in rigidity and not the underlying cause of rigidity [22;25;26].

B. Modification of neural mechanisms

Since the observation of disappearance of rigidity after transsection of a dorsal root by Walshe in 1924 the role of altered neural pathways has been investigated. These neural pathways can be divided grossly into pathways that relay in the brain, or long loop reflexes, and in pathways at the spinal level, or short reflex pathways. The latter can be influenced by several descending pathways.

B1. Basal ganglia circuitry

PD is pathologically characterized by a dopamine deficit in the striatum as a result of degeneration of dopaminergic substantia nigra neurons. This deficit influences a large circuitry in which the basal ganglia play a major role. This circuitry was first described by De Long. The most important input nucleus of the basal ganglia is the putamen. The most important output nuclei are the internal segment of the pallidum (Gpi) and the reticular part of the substantia nigra. Two important connections between these input and output nuclei exist: an indirect and a direct pathway. The dopamine deficit in the substantia nigra as seen in PD has a different effect on these two pathways. The end effect is an overactivity of the basal ganglia output which results in an over-inhibition of the thalamus. The glutaminergic thalamocortical neurons are thus less activated [18;30].

According to Rinne the loss of dopaminergic neurons correlated with the degree of rigidity and akinesia [31]. However, an association between the fluctuations of rigidity and dopaminergic activity cannot be explained by the static loss of nigral dopaminergic neurons.

Although the altered function of the basal ganglia circuitry is widely accepted, it provides no single explanation for rigidity. The basal ganglia circuitry is influenced by other neural structures and the more peripheral mechanisms are in turn affected by the abnormal neural activity within the basal ganglia [18].

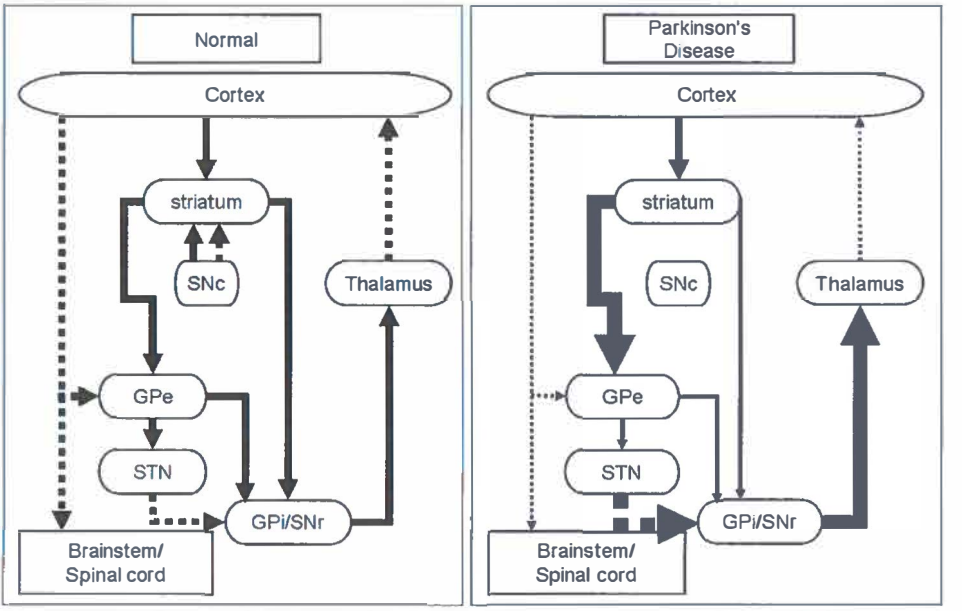

Figure 1: Dopamine deficit in the substantia nigra has a different effect on the direct and indirect pathways between the input and output nuclei of the basal ganglia. At the end an overactivity of the basal ganglia gives an overinhibition of the thalamus resulting in inhibition of thalamocortical neurons.
SNc: Substantia Nigra – pars compacta. STN: Subthalamic Nucleus. GPe: Globus Pallidus externus. GPi: Globus Pallidus internus. SNr: Substantia Nigra – pars reticularis.
--- activation
___ inhibition

B2. The long loop reflex

When a passive movement of a limb in a subject is abruptly stopped, the EMG of the stretched muscle shows three consequent responses: M1, M2 and M3. The M1 response occurs after ±25-30 ms, and is the myotatic reflex of the muscle. The second reflex response, M2, appears after a delay of ±50 ms. The M3 response (in wrist and elbow) occurs at about 100 ms [29]. The M2 response is considered to reflect the activity in long loop pathways. In parkinsonian patients M2 and M3 form one complex and are not always separately distinguishable [32].

For a long time, alterations in the long loop reflex (LLR) were thought to form the functional anatomical basis of rigidity. A number of authors found the M2-3 complex to be increased in parkinsonian patients [27-29;32-36]. The correlation of an increase in rigidity with an increase in M2-3 amplitude however has been uncertain and dependent on the presence of relaxed muscles or background contraction. As a result of the studies showing an increase in M2, a more excitable long loop pathway in parkinsonian patients was suggested.

The origin of the LLR is still not fully understood, but is thought to involve a transcerebral pathway [7;37-40]. The long loop is considered to arise in the primary endings of neuromuscular spindles. An action potential travels in Ia fibers to the spinal cord where they activate the motor neurons. Action potentials are also

transmitted to the brain via the posterior columns of the spinal cord and influence the sensorimotor cortex. The sensorimotor cortex sends a message back to the spinal motor neurons via the corticospinal tract [3].

In this theory, the hyperexcitability of the LLR is located at the level of the sensorimotor cortex. The sensorimotor cortex is facilitated as well as inhibited in parkinsonian patients and hence can influence the long loop reflex [4]. The sensorimotor cortex is influenced by the basal ganglia circuitry and the supplementary motor area (SMA); the SMA normally inhibits the motor cortex. Another loop starting in the motor cortex, relaying in the basal ganglia and then returning to the SMA is thought to be less inhibitory in parkinsonian patients and a permanent inhibition from the sensorimotor cortex to be removed [41]. This explanation is compatible with the classical scheme as mentioned before. In this scheme the basal ganglia project essentially to the cerebral cortex [3].

There are a number of drawbacks for the long loop theory and long loop reflexes alone cannot explain all facets of rigidity and neurophysiological findings in rigidity [3;4]. It is possible that the increase in M2 is not the only mechanism [4;7] or is even a compensatory mechanism in, instead of a causative determinant of rigidity.

B3. Spinal pathways

Other neural pathophysiological circuitries which were investigated are the stretch reflex, autogenic inhibition, reciprocal inhibition, shortening reaction and tonic stretch reflex [2;8;12;21;33;35;42-48]. The most recent theory, which can explain part of the (neurophysiological) findings in parkinsonian rigidity is the spinal hypothesis by Delwaide, which concerns autogenic inhibition [2;3;11;12].

In PD the activity of the Ia inhibitory interneurons responsible for the first phase of autogenic inhibition, is increased. The activity of the Ib interneurons responsible for non-reciprocal inhibition is reduced. The increase of activity of the Ia interneurons, the reduction of activity of the Ib interneurons and the appearance of rigidity are correlated. Ia and Ib interneurons are influenced by peripheral afferents and descending pathways (corticospinal and reticulospinal tracts). In normal subjects the Ib interneuron integrates all these influences and exerts a tonic inhibition on the motor neurons. If this interneuron is less active, the inhibition of the motor neuron is decreased therefore causing hyperactivity of the motor neurons, which translates clinically into rigidity. The reticulospinal tract is the only known descending pathway that exerts opposite effects on the Ia and Ib interneurons. The nucleus reticularis giganto cellularis (NRGC), from which this tract descends, is therefore likely to play a role in rigidity.

By stimulation of the NRGC the Ib interneurons are facilitated and the Ia interneurons are inhibited via a polysynaptic pathway. In PD the NRGC is probably less active, resulting in a reduced facilitation of Ib interneurons and increased facilitation of Ia interneurons. A reduction of Ib activity is then proposed as the final mechanism for rigidity at spinal level.

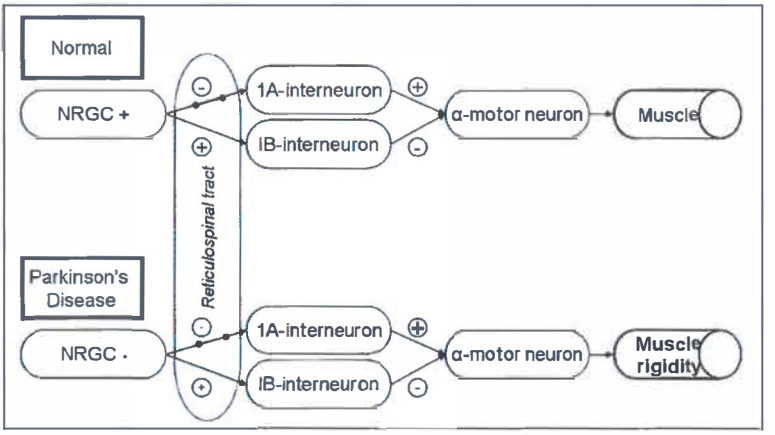

Figure 2: Motor neurons integrate influences of many different inputs, under which are Ia and Ib interneurons. The Ia and Ib interneurons are influenced by descending pathways.
In Parkinson's disease, the NRGC is probably less active, resulting in a reduced facilitation of Ib interneurons and facilitation of Ia interneurons via the reticulospinal tract. A reduction of Ib activity is then proposed as the final mechanism at spinal level for rigidity.
NRGC: Nucleus Reticularis Giganto Cellularis.
(Modified from Delwaide 2001 [3])

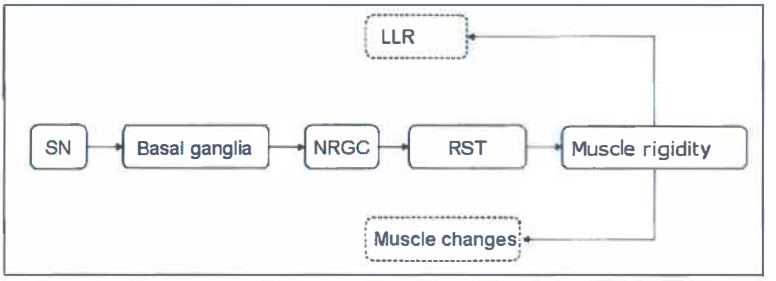

Figure 3: Simplified proposed model of pathophysiology of parkinsonian rigidity. Dopamine deficit in the substantia nigra leads to alterations in the output of the basal ganglia. The basal ganglia project to the reticular formation in which the NRGC is present. The reticulospinal tract is descending from the NRGC and leads to a reduced facilitation of Ib interneurons. The reduction of Ib activity is proposed as final mechanism at spinal level for rigidity.
Changes in LLR and muscle changes in this model may be explained as compensatory mechanisms.
SN: substantia nigra.
NRGC: Nucleus Reticularis Giganto Cellularis.
RST: reticulospinal tract.
LLR: long loop reflexes.

Discussion and conclusion

Despite the fact that parkinsonian rigidity is a major symptom and problem, the pathophysiology is still not fully understood. The models mentioned above do not act separately, but probably are synergistic to each other.
It is proposed that modifications in the basal ganglia circuitry due to dopamine deficit in the substantia nigra indirectly influence the Ib interneurons through relays in the tegmentum and reticular formation, in which the NRGC is to be found. In parkinsonian patients changes in subcortical pathways can lead to compensatory changes in the corticospinal tract; and the changes in LLR and muscle changes can be explained as a compensatory mechanism (figure 3).
The response of rigidity to L-dopa substitution, which aims at restoring dopaminergic function in the striatum [49], can be explained in the above simplistic model.
The pathophysiology of rigidity remains under investigation; current theories confirm that the lower motor neuron is the final common pathway resulting in rigidity at muscle level. Since the output activity of motor neurons is directly conveyed to muscle fibers it can be recorded by electromyographic electrodes. Registration of motor unit potentials by EMG thus integrates all and hence could provide a useful tool for quantification of rigidity and further insight in pathophysiology. Many investigators have been using EMG for quantification of parkinsonian rigidity during passive stretch as well as in rest [21;27;50]. The results of quantification of unprocessed EMG in relation to rigidity thus far are not unambiguous. The presence of the cogwheel phenomenon as a separate component within parkinsonian rigidity could play a role. The pathophysiology of the lead pipe phenomenon and the cogwheel phenomenon is different. Maybe application of signal processing before quantification can aid in further understanding of the pathophysiology of both components.

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Chapter 3

General Material and Methods

The evaluation of the various methods for analysis and quantification of parkinsonian rigidity in this thesis is based on routinely performed neurophysiological assessment of patients referred for functional stereotactic neurosurgery.
The neurophysiological recordings comprise a digital data bank, out of which a selection for off-line analysis is made for the specific studies in the subsequent chapters. This chapter gives an overview of the common part of the material and methods pertaining to the creation of the data bank.

During 1997-2001, 33 patients were referred to our department of neurosurgery. Eight were referred for pallidotomy, one for thalamotomy, 20 for implantation of deep brain stimulation (DBS) electrodes of which 2 unilateral in the thalamus, 3 unilateral in the pallidum and 14 bilateral and 1 unilateral in the subthalamic nucleus (STN). Four patients were admitted for adjustment of DBS stimulation parameters (2 thalamus, 2 STN). Two patients underwent additional surgery for repositioning of the electrode (patient 18 and 25, table 1). The age of the patients was in a range of 47-78 yr (mean 61,6 yr; sd 8,4 yr).
The patients underwent routine neurophysiological assessment of tremor, rigidity and bradykinesia. This was part of clinical pre- and postoperative evaluation. Assessment started four hours after the last intake of dopaminergic medication, or at the end of an inter-medication interval when smaller. This was used as a practical approximation of 'off-state' in this study, instead of the medication free overnight usually used, since the measurements were carried out in a routine preoperative evaluation that was done in this way. EMG recordings were made simultaneously during rigidity and tremor testing as part of the pre- and postoperative evaluation. All patients gave informed consent, where they agreed that the data from the routine measurements were to be used for research.

The neurophysiological data were recorded during a clinical rigidity test of the wrist. Rigidity was scored according to the descriptions in the rigidity section of the UPDRS (table 1) [1]. In this test the examiner (AJP or LJ) flexes and extends the wrist repeatedly, while the patient is seated in a relaxed position. The flexion and extension movements were carried out between 1 and 2 Hz by the examiner [2]. Sometimes, the frequency of the test cycle was smaller than 1 Hz in case of severe rigidity.
The clinical rigidity scores were documented upon completion of each assessment. Special observations as tremor, cogwheel phenomenon or a change in rigidity were documented as well.

Table 1: Definition of the rigidity scoring according to the UPDRS. The testing is performed "sitting in a relaxed position, while cogwheeling is ignored" [1].

0	Rigidity absent
1	Rigidity slight or detectable only when activated by mirror or other movements
2	Mild to moderate rigidity
3	Marked rigidity, but full range of motion easily achieved
4	Severe rigidity, range of motion achieved with difficulty

In the first 13 patients, two pre-operative and two postoperative measurements were recorded during rigidity testing. In the subsequent patients, four measurements were added to the protocol (extended session, see table 2), so that each session comprised three pairs of rigidity recordings. The first and third recording pairs were performed with a patient in relaxed position to test passive rigidity. The rigidity of the second pair of measurements was reinforced by contralateral activation (CLA) where the patient was asked to repetitively squeeze a ball in the opposite hand. The postoperative session to assess improvement of rigidity was also carried out with an external stimulator switched on, unless when a microlesion effect had completely suppressed rigidity and other symptoms or the patient had underwent lesioning. Table 2 summarizes the measurements performed in the individual patients.
Five patients did not undergo postoperative measurements because of: an interrupted procedure of electrode implantation (1), postoperative suboptimal clinical condition (3), and early discharge of the patient (1). Two of these were assessed 2 and 8 weeks after the procedure (marked * in table 2).
After unilateral lesioning or DBS, the contralateral arm was assessed, after bilateral procedures both arms were assessed. The data bank of 33 patients comprises extended bilateral measurements in 15 patients referred for DBS STN of whom 14 patients were assessed pre- and postoperatively as is summarized in table 1. In total 577 files from the same number of measurements were obtained from 48 arms (25 right, 23 left) of 33 patients.

During rigidity testing, simultaneous surface EMG's of the forearm muscles were recorded. The electrodes, 3M Scotch ECG Ag/Cl2 (diameter 19 mm) were placed in a longitudinal orientation over the bellies of the flexor carpi radialis and the extensor carpi radialis muscles. The interelectrode spacing (center to center) was ±6 cm. The length of the epoch of each measurement was 12 seconds.
A goniometer for recording the angular excursions between the hand and the forearm during clinical rigidity testing, was constructed from a potentiometer. The signal from the potentiometer was connected to a 1 mV, 256Hz oscillator circuit and a third physiological amplifier.

The amplifiers were part of an 8 channel intra-operative neurophysiological measuring system, Neurogard®. All three channels used had equal amplification and filter settings. The high pass filters were set to 10 Hz and the low pass filters to 1 kHz. The signals were digitized by a 12 bit AD converter at 4.35 kHz and down sampled by replacing the average of 4 samples into one sample. The signals were stored on hard disk for later retrieval.
Except for chapter 5 all off-line post-processing software start with a high pass filter, to suppress low-frequency movement artefacts in the EMG signal, using a 12-coefficient Daubechies wavelet filter not zeroing the upper 3 scaling bands. The equivalent 6dB cut-off frequency is determined by applying a white noise input signal of 60 Hz bandwidth. Further processing steps on the EMG data are described in the chapters concerned.
Further signal analysis was carried out by user-made computer programs dedicated to the rigidity measurements and written by dr. H.L. Journée, neurophysiologist. These are further described in the specific chapters.
For statistical analysis, the statistical package SPSS 11.0.1 was used. The specific tests used, are described in the subsequent chapters.

Table 2: Patient information.

Survey of the patients of the databank. The data are given in chronological order.

The table shows when the patients underwent the measurements. Further explanation is given in the text.

m: male, f: female; l: left; r: right

*1 out patient postoperative measurement 2 months after operation.

*2 out patient postoperative measurement 2 weeks after operation.

					Measurements					
Patient	Intervention	Age	Gender m/f	Unilateral	Pre-operative	Post operative	Stim on	Stim off	Side	Extended session
1	Pallidotomy	47	f	x	x	x	.	.	l	.
2	Pallidotomy	71	m	x	x	x	.	.	l	.
3	Pallidotomy	67	f	x	x	x	.	.	r	.
4	Pallidotomy	66	f	x	x	x	.	.	r	.
5	Pallidotomy	72	f	x	x	x	.	.	l	.
6	DBS thalamus	60	m	x	x	x	x	x	l	.
7	Adjustment DBS thalamus	78	m	x	.	.	x	x	r	.
8	Adjustment DBS thalamus	64	m	x	.	.	x	x	r	.
9	Adjustment DBS STN	68	f	x	.	.	x	x	l	.
10	DBS pallidum	69	f	x	x	x	x	x	l	.
11	Pallidotomy	67	m	x	x	x	.	.	r	.
12	Thalamotomy	63	m	x	x	x	.	.	l	.
13	DBS pallidum	54	m	x	x	x	.	.	l	x
14	DBS STN	71	f	x	x	.	.	.	r	x
15	Pallidotomy	54	m	x	x	.	.	.	r	x
16	Pallidotomy	63	f	x	x	x	.	.	r	x
17	DBS thalamus	75	f	x	x	x	x	x	l	x
18	Adjustment DBS STN	49	m		.	x	x	x	l+r	x
19	DBS pallidum	54	m	x	x	x	x	x	r	x
20	DBS STN	56	f		x	x	x	x	l+r	x
21	DBS STN	55	m		x	.	.	.	l+r	x
22	DBS STN	62	f		x	x	.	x	l+r	x
23	DBS STN	52	f		x	x *1	x	.	l+r	x
24	DBS STN	63	f		x	x	.	x	l+r	x
25	DBS STN	48	f		x	x	.	x	l+r	x
26	DBS STN	68	f		x	x	.	x	l+r	x
27	DBS STN	56	f		x	x	.	x	l+r	x
28	DBS STN	69	f		x	x	.	x	l+r	x
29	DBS STN	51	f		x	x *2	.	x	l+r	x
30	DBS STN	60	f		x	x	.	x	l+r	x
31	DBS STN	63	f		x	x	x	x	l+r	x
32	DBS STN	49	m		x	x	x	x	l+r	x
33	DBS STN	68	f		x	x	x	x	l+r	x

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Chapter 4

Study for the applicability of EMG in quantification of parkinsonian rigidity

Abstract

Introduction

Rigidity in parkinsonian patients to date is scored according to a clinical rating scale. The need for quantification is generally recognised, but so far this has not resulted in widespread application of a suitable method.

We studied the applicability of EMG in the quantification of rigidity in parkinsonian patients referred for neurosurgical intervention.

Methods and Material

5 patients underwent clinical rigidity measurements with simultaneous EMG registration of flexor and extensor muscles of the forearm. 5 control subjects were used as a reference group.

EMG signals were evaluated for presence of EMG activity related to the rigidity testing, the lead pipe phenomenon and the cogwheel phenomenon.

EMG amplitudes in pre- and postoperative recordings were compared with clinical rigidity scores.

Results

In rigidity an increase in EMG activity was present during muscle lengthening.

The cogwheel phenomena can be detected in the EMG signals of parkin-sonian patients as bursts of EMG activity. Fourier Transformation of the COGWHEEL PHENOMENON resulted in an increased power over a broad distribution of frequencies.

EMG amplitudes in flexor muscles were higher in patients than in control subjects.

EMG amplitudes in extensor muscles did not differ significantly between patients and controls. Postoperative flexor EMG amplitudes showed a decline corresponding to the decline in clinical rigidity score.

Discussion and conclusion

The increase in rigidity in parkinsonian patients was predominantly present in the lengthening phase. Changes in rigidity could be quantified from the EMG amplitudes in the flexor muscles of the forearm during passive movements of the wrist. Besides this cycle-related increase in EMG activity a burst pattern related to the cogwheel phenomenon was present. Despite the clear visibility of the characteristic components of parkinsonian rigidity, namely the cogwheel phenomenon and the tonic background contraction, or the lead pipe phenomenon, conventional filtering methods failed in detection, extraction and quantification of the cogwheel bursts.

Introduction

The need for objective measurement of rigidity and other parkinsonian symptoms has been mentioned by several authors [1-4]. The Unified Parkinson's Disease Rating Scale (UPDRS), a semi-quantitative subjective scale [5;6], has gained world wide acceptance and is widely used in pharmacological and clinical studies and in peri-operative assessment. It assesses a broad spectrum of symptoms which are divided into different sections [7]. In the motor section, rigidity is scored in a five point-scale (table 2, chapter 3), while cogwheeling is ignored.
The inter-rater reliability of the UPDRS in the motor part is good, explaining its wide spread acceptance and use as gold standard [5]. However, rigidity scoring shows a less consistent inter-rater reliability [8]. High scores of marked rigidity are most consistent, whereas mild rigidity has a disappointingly poor inter-rater reliability [5;9-11]. This explains in part the ongoing search for alternative methods to quantify parkinsonian rigidity. Objective measurement of parkinsonian rigidity still remains a challenge however. Since 1959 several methods have been introduced, but none are generally accepted and implemented so far [12].
Techniques for objective quantification of parkinsonian rigidity can be divided into mechanical and non-mechanical methods.
Since rigidity is experienced by the resisting force of a body part, it is most straightforward to design a device that measures directly the resisting force opposing an externally acting force [3;13-16]. Direct measurement of the resisting force can be replaced by quantified electromyographic (EMG) recordings. Reliable results can be expected from this since the amplitude of the EMG signal correlates with muscular force under static conditions as well as during locomotion [17-20].
External forces can be applied by mechanical systems or manually. Mechanical systems usually apply a torque motor that administers impulse type and linear ramp [21-23], square wave [24] or sinusoidal perturbations [12;25-34]. Other force-driving devices have been developed for measurement of rigidity in the orofacial system [35]. Examiner-driven forces offer no calibrated input functions, but provide a closer relation to clinical rigidity testing methods [3;36-39].
The mechanical methods have their limitations or cannot be used at all in the operating room. Methods using mechanical devices for initiation of movements such as torque motors and most force recording devices are inappropriate because of unacceptably large dimensions and other cumbersome aspects such as continuous fixation of the patient to the device for several hours.
EMG measurements during clinical testing have the advantage of providing little disturbance of the patient during and between measurements due to the small measuring device and the close relation to clinical rigidity testing.

EMG recording is often used in reflex studies initiated by a short mechanical perturbation, for example by a torque motor, or electrically by nerve stimulation.

In contrast to the short (M1) latency reflex [40-43], the long (M2-3) [23;29;44-51] latency reflexes are increased in clinically rigidity. However, the correlations with rigidity vary markedly between studies [46]. H-reflexes are produced by electrical stimulation of Ia fibers in the parent nerve. In rigid parkinsonian patients, H-reflexes show a significant increase of amplitude at interstimulus intervals (ISI) over 30ms [52] and a significant depression at short ISI's of 5-9 ms [50;53], when testing reciprocal inhibition. A significant linear correlation of the soleus H-reflex with rigidity is reported [50;54]. However, this H-reflex has to be measured in specific positions of the limb and is often difficult to elicit in muscles of the upper limb.
Measurements of reflex activity have mostly been used to study the neurophysiological basis of parkinsonian rigidity but have not been applied specifically for quantification of parkinsonian rigidity.
The average area of the surface EMG at rest has also been described to correlate with rigidity [55;56], however this increase has also been reported to exist only temporarily, or not to be correlated with clinical rigidity [57].
Quantification of EMG signals during passive movements of the upper limb in a clinical test can be useful for objective assessment of parkinsonian rigidity. Meara and Cody reported a decreased EMG response amplitude when a rigid status of a parkinsonian patient changed into a non-rigid status after intake of medication [58].
The same authors found improved correlation between quantified EMG and grade 0-2 rigidity by selectively quantifying EMG activity in the stretching phases [59].
Benabid and Landy used EMG activity from cyclic movements of the limb in the operation room to demonstrate the post operative decrease in rigidity [60;61]. More recently, Liu introduced the EMG amplitude during hand opening and closing exercises in neuromonitoring for stereotactic surgery [62]. The amplitude of the EMG has also been used to assess changes in rigidity in pharmacological and surgical animal experiments [63;64].
In spite of varying correlations of quantified EMG activity with parkinsonian rigidity, this technique still seems most appropriate for intra-operative rigidity monitoring during standard clinical rigidity testing.
The increase in resistance during passive mobilisation of a limb can be reproduced in the EMG as a continuous increase in muscle activity due to increased α-motor neuron activity. Features of rigidity which can be felt by the examiner are the background contraction of the characteristic lead-pipe phenomenon and cogwheel phenomenon. These can be recognized in the EMG as background noise and cogwheel bursts [65;66]. Quantification of these separate signal components has not yet been elaborated for the quantification of parkinsonian rigidity.

In this study we tested the applicability of EMG as a method for intra-operative assessment of parkinsonian rigidity.
The objective was to explore the validity of surface EMG quantification of parkinsonian rigidity using pre- and post-operative measurements in patients who underwent stereotactic neurosurgery for Parkinson's disease. The changes in EMG

amplitude are discussed in the perspective of UPDRS changes. Furthermore the presence of characteristics of parkinsonian rigidity, the lead pipe phenomenon and the cogwheel phenomenon in the EMG are considered.

Material and Methods

EMG data in this study were obtained from routine clinical neurophysiological measurements in patients who were referred for pallidotomy. The first five parkinsonian patients (mean 64,6 yr, one male, four female) from our clinical series were selected (Patient 1-5, chapter 3 table 1). All patients underwent neurophysiological evaluation. Rigidity was scored clinically with simultaneously recorded EMG of the extensors and flexors of the forearm, during passive movement of the wrist. The sessions were performed one day prior to, and two days after the operation.
The EMG signals of the first 5 consecutive healthy control subjects (mean age 54,8 yr) were used as reference. These subjects underwent a single session of the same measurement procedure as the patient group. The controls had no clinical signs of rigidity.

The set-up for recording the EMG signals and angular excursions of the wrist by a goniometer, definitions for recording length, analogue and digital signal data handling are described in chapter 3.

The unprocessed EMG signals were interpreted by two examiners in consensus (AP and HLJ). Both examiners were acquainted with neurophysiological data of parkinsonian rigidity.

The recorded signals of patients and control subjects were scrutinised for presence of cyclic EMG activity related to the wrist movements and the presence of burst phenomena from cogwheel phenomenon and tremor.
To determine the frequency of the bursts, the signals underwent digital processing by subsequent full-wave rectification and fast Fourier transform to obtain power spectra. When the signal to noise ratio permitted, the power spectra were used to retrieve the frequency band of the cogwheel bursts from their location of the power spectral peaks along the frequency axis.
EMG data were converted into root-mean square (rms) values for quantification of their amplitudes. The EMG amplitudes of pre- and post-operative recordings were compared with clinical rigidity scores. The amplitude of the EMG signals of the control subjects were compared to EMG signals of the parkinsonian patients.

Agonist and antagonist muscles during the study were defined as follows:

During extension of a limb the extensor muscles are shortened and the flexor muscles are lengthened. The extensor muscles are the agonist muscles and the flexor muscles are the antagonist muscles. In flexion the flexor muscles are the agonist muscles and the extensor muscles the antagonist muscles.
A software package SPSS 11.0.1 was used for statistical evaluation. The Mann-Whitney test for unpaired non-parametrical variables was used to compare the rms values between patients and control subjects.

Results

Cycle-related EMG activity
All patients showed increase in EMG activity during muscle lengthening in the pre-operative measurements. On the contrary, the postoperative measurements, showed no consistent increase in EMG activity during lengthening of the muscle.
Figure 1 shows a representative example of recordings of the flexor and extensor EMG's together with the goniometer signal of patient 4, during manipulation of the wrist by the examiner. An increase in EMG activity was present in the lengthening phases of the muscle resulting in an alternating pattern of EMG activity in flexors and extensors of the forearm. The increases in EMG amplitude in the lengthening phases, indicated by grey boxes, was most pronounced in the flexor signal.

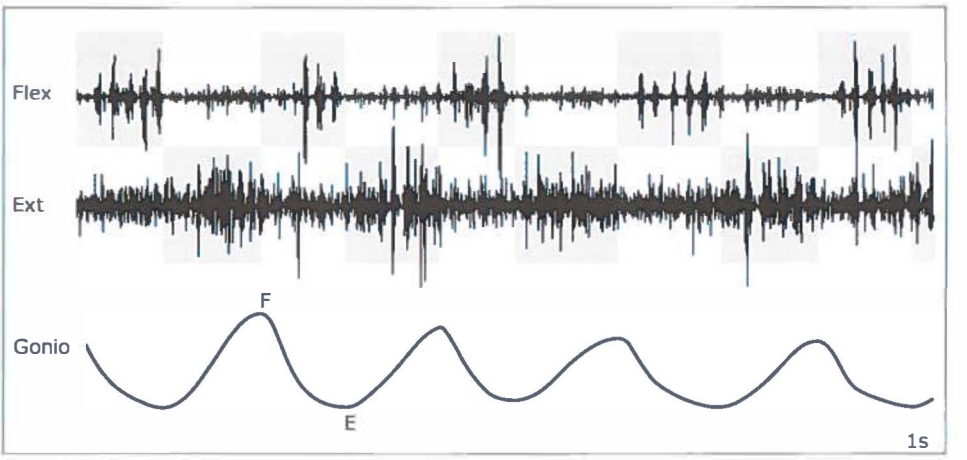

Figure 1: An example of the EMG during manipulation of the wrist by the examiner of patient 4. The upper signal shows the flexor EMG. The extensor EMG is shown in the second row. The signal of the goniometer is shown at the bottom. E and F resemble maximal extension and flexion. The grey shadings mark the lengthening phases of the muscles; an alternating pattern of increase in EMG activity in flexor and extensor signals can be noticed. Burst patterns from the cogwheel phenomenon can also be distinguished. The flexor EMG shows most clearly increases of EMG activity during the lengthening phases.

None of the control subjects showed clinical signs of rigidity (UPDRS=0). The movements by the examiner were performed somewhat faster than in (rigid) parkinsonian patients, but the repetition frequency remained between 1 and 2 Hz. The control subjects showed no increase in EMG activity during muscle lengthening. In contrast, all control subjects showed an increase in EMG activity during shortening, 4 out of 5 in flexor muscles and 3 out of 5 in extensor muscles. In 3 control subjects sometimes co-contraction patterns were visible during extension of the wrist.

Characteristics of EMG bursts

In the parkinsonian patients repetitive burst series could clearly be seen in the flexor as well as extensor EMG's. These bursts usually appeared simultaneously with a cogwheel phenomenon noted by the examiner.

In the pre-operative recordings, 9 out of 10 flexor EMG's showed bursts in the lengthening phase, whereas in one measurement, bursts were present during shortening as well as lengthening of the recording epoch. The extensor muscles showed predominantly bursts in lengthening phase in 6 of 10 recordings, in the other four recordings bursts continued in the shortening phase. In the postoperative recordings bursts in lengthening phase were present in 17 of 20 recordings.

The power spectra (after Fourier Transformation) showed, for the flexors in 7 out of 10 recordings and for the extensors in 5 out of 10 cases, elevated levels over a broad frequency band corresponding with the range of reciprocal values of the burst intervals in the EMG's. These elevated levels were superimposed on a masking background noise. In the other cases the noise completely camouflaged the power spectral components of the repetition times of the EMG bursts.

Examples are shown in figure 2. In both the flexor and extensor EMG of patient 4, one can easily recognize repetitive tremor bursts with burst interval lengths in a range of 90–130 ms. In the power spectrum of the flexor EMG (figure 2a, left lower panel) one can distinguish a peak at about 1 Hz from cyclic movements of the wrist driven by the examiner. Furthermore, the spectrum shows increased power in a frequency band of 7.5-10 Hz superimposed on broad band noise. The background noise of the extensor EMG is higher when compared to the flexor EMG. Consequently, the background noise in the power spectrum of figure 2a (right lower panel) completely masks the frequency band where an elevation of power from the burst repetitions is expected.

Patient 2 (figure 2b) showed a resting tremor of about 5 Hz in standard clinical tremor testing. The power spectrum of both the extensor and flexor muscles EMG showed a narrow peak at 5 Hz. During rigidity testing the EMG showed, instead of a regular burst pattern of 200 ms intervals, irregular burst patterns during lengthening of the muscle.

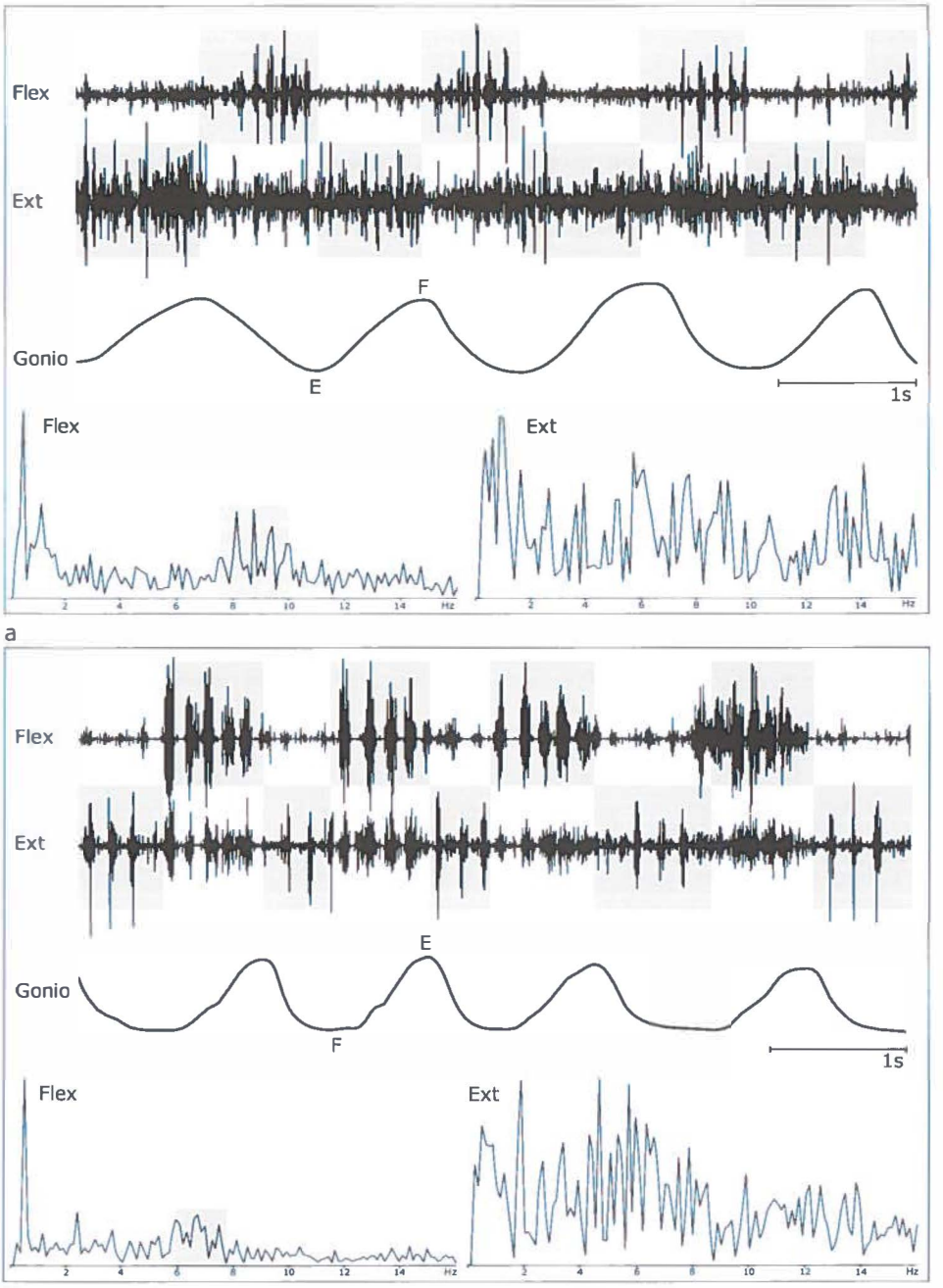

Figure 2: The EMG signals of the flexor (Flex) and extensor (Ext) muscles in the forearm of patient 4 are shown in (a), together with the signal of the goniometer. E and F resemble maximal extension and flexion. The grey shadings mark the lengthening phases of the muscles. Below the power spectra (after Fourier Transformation) of the flexors (left) and extensors (right) are shown. The cogwheel bursts can clearly be recognized in the original signals. However their presence in the power spectra is masked by demodulation noise from the full wave rectified EMG.

Only the cogwheel busts from the flexor signals can be distinguished by an elevation of energy in the band between 7.5 and 10Hz. The peak at about 1 Hz is the frequency of the applied excursions of the examiner.
The EMG signals and goniometer of patient 2 with the associated power spectra are shown in (b). The cogwheel bursts in the original signal are clearly present. The power spectra of only the flexor EMG shows a subtle increase of power in a frequency band of 6 – 8 Hz superimposed on broad band background noise. The background noise in the power spectrum of the extensor EMG completely masks the frequency band where an elevation of the spectrum is expected from the interburst intervals.

The power spectra of only the flexor EMG showed an increase of power in a frequency band of 6–8 Hz superimposed on broad band background noise. The background noise in the power spectrum of the extensor EMG completely masked the frequency band where an elevation of the spectrum was expected from the interburst intervals.

Changes in EMG activity following surgery

Figure 3 shows the rms amplitudes of the EMG in the pre- and post-operative measurements of the patients during clinical rigidity testing. The amplitudes in the control subjects are shown at the right. The left panel is from the flexor muscles and the right panel from the extensor muscles. The patients had rigidity scores (UPDRS) of pre-operatively (p1-5) 3, 2, 0, 4, 2 and postoperatively 0, 0, 0, 0, 2 respectively. All UPDRS scores for the control subjects were 0.

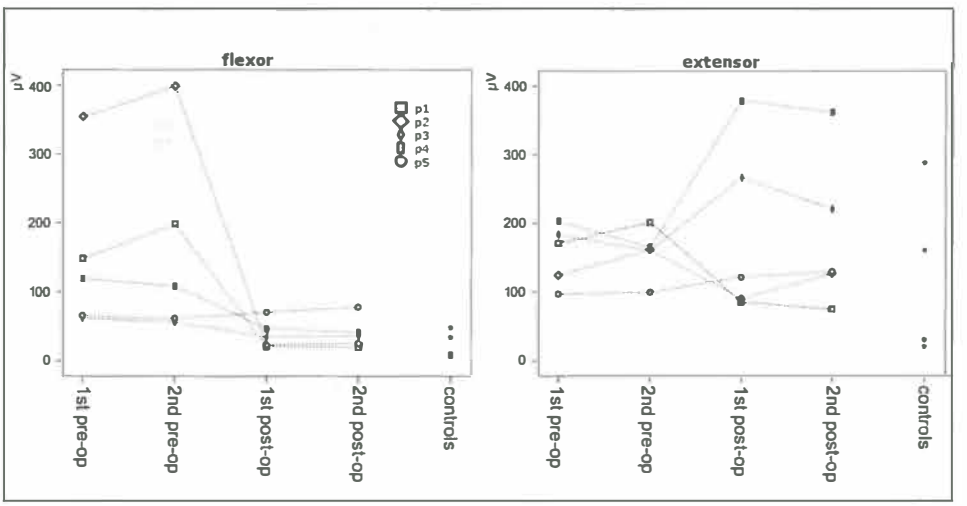

Figure 3: Diagrams of amplitude course of two subsequent recordings of the flexor and extensor muscles of 5 parkinsonian patients (p1-5) before and after surgery and 5 control subjects (c1-5).
On the horizontal axis the timing of the measurement is plotted.
UPDRS changed from 3 pre-operative to 0 post-operative in patients p1 and p4 and from 2 to 0 in patient p2. In patient p3 and p5 the UPDRS remained unchanged 0 and 2 respectively.
In all patients the flexor activity drops in decreasing rigidity postoperative. In patient p3 and p5, the flexor activity remains unchanged. The extensor activity shows heterogeneous changes: patient p1 and p2 show a decrease in extensor activity, whereas patient p3 and p4 show an increase in extensor activity, despite unchanged or decreased rigidity postoperative.

Three patients showed a decrease in clinical rigidity after the pallidotomy procedure whereas two patients (3 and 5) did not show any changes in rigidity postoperatively. The flexor recordings showed a decline in amplitudes in the first 3 patients, patient 3 and 5 showed only minor changes in EMG amplitude.
In patients 1 and 2 the amplitude of the extensor signals decreased. Patient 5 showed a mild increase. However, two patients (3 and 4) showed an increase in amplitude of extensor muscles in spite of a decreased or unchanged clinical rigidity. When the extensor EMG activity of these patients increased, a simultaneous increase in EMG activity was present during extension of the wrist in the flexors due to co-contraction.

The mean amplitudes of the control subjects are shown at the most right. In flexor muscles the control subjects show smaller amplitudes than pre- and postoperative parkinsonian measurements. In extensor muscles there is a wide range of amplitudes.

Discussion

Rigidity, which is perceived by the examiner during a clinical test as an increase in resistance to passive movement, can be interpreted as a resistive force opposing the movement. EMG provides information on mechanical action of muscles. Many authors have previously described the relationship between the integrated EMG and muscle contraction force. A linear relationship between EMG amplitude and force in isometric muscle contraction is presently accepted [17;67]. A less linear relationship is described in the literature when antagonist muscles contribute to the contraction [68]. During a rigidity test, the muscle force exerted by the patient is not isometric since the muscles are stretched and shortened during the extension and flexion excursions of the movements made by the examiner. Moreover, the force changes in time. It is defined as 'dynamic force'. It is not known how linear the relationship between EMG and force will be during the test. Guimaraes et al [20] found a non-linear proportional relationship between integrated EMG and force during walking. A linear relationship between EMG amplitude and force are of relatively limited importance since the UPDRS scale is also probably not linearly related with force of the resistance felt by the examiner. The way in which a clinical examiner perceives resistance will depend on many factors and the subjective interpretation of resistance probably also is not linearly related to the actual force.
The most important requirement determining the utility of EMG for quantification of rigidity is the existence of a proportional relationship between EMG amplitude and force. This condition seems to be fulfilled in this small patient group in which we were able to detect EMG changes in clinical rigidity. The amplitude of the flexor EMG dropped in the post-operative recordings, confirming the decrease in

clinical rigidity. The extensor muscles showed a less consistent decrease in EMG amplitude with sometimes paradoxical increases. This has probably to be ascribed to active contraction during extension of the wrist.

EMG amplitudes in patients and control subjects varied significant in the flexor muscles, whereas extensor muscles showed a large overlap. Also the decrease in rigidity in the patient group is best depicted in the flexor muscles. Rigidity was considered to be equally present in flexor and extensor muscles [46;69;70], however, more recent studies describe an asymmetric distribution of the muscles in rigidity [71].
The increase in EMG amplitude was predominantly present in the lengthening phase, confirming the findings of Meara et al. [72;73]. Next to this increase a burst pattern was present in the EMG. The increase of EMG with bursts in the lengthening phase was not noticed in the control subjects. However, the control subjects showed an increase of EMG activity during muscle shortening, indicating active contraction. When control subjects were asked to simulate rigidity, the increase in EMG amplitude started before the onset of the lengthening phase while both muscle groups showed more pronounced co-contraction patterns, compared to parkinsonian patients.

In clinical rigidity testing, two components of rigidity can be felt: the tonic part of rigidity -or the lead-pipe phenomenon- which can be interrupted by the other part: the cogwheel phenomenon. The cogwheel phenomenon is believed to represent an underlying action tremor, since its frequency between 7-14 Hz is the same as the cogwheel burst frequency [74-76]. When visible in the power spectrum in this study, the power of cogwheel bursts was present in a frequency band of 7-10 Hz. This is within the range of 7-14 Hz reported in the literature. The spectra of cogwheel bursts may show multiple peaks (left spectrum in figure 2b) as well as a continuous elevation in the frequency band.
The background contraction reflects the static component of rigidity whereas the bursts relate to the cogwheel phenomenon. Despite its characteristic (but not pathognomonic) appearance in parkinsonian rigidity, the cogwheel phenomenon has to be excluded in clinical rigidity testing according to the UPDRS-definition of rigidity.

It is shown in this study that power spectra were inappropriate for retrieving the power spectral components of cogwheel bursts. The main reason is the presence of demodulation noise. This noise results from demodulation of amplitude modulated noise by full wave rectification [77]. In power spectra, tremor signals have narrow band frequency peaks that can often be distinguished from the broad band demodulation noise [62;78;79]. However, when the bandwidth of irregular pacing bursts series is higher than 1 or 2 Hz and when bursts are not continuously present, as is the case during rigidity testing, the power spectrum of the bursts

becomes invisible due to the masking effect of the power spectrum of the demodulation noise. In contrast to the invisibility of the power spectral component of the bursts in a spectrum, they can clearly be recognized in the EMG signals. This failure of spectral analysis is ascribed to inevitable causes; in the first place the essential presence of demodulation noise resulting from full wave rectification of amplitude modulated noise of EMG bursts. Secondly, the power spectral analysis is designed for stationary signals. Instead of being present throughout the whole recording epoch, cogwheel bursts are usually present during the muscle stretching phases. A stationary background noise will then overrule the power spectrum.
We conclude that linear filtering and power spectral analysis are inappropriate to detect and analyse EMG bursts of the cogwheel phenomenon. Non-linear and time variant filtering techniques using wavelet transform [67;80;81] or statistical detection algorithms [81] that are primarily designed to detect non-stationary events seem to be appropriate choices for detection and analysis of cogwheel EMG bursts. When these techniques permit separation of bursts from the background EMG activity, it may theoretically be possible that errors in EMG quantification for rigidity by interfering bursts of a tremor could be reduced. In this way, a false positive detected rigidity from tremor, in patients with clinically none or mild rigidity, could possibly be prevented.

Conclusion

This study showed in a small patient group that changes in clinical rigidity can be quantified from the EMG amplitude of predominantly the flexors in the forearm during passive movements of the wrist.
In contrast to the clear visibility of the characteristic components of parkinsonian rigidity of the tonic background activity and cogwheel bursts in the unprocessed EMG signals, linear filtering and power spectral analysis techniques often fail in detection, extraction and quantification of cogwheel bursts in EMG signals. The reasons for this are the unavoidable presence of demodulation noise and the non-stationary characteristics of the bursts. One can expect an optimal performance from a cogwheel burst detector using digital analysis techniques that are primarily designed to detect non-stationary changes in signals. Such a detector may be used to separate the cogwheel bursts from background activity which represents the lead pipe phenomenon, before quantification of the EMG. Then the clinical definition of parkinsonian rigidity according to the UPDRS, in which the cogwheel phenomenon has to be excluded, will be approximated most closely.

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Chapter 5

Time variant wavelet filtering for separation of static and dynamic components in rigidity EMG and correlation with clinical rigidity

Abstract

Introduction
Parkinsonian rigidity consists of the lead pipe phenomenon and the cogwheel phenomenon. These two components can be identified in EMG recordings of parkinsonian patients. In quantification of parkinsonian rigidity, separation of these two components seems obligatory to conform with the widely used UPDRS rigidity scale.
This study investigates the capability of time variant wavelet filtering, a method of non-linear signal analysis, for separation of these two components of parkinsonian rigidity in EMG recordings, after determination of optimal filtering settings in parkinsonian patients.

Methods and Material
Optimal filter parameters were determined in a single parkinsonian patient, these parameters were then used for the entire patient group. A threshold factor, TF, was the wavelet transform filter parameter controlling the separation of the static (background EMG) and dynamic (bursts) components. Amplitudes of the 'static' and the 'dynamic' components of the filtered EMG as well as the unprocessed EMG were computed. Amplitudes of 33 parkinsonian patients and 10 control subjects were compared with clinically assessed rigidity.

Results
The choice of the wavelet type did not appear critical, the least distortion of the bursts was noted with Daubechies wavelet D12. At TF=0.08, the selectivity between static background contraction and dynamic bursts was optimal. These were chosen as filter parameters for the study. Patients with rigidity showed higher amplitudes in flexor signals when compared to control subjects. The reproducibility between two subsequently performed measurements was good.
In contrast to signals in extensors, in flexors a significant correlation was found between the amplitudes of unprocessed and static part of EMG, and clinically assessed rigidity (Spearman's correlation coefficient 0.34 and 0.42 respectively). An increase in clinical rigidity by contralateral activation was accompanied by an increase in EMG amplitude in extensor muscles, but not in flexor muscles.
Decrease in rigidity post-intervention was significant in all parts of flexor muscles.

Discussion and conclusion
Wavelet filtering is a novel technique for detection and separation of cogwheel bursts from the background EMG. The amplitude of the static filtered 'background' EMG offers a mild improvement of correlation with clinical rigidity, compared to quantification of non-processed EMG.
The changes in clinical rigidity were best reflected in flexor muscles
In the presence of 'negative rigidity' high amplitudes were found in patients with clinically no or only mild rigidity; this problem has to be resolved in a future study before wavelet filtering will be successful in EMG quantification of rigidity.

Introduction

Parkinsonian rigidity has been noted as an increase in resistance to passive stretch. It consists of a static background contraction, the lead-pipe phenomenon (LPP), which can be interrupted by a tooth-like fashion, the cogwheel phenomenon. These two components of parkinsonian rigidity, the lead-pipe phenomenon and the cogwheel phenomenon, can be separately identified in the electromyography (EMG) recordings of parkinsonian patients as a background contraction with superimposed bursts.

In developing a method for quantification of parkinsonian rigidity, separation of these two components seems obligatory since the definition for clinical rating of rigidity according to the UPDRS states that the observer has to ignore the cogwheel phenomenon. Since cogwheel bursts may contribute substantially to the amplitude of the EMG, it is important to separate these bursts from the static background contraction before quantification of the EMG for scoring of rigidity.

It was concluded in the previous chapter that linear filtering and power spectral analyzing techniques often fail in detection or selective separation of cogwheel bursts in EMG signals. Reasons for this are the essential presence of demodulation noise and non-stationary characteristics of the bursts, as well as the irregularly-paced burst pattern. This means that in a spectrum the bursts are barely visible because they are spread out over a wide frequency band that is superimposed on the underground of the demodulation noise. This is in contrast to the easily recognizable narrow band peaks of tremor EMG's. One can expect an optimal performance from a cogwheel burst detector using digital analysis techniques that are primarily designed to detect non-stationary changes in signals such as EMG-bursts. One of these techniques is the wavelet transform (WT). This relatively new technique has gained widespread use in speech and image processing, and also in surface EMG analysis [1-3]. A cogwheel burst is a non-stationary transition from a stationary background noise. WT is primarily sensitive to non-stationary events. Wavelet filtering was recently shown to be successful in separating burst patterns in unprocessed EMG signals of parkinsonian patients with dystonia [4]. These methods probably also will be successful for detection, timing or filtering of regular pacing EMG bursts in pathological tremor as well as irregular pacing bursts in rigidity to separate them from the EMG of background contraction. Wang et al applied adaptive soft-thresholding wavelet shrinkage according to Donoho et al [5;6] for extraction of burst from tonic components from surface electromyograms in patients with dystonia [4]. In parkinsonian rigidity this application has still not been reported to our knowledge.

The hypothesis of this study is based on the UPDRS definition of rigidity and states that the background activity of the EMG correlates better with clinical rigidity than unprocessed EMG. This study investigates the capability of time variant wavelet filtering, a method of non-linear signal analysis, for separation of

the two components of parkinsonian rigidity in EMG recordings after determination of optimal filtering settings in parkinsonian patients.
The hypothesis will be tested by quantification of the unfiltered and filtered parts of the EMG and correlated with clinical rigidity scores.

Background of wavelet filtering and choice of parameters

Filters can be developed from both Fourier transform and wavelet transform. One can construct two types of filters by means of wavelet transform: time invariant and time variant types. Classic filters are time invariant which means that their characteristics do not change in time. Time variant filters result from developments in the past two decades; the characteristics of time variant filters vary in time and are suitable for detection of bursts.
Filters are designed to separate or undo specific signal components from a signal. Most used are linear harmonic filters. Such filters can block specific frequencies while preserving a predefined filtered frequency band. These can be designed using Fourier transform. In Fourier transform, a signal becomes decomposed into a finite or infinite set of sine and cosine waves of different frequencies. The amplitudes are represented by spectral coefficients in the frequency domain. These coefficients can be visualized by amplitude- or power spectra [7]. A filter can be constructed by taking out a set of frequencies by zeroing a selected part of spectral coefficients followed by a Fourier back transform resulting in the filtered signal. This filter is based on sine waves of infinite length. A spectrum gives only information about the presence of a set of sine functions during the recording length, but one can not tell if peaks or a power band in a spectrum results from the continuous (stationary) or temporary (non-stationary) presence of a signal. A spectrum has no time dimension and therefore this information is lost. In Short-time-Fourier transform (STFT) [8] and Gabor [9;10] transform, sine functions and therefore the analysis epochs, are made of finite length by separating a data array of a digitized signal into a series of short epochs in which the signals are truncated by a Gaussian or other tapering functions. These truncated parts may overlap. Transforms of these truncate pieces of the signal are repeatedly performed along the recording length of a signal. The locations of burst can be retrieved by comparing subsequent spectra's. This type of analysis is time invariant, but one can recognize time variant patterns when amplitude spectra are displayed along a time axis. A well known widespread application STFT in physiology is ultrasound spectral Doppler for measurement of the velocity of particles in blood vessels.
However, since the frequency spectra of the background EMG and bursts are the same, classic filters and STFT offer no opportunity to separate bursts from the background noise.

Discrete wavelet transformation (DWT), which algorithm has been described by Daubechies [11], offers a solution for this problem. The transform has similarities with the Fourier transform. Instead of sine functions of infinite length, wavelet transform applies wavelets of different types of mother wavelets. They have a finite length, 'compact support' and most of their shapes differ from sine functions. The wavelet transformation is like the Fourier transform ortho-normal for a specific set of mother wavelet types. This makes it possible to construct filters similar to Fourier transform. Wavelet transform converts the signals into coefficients in a 'time-scale' band which is similar to a frequency spectrum. The scale bands reflect octave-wise arranged 'frequency bands'. One time-scale band belongs to a wavelet of a given width. This wavelet is a family member that is derived from the mother wavelet. The width of the wavelet in each lower scaling band is doubled, defining a lower octave band. In contrast to a spectrum, which has no time dimension, coefficients in the time-scale bands are represented along a time axis. This means that the coefficients in the time-scale are preserved in time. In this way, the occurrence of events in time can be derived from the location of the coefficients in the time-scale domain. Wavelet transform is primarily suited for detection of nonstationary events.

As in Fourier transform, a wavelet filter can be constructed by modifying the coefficients, for example by zeroing, before back transform. On can design a time invariant filter by attenuation or zeroing coefficients in a specific selection of time-scale bands. For example, if one desires to create a high-pass filter, one can zero the lower octave bands while preserving the upper bands, or a band-filter by zeroing coefficients in the upper and lower time scale bands. Time variant filters can be constructed by modification of specific selection coefficients in a time-scale domain. Examples are evoked potentials where coefficients outside a time-scale domain are zeroed before back-transform. Such a template is usually obtained from a de-noised average over a large number of sweeps. Since in a template a relative small number of wavelet coefficients are preserved, the noise which is usually spread over all coefficients, can be removed very efficiently. This results in a significant reduction of measuring time since only a fraction of the number of sweeps is required to obtain the required signal to noise ratio of the response.

Time variant wavelet filters have been applied in evoked potentials (SEP's) [12] and in auditory evoked potentials (AEP) [13].

Another time variant filter is based on thresholding, where a threshold is used to decide whether coefficients in the time-scale domain are zeroed or attenuated. In thresholding techniques such as wavelet shrinkage, the majority of coefficients - each carrying a small part of the background EMG - are shrunk to zero so that only the few larger coefficients above a predefined threshold level, representing the signal of the bursts, are maintained. The size of the coefficients controls the characteristics of the filter. This means that the filter characteristics depend on amplitude and therefore are non-linear. The time dependent zeroing of coefficients makes the filter time-variant.

The threshold amplitude is the filter parameter and handles the selectivity. The selectivity depends on the signal-to-noise (SNR) ratio of the amplitudes of the bursts and the background noise. When the amplitude of the background noise increases, the selectivity may decrease. This problem can be solved by adapting the threshold level to the amplitude. Several adaptive soft-thresholding techniques have been developed and described by Donoho et al [5]. Wang et al demonstrated adaptive soft-thresholding wavelet shrinkage for extraction of burst from tonic components from surface electromyograms in patients with dystonia [4]. For a mathematical description of the discrete wavelet transform (DWT) and the soft-thresholding technique we refer to the paper of Daubechies [11], Donoho [5;6] and Wang et al [4].

Material and Methods

Surface EMG's of 33 Parkinson patients, referred for ablation or deep brain stimulation of thalamus, pallidum or subthalamic nucleus were analyzed retrospectively. Twenty-nine patients were referred for surgery, these patients were recorded in pre- and postoperative situations, 3 patients did not undergo postoperative recordings because of their clinical condition or early discharge; 4 additional patients were referred for adjustment of stimulator and were recorded with the stimulator switched off and on. The patients and characteristics are described in chapter 3. Of each patient, recordings of one arm were used in this study. In patients in whom both arms were recorded only recordings of the right arm were used. EMG recordings of the right arm of 10 healthy control subjects were made for comparison.
Recordings were made during standard pre- and postoperative rigidity testing by passive movement of the wrist by the examiner, followed by rigidity testing during contralateral activation (CLA), in which the patient was asked to squeeze a ball with the contralateral hand during rigidity testing. Both tests were performed twice by the same examiner (HLJ or AJP). The clinical rigidity scoring according to the rigidity part of the Unified Parkinson's Disease Rating Scale (UPDRS) and the EMG recordings were executed simultaneously.

Off-line analysis of the retrieved EMG recordings was carried out with the software package 'FYSTOOLS-WT' of the Neuro-Guard® neurophysiological equipment. This package is designed for interactive use on physiological signals and comprises a wavelet transform toolbox which was adapted to the experiments of this study.
The discrete wavelet transform (DWT) was performed by a pyramid algorithm according to a multi-resolution scheme [14-16]. The software package has the possibility to perform time variant and time invariant wavelet filtering. The time variant filter can be defined by the user making a selection out of 9 time-scale

bands that are to be zeroed. The user also can select Daubechies wavelet types of lengths of 2 (Hair wavelet) (D2), 4 (D4), 12 (D12) and 20 points (D20).
In the time variant filtering, the filtered signals were obtained by stepwise computation of the wavelet transform over epochs of 1024 points. The 1024 samples cover a nearby 2 s epoch length after they were down-sampled by a factor of 2. The blocks overlapped by a factor of 50%. Time variant wavelet filtering was performed using a uniform threshold. The filtering procedure zeroed all coefficients in the time-scale domain of which the absolute value is below a user-defined threshold level before a wavelet back-transform was performed. The time variant filter resulted in two filtered signals: the 'dynamic' signal and the complementary 'static' signal. Due to the ortho-normal characteristics of the wavelet transform with the Daubechies wavelets, the sum of the dynamic and static signal is equal to the original signal before time variant filtering. The threshold level is defined by a threshold factor, TF, relative to the maximum top-top amplitude $V_{t\text{-}t\ max}$ of the signal over 1024 points. The optimum factor was determined by visual inspection of a threshold series of TF=0–0.5 of flexor and extensor signals of patient 1.
These choices of the threshold and wavelet type were used in statistical study on the group of 33 patients. The signal blocks of 1024 samples were repetitively processed in sequential steps:
Adaptation of the threshold level according to: $TF=0.08 \cdot V_{t\text{-}t\ max}$ by determination of $V_{t\text{-}t\ max}$ of the next epoch.
Extraction of static and dynamic components from the EMG by time variant wavelet analysis using a Daubechies 12 wavelet filter. In this way 3 signals per EMG recording were obtained: an 'unprocessed' EMG, a 'static' or background EMG and a 'dynamic' or burst EMG.
Computation of root-mean-square (rms) amplitude values over 2 seconds in a series of 6 and the average of these three signals.
The EMG amplitudes in flexor and extensor muscles were evaluated separately in the study, because of the difference in amplitudes between flexor and extensor muscles.

The EMG amplitudes of the unprocessed EMG, the background EMG and the burst EMG were compared to clinical rigidity scoring.
- EMG scores of flexor and extensor muscles of patients and control subjects were compared using the Mann-Whitney test for unpaired non-parametric variables to investigate whether the expected increase in EMG amplitudes in (rigid) parkinsonian patients is true in our population.
- The first and second passive rigidity measurements in the patient group were used to calculate reproducibility of EMG amplitudes and UPDRS rigidity scores; Spearman's correlation coefficient was calculated for UPDRS rigidity and for the three parts of the EMG.

- To investigate whether an increase in UPDRS rigidity was accompanied by an increase in EMG amplitudes, the first rigidity measurements of each session were used for correlation studies between the EMG amplitudes of the static and dynamic filtered signal as well as the unprocessed EMG, with clinical rigidity scores. Correlations between clinical rigidity scores and amplitudes of the EMG were analyzed by calculating Spearman's correlation coefficients (for non-parametric distribution). P-values <0.05 were considered statistically significant.
- During contralateral activation, an increase in rigidity is expected. The Wilcoxon signed ranks test for paired non-parametric variables was used to assess the changes in clinical rigidity and EMG amplitudes during contralateral activation. Since rigidity tests with contralateral activation was added later in the standard measurements protocol, recordings of 21 cases were available for comparison with passive rigidity testing. In one of these patients (#18) one file was overwritten and recorded as missing file. The tests with contralateral activation were performed in every patient irrespective to the first UPDRS score.
- In order to ascertain whether changes in clinical rigidity are reflected in EMG amplitudes, the difference between EMG amplitudes of the first pre- and postoperative recordings of the patients were plotted against the change in UPDRS rigidity, and regression was calculated.

Statistics were performed with the statistical package SPSS 11.0.1.

Results

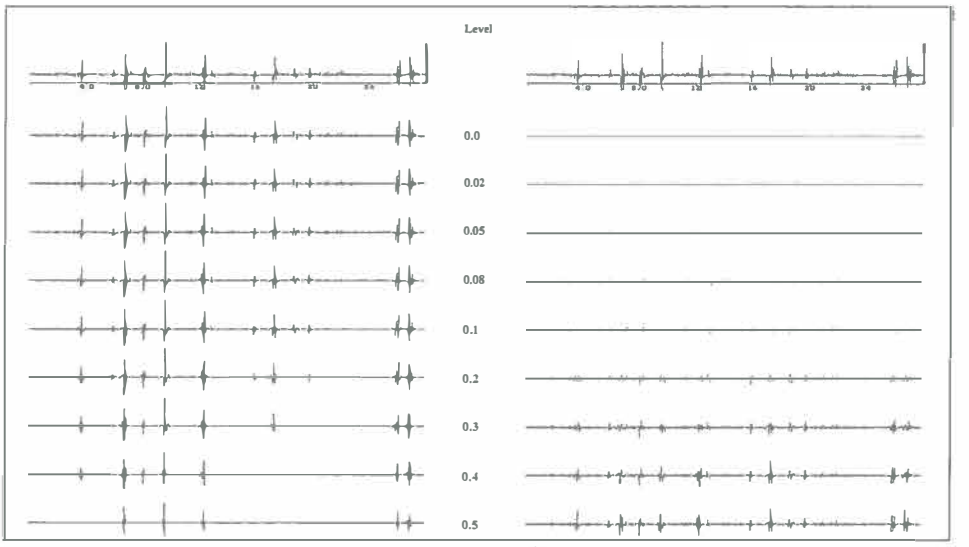
Pilot study for the selection of the threshold level and wavelet type.

Figure 1 shows four stacked plots of the WT-filtered EMG signals of patient 1 for a threshold series of TF=0–0.5. The high-pass filtered EMG signal before time variant filtering is shown above the plot. The stacked plots at the left (figure 1a and 1c) resemble the filtered 'dynamic' part and at the right the background 'static' part (figure 1b and 1d). Figure 1a and b belong to the recordings of the flexor EMG and figure 1c and 1d to the extensor EMG.

For TF=0, all coefficients were unchanged so that the original signal is present in the dynamic signal, leaving no complementary static signal in the plots at the right. With increasing TF, the signals at the right showed gradually a build-up of the background noise without bursts in the static plots until TF=0.08. At TF=0.08 the selectivity is optimal since bursts in the dynamic signal are retained, whereas in the static filtered signals the background noise is present. Further increase of TF above 0.2 showed a reduction and finally complete disappearance of the number of bursts in the dynamic signal, while the complementary unfiltered parts of the bursts appear in the stationary filter part. This was seen in the extensor as well as flexor EMG's.

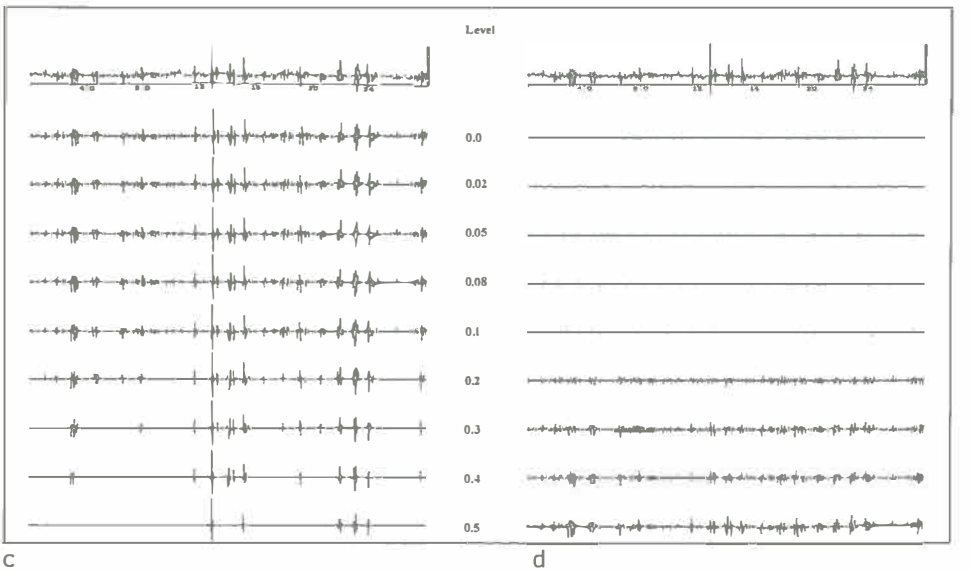
We concluded that TF=0.08 was an optimal choice for the statistical study.

Flexor



a b

Extensor

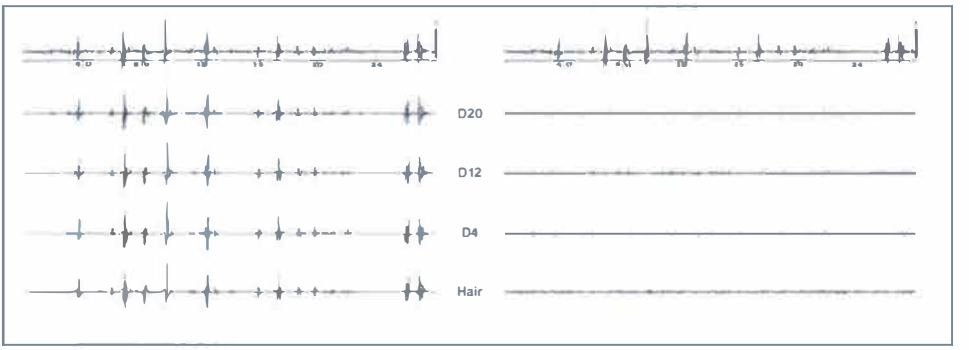


c d

Figure 1: EMG signal of patient 1. Four stacked plots are shown from the EMG signal (top) of patient 1 after application of a time invariant wavelet filtering with different threshold factor.
The upper stacked plots belong to the flexor muscles and the lower plots belong to the extensor muscle. The left stacked plots are the filtered signals after time variant wavelet filtering. The level of the threshold increases from top to bottom. The complementary signals, the filtered part, is shown at the right.
With increasing threshold, the interburst signal decreases to 'zero'. The bursts remain present until the threshold becomes too high; then bursts also disappear from the signal and will be present in the complementary signal. The optimal threshold is shown at 0.08: the interburst signal is flat and no bursts become present in the complementary signal.

Figure 2 shows in the same patient the effects of different Daubechies wavelet types D2, D4, D12 and D20 on the dynamic filtered signal at TF= 0.08. In all four dynamic filtered signals the stationary background EMG was sufficiently removed whereas no differences between the filtered signals were present. In two other EMG signals of patients 2 and 3 (not shown here) there were minor differences visible, whereas the D12 filter showed the least distorted bursts. Therefore the D12 wavelet was chosen for the statistical evaluation of the patient group.

Flexor



Extensor

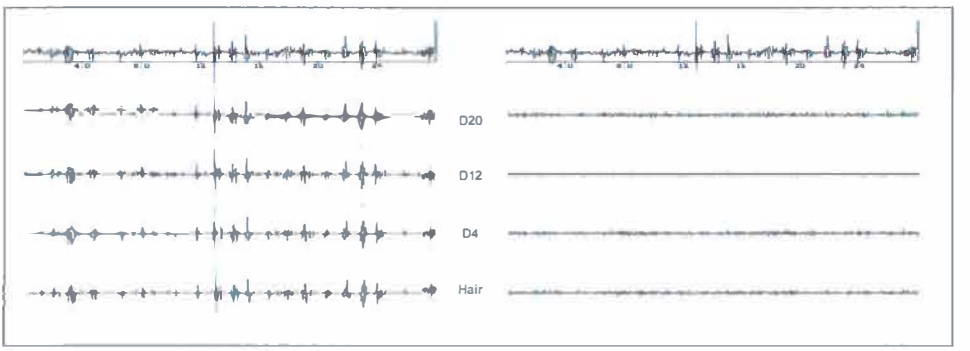


Figure 2: Time variant wavelet filtering of the EMG signal of the same patient as figure 1 is shown for different wavelet types. A Daubechies 4, 12, 20 and a Hair wavelet are subsequently shown for filtering at TF = 0.08 in flexor (a) and extensor muscle (b).
No marked changes are present between the four wavelet types.

Separation of EMG components

In pre-operative recordings bursts were reasonably well separated from background EMG activity by time variant WT filtering at TF=0.08 whereas the SNR was sufficiently high for filtering. In post-operative recordings the bursts were not always visible or less distinct at smaller SNR's. Consequently, the dynamic signal showed no or occasional burst patterns. In control subjects no EMG bursts were noted in the dynamic filtered signals.

Patients and control subjects

All control subjects had UPDRS rigidity scores of zero, while patients had higher UPDRS scores between zero and 3 (UPDRS 0: 13 patients; UPDRS 1: 1 patient; UPDRS 2: 14 patients; UPDRS 3: 5 patients, UPDRS 4: 0 patients).

In patients generally higher EMG amplitudes in flexor signals were seen when compared to healthy control subjects. These differences were significant for the two filtered components as well as in the unprocessed EMG. (Mann-Whitney unprocessed EMG $p=0.003$, static: $p=0.001$ and dynamic $p=0.000$). The extensors of patients did not show significant higher EMG amplitudes when compared to control subjects (Mann-Whitney unprocessed EMG $p=0.47$, static: $p=0.20$ and dynamic $p=0.09$).

Reproducibility

In the patients as well as control subjects, all rigidity measurements were immediately followed by a subsequent similar measurement. Table 1 shows the UPDRS rigidity scores in the first and second measurements in a cross-tab. The clinical rigidity scoring according to the UPDRS showed good reproducibility in patients (Spearman's Correlation coefficient: 0.92).

Reproducibility of amplitudes of the three parts of the EMG was expressed in correlation factors from 0.79 to 0.96 (Spearman's Correlation coefficient) and were significant at $p<0.01$, for all muscle groups in filtered and unfiltered signals. Table 2 shows a survey of the results.

Table 1: Reproducibility of the first and second clinical rigidity measurements of passive rigidity testing, according to the UPDRS definition. (Spearman's correlation coefficient 0.92).

		UPDRS 2nd measurement				
		0	**1**	**2**	**3**	Total
UPDRS 1st measurement	**0**	12		1		13
	1		1			1
	2			11	3	14
	3				5	5
	Total	12	1	12	8	33

Table 2: Reproducibility of first and second passive rigidity measurements of the patient group (n=33). Correlation factors were calculated with Spearman's correlation coefficient. All correlation factors are significant for $P<0.01$.

	Flexor	**Extensor**
Unprocessed EMG	0.86	0.93
Static part	0.86	0.89
Dynamic part	0.79	0.96

Correlation of EMG amplitudes with clinical rigidity

The amplitudes of EMG signals in the patients and control groups showed a wide spread distribution. The correlation factors of EMG amplitudes for each part of the EMG with the clinical rigidity scores are shown in table 3.

In flexor EMG a correlation between the clinical rigidity and EMG values was present in each part of the EMG. The static component showed the strongest correlation (R:0.42, p=0.02); for extensor signals no correlation was found between EMG values and clinically assessed rigidity.

Tabel 3: Correlation of the amplitudes of EMG signals with clinical assessed rigidity according to the UPDRS in patients (n=33, Spearman's correlation coefficient).
* indicates a significant correlation (p<0.05)

	Flexors			**Extensors**		
EMG component	Spearman's Correlation coefficient	p	Sign.	Spearman's Correlation coefficient	p	Sign.
Unprocessed EMG	0.34	0.05		0.06	0.74	
Static part	0.42	0.02	*	0.13	0.47	
Dynamic part	0.24	0.18		0.04	0.82	

Passive rigidity versus contralateral activation

Contralateral activation (CLA) induces a conditioning facilitation resulting in an increase in clinical assessed rigidity. This was confirmed in the patient group. There was an increase of clinical rigidity scores during CLA. Table 4 shows the UPDRS rigidity scores in passive rigidity testing and in subsequent CLA (Wilcoxon signed ranks test p=0.00).

The expected increase in rigidity after CLA was seen for each part of the extensor EMG. No significant changes were seen in flexor EMG. The median amplitudes of passive testing and contralateral activation are given in table 5.

Table 4: The increase in clinical rigidity score of contralateral activation versus passive rigidity testing (n=20).

		CLA					
		0	1	2	3	4	Total
Passive rigidity	0	1	6		1		8
	1			1			1
	2			3	5		8
	3				2	1	3
	Total	1	6	4	8	1	20

Table 5: Median amplitude of EMG (μV) in passive rigidity testing and contralateral activation (n=20).

		Passive rigidity	**CLA**	
		Median	median	p
Flexor	Unprocessed	97.13	102.63	0.17
	Static	30.91	29.65	0.26
	Dynamic	176.22	161.66	0.68
Extensor	Unprocessed	167.88	273.77	0.002
	Static	49.56	63.15	0.005
	Dynamic	363.34	390.67	0.04

Pre- and postoperative changes in rigidity

In order to evaluate whether changes in clinical rigidity reflect themselves in EMG amplitudes, the change in EMG amplitudes of the first pre- and postoperative recordings of the patients were plotted against the change in UPDRS rigidity, and regression was calculated. The scatter plot is shown in figure 3. Regression lines are summarized in table 6.

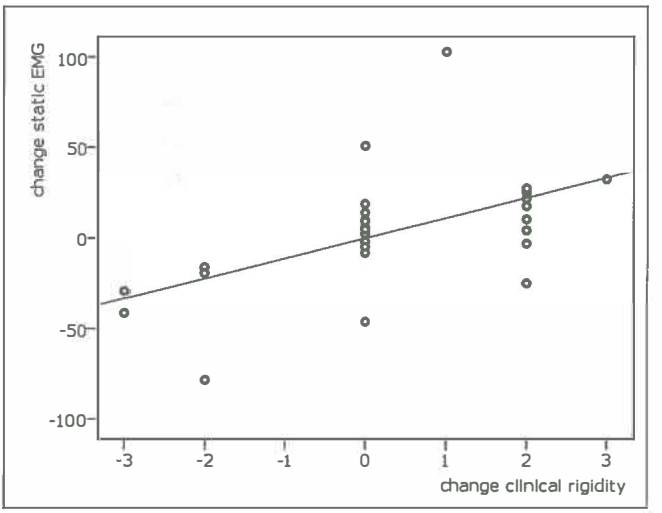


Figure 3: Scatter plot of the change in static EMG in μV of flexor muscles with change of UPDRS rigidity in post-operative measurements, compared to pre-operative measurements. The change in UPDRS is reflected by the change in EMG amplitudes.

Table 6: Regression lines of changes in EMG amplitudes in postoperative recordings versus pre-operative recordings for simultaneous change in UPDRS rigidity.

		R	Intercept (b)	Slope (a) μV/ point UPDRS	p
Flexor	Unprocessed	0.44	-1.84	39.14	0.02
	Static	0.54	-0.20	11.07	<0.01
	Dynamic	0.42	12.3	62.70	0.02
Extensor	Unprocessed	0.03	-23.16	2.66	0.89
	Static	0.07	-3.48	1.64	0.71
	Dynamic	0.01	-39.75	1. 43	0.96

Discussion

Since the publication of Webster in 1959 [17] many investigators have attempted to quantify rigidity by measurements. So far none of these methods have been accepted in a routine neurophysiological assessment of parkinsonian rigidity. Some authors described the use of intra-operative EMG to illustrate induced effects on parkinsonian rigidity [18;19]. In pharmacological animal studies, the amplitude of EMG is used as an objective reference of clinical rigidity [20;21]. A correlation between EMG and rigidity is published for stretch reflexes with varying results [22-24]. Since an EMG is proportionally related to force one would expect that EMG offers an entry for a method to measure rigidity. The continuous surface EMG activity from sustained muscular activity has proved very effective for quantifying muscular activity in dystonia [25]. However, the complexity of EMG's during clinical rigidity testing with rapid changes in continuous EMG activity have only met modest applications for recording of parkinsonian rigidity.
This study presents a further insight in the applicability of EMG recordings for quantification of parkinsonian rigidity.

Technical aspects

Performance of a time-varying wavelet filter in rigidity EMG's
The study showed that a time variant wavelet filter is able to effectively separate cogwheel bursts from the stationary background noise in an EMG. This separation cannot be accomplished by classical filters since these only would be successful when the frequency bands of the EMG bursts and background EMG would not largely overlap. Also not effective are all other linear filters that are based on the characteristics of harmonic sine functions in regard to infinite length.
The success of wavelet filtering depends on the choice of a threshold by which it is decided which time-scale coefficient will be preserved or nulled. This makes the

filter sensitive to amplitude level. The filter would function properly if the background EMG is a stationary noise of constant amplitude on which noise bursts are superimposed. The bursts act as non-stationary events for which detection by wavelet transform is well suited. For optimal separation of bursts one can chose a statistical probability level by which leakage of background noise can be minimized while most of the burst passes the dynamic filter. In this way the filter can be optimized to detect bursts of relative low signal-to-noise ratios.

A few characteristics of the EMG signal in rigidity assessment complicate a useful design of a wavelet filter.

1. In practice, signal amplitudes are different in various muscles and between various patients. One can relate a threshold level to the amplitude of signals by a threshold adaptation technique using a universal threshold factor that relates to an amplitude reference. Such a factor desensitizes a filter design for amplitude differences between muscles and between patients. The quality of the filter depends on the definition of amplitude reference. The definition of TF in this study is an example, which is not optimally adapted to the flexion-extension cycles of a rigidity test.
2. The cyclic flexion-extension excursions during the passive movements of the wrist showed an EMG pattern with varying amplitudes in which the static background EMG cannot be considered as a stationary noise since it usually is only present during muscle stretching phases and shows a varying amplitude over the varying epoch lengths. A background EMG activity may sometimes be present during muscle shortening as well. There are often marked cycle-to-cycle variations in clinically scored rigidity during passive movements. These variations were also recognized in EMG amplitudes of the background EMG.

Also noted are bursts patterns without background noise. These bursts are separated by silent periods. Subsequent cogwheel bursts may show marked irregular variations of inter-burst intervals, burst widths and burst amplitudes. Inter-burst intervals vary between 80 and 180ms which agrees with the frequency range of 7-14 Hz mentioned in the literature [26-28] whereas burst widths may vary between 30 and 80ms.

This variety in parameters of the bursts as well as in the background EMG, which is not really stationary, complicate a design for a time variant wavelet filter. Adaptive soft-thresholding wavelet filtering techniques seem to be essential to overcome variations in the amplitude of the background signal. One is forced to design algorithms that adapt a threshold, most preferably burst-to-burst, to cope optimally with variations in duration and amplitude of the background noise. Such short time intervals may introduce relative large in mean square errors in the minimax principle or in Stein's unbiased risk estimates (SURE). This and other methods have successfully been applied by Wang et al [4] in patients with dystonia where an excellent adaptation to slow, gradual increasing amplitudes of background EMG and bursts has been shown. The authors did not discuss how rapidly their adaptive window shrinkage techniques adapt to sudden changes in

burst amplitudes and background noise as may occur in rigidity testing. The universal threshold and the minimax principles in their paper show that a few small bursts intermediate between large bursts did not pass the filter. It is not known to us if an improvement of the selectivity of their soft-threshold adapting algorithms in rigidity EMG's can be expected when compared to the thresholding method used in our study. Our method applies adaptive soft thresholding with a 1 second refresh interval. The method more or less copes with extension-flexion-extension cycle-to-cycle variations of EMG amplitudes. A drawback of our method is sensitivity to large instantaneous variations in burst amplitudes.

3. Ortho-normal transformations like the Fourier and wavelet transform are based on independence of sine- or wavelet functions that are used to decompose a signal. The coefficients in frequency and time-scale domains can be manipulated independently and the filtered results obey a superposition principle. The filtered background EMG is independent of the EMG bursts. When burst amplitudes increase, the filtered background EMG remains unaffected. This assumption is correct as long as the background noise is also neurophysiologically independent of the bursts and not modulated by them. In a few recordings, one can recognize a modulation effect. Figure 4 shows an example of an extensor EMG of a parkinsonian patient during a rigidity test. The initial part of the recording shows a continuous EMG signal that in the second part becomes interrupted by cogwheel bursts. In 4 places one can notice 'pinching' effects by which the amplitude of the background noise is reduced between bursts. A wavelet filter would underestimate the background noise amplitude especially when soft-threshold adaptation wavelet shrinkage is dimensioned for fast adaptation acting within intervals as small as 200ms or below. The pinching effects from bursts can sometimes be so marked, that background noise is reduced to silent periods around bursts. These background attenuating effects seem to result from a modulation mechanism. This complies with the description in the review of Ghilione et al that the hypertonicity of parkinsonian rigidity is interrupted as a cogwheel mechanism at a 6- to 9-Hz frequency [29].

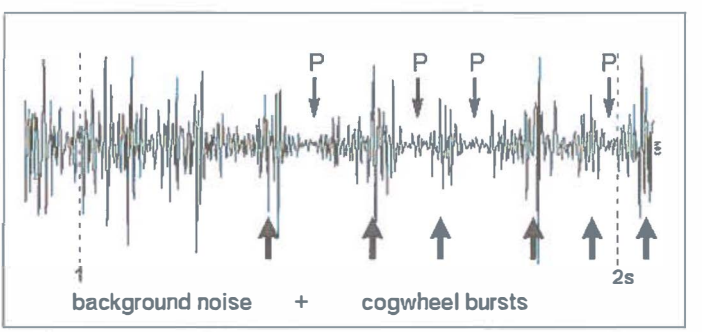


Figure 4: Example illustrating the amplitude modulating effect of burst where the amplitude of the background noise is reduced in between two bursts. This pinching effect is indicated by the down pointing P-labeled arrows. The up pointing arrows indicate the instants of the cogwheel phenomenon bursts.

Choice of wavelet base

Considering the Daubechies wavelet bases used in this study, the choice of the wavelet type is concluded to be of less importance than definitions of threshold factors or algorithms for adaptive thresholding. The disadvantage of significant no zero-phase properties of the Daubechies wavelets would affect the accuracy of timing of detected bursts which is beside the purpose of this study.

Choice of threshold factor for burst detection

It is concluded that time-variant wavelet filtering is an excellent technique for detection of cogwheel burst. Bursts are detectable for TF=0.08–0.15. When bursts only have to be detected and not quantified, maximal removal of the background EMG prevails so we recommend TF=0.12-0.15 where almost all visually recognized bursts pass the dynamic filter whereas the background noise is almost completely blocked.

Choice of threshold factor quantification of rigidity

For the statistical evaluation in the second part of this study it is important to exclude bursts sufficiently from the background noise and this can be accomplished by a lower TF. This would comply with the UPDRS definition for rigidity where cogwheel bursts are excluded. Moreover interference from persistent tremor bursts would also be suppressed. Removal a part of the background EMG amplitude due to a low threshold factor is considered as less important then the interference of bursts on EMG. TF=0.08 fulfills these conditions.

Statistical study

I) Reproducibilty

Rigidity is known to vary from day to day within a single day and between subsequent measurements [29]. Rigidity may change from cycle to cycle during passive testing of rigidity [30;31]. We encountered patients with cycle-to-cycle variations of rigidity of more than 2 scales. The duration of a test and how cycle-to-cycle differences of rigidity have to be interpreted, are not defined in the UPDRS. One can expect that these variations are also visible in the two succesive rigidity tests which are used to check the UPDRS reproducibility. Table 1 shows the transitions of UPDRS scores from the first to the second measurement. The maximum variation is 2 scales.

The reproducibility indicates a limit to the accuracy or selectivity of the UPDRS score. Since in this study the UPDRS score was used as reference, this limit also influences the accuracy of rigidity measurements using quantified EMG amplitudes. When comparing an objective method to a clinical rating scale, the tested method never can be proven to be better than the clinical rating scale. This

problem was already discussed by Patrick and Prozachka, who advocated against the clinical rating scale [30;31]. Unfortunately, no better gold standard for rigidity testing is available.

The kappa value of the clinical rigidity test according to the UPDRS for two subsequent assessments is 0.82. Reproducibility for EMG amplitudes showed high correlation factors between 0.79 and 0.86 for flexor EMG and between 0.89 and 0.93 for extensor EMG. EMG amplitudes therefore showed a good reproducibility. When EMG amplitudes increased, the difference between the first and second measurement increased.

It is concluded that the reproducibility of the EMG signals and their filtered components is sufficient to be useful for neurophysiological assessment of rigidity.

II) Correlation of EMG amplitudes with clinical rigidity

When compared to the extensors, the values obtained in flexor muscles correlated the best with clinical rigidity scores of the patients in both the pre- and post-operative assessments. This is shown in table 3 where moderate significant correlation factors ($p<0.01$) are found for the flexor EMG's whereas the correlation factors for extensors were below 0.2 and non-significant ($p>0.2$). Our results are not in agreement with the literature, where flexor and extensor muscles are said to equally reflect parkinsonian rigidity [32]. The moderate correlation between the quantified flexor EMG's and UPDRS scores in the patient group may have different causes which are discussed below.

1) The influence of local anatomical properties of the tested body part that relate to parameters like muscle mass and skin thickness. This influences EMG amplitude and contributes to the large inter-individual differences. This will play no role in intra-operative assessments.

2) The UPDRS=1 score can be troublesome due to the addition of contralateral activation when no or slight rigidity is found. When EMG recordings are performed during passive tests and when the examiner perceives no resistance during testing, the UPDRS score can be equal to 1 while there is no muscular activity, since the score of 1 becomes established in a subsequent test with contralateral activation. Incorporating the contralateral activation may increase rigidity levels comparable to UPDRS scores of 2 and 3. This is also shown in table 4.

3) Sometimes a tremor can be predominantly present and may affect the EMG amplitude and introduce erroneous results and bias the quantified rigidity. Like the bursts from cogwheeling, EMG bursts can be removed from the signal by means of static time variant wavelet filtering.

4) The presence of negative rigidity. In negative rigidity relative high EMG amplitudes are due to active participation of the patient. The EMG signals showed an increase in EMG amplitude in the shortening phase instead of the lengthening phase. The increase in amplitude started usually just before the transition to the shortening phase. This may explain why this effect only was seen when the examiner noticed no rigidity (UPDRS=0). Obviously, CLA blocks anticipation of a

patient in the cyclic movements so that negative rigidity transits into positive rigidity of non-zero UPDRS scores. Meara and Cody originally described the phenomenon of negative rigidity [33]. Patrick et al excluded all patients with negative rigidity in their study for quantification of rigidity by force transducers [31]. In this study we were not able to exclude patients since the applied wavelet filtering software did not permit separation of signals in lengthening and shortening phases.

5) Inter-individual differences in the relationship between EMG amplitude and UPDRS score may decrease correlation. We noticed three categories in our group of 33 patients. A first category shows a positive proportional relationship between EMG amplitudes and UPDRS scores. This was seen in 17 static flexor EMG's and in 12 static extensor EMG's. A second category with an inverse relationship between EMG amplitude and UPDRS rigidity score was seen in 3 flexor- and 4 extensor EMG's. A third category with no obvious differences between EMG amplitudes for different UPDRS scores was found in 10 flexor and 14 extensor EMG's. In the remaining three patients, the UPDRS scores before and after surgery were unchanged.

The second and third category may result from negative rigidity as discussed above. We believe that the inverse proportional relationship between EMG amplitude and UPDRS can mainly be attributed to negative rigidity and was the main factor contributing to the impaired correlation factors.

Contralateral activation

Contralateral activation is a conditioning effect resulting from active participation of the patient by voluntary movements or muscle contractions in the contralateral upper extremity. This obviously disinihibits neural circuits involved in the genesis of parkinsonian rigidity.

Occasionally, slight rigidity was noticed during CLA in patients with essential tremor (not included in this study) and control subjects, although less pronounced than in parkinsonian patients. Obviously parkinsonian rigidity seems to result from same neural circuits, but the effects from CLA on parkinsonian rigidity are more pronounced. The mean clinical rigidity score of 1.2 was increased to 2.1 during CLA. Table 5 shows that the increase of EMG amplitudes from passive testing to CLA was significant for extensor muscles. No significant differences were shown for flexor muscles. The disappearance of negative rigidity and the introduction of rigidity, probably adds to the unchanged EMG amplitude in flexor muscles. The blocking effect on negative rigidity was discussed previously.

The addition of CLA in an extra test, when in a clinical first test no resistance is felt, complicates the design of method that should provide a gradual increasing parameter for rigidity and which was intended to be simple and not requiring active cooperation of a patient. The troublesome presence of CLA in the definition for a UPDRS score of 1 is also discussed in literature [30].

In summary, correlation with clinical rigidity in a group of individuals is maximal for flexor EMG amplitudes compared to extensors. The flexor EMG amplitudes also showed a higher correlation with clinical rigidity scores when considering pre- and postoperative measurements. Our results are not in agreement with the literature, where flexor and extensor muscles are said to equally reflect parkinsonian rigidity [32], although more recent publications also propagate an asymmetric distribution [34,35].

Table 3 showed slight differences of correlation coefficients of 0.34 for the unprocessed flexor EMG's and 0.42 for the static filtered EMG's. For the extensors the correlation coefficients were 0.06 and 0.13 respectively. The highest correlation factors were from the static filtered EMG. This supports the hypothesis that cogwheel bursts have to be ignored.

We expect that wavelet filtering can offer only a modest improvement for quantification of rigidity, even when optimal soft-thresholding algorithms for wavelet shrinkage are available, unless main causes of impaired correlation factors, like negative rigidity, are resolved. However, wavelet filtering is a superior technique for detection of the presence of cogwheel bursts and may improve the accuracy of the method when tremor busts are present in the EMG.

The relatively fast-changing amplitudes of background noise and irregularly varying signal-to-noise ratio between cogwheel bursts and background EMG makes it necessary to design soft-thresholding techniques with cycle-to-cycle adaptation performance. Such methods are not available yet.

Wavelet filtering is based on the assumption that cogwheel bursts are superimposed on a background contraction. However, one should be aware that this assumption in practice could be affected by modulation effects from neural activity from long-loop reflexes on the static background EMG, so that background EMG and burst cannot be considered as absolutely independent phenomena.

Conclusion

Time variant wavelet filtering is a novel technique for successful detection or separation of cogwheel bursts from the static background EMG. The static filtered background EMG offers only a modestly improved correlation with clinically scored rigidity, which supports the hypothesis of the study. After resolving the problem of negative rigidity and optimizing of a soft-thresholding algorithm, a further explorative study will be necessary to obtain a realistic opinion on the features of a time variant wavelet filter in an intra-operative method for quantification of parkinsonian rigidity by means of EMG recording.

Based on the observation that all filtered and unprocessed EMG amplitudes of both muscles show good reproducibility, it is concluded that EMG recordings will be useful for quantification of rigidity. This study revealed a poor selectivity for

UPDRS scores in the range of 0-2, which implies that EMG amplitudes are not useful for inter-patient comparison of rigidity. However, it is expected that flexor EMG's can be used to monitor intra-individual changes in rigidity during functional stereotactic surgical procedures. When the causes of the moderate correlation between EMG amplitudes and UPDRS scores can be deducted and resolved in a redesign of the measurement method, it is expected that the accuracy of the UPDRS becomes approximated or even aqualled. When quantified EMG's are to be compared with clinical rigidity scores, it is recommended to remove the additional test with contralateral activation out of the definition of a UPDRS score of 1, leaving the gradation of slight resistance.

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Chapter 5

Quantification of parkinsonian rigidity and detection of tremor and negative rigidity in electromyographic recordings by a balance coefficient and amplitude

For reasons of legibility and comprehension, the text has been written as a chapter. Parts of this chapter are published in:

Postma AA, Staal MJ, Arle J, Sils JL, Leenders KL, Journée HL. Quantification of parkinsonian rigidity and detection negative rigidity in electromyographic recordings by a balance coefficient and amplitude.
Submitted

Journée HL, Postma AA, Staal MJ. Intraoperative neurophysiological assessment of disabling symptoms in DBS surgery.
Neurophysiol.Clin. 2007;37:467-75.

Abstract

Introduction

Quantification of rigidity with EMG may become complicated when negative rigidity and tremor are present.

A balance coefficient (BAL) is introduced to detect these interfering phenomena and will be tested regarding its applicability in rigidity scoring.

Methods

The BAL is defined as the logarithm of the quotient of EMG amplitudes in the lengthening and shortening phases of flexor and extensor muscles during passive movement of the wrist. Positive values of the BAL denote positive rigidity, whereas negative values refer to negative rigidity. EMG amplitudes in the shortening and lengthening phases as well as the BAL, are compared to clinically scored rigidity in 14 patients referred for implantation of DBS STN as well as in 11 healthy control subjects.

Results

The EMG amplitudes in lengthening phase of both flexor and extensor muscles showed the highest correlation with clinical rigidity (spearman's correlation coefficient of 0.76 and 0.75 ($p=0.002$)). BAL detected negative rigidity in all control subjects simulating negative rigidity. BAL detected negative rigidity in 1 of 2 patients who were clinically suspected of negative rigidity. In the second patient tremor bursts interfered with the EMG measurements.

The BAL was zero to negative in non-rigid patients, increased to a maximum level in moderate rigidity and showed a slight decline in severe rigidity.

Discussion and conclusion

EMG amplitudes in lengthening phases correlated with clinical rigidity.

A positive BAL indicates whether EMG amplitudes are useful for quantification of rigidity. Negative BAL values indicate possible negative rigidity which may result in false high EMG amplitudes unrelated to rigidity. The balance coefficient is useful for detection of negative rigidity, is unsuitable for tremor detection and shows limitations for quantification of rigidity.

Introduction

Rigidity is clinically assessed by an examiner moving the limb of a patient while the patient is relaxed. The examiner feels a continuous resistance, sometimes interrupted by the cogwheel phenomenon. When a relationship is assumed between surface electromyographic (EMG) recordings and muscular force, EMG recordings may be useful for objective assessment of parkinsonian rigidity since rigidity is the resistance that is perceived by the physician during passive stretching of a limb and is accompanied by an increase in EMG amplitude in the stretched and thus lengthened muscle [1;2].

By visual inspection of these EMG recordings one can distinguish burst patterns of the cogwheel phenomenon from a tonic background contraction [1]. Both the cogwheel phenomenon and the tonic contraction can be felt by the examiner. It is possible to separate these two signal components by digital signal analyzing algorithms. For example, we applied a filter that is based on wavelet transform to separate the cogwheel burst from stationary background noise of the tonic muscle contraction [3]. The amplitudes of these separated signals corresponded to clinical rigidity. However, as described in chapter 5, we noticed that the amplitude of these EMG signal components is not always useful for quantification of rigidity. In one subgroup of patients we measured paradoxically large EMG amplitudes in patients with clinically no or only minor rigidity. This phenomenon has been described by Meara et al. (1992) and named negative rigidity [1]. Patrick et al. also recognized the problem of negative rigidity and in their study excluded those patients [10;11].

Negative rigidity is explained by assistance of the patient in the movement by active muscle contraction. This contraction occurs during muscle shortening instead of lengthening. The muscle assists in the passive movements of the tests and, therefore, reduces the mechanical resistance that is felt by the physician. This results in a low clinical rigidity score and explains the paradoxically high EMG amplitude. Visual explanations of positive and negative rigidity are shown in figure 1a.

Another complicating phenomenon we noticed in some parkinsonian patients was a continuous presence of tremor burst activity throughout the cyclic extension-flexion excursions in a rigidity test. This activity, which does not result from rigidity, was present during muscle shortening as well as during lengthening. In an algorithm for assessment of rigidity both phenomena should be detected.

To detect negative rigidity, the EMG should be split into separate epochs referring to muscle lengthening and shortening respectively.

In this chapter, a balance coefficient (BAL), which compares EMG activity of muscles in the lengthening and shortening phases, is introduced and its characteristics studied when used for quantification of parkinsonian rigidity and detection of negative rigidity and tremor. The quantification of rigidity by the EMG

amplitude separated into lengthening and shortening phases, will also be considered.

Balance coefficients are defined as the ratios of quantified EMG in the lengthening phase to the quantified EMG in the shortening phase. The ratios are converted into logarithms and expressed in Decibel units (dB). This has the feature that a positive logarithmic value will indicate positive rigidity and a negative value negative rigidity. The balance coefficients are computed cycle-to-cycle from wrist movements for each muscle group. A total ratio of both muscle groups is obtained by averaging of the balance coefficients of the two muscle groups. It is supposed that the total balance coefficient represents the net resistance of the force of the antagonistic muscle groups that is felt by a physician.

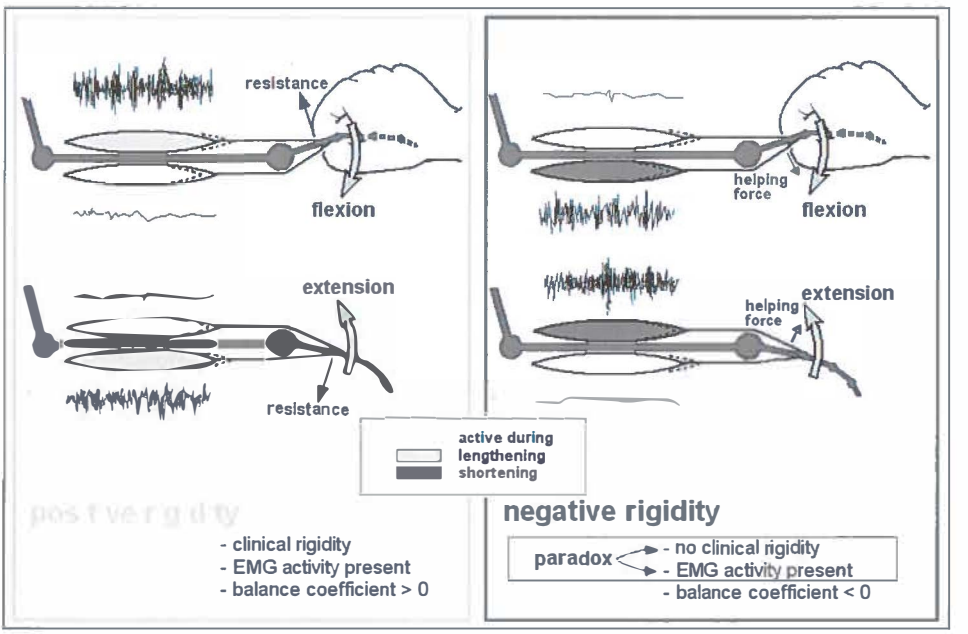

Figure 1: Theoretical expectations of the relation of the EMG and balance coefficient as a function of rigidity scores in parkinsonian patients.

a. Cartoons explaining positive and negative rigidity in extension to flexion and flexion to extension phases of the wrist during a clinical rigidity test. Positive rigidity is shown in the left panel. During lengthening the muscles (extensors during flexion of the wrist and flexors during extension) show contraction which is measured as EMG activity as shown near the muscle. This contraction is noticed by the clinical examiner as a mechanical resistance or rigidity leading to a positive balance coefficient. The right panel shows negative rigidity when muscles are active during shortening. This results in unnoticed helping effects that go undetected by the observer leaving a paradox of EMG activity when no clinical rigidity is observed. The balance coefficient is negative.

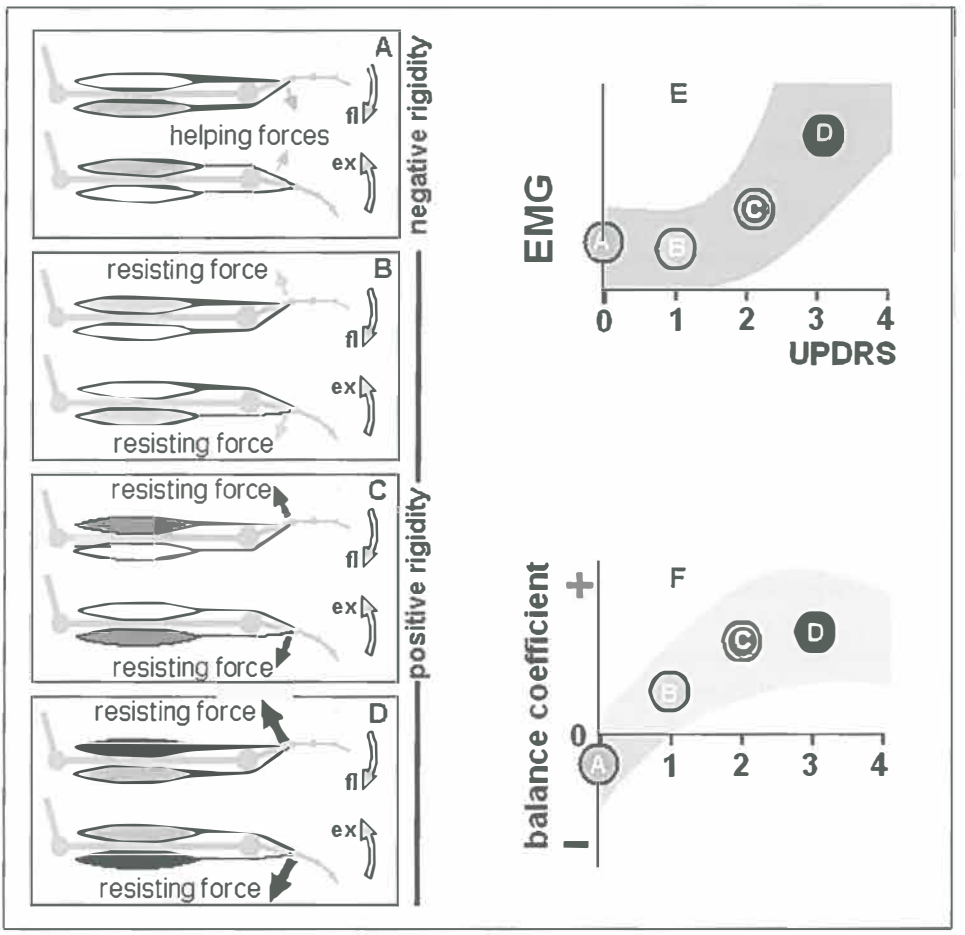

Figure 1b. Cartoons showing the features of the balance coefficient for quantification of rigidity from theoretical expectation. The left panels show from top to bottom conditions at increasing rigidity scores of 0 to 3. A score of 0 may result from negative rigidity, which implies presence of EMG activity during muscle shortening, while due to the helping effects no rigidity is observed resulting in a zero UPDRS score. EMG activity still is present at higher rigidity scores, but now apply to muscle lengthening whereas the EMG amplitude increases with rigidity.

The expected course of the EMG amplitudes as function of rigidity score is shown in the upper panel at the right where the grey area indicates the expected variability around mean values of the circles. The presence of EMG due to negative rigidity is prone to fail to differentiate between rigidity scores in the low range between 0-1, whereas expected differentiation in the higher range is more successful.

The expected course of the balance coefficient as function of rigidity score is shown in the lower panel at the right. Since the balance coefficient is selective for negative rigidity it will be most sensitive in the lower rigidity range and decrease at higher rigidity scores due to co-activation of antagonists.

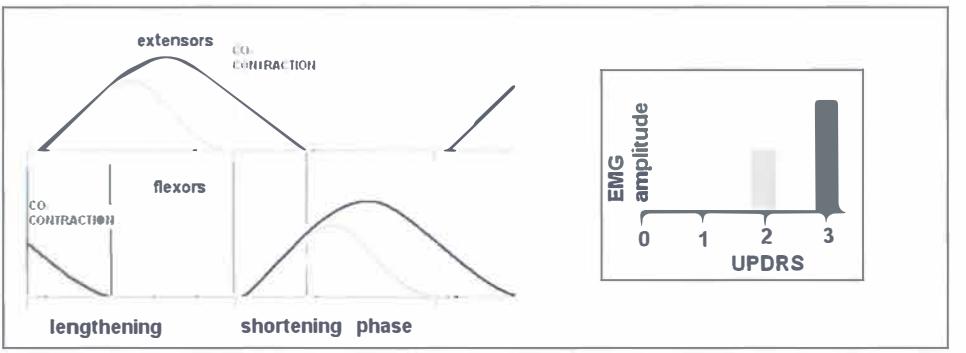

Figure 1c. Co-activation increases with rigidity and may result from: A overflow of EMG of tonic contraction in time from muscle lengthening into the shortening phases; B simultaneous muscle contraction in both muscle groups not caused by volume conduction cross-talk of EMG's and C simultaneous presence of EMG cogwheel bursts in both muscle groups. Figure 1c illustrates the first possibility of overflow as function of the UPDRS at rigidity scores of 1, 2 and 3. The plots show the course of the quantified EMG of the extensors (upper traces) and flexors (lower traces), where in this example only an overlapping interval with co-activation is present at a rigidity score of 3.

The EMG signals are quantified by averaging the full-wave rectified EMG over the length of each lengthening or shortening phases and are described by four parameters. These are defined for the extensors (EXT) and flexors (FLEX) according to: EXT_{len}, EXT_{sh}, $FLEX_{len}$ and $FLEX_{sh}$. The indices 'len' and 'sh' refer to respectively the lengthening and shortening phase.

The balance coefficients for the extensors and flexors for these muscle groups are given by the subsequent equations:

$$BAL_{EXT}=20\cdot^{10}\log\{EXT_{len}/EXT_{sh}\} \quad (1)$$

and

$$BAL_{FLEX}=20\cdot^{10}\log\{FLEX_{len}/FLEX_{sh}\} \quad (2)$$

whereas a total balance coefficient is defined as:

$$BAL=20\cdot^{10}\log\{EXT_{len}\cdot FLEX_{len}/EXTt_{sh}\cdot FLEX_{sh}\} \quad (3)$$

When the quantifications of EMG activity in both phases are equal or, so to speak, 'in balance', then the ratio is equal to 1 and thus the logarithm is equal to zero. When the quantified EMG in the lengthening phase is higher compared to the shortening phase, the ratio is higher than 1 and thus the logarithm is positive. For the opposite situation: more EMG activity in the shortening phase when compared to the lengthening phase, the ratio will be smaller than 1 resulting in a negative logarithmic value (figure 1b).

Since the EMG's are quantified based on amplitudes, the logarithmic values are expressed in decibels (dB).
Another feature of the logarithmic notation is that the total balance coefficient can be obtained simply by summation of the balance coefficients of each muscle group:

$$BAL=BAL_{EXT}+BAL_{FLEX} \quad (4)$$

The total balance coefficient expresses the net result of both muscle groups.

The balance coefficient theoretically offers two possibilities for measurement of rigidity in patients with Parkinson's disease.

1) The coefficient may distinguish disturbing effects from rigidity according to the next hypotheses:
- A positive misbalance indicates parkinsonian rigidity.
- Zero balance indicates phase independent muscular activity as may result from tremor.
- A negative misbalance indicates negative rigidity.

Besides resulting from tremor as previously discussed, a zero or reduced balance could also result from co-contraction at the segmental motor neuron level, local EMG cross-talk and background noise. Co-contraction patterns have been reported of EMG bursts from tremor and from the cogwheel phenomenon [4].
Co-contraction and cross-talk add EMG activity in the shortening phase causing increase denominators in equations (1-3), which results in a decrease of the balance coefficient as shown in figure 1c.

2) The balance coefficient may be useful for quantification of parkinsonian rigidity. One can expect a non-linear relationship of balance coefficient values with clinical rigidity scores. The balance coefficient is defined by the ratio of the EMG amplitudes of the lengthening and shortening phases. At low rigidity levels, when in the shortening phase the signal consists of only background noise with no or minimal EMG activity, one can expect that the EMG amplitude from parkinsonian rigidity in the lengthening phase controls the magnitude of the balance coefficient. The initially increasing course of the magnitude of the balance coefficient may even turn into decrease at high rigidity scores. This is theoretically possible when co-contraction and overflow by prolonged EMG activity to the shortening phase become evident. At the start of a scatter diagram at 0, when there is clinically no rigidity, the balance coefficient is theoretically zero or even negative in negative rigidity. The theoretical expectation of the relationship between the balance coefficient and clinical rigidity score is schematically shown in figure 1b.

This hypothesis will be tested by exploring the relationship between the data pairs of the balance coefficient and the clinical rigidity that was scored simultaneously with the EMG recordings.

Material and methods

In the period 1997-2001, 14 consecutive patients were referred for implantation of electrodes for bilateral deep brain stimulation of the subthalamic nucleus (Chapter 3: patient 20-33), the age range was 47-70 years (mean 58,7 yrs). The patients underwent routine testing for rigidity one day before implantation of a programmable stimulator, and simultaneous EMG registrations were made during rigidity testing.
The patients subsequently underwent two measurements during a rigidity test without contralateral activation followed by two measurements during contralateral activation. For contralateral activation the patient was asked to squeeze a ball in the opposite hand to reinforce rigidity. Clinical rigidity was scored according the Unified Parkinson's Disease Rating Scale (UPDRS).
Eleven age-matched healthy control subjects (48-87 years, mean: 64,5 yrs) underwent rigidity measurements without and with contralateral activation of the opposite arm. In addition, two extra measurements were carried out after the subject was asked to assist in the cyclic movement that was performed by the examiner. These measurements were intended to validate the assumption of a negative balance coefficient in negative rigidity.
All patients and control subjects gave informed consent for their participation in this study.
EMG recordings were made as mentioned in the general material and methods section (chapter 3).
The lengthening and shortening phases of flexors and extensors during wrist movements were retrieved from the goniometer signal. The EMG signal parts were rearranged and assigned to four groups distinguished by phase (shortening or lengthening) and muscle group (flexor or extensor). The EMG signal parts were stripped over 50 ms from both ends of the movement phases to restrict artefacts due to EMG overflow from the preceding phase in the movement cycle.
From the retrieved EMG signals calculation of mean full wave rectified amplitudes for the shortening and lengthening phases for both muscle groups (4 values per extension-flexion cycle) was performed prior to computation of the balance coefficients according to equations 1-3.
These cycle-specific balance coefficients were plotted in a graph over the length of the measurement. The EMG signals and the balance coefficients of three patients with rigidity, negative rigidity and tremor will be presented as example of each condition.

In the control subjects the balance coefficients were calculated for rigidity testing, for testing with contralateral activation and for testing with assistance in the movement by the test subject.
Mean EMG amplitudes of each lengthening and shortening phase in the parkinsonian patients were calculated for all first right arm measurements and compared to the simultaneously-assessed clinical rigidity UPDRS scores.
Balance coefficients were computed for all pre-operative measurements of the patients. The median scores of BAL were plotted to UPDRS rigidity to verify the theory of initial increment and later decline of BAL with increasing rigidity scores.
Statistical analysis and drawing of scatter plots was carried out using statistical package SPSS 11.0.1. For correlation of non-parametric data spearman's correlation coefficient for bivariate correlation was used. The Wilcoxon signed rank test was used for non-parametric comparison of paired data (balance coefficient in passive rigidity versus contralateral activation).

Results

Examples of balance coefficient in rigidity, negative rigidity and tremor
A survey of EMG signals and the balance coefficients of three patients with rigidity, negative rigidity and tremor as example of each condition are shown in figure 2.
In each survey, the EMG signal parts are grouped in four columns. The first two columns concern the flexion to extension phase (Flex>Ext) and the last two columns comprise recordings of the phases from flexion to extension (Ext>Flex). The EMG signal parts are waterfall plots where the signals at the bottom correspond with the end of the measurement. The flexor EMG's are presented in the first and third columns and the extensor EMG's in the second and fourth columns. The original flexor EMG runs from the first line of the first column to the first line of the third column, and continues at the second line of the first column etcetera. The columns define respectively the flexor lengthening phase, the extensor shortening phase, the flexor shortening phase and the extensor lengthening phase. A calibration mark of the amplitude is given at the right side of each column.
Figure 2a shows a typical example of a recording of a patient (chapter 3: patient 25) with mild rigidity (UPDRS=2) in which both muscle groups show rigidity. When the wrist is moved from flexion to extension the highest amplitudes are found in the lengthening flexor muscle; when moving from extension to flexion, the highest amplitudes are found in the lengthening extensor muscle as is to be expected in rigidity. The muscles show the lowest EMG amplitudes in the shortening phases. The total balance coefficient is 16.
(BAL_{FLEX}=8.83; BAL_{EXT}=7.18).

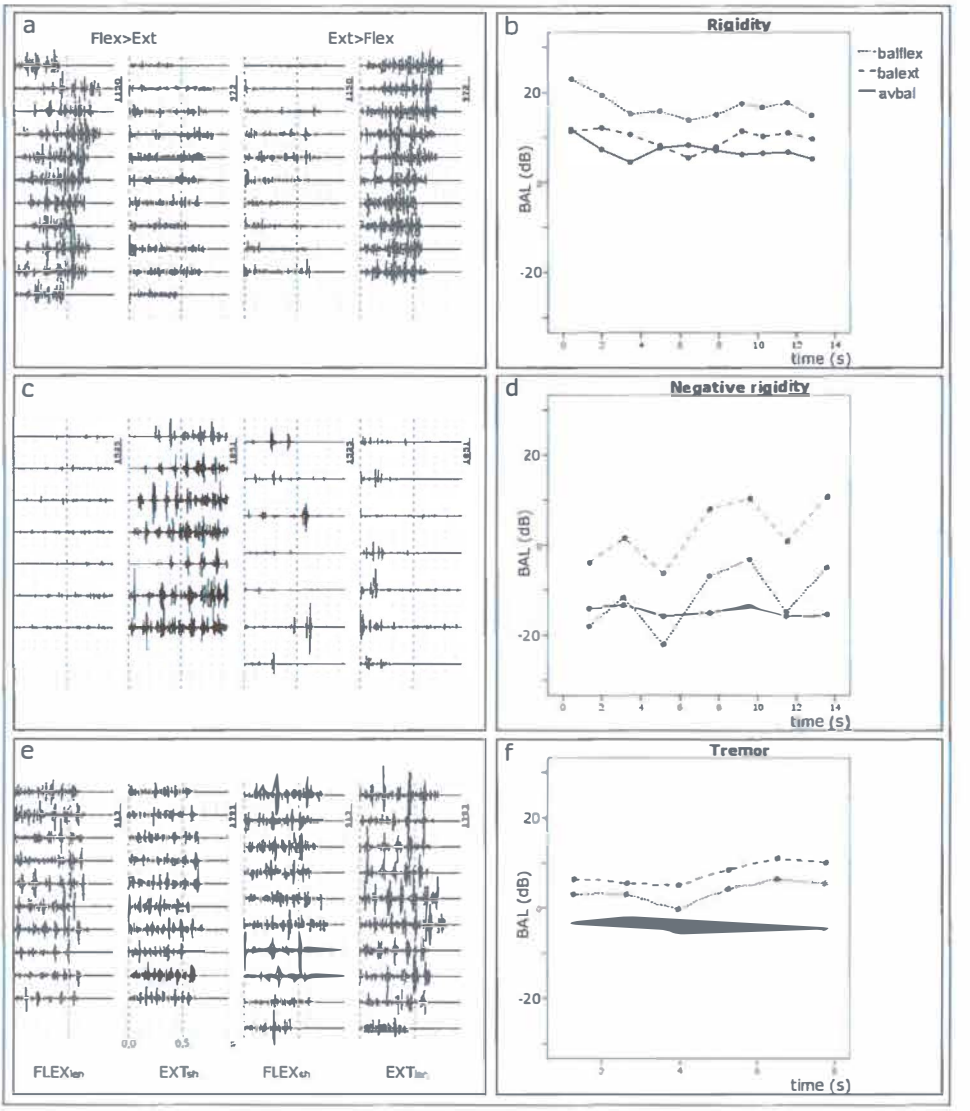

Figure 2: EMG signals of forearm extensors and flexors during a clinical rigidity test of parkinsonian patients showing (a): positive and (c): negative rigidity and (e) tremor.

Cycle-to-cycle EMG parts are split and placed in columns below each other. EMG column pairs show at the left flexors and at the right extensors. The left EMG column pairs are assigned to the flexion to extension phases (Flex>Ext) and the right pairs to the extension to flexion phases (Ext>Flex). The BAL_{flex} and BAL_{ext} as well as the total score BAL are calculated as logarithms and expressed in decibels (dB) so that positive values indicate positive rigidity and negative values negative rigidity. The values are given per flexion-extension cycle of the test and plotted as functions of time (s)(horizontal axis).

(a): EMGs of positive rigidity have high amplitudes during muscle lengthening and relatively low amplitudes during muscle shortening. Cogwheel bursts can easily be recognized throughout the measurements. The UPDRS for rigidity was 2.

(b): positive balance coefficient functions of the EMG signals of a indicate positive rigidity.

(c): EMGs reflecting negative rigidity have low amplitudes during muscle lengthening and high amplitudes during muscle shortening. The UPDRS for rigidity was 0 (no rigidity, even during contralateral activation).

(d): negative balance coefficient functions of the EMGs of c indicate negative rigidity.
(e): EMGs reflecting tremor bursts being present during muscle lengthening and during muscle shortening.
(f): In the patient with tremor the BAL was about 2, while the UPDRS for rigidity was 3.

Figure 2c shows an example of negative rigidity. In clinical testing no rigidity was present (UPDRS=0). The highest amplitudes were found in the extensor EMG's in the shortening phase, indicating active contraction of the extensor muscle during extension of the wrist. The amplitudes in the lengthening phase of the extensors and of the other parts are much lower.
The total balance coefficient is -11.5 (BAL_{FLEX}=-2.67; BAL_{EXT}=-8.86).
A signal which seems to contain tremor is shown in figure 2e. Bursts, like that in tremor EMG, are shown in extensor, as well as flexor muscles, in both lengthening and shortening phases. The bursts are, however, not as regular as expected in normal tremor EMG. The tremor signal is modulated by the flexion and extension movements of the wrist.
Spectral analyses of both flexor and extensor signals showed a broad increase in frequency between about 8 to 10 Hz without any characteristic tremor peak at about 4 Hz. Clinical rigidity scoring in this patient showed an UPDRS of 3. Balance coefficient was 2.07 (BAL_{FLEX}=-0.3; BAL_{EXT}= 2.37).
In figure 2b, 2d and 2f, computations of the balance coefficients of the three patients according to equations 1, 2 and 3 were carried out for each cycle and plotted in a graph over the length of the measurement. The balance coefficient is, like rigidity, fluctuating slightly over the epoch, instead of remaining constant. This is seen in total balance coefficient and in BAL_{FLEX} and BAL_{EXT}.

Balance coefficient control subjects
During rigidity testing, control subjects were asked to assist the wrist movement made by the examiner in such a way that the examiner would not notice the assistance. In all control subjects the total and muscle specific balance coefficients were negative, indicating active contraction of the shortening muscles. This active contraction was seen most strongly in extensor muscles and less in flexor muscles. This is reflected in the balance coefficients of the separate muscle groups as shown in table 1.
In normal passive rigidity testing, all control subjects showed negative balance coefficients, also indicating assistance in the movement. None of the control subjects showed clinical rigidity.
During contralateral activation, 2 out of 11 controls showed positive balance coefficients (0.42 (UPDRS=0) and 3.3 (UPDRS=1)), the other 9 had negative balance coefficients.
There was a significant difference in balance coefficient between passive rigidity testing and testing with contralateral activation (p=0.003, Wilcoxon signed rank test). No differences in balance coefficients were detected between the first and second measurement of passive testing, testing with contralateral activation and

testing with active assistance. Also no significant differences were present between passive testing and assistance in the control subjects.

Table 1: Total and muscle specific balance coefficients of control subjects during passive rigidity testing (passive), during contralateral activation (CLA) and during assistance (Assistance) of the subject in the movement made by the examiner.
All measurements were done twice; 1st and 2nd refer to the first and second measurement. Median balance coefficient, 25 and 75 percentile are shown.

	BAL		**BALflex**		**BALext**	
	median	*25/75*	*median*	*25/75*	*median*	*25/75*
passive 1st	-9.6	-16.3/-5.3	0	-1.8/4.7	-10	-18.4/-7.9
passive 2nd	-8.1	-11.7/-6.3	0.4	-0.7/2.5	-8.7	-14.6/-5.7
CLA 1st	-4.3	-6.6/-1.1	2.9	-0.6/3.5	-5.2	-9.5/-3.2
CLA 2nd	-3	-6/0	1	-2.6/2.7	-3.4	-6.9/-2.4
Assistance 1st	-8.6	-18.7/-8.1	4	-5.4/9.5	-15.2	-20.9/-10.7
Assistance 2nd	-7.6	-11.3/-6.5	4.6	-0.2/8.6	-13	-15.9/-11.1

Mean EMG amplitudes of flexion and extension phases and correlation with UPDRS in parkinsonian patients

In figure 3 the EMG amplitudes of each phase (EXT_{len}, EXT_{sh}, $FLEX_{len}$ and $FLEX_{sh}$) are plotted against the UPDRS. A gradual increase in amplitude is shown in increasing rigidity. Amplitudes are larger for lengthening phase of the muscles compared to shortening, and for extensor muscles compared to flexors. Correlation factors (spearman's correlation coefficient) were as follows: flexor lengthening phase: 0.76 (p=0.002); extensor lengthening phase: 0.75 (p=0.002); flexor shortening phase: 0.62 (p=0.018) and extensor shortening phase: 0.62 (p=0.019). All correlations were significant and maximal for lengthening phases. An overlap in scores is present, no UPDRS score can be predicted from the individual EMG amplitudes.

Balance coefficient in parkinsonian patients

In the first right-sided passive measurements, 6 out of 14 patients showed negative balance coefficients (table 2). 4 of these 6 patients had UPDRS scores of 0, 1 patient had UPDRS of 2 and 1 patient had a UPDRS of 3. Eight out of 14 patients had positive balance coefficients, of which 6 were in a range of 0.1–2.7. Two patients had balance coefficients larger than 10. In two patients assistance of the patient was suspected by the examiner. In one of these patients the balance coefficient was -11.4, in the other the balance coefficient was 2.0. In this last patient, a tremor was also clinically suspected and seen in the EMG.

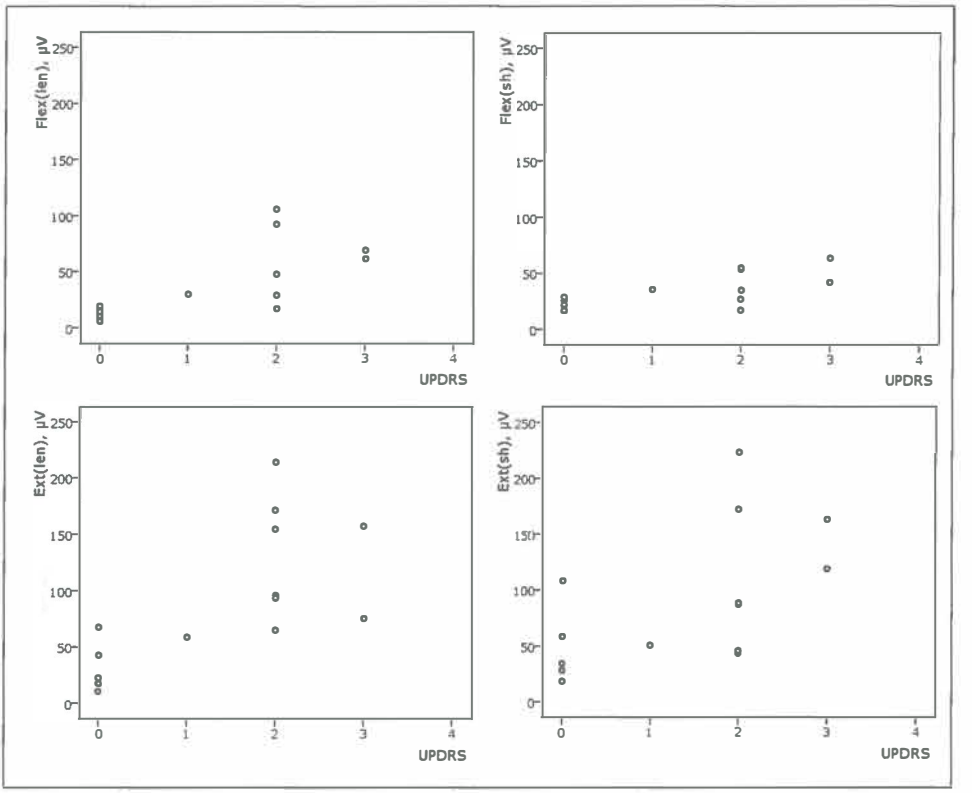

Figure 3: Plots of EMG amplitudes (in µV) of the flexor (Flex)-(upper panels) and extensor muscles (Ext)-(bottom panels) as function of the UPDRS scores for rigidity of the lengthening (len)-(left panels) and the shortening (sh)-(right panels) phases separately in parkinsonian patients. All graphs show an increase of EMG amplitude with rigidity scores, which is most pronounced during lengthening phase. The differences between lengthening and shortening phases are most prominent in flexor muscles.

Table 2: Survey of positive and negative scored rigidity related to the sign of the total balance coefficient (BAL) of patients during passive rigidity testing (left) and at contralateral activation (right).

BAL	Rigidity score passive		Total
	Positive	Negative	
≥ 0	7	1	8
< 0	5	1	6
	12	2	**14**

BAL	Rigidity score CLA		Total
	Positive	Negative	
≥ 0	13	0	13
< 0	1	0	1
	14	0	**14**

In rigidity testing during contralateral activation 1 of 14 patients showed a negative balance coefficient, the UPDRS score in this patient was 1. All other patients showed positive balance coefficients.

During reinforcement by contralateral activation an increase in rigidity was clinically detected. This was recognized as an increase in mean UPDRS from 1.4 in

passive rigidity, to 2.1 during contralateral activation. The median balance coefficient increased from 0.1 to 5.2 during reinforcement (Wilcoxon signed rank test p=0.002).
No significant differences in UPDRS scoring or balance coefficient were detected between the first and second measurements of passive rigidity, between the first and second measurements with reinforcement, or between the first passive rigidity measurements and the passive rigidity measurements following reinforcement.
The patient group showed an overlap of balance coefficients between clinical rigidity score classes. The overlap at the highest two score levels of 2 and 3 permitted no differentiation. Figure 4 shows the median total balance coefficients plotted against UPDRS scores of all preoperative measurements.

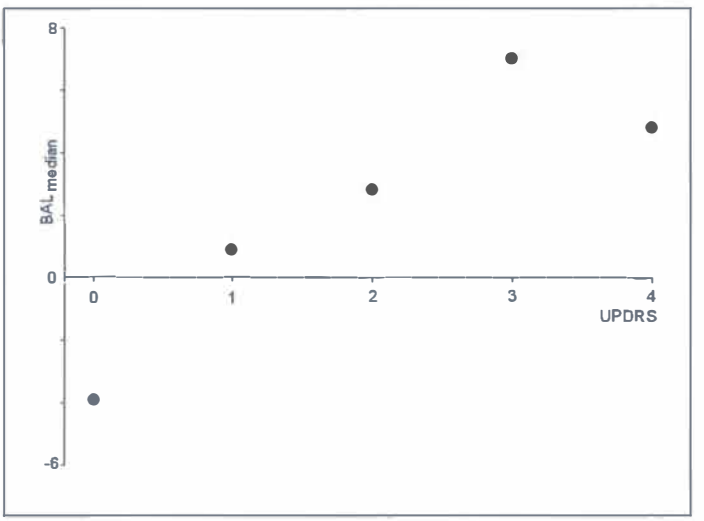

Figure 4: Balance coefficient (median) plotted against the UPDRS rigidity scale from the pre-operative measurements of the parkinsonian patients. In non-rigid patients all, but one, showed negative balance coefficients. An initial increase in BAL is followed by a slight decrease above UPDRS 3.

Discussion

The use of EMG for objectification of parkinsonian rigidity during a clinical test appears attractive for intra-operative use during surgical intervention.
In a previous study aiming at quantification of rigidity, however, there were several complicating factors that would render EMG based methods inaccurate if not taken into account. Important factors were the presence of EMG activity at low rigidity scores resulting from active assistance, tremor and co-activation of antagonistic muscle groups.

Detection of these complicating factors is of considerable importance since erroneously quantified rigidity may negatively influence the decisions regarding the interventions in the patient. Stretch related increase in rigidity has been described by many authors [1;1;2;5-9]. Analysis of the EMG in rigidity showed that increase in EMG is more pronounced during lengthening than during shortening of the muscle, which is in agreement with the clinical definition of rigidity, 'an increase in resistance in muscle stretch'. Essential for detection and proper quantification of rigidity is the ability to distinguish EMG signals from muscle lengthening and shortening phases. Only then does it become possible to analyze specifically how parkinsonian rigidity contributes to the EMG in the lengthening phase in comparison to the shortening phase. The balance coefficient which is introduced in this study basically compares of EMG amplitudes of the lengthening phases to EMG amplitudes of the shortening phases by a ratio. Meara and Cody introduced an EMG ratio between the stretched and simultaneously released muscle and showed only a decrease of the ratio from strong to mild rigidity [1]. However, there were no significant changes in the lowest scoring range. In our opinion, this may be explained in part by not explicitly considering the phenomenon of negative rigidity in this ratio, despite the fact that these authors introduced the term. Application of their ratio in our patient group also did not show a significant correlation with clinical rigidity.

The balance coefficient is primarily designed to distinguish between positive and negative rigidity by taking the logarithm of EMG ratios (equations 1-3) and in the second place for quantification of rigidity. Furthermore the total balance coefficient reflects the net result of activation of agonist and antagonist muscle groups together, which presumably reflects the mechanical resistance observed by a clinical examiner performing a rigidity test, whereas muscle specific balance coefficients (equations 1-2) specify the contribution of each muscle group in the total balance coefficient (equation 4).

The characteristics of the balance coefficients will be discussed with regard to detection of interfering phenomena of negative rigidity, tremor and muscular co-activation and subsequently its use in quantification of parkinsonian rigidity.

A. Characteristics of the balance coefficient for detection of interfering phenomena

Detection of negative rigidity

Figures 2c and 2d are typical examples of the EMG signals and balance coefficients of negative rigidity. The EMG activity is mainly present during shortening phases of the muscle which indicate that muscles contract during muscle shortening. In other words, the patient anticipates in the movement and "helps" the clinical observer. This results in a score 0 for rigidity whereas the total balance coefficient is negative (figure 2d). The helping effect originates mainly in

the extensors. This is also visible in the balance coefficients. The balance coefficients of the extensors are relatively stable in a range of –12 to –15 dB whereas the values of the flexors have a swinging course in a wide range between –5 and +10dB which is caused by incidental bursts. Both courses are present in the total balance coefficient which in spite of the large swinging excursions is negative throughout the measurement. This example agrees with the schematic drawing in figure 1a at the top.

This example of negative rigidity is opposite to the typical example in figures 2a and 2b of positive rigidity with positive balance coefficients in a parkinsonian patient with UPDRS=2 for rigidity. The EMG is predominantly present during the lengthening phases of both muscle groups whereas the positive balance coefficients of both muscle groups are about equal to one other throughout the measurement. The muscle specific positive balance coefficients between 5–12 dB correspond to the simultaneously scored UPDRS of 2.

The assumption that a negative balance coefficient reflects anticipation in the movements applied by an examiner was confirmed in control subjects. The threshold level for distinction between positive and negative rigidity has a theoretical mean value of zero. In practice, the decision level for negative rigidity of the balance coefficient was shifted to about –5dB. From this level, all control subjects showed negative balance coefficients when simulating negative rigidity. This suggests that the balance coefficient is a good predictor of negative rigidity. Table 1 shows that when control subjects did not actively participate in the movements and no rigidity was detected by the examiner all measurements showed again negative balance coefficients. Contralateral activation obviously induced an increase of the balance coefficients towards more positive values. The muscle specific balance coefficient showed that the extensor group is specifically involved, since BAL_{ext} contributed mainly to the total BAL, whereas the BAL_{flex} values from the flexor groups had near zero values. All measurements in table 1 showed good reproducibility. Participation in passive tests goes unnoticed by the subjects and examiners. It should be emphasized that the EMG amplitude is invisible in the balance coefficient since the balance coefficient basically compares amplitudes irrespective to their magnitude. The phenomenon of negative rigidity was also encountered in parkinsonian patients with no or mild rigidity. Most of these patients also showed negative balance coefficients. We experienced that it is very difficult for these patients and control subjects not to assist the movement made by the examiner. The examiner can check the presence of negative rigidity by introducing an unannounced brisk cessation during the cyclic movements. Anticipation by the subject on the cyclic movements of the test due to negative rigidity then is detected by active continuation of the movements of the patient or control subject. Reinforcement of rigidity by contralateral activation can be a powerful method to suppress negative rigidity. In our group of parkinsonian patients, negative rigidity was never detected during CLA in clinical rigidity tests

and balance coefficients were positive in 13/14; whereas in passive rigidity testing only 8/14 of these patients showed positive balance coefficients.

Detection of tremor and co-contraction

Tremor bursts may interfere with EMG measurements, as was shown in chapter 5. When one assumes equal strong EMG activity from tremor throughout all flexion and extension cycles of a clinical rigidity test then one would predict near zero balance coefficients. A typical illustration of a near zero effect of the balance coefficient (figure 2f) with a slight cycle modulated tremor is shown in figure 2e. The balance coefficient in this patient was about 2. In fact, this patient was very rigid (UPDRS=3) so that a larger positive balance coefficient was expected. The balance coefficient may possibly be useful to detect tremor when balance coefficients are near zero. However, this is not always the case.

1) A tremor is often modulated by cyclic movements of rigidity tests. This causes asymmetry of tremor bursts in muscle lengthening and shortening phases which implies that the balance coefficient may differ from zero. By movement of the wrist, tremor amplitude and frequency may be modulated [15-17]. The repetitive bursts from the cogwheel phenomenon are modulated anyway by cyclic movements of a rigidity test since they are predominantly present during lengthening phases. In a larger group of 29 patients, where balance coefficients were in a range of –12 to 7, we noted that balance coefficients in tremor can significantly differ from zero and consequently were not detectable.

2) Tremor is not the only phenomenon that could generate around zero balance coefficients. Co-contraction of antagonistic muscle groups can reduce balance coefficients. Co-contraction at high rigidity scores may show overflow effects from muscle lengthening to a shortening as shown in figure 1c. Also instantaneous co-contraction from simultaneous firing motor neurons of agonists and antagonists is possible. In more pronounced co-contraction the balance coefficient may theoretically further be reduced and approximate the value of zero.

It is concluded that near zero balance coefficients of the balance coefficient do not permit clear differentiation between tremor, muscular co-contraction and low rigidity scores.

B. Quantification of rigidity by the balance coefficient

It has been shown that the balance coefficient can successfully be applied as detector for negative rigidity. Therefore a negative balance coefficient may be used to exclude EMG from further quantification and refers to clinical low rigidity scores of 0 or 1.

Besides its use as detector for negative rigidity, the balance coefficient also can be considered as a parameter for quantification of rigidity.

We have shown a correlation between clinical rigidity and amplitude of the EMG in both muscles in both phases of the cyclic movements. As expected from literature, the strongest correlation between EMG amplitude and rigidity score was found for lengthening phases. The shortening phase, however, also showed an increase in EMG amplitudes at increase of rigidity, but smaller. The increase in EMG activity in rigidity in the shortening phase is likely caused by co-contraction effects that depend on rigidity like the example as shown in figure 1c or due to an increase in shortening reaction [18;19]. Cantello already showed an increase in EMG activity in rigid patients at rest, whereas most authors with passive movement related rigidity testing showed cycle related EMG activity [20].
Since the highest correlation factors were found during muscle lengthening phase, it can be expected that, in addition as a detector for negative rigidity, the balance coefficient also may be used for measurement of rigidity in rigid patients. The balance coefficient is indeed correlated with clinical rigidity. However, it is not possible to predict the clinical rigidity from balance coefficients over the full range of the rigidity scale.
An optimal solution for quantification of parkinsonian rigidity may be obtained by using characteristics of the balance coefficient which performs optimally in the low rigidity range of 0-2, and combine this with quantified EMG recordings in the lengthening phase in the high rigidity range where negative rigidity is absent. The decision level of –5dB of the balance coefficient can be used to decide whether EMG amplitudes are amenable for quantification.
We also created a single parameter for quantification of rigidity by multiplication of the EMG amplitude by the balance coefficient after correction of the –5dB bias of the decision level. This would create negative EMG amplitudes at negative rigidity. This did not improve the afore mentioned correlation. This may be ascribed to the non-linear influence of relative attenuation of the balance coefficient at the high rigidity scores on the product. It was concluded that this method offered no additional value.

In addition to the findings of Meara et al., using the EMG ratio between the stretched and released muscle that was useful for differentiation only between strong and mild rigidity[1], the balance coefficient can in theory be useful to differentiate between lower rigidity scores in a range of 0-2 as shown in figure 1b. When rigidity increases above UPDRS=2, then co-contraction such as may occur from overflow effects in severe rigidity (figure 1c) gradually may become important so that with increasing rigidity the balance coefficients theoretically may reach a maximum followed by a decrease as shown in figure 1c. This decrease of the balance coefficient at the highest rigidity score was confirmed in our patient group (figure 4).

When rigidity scores are 2 or higher, one would expect no negative rigidity and consequently positive balance coefficients. This was not the case in two out of 14 patients with UPDRS rigidity scores of 2 and 3. These patients had balance coefficient values of respectively –4 and –2.8. This paradox in both patients was caused by large bursts in the EMG signals that were unevenly distributed between flexor and extensor muscles and shortening and lengthening phase. The frequency spectra of the bursts showed peaks between 10 and 12 Hz in one patient and a wider spectrum in the other. These are within the 7-14 Hz range of action tremor and cogwheel phenomenon [12;13]. When these bursts are intercepted and masked, the balance coefficients would not be negative anymore. This finding stresses the need for recognition of the bursts in the EMG's.

Clinical application of the balance coefficient

A balance coefficient is sensitive to tremor, cogwheel phenomenon, negative rigidity and rigidity. In the control subjects and patients the balance coefficient gives additive information in clinically non-rigid status. A negative balance coefficient should be taken into account in a procedure for quantification of rigidity using EMG amplitudes. Only quantified EMG values at positive balance coefficients can be used for quantification of rigidity. A negative balance coefficient is a warning that EMG amplitudes may lead to false overestimations of low clinical rigidity scores. In this study, negative rigidity was never encountered in rigid patients and only noticed in the groups of healthy subjects and patients with no or very mild rigidity. In other words, when relatively high EMG amplitudes are measured in EMG recordings in rigidity testing, while clinical testing results in absent or slight rigidity scores, one can expect the presence of negative rigidity. This stresses the importance of incorporation of detection of negative rigidity, for example by means of the balance coefficient, in an automated method for objective quantification of rigidity.

In the previous chapter it was concluded that cogwheel bursts may play a role in parkinsonian rigidity. In contrast to the hypothesis, in this small patient group the balance coefficient was not sensitive enough to exclusively detect the presence of cogwheel bursts and interference by tremor. When bursts from the cogwheel phenomenon could selectively be detected in time, quantified and separated into a group of muscle lengthening and a group of shortening like in this study, one might obtain a quantifying parameter from the cogwheel bursts resulting in an improved correlation with the rigidity scores according to the UPDRS. Bursts can effectively be intercepted by a second order moment function and masked, so that the continuous parts of the background EMG are preserved [14]. This is further explored in the next chapter.

Conclusion

The balance coefficient detects the presence of negative rigidity when clinically no or mild rigidity is scored. Negative rigidity is detected when balance coefficients are below a small negative bias. The balance coefficient is useful to handle the paradox of high EMG amplitudes of negative rigidity in order to obtain an improved correlation between quantified EMG and UPDRS rigidity score. The hypothesis that the balance coefficient identifies positive and negative rigidity is confirmed in a small patient group and control subjects, however the balance coefficient is not sensitive for selective detection of tremor or for quantification of rigidity. A further improvement of the correlation is expected from individual detection and removal of cogwheel bursts and, as in this study, group-wise separation into lengthening and shortening phases of the cyclic movements in rigidity tests.

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Chapter 4

Assessment of rigidity in parkinsonian patients by selective quantification of cogwheel bursts and interburst intervals in myograms using a second order moment function

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Abstract

Introduction
The continued development of therapeutic options for Parkinson's Disease (PD) increasingly calls for more precise and reliable neurophysiological methods to assess individual parkinsonian symptoms, such as rigidity. Electromyography (EMG) has already been used for quantification of rigidity with varying accuracy.
Next to the lead pipe phenomenon the cogwheel phenomenon is one of the characteristics of parkinsonian rigidity. A method of analysis such as second order moment filtering (SOMF) is needed to separate the cogwheel phenomenon from the static background contraction before quantification of the EMG, to conform to the clinical scoring of rigidity according to the UPDRS rating scale.

Material and Methods
14 consecutive patients referred for implantation of DBS electrodes in the STN underwent pre- and postoperative assessment of rigidity with simultaneous EMG recording of the forearm muscles. Separation and characterization of the EMG components were carried out with off-line analysis by SOMF. The quantified components were compared to clinical assessment of rigidity.

Results
The bursts of the cogwheel phenomenon were detected by SOMF.
The spearman's correlation coefficient between UPDRS rigidity rating and interburst minimum (MBAF (Tmin)), as representative of the static background contraction, was 0.85/0.79 for flexor/extensor muscles during lengthening of the muscle ($p<0.001$) and 0.75/0.61 for the shortening phase (p:0.002/0.02) respectively.
The correlation coefficient between the burst amplitude (MBAF(T0)) in the lengthening phase was 0.71/0.78 (p:0.004/0.001), and for shortening phase 0.32/0.38 ($p>0.05$).
Timing of the bursts, burst width and location of the minimum between the bursts showed no correlation with clinical rigidity.

Discussion
The cogwheel phenomenon is one of the hallmarks of parkinsonian rigidity, which has to be ignored in clinical scoring. Second order moment filtering is important for recognition and characterization of the cogwheel burst as component of rigidity and determination of moments of background activity.
Both components correlated with clinical rigidity during the lengthening phase of the muscle, but only the background contraction has high correlation during shortening phase.
The addition 'cogwheeling ignored' in the UPDRS definition of rigidity ignores one of the major hallmarks of parkinsonian rigidity, but by ignoring this phenomenon the correlation of quantified rigidity compared to clinical rigidity is increased and interference of tremor bursts is prevented.
This study provides complementary tools for the design of a method for intra-operative monitoring of parkinsonian rigidity.

Introduction

In clinical assessment of parkinsonian rigidity the examiner feels a continuous resistance, sometimes interrupted in a tooth-like fashion by a cogwheel phenomenon. The cogwheel phenomenon is a hallmark of in parkinsonian rigidity.
However, according to the UPDRS, the cogwheel phenomenon has to be excluded in clinical quantification of rigidity.
In EMG recordings the cogwheel phenomenon can be distinguished as a series of burst patterns superimposed on a tonic background contraction [1]. Since the EMG of the cogwheel phenomenon and the static background contraction share the same power spectral frequency band, conventional band pass filters fail to separate these two components. An additional shortcoming of power spectral analyzing techniques which are successful in retrieving the frequency components of regular paced tremor EMG bursts, is that these are inappropriate for analysis of the irregularly paced patterns of cogwheel bursts. The repetition frequencies of these cogwheel bursts are spread out over a wide frequency band [2] so that their power spectrum becomes invisible due to immersion in EMG demodulation noise [3].
A relatively new technique, the wavelet transform (WT), is able to detect non-stationary cogwheel burst in stationary background noise. The bursts can be selectively filtered from the background noise. The separating power depends on a discriminating amplitude level. We found a good correlation between EMG amplitude and clinical rigidity of both components (chapter 5) [4]. Wavelet shrinkage techniques adapt the discrimination level of WT filters to gradual changes in amplitude. These techniques are successful in dystonia EMG's when time for adaptation is sufficiently long [5]. However, the short time intervals of muscle shortening phases in clinical rigidity tests appeared to be too short for reliable selective separation of cogwheel bursts from the background EMG. This adaptation problem is not present in a new method, based on a statistical computation using a running second order moment function (SOMF). The SOMF can be used to primarily detect cogwheel bursts as locally increased densities of energy in an EMG like points of gravity [6]. Since the amplitude is ruled out by burst wise normalization, detection levels are independent and thus insensitive for amplitude. Since the SOMF based method delivers the instants of detected bursts, it is possible to compute the energy of cogwheel bursts and the energy of the EMG of the surrounding background contraction separately.

Separation of cogwheel bursts from the background EMG by a wavelet filter was based on the presumption that cogwheel bursts are independent from and superimposed on the background EMG. This seems in concordance with the statement 'cogwheeling to be ignored' in the UPDRS definition for parkinsonian rigidity. From a neurophysiological view, however, it is more likely that at motor neuron level the background EMG is modulated by central neural mechanisms that

generate action tremor and cogwheel bursts. The cogwheel phenomenon is related to action tremor [2;7]. This would imply that the assumption of superposition does not hold since the background EMG essentially depends on bursting events. A modulation model instead of superposition model would therefore be more appropriate.
The distinction between superimposition and modulation appears irrelevant when bursts are detected by a method identifying EMG bursts at locations with relative condensation of energy. In this chapter, a new method, based on a statistical computation using a second order moment function SOMF, is used to detect the cogwheel bursts by detection of the condensations of energy in the EMG. The SOMF is explained in more detail in the paragraph background. In this study the sensitivity and positive predictive value of the burst detection with different parameters of the SOMF are determined. After identification of cogwheel bursts, the mean amplitude of the interval between bursts can be calculated. To comply with the UPDRS definition of rigidity which excludes the cogwheel phenomenon, we consider this EMG sections between the bursts to represent the static part of parkinsonian rigidity, whereas the interval over the width of the burst refers to the cogwheel burst.

Background of second order moment function and choice of parameters

Description
For the detection and timing of EMG bursts a running second order moment function is used. The computation of the running second order time function SOMF(W,t_i) starts with a window with a width of W seconds directly at the beginning of the full wave rectified EMG signal $|x(t_i)|$ at t_i=W/2.
After computation of SOMF(t_i), which is given in formula (1), the window is repeatedly shifted one sample interval forward and a new SOMF computation made until $t_i=t_N$-W/2 in which t_N is the instant of the last sampled value. N is the number of samples, and n refers to individual samples.

$$SOMF(W, t_i) = \frac{\sum_{t_n=t_i-W/2}^{t_i+W/2} |x(t_n)|.(t_n-t_i)^2}{\sum_{t_n=t_i-W/2}^{t_i+W/2} |x(t_n)|} \qquad (1)$$

This is a computation of the second order moment from the centre of the time window. The denominator is for normalisation which makes the result independent of the amplitude. When no bursts are present within a window only a background noise will be left. It is assumed that this noise will be approximated by a homogeneous distribution function whose second order moment function has an expectance value of $SOMF(W,t_i)=W^2/12$. When $x(t_n)=0$ (no signal) within the window, $SOMF(W,t_i)$ is given the value: $W^2/12$. Figure 1 shows a drawing of an EMG burst x(t), enclosed by silent periods such as are often seen in EMG's from a resting tremor in patients with PD. The width of the time window shown is sufficient to enclose the burst width. SOMFx in figure 1 shows a parabolic course around the 'point of gravity' of the burst at the minimum.
At the minimum t_{min} ($=t_{burst}$ in figure 1) the $SOMF(W,t_i)$ is equal to the variance (VAR) of the distribution function $|x(t_i)|$ of the burst. The parabolic course, which is synonymous to Steiners law in mechanics, is given by:

$$SOMF(W, t_i)=VAR+(t_i-t_{min})^2=SOMF(W,t_{min})+(t_i-t_{min})^2 \qquad (2)$$

The minimum of the second order moment function is at the same location as the 'point of gravity' which is equal to the first order moment of the burst when there is no background activity.

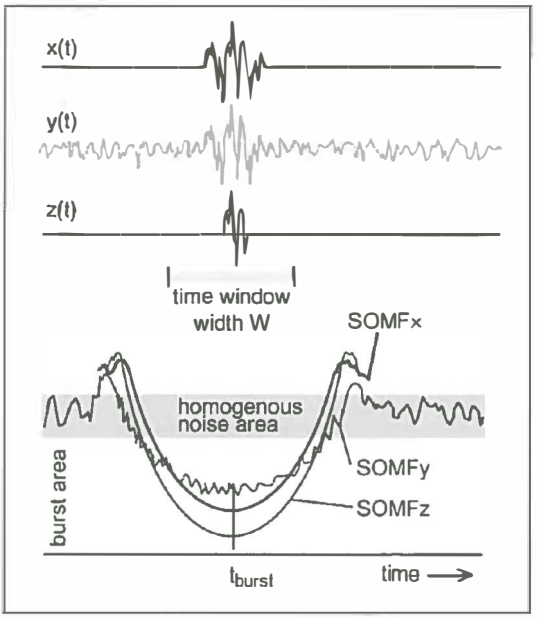

Figure 1: Three burst EMG signals with their running second order moment functions, x(t) en z(t) are burst signals without background noise. The burst width of x(t) is larger than the width of the burst in z(t). y(t) is the burst of x(t) superimposed on a background noise. SOMFx, SOMFy and SOMFz are the respective running second order moment functions of x(t), y(t) and z(t). The grey band shows a confidence interval for stationary noise.

When the burst width is smaller than the window width W, the second order moment function at the minimum, SOMF(W,t_{min}), is equal to the variance VAR of the distribution function of the enclosed burst. The quadratic term $(t_i-t_{min})^2$ describes the parabolic course of SOMF(W,t_i) in the region around t_{min}. The width of the parabolic course is truncated by the window and burst widths. The noisy effects at both ends of the parabolic curve are caused by burst shift-out, since the variance VAR is linearly related to the square of the standard deviation of distribution function of the burst. The narrow burst of signal z(t) has the parabolic function with the lowest minimum. As in this example, when there is no background noise, the parabolic function is independent of the shape of the burst. However, there is background noise to be considered. This is shown in signal y(t). The noise will flatten the parabolic course of SOMFy as shown in figure 1. The location of the minimum at t_{burst} will be affected due to random variations in shape of the distribution function of the part of the background noise enclosed within the moving window. Moreover, the parabolic curve becomes contaminated with noise. The minimum SOMF(W,t_{min}) is elevated due to the width of the background noise that contributes to the distribution function of the burst.

Detection and timing of EMG-burst

EMG bursts can be detected by the magnitude of the minimum values of the SOMF. However, when the signal to noise ratio (SNR) of the burst to the background noise is poor, or when no burst is captured within the sliding window, SOMF minima become too high for proper burst detection. This may occur when SOMF minima are in the grey band in figure 1. The grey band is a confidence interval of SOMF minima of stationary EMG noise without bursts. The SOMF(t_i) of stationary noise within window W has a expectance value $\varepsilon_{SOMF:noise}$ of:

$$\varepsilon_{SOMF:noise}(W)=W^2/12 \qquad 3)$$

The width of the confidence interval has an inverse relationship with the number of degrees of freedom v of the noise. For stationary Gaussian noise, v is equal to the product of the SOMF window width W and the noise bandwidth B_n [16].
L defines a factor for threshold Th relative to $\varepsilon_{SOMF:noise}$:

$$Th=L\cdot\varepsilon_{SOMF:noise} \qquad (4)$$

where $L\leq 1$. A burst is detected when SOMF(t_{min})<Th. The sensitivity of burst detection by the SOMF method increases with L, but the selectivity and the positive predictive value (PPV) of a detected burst decrease when Th reaches the grey region due to false detection of bursts (false positive).

Scanning procedure for automated burst detection

The subsequent series of detected minima of the SOMF are obtained by an automated procedure with predefined level factor L. Initially $SOMF(W,t_i)$ is scanned until $SOMF(W,t_i)>1.2$ Th (starting condition). Subsequent SOMF minima are determined starting at $SOMF(W,t_i)<Th$ until $SOMF(W,t_i)<1.2$ Th. Th and 1.2Th define levels of a Schmidt-trigger comparator with empirically determined hysteresis of 20%. The Schmidt-trigger prevents detection of false minima near crossings at level Th due to noise that is superimposed on the SOMF.

Choice of the SOMF window width

W is a time scale parameter. It has to be tuned on basis of burst width and burst repetition frequency.

The window width W must at least cover the EMG bursts whereas the maximum width is restricted, since only one burst should be admitted within a window. The detector performs well when the frequency of the bursts lie within an octave band of about 1.5.

Optimal sensitivity and selectivity for burst detection are expected when performing analysis with window dimensions of W=200 ms for a 3–8Hz band and W=120 ms for a 5-12Hz band.

Choice of the detection level

A high detection level L will result in a high burst count that also includes false bursts which originate from background noise as L lies within the noise band in figure 1.

By contrast, a low level will have a high PPV and a low sensitivity. Based on tremor recognition, the optimum expected detection levels are L=0.75–0.8 [6].

Material and methods

In the period from 1997 to 2001, 14 consecutive patients were referred for implantation of electrodes for bilateral deep brain stimulation of the subthalamic nucleus (Chapter 3: patient 20-33), age range 47-70 years (mean 58,7 yrs). The patients underwent routine testing for rigidity one day before implantation and postoperatively. During clinical rigidity testing, scored according to the UPDRS, simultaneous EMG registrations were made.

The right sided measurements were used in this study. The patients subsequently underwent two measurements during a rigidity test without, and two during contralateral activation and finally two measurements again without contralateral activation. For contralateral activation the patient was asked to squeeze a ball in the opposite hand to reinforce rigidity.

EMG recordings were made as mentioned in the general material and methods (chapter 3).

Off-line analysis was carried out in the following steps:
1) Suppression of low-frequency movement artefacts by a high-pass wavelet filter using a 12-coefficient Daubechies wavelet filter of which the lower five scaling bands were blocked. 2) Full wave rectification of the EMG signal. 3) Identification of the bursts of the cogwheel phenomenon by second order moment filtering (SOMF) employing a 120ms time window and detection level of 0.75. 4) Splitting up of EMG epochs according to extension to flexion and vice versa and reassembling of the EMG chunks into two groups representing the lengthening and shortening phases by means of the goniometer signal. This was performed for both muscle groups. The EMG chunks were truncated (zeroed) 50 ms from both ends to suppress artefacts from EMG overflow to complementary movement phases. 5) A mean burst amplitude function $MBAF_{muscle,phase}(T)$ was calculated for both movement phases and muscle groups. The mean maximum and minimum values with their standard deviations resulted from averaging of the maximum and minimum values of individual bursts. These individual extremes were obtained by averaging over a width of 25ms. The choice of the width was an empirical compromise between accuracy and width of the MBAF. The mean location in time and standard deviation were similarly obtained from averaging of the locations of the individual minima. $T_0=0$ represents the centre of the cogwheel burst, whereas T_{min} represents location of the minimum amplitude in the interburst interval.

The identification of bursts with SOMF in the EMG signal is demonstrated in the EMG signal of patient 33 (figure 2).
Sensitivity and positive predictive value for detection of bursts were determined in 5 randomly selected patients (13,23,28,32,33 from table 1, chapter 3) for window widths 50, 80, 100, 120, 150 and 200 ms and level 0.05; 0.40; 0.50; 0.60; 0.70; 0.75; 0.80; 0.90 and 1. The visually identified bursts in the EMG signal were used as standard reference. The specificity could not be determined since bursts that go undetected by visual inspection would be missed.

Five parameters that characterize a repetitive cogwheel burst and its environment were derived from the MBAF for comparison with clinical rigidity scores at pre-operative measurements.
1) the minimum values of the MBAF representing background EMG activity excluding the burst: $MBAF_{muscle,phase}(\tau_{min})$,
2) the maximum MBAF at the 'gravity' center of the burst: $MBAF_{muscle,phase}(0)$,
3) the burst widths $BW_{muscle,phase}$,
4) the locations where the MBAF is minimal: τ_{min} and
5) the interburst time intervals that are determined at the first peak next from the center peak in the auto interburst time histograms (auto-IBTH) as described by Journée et al [6]. All these values are computed for the lengthening and shortening phases of both muscle groups.

The increase in $MBAF_{muscle,phase}(\tau_{min})$ and MBAF(0) by contralateral activation (CLA), was studied by comparison of first of two rigidity measurements during reinforcement with the reference first rigidity measurement without reinforcement.

To judge the effects of stereotactic treatment, post- and pre-operative measurements were compared in individual patients.
The set of $MBAF_{muscle,phase}(\tau)$ values from 4 pre- and 4 post operative passive rigidity measurements were used for computation of Spearman's correlation coefficients and regression lines of each individual patient.

Statistical analysis and drawing of plots was carried out using statistical package SPSS 11.0.1. Correlation factors were calculated with the Spearman's correlation coefficient for non-parametric variables. The Wilcoxon signed rank test was used for comparison of passive rigidity and contralateral activation.

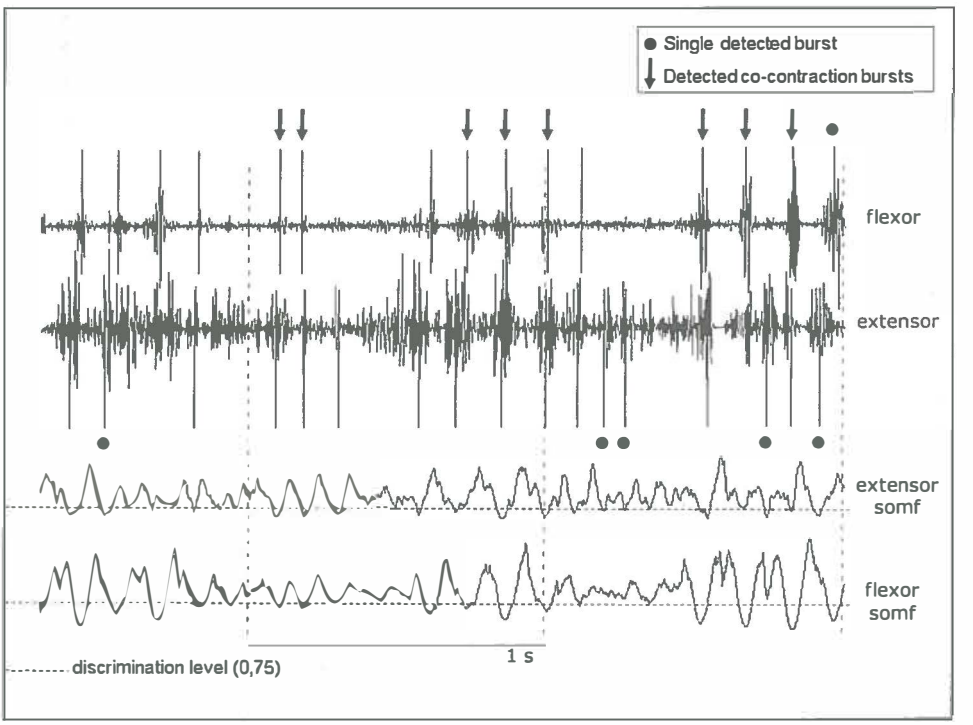

Figure 2: Example of the filtering effects of a second order moment function (SOMF) on cogwheel bursts in EMG's of flexors (upper trace) and extensors (second trace) in he forearm of a patient with Parkinson's disease during clinical rigidity testing. The third and bottom traces are the SOMF's of respectively the extensors and flexors. Bursts represent locations with increased energy densities and can be recognized by their parabolic course in the SOMF signals. Minima denote locations of detected bursts. Vertical time mark lines indicate these minima in the cogwheel burst. SOMF window width is 120 ms and detection level: 0.75. The vertical arrows indicate some recognized co-contracting bursts whereas the spherical dot denote some detected bursts without co-contracting counterpart.

Results

Burst detection with second order moment filtering

The bursts of the cogwheel phenomenon in the EMG were detected by second order moment filtering (SOMF). Figure 2 shows an example of the EMG. The uppermost two signals show the unprocessed EMG of flexors and extensors. The subsequent SOMF's of the extensors and flexors are shown below. Parabolic parts denote cogwheel bursts. Bursts are recognized when their minima are below the 0.75 detection level (dashed lines). The time marks of these minima mark the location of the cogwheel burst and are drawn in the original EMG. The burst width of the EMG burst is proportionally related to the level of the minimum of the SOMF. The cogwheel bursts in the flexor EMG are all identified while bursts in the extensor EMG are harder to recognize due to impaired signal to noise ratio by a relatively high background noise level. The cogwheel bursts show occasionally patterns of co-contraction having equal minimum SOMF timings as indicated by the vertical arrows. However, bursts can also be present asynchronously in both EMG's. Some examples are given by the spherical dots.

Optimum window width and level

Figure 3 shows the sensitivity and positive predictive value (PPV) plotted for different window width and level for bursts detected in flexor and extensor EMG's. A level of 1 will detect most bursts, but will indicate more false positive bursts and thus results in a lower PPV. Window widths of 100, 120 and 150 ms can detect most bursts. The optimum window width and level combination lies in the right upper quadrant. Window widths of 120 and 150 ms with levels of 0.75, 0.8 and 0.85 are optimal. The sensitivity and PPV of these combinations are given in table 1. A window width of 120 ms with level 0.75 and a window width of 150 ms with level 0.8 have about equal sensitivity and PPV. We chose a window width of 120 ms and a level of 0.75 for further use in this study. This combination had a sensitivity of 85.6% and a positive predictive value of 71%.

Figure 3: Statistical summary of the sensitivity, PPV and the product of sensitivity by PPV of the flexor EMG's at the left and of the extensor EMG's at the right of 5 patients (in %). Sensitivity and selectivity of the flexor EMG's reach nearby 100% levels and is less critical dependant on the parameter choice whereas the extensor EMG's reach lower maximal levels and optimal results depend more critical on the choice of both SOMF parameter settings. The product plots of the PPV and sensitivity at the bottom show for all window width optimum values of the threshold level between 0.7–0.75 for the flexors and at 0.8 for the extensors, whereas the optimal width of the time window for both muscle groups is 120-150 (flexors) or 150 (extensors).

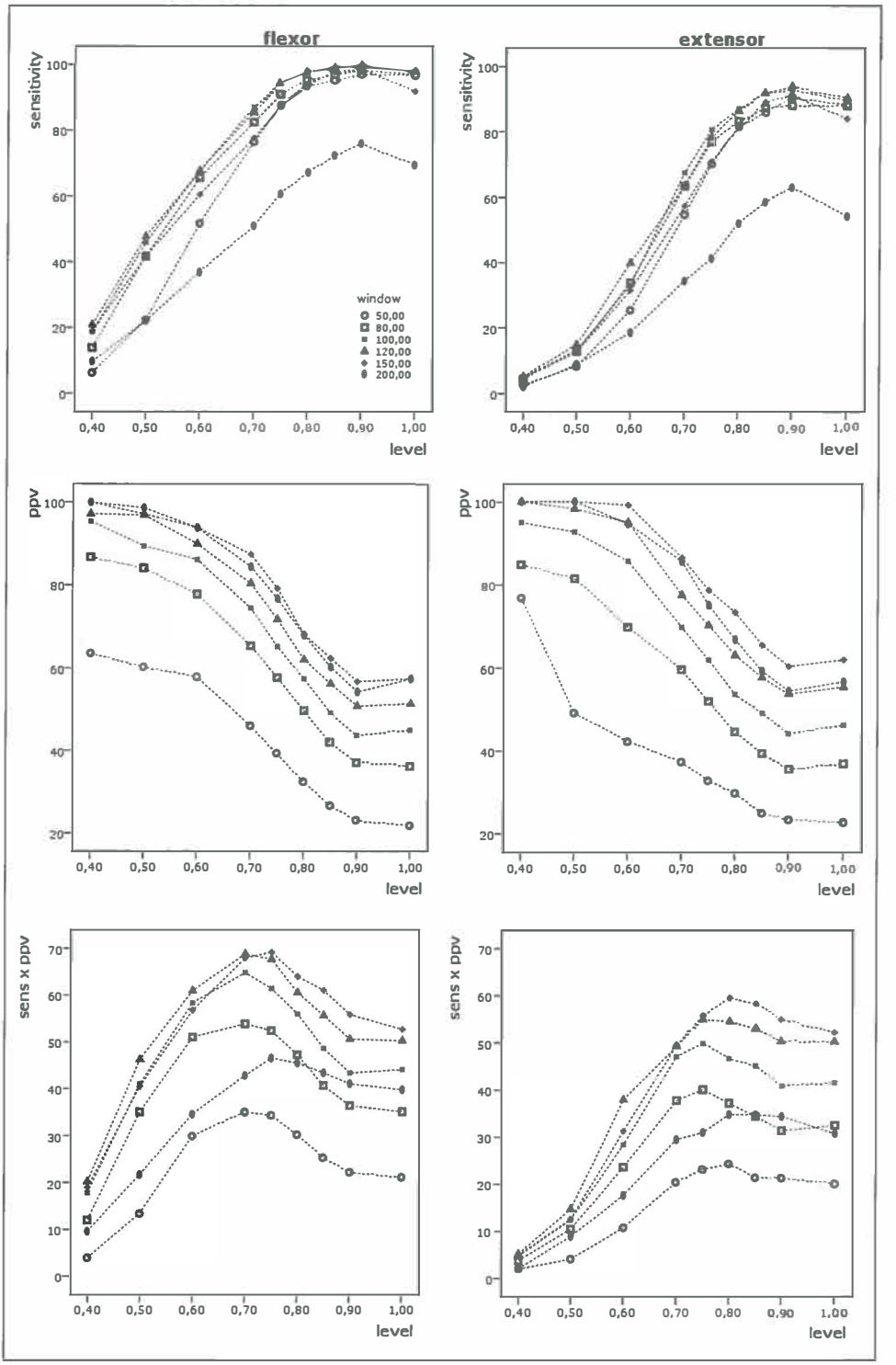
flexor
extensor
sensitivity
ppv
sens x ppv
level
window
50,00
80,00
100,00
120,00
150,00
200,00

Table 1: The sensitivity and positive predictive value (PPV) for a given window width and level.

Window width, level	Sensitivity (%)	PPV (%)
120 ms, 0.75	85.6	71.0
120 ms, 0.8	91.6	62.7
120 ms, 0.85	95.2	57.0
150 ms, 0.75	78.5	79.0
150 ms, 0.8	87.1	70.6
150 ms, 0.85	93.1	63.9

Table 2: Correlation of cogwheel EMG burst parameters with clinical rigidity. len: lengthening and sh: shortening phases; flex: flexors and ext: extensors forelimb, R: Spearman's correlation coefficient and p-value *) significant for $p<0.05$.

$MBAF_{muscle,\ phase}(\tau)$	R	p
$MBAF_{flex,len}(\tau_{min})$	0.845	0.000 *
$MBAF_{ext,len}(\tau_{min})$	0.791	0.001 *
$MBAF_{flex,sh}(\tau_{min})$	0.749	0.002 *
$MBAF_{ext,sh}(\tau_{min})$	0.606	0.022 *
$MBAF_{flex,len}(0)$	0.713	0.004 *
$MBAF_{ext,len}(0)$	0.779	0.001 *
$MBAF_{flex,sh}(0)$	0.317	0.270
$MBAF_{ext,sh}(0)$	0.380	0.180
$Burst\ width_{muscle,\ phase}$		
$burst\ width_{flex,len}$	0.195	0.505
$burst\ width_{ext,len}$	0.122	0.677
$burst\ width_{flex,sh}$	0.151	0.607
$burst\ width_{ext,sh}$	0.187	0.522

Comparison of burst parameter with clinical rigidity scores according to the UPDRS

1. Comparison of interburst minimum amplitude $MBAF_{muscle,phase}(\tau_{min})$

Table 2 summarizes the correlation coefficients between the UPDRS scores and the $MBAF_{muscle,phase}(\tau_{min})$, the $MBAF_{muscle,phase}(0)$ and $BW_{muscle,phase}$ for the lengthening and shortening phases of both muscle groups. All correlation coefficients with

$MBAF_{muscle,phase}$ (τ_{min}) have significant p values ≤0.022 for all phases and muscles. However, the highest correlation factors were found in the lengthening phase.
The interburst minimums $MBAF_{muscle,phase}(\tau_{min})$ denoting the EMG energy of the background EMG between the bursts showed the highest and most significant correlation with the UPDRS rigidity scores. The highest correlation of 0.845 was found for the flexors in the lengthening phase followed by the extensors with a correlation of 0.791. The correlations were significant at p≤0.001. The correlation and significance levels were lower in the shortening phases: 0.749; p=0.002 for the flexors and 0.606; p=0.22 for the extensors.
Figure 4 shows a scatter plot of $MBAF(\tau_{min})$ and the UPDRS rigidity scores from the first rigidity measurements in all patients. An increase in amplitudes with increasing rigidity is visible. However, there is overlap in the amplitude distribution of the MBAF values of subsequent rigidity scores.

2. Comparison of burst amplitude with rigidity score

The maximum burst amplitude at $\tau=0$, $MBAF_{muscle,phase}(0)$, includes the EMG burst energy. The correlation factor for flexors and extensors has dropped slightly to respectively 0.713 and 0.779 at somewhat increased p levels and has remained significant at p<0.005. However, for muscle shortening the correlation factor has dropped to insignificant low levels.

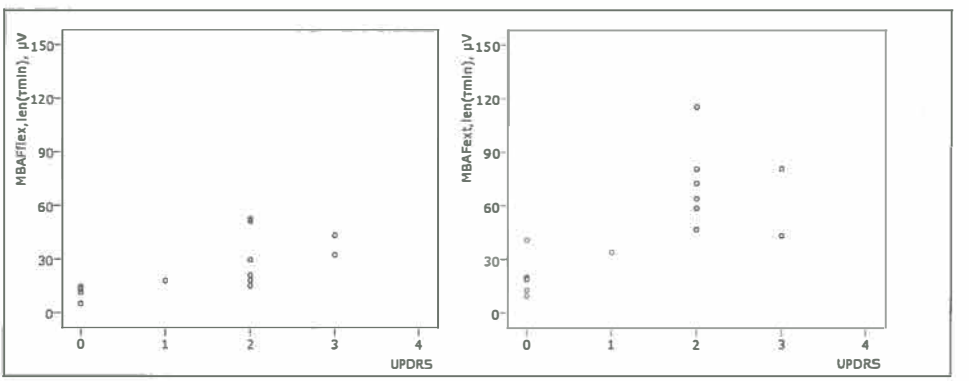

Figure 4: The interburst minima and the UPDRS rigidity scores are plotted for (a) flexor ($MBAF_{len,flex}(\tau_{min})$) and (b) extensor ($MBAF_{ext,len}(\tau_{min})$) antagonist muscles in 14 parkinsonian patients. An increase in interburst minima is detected with increasing rigidity scores.

3. Comparison of burst width with rigidity score

The four bottom rows in table 2 show no correlation between burst width and clinical rigidity scores for all muscles and excursion phases.

4. Comparison with interburst minimum MBAF(τ_{min})

The median locations of the interburst minima after de cogwheel phenomenon maximum are given in table 3 for the muscle groups in both excursion phases. The mean values are in a range of 47-60 ms and show no significant correlation with clinical rigidity.

Table 3: Statistical survey of the location of interburst minimum τ_{min} of the burst amplitude function MBAF(τ_{min}).and correlation with clinical rigidity: R: Spearman's correlation coefficient p: significance level. len: lengthening and sh: shortening phase; flex: flexors and ext: extensors forelimb. All correlation coefficients are not significant for $p<0.05$.

	Location interburst minimum τ_{min}			Correlation with clinical rigidity	
muscle, phase	Median (ms)	Minimum (ms)	Maximum (ms)	R	p
flex, len	48	48	52	-0.286	0.64
ext, len	49	47	54	-0.068	0.27
flex, sh	48.5	48	60	0.225	0.47
ext, sh	49	48	56	-0.211	0.92

5. Comparison of interburst time differences

According to table 4, the interburst time ranges from 88 to 122 ms. This corresponds to a frequency band of 8.2–11.4 Hz. Columns 4 and 5 show no correlation between the IBI and clinical rigidity scores for all muscles and excursion phases in pre-operative recordings.

Table 4: Survey of interburst time intervals, IBI, and correlation with clinical rigidity: R: Spearman's correlation coefficient p: significance level. len: lengthening and sh: shortening phase; flex: flexors and ext: extensors forelimb. All correlation coefficients are not significant for $p<0.05$.

	IBI			Correlation with clinical rigidity	
muscle, phase	Median (ms)	Minimum (ms)	Maximum (ms)	R	p
flex, len	102.9	93.2	122.0	-0.251	0.386
ext, len	106.8	92.6	121.4	0.312	0.277
flex, sh	110.3	91.9	121.1	0.381	0.179
ext, sh	99.4	88.2	119.1	-0.331	0.248

Amplitude increase in contralateral activation

During contralateral activation the muscle groups show opposing changes: all MBAF's of the flexor muscles show an increase of amplitudes during reinforcement procedure (Wilcoxon signed rank, $MBAF_{flex,len}(\tau_{min})$ p=0.001; $MBAF_{flex,sh}(\tau_{min})$ p=0.001; $MBAF_{flex,len}(0)$ p=0.001 and $MBAF_{flex,sh}(0)$ p=0.006).
The amplitudes in extensor muscles have decreased ($MBAF_{ext,len}(\tau_{min})$ p=0.016; $MBAF_{ext,sh}(\tau_{min})$ p=0.016 and $MBAF_{ext,len}(0)$ p=0.008).

Detection of rigidity changes within a patient

Figure 5 shows an example of the individual graph of $MBAF_{flex,len}(T_{min})$ and $MBAF_{ext,len}(T_{min})$ plotted against clinical rigidity scores for all recordings during passive rigidity testing of patient 26. In increasing rigidity scores an increase in $MBAF_{flex,len}(T_{min})$ and $MBAF_{ext,len}(T_{min})$ is present. 11 out of 14 patients show an increase in $MBAF_{(}T_{min})$ in both flexor and extensor muscles in lengthening phase. This is significant in 9 patients for flexor muscles and 7 for extensor muscles (Table 5). Still some overlap between scores is present. 2 patients show high $MBAF_{flex,len}(T_{min})$ and $MBAF_{ext,len}(T_{min})$ scores in UPDRS rigidity score of 1. 1 patient shows an increase from UPDRS rigidity from 0 to 1 and from 2 to 3, but no overall increase.

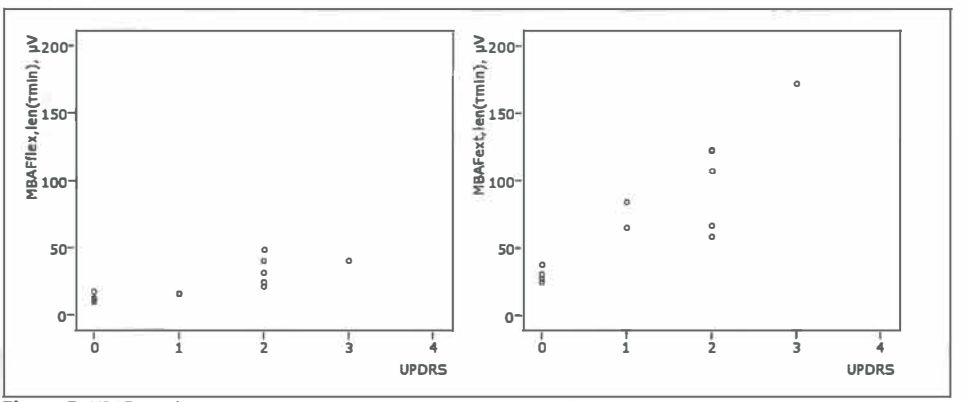

Figure 5: $MBAF_{flex,len}(\tau_{min})$ (a) and $MBAF_{ext,len}(\tau_{min})$ (b) are plotted to the simultaneous scored clinical rigidity score in pre- and post operative recordings of patient 7.

Correlation between MBAF(T_{min}), (MBAF(T_0), burst width and mean location

The MBAF(T_{min}) and (MBAF(T_0) in the corresponding phases of the muscles have been correlated (len, flex: 0.912 p=0.000; len,ext:0.908 p=0.000; sh,flex: 0.560 p=0.037; sh,ext 0.868 p=0.000). The burst width and mean location and the burst width and the interburst interval are not significant correlated.

Discussion

The second order moment function (SOMF) provides a powerful technique for detection of EMG bursts even in the presence of background noise.
The parameters of the SOMF have to be tuned on basis of burst width and burst repetition frequency. The window width should be sufficient large to enclose the burst width. On the other hand, the maximum width will be limited by the burst repetition time since only one burst should be admitted within a window. The detector performs well when the frequency of the burst patterns lies at about a 1.5 octave. Pathological tremor frequencies in parkinsonian patients are in the range of 3.5-7 Hz for rest tremor and 7-14 Hz for action tremor and cogwheel phenomenon [2;8]. These frequency bands could be covered by one SOMF window width. Optimal sensitivity and selectivity for burst detection are expected using a window dimension of W=200 ms for a 3–8Hz range for tremor and W=120 ms for a 5-12Hz range for analysis of the cogwheel phenomenon.
The level parameter controls which SOMF minima will be detected and marked as bursts. A high level will detect all SOMF minima, but falsely detected minima from background noise may also be found. Optimum detection levels are L=0.75–0.8. The SOMF method for burst detection appears to agree with results of visual inspection.
SOMF burst detection is primarily sensitive for the detection of non-stationary events. This is also a characteristic of methods that are based on wavelet transform, short-time-Fourier transform, Gabor transform and Wigner Ville algorithms [9;10]. Wavelet filtering has recently proved to be successful in separating burst patterns in unprocessed EMG signals of parkinsonian patients with rigidity [4] or dystonia [5]. These methods probably will be successful also for detection and timing of EMG bursts in pathological tremor by addition of computational procedures, and can be useful in detection of cogwheel bursts. The second order moment function offers the advantage that the instants of occurrence of bursts are available.
This characteristic of SOMF is used in this chapter for identification of the cogwheel phenomenon. When identified in an automatic procedure, the cogwheel phenomenon and the background contraction can be separately investigated. As mentioned before, cogwheel phenomenon and static background contraction are not two independent phenomena since the cogwheel bursts modulate the background EMG. The silent period following a burst, which results from modulation of the membrane potential of motor neurons, will affect the interburst minimum amplitude. Furthermore, a cogwheel burst is not as sharply delineated as a block, but acts as a Gaussian curve. Despite these two characteristics, it is our opinion that the interburst interval can give a good impression of the static background contraction of rigidity. By calculating the burst amplitude over an interburst interval of 50ms centred at the minimum, these characteristics will have an insignificant influence on the results.

According to the definition of UPDRS rigidity it was expected that the interburst minimum amplitude relates to the lead pipe phenomenon of rigidity and therefore is correlated with rigidity. A significant correlation was found for lengthening phase, and to a lesser extent also for the shortening phase of the muscle. The highest correlation factors were obtained from flexor signals.

Although deliberately ignored in the UPDRS definition, the cogwheel phenomenon should be considered a hallmark of parkinsonian rigidity. Therefore we chose to explore also the characteristics of the cogwheel bursts in relation to rigidity. The cogwheel burst amplitude is only correlated with clinical rigidity in lengthening phase of the muscle, but not in the shortening phase. The width of the bursts and the interburst time interval did not change with increasing rigidity. The interburst minimum amplitude and the cogwheel bursts were highly correlated. This supports the modulation model and contradicts an independent superimposition of cogwheel bursts on background EMG. The cogwheel phenomenon during muscle lengthening is a genuine characteristic of parkinsonian rigidity in which the burst amplitude correlates like the interburst minimum amplitude with rigidity scores, therefore separation of the two phenomena does not seem a necessity. However, tremor bursts could still be an interfering problem if no selection between the bursts and minima is carried out.

The recent updated version of the UPDRS, the MDS-UPDRS does not mention the inclusion or exclusion of the cogwheel phenomenon anymore [11].

Separation in lengthening and shortening phase is obligatory to overcome interference by negative rigidity, as already stated in previous chapters.

Flexor and extensor muscles are said to be equally involved in parkinsonian rigidity [12]. We found that both muscle groups reflect the changes in rigidity, however, in contralateral activation, the increase in rigidity was solely reflected in flexor muscles. This has recently been confirmed by Xia et al, who found that rigidity, measured as torque resistance, was more readily elicited during extension movement, although this was clinically not evident [13].

Despite the positive relationship between the amplitude of the background EMG and rigidity, there still is an overlap of amplitudes. One cannot accurately predict the UPDRS rigidity score from the minima or bursts in the lengthening phase. This is to be expected since many factors that vary between patients such as skin thickness, muscle mass etc. influence the amplitude of the EMG [14]. One can compensate for some of these factors by normalizing the EMG amplitude for example by dividing measured EMG amplitudes by the amplitude at maximum contraction force [1]. Because a maximum contraction often cannot be obtained in a reliable manner in practice in parkinsonian patients, we chose not to add such a normalisation procedure. Moreover, our method is designed for future application in intra operative neuromonitoring where only intra-individual changes in rigidity are important and not absolute values. We showed that individual changes in rigidity in pre- and postoperative recordings in our small patient group were adequately reflected in the lengthening phase of flexor and extensor interburst

minima. Outliers were largely found at a UPDRS rigidity score of 1. Clinical scoring of slight rigidity has a moderate inter- and intra-rater reproducibility, in contrast to moderate to severe rigidity [15;16]. This can be an explanation of the discrepancy in 2 patients (8,11). Other authors have already advocated against the use of UPDRS rigidity ratings and recommended implementation of objective quantification of rigidity [17;18]. Most recently Liu implemented EMG recordings in intra-operative neuromonitoring for tremor, dystonia and rigidity. He used the co-contraction as parameter of rigidity and dystonia [19]. Landy and Benabid used the visual decrease in amplitude of EMG during passive rigidity testing as outcome [20;21].

We believe that EMG can provide an useful assistance during intra-operative neuromonitoring in parkinsonian patients undergoing DBS procedures. Quantification of the EMG is in our opinion, necessary for objective interpretation of the results. Separation of the EMG in lengthening and shortening phase and in background contraction and cogwheel bursts add to reliable assessment of clinical rigidity.

The implementation of the SOMF method in an intra-operative neuromonitoring method will be evaluated in a prospective study.

Conclusion

The second order moment function is appropriate for detection of individual EMG noise bursts of the cogwheel phenomenon and is a powerful tool in separation of the bursts from the static background contraction. The interburst minima in the lengthening phase seem a good measure for the static background contraction of parkinsonian rigidity and can be used as such in a future intra-operative neuromonitoring. The addition 'cogwheeling ignored' in the UPDRS definition of rigidity ignores one of the major hallmarks of parkinsonian rigidity, but by ignoring this phenomenon the correlation of quantified rigidity measurement compared with clinical assessment of rigidity is increased.

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Chapter 8

General discussion and conclusion

General discussion

Parkinsonian rigidity, an increase in resistance to passive stretch of a limb is one of the major symptoms of Parkinson's disease (PD). The need for quantification of parkinsonian symptoms, in connection with objective evaluation of therapies, has been recognized for decades by many authors [1-4]. Some of these symptoms, like tremor and bradykinesia, can be quantified by accelerometers or with EMG. So far, no objective method for quantification of parkinsonian rigidity has achieved widespread implementation.

The ongoing development of neurosurgical techniques in the therapeutic armamentarium against PD and the demand for intra-operative neuromonitoring stress the need of quantification of rigidity, since in some cases rigidity is the only parkinsonian symptom present.

Large mechanical devices, measuring the resistive force or torque are hard to implement in an office setting or in an operating theatre [5-8]. EMG has played a major role in unraveling the pathophysiology of parkinsonian rigidity: different reflexes were found to correlate with a larger or lesser degree to rigidity. The long loop reflexes were thought for a long time to play a major role in parkinsonian rigidity [9-13]. More recently a prominent role has been ascribed to autogenic inhibition [14-17]. EMG in the research setting thus provides information about parkinsonian rigidity. The large arrangements for these settings, together with the variable correlations to rigidity, limit its implementation in a intra-operative setting.

To prevent these implementation drawbacks we decided to stay as close as possible to routine clinical rigidity testing. This has the advantage of being easy to implement in an intra-operative setting with the least disturbance of the patient, the best compliance of patient and doctors and the direct correspondence to the clinically applied rigidity testing.

Because rigidity is known to show fluctuations - over the day, in subsequent measurements and even within the measurement [2;3] testing during clinical rigidity measurement will minimize repercussion of rigidity fluctuations in subsequent measurements. Two methods are present for simultaneous clinical and instrumental measurement of rigidity. We chose to use EMG measurements of the agonist and antagonist muscle during movements of the limb by the examiner. The second possibility, as later was introduced by Patrick and Prochazka, is the use of force transducers during passive movements of the elbow [3;4].

Because of the wide range of correlations of EMG to parkinsonian rigidity in literature [9;10;15;18-20], we decided to analyze the EMG, before quantification, in correspondence with the definition of rigidity according to the widely used Unified Parkinson's Disease Rating Scale (UPDRS). In this clinical rating scale, rigidity is scored while the cogwheel phenomenon has to be ignored [21].

When an examiner applies large excursions, he may perceive rigidity as a continuous resisting force, the so-called lead-pipe phenomenon, sometimes interrupted in a tooth-like fashion, the cogwheel phenomenon.
The two components of rigidity, the lead pipe phenomenon and the cogwheel phenomenon could be distinguished in the EMG signal. The cogwheel phenomenon was visible as a burst pattern with an irregular interval. The increase in EMG amplitude, as expected from the definition 'during stretch of the muscle', was most markedly present in the lengthening phase of the muscle. The cogwheel phenomenon was also more pronounced in the lengthening phase of the muscle. After a surgical intervention in which rigidity was abolished, EMG amplitudes decreased, thereby confirming the applicability of EMG in rigidity quantification. It was decided that – in concordance with the UPDRS - the cogwheel phenomenon should be filtered from the EMG signal before calculation of amplitudes. Because of the irregular occurrence of the cogwheel phenomenon, conventional filtering methods like Fourier Transform failed.
In chapter 5 the cogwheel phenomenon was filtered from the background EMG by use of time variant wavelet transform. The power of the filter was determined by the level setting. An optimum filter level for extracting the static component from the EMG was found at level 0.08. No cogwheel bursts were present in the static component at this level. Quantification of this static component showed moderate correlation with simultaneously-assessed clinical rigidity for flexor muscles. However, the unprocessed EMG and to a lesser extent the dynamic component of the EMG of the flexor muscles also showed correlations with clinical rigidity, although not as high as the static component. The extensor muscles did not show significant correlations between EMG amplitude and clinical rigidity. The implementation of the technique as an intra-operative neuromonitoring method however, was restricted by two problems. Tremor and negative rigidity yielded high amplitudes in patients with no or slight rigidity. It was not expected beforehand that tremor would interfere with the static component amplitude because of the filtering, but for tremor EMG a level of 0.08 was not suitable. In negative rigidity the patient assisted in the movement made by the examiner. This was previously recognized by Meara and Cody [9], who calculated a ratio between lengthened muscle and the simultaneous shortened muscle and correlated this to rigidity. They found that the stretch-related EMG corresponded to rigidity in the more rigid patients. The ratio improved the correlation with clinical rigidity, but only in patients with high clinical rigidity scores.
This ratio is susceptible to basic amplitude differences between flexor and extensor muscles as in our patient group. Division of the EMG into shortening and lengthening phases for each muscle showed high correlations of the lengthening phases of flexor and extensor muscles with clinical rigidity. However, also the shortening phase of the muscle was increased in increasing rigidity and showed a correlation with clinical rigidity, although to a lesser extent. The ratios used by

Meara, did not have a significant correlation with clinical rigidity in our patient group.

To overcome the problems of negative rigidity and tremor, we developed a balance coefficient between lengthened and shortened muscles, in which both muscle groups were concerned. By using a logarithmic function, a balance coefficient of zero would imply the muscles to be in balance. The theory would imply a negative ratio to represent negative rigidity and a positive balance coefficient to represent rigidity. The balance coefficient was expected to increase with increasing rigidity, reaching a platform followed by a decrease due to co-contraction. The study confirmed this pattern. However, the values of the balance coefficient were shifted towards zero and negative balance coefficients. The flexor and extensor muscles did not contribute equally to rigidity. The balance coefficient proved a useful tool for identification of negative rigidity and subsequent exclusion of the high EMG amplitudes. The balance coefficient as a quantification tool in rigidity testing seemed less useful. The balance coefficient of around zero could not assist in identifying tremor interference, as had been one of our hypotheses. We concluded that the balance coefficient is a helpful tool in identifying negative rigidity, but not suitable for quantification of rigidity. The division of the epoch into lengthening and shortening phases seemed obligatory to avoid interference of negative rigidity. In splitting the epoch, the cogwheel phenomenon was still present in the EMG segments. A method for individual identification of the bursts was developed in chapter 7. The second order moment function (SOMF) is based on the assumption that the bursts and the background contraction are modulated instead of superimposed. The parameters of the SOMF concerning the window width and the level were adapted to the expected burst width and repetition time of the bursts, but these cover a large frequency range. After identification of the bursts, characterization of the cogwheel phenomenon bursts and of the interburst amplitudes were carried out. The interburst amplitudes showed a good correlation with clinical rigidity, especially in the lengthening phase. The silent period could in theory influence the interburst amplitude, but in practice this was not the case.

The cogwheel phenomenon bursts in the lengthening phase of the muscle movement showed a correlation with clinical rigidity, in contrary to the shortening phase. We concluded that the cogwheel phenomenon plays a role in rigidity. The phrase 'cogwheeling ignored' in the definition of rigidity in the UPDRS therefore ignores one of the major characteristics of parkinsonian rigidity. Filtering of the cogwheel phenomenon from the background contraction therefore seemed not necessary in the lengthening phase. The additional value of SOMF compared to amplitude of unprocessed EMG in lengthening phase is the slight improvement of correlation with rigidity, and the possibility of filtering of tremor components from the EMG signal. For future use in an intra-operative neuromonitoring method both the SOMF method and the EMG amplitude in lengthening phase would yield acceptable results. The latter is more easy to implement and thus preferred.

The use of clinical rigidity scales in this study as a 'gold' standard is a compromise between accepted rigidity scoring and the absence of an objective standard. The UPDRS is widely accepted and used and has shown good reproducibility for most items, whereas reproducibility for the rigidity item is fair [22-24]. The use of contralateral activation in rigidity testing adds to the non-linearity of the UPDRS rigidity scoring. The use of contralateral activation in a study should be limited to comparison of rigidity testing without and with contralateral activation to explore an increase in rigidity and not for determining the presence of 0 or 1 rigidity. In 2008 an update on the UPDRS, the MDS-UPDRS was published, in which a score of 1 concerns rigidity only during contralateral activation. A score of 2 concerns mild rigidity without contralateral activation [25]. Prochazka and Patrick advocated the use of Système International (SI) units instead of the use of the UPDRS rigidity scale, but questioned the acceptance of the SI units in daily practice [3;4].
The use of EMG amplitudes expressed as μV is according to the terms of SI units and would provide clear results, which can easily be interpreted by the clinician, especially in follow-up measurements.
To our knowledge few other groups have been using EMG in the operating theatre and have used the decrease of the amplitude as outcome measure of rigidity [26-28]. Recently Levin et al. used EMG as objective measurement of rigidity in patients treated with subthalamic stimulation and concluded that EMG can potentially be useful for quantifying rigidity in the operating setting [29]. Further prospective studies will be necessary to study the correlation with clinical rigidity in a larger patient group, and the implementation of quantified EMG in intra-operative neuromonitoring and its implications in decision making. The use of EMG amplitude in lengthening phase can be used as an outcome measure in these studies.
Further development of techniques for anatomical positioning and microelectrode recordings until now have not made rigidity assessment as outcome measure superfluous, but rather have increased the need for ongoing attempts of quantification of rigidity.

Conclusion of this thesis

The ongoing development of neurosurgical therapies for parkinsonian patients stresses the need for quantification of rigidity. EMG seems useful as an outcome measure since the EMG contains information regarding the lead pipe phenomenon and the cogwheel phenomenon in parkinsonian rigidity. Wavelet analysis proved suitable for separation of the background contraction of the EMG and the burst pattern of the cogwheel phenomenon. Separation of these parts by wavelet transform did however not improve quantification of rigidity, because negative rigidity and tremor disturbed correlation with clinical rigidity.

The balance coefficient was computed from lengthening and shortening phases and was developed for detection of tremor and negative rigidity; it was not suitable for rigidity detection, but provided a cut-off under which the EMG amplitudes could be attributed to negative rigidity and thus could be rejected or nulled.

Second order moment filtering, a new developed method for signal analysis, was effective in separation of background EMG and cogwheel phenomenon. In the lengthening phase of the muscle movement, both parts of the EMG showed high correlations with clinical rigidity suggesting that the addition 'cogwheeling ignored' in UPDRS rigidity scoring is not a necessity. Correlation was however slightly improved by filtering the cogwheel phenomenon and tremor interference diminished. The methods for separation of cogwheel phenomenon from background contraction can furthermore be used to improve understanding of pathophysiology of cogwheeling.

Both the unfiltered and the static component of the EMG in lengthening phase can be used as outcome measure for parkinsonian rigidity in intra-operative neuromonitoring in future studies.

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Chapter 9

Summary

Parkinson's Disease (PD) is characterized by typical motor and non-motor symptoms one of which is rigidity. Today numerous therapy strategies exist. In the last decades, patients with symptoms refractory to medical therapy became candidates for neurosurgical interventions. Targeted areas for ablation or deep brain stimulation are thalamus, pallidum and subthalamic nucleus (STN).
Next to anatomical positioning, neurophysiological assessment is essential for optimal positioning of the electrodes in these procedures. Proper positioning of the electrodes is based on MR/CT based anatomical positioning in a stereotactic frame, micro-electrode recordings for neurophysiological positioning, low frequency stimulation to detect interference with internal capsule fibers and high frequency stimulation for evaluation of clinical improvement of the symptoms and of side effects.
The ongoing development of neurosurgical therapies and consequent demand for intra-operative neuromonitoring have stressed the need for quantification of rigidity, since in some procedures (targeted pallidum and STN) rigidity is one of the few parkinsonian symptoms which are present.
Rigidity to date is assessed clinically by flexion and extension of the limb by the examiner and scored according to the rigidity item of the Unified Parkinson Disease Rating Scale, on a 5 point scale as mentioned in chapter 3.
The need for objective rigidity testing has been recognized for a long time, but has not resulted in a generally accepted method. This thesis focuses on a method for quantification of rigidity which is applicable in intra-operative neuromonitoring.
The definition and the pathophysiology of rigidity are described in chapter 2.
Rigidity is an increased resistance to passive stretch, irrespective of the direction and the velocity of the movement. Flexor and extensor muscles are both involved. Parkinsonian rigidity consists of the lead pipe phenomenon, a continuous resistance, sometimes interrupted in an intermittent fashion, the cogwheel phenomenon. Despite abundant clinical and neurophysiological data the patho-physiology of rigidity is still not fully understood. The cogwheel phenomenon may represent action tremor, because of its frequency between 7 and 14 Hz. The lead pipe component is thought to be the result of altered neuronal mechanisms. The basal ganglia circuitry plays a major role in PD and influences descending pathways, but can not solely explain rigidity. The alteration of long loop reflexes were thought for a long time to form the pathophysiological mechanism of parkinsonian rigidity, but nowadays a large role is attributed to autogenic inhibition. Descending pathways act in different ways on Ia and Ib interneurons at the spinal level and give rise to increased firing of alpha motor neurons. The basal ganglia circuitry influences the Ib interneurons indirectly via relays in the tegmentum and reticular formation. From the nucleus reticularis giganto cellularis (NRGC) the reticulospinal tract descends and acts in different ways on the Ia and Ib interneurons. The long loop reflexes in this model are thought to act as a compensatory mechanism.

In this pathophysiological model the firing of the alpha motor neurons is altered. Since EMG measures activity of motor-units; the motor neuron and the population of muscle fibers it innervates, EMG should be able to quantify rigidity.
Chapter 3 describes the general material and methods used in this thesis.
In chapter 4 a pilot study of parkinsonian patients and control subjects showed that the cogwheel phenomenon was present in the EMG's of the parkinsonian patients as a burst pattern. Control subjects did usually not show this burst pattern. This cogwheel phenomenon was predominantly present during lengthening of the muscle. Traditional filtering methods were not appropriate for retrieving the power spectral components of cogwheel bursts due to the irregular pattern of the bursts and the presence of demodulation noise.
In parkinsonian patients the amplitude of the EMG was larger in lengthening phase of the muscle, than in shortening phase. No significant differences in amplitudes of patients and control subjects were identified in this small group. The patient group showed a decrease in clinical rigidity in postoperative recordings compared to preoperative recordings. This was reflected in a decrease of EMG amplitude of flexor muscles.
Since the clinical definition of rigidity states that the cogwheel phenomenon should be ignored, we decided to split the EMG signal into a background contraction component and a burst pattern component. Since traditional filtering methods failed in such a separation of the cogwheel phenomenon, we introduced an application of wavelet filtering, described in chapter 5, to achieve this goal.
A time variant wavelet filter was adapted for use in EMG signals. The separating power between background and burst pattern component is dependent on the discrimination level selecting the wavelet coefficients. A discrimination level of 0.08 showed a good separation between background activity and the bursts. The choice of the wavelet type did not contribute significantly to the separation of bursts.
After separation of bursts and background contraction, the amplitude of the unprocessed EMG, the static background EMG and the dynamic EMG (bursts) were calculated and compared to clinical rigidity. Maximum correlation was found for static background EMG of flexor muscles, whereas extensor muscle EMG did not show any correlation with clinical rigidity. The moderate correlation was mainly attributed to assistance of the patient in the movement made by the examiner in non-rigid states: so-called negative rigidity. A minor role was due to interference of tremor.
To overcome these problems we developed the balance coefficient as described in chapter 6. Since rigidity is predominantly present in the lengthening phase in the muscle, and active contraction is present in the shortening phase of the muscle, the balance coefficient is a logarithm of a ratio of EMG amplitudes of lengthening and shortening phase of the muscles. A positive balance coefficient indicates rigidity, whereas a negative balance coefficient indicates negative rigidity. The balance coefficient was not able to predict presence of tremor. There appeared to

be a proportional relationship between the balance coefficient and clinical rigidity in the range of rigidity scores of 0 - 2. However the balance coefficient did not correlate to rigidity when taking into account the whole rigidity scale. EMG amplitudes in the lengthening phase of both flexor and extensor muscles correlated with clinical rigidity, underlining the need for separation in lengthening and shortening phase. In the methods so far studied, the cogwheel bursts were not selectively excluded from the EMG signals in conformation with the UPDRS definition for rigidity. A more precise comparison was expected from a new analytical method in which burst detection is pivotal.

In chapter 7 second order moment filtering (SOMF) as a tool for cogwheel burst recognition was introduced. By individual recognition of bursts in the lengthening and shortening phases of the muscles, the characteristics of the bursts and the interburst amplitudes could be investigated. Amplitudes of the bursts as well as interburst amplitudes in the lengthening phases of the muscles proved to correlate with clinical assessment of rigidity, in contrast to the burst amplitudes in the shortening phase. The background contraction in the shortening phase correlated with rigidity to a lesser extent.

Other individual characteristics of the bursts – such as burst width - did not correlate to clinical rigidity. We concluded that, despite the phrase 'cogwheeling ignored' the cogwheel burst is one of the hallmarks of parkinsonian rigidity. The correlation between quantified EMG and clinical rigidity scores improves when cogwheel bursts are selectively removed. Moreover, removal of bursts also applies to tremor bursts, which reduces the interference of tremor.

It is concluded that both the EMG amplitude in the lengthening phase of the muscle and the interburst minimum in the lengthening phase can be used for quantification of parkinsonian rigidity and seem to be applicable for intra-operative neuromonitoring of stereotactic neurosurgical interventions in parkinsonian patients.

Chapter 10

Samenvatting
Dankwoord
Curriculum Vitae

Samenvatting

De ziekte van Parkinson wordt gekenmerkt door specifieke motore en niet-motore symptomen, waaronder rigiditeit. Naast de uitgebreide medicamenteuze therapieën bestaat tegenwoordig ook de mogelijkheid tot neurochirurgisch ingrijpen bij patiënten met pathologische adaptatie aan de medicatie. Hierbij kan een electrode worden ingebracht in de diepe delen van de hersenen, waarna een kleine laesie kan worden aangebracht (coagulatie) of een electrode definitief kan worden achtergelaten om deze gebieden te stimuleren (DBS). De doelgebieden voor coagulatie of stimulatie in het brein zijn de thalamus, de globus pallidus en de subthalamische nucleus (STN).
Tijdens deze procedures wordt gebruik gemaakt van anatomische positionering. Hiernaast speelt neuromonitoring een essentiële rol voor de optimale plaatsing van de elektrode.
De anatomische positionering maakt gebruik van beeldvormende technieken zoals CT en MRI, waarbij het hoofd van de patiënt in een stereotactisch frame is geplaatst. Micro-elektrode registraties worden gebruikt om de elektrische signalen vanuit de diverse structuren te registreren, om op deze manier zorg te dragen voor een optimale neurofysiologische positionering. Laagfrequente stimulatie van de elektrode dient om mogelijke interferentie met de vezels van de capsula interna op te sporen. Hoogfrequente stimulatie wordt gebruikt om het gewenste effect op de symptomen te controleren en eventuele bijwerkingen te detecteren.
De verdergaande ontwikkelingen van de therapeutische mogelijkheden hebben geleid tot een toegenomen vraag naar objectieve vastlegging van de symptomen. In onze huidige intra-operatieve monitoring kunnen tremor, fingertapping en diadochokinese reeds worden geobjectiveerd. Voor rigiditeit, in sommige procedures een van de weinig aanwezige symptomen, is nog geen objectieve meetmethode beschikbaar.
Op dit moment wordt de rigiditeit klinisch bepaald door het flecteren en extenderen van een ledemaat door een onderzoeker. Hierna wordt gescoord volgens een 5-punts schaal van de Unified Parkinson's Disease Rating Scale (UPDRS).
Alhoewel al zeer lange tijd de noodzaak wordt erkend om rigiditeit te objectiveren, heeft dit tot op heden niet geleid tot een geaccepteerde objectieve meetmethode.
Dit proefschrift richt zich op het ontwikkelen van een methode voor objectieve bepaling van de rigiditeit bij parkinsonpatiënten, passend binnen de huidige intra-operatieve neuromonitoring.
De definitie en pathofysiologie van rigiditeit worden beschreven in hoofdstuk 2. Rigiditeit is een toegenomen weerstand op passieve rek van de spier, onafhankelijk van de richting en de snelheid van de beweging. Zowel flexoren als extensoren zijn betrokken.

Parkinsonrigiditeit bestaat uit een loden pijp fenomeen, een zogenaamde continue weerstand, soms onderbroken door het tandrad fenomeen. Ondanks de uitgebreide klinische en neurofysiologische data is het pathofysiologische mechanisme nog steeds niet ontrafeld. Het tandrad fenomeen wordt toegeschreven aan het dóórbreken van actie tremor, gezien de overeenkomst in frequentiegebied tussen de 7 en 14 Hz. Veranderde neuronale mechanismen zouden ten grondslag liggen aan het loden pijp fenomeen. Een verandering in het circuit van de basale kernen speelt een belangrijke rol bij de ziekte van Parkinson en beïnvloedt meerdere afdalende banen, maar kan op zichzelf de rigiditeit niet verklaren. Lange tijd werd gedacht dat veranderingen in de 'long loop reflexen' ten grondslag lagen aan de parkinsonrigiditeit, maar tegenwoordig wordt een belangrijke rol toegeschreven aan autogene inhibitie. Verschillende afdalende banen hebben verschillende invloed op Ia en Ib interneuronen op spinaal niveau en leiden tot een toegenomen vuren van alfa-motorneuronen. Het circuit van de basale kernen beïnvloedt de Ib interneuronen indirect via relais in het tegmentum en de reticulaire formatie. Vanaf de Nucleus Reticularis Giganto Cellularis daalt de tractus reticulospinalis af en beïnvloedt op verschillende manieren de Ia en Ib interneuronen. De veranderingen die worden waargenomen in de long loop reflexen worden in dit model verklaard als compensatoir mechanisme.
In dit pathofysiologische model is het vuren van de alfa-motorneuronen veranderd. Aangezien EMG het resultaat is van de activiteit van motorunits, zou dit de mogelijkheid moeten bieden om hieruit een maat voor rigiditeit te herleiden.
Hoofdstuk 3 beschrijft in het algemeen het materiaal en de methoden welke werden gebruikt in dit proefschrift.
In hoofdstuk 4 is een pilot studie gedaan met parkinsonpatiënten en een controle groep.
Deze toonde aan dat het tandrad fenomeen kon worden geïdentificeerd in het EMG als een burstpatroon. De controlepersonen toonden dit burstpatroon niet. Het tandrad fenomeen was met name zichtbaar tijdens verlengen van de spier. Traditionele filtermethoden bleken niet in staat om het tandrad fenomeen te karakteriseren en te filteren. De oorzaak was gelegen in het onregelmatige aspect van de bursts, tezamen met de aanwezigheid van demodulatie ruis.
Bij parkinsonpatiënten was de amplitude van het EMG groter tijdens de verlengingsfase van de spier dan tijdens de verkortende fase. In deze kleine groep bleken geen significante verschillen te bestaan tussen de patiënten en de controlepersonen. De patiëntengroep toonde een afname van de klinische rigiditeit in de postoperatieve metingen in vergelijking met preoperatief. Dit was zichtbaar in een afname van de EMG amplitude van de flexor spieren.
De klinische definitie van rigiditeit vermeldt dat het tandrad fenomeen moet worden uitgesloten, om deze reden werd besloten om de achtergrondcontractie en het burst patroon te scheiden.

Aangezien traditionele filter methoden, zoals fourier transformatie, niet in staat bleken tot een goede scheiding, introduceerden we een toepassing van wavelet filtering in hoofdstuk 5.
Een tijdsvariant wavelet filter werd aangepast voor het gebruik in de EMG signalen. Het scheidend vermogen tussen de achtergrondscontractie en de burstpatronen bleek afhankelijk van het discriminerende level welke de wavelet coëfficiënten selecteert. Een discriminatie level van 0.08 toonde een goede scheiding tussen de achtergrondscontractie en de bursts. De keuze van het wavelet type bleek niet duidelijk bij te dragen aan de mate van scheiding van de bursts.
Na scheiding van bursts en achtergrondcontractie, werden een drietal amplitudes berekend: van het onbewerkte EMG, de statische achtergrondcontractie en het dynamische EMG (de bursts). Deze werden vergeleken met de klinische rigiditeit.
De hoogste correlatie werd gevonden voor de statische achtergrondcontractie van de flexoren, terwijl de extensoren geen correlatie vertoonden met de klinische rigiditeit. De matige correlatie werd toegeschreven aan een aantal factoren, waarvan de belangrijkste negatieve rigiditeit leek te zijn, het actief aanspannen van de spieren bij afwezigheid van klinische rigiditeit, terwijl interferentie met tremor in mindere mate leek bij te dragen.
Om voor deze problemen een oplossing te vinden, ontwikkelden wij de balance coefficient (BAL), welke wordt beschreven in hoofdstuk 6. Rigiditeit is met name aanwezig in de verlengingsfase van de spieren. Actieve contractie bij negatieve rigiditeit is met name aanwezig in de verkortingsfase van de spieren. De BAL is een logaritme van de verhouding tussen de verlengingsfase en de verkortingsfase van de spieren. Een positieve BAL geeft op deze manier rigiditeit aan, terwijl een negatieve BAL negatieve rigiditeit impliceert.
De hypothese dat de BAL de aanwezigheid van tremor zou kunnen detecteren, bleek niet te worden bevestigd. Er was een proportionele relatie tussen de BAL en de klinische rigiditeit in de lagere range van rigiditeitsscores (0-2). De BAL correleerde echter niet met rigiditeit als de gehele rigiditeitsschaal inclusief de hogere rigiditeitswaarden werd betrokken bij de analyse.
De amplitude van het EMG tijdens de verlengingsfase van zowel flexoren als extensoren correleerde met de klinische rigiditeit, waarmee de noodzaak van scheiding in een verlengingsfase en verkortingsfase werd bevestigd.
Het bleek erg lastig om in de hierboven gebruikte signaal analyse methoden een selectieve exclusie te bereiken van de (tandrad) bursts. Een nauwkeurigere analyse van de bursts werd verwacht van een nieuwe methode van signaalanalyse, waarin burst detectie centraal staat.
In hoofdstuk 7 werd de second order moment filtering (SOMF) geïntroduceerd. Door individuele herkenning van de bursts in de verlengings- en verkortingsfase van de spieren, konden zowel de karakteristieken van de bursts als de amplitude tussen de bursts (interburst) worden onderzocht. Amplituden van zowel de bursts als de interburst amplituden correleerden met de klinische rigiditeit. De

achtergrondcontractie in de verkortingsfase (interburst) correleerde in mindere mate met de klinische rigiditeit, terwijl de bursts in de verkortingsfase niet correleerden.
Andere individuele karakteristieken van de bursts, zoals de wijdte van de burst, correleerden niet met de klinische rigiditeit.
Wij concludeerden dat, ondanks het feit dat in de UPDRS definitie staat dat het tandrad fenomeen moet worden buitengesloten, dit een van de kenmerken is van parkinsonrigiditeit. De correlatie van EMG amplituden en klinische rigiditeit verbeterde echter wel wanneer de bursts selectief werden verwijderd. Ook is er minder interferentie van tremor bij selectieve verwijdering van de bursts.
Zowel de EMG amplitude in de verlengingsfase van de spier en de interburst amplitude kunnen worden gebruikt voor kwantificering van parkinsonrigiditeit en zijn geschikt voor intra-operatieve neuromonitoring.

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Curriculum vitae

De auteur van dit proefschrift werd geboren op 1 april 1970 te Grijpskerk. Van 1982 tot 1988 doorliep zij het Atheneum aan het Lauwers College te Buitenpost. Ze volgde ze de inservice opleiding voor radiodiagnostisch laborant in het Medisch Centrum Leeuwarden (MCL) te Leeuwarden van 1989-1992. Vervolgens werkte ze als radiodiagnostisch laborante in het MCL tot 1994. Vanaf 1994 studeerde ze geneeskunde aan de faculteit Medische Wetenschappen van de Rijksuniversiteit van Groningen waar ze in 1998 haar doctoraal examen haalde ('cum laude') en in 2000 haar artsexamen ('cum laude').
Tijdens haar studie begon ze met wetenschappelijk onderzoek op de afdeling neurochirurgie wat uiteindelijk resulteerde in dit proefschrift. Na haar studie werkte ze van 2000 tot en met 2001 als AGNIO op de afdeling neurochirurgie van het Academisch Ziekenhuis Groningen (thans UMCG). In 2002 begon ze aan haar opleiding tot radioloog in het Academisch Ziekenhuis te Maastricht, welke ze voltooide in april 2007. Tijdens het laatste jaar van haar opleiding startte ze met het twee jaar durende fellowship neuroradiologie te Maastricht.
Momenteel is ze werkzaam als neuroradioloog in het MUMC+ in Maastricht.
Ze is getrouwd met Foppe Jacobi en heeft twee dochters Gerianne (2004) en Rixt (2006) en een zoon Willem-Thijs (2008).