Multi-channel array EMG in chronic neck-shoulder pain

Laura A.C. Kallenberg

Address of correspondence:

Laura Kallenberg
Roessingh Research and Development
PO Box 310
7500 AH Enschede
The Netherlands
+31-(0)53-4875767
l.kallenberg@rrd.nl

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MULTI-CHANNEL ARRAY EMG IN CHRONIC NECK-SHOULDER PAIN

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Voorzitter:

Prof. dr. ir. A.J. Mouthaan	Universiteit Twente

Promotor:

Prof. dr. ir. H.J. Hermens	Universiteit Twente

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Dr. M.M.R. Vollenbroek-Hutten	Roessingh Research and Development

Paranimfen:
Dr. Gerlienke Voerman
Ir. Cornelie van Driel

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Chapter 1

Introduction

Introduction

Chronic muscular pain has become an important problem in the industrialised countries, affecting a considerable part of the working population. The Third European Survey on working conditions in acceding and candidate EU countries in 2000 revealed that 23% of the workers in the EU countries report muscular pain in the neck-shoulder region (Paoli & Parent-Thirion 2003). In terms of prevalence, muscular pain is the third work-related health problem in the EU, only preceded by backache (34%) and stress (28%). Comparable figures have been reported for the United States (Bernard 1997) as well as for Australia and Japan (Bammer 1990). The prevalence is higher in females than in males (Strazdins & Bammer 2004).
Punnett and Wegman in a recent review state that the term musculoskeletal disorders refers to

"a wide range of inflammatory and degenerative conditions affecting muscles, tendons, ligaments, joints, peripheral nerves, and supporting blood vessels. [...] Body regions most commonly involved are the low back, neck, shoulder, forearm, and hand, although recently the lower extremity has received more attention."
(Punnett & Wegman 2004)

This definition stresses that the term 'musculoskeletal disorders' is an umbrella term for a range of conditions that are not all clinically well-defined. Subjective symptoms include constant muscle pain, muscle fatigue and/or stiffness, and radiating pain. Various related terms, such as chronic pain, repetitive strain injury and self-reported musculoskeletal complaints are also commonly used in the literature.
Several risk factors, related to development of musculoskeletal disorders have been identified. In 1997, the National Institute of Occupational Health in the United States performed an extensive systematic review of the epidemiologic literature on upper extremity musculoskeletal disorders and workplace factors, including over 600 studies (Bernard 1997). Evidence was found for causal relations between musculoskeletal disorders in neck and/or shoulder and exposure to awkward posture, repetitious movements and/or high force demands. Furthermore, despite the low force levels required, computer workers are particularly at risk to develop neck-shoulder complaints (Bongers et al. 2002, Jensen 2003). Beside physical work factors, psychosocial risk factors such as stress, high job demands and low vocational satisfaction have been identified (Bongers et al. 2002). Stress may keep a muscle activated even if there is no demand for muscle activity from a biomechanical perspective (Lundberg et al. 2002). A variety of

individual factors such as age, body mass index and perception of intensified work load are also considered to play a role in the development of chronic pain complaints (Bernard 1997).

Despite the identification of these risk factors, the etiology of the development of chronic pain is unclear. Several pathophysiological models describing the underlying mechanisms have been proposed (Hägg 1991, Johansson & Sojka 1991, Lund et al. 1991). These models have in common that they predict changes in motor control, reflected in muscle activation patterns. However, these models propose different working mechanisms and consensus on the nature of the changes in motor control is lacking. A better understanding of the underlying mechanisms is an important prerequisite for development of effective treatment methods. Model-based experimental studies assessing motor control in chronic pain cases in a non-invasive way may provide more insight into these mechanisms.

Chronic neck-shoulder pain

Extensive research during the last decades has been directed towards unravelling the mechanisms that underlie the development of chronic pain. Several models have been proposed and experimental evidence that supports some of them has been reported, but the etiology of the development of chronic pain remains controversial. In this section, the most important models that have been proposed are presented.

As early as 1942, Travell et al. proposed the pain-spasm-pain model as explanation for the development of chronic muscle pain (Travell et al. 1942). This model suggests a positive feedback loop consisting of muscle pain, causing a spasm which in turn leads to increased muscle pain. The spasm is proposed to occur as a result of local ischemia. The authors did not elaborate on possible neural pathways that would constitute this vicious circle. In 1987, Berberich et al. suggested the γ-motor neuron system to play a role: muscle tone would lead to ischemia, which would activate nociceptors, projecting to the γ-motor neuron system (Berberich et al. 1987). Increased activity of the γ-motor neuron system would lead to Ia muscle afferent activation that results in excitation of the α-motor neurons, leading to increased muscle tone. Johansson and Sojka (1991) extended this model with a chemical and/or mechanical interaction on the γ-motor neuron system via group III (or Aδ) and IV (or C) muscle afferents, that are sensitive to metabolites resulting from muscle contraction. Their model also includes the projection of III and IV afferents on the γ-motor neuron system of heteronymous muscles. The model was further extended with a second positive feedback loop, related to the role of group II afferents. Activity of group III and IV afferents would not only lead to more activity of Ia afferents, but also to more activity of group II afferents. Group II afferents project on the γ-motor neuron

system, thereby increasing the sensitivity of the muscle spindles, which would in turn lead to higher activity of the group II afferents. Johansson and Sojka suggested that once a threshold has been exceeded, this loop would not depend on input from group III and IV afferents, but would be able to maintain itself.

The vicious circle model that Johansson and Sojka proposed aims at explaining the spread of pain to other muscles, as well as the prolonged duration of the pain after contractions. In a review of the vicious circle model, Knutson (2000) concluded that although there is evidence from animal experiments that support the hypothesis, it cannot yet be considered proven due to lack of data in human subjects. A few years later however, it was shown that experimental pain, induced by insertion of hypertonic saline leads to changes in reflex activity of muscle spindle afferents from homo- and heteronymous muscles in humans (Thunberg et al. 2002).

The vicious circle model as proposed in 1991 was adapted by Johansson et al. (2003) to reflect another feedback mechanism that relates pain to muscle activity. This mechanism consists of a decreased propriocepsis due to nociception, which leads to less precision in motor control tasks. To reach high precision in spite of this, co-contraction levels are increased, which means that muscle activity is increased. Experimental findings supporting a decreased propriocepsis have been found by Revel et al. (1991) who showed a decreased ability to relocate the head position with respect to the trunk after an active head movement in cases with cervical pain. Similar results were found by Sarnoch who showed a decreased ability to discriminate different levels of muscle activity of the trapezius muscle in cases with fibromyalgia (Sarnoch 1995). In a study with primates was shown that highly repetitive, articular finger squeezing can lead to deterioration of the hand representation on the primary sensory cortex (Byl et al. 1997).

In contrast to the vicious circle model, which predicts increased activity of the painful muscle as well as secondary muscles, the pain adaptation model, proposed by Lund (1991) predicts a task-dependent decrease in activity of the agonist together with an increase in antagonistic activity as a result of pain. These changes in muscle activation will cause a reduction of movement, which may act as protection of the painful muscle. In this model is assumed that group III and IV afferents project to α-motor neurons via both excitatory and inhibitory interneurons. The increase in antagonist activity and the decrease of agonist activity is assumed to be caused by the central motor command, that includes excitation of the inhibitory interneuron of the agonist, and inhibition of its excitatory interneuron, while it also includes inhibition of the inhibitory interneuron of the antagonist, and excitation of its excitatory interneuron.

Several indications that support the pain adaptation model have been found. Recently, a study with patients with whiplash-associated disorder showed a decreased muscle activity in the trapezius muscle during a 90 degrees shoulder abduction task (Nederhand et al.

2003). Furthermore, the effect of experimental muscle pain has been shown to be supportive of the pain adaptation model. Graven-Nielsen et al. (1997) found decreased agonistic and increased antagonistic activity during gait in response to experimental pain, elicited by insertion of hypertonic saline. A similar reorganization of muscle synergy was found in a study by Madeleine et al. (1999).

Probably the most widely used hypothesis for the development of chronic muscular pain in work requiring low force levels is the Cinderella hypothesis, proposed by Hägg (1991). This hypothesis suggests that muscle fibres of low-threshold motor units (MUs) are getting damaged because of lack of sufficient muscle relaxation. The hypothesis is based on two corner stones. The first one is the Henneman principle, which states that MUs are recruited in a stereotyped way (Henneman et al. 1965). The second one is the finding of an increased percentage of ragged red fibres, indicative of structural cell membrane damage, in cases with trapezius myalgia.

Substantial empirical findings support this hypothesis. MUs that stay continuously active for long periods of time (several hours) during low-level, static contractions have been found in studies using intramuscular electromyography (EMG) recordings (Forsman et al. 2002, Lundberg et al. 2002, Thorn et al. 2002, Zennaro et al. 2003a, Olsen et al. 2001). It has also been shown that the same MUs stay active when task requirements change (Kadefors et al. 1999).

Further support of the Cinderella hypothesis emerged from EMG studies in cases with chronic pain. Elert et al. (1992) demonstrated an inability to relax in trapezius myalgia patients. This was confirmed by a study of Nederhand et al. (2000) in cases with whiplash associated disorder. This study showed that the time before the EMG activity reached baseline level again after performing a physical task was longer in pain cases than in healthy controls. Other authors reported a decreased percentage of muscle rest, measured as short silent periods in the EMG ('gaps'), in chronic pain patients (Veiersted 1994; Hägg and Åström 1997). In another study was shown that lack of gaps was a weak but significant predictor for the development of pain (Veiersted et al. 1993).

Although there is a substantial amount of empirical findings that supports the Cinderella hypothesis, the hypothesis itself does not clarify the underlying mechanisms that cause changes at the level of the muscle cells, and how this leads to development of pain. Biopsy studies might give more insight in such mechanisms. In a review (Hägg 2000) of biopsy studies it was concluded that the percentage of type I fibres is higher cases with myalgia. The fibre diameter of both type I and type II fibres was increased in cases with myalgia as well as in subjects exposed to occupational risk factors, compared to unexposed healthy subjects. Metabolic homeostatis (measured by ATP content and presence of COX negative fibres) was more disturbed in subjects with myalgia and in exposed subjects than in unexposed healthy subjects. A higher number of so-called ragged red fibres, indicative

of structural damage to cell membrane and mitochondria, was found in cases with myalgia and exposed subjects compared to healthy unexposed subjects.
Furthermore, there is evidence for development of muscle damage in rabbits due to low-intensity loading (Lexell et al. 1993). Low-frequency stimulation experiments showed that muscles that were continuously stimulated showed more degeneration than intermittently stimulated muscles. Additionally, a low-level repetitive reaching task that was performed by rats for up to 8 weeks resulted in increased levels of cytokine and macrophages, indicative of tissue responses associated with inflammation (Barbe et al. 2003). Other studies found that arterial blood flow and micro-circulation were decreased in cases (Larsson et al. 1990; 1999, Sharma et al. 1997, Pritchard et al. 1999, Gold et al. 2004). Based on the finding that long-term low-frequency stimulation leads to accumulation of Ca^{2+} in rat skeletal muscles, Gissel (2000) suggested that Ca^{2+} accumulation plays a causative role in the development of chronic muscle pain. In a recent review was concluded that limitation of the blood circulation plays a role, but it remains unclear whether this is a cause or rather a consequence of the musculoskeletal disorder (Visser & van Dieën 2006). These authors further concluded that there is indication that disorders of muscle cells, such as e.g. damage to the cell membrane or disturbed mitochondrial activity underlie musculoskeletal disorders in the upper extremity.
In summary, a considerable number of empirical findings support the Cinderella hypothesis. Regarding the two other models, describing the underlying neurophysiological pathways that are involved in chronic pain development, there seems to be more evidence for the vicious circle model than for the pain adaptation model. Additional research is needed to obtain more insight into the pathophysiology, which is a prerequisite for development of effective diagnosis and treatment possibilities. A more precise investigation of muscle activity at the level of MUs might be of help to clarify part of the complicated mechanisms that underlie the development of chronic pain.

Assessment of muscle activity

Muscle activity of muscles that are located superficially can be assessed non-invasively with surface EMG by placing two electrodes at the skin above a muscle, parallel to the direction of the muscle fibres. The signal that is obtained in this manner consists of a weighted summation of the spatial and temporal activity of many MUs that is volume conducted from the muscle to the skin.
When a MU is activated, an action potential propagates along the α-motor neuron from the spinal cord to the neuromuscular junction, where it is transferred to the muscle fibres. When the action potential reaches the muscle fibres, their membranes, that are polarized with negative Cl^- ions at the inside and Na^+ ions at the outside of the cell, become

depolarized. The depolarization wave propagates along the fibre in two directions away from the neuromuscular junction, causing the fibre to contract. The depolarization wave extinguishes at the tendons. The electrical signal that accompanies the depolarization wave is the single fibre action potential. The single fibre action potentials of all muscle fibres of one MU together constitute its motor unit action potential (MUAP).

The activity of the α-motor neurons is regulated by the Central Nervous System (CNS). Basically, the CNS controls the force that is generated by the muscle by changing the number of MUs, i.e. recruitment, and the firing rate with which the MUs are activated. Motor neurons with a small cell body are the first ones to be activated. These motor neurons belong to small MUs in terms of the force they generate as a consequence of the number and type of fibres and their fibre diameter. When the central drive from the CNS increases, larger α-motor neurons and thus larger MUs are recruited. This distinctive recruitment pattern is called the 'Henneman principle' or 'size principle' (Henneman et al. 1965).

The surface EMG signal reflects the temporal and spatial summation of the electrical activity generated by all active MUs together. The contribution of a MU to the surface EMG signal depends a.o. on the distance to the electrodes, which in turn depends on its spatial location in the muscle, in particular its depth. The surface EMG signal that is obtained in this way is commonly used in e.g. movement analysis and exercise physiology.

Because of the large pick-up area of such a surface EMG recording system, the number of MUs that contribute to the signal is large, resulting in a signal of a stochastic nature in which the activity of individual MUs cannot be distinguished. Quantification of the surface EMG signal therefore typically is done with variance-based parameters such as root-mean-square value (RMS). Furthermore, parameters related to the power spectrum are often used, especially in fatigue studies (De Luca 1984, Merletti et al. 1990).

During the last decades, different research groups have directed their research to the development of a spatially more selective, non-invasive recording technique (Merletti et al. 2003, Zwarts & Stegeman 2003, Rau & Disselhorst-Klug 1997, Zhou & Rymer 2004a). With multiple electrodes, arranged in an array with short inter-electrode distances, the spatial selectivity of the recording can be enhanced. The selectivity can be further improved by applying spatial filters that consist of linear combinations of electrodes (Disselhorst-Klug et al. 1997). With these spatial filters, the activity of superficially located MUs is enhanced while the activity of deeper located MUs is suppressed. The presence of propagating motor unit action potentials (MUAPs) is clearly visible in multi-channel array recordings (see Figure 1.1).

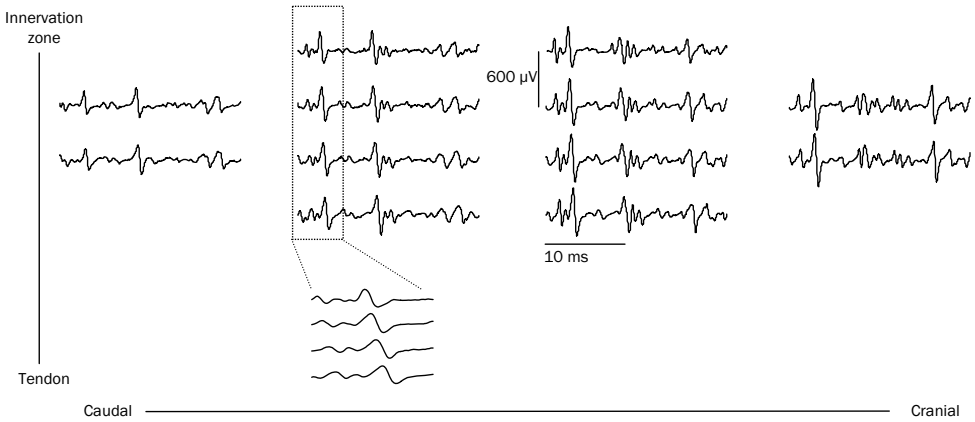

Figure 1.1 Example of a multi-channel EMG recording. A two-dimensional array with 16 electrodes was placed on the upper trapezius. Bipolar derivations are shown. The array was placed between the innervation zone (towards the upper side of the figure) and the tendon (towards the lower side). Motor unit action potentials (MUAPs) originating from different motor units (MUs) can be seen. The shape of the MUAP depends on the location of the MU and its physiological properties such as size.

The possibility to obtain spatial information and in particular to estimate the muscle fibre conduction velocity (CV) from multi-channel recordings led to substantial effort in array development in several research groups (e.g. Rau et al. 1997, Blok et al. 2002, Merletti et al. 2003). Electrodes arranged parallel to the muscle fibres show the propagation of the MUAP from innervation zone to tendon. Extensive research directed at optimal estimation of CV from multi-channel recordings has resulted in algorithms that are able to extract single MU CV (Schulte et al. 2003, Farina et al. 2002a, Farina et al. 2002b, Farina et al. 2000).

Because of the spatial selectivity of multi-channel array EMG recordings, the signal consists of the summed activity of a limited number of MUs. Recently, sophisticated signal processing algorithms that can decompose the EMG signals into the MUAP trains of the contributing MUs have been developed (Holobar & Zazula 2004, Gazzoni et al. 2004, Kleine et al. 2000). Complete decomposition provides important information related to motor control: e.g. recruitment and derecruitment of MUs and firing rates of individual MUs as well as morphological MUAP characteristics. Different automatic software packages for decomposition of needle or wire EMG signals exist (Zennaro et al. 2003b, McGill et al. 2005, Mambrito & De Luca 1984). However, complete decomposition of surface EMG signals is much more complicated due to the properties of the volume conductor, that lead to highly similar MUAP shapes of different MUs. Two-dimensional topographical information related to the geographical distribution of different MUs gives

additional information that is beneficial for decomposition of surface EMG signals (Kleine et al. 2000).
Most decomposition algorithms use a segmentation-classification approach; i.e. decomposition starts with detection of segments containing activity, that are subsequently assigned to classes that ideally correspond to the MUs (e.g. De Luca et al. 2006, Gazzoni et al. 2004, Zhou & Rymer 2004b, Kleine et al. 2000). Due to the high level of similarity between MUAPs from different MUs, classification of the segments is complicated in surface EMG. However, the detection of the active segments (corresponding to the MUAPs from all MUs that contribute to the signals) alone also provides relevant information. Detection of the MUAPs enables the estimation of the total number of MUAPs per second, or MUAP Rate, that may be used as a measure for motor control, since it reflects the sum of the firing rates of the active MUs. Besides the detection of the time instants where a MUAP occurs, MUAP shapes can be extracted from the signal. The morphological MUAP characteristics may provide information about peripheral properties of the muscle. Parameters related to the amplitude of the MUAPs may reflect MU size, while parameters related to the frequency content of the MUAPs may reflect duration of the MUAP and CV.
In summary, the application of non-invasive multi-channel array EMG recording systems provides information about muscle activity and motor control at a more detailed level than conventional surface EMG. This type of recordings may provide new insights into the mechanisms of disorders related to the neuromuscular system.

Thesis objectives and outline

The aims of this thesis were twofold:

1. To develop and evaluate a non-invasive method to enable assessment of motor control at the motor unit level;
2. To investigate whether there are differences in motor control between chronic pain cases and healthy subjects and to what extent these differences can be used to distinguish these groups in an objective way.

In subjects with work-related chronic neck-shoulder pain, in particular the descending part of trapezius muscle is often affected (Kuorinka & Koskinen 1979, Luopajarvi et al. 1979, Viikari-Juntura 1983). Therefore, the upper trapezius muscle was investigated in the research described in this thesis.
The outline of this thesis follows these aims. In Chapter 2 and 3, the development and evaluation of a new measure for motor control (MUAP Rate) is described. EMG parameters that are commonly used to describe muscle activation are influenced by

changes in motor control as well as by peripheral muscle properties, which complicates their use as a measure for motor control solely. MUAP Rate however would not be affected by peripheral muscle properties. This was investigated in a simulation study (Chapter 2). The relation between MUAP Rate and the two parameters with which the CNS performs motor control (number of MUs and firing rate) was explored as well in this study.

Subsequently, the behaviour of MUAP Rate in experimental conditions was investigated (Chapter 3). MUAP Rate was compared to the commonly used EMG parameters RMS and FMED during a step contraction with different force levels and during a fatiguing contraction.

After the evaluation of the proposed measure for motor control by means of simulation and experiments, it was applied to investigate motor control in subjects with chronic pain compared to healthy controls (Chapters 4 to 6). Because of the work-related character of the pain, Chapter 4 presents a study investigating motor control in pain cases during computer tasks.

Although the Cinderella hypothesis states that low-threshold MUs get damaged, it does not explain how development of damaged MUs proceeds. We assumed that before a MU gets damaged, there might be a stage in which it gets chronically fatigued. Therefore, the next study was directed towards the investigation of muscle fatigue development in the two groups (Chapter 5).

Both of these studies showed differences in EMG parameters between the two groups. Since clinical diagnostic tools generally cannot reveal deviations in chronic pain cases, the next study investigated the discriminating ability of the EMG parameters. Chapter 6 presents a pilot study investigating if a combination of multiple EMG parameters can objectively distinguish between chronic pain cases and controls at the level of individual subjects.

Finally, the thesis is concluded with a general discussion of the differences in muscle activation that were found in chronic pain cases in relation to the neurophysiological models. Secondly, the benefits and limitations of the newly developed measure for motor control are discussed.

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Chapter 2

Behaviour of motor unit action potential rate, estimated from surface EMG, as a measure of muscle activation level

Laura A.C. Kallenberg, Hermie J. Hermens
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Abstract

Surface electromyography (EMG) parameters such as root-mean-square value (RMS) are commonly used to assess the muscle activation level that is imposed by the central nervous system (CNS). However, RMS is influenced not only by motor control aspects but also by peripheral properties of the muscle and recording setup. To assess motor control separately, the number of motor unit action potentials (MUAPs) per second, or MUAP Rate (MR) is a potentially useful measure. MR is the sum of the firing rates of the contributing MUs and as such reflects the two parameters that the CNS uses for motor control: number of MUs and firing rate.

MR can be estimated from multi-channel surface EMG recordings. The objective of this study was to explore the behaviour of estimated MR (eMR) in relation to number of active MUs and firing rate. Furthermore, the influence of parameters related to muscle properties and recording setup (number of fibres per MU, fibre diameter, thickness of the subcutaneous layer, signal-to-noise-ratio) on eMR was compared with their influence on RMS.

Physiological parameters were varied in a simulation model that generated multi-channel EMG signals. The behaviour of eMR in simulated conditions was compared with its behaviour in experimental conditions. Experimental data was obtained from the upper trapezius muscle during a shoulder elevation task (20-100 N).

The simulations showed strong, monotonously increasing relations between eMR and number of active MUs and firing rate ($r^2>0.95$). Because of unrecognized superimpositions of MUAPs, eMR was substantially lower than the actual MUAP Rate (aMR). The percentage of detected MUAPs decreased with aMR, but the relation between eMR and aMR was rather stable in all simulated conditions. In contrast to RMS, eMR was not affected by number of fibres per MU, fibre diameter and thickness of the subcutaneous layer. Experimental data showed a strong relation between eMR and force (individual second order polynomial regression: $0.96<r^2<0.99$).

Although the actual number of MUAPs in the signal cannot be accurately extracted with the present method, the stability of the relation between eMR and aMR and its independence of muscle properties make eMR a suitable parameter to assess the input from the CNS to the muscle at low contraction levels non-invasively.

Background

By means of surface electrodes placed at the skin above a muscle the electrical activity accompanying muscle contractions can be measured non-invasively (surface electromyography, EMG). Parameters based on the amplitude of the signal such as root-mean-square value (RMS) are commonly used in e.g. movement analysis to assess the muscle activation level that is imposed by the central nervous system (CNS) (Winter & Yack 1987, Mathiassen & Aminoff 1997, Bilodeau et al. 2003, Farina et al. 2002). However, RMS is influenced not only by motor control aspects but also by peripheral properties of the muscle and recording setup parameters.

At the single muscle level, motor control is performed by the CNS by regulating the number of active MUs and their firing rate. The number of motor unit action potentials (MUAPs) per second, or MUAP Rate (MR), is the sum of the firing rates of all active MUs and it would therefore directly reflect motor control. In contrast to RMS, MR would not be affected by peripheral muscle fibre properties.

From signals measured with conventional EMG electrodes, arranged in a traditional bipolar configuration, MUAPs can hardly be extracted because of the large number of MUs that contribute to the signal, which consequently results in a high degree of overlap of the MUAPs in the signal. During the past years, several groups have explored the use of array electrodes, consisting of multiple contact points in different configurations (e.g. Disselhorst-Klug et al. 1997, Zwarts & Stegeman 2003, Farina et al. 2003, Merletti et al. 2003, Blok et al. 2002, Zhou & Rymer 2004, Roeleveld et al. 1997a). With such arrays spatial filters can be applied to increase the selectivity of the recording system, thereby decreasing the number of MUs that contribute to the EMG signal. In combination with advanced signal processing techniques, this creates the possibility to examine individual MUAPs in a non-invasive way.

Recently, Gazzoni et al. (2004) proposed a method for detection of MUAPs and their classification to the corresponding MUs, that was shown to be able to classify a small but representative sample of MUs. The detection part of this algorithm (based on the Continuous Wavelet Transform; CWT) can be used to obtain an estimate of MR (eMR). A previous study showed significantly higher eMR values in EMG recordings from the upper trapezius during computer tasks in cases with chronic neck-shoulder pain than in healthy controls, while RMS did not show differences (Kallenberg & Hermens 2006). This was attributed to the sensitivity of RMS for peripheral properties and properties of the recording setup, which may have masked differences in motor control.

The objective of this work was to explore to what extent eMR, estimated from the surface EMG by using an electrode array combined with an algorithm based on the CWT, is

suitable as a measure of the input of the CNS to a muscle. For this purpose, we investigated 1) the relation between eMR and the two parameters with which the CNS controls muscle activity (number of MUs and firing rate) and 2) to what extent eMR is affected by parameters related to muscle properties and to the recording setup in comparison to RMS.
As information about the actual number of MUAPs in experimental signals is not directly available and physiological variables cannot be controlled experimentally, multi-channel EMG signals were generated with a simulation package. To compare the behaviour of eMR in simulation conditions with its behaviour in experimental conditions, eMR was calculated from experimental multi-channel EMG signals recorded from the upper trapezius muscle during a shoulder elevation task at different force levels.

Methods

Simulations

Simulation model To generate EMG signals, a simulation package developed for evaluation of signal processing algorithms for extracting EMG features was used (Duchene & Hogrel 2000). The model includes the complete transformation from the intracellular action potential to the signal recorded at the surface. First, the extracellular action potential of one muscle fibre is calculated by convoluting an analytical description of the intracellular action potential with a weighting function depending on distance between fibre and detection site, the position along the fibre of the detection site and volume conduction properties. The muscle is modelled as a one-layer cylindrical shape with a high axial and lower radial conductivity. Fat and skin tissue is modelled as a peripheral layer (referred to as subcutaneous layer) where no muscle fibres can be located. Muscle fibres are defined as finite length line sources, located parallel to the skin surface. The muscle fibre conduction velocity is assumed to be linearly related to fibre diameter (Nandedkar & Stalberg 1983). Next, a MUAP is obtained by combining the extracellular action potentials of all fibres belonging to one MU. This MUAP is convoluted with a pulse train, resulting in the MUAP train for that MU. Finally, the generated signal consists of the combination of MUAP trains of all contributing MUs. For more details see Duchene & Hogrel 2000.

Five categories of model parameters can be varied:

1. experimental parameters (describing the detection system),
2. morphological parameters (describing the muscle anatomy),

3. physiological parameters (number of MUs, number of fibres per MU, fibre characteristics),
4. electrical parameters (tissue conductivities),
5. statistical parameters that define the variability in firing behaviour and in anatomical properties of the MUs.

The algorithm for detection of MUAPs must be applied to a set of signals from adjacent locations in the direction of the muscle fibres, so that propagating MUAPs are identifiable. The configuration of the simulated recording setup was chosen to resemble one row of a two-dimensional electrode array (Helmholtz Institute for Biomedical Engineering, Technical University Aachen, Germany) that was used in the experimental part of the study. It consists of a linear electrode array with 5 contact points (point electrodes) with an inter-electrode distance of 10 mm. The detection area was assumed to be circular. The radius of the detection area (10 mm) was estimated based on Roeleveld et al. (1997b) and Barkhaus & Nandedkar (1994). The simulated location of the electrode array was between the innervation zone and tendon, aligned with the muscle fibre direction.
Morphological, electrical and physiological parameter values were based on data of the biceps brachii (default values of the software package). For a full list of parameter settings, see Table 2.1.

Table 2.1 Settings of parameters used in the simulation package

Sample frequency	2000 Hz
Signal duration	10 seconds
Muscle length	100 mm
Muscle radius	20 mm
Motor point location	60 mm
Maximal detection distance	10 mm
Electrode diameter	1.8 mm
Intracellular action potential duration	5 ms
Mean muscle fibre conduction velocity	4 m/s
Intracellular conductivity	1.010 S/m
Radial conductivity	0.063 S/m
Longitudinal conductivity	0.330 S/m
Motor unit radius	Mean 4 mm, SD 0.2 mm

Simulation protocol Two sets of simulations were performed: in the first set, the influence of the determinants of MR (number of MUs, firing rate and a combination of both) was investigated while the second set was directed at the influence of parameters, related to peripheral muscle properties and to the recording setup that should affect RMS but not MR (number of fibres per MU, fibre diameter, thickness of the subcutaneous layer, signal to noise ratio).

The simulation protocols are summarised in Table 2.2. In simulation 1, the number of MUs was varied. To obtain a good estimate of the number of MUAPs in the simulated signals, all MUs had to be located within the detection area of the electrode; else, the number of MUs that contributed to the signal could not be tracked exactly.
An estimate of the generated number of MUAPs per second in the simulated signal (actual MR, aMR) was estimated by multiplying the number of MUs with the mean firing rate:

$$aMR \approx FR \cdot nrMUs \quad (1)$$

Where FR = mean firing rate of all active MUs
nrMUs = number of MUs

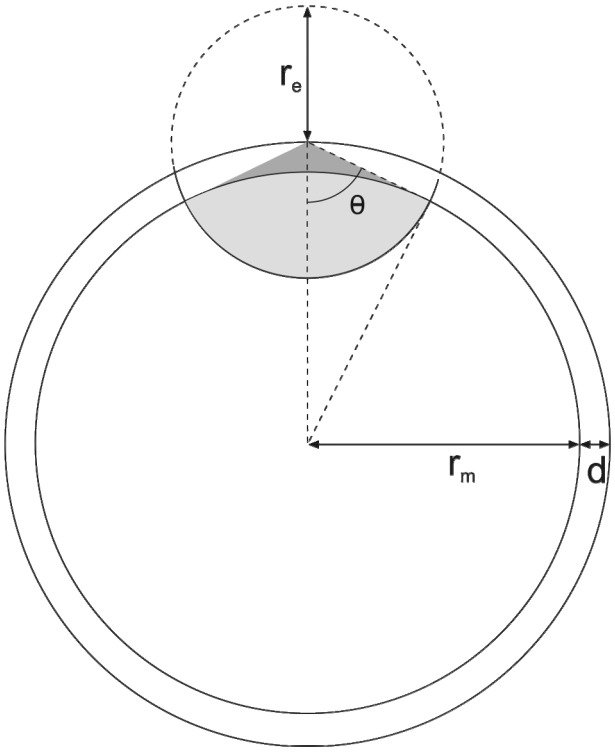

Figure 2.1 Schematic representation of the muscle and the electrode detection area. Upper circle indicates the electrode detection area; lower circle indicates the muscle and the subcutaneous layer. r_e: radius of electrode detection area (10 mm), r_m: muscle radius (20 mm), d: thickness of the subcutaneous layer (2mm). The ratio between the part of the muscle within the electrode detection area (light grey) and total muscle cross-section area was calculated for estimation of the number of MUs that contribute to the EMG signal in relation to the total number of MUs, located throughout the muscle. The triangle used for calculation of θ is indicated with interrupted lines. Dark grey area indicates the part of the electrode detection area that lies within the subcutaneous layer and does not contain MUs.

Because the location of the MUs was constrained to the detection area, in the first simulation, the number of MUs was varied over a limited range (from 1 to 30, simulation 1a). To judge the effect of this constraint, in simulation 1b the location of the MUs was not restricted to the detection area, and the number of MUs was varied from 12 to 300. In this case, the ratio between the detection area and the muscle cross-section area was included in the estimation of aMR (see Figure 2.1):

$$aMR \approx FR \cdot nrMUs \cdot RatioAreas \qquad (2)$$

Where RatioAreas = ratio between part of the muscle within the electrode detection area and total muscle cross-section area
The detection area contains both skin and muscle tissue. The skin part of the detection area (shaded in Figure 2.1) is approximately 10%. Because MUs can only be located in the muscle tissue, which is 90% of the detection area, equation (2) becomes:

$$\begin{aligned} aMR &\approx FR \cdot nrMUs \cdot \frac{DetectionArea}{MuscleCrossSection} \cdot 0.9 \\ &\approx FR \cdot nrMUs \cdot \frac{2\theta/2\pi \cdot \pi \cdot r_e^2}{\pi \cdot r_m^2} \cdot 0.9 \\ &\approx FR \cdot nrMUs \cdot \frac{\theta \cdot r_e^2}{\pi \cdot r_m^2} \cdot 0.9 \end{aligned}$$

Where r_e= detection area radius and r_m= muscle radius

θ can be calculated with the law of cosine for the triangle indicated in Figure 2.1 with dotted lines:

$$aMR \approx FR \cdot nrMUs \cdot \arccos \frac{r_m^2 - r_e^2 - (r_m+d)^2}{-2r_m+d} \cdot \frac{r_e^2}{\pi \cdot r_m^2} \cdot 0.9$$

Where d = thickness of the subcutaneous layer
With r_e = 10 mm, r_m = 20 mm and d = 2 mm this becomes:

$$\begin{aligned} aMR &\approx FR \cdot nrMUs \cdot 0.069 \cdot 0.9 \\ &\approx 0.062 \cdot FR \cdot nrMUs \end{aligned}$$

In summary, in simulation 1a, aMR is estimated by FR · nrMUs and in simulation 1b by 0.062 · FR · nrMUs.

In simulation 2, firing rate was varied in two conditions: with 5 active MUs (simulation 2a) and with 10 active MUs (simulation 2b). Each MU was assigned an individual firing rate; see Section 2.1.3. Mean firing rate was varied from 8 to 20 pulses per second (pps). In these simulations, all other variables were held constant so that variation in eMR could exclusively be related to variation in one input variable.
In physiological circumstances, the number of MUs and firing rate are not independent of each other. Therefore, in simulation 3 these two variables were varied simultaneously to simulate an increasing force production. Different authors have shown that rate coding mainly contributes to force production at higher force levels (above 30% of the maximal voluntary contraction force, MVC), especially for large muscles (Kukulka & Clamann 1981, Conwit et al. 1999). Therefore, in the first simulation steps only the number of MUs was increased while in the later steps, both the number of MUs and the mean firing rate were increased simultaneously (see Table 2.2). The firing rate values were based on experimental research by Conwit et al. (1999), who investigated average firing rate in relation to percentage of MVC.

The second set of simulations was directed at the influence of parameters related to peripheral muscle properties and to the recording setup. These parameters do not affect aMR, but they do affect the amplitude and frequency content of the signal. One of the most important peripheral muscle properties is MU size, which is a combination of the number of fibres per MU and their diameter. In simulation 4, the influence of the number of fibres per MU (range 5 - 1000) was investigated while in simulation 5 fibre diameter (40 - 100 μm) was addressed. According to the Henneman principle (Henneman et al. 1965), in physiological circumstances small MUs are always recruited first, and when more force is required, larger MUs are recruited additionally. To simulate this behaviour, the mean and the standard deviation of the distribution from which the mean fibre diameter was drawn were increased simultaneously (see Table 2.2).
Furthermore, in simulation 6 the influence of thickness of the subcutaneous layer (range 0.1 - 5 mm) was evaluated when 5 MUs (6a) and 10 MUs (6b) were active. Due to filtering effects of the subcutaneous layer, the EMG signal is attenuated (Nordander, et al. 2003) and the duration of the MUAPs may become longer, which could lead to an increase in MUAP superimposition. These effects may affect the performance of the algorithm to detect MUAP shapes.
Finally, since the performance of the algorithm was expected to depend on the signal to noise ratio (SNR) as well, this variable was varied from 3 dB to 1000 dB in simulation 7. This simulation was performed with 5, 10 and 15 MUs (simulations 7a – c).

Table 2.2 Simulation protocols

Simulation number	Number of MUs	Firing rate (pps)	Number of fibres per MU	Fibre diameter (µm)	Thickness subcutaneous layer (mm)	SNR (dB)
1	a: 1- 10 in steps of 1, 15-30 in steps of 5 b: 12 -120 in steps of 12, 120-300 in steps of 60	Mean: 12, SD: 1	750	55	2	1000
2	a: 5 b: 10	Mean: 8 to 20 in steps of 2, SD: 1	750	55	2	1000
3	1 2 4 5 6 7 8 10 11 12	10 10 10 11 12 12.75 13.5 14 15 16	750	55	2	1000
4	5	Mean: 12, SD: 1	5, 50, 100, 250, 400, 600, 750, 800, 900, 1000	55	2	1000
5	5	Mean: 12, SD: 1	750	Mean: 40 to 100 in steps of 10, SD: 5 to 35 in steps of 5	2	1000
6	a: 5 b: 10	Mean: 12, SD: 1	750	55	0.5, 1, 2, 3, 4, 5	1000
7	a: 5 b: 10 c: 15	Mean: 12, SD: 1	750	55	2	3, 6, 10, 15, 20, 50, 100, 1000

Each row represents a simulation. The simulation number is shown in the left column; the settings of all variables are shown in the other columns. In the third simulation, the number of MUs and firing rate are increased simultaneously in steps; each row in the first two columns represents a step.

Simulation settings See Table 2.2. In case the number of MUs was not varied (simulations 2, 4-7), it was set to 5, 10 or 15. The default value of SNR was set to 1000 dB, resembling a signal without noise. The default number of fibres per MU was set to 750, which corresponds to the average MU size in the biceps brachii (Buchthal 1961). Fibre diameter was set to 55 μm and thickness of the subcutaneous layer to 2 mm.
When firing rate was kept constant (simulations 1, 4-7), for each MU, its mean inter-pulse interval (IPI) was drawn from a Gaussian distribution with a mean of 83.3 ms and a standard deviation (SD) of 7 ms (corresponding to a mean firing rate of 12 pps with an SD of 1 pps). The variation within a pulse train (belonging to one MU) was set to ten percent.
The influence of fibre diameter was investigated in simulation 5. For each MU, a mean fibre diameter was drawn from a normal distribution (bounded at ±3 SDs) with a user-defined mean and SD. Next, the individual fibre diameters within the MU were drawn from a normal distribution (bounded at ±2 SDs) with the drawn fibre diameter as mean and a SD of 1 μm (default setting of the simulation package).
SNR could not be varied in the simulation package. Therefore, Gaussian noise was added to the simulated signals by using custom-made software written in Matlab (The MathWorks, Inc., Natick, MA, USA).
Each step in the simulations was repeated three times and outcome values were averaged to decrease the variability introduced in the input parameters.

Experimental set-up

Subjects The study was approved by the local medical ethics committee. Five subjects (three female, two male, mean (SD) age 26.6 (2.70) years, weight 68.4 (10.9) kg, height 175.8 (11.3) cm, body-mass index (BMI) 22.1 (1.9) kg/m^2) without known disorders took part in this study. All subjects gave their written informed consent.

General procedures Subjects performed a stepwise increasing contraction consisting of five force levels of 20 to 100 N in steps of 20 N. The force levels were shown on a laptop screen and subjects were instructed to keep the force level as constant as possible for each step. Each level was maintained for ten seconds. Between the levels, one second was allowed for transition to the next level.
Subjects were seated on a chair that was adjusted in height to prevent them from touching the floor with their feet. The chair was attached to a frame that was fixed to the wall. Two force transducers (Thermonobel, Karlskoga, Sweden) were attached to the frame for measuring the force from the trapezius muscle. The position of the force sensors was adjusted to body size, such that the sensor centre was located slightly above the acromion.

In rest, the force sensors were just not touching the subject. The force signals were sampled with 1 kHz and digitised with a 16-bits A/D converter, and stored on a laptop.
Subjects were instructed not to speak or move the head during the recordings, to sit straight, and to keep their hands rested in the lap. Subjects were not allowed to cross their feet.

EMG recordings EMG of the dominant upper trapezius was recorded using a two-dimensional 16-channel electrode array (Helmholtz Institute for Biomedical Engineering, Technical University Aachen, Aachen, Germany). The array consisted of four rows, the first and fourth containing three contact points and the middle two containing five contact points. The distance between the rows was 10 mm, as was the distance between the adjacent electrodes within a row. The inter-electrode distance is relatively small in comparison with conventional surface EMG measurements, which increases the spatial selectivity.
Before electrode placement, the skin was cleaned using abrasive paste. Electrodes were placed with the rows parallel to the line from the spinous process of the seventh cervical vertebra (C7) to the acromion with the centre of the electrode 2 cm lateral from the midpoint, in accordance with the SENIAM recommendations (Hermens et al. 2000). A ground electrode was placed on the wrist of the dominant side.
The monopolar signals were amplified 1000 times, sampled at 4000 Hz and band-pass filtered (10-500 Hz) with a custom made EMG amplifier (Helmholtz Institute for Biomedical Engineering, Technical University Aachen, Aachen, Germany). The signals were digitised using a 16 bit A/D-converter and stored on a laptop. Before the measurement started, the signal quality was inspected visually. Criteria for correct electrode placement were presence of propagating MUAPs across the channels, similarity of the MUAP shapes in all channels and absence of excessive noise. Adjustments were made when necessary until signals with good quality could be obtained.

Data analysis Monopolar signals with an inter-electrode distance of 10 mm from adjacent electrodes from the middle two rows of the array were subtracted, resulting in two sets of four single differential signals. For both sets, cross-correlation between adjacent signals was calculated, resulting in three values from each set. Adjacent signals are expected to show a high degree of similarity when there are no artefacts present. The set with the highest average correlation coefficient was therefore selected for further processing.
For the simulated signals, analogous to the experimental signals, a set of four single differential signals was constructed by subtracting signals from adjacent electrodes.

For detection of MUAPs, a wavelet-based algorithm that uses multi-channel information was applied (Gazzoni et al. 2004, Farina et al. 2000). The algorithm uses the continuous wavelet transform (CWT) to identify shapes that are similar to a mother wavelet. As mother wavelet, the first order Hermite-Rodriguez function was used. The CWT uses two parameters, being a time shift (related to the location in time where a similar shape occurred) and a scale factor that is related to the amplitude and width of the wavelet. The CWT of each single signal is calculated for a range of different values for both parameters. The squared output of the CWT (ranging from 0 to 1) is a measure for the similarity between the mother wavelet and the signal at a certain time instant. This output can be plotted in a three-dimensional graph against the time instant and the scale factor, resulting in a so-called scalogram.

The algorithm started with calculating the CWT for the first channel. When the scalogram reached a maximum that was higher than a user-defined threshold (set to 0.1 in this study), a candidate MUAP was found at the time instant and scale factor corresponding to the maximum. The algorithm then searched for candidate MUAPs that were located in the surrounding channels within a time delay corresponding to a conduction velocity between 2 and 8 m/s. When the candidate was present in a minimal number of channels (set to 3 in this study), the candidate was considered a MUAP. Then, the CWT was calculated for the next channel. The algorithm cycled through the channels in this way. Outputs of the algorithm were the firing times and the corresponding MUAP shapes on each channel. For more details, see Gazzoni, et al. (2004) and Farina et al. (2000).

From the firing instances, the number of MUAPs (resulting from all MUs together) was extracted for time windows of one second. The mean value (across time) was calculated and is reported as eMR. aMR is estimated by multiplying the average firing rate with the number of MUs.

Root-mean-square values (RMS) were calculated from each signal for time windows of one second. Values were calculated for each channel and averaged both across channels and across time.

The algorithms were implemented in Matlab software (The MathWorks, Inc., Natick, MA, USA).

Results

Throughout the results section, eMR, aMR and RMS are compared.

In Figure 2.2, an example of a simulated signal is shown for ten active MUs, together with an example of an experimentally recorded signal from the upper trapezius muscle at 100 N for comparison. The appearance of the simulated signal is similar to the experimentally recorded signal. The median frequency of the power spectrum of the simulated signals

(first channel) is 64.7 Hz, while that of the experimental signal (first channel) is 63.5 Hz. When less active MUs are simulated, individual MUAPs can easily be recognised.

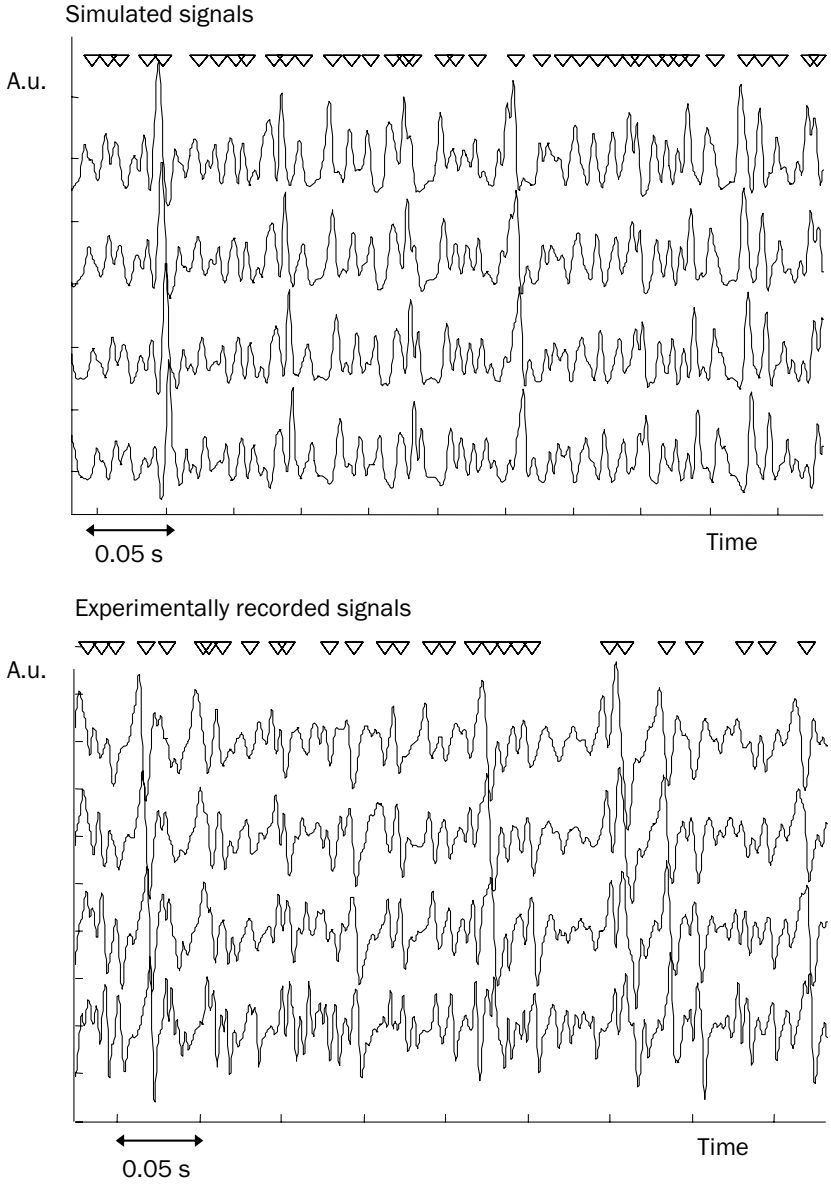

Figure 2.2 Simulated signals with ten active MUs (upper graph) and experimentally recorded signal at a force level of 100 N (lower graph). Four single differential signals with 10 mm inter-electrode distance, recorded parallel to the muscle fibres are shown. Fibre direction is from innervation zone (upper signal) to tendon (lower signal). Triangles indicate detected MUAPs. A.u.: arbitrary units.

Determinants of MR

In Figure 2.3 (upper graphs), the relation between the number of active MUs and both eMR and RMS when the MUs are located within the detection area of the electrodes is shown (simulation 1a). eMR increases with the number of active MUs, but the percentage of detected MUAPs decreases. Visual inspection of the signals underlines that this is related to the increasing occurrence of superimpositions that are detected as single MUAPs. The best fit of a second order polynomial trend line resulted in an explained variance (squared Pearson's correlation coefficient, r^2) of 0.99 ($p<0.001$).
RMS also increases with number of active MUs. The best trend line was a square root relation which resulted in an explained variance of 0.86 ($p<0.001$).

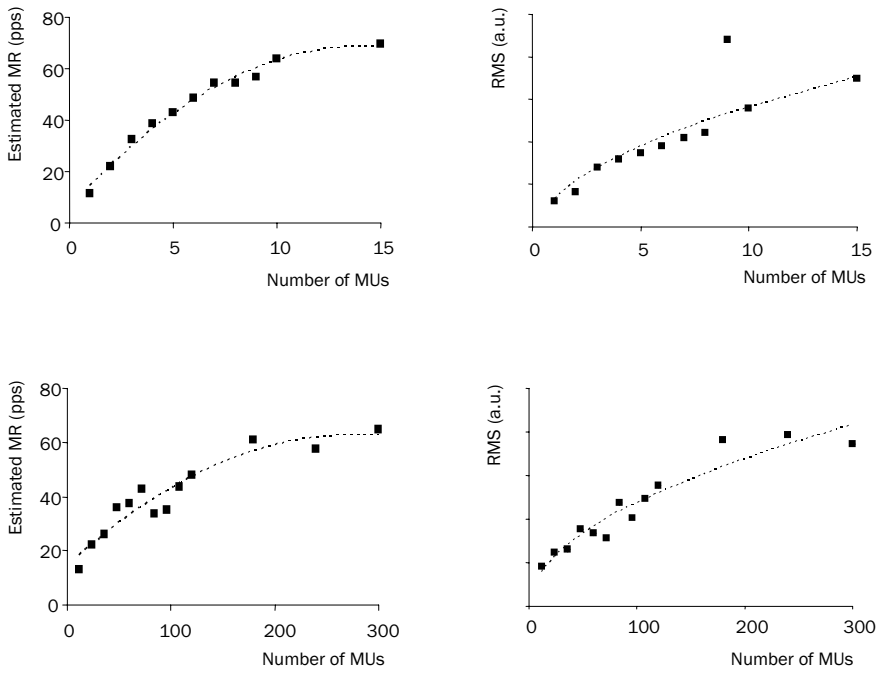

Figure 2.3 Relation between number of active MUs and both estimated MR and RMS in simulated conditions. Upper graphs show the relations when MUs were restricted to be located within detection area of electrode. Lower graphs show the relations when MUs were located throughout the whole muscle. Scales of the y-axis are the same in both RMS graphs.

Figure 2.3 also shows the relation between number of MUs and both eMR and RMS when the location of the MUs was not restricted to the detection area (simulation 1b, lower graphs). The shape of the curve is similar as for simulation 1a, but the variability of the measurements is larger, as is reflected in the somewhat lower explained variance: the best

fit was a second order polynomial trend line with an explained variance of 0.91 ($p<0.001$). RMS was best approximated by a square root relation, with an explained variance of 0.92 ($p<0.001$).

In simulation 2 firing rate was simulated in two conditions: 1) while five MUs are active, 2) while ten MUs are active. aMR increases linearly with firing rate in both situations, with a steeper slope when ten MUs are active. eMR increases linearly as well, but the slope of the curve is less steep than for aMR. Fitting of a linear regression line through the eMR curves resulted in a line with a slope of 2.18 and an intercept of 41.7 pps ($r^2 = 0.96$, $p<0.001$) for five active MUs and a slope of 1.72 and an intercept of 16.6 pps ($r^2 = 0.95$, $p<0.001$) for ten active MUs. The curve for ten active MUs is shifted to higher values than the curve for five active MUs.

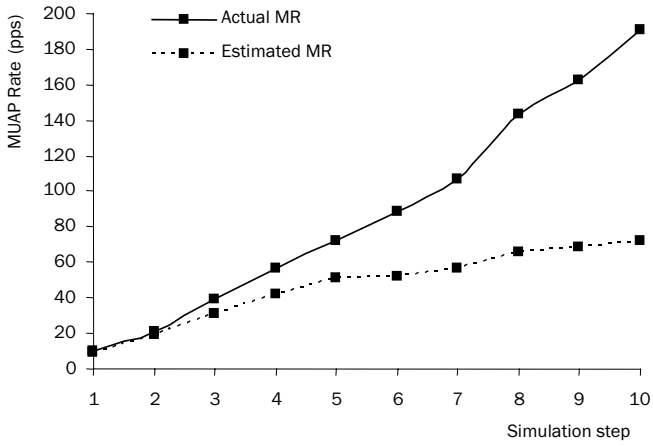

Figure 2.4 Actual and estimated MR in relation to simulated force production. To simulate an increasing force, the number of MUs and their firing rate were increased simultaneously. See Table 2.2 for the parameter values at each step.

Figure 2.4 shows the behaviour of MR when increasing force production is simulated as a combined increase of firing rate and number of MUs. Both aMR and eMR increase with simulated force. The increase is less for eMR than for aMR, similar to the results of simulation 1 and 2.

In Figure 2.5, the influence of the determinants (number of MUs and firing rate) on eMR in different conditions is summarized. This figure provides an impression of the stability of the relation between eMR and aMR in different conditions. It shows that this relation is very similar for the different simulations. The results from simulation 1b, number of MUs with MUs located throughout the whole muscle, deviate somewhat from the curve with slightly lower eMR values, but the shape of the relation is similar. For the pooled data, a

logarithmic trend line explained 94% of the variance while a second order polynomial trend line explained 92%.

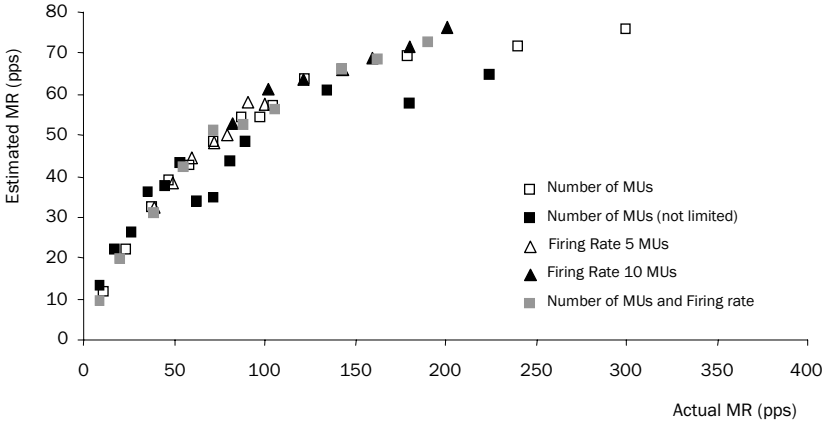

Figure 2.5 Relation between actual and estimated MR in different conditions. Results of simulations with varying number of active MUs, firing rate, and a combination of both. The relations with number of MUs were simulated in two conditions: when MUs were restricted to be located within the detection area of the electrode and when MUs were located throughout the whole muscle (indicated as "number of MUs (not limited)" in the legend). The relations with firing rate were investigated in case of five and ten active MUs.

Parameters related to muscle properties and recording setup

Except from the relation between RMS and thickness of the subcutaneous layer, the relations between aMR, eMR and RMS on one hand and number of fibres, fibre diameter and thickness of the subcutaneous layer on the other hand were best approximated with a linear fit. Linear regression analysis was applied to estimate the coefficients of the relations, and the explained variance. In contrast, the relation between RMS and thickness of the subcutaneous layer was obviously non-linear. This relation could best be approximated by a logarithmic relation. Explained variance and coefficients were in this case estimated with non-linear regression. Table 2.3 shows that number of fibres, fibre diameter and thickness of the subcutaneous layer explain a high percentage of variance of RMS values ($r^2>0.94$) but not of eMR and aMR ($r^2<0.13$). There is no significant in- or decrease in aMR and eMR with these parameters, while RMS increases strongly with number of fibres and fibre diameter. RMS decreases logarithmically with thickness of the subcutaneous layer.

The aMR and corresponding eMR intercept values (β_0) that were found in simulations 4 tot 7 are consistent with the relation between eMR and aMR as was found in simulations 1 to 3 (Figure 2.5).

Table 2.3 Influence of peripheral properties on aMR, eMR and RMS

	aMR (pps)				eMR (pps)				RMS (a.u.)			
	β_0	β_1	r^2	p	β_0	β_1	r^2	p	β_0	β_1	r^2	p
Number of fibres	62.2	-0.0011	0.11	0.35	41.4	0.0027	0.13	0.31	1.15	0.14	0.96	0.001
Fibre diameter	57.2	0.018	0.046	0.65	37.0	0.048	0.11	0.47	118	4.5	0.97	0.001
Thickness subcutaneous layer:												
- 5 MUs	59.9	0.072	0.038	0.57	42.5	0.24	0.062	0.46	132	-37	0.94	0.001
- 10 MUs	122	-0.36	0.073	0.42	61.3	0.31	0.027	0.63	195	-63	0.98	0.001

Linear regression was applied for estimation of the percentage of explained variance (r^2) and of the intercept β_0 and slope β_1. The relation between RMS and thickness of the subcutaneous layer could best be approximated with a logarithmic relation. Nonlinear regression was performed to estimate the coefficients of this relation.

The influence of signal-to-noise ratio is shown in Figure 2.6 for five, ten and fifteen active MUs. Obviously, aMR does not change with SNR. For values lower than 15 dB, eMR increases. In case of five active MUs, eMR is even higher than aMR. RMS shows a similar behaviour.

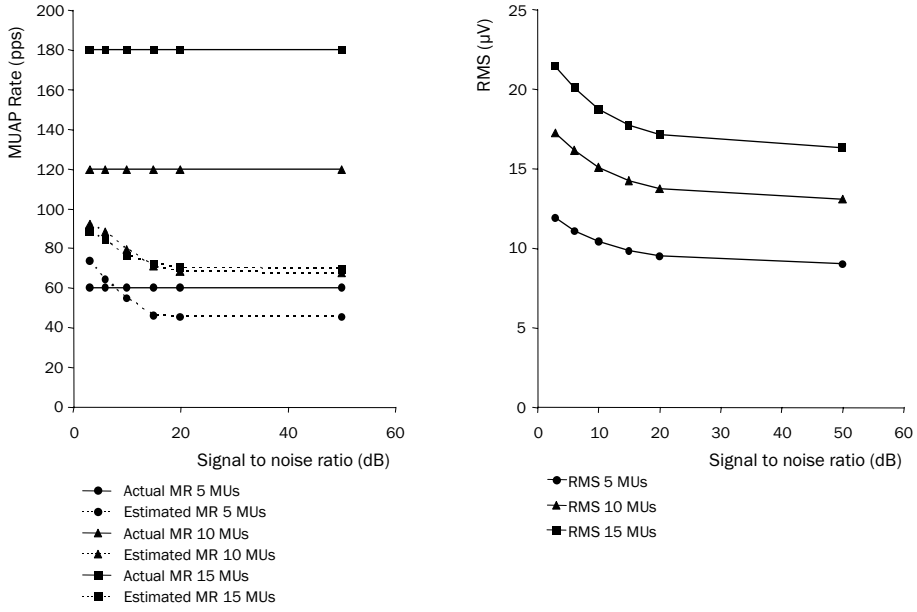

Figure 2.6 Influence of signal to noise ratio on estimated MR. Simulations were performed in case of 5, 10 and 15 active MUs.

Experimental results

The experimental results are reported in Figure 2.7. The relation between eMR and force is approximately linear, although the increase in eMR flattens for the force levels of 80 and 100 N. Individual second order polynomial trend lines resulted in an average explained variance of 0.98 (range 0.97-0.99, $p<0.001$). Linear trend lines explained slightly less variance (mean $r^2=0.94$, range 0.88-0.97).

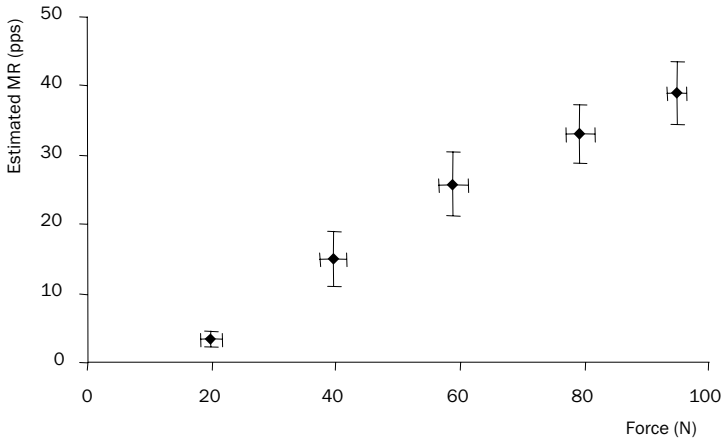

Figure 2.7 Relation between estimated MR and force in experimental conditions during a step contraction of the trapezius muscle (force levels from 20 to 100 N). Mean values of 5 subjects are shown. Bars show inter-subject standard errors of the mean both in force and estimated MR.

Discussion

The objective of this work was to explore to what extent eMR, estimated from the surface EMG by using an electrode array combined with an algorithm based on the continuous wavelet transform, is suitable as a measure of the input of the CNS to a muscle. For this purpose, we investigated 1) the relation between eMR and the two parameters with which the CNS controls muscle activity (number of MUs and firing rate) and 2) the influence of parameters related to muscle properties and to the recording setup on eMR in comparison to RMS.

Determinants of MR

In simulations 1 to 3, the influence of the number of MUs and firing rate on eMR were investigated. The high percentages of explained variance show that although eMR diverges widely from aMR, eMR is strongly related to number of active MUs (simulation 1) and

firing rate (simulation 2), as well as to a combination of both (simulation 3). The results from the different simulations are consistent (Figure 2.5), which gives an indication of the stability of the relation between aMR and eMR. Increases in the number of MUs and firing rate seem to be interchangeable; eMR only depends on the total number of MUAPs per second.

The increase of eMR with number of MUs could well be approximated ($r^2 = 0.99$) by a second order polynomial fit with a negative coefficient for the quadratic term. This indicates that the percentage of detected MUAPs decreases when the number of MUs increases. Visual inspection of the signals reveals that this is related to the occurrence of superimpositions that are either not recognized, or detected as single MUAPs. Assuming that the number of superimpositions increases linearly, the percentage of detected MUAPs decreases linearly as well, which would indeed result in a second order polynomial relation. Several algorithms aiming at full EMG decomposition contain a method for resolving superimpositions (Stashuk 2001, McGill et al. 2005, Loudon et al. 1992, Zennaro et al. 2003). These algorithms are developed for invasive needle or wire recordings and are based on the shape differences between MUAPs from different MUs. However, for surface EMG recordings, the MUAP shapes from different MUs are rather similar. Other approaches to resolve superimpositions such as algorithms based on independent component analysis (Nakamura et al. 2004a, 2004b), that do not necessarily rely on the occurrence of temporally isolated MUAPs in the signal may prove to be more successful.

In order to make a reliable estimate of aMR, MUs were restricted to be located within the detection area. When the location of the MUs was not restricted, the variability of both RMS and eMR was higher. Probably, part of this variability is related to errors in the estimate of the number of MUs that contribute to the signal. MUs may partly lie within the detection area and it depends on the location of the centre of the MU whether it is included in the estimate of the number of MUs or not. Furthermore, contribution of parts of MUs is likely to increase background activity. However, despite the increased variability, the shape of the relation between eMR and number of MUs was the same for simulations 1a and 1b. Thus, the restriction of the location of MUs to the detection area of the electrode had a rather limited effect.

In conclusion, the simulation results show that eMR considerably diverges from aMR. This implies that eMR cannot directly be used to estimate the true number of MUAPs in the EMG signal. However, the relation between eMR and aMR is rather stable in different conditions and eMR is strongly related to the number of MUs and firing rate.

Parameters related to muscle properties and recording setup

In contrast to RMS, eMR was not affected by number of fibres per MU, fibre diameter and thickness of the subcutaneous layer. This underlines that eMR specifically reflects

parameters related to the input of the CNS to the muscle, whereas RMS also depends on peripheral muscle and subcutaneous layer properties. In a previous study differences between cases with chronic neck-shoulder pain and healthy controls were found in eMR, while RMS did not show any differences (Kallenberg & Hermens 2006). This was attributed to the sensitivity of RMS for peripheral properties, which the present findings confirm. The influence of peripheral properties may have masked subtle differences in motor control. The sensitivity of RMS for peripheral properties may be decreased by normalising the RMS values to an individual's RMS value during MVC, as is often done in experimental studies. However, especially in subjects with pain or fear of pain, it may be difficult to assess an individual's maximal capacity reliably.

Two aspects of MU size were investigated: the number of fibres per MU and fibre diameter. Both parameters did not affect eMR, while they showed a linear relation with RMS. Because in physiological circumstances, additionally recruited MUs in general will be larger (Henneman et al. 1965), MU size also affects the relation between RMS and force. The sensitivity of RMS for peripheral properties in general may lead to a higher inter-subject variability for RMS than for eMR.

The percentage of detected MUAPs remained constant when fibre diameter was varied.

By increasing the mean muscle fibre diameter within a MU as well as the width of the distribution of mean fibre diameter across MUs simultaneously, the recruitment of larger MUs was simulated while the smaller MUs remained present in the signal. In this way it was shown that small MUAPs are still detected in the presence of large MUAPs. This is in agreement with simulation results of Gazzoni et al. (2004), who also reported that both small and large MUs were simultaneously detected.

It was shown that estimation of MR is hampered when the SNR becomes lower than 15 dB, independent of the number of active MUs. In this case, apparently noise is generating false positives. RMS was also over-estimated for lower SNRs. This implies that the SNR in experimental conditions should be higher than 15 dB. In the experimental part of this study SNR (estimated from the signal variance during contraction divided by the signal variance during rest) typically ranged from 40 to 100 dB for the applied force range, indicating that noise did not hamper the estimation of MR.

Experimental results

The experimental results showed strong, second order polynomial individual relations between eMR and contraction force ($0.97<r^2<0.99$). In comparison, individual linear relations between RMS and shoulder elevation torque with explained variances of 88-97% have been reported (Louhevaara et al. 1990).

The maximal force that was measured was 100 N, which corresponded to an eMR of approximately 40 pps. From Figure 2.5 can be seen that in the range from 0 to 40 pps, the

increase of eMR is approximately linear. A force of 100 N corresponds to 25-30% of MVC that was 357 N for healthy subjects in the same experimental setup (Schulte et al. 2005). For higher force levels, the eMR-force curve will probably flatten, due to the increased occurrence of superimpositions.

Absolute rather than relative force levels were used in this study, since in daily life conditions, experienced loads are also not scaled to an individual's capacity. Relative force levels are often used to decrease inter-subject variability. When the force levels would have been normalised, the relation between eMR and force might have been even stronger.

The number of MUs that contribute to the signal is strongly dependent on the spatial selectivity of the recording system (Disselhorst-Klug et al. 1997). Selection of the recording system involves a trade-off between representation of all MUs and optimal MR estimation. The single differential configuration with the relatively small inter-electrode distance (10 mm) that was applied for this study appeared to be suitable for the range of investigated force levels. For higher force levels, MR estimation might improve by applying a more spatially selective filter, which can be reached with a more selective electrode configuration or with a smaller inter-electrode distance. When recordings are made with a two-dimensional array, as was done in this study, the spatial selectivity can be increased by using the Laplacian configuration (Farina et al. 2003). With linear electrode arrays (Merletti et al. 2003), the inter-electrode distance could be shortened.

Methodological aspects

MR is a combination of the number of active MUs and their firing rates and does not give information about each of these variables separately. Many research groups are working on algorithms for complete EMG decomposition (e.g. Gazzoni et al. 2004, Kleine et al. 2000, Chauvet et al. 2003, Holobar & Zazula 2004). In most algorithms, the first step of decomposition is the detection of MUAPs in the signal. The second step consists of the assignment of the detected MUAPs to the MU that generated them (classification). Other algorithms are based on higher-order statistical features of the EMG signals (Nakamura et al. 2004).

Complete decomposition would result in clinically relevant information that can easily be interpreted. However, most methods are only able to decompose very few MUs (about 5) completely from surface EMG signals. Furthermore, decomposition of MUs with small MUAP amplitude is difficult, whereas the results of simulation 5 show that detection of small MUAPs is possible even in the presence of big MUAPs.

Zhou and Rymer (2004) also developed a method for MUAP counting based on template matching. They obtained MUAP templates of each MU from spike-triggered averaging of the surface EMG signal by using decomposed intramuscular EMG signals as trigger. These templates were then used to generate a simulated EMG signal. Their MUAP

counting algorithm was able to estimate MR reliably up to 100 pps from these signals, which seems a better performance than that of the algorithm we applied. For higher values, the performance of the algorithm also decreased. It should be taken into account that the templates used for generation of simulated signals were used for detection as well in the algorithm of Zhou and Rymer. Since such templates are not a priori known in an experimental setting without intramuscular recordings, the performance of the algorithm in such conditions remains to be investigated.

Conclusions

The simulations showed rather stable, monotonously increasing relations between eMR and both number of active MUs and firing rate. In contrast to RMS, eMR is hardly influenced by the number of fibres per MU, fibre diameter and thickness of the subcutaneous layer. eMR therefore seems to specifically reflect input from the central nervous system to the muscle while it is not affected by peripheral aspects. Experimental data showed a strong, approximately linear relation between eMR and force.
Although the actual number of MUAPs in the signal cannot be accurately extracted with the present method, eMR seems to be a suitable non-invasive tool to study the input of the central nervous system to the muscle at low contraction levels.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LK participated in the conception and design of the study, carried out the experimental part of the study, analysed and interpreted the data and drafted the manuscript. HH participated in the conception and design of the study, helped in interpreting the data and revised the manuscript. All authors read and approved the final manuscript.

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Chapter 3

Behaviour of a surface EMG based measure for motor control: motor unit action potential rate in relation to force and muscle fatigue

Laura A.C. Kallenberg, Hermie J. Hermens
J Electromyogr Kinesiol, in press

Abstract

Surface electromyography parameters such as root-mean-square value (RMS) and median power frequency (FMED) are commonly used to assess the input of the central nervous system (CNS) to a muscle. However, RMS and FMED are influenced not only by CNS input, but also by peripheral muscle properties. The number of motor unit action potentials (MUAPs) per second, or MUAP Rate (MR), being the sum of the firing rates of the active motor units, would reflect CNS input solely. This study explored MR behaviour in relation to force and during a fatiguing contraction in comparison to RMS and FMED. In the first experiment (n=10) a step contraction of shoulder elevation force (20-100 N) was performed while multi-channel array EMG was recorded from the upper trapezius muscle. The sensitivity of MR for changes in force (1.8%/N) was almost twice as high as that of RMS (0.97%/N), indicating that MR may be more suitable for monitoring muscle force. The second experiment (n=6) consisted of a 15-min isometric contraction of the biceps brachii. MR increased considerably less than RMS (0.9% vs. 4.1%), suggesting that MR selectively reflects central motor control whereas RMS also reflects peripheral changes. These results support that, at relatively low force levels, MR is a suitable parameter for non-invasive assessment of the input of the CNS to the muscle.

Introduction

The electrical activity accompanying muscle contractions can be measured non-invasively by means of surface electrodes placed at the skin above a muscle (surface electromyography, SEMG). Variables related to the amplitude of the SEMG signal (e.g. root-mean-square (RMS) value) and to its frequency content (e.g. median frequency of the power spectrum, FMED) are commonly used in movement analysis to assess physiologically relevant aspects such as muscle activation level and development of muscle fatigue.

It is well-known that RMS increases with force, but different shapes of this relationship have been reported. Gerdle et al. (1991) reported a linear relation between normalized RMS and normalized torque for rectus femoris, vastus medialis and vastus lateralis over the complete range of force. In contrast, another study reported a lower slope of the RMS-force relation at force levels up to 40% MVC than for higher force levels (Hagberg and Hagberg, 1989). A similar pattern was found for the back muscles (Kumar and Narayan 2001).

During isometric, isotonic sustained contractions, in general RMS increases and FMED decreases (see e.g. De Luca 1984, Merletti et al. 1990, Merletti et al. 2002, Madeleine et al. 2002, Öberg et al. 1992). These changes are considered to be myoelectric manifestations of muscle fatigue, related to additional motor unit recruitment and/or a decrease of muscle fibre conduction velocity.

When interpreting changes in RMS and FMED it should be considered that they are influenced by both central motor control properties (e.g. changes in recruitment) as well as peripheral muscle properties (e.g. changes in shape and duration of the intracellular action potential, motor unit size and muscle fibre conduction velocity). Interpretation of the changes in RMS and FMED in terms of specific physiological mechanisms is therefore not straightforward.

Recent research has shown that motor unit action potentials (MUAPs) can be isolated from the surface EMG when recorded with electrode arrays (Gazzoni et al. 2004, Disselhorst-Klug et al. 2000, Stegeman et al. 2000, Merletti et al. 2003). This provides the opportunity to selectively assess the input from the central nervous system (CNS) to a muscle (Kallenberg & Hermens 2006a). The CNS controls muscle activity by recruitment of MUs and by changing their firing rate. The number of MUs and their firing rate are reflected in the number of motor unit action potentials (MUAPs) per second (MUAP Rate, MR).

A previous simulation study showed that there is a strong, monotonously increasing relation between MR and both number of MUs and firing rate, while MR is not affected

by MU size (a peripheral property). The objective of the present study was to explore the behaviour of MR in experimental conditions in comparison to two conventional EMG parameters (RMS and FMED). This was performed during a step contraction with increasing force levels, and during a fatiguing contraction.

Methods

Two experiments were performed. In the first experiment, the relations of MR and RMS with force were investigated. Subjects had to perform a step contraction consisting of shoulder elevation force steps from 20 to 100 N.
The behaviour of MR, RMS and FMED during a fatiguing contraction was investigated in the second experiment, which consisted of a sustained isometric contraction of 15 min at 10% MVC of the biceps brachii.

Subjects

A Dutch questionnaire about work and health (Hildebrandt et al. 2001) was used to select subjects. This questionnaire comprised questions about work history and vocational satisfaction, as well as questions about health, i.e. history, duration and location of complaints and history of therapy. Only the health-related questions were used to select subjects. Subjects were included when they did not have any self-reported complaints in the neck, shoulders, arms or upper back during the last year. Ten subjects (5 male, 5 female, mean age 31.0, standard deviation (SD) 11.6 years, mean height 179.7, SD 10.9 cm, mean weight 69.6, SD 9.8 kg, mean body mass index 21.5, SD 1.6 kg/m^2) participated in the first experiment. Six subjects (3 male, 3 female, mean age 22.9, SD 2.2 years, mean height 179.5, SD 4.2 cm, mean weight 67.8, SD 6.1 kg, mean body mass index 21.1, SD 1.8 kg/m^2) participated in the second experiment. The study was approved by the local medical ethics committee and all subjects signed a written informed consent.
Part of the data has been used for an earlier publication (Kallenberg et al. 2006).

General procedures

In the first experiment, shoulder elevation force and SEMG of the upper trapezius muscle were measured simultaneously. Subjects performed a step contraction consisting of five force levels (20, 40, 60, 80, 100 N, corresponding to approximately 5 to 30% MVC, Schulte et al. 2006). A repetition of the second step (40 N) was added as sixth step to investigate possible myoelectric manifestations of fatigue, reflected as differences in the EMG parameters of the second and sixth steps. Each step had to be maintained for 10 s while one second was used for transition to the next step.

Subjects were seated on an adjustable chair that was high enough to prevent them from touching the floor with their feet. The chair was attached to a frame that was fixed to the wall. Two force transducers (Thermonobel, Karlskoga, Sweden) were attached to the frame for measuring shoulder elevation force on both sides. Subjects were instructed to perform the contractions symmetrically. They were not allowed to speak or to move the head during the recordings, they had to sit straight and keep their hands rested in their lap. Subjects were not allowed to cross their feet. The position of the force sensors was adjusted to body size, such that the sensor centre was located slightly above the acromion. In rest, the force sensors were just not touching the subject.

In the second experiment, subjects had to maintain a force level of 10% of the maximum voluntary contraction (MVC) of the biceps brachii for 15 min. A low force level was chosen because in such conditions conventional EMG parameters give inconsistent results; the decrease of muscle fibre conduction velocity of the fatiguing MUs might be counteracted by additional recruitment of fresh MUs. MR seems especially suitable in this condition because it would selectively reflect the input of the CNS to the muscle.

Before the electrodes were placed, MVC was determined according to the recommendations of Mathiassen et al. (1995). Subjects were asked to perform a maximal contraction three times with two minutes rest in between. Verbal encouragement as well as real-time feedback of the force level was provided. When the third measurement was more than 10% higher than the first two, a fourth and if necessary, fifth measurement was performed. The force signal was averaged with a 100 ms moving window. The maximum value was considered the MVC.

Subjects were seated on a chair with adjustable height. The lower arms were supported in a horizontal position with the hand in the neutral position (midway between pronation and supination). The elbow was kept in 90° flexion and the upper arm was slightly abducted while it remained in the plane of the trunk. A non-elastic strap was used to connect the wrist to the force transducer, which was fixed to the floor. During the isometric contractions of the biceps brachii, subjects were asked to pull on the strap without changing the elbow position. Subjects were instructed to relax their lower arms. Perceived fatigue was measured with a 10-point Likert scale before and after the 15 minutes contraction.

In both experiments, force feedback was provided on a laptop screen in front of the subject. The gain of the force feedback was adapted such that deviations of 1 N could clearly be seen. The force signals were sampled with 1 kHz, digitized with a 16-bits A/D converter, and stored on a laptop.

SEMG recordings

SEMG of the dominant upper trapezius was recorded using a two-dimensional 16-channel array developed by the Helmholtz Institute for Biomedical Engineering, Technical University Aachen, Aachen, Germany (Disselhorst-Klug et al. 2000), see Figure 3.1. The array consisted of four columns of gold-coated pin-electrodes with a diameter of 1.5 mm, the first and fourth containing three contact points and the middle two containing five contact points. The inter-electrode distance (IED) was 10 mm in both directions.

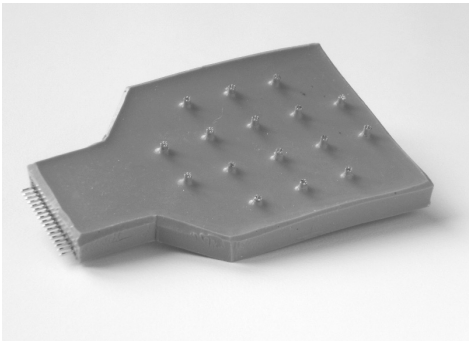

Figure 3.1 Two-dimensional 16-channel electrode array used for EMG recordings. The inter-electrode distance is 10 mm. The array was placed parallel to the line from C7 to the acromion.

Before electrode placement, the skin was cleaned using abrasive paste. Electrode placement was done in accordance with the SENIAM recommendations for SEMG recordings (Hermens et al. 2000). In the first experiment, electrodes were placed on the trapezius of the dominant side with the columns parallel to the line from the spinous process of the seventh cervical vertebra (C7) to the acromion with the centre of the electrode 2 cm lateral from the midpoint. In the second experiment, electrodes were placed on the biceps brachii with the columns parallel to the line from the acromion to the fossa cubit, with the centre of the electrode placed at one third from the fossa cubit. For both muscles, this resulted in placement of the electrode between the innervation zone and the tendon, such that propagating MUAPs were recorded. This was checked by visual inspection, and if necessary electrodes were repositioned. The side on which the electrode was placed (dominant or non-dominant) was randomised. In both experiments, a ground electrode was placed at the wrist.

The monopolar signals were amplified with a gain of 1000 and band-pass filtered (10-500 Hz) with a custom made SEMG amplifier (Helmholtz Institute for Biomedical Engineering, Technical University Aachen, Aachen, Germany, input resistance 10^{12} Ω, common mode rejection ratio 78 dB, signal to noise ratio 84 dB). The signals were sampled at 4000 Hz, digitised using a 16 bit A/D-converter (National Instruments) and

stored on a portable PC. The signals were visually inspected online. Propagation of signals and minimal shape differences between subsequent signals were used as criteria for correct alignment of the electrode columns in parallel to the muscle fibres.

Data analysis

All data was offline band-pass filtered with a second order zero phase shift Butterworth filter (10-400 Hz). For calculation of MR and MUAP shape properties, single differential signals with an IED of 10 mm were constructed from the two middle rows of monopolarly recorded signals (see Figure 3.2). This resulted in two sets of four unidirectionally propagating single differential signals. For both of these sets, cross-correlation between adjacent signals was calculated (resulting in three values from each set) and the set with the highest average correlation coefficient was selected for further processing.

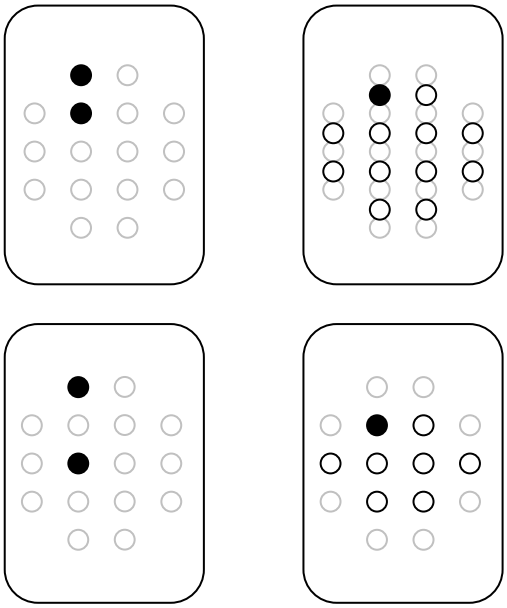

Figure 3.2 Construction of single differential signals with 10 mm (upper) and 20 mm (lower) inter-electrode distance from the monopolar recordings. The locations of the monopolar recordings are shown on the left part. The grey circles on the right part indicate the location of the original monopolar recordings. The black-lined circles indicate the (virtual) location of the constructed signals. The filled circles show an example of the construction.

MUAPs were detected with a method that used the Continuous Wavelet Transform to identify shapes that were similar to a mother wavelet (i.e. the first order Hermite-

Rodriguez function). The algorithm separated the MUAPs from the surrounding background activity. The algorithm searched for candidate MUAPs on all channels. A candidate had to occur in at least three channels before being called a MUAP. Outcome of the detection algorithm were the times of occurrence of the MUAPs detected, and the MUAP shapes on all channels. For more details, see (Gazzoni et al. 2004, Farina et al. 2000, Kallenberg & Hermens 2006b).

MR was calculated for adjacent, non-overlapping epochs of one second throughout the duration of the contractions as the number of detected MUAPs per second. Thus, MR reflects the sum of the firing rates of all contributing MUs.

In addition, the RMS value (RMS_{MUAP}) and the median frequency of the power spectrum ($FMED_{MUAP}$) of each detected MUAP was calculated (Kallenberg & Hermens 2006b). Histograms of these parameters were used to examine peripheral properties of the MU population. RMS_{MUAP}, related to the depth under the electrode and to the size of the MUs, was calculated by taking the square root of the sum of all squared data samples of the MUAP, divided by the number of samples. $FMED_{MUAP}$ reflects the frequency content of the MUAPs, which is mainly related to the MUAP duration (Hermens et al. 1992) and muscle fibre conduction velocity (Lindstrom & Magnusson 1977, Dumitru et al. 1999, Arendt-Nielsen & Mills 1985). $FMED_{MUAP}$ was calculated as the median value of the power spectrum, obtained using the fast Fourier-transform with a rectangular window. The MUAP shapes were zero-padded to obtain a frequency resolution of 1 Hz. $FMED_{MUAP}$ and RMS_{MUAP} were calculated from each of the four single differential channels, and the values were averaged across the channels afterwards.

For analysis of global SEMG parameters, three single differential signals with an IED of 2 cm were constructed from the monopolar signals by subtracting signals with 2 cm in between in the direction parallel to the muscle fibres, in accordance with the SENIAM guidelines for conventional SEMG (Hermens et al. 2000); see Figure 3.2. The signals were constructed from the same set of monopolar signals as used for MR estimation. The signals were inspected visually for the presence of artefacts and noise. Epochs containing artefacts were removed and channels with noise were discarded. Global RMS (RMS_G) and median power frequency ($FMED_G$) were calculated from adjacent, non-overlapping signal epochs of one second for each of the three signals. Average values across the three signals were calculated.

For the step contraction of the trapezius muscle, the EMG parameters (RMS_G, $FMED_G$, MR, RMS_{MUAP}, $FMED_{MUAP}$) were averaged for each force step (across the ten seconds duration). For the sustained contraction of the biceps brachii, averages were calculated per 30 s.

Statistical analysis

Linear regression analysis was applied for each individual subject for investigating relations between SEMG parameters and force (excluding the sixth step of the step contraction, that was a repetition of the second step). The slopes of the regression lines (normalized to the value at the third force step) are reported as measure for the sensitivity of the SEMG parameters for changes in force.

For comparison of the sixth and second step of the step contraction, normality of the distributions of RMS_G and MR was checked with the Kolmogorov-Smirnov test prior to statistical testing. This data was normally distributed; therefore a Student's t-test for paired samples was used to test for differences.

A mixed linear model was chosen to analyse the SEMG parameters during the sustained contraction. Mixed linear models are designed to handle correlated data, e.g. including multiple observations within each subject. For the 15 min sustained contraction, parameters were extracted for 30 s windows, resulting in 30 observations per subject. Besides factors that describe the average behaviour of the group of subjects (fixed factors), the model allows the inclusion of separate noise terms for each subject and for each measurement within a subject (random factors). Restricted maximum likelihood estimation was used for estimation of the parameters. Time was included as a covariate because it is a continuous factor, arbitrarily quantified in 30 s periods. Because of its influence on RMS (Nordander et al. 2003), body mass index was included as covariate as well. A random intercept for each subject was included. Furthermore, since the in- or decrease in SEMG parameters may be different for each subject, a random term for the slope in time for each subject was included. The model can mathematically be described as:

$$K=\beta_0 + \beta_1 \cdot \text{time} + \beta_2 \cdot \text{BMI} + \mu_0 + \mu_1 \cdot \text{time} + \varepsilon$$

With k the measurement data, β_i the coefficients for the fixed factors, μ_0 the random intercept per subject, μ_1 the random term for the slope per subject and ε the remaining noise.

The model was applied to calculate the significance of the factors. In- or decreases in parameters were estimated by applying the model again with only the significant factors included (manual backwards elimination). Means and confidence intervals (CI) of the parameter estimates are reported.

Results

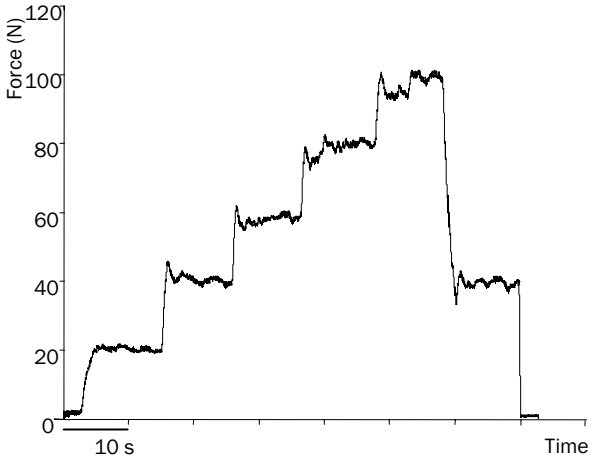

Figure 3.3 Typical example of force curve. Force steps of 20, 40, 60, 80 and 100 N were maintained for 10 seconds each, with one second in between for transition to the next step. The sixth step was a repetition of the second step (40 N).

The cross-correlation coefficient between the channels was 0.87 (SD 0.13) for the data of the first experiment. It was only in one case necessary to exclude a signal epoch (3 s) from the analysis due to artefacts in the SEMG signals. All subjects were able to follow the force steps of the step contraction to a reasonable extent: the mean force levels were within 2% of the required force levels. Standard deviations were less than 5% of the mean force levels. See Figure 3.3 for an example of a force curve.

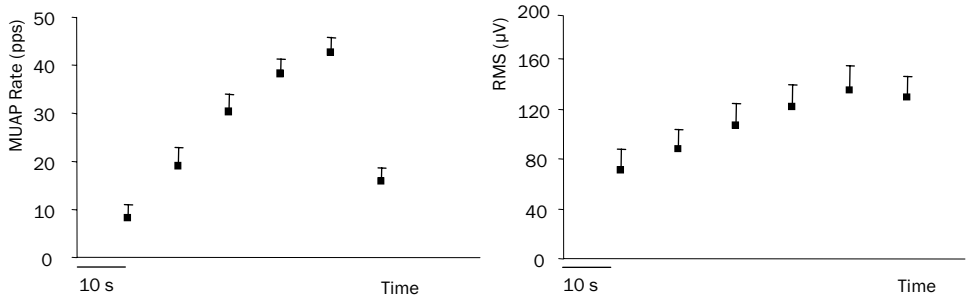

Figure 3.4 Global RMS (left) and MR (right) calculated from EMG recordings of the upper trapezius during the step contraction of shoulder elevation force. Force increased from 20 to 100 N in steps of 20 N. The sixth step was a repetition of the second step (40 N). Black squares show the average RMS and MR values for each force step, bars show standard errors of the mean.

In Figure 3.4, RMS_G and MR during the step contraction are shown. In the first five steps, the increase of RMS_G is approximately linear. Remarkably, RMS_G of the sixth step (i.e. the repetition of the second step) was much higher than that of the second step (Student's t-test for paired samples, $p<0.001$). Individual linear regression models including force and an intercept explained on average 96% (range 79-99%, $0.001<p<0.11$) of the variance in RMS_G. The sensitivity of RMS_G for changes in force, expressed as the normalised slope of the regression line, was on average 0.97%/N (range 0.27-1.8%/N).
MR increased linearly with force up to 80 N, while the increase in the last step was smaller. The values of MR for the second and the sixth step (both 40 N) were not different (Student's t-test for paired samples, $p=0.39$). Individual linear regression models including force and an intercept explained on average 94% (range 88-97%, $0.002<p<0.019$) of the variance in MR. The sensitivity of MR for force, expressed as the normalised slope of the regression line, was almost twice as high as the sensitivity of RMS_G: on average 1.8%/N (range 0.73-3.1%/N).
Note that for both RMS_G and MR the standard errors of the mean are rather constant across the whole force range. The standard errors of MR are relatively small compared to its dynamic range.

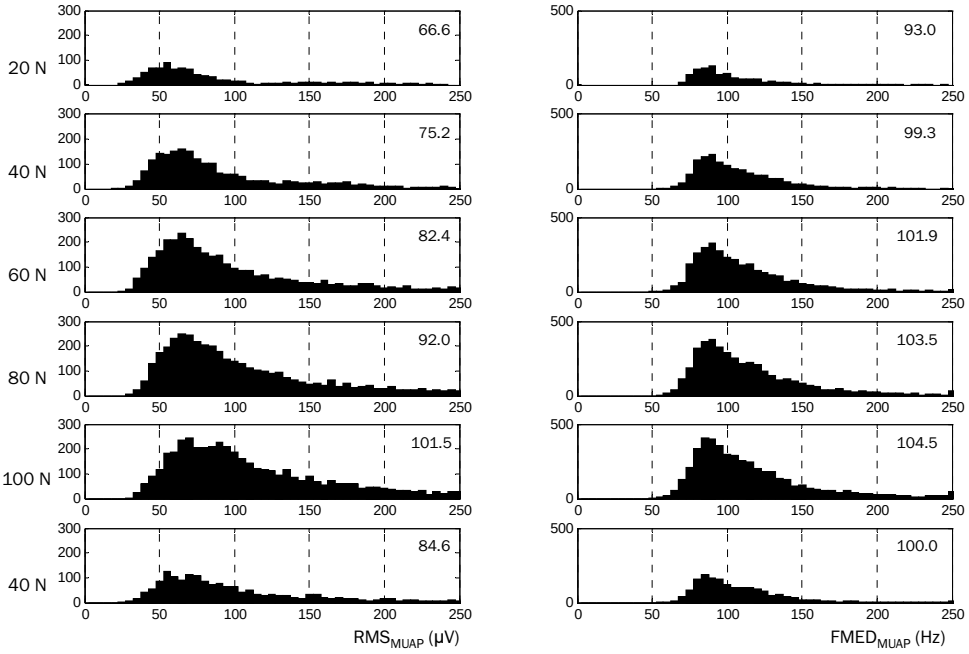

Figure 3.5 Distributions of RMS_{MUAP} and $FMED_{MUAP}$ of the MUAPs detected in EMG recordings of the trapezius muscle for the five different force steps (20-100 N). The sixth step was a repetition of the second step (40 N). Median values of the histograms are reported in the upper right corners.

In Figure 3.5, histograms of RMS_{MUAP} (left) and $FMED_{MUAP}$ (right) of the detected MUAPs are shown for each step. The distribution of RMS_{MUAP} expands towards higher values when the force increases, as is also reflected in the median values of the RMS_{MUAP} histograms. The low RMS_{MUAP} values are still present at higher force steps while higher RMS_{MUAP} values are added to the distribution when the force increases. The distribution of $FMED_{MUAP}$ changes less with force than that of RMS_{MUAP}. The median values of the histograms show that there is a slight shift towards higher $FMED_{MUAP}$ values with force. The shapes of the histograms of $FMED_{MUAP}$ for the second and sixth step are rather similar, while there are relatively more high RMS_{MUAP} values at the sixth than at the second step.

The behaviour of MR during a fatiguing contraction was investigated in the second experiment. The Likert scale scores (range 0-10) of perceived fatigue were 1.0 (SD 1.55) before, and 6.0 (SD 2.37) after the contraction. The mean MVC of the biceps brachii was 184 N (SD 45.6).
For the data of the second experiment, the cross-correlation coefficient between the channels was 0.73 (SD 0.14). For two subjects, there were a few (1-3) short periods of the signal that contained artefacts. These periods were left out from the data analysis.
MR and RMS_G both increased and $FMED_G$ decreased with time (Figure 3.6). MR increased significantly with time with 0.91%/min (0.39 pps/min, CI 0.0076 to 0.78, $p<0.043$). The intercept at the beginning of the contraction was 43.0. The mean SD across subjects averaged over time was 9.91 pps. RMS also increased significantly with time with 4.1%/min (2.0 μV/min, CI 0.42 to 3.5, $p<0.022$) and its intercept was 47.6 μV. The mean SD was 15.5 μV. FMED decreased significantly with time with 0.88%/min (0.49 Hz/min, CI -0.70 to -0.28, $p<0.002$) with an intercept of 55.7 Hz. The mean SD was 9.04 Hz.

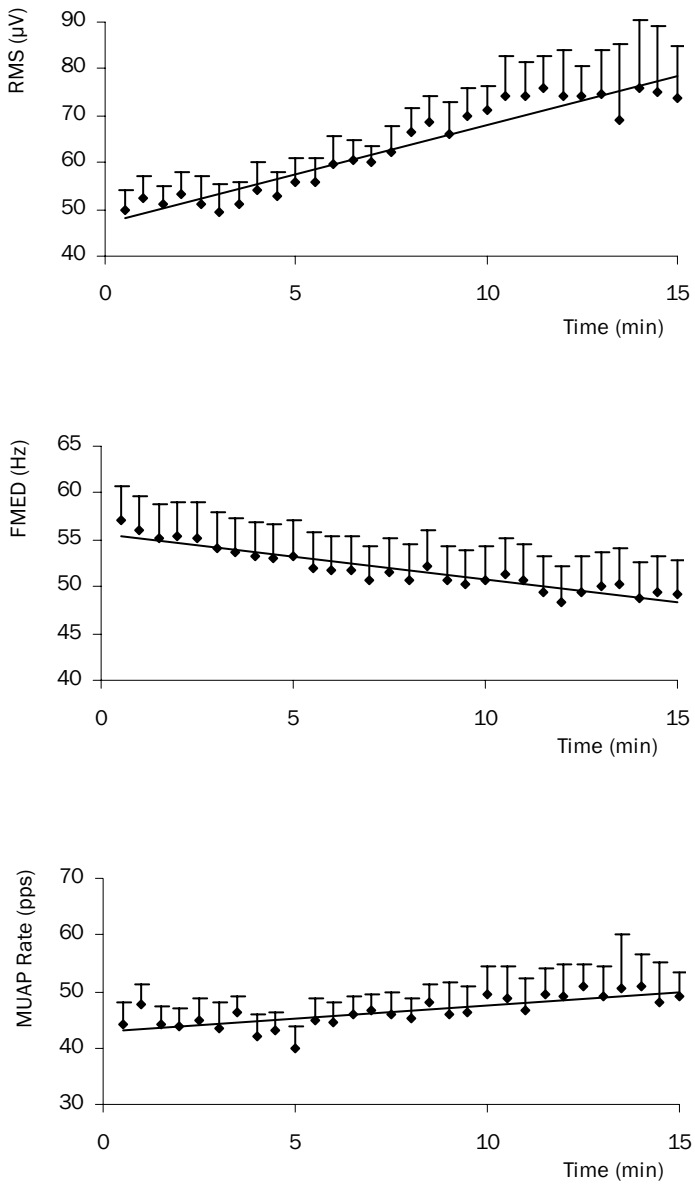

Figure 3.6 Changes in time of global RMS, global FMED and MR during a 15-min sustained contraction of the biceps muscle at 10% MVC. Diamonds show mean values, bars show standard errors of the mean.

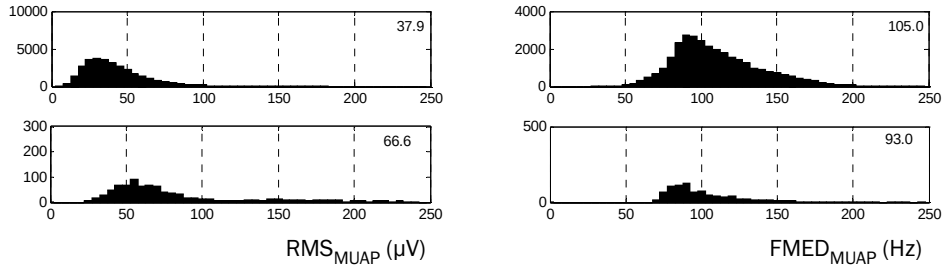

Figure 3.7 Distributions of RMS_{MUAP} and $FMED_{MUAP}$ of the MUAPs detected in EMG recordings of the biceps muscle during the first 30 seconds of a sustained contraction at 10% MVC (upper graphs). The distributions of RMS_{MUAP} and $FMED_{MUAP}$ from the trapezius muscle at the force step of 20 N are shown below for comparison (lower graphs). Median values of the histograms are reported in the upper right corners.

The distributions of RMS_{MUAP} (left) and $FMED_{MUAP}$ (right) of the detected MUAPs during the first 30 seconds of the contraction are shown in Figure 3.7 (upper graphs). The RMS_{MUAP} values are lower than the RMS_{MUAP} values extracted from the trapezius signals at 20 N (lower graphs), while the force level is similar: the biceps brachii contraction was performed at 10% MVC, which on average corresponds to 18 N. The median RMS_{MUAP} value of the biceps (37.9 μV) is also much lower than that of the trapezius (66.6 μV), while in contrast the median $FMED_{MUAP}$ value is somewhat higher in biceps (105.0 Hz) than in trapezius (93.0 Hz).

In Figure 3.8, the changes over time in MUAP properties are reported. RMS_{MUAP} increases over time while $FMED_{MUAP}$ decreases. RMS_{MUAP} increased significantly with time with 3.5%/min (1.26 μV/min, CI 0.148 to 2.38, $p<0.034$). The intercept at the beginning of the contraction was 36.3 μV. The mean SD across subjects, averaged over time was 12.1 μV. There was trend for a decrease of $FMED_{MUAP}$ with time with 0.45%/min (0.40 Hz/min, CI -0.83 to 0.020, $p<0.058$) and its intercept was 89.6 Hz. The mean SD was 12.5 Hz.

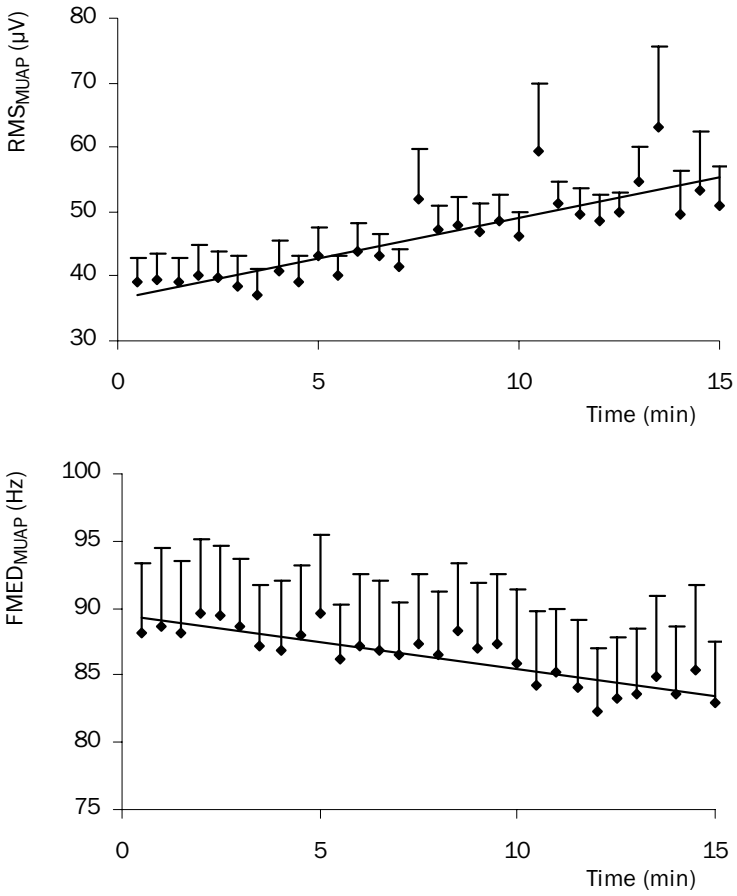

Figure 3.8 Changes in time of RMS_{MUAP} and $FMED_{MUAP}$ during a 15-min sustained contraction of the biceps muscle at 10% MVC. Diamonds show mean values, bars show standard errors of the mean.

Discussion

The objective of this study was to explore the behaviour of MR in comparison with RMS_G and $FMED_G$ in experimental conditions. MR was found to increase linearly with force up to a level of 80 N, probably due to a combined effect of recruitment of new motor units and an increase of firing rates of already recruited units. For higher force levels, the curve starts to flatten. This flattening may be related to at least two phenomena. Firstly, when the number of MUAPs in the signal increases, the MUAPs will start to overlap each other, causing underestimation of the number of MUAPs (see also Kallenberg & Hermens 2006a). Secondly, when a higher force is required, generally bigger MUs are recruited

(Henneman et al. 1965). These bigger MUs have a higher force output per firing, and thus, for a same increase in force, less additional MUs and/or firings are needed.
In contrast, the relation between RMS_G and force was linear over the whole range of investigated force levels, which is in agreement with findings for the upper leg muscles (Gerdle et al. 1991, Karlsson & Gerdle 2001). Hagberg and Hagberg (1989) reported that the slope of the RMS-force curve was steeper for high force levels than for low force levels in the upper trapezius. We only measured a force range of low to moderate levels: a force of 100 N corresponds to about 25-30% of MVC, that was 357 N for healthy subjects in the same experimental setup (Schulte et al. 2006).
The sensitivity of MR to force was about twice as high as that of RMS_G. The inter-subject variability was smaller for MR than for RMS_G, as indicated by the standard errors of the mean, relative to the dynamic range. Furthermore, MR reflected the repetition of the second step better than RMS_G. These findings suggest that for low to moderate shoulder elevation force levels, MR is a better force estimator than RMSG in the present setup.
The distribution of RMS_{MUAP} expands to higher values with increasing force. The amplitude of the MUAP depends on the size of the MU (Roeleveld et al. 1997) and on the distance between MU and electrode. Assuming a homogeneous distribution of the MUs in the muscle, the increase of RMS_{MUAP} may indicate recruitment of larger MUs. This is further supported by the increase of $FMED_{MUAP}$ with force. It was shown that $FMED_{MUAP}$ is mainly determined by muscle fibre conduction velocity (Lindstrom & Magnusson 1977, Dumitru et al. 1999, Arendt-Nielsen & Mills 1985) and by the duration of the MUAPs (Hermens et al. 1992). Since conduction velocity of a motor unit is correlated with its recruitment threshold (Andreassen & Arendt-Nielsen 1987), the higher $FMED_{MUAP}$ values indicate the contribution of higher threshold MUs.
A remarkable difference was found between the second level of the step contraction and its repetition (sixth step). At the sixth step, MR returned to the value for the second step, whereas RMS_G remained much higher. This discrepancy could be related to peripheral changes caused by muscular fatigue, which affect RMS_G (Merletti et al. 1990, De Luca 1984) but not MR. In addition, the RMS_{MUAP} histograms also show a higher median value at the sixth than at the second step. Although the explanation of these findings is not straightforward, one possibility might be that the lowering of the force step during the contraction is largely caused by a decrease in firing rate of the contributing MUs, while derecruitment of the large MUs only occurs to a limited extent. Another explanation might be that the duration of the MUAPs at the sixth level is elongated because of muscle fatigue, which would lead to an increased RMS_G, while it does not affect MR.

The second objective was to explore the behaviour of MR in comparison with RMS_G and $FMED_G$ in relation to fatigue. Subjects had to perform a 15-min isometric contraction of

the biceps brachii at 10% of their MVC. Although this is a rather low force level, the results of the Likert scale (mean score 6.0 after the contraction) show that the contraction was indeed perceived as fatiguing. Further indications for muscle fatigue development were found in the EMG variables: RMS_G, RMS_{MUAP} and MR increased while $FMED_G$ and $FMED_{MUAP}$ decreased with time. The increase of RMS_G, RMS_{MUAP} and MR is most likely related to recruitment of fresh MUs. Particularly at low force levels, additional recruitment may compensate the loss of force of already active MUs.
RMS_G increased with 4.1% per minute while there was only a 0.9% per minute increase of MR. The stronger increase of RMS_G is in line with the hypothesis that RMS_G, in contrast to MR, is also influenced by peripheral properties. Balog et al. (1994) reported changes in shape, size and duration of the intracellular action potential in relation to fatigue. These peripheral changes are probably reflected in the surface recorded MUAPs (which is shown by the increase in RMS_{MUAP}) and thereby also in RMS_G.

When the biceps brachii contraction is compared to the trapezius contraction (first step), a remarkable finding is that RMS_G is lower for the biceps than for the trapezius, while MR is higher in biceps. This might be explained by considering the substantially lower RMS_{MUAP} values in the biceps, because RMS_G is directly related to the size of the MUAPs, while MR is not affected by MUAP size. Lower RMS_{MUAP} values may point at more deeply located or smaller MUs. In agreement, an autopsy study showed a smaller average MU diameter in biceps than in trapezius (Polgar et al. 1973). This may be related to the function of the biceps, that is involved with precise control of movements, while trapezius has a more postural function.

Another method for MUAP counting, using an amplitude-based detection algorithm was developed by Zhou et al. (2003). They illustrated the relation between MR and force with recordings from three subjects, indicating an increase of MR with increasing force as well. However, they found that MUAPs with small peak amplitude that were detected at relatively low force steps (20% MVC) were not detected at higher force steps (40% MVC). They attributed this finding to the intrinsic properties of the measurement system. Contrary to this, in our study the low values of RMS_{MUAP} remain present in the distributions even at higher force steps, indicating that the algorithm is able to detect small MUAPs, even in the presence of larger MUAPs. This might be caused by differences between the algorithms. In the study of Zhou et al., in the first stage, candidate MUAPs (peaks) are detected. A threshold, derived from the amplitude distribution of the candidates is used for deciding which candidates are real MUAPs. If the candidates generally are bigger, this threshold will become higher, thus excluding small MUAPs from

being selected. In the present method, the threshold is not based on amplitude, but on similarity of the MUAP with a scalable mother wavelet.
A limitation of the algorithm is its inability to resolve superimpositions of MUAPs. Superimposed MUAPs are either not recognized or detected as single MUAP. For application to higher force steps, where superimpositions occur more often, the algorithm needs to be extended with a module that can handle superimpositions as is applied in software packages for decomposition of intramuscular EMG recordings (Zennaro et al. 2003, McGill et al. 2005).
Assessment of muscle activity with electrode arrays has several advantages when compared to conventional bipolar EMG. Recordings with an array in general can provide a more complete view of muscle activity because not only temporal, but also spatial information becomes available. The combination of array recordings with decomposition algorithms allows the extraction of information at the level of MUAPs, or even at the level of individual MUs (Holobar & Zazula 2004, Gazzoni et al. 2004, Kleine et al. 2000). Array EMG recordings are particularly suitable for low to moderate force levels. For higher force levels, superimposed MUAPs complicate the extraction of information. To overcome this, higher order spatial filters may be used to limit the number of MUs that contribute to the signal. However, this also limits the view of the electrode, which might make the recording less representative of the whole muscle.

Conclusion

In this study the behaviour of MR and MUAP shape properties in relation to force and fatigue development was explored in comparison with the commonly used SEMG measures such as RMS_G and $FMED_G$. The results suggest that MR is more sensitive to changes in shoulder elevation force than RMS_G. In a sustained contraction of the biceps brachii, MR showed a slight increase while RMS_G increased strongly. This is in line with the hypothesis that MR is largely determined by motor control properties whereas RMS_G is also strongly influenced by MU size. A limitation of the present implementation of MR estimation is that it can only be used for contractions at low to moderate force steps. Further research to explore the applicability of MR for other muscles is underway.

Acknowledgements

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Chapter 4

Motor unit action potential rate and motor unit action potential shape properties in subjects with work-related chronic pain

Laura A.C. Kallenberg, Hermie J. Hermens
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Abstract

The objective of this study was to investigate differences in motor control of the trapezius muscle in cases with work-related chronic pain, compared to healthy controls. Ten cases with chronic pain and thirteen controls participated in the study. Electromyographic (EMG) signals were recorded from the upper trapezius during five computer work-related tasks. Motor control was assessed using global root-mean-square value (RMS_G), motor unit action potential (MUAP) rate (number of MUAPs per second, MR) and two MUAP shape parameters, i.e. root-mean-square (RMS_{MUAP}) and median frequency ($FMED_{MUAP}$). MR and $FMED_{MUAP}$ were higher for the cases than for the controls ($p<0.05$). RMS_{MUAP} showed a trend for higher values in the chronic pain group ($p<0.13$), whereas RMS_G did not show a significant difference between the groups. The higher MR, $FMED_{MUAP}$ and the trend for higher RMS_{MUAP} suggest that more high-threshold MUs contribute to low-level computer work-related tasks in chronic pain cases. Additionally, the results suggest that the input of the central nervous system to the muscle is higher in the cases with chronic pain.

Introduction

The prevalence of work-related disorders (WRD) has increased significantly during the last few decades. Since the majority of people with WRD are limited in their working abilities by chronic pain, this results in high costs for health care and society.

The mechanisms behind the development of chronic pain are poorly understood (Bongers et al. 2002b). The Cinderella hypothesis, which states that low-threshold motor units (MUs) are damaged due to lack of sufficient muscle rest (Hägg 1991), is a commonly used model related to work at low force levels. Some evidence for this hypothesis has been found. So-called Cinderella MUs (defined as MUs that stay active for periods of over 30 min without rest) have been reported by different authors (e.g. Thorn et al. 2002; Forsman et al. 2002; Zennaro et al. 2003; Søgaard 1995). Other authors found a decreased percentage of muscle rest, measured as gaps in the electromyogram (EMG), in chronic pain patients (Veiersted 1994; Hägg and Åström 1997). In another study, Veiersted showed that lack of gaps was a weak but significant predictor for the development of pain (Veiersted et al. 1993).

However, the Cinderella hypothesis does not explain how the low-threshold MUs are getting damaged. It can be hypothesised that the development of damaged MUs is either caused by, or at least accompanied by, changes in motor control. Assuming this, it is desirable to assess motor control in chronic pain cases in a direct and detailed way.

Usually, bipolar surface EMG is used for investigating motor control. However, extraction of motor control aspects from bipolar EMG is not straightforward since the EMG signal, which is measured with relatively large electrodes, consists of the summed activity of many MUs. More detailed information about single MUs can be obtained using needle electrodes. For example, Linnamo et al. (2003) used an index based on the number of motor unit action potentials (MUAPs) within different amplitude bands for describing the motor neuron pools during different contraction types. However, measuring EMG with needles is invasive, and only a few MUs contribute to the recorded signal, which limits the use of this method for assessing motor control.

Recently, we have proposed the assessment of the number of MUAPs per second, or MUAP rate (MR), for investigating motor control (Kallenberg and Hermens 2004), since this parameter is directly related to the input of the central nervous system to the muscle. In addition to information about motor control, MUAP shape properties are provided by this method. The MUAP rate and MUAP shape properties can be assessed non-invasively with this method using multi-channel electrode arrays in combination with advanced signal processing methods (e.g. continuous wavelet transform).

The aim of the present work was to investigate differences in motor control between chronic pain cases and healthy controls during computer work-related tasks, using the MR and MUAP shape properties.

Methods

Subjects

This study was approved by the local medical ethics committee. All subjects gave their written informed consent.

EMG of the dominant upper trapezius from a control group (n=13; 2 males, 11 females, mean age 38.9, range 20–54 years, mean body mass 67.5, range 55–80 kg, mean height 173.1, range 158–183 cm, mean body mass index 23.0, range 18.2–27.1 kg/m^2) and a case group (n=10; 4 males, 6 females, mean age 36.1, range 24–51 years, mean body mass 71.2, range 57–86 kg, mean height 176.2, range 164–195 cm, mean body mass index 23.0, range 19.4–28.3 kg/m^2) was recorded during computer work-related tasks. All subjects were computer workers. Subjects were recruited from a local university and a local library. Their history of neck-shoulder complaints was assessed by means of a questionnaire (an adapted version of the Standardized Nordic Questionnaire, Kuorinka et al. 1987). Subjects were included in the control group if they did not have any self-reported complaints in the neck or shoulder region for at least 3 years. Subjects were included in the case group if they reported neck or shoulder complaints for more than 30 days during the last year. Furthermore, to be included, cases had to report that their complaints restricted their ability to work.

General procedures

Five visual analogue scales (VAS) were used to measure the levels of stress and discomfort experienced in the arms, shoulders, neck and upper back before the experiment started. The protocol consisted of a unilateral dynamic hand task (referred to as the dots task), a typing task, an editing task, a mouse task and a stress task. The duration of each task was set to 5 min. During the dots task, subjects were asked to continuously move the dominant arm between three target areas by putting marks in circles with a diameter of 12 mm with a pencil (see Fig. 4.1). The pace was kept constant at 88 marks/min by a metronome.

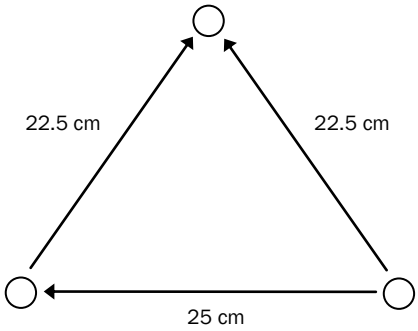

Figure 4.1 Dots task. Circles indicate the target areas (diameter 12 mm). The subject had to mark the target areas with a pencil at a pace of 88 marks/min. The arrows indicate the direction for right-handed subjects.

The typing task consisted of re-typing a standard text. During the editing task, subjects had to make the first word with five characters or more bold and capitalise the first character of the next word with five characters or more. This had to be repeated throughout the whole text or until the time was finished. The mouse task was performed using a drawing program on the PC, where subjects had to draw a pattern by clicking on small circles (7 mm diameter). During the stress task (the STROOP test, Faucett and Rempel 1994), the Dutch words for 'blue', 'yellow', 'green' and 'red' were shown in different colours. Subjects had to point the mouse to an icon with the colour of the word in black characters as quickly as possible. If a mistake was made or if a time limit was passed, a beep sounded.

EMG recordings

EMG recordings were made with linear eight-channel electrode arrays (LISiN-SPES Medica, S. Pedrino di Vignate, Milano, Italy) with a 5-mm inter-electrode distance. The arrays were placed on the upper trapezius muscle, on the line from the spinous process of the seventh cervical vertebra to the acromion, with the most medial electrode 5–10 mm lateral from the midpoint, such that unidirectionally propagating signals were recorded (Farina et al. 2003). The part of the skin where the electrodes were placed was cleaned with alcohol. Conductive gel (20–30 μl for each electrode of the array) was used to assure proper electrode–skin contact and was inserted with a gel dispenser (model Eppendorf AG-Multipette plus, Hamburg, Germany) into the cavities of the adhesive electrode array (see Farina et al. 2003). A ground electrode was wrapped around the wrist. The signals were bipolarly amplified 3,500 times, analogue band-pass filtered (cut-off frequencies 6–500 Hz) and sampled at 2,048 Hz. The signals were digitised using a 12 bit A/D-converter and stored on a data logger (LISiN-Sirio Automazione, Rivoli, Turin, Italy). Before the

measurement started and in between the recordings, the signal quality was inspected visually and adjustments were made when necessary.

Signal processing

Root-mean-square (RMS) values were calculated for adjacent non-overlapping epochs of 1 s from a bipolar signal with an inter-electrode distance of 2 cm, according to the recommendations of Mathiassen et al. (1995) and Hermens et al. (2000). The four channels that were used to construct this bipolar signal were selected from all available channels according to a previously described method that minimises the sensitivity to changes in electrode position (Farina et al. 2002). In order to identify possible fatigue-related changes during the tasks, a linear regression line was fitted through the RMS values of the 1 s epochs, and its intercept and slope were calculated (Farina and Merletti 2000). The global RMS (RMS_G) was defined as the intercept of the regression line.

For calculation of the MR, at least five consecutive bipolar signals that showed propagating MUAPs with high quality were selected manually. MUAPs were detected with a method that uses the continuous wavelet transform to identify shapes that were similar to a mother wavelet (i.e. the first order Hermite-Rodriguez function, depicted in Fig. 4.2). The algorithm separated the MUAPs from the surrounding background activity. The algorithm searched for candidate MUAPs on all channels. A candidate had to occur in at least three channels before being called a MUAP. The outcomes of the detection algorithm were the times of occurrence of the MUAPs detected, and the MUAP shapes on all channels (See Fig. 4.2). An example of 400 ms of a recorded signal is shown in Fig. 4.2. The triangles indicate the MUAPs that were detected and correspond to the time instances where the detected MUAPs occurred in the second channel. The times of occurrence in all channels were stored. The extracted MUAP shapes are shown for a few examples. For more details about the method, see Farina et al. (2000) and Gazzoni et al. (2004).

The detected MUAPs were not classified into single MU firing trains. MR was calculated from all detected MUAPs. Thus, MR reflects the product of the number of MUs and their average firing rate. MR was calculated for adjacent, non-overlapping epochs of 1 s throughout the duration of the tasks as the number of detected MUAPs per second from the middle one of the signals selected for MUAP detection. The mean and standard deviation of MR within each subject (across seconds) were calculated. In addition, root-mean-square value (RMS_{MUAP}) and median power frequency ($FMED_{MUAP}$) of all detected MUAP shapes were calculated from the same signal. Subsequently, RMS_{MUAP} and $FMED_{MUAP}$ were averaged per subject.

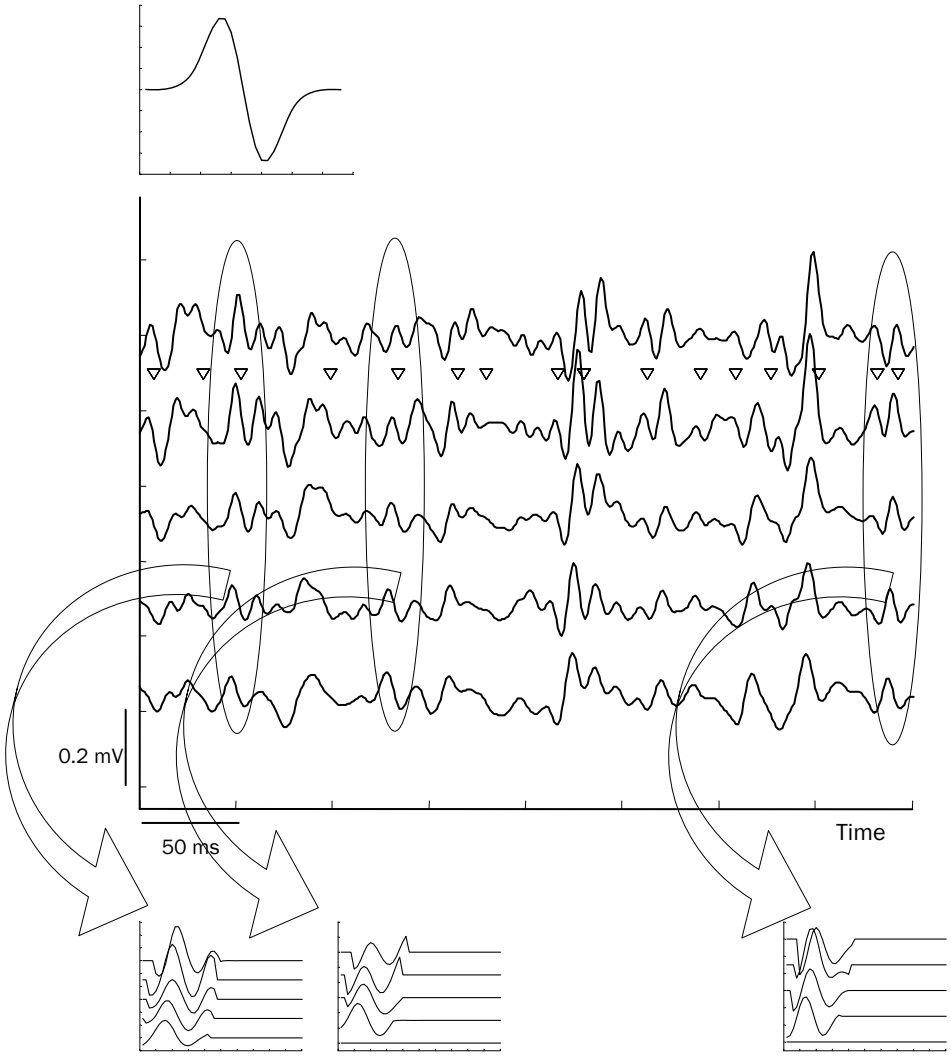

Figure 4.2 Top First-order Hermite-Rodriguez function, used as mother wavelet for the detection of MUAPs. Bottom Recorded signal (400 ms) with detected MUAPs (indicated with triangles) and some examples of extracted MUAP shapes (the zeros surrounding the MUAP shapes are not included in the analysis).

The data were analyzed using two-way (task, group) analysis of variance (ANOVA), followed by post hoc Bonferroni tests, when required. When means between the two groups were compared, the normality of the distributions of the data was assessed with a Kolmogorov-Smirnov test prior to statistical testing. If the data were non-normally distributed, the Mann-Whitney test for independent samples was used. If the data were normally distributed, the Student t-test for independent samples was used. Differences in variance between the groups were tested with Levene's test for equality of variance. Statistical significance was set to $p<0.05$.

Results

The VAS scores for the overall stress level and discomfort experienced in the arms, shoulders, neck and upper back of both groups are presented in Table 4.1. The VAS scores in the case group are much higher than those of the control group for all items ($p<0.05$, Mann-Whitney test).

Table 4.1 VAS scores of the two groups (SD: standard deviation)

	Controls		Cases	
	Mean	SD	Mean	SD
Stress level	0.3	0.4	3.8	1.8
Experienced discomfort in arms	0.3	0.6	1.7	1.8
Experienced discomfort in shoulders	0.1	0.4	4.6	2.7
Experienced discomfort in neck	0.2	0.4	4.4	3.0
Experienced discomfort in upper back	0.2	0.4	3.8	3.0

The mean MR and the inter-subject standard deviation of both groups during the tasks are shown in Fig. 4.3. A two-way (task, group) ANOVA revealed a statistically significant dependency for both variables (task: $F=3.92$, $p<0.005$, group: $F=6.67$, $p<0.02$). As can be seen from the figure, the difference between the two groups is most pronounced for the stress task. Mann-Whitney tests for each task analysed separately revealed a significant difference between the groups for the stress task ($p<0.05$).

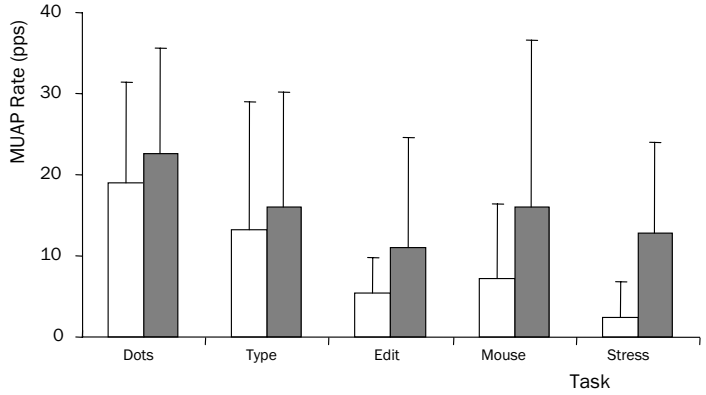

Figure 4.3 MR for the control group (white bars, n=13) and the chronic pain group (black bars, n=10) for all tasks. The error bars show inter-subject standard deviations. MR is significantly higher for chronic pain cases than for controls.

The RMS_G is presented in Fig. 4.4. The differences between the groups are rather small. A two-way (task, group) ANOVA revealed a dependency only on task, not on group (task: $F=10.7$, $p<0.000$, group: $F=0.972$, $p>0.32$). A post hoc Bonferroni test revealed significant differences between the dots task and all other tasks ($p<0.02$). The rates of change of the RMS_G during the tasks (slopes of the regression lines) were not significantly different from zero for both groups.

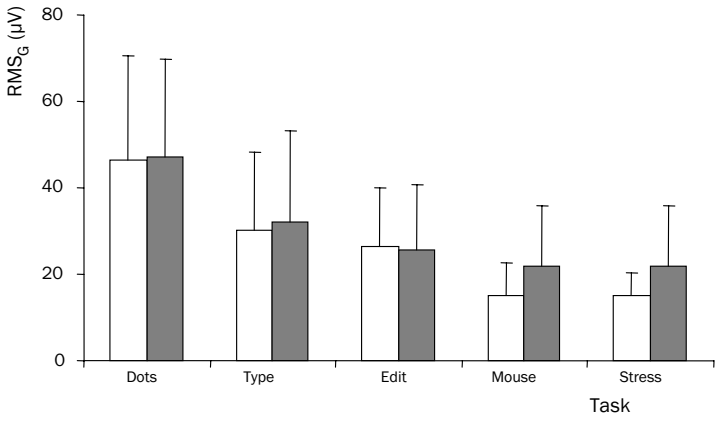

Figure 4.4 RMS_G for the control group (white bars, n=13) and the chronic pain group (black bars, n=10) for all tasks. The error bars show inter-subject standard deviations. No significant differences were found between the groups.

The RMS_{MUAP}, mean per subject, is presented in Fig. 4.5. A two-way (task, group) ANOVA revealed a trend ($p<0.13$) for higher RMS_{MUAP} values in the case group. Mann-Whitney tests for each task analysed separately revealed a significant difference between the groups for the mouse task ($p<0.03$). The distribution of RMS_{MUAP} seems to be shifted to higher values for the case group, compared to the controls. The variance in the two groups did not differ (Levene's test for equality of variance, $p>0.77$).

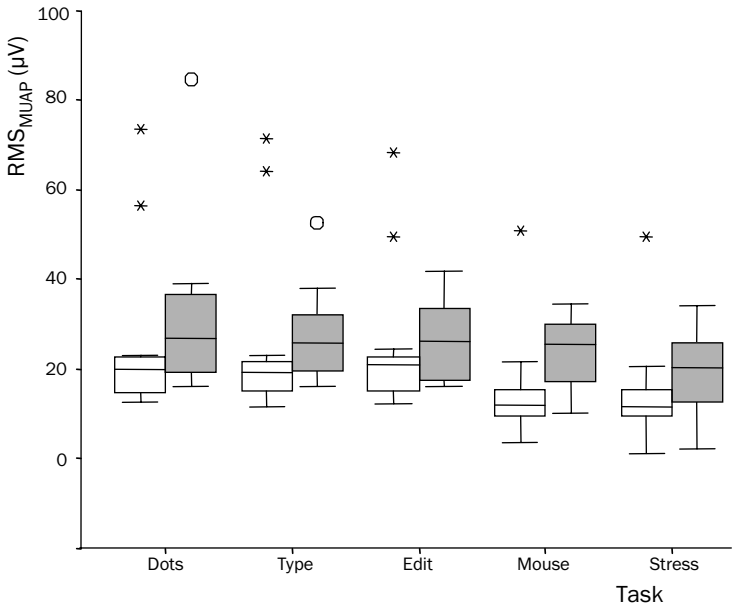

Figure 4.5 Mean RMS (per subject) of the detected MUAPs (RMS_{MUAP}) per subject group (white bars control group, n=13; grey bars chronic pain group, n=10) for all tasks. There is a trend for higher values in the chronic pain group (ANOVA, $p<0.13$). The bar length is the interquartile range. Asterisks indicate outliers (values between 1.5 and 3 bar lengths from the upper or lower edge of the bar). Circles indicate extremes (values more than 3 bar lengths from the upper or lower edge of the bar).

$FMED_{MUAP}$, mean per subject, is presented in Fig. 4.6. It can be seen that the distribution of $FMED_{MUAP}$ is shifted to higher values for the case group. In addition, the variability is larger in the case group. A two-way (task, group) ANOVA revealed a dependency only for group ($F=22.1$, $p<0.001$). Mann-Whitney tests for each task analysed separately revealed significant differences between the groups for all tasks except for the editing task ($p<0.05$). Levene's test for equality of variance revealed a significantly higher variance in the case group than in the control group ($p<0.02$).

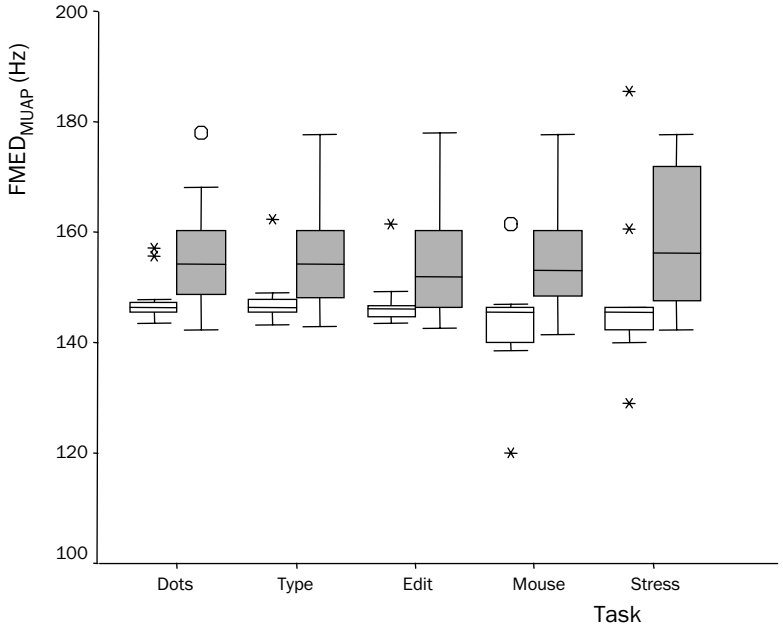

Figure 4.6 Mean FMED (per subject) of the detected MUAPs ($FMED_{MUAP}$), per subject group (white bars control group, n=13; grey bars chronic pain group, n=10) for all tasks. There is a significant difference between the two groups (ANOVA, $p<0.001$). The bar length is the interquartile range. Asterisks indicate outliers (values between 1.5 and 3 bar lengths from the upper or lower edge of the bar). Circles indicate extremes (values more than 3 bar lengths from the upper or lower edge of the bar).

Discussion

The objective of this study was to investigate differences in motor control in chronic pain cases compared to healthy controls. The results show a higher mean MR for cases with chronic pain than for controls during computer work-related tasks. This finding would suggest a higher input from the central nervous system in the cases, due to increased recruitment and/or a higher average firing rate. The higher $FMED_{MUAP}$ and the trend for higher RMS_{MUAP} in the chronic pain cases suggest that more high-threshold MUs contribute to the contractions. According to the Henneman principle (Henneman et al. 1965), this would suggest that the motor unit recruitment during an imposed task is increased in chronic pain cases compared to controls, although the biomechanical demand is the same. This is in agreement with the pain-spasm-pain model (Turk and Flor 1984; Gentry and Bernal 1977) that suggests a stiffening of the painful area through contraction of the painful muscle to prevent further muscle damage caused by movement.

Another explanation of the higher MR and higher $FMED_{MUAP}$ and RMS_{MUAP} values would be a lower force output of the low-threshold MUs in chronic pain cases, thereby necessitating additional recruitment. To the authors' knowledge, information about force output per MU at low contraction levels is not available in relation to chronic pain. Some evidence pointing to a decreased force output in cases with chronic pain has been found by Schulte et al. (2006), who reported a decrease in maximal voluntary contraction force in cases.

The higher MR in combination with the trend for higher RMS_{MUAP} values in chronic pain cases is expected to result in higher global RMS values. However, no significant difference was found between the two groups for RMS_G. RMS_G is an estimate of the variance of the EMG signal, and therefore more sensitive to noise and background activity than MR. In addition, RMS_G is highly influenced by the detection system parameters (e.g. inter-electrode distance), thickness of the subcutaneous layer etc. Differences in MR and RMS_{MUAP} between the two groups might be masked by these factors. A possible confounding influence on the present results could be the body mass index as this would especially affect the RMS_G and RMS_{MUAP}. However, the body mass index was very similar in the two groups.

The observed differences in MR were most pronounced in the stress task. The stress task requires a low biomechanical demand, as can be seen from the MR values of the control group. In spite of this low demand, the chronic pain cases showed much higher MR values than controls, suggesting that they are more sensitive to stress than controls. This is in agreement with reports of increased sensitivity to stress in chronic pain cases (Bansevicius et al. 2001; Bongers et al. 2002a; Huang et al. 2002) and the finding that stress can keep

low-threshold MUs active, even when there is no biomechanical demand (Lundberg 2002).

Contrary to the present results, Birch et al. (2000) found a decreased EMG activity in relation to pain. They inserted hypertonic saline in the extensor carpi ulnaris (ECR) before starting a mouse task with either high or low precision. For the low precision task, the EMG amplitude of the ECR was less in the pain condition than in the control condition. The contradiction between these results and the present results is most likely related to the type of pain. In the study of Birch et al. (2000) experimental pain was induced in healthy subjects, resulting in acute pain, while the present study investigated chronic pain.

Other authors (Moffroid 1997) have suggested that chronic pain is accompanied by muscle deconditioning. Deconditioning leads to a decrease in fibre diameter, thereby decreasing conduction velocity. This would in turn result in a decreased $FMED_{MUAP}$. In contrast, we found a higher $FMED_{MUAP}$. No evidence for deconditioning was found in the cases in our study.

Conclusion

The aim of the present work was to investigate differences in motor control of cases with chronic pain compared to healthy controls. The results show that MR is higher for chronic pain cases than for controls in computer work-related tasks. Furthermore, the higher $FMED_{MUAP}$ and the trend for higher RMS_{MUAP} suggest that more high-threshold MUs contribute to the contractions in cases with chronic pain. This indicates that the input of the central nervous system to the muscle is higher in chronic pain cases, while the biomechanical demand is the same. MR seems to be a promising way to assess motor control of a muscle in a non-invasive way.

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Chapter 5

Myoelectric manifestations of fatigue at low contraction levels in subjects with and without chronic pain

Laura A.C. Kallenberg, Elke Schulte, Catherine Disselhorst-Klug, Hermie J. Hermens
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Abstract

The aim of the present study was to investigate differences in myoelectric responses to fatigue development between cases with chronic neck-shoulder pain (n=10) and healthy controls (n=10) during a low force level sustained contraction.

Subjects performed a 15-minute isometric shoulder elevation at a force level of 40 N (sustained contraction), preceded and followed by a step contraction, consisting of five force levels from 20 to 100 N.

EMG recordings were made with a two-dimensional electrode array on the upper trapezius of the dominant side. Root-mean-square (RMS_G), median power frequency ($FMED_G$), conduction velocity (CV), number of motor unit action potentials per second (MUAP Rate) and MUAP shape properties were estimated. Changes over time and differences between the groups were statistically evaluated with a linear mixed model.

During the sustained contraction, cases showed less increase in RMS_G than controls (controls: 58.5%, cases: 33.0%). $FMED_G$ and CV decreased in controls ($FMED_G$: -6.3%, CV: -5.3%) and stayed constant ($FMED_G$) or slightly increased (CV, 3.15%) in cases. Overall, cases showed a less pronounced myoelectric response to the fatiguing task than controls, which may be related to additional recruitment of higher-threshold MUs. A possible explanation might be that cases were already (chronically) fatigued before the experiment started.

Introduction

Chronic muscular pain is becoming an increasingly important problem in western countries. The Third European Survey on working conditions in acceding and candidate EU countries in 2000 (Paoli and Parent-Thirion, 2003) revealed that 23% of the workers in the EU countries report muscular pain in the neck-shoulder region. Muscular pain is the third important work-related health problem in the EU, only preceded by backache (34%) and stress (28%).

Chronic pain has been studied in relation to muscle activity patterns by surface electromyography (EMG). Several authors reported that EMG activity during work tasks was increased in patients with neck-shoulder complaints (Veiersted et al. 1990, Veiersted 1994, Lundberg et al. 1999, Madeleine et al. 2003). Other studies demonstrated an inability to relax in trapezius myalgia patients (Elert et al. 1992). Furthermore, a decreased percentage of muscle rest, measured as short silent periods in the EMG ('gaps'), has been demonstrated in chronic pain patients (Veiersted 1994, Hägg and Åström 1997). In another study, Veiersted showed that lack of gaps was a weak but significant predictor for the development of pain (Veiersted et al. 1993).

Other authors have investigated the development of muscle fatigue in chronic pain patients. Fatigue is known to be reflected in the EMG signal as an increase of its amplitude and a decrease of its characteristic spectral frequencies (De Luca 1984; Merletti et al. 1990, 2002; Madeleine et al. 2002). In a study on fatigue development in patients with unilateral myalgia was found that the affected side showed less myoelectric signs of fatigue than the healthy side (Öberg et al. 1992). Other studies of fatigue in relation to chronic pain did not reveal differences in EMG parameters, but showed that endurance time was shorter for chronic pain cases (Hagberg and Kvarnström 1984, Hansson et al. 1992, Larsson et al. 2000).

Pain in the neck-shoulder region relatively often occurs in relation to computer use (Bongers et al. 2002, Jensen 2003), where the force levels generated by the muscles are very low. Nevertheless, studies of the development of fatigue in pain patients usually are performed at relatively high force levels: for example, Öberg et al used 0 kg, 1 kg and 2 kg hand loads while subjects held the arms straight at 90 degrees of elevation in the scapular plane (Öberg et al. 1992). It is questionable whether the development of fatigue during such contractions represents the fatigue that occurs during computer work sufficiently. Therefore, in this study we focused on investigating the myoelectric manifestations of fatigue at low force levels.

A hypothesis that is often used to explain chronic pain development is the Cinderella hypothesis (Hägg 1991). This hypothesis states that low-threshold motor units (MUs) are

getting damaged because of too long activation and lack of muscle rest in chronic pain patients (Hägg 1991). However, the Cinderella hypothesis does not explain how development of damaged MUs proceeds. A possible mechanism could be that healthy MUs first become chronically fatigued, i.e. their force production is reduced, before getting damaged. Assuming this, one would expect that part of the (low-threshold) MUs of cases with chronic pain is already fatigued before the start of a contraction, or that they would get fatigued very early during the contraction. To compensate for the loss of force, higher-threshold MUs would be recruited. This additional recruitment may mask the myoelectric manifestations of fatigue (Houtman et al. 2003). We therefore hypothesize that cases with chronic pain respond less pronounced than healthy controls to a low-level fatiguing contraction in terms of changes in EMG.

To investigate this hypothesis, computer workers with and without chronic pain performed a low force level fatiguing contraction. Multi-channel surface EMG was recorded from the upper trapezius before, during and after the fatiguing contraction. Besides commonly used EMG parameters, conduction velocity (CV) and the number of motor unit action potentials per second (MUAP Rate, MR) were assessed.

Methods

Subjects

Ten healthy subjects (control group, 5 male, 5 female, mean (SD) age 31.0 (11.7) years, weight 69.6 (9.8) kg, height 180 (11) cm, body-mass index (BMI) 21.5 (1.6) kg/m^2) and ten cases with chronic pain (case group, 6 male, 4 female, mean (SD) age 36.7 (9.3) years, weight 70.6 (6.5) kg, height 178 (10), BMI 22.5 (2.8) kg/m^2) took part in this study. The two subject groups were not different with respect to their demographic characteristics (Student's t-test for independent samples, $p>0.24$). All subjects signed an informed consent. The study was approved by the local medical ethics committee.

A Dutch questionnaire about work and health (Hildebrandt et al. 2001) was used to select subjects. This questionnaire comprises questions about work history and vocational satisfaction, and questions about health, i.e. history, duration and location of complaints and history of therapy.

Subjects were included when they performed predominantly computer work for at least 20 hours per week. Subjects were excluded if they reported non-work related neuromuscular disorders. Subjects were included in the control group when they did not have any self-reported complaints in the neck, shoulders, arms or upper back during the last year. Subjects were included in the case group when they reported more than 30 days during the last year with pain in the neck and/or shoulders. Subjects were excluded if they had

complaints in more than three body regions. Cases were recruited from the Dutch society for patients with Repetitive Strain Injury.

General procedures

Shoulder elevation force and EMG of the m. trapezius were measured simultaneously during two step contractions and an isometric sustained contraction of 15 minutes at a force level of 40 N (further referred to as sustained contraction). The step contractions were performed before and after the sustained contraction to examine possible changes in motor control. The step contractions consisted of five force levels (20, 40, 60, 80, 100 N) with a duration of 10 seconds each. In between the levels, one second for transition to the next level was given. The first step contraction was followed by 15 minutes rest (see Figure 5.1). After that, the sustained contraction was performed, directly followed by the second step contraction.
When the exerted force tended to decrease, subjects were encouraged to maintain the required force level.

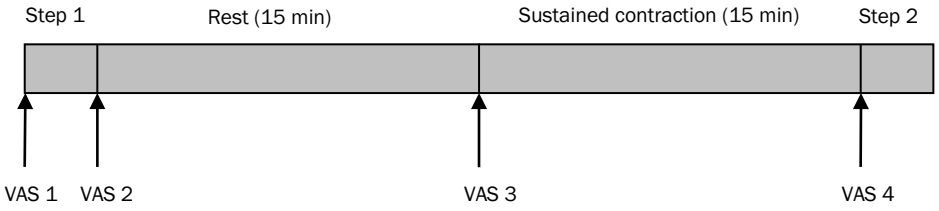

Figure 5.1 Experimental protocol. Subjects had to perform a step contraction (levels of 20-100 N in steps of 20 N, duration of each level 10 s), followed by 15 min rest. After that, a sustained contraction with a duration of 15 min at a level of 40 N was performed, immediately followed by a second step contraction. VAS: Visual Analogue Scales of perceived fatigue. Arrows indicate time instances when the VAS scores were recorded.

Subjects were seated on an adjustable chair that was high enough to prevent them from touching the floor with their feet. Subjects were instructed not to speak or move the head during the recordings, to sit straight, and to keep their hands rested in their lap. Subjects were not allowed to cross their feet.
The chair was attached to a frame that was fixed to the wall. Two force transducers (Thermonobel, Karlskoga, Sweden) were attached to the frame for measuring the shoulder elevation force. The position of the force sensors was adjusted to body size, such that the sensor centre was located slightly above the acromion (see Figure 5.2). In rest, the force sensors were just not touching the subject. The distance between the spinous process of the seventh cervical vertebra (C7) and the acromion was measured. Force feedback was provided on a laptop screen in front of the subject. The force signals were sampled with 1 kHz, digitized with a 16-bits A/D converter, and stored on a laptop.

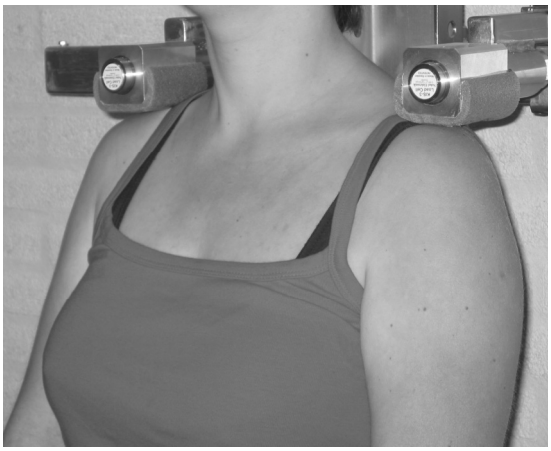

Figure 5.2 Measurement set-up with the two force transducers located slightly above the acromion at both sides. Force and EMG (not visible) were measured simultaneously from the trapezius muscle. Force feedback was provided on a laptop in front of the subject.

Perceived fatigue in the neck-shoulder region was measured with Visual Analogue Scales (VAS, Gift 1989) before the experiment started, after the first step contraction, after the rest period and after the second step contraction (Figure 5.1). The minimal VAS score (0) corresponded to 'not fatigued at all', the maximum VAS score (10) corresponded to 'as much fatigued as possible'.

EMG recordings

EMG of the dominant upper trapezius was recorded using a two-dimensional 16-channel electrode array developed by the Helmholtz Institute for Biomedical Engineering, Technical University Aachen, Aachen, Germany (Schulte et al. 2006). The array consisted of four rows of gold-coated pin electrodes with a diameter of 1.5 mm, the first and fourth containing three contact points and the middle two containing five contact points. The inter-electrode distance (IED) was 10 mm in both directions (see Figure 5.3).

Before placement of the electrode array, the skin was cleaned using abrasive paste. The electrode array was placed with the rows parallel to the line from C7 to the acromion with the centre of the electrode array 2 cm distally from the midpoint, in accordance with the SENIAM recommendations (Hermens et al. 2000). The signals were visually inspected online. Propagation of signals and minimal shape differences between subsequent signals were used as criteria for correct alignment of the electrode array rows in parallel to the muscle fibres. A ground electrode was placed on the wrist of the dominant side.

The monopolar signals were amplified with a gain of 1000 and band-pass filtered (10-500 Hz, Butterworth filter) with a custom made EMG amplifier (Helmholtz Institute for

Biomedical Engineering, Technical University Aachen, Aachen, Germany, input resistance $10^{12}\Omega$, common mode rejection ratio 78 dB, signal to noise ratio 84 dB). The signals were sampled at 4000 Hz, digitised using a 16 bit A/D-converter (National Instruments) and stored on a laptop.

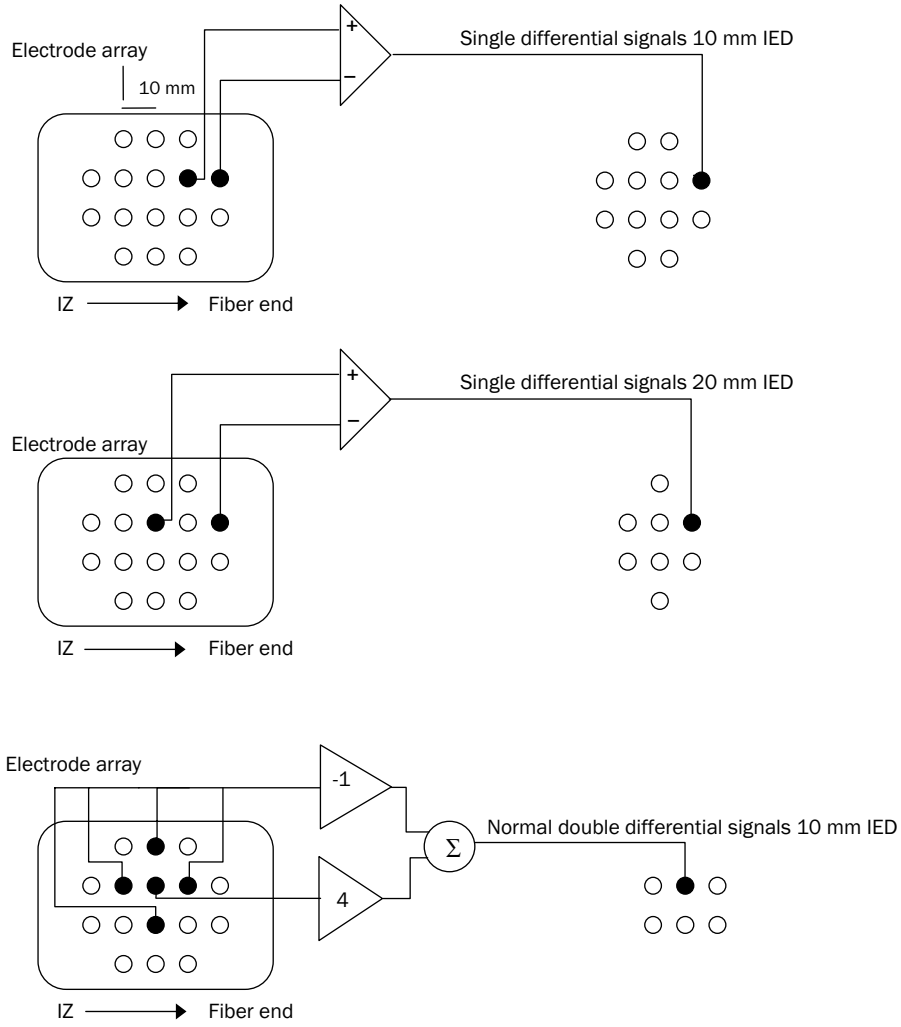

Figure 5.3 Schematic representation of the electrode and the construction of several spatially filtered signals from the monopolar recordings. IZ: innervation zone. IED: Inter-electrode distance

Data analysis

For analysis of global EMG parameters, six single differential signals with an IED of 2 cm were constructed offline from the monopolar signals of the middle two rows of the array by subtracting signals from electrodes with 2 cm in between in the direction parallel to the muscle fibres, in accordance with the SENIAM guidelines for conventional surface EMG (Hermens et al. 2000; see Figure 5.3). The signals were inspected visually for the presence of artefacts and noise. Epochs containing artefacts were removed and channels with noise were discarded.

Global RMS (RMS_G) and median power frequency ($FMED_G$) were calculated from adjacent, non-overlapping signal epochs of one second for each of the six signals. Since averaging across multiple electrodes increases the stability of the RMS_G estimates (Staudenmann et al. 2005), average values across the six signals were calculated for RMS_G as well as $FMED_G$.

Estimates of conduction velocity (CV) have been shown to be dependent on the applied spatial filter. Longitudinal (parallel to the muscle fibres) and 2D-filters are supposed to reduce end-of-fibre components (that bias CV estimation) to a larger extent than transverse filters (Schulte et al. 2003). Furthermore, the 2D normal double differential filter (NDD) has been shown to result in a high spatial selectivity in both longitudinal and transverse direction (Farina et al. 2003). Therefore, NDD-filtered signals were used for CV estimation. The number of MUs that contribute to the NDD signals is limited. The CV estimate that results from the interference pattern of the contributing MUs is a weighted average value of the single MU CVs, with weights depending on the location and size of each MU.

Two sets of NDD signals were constructed from the monopolarly recorded signals (see Figure 5.3). From each set, the first and last channel was used for CV calculation. CV was estimated using a cross-correlation based algorithm that calculated the time delay corresponding to the maximum of the cross-correlation function, using its time derivative. The two CV estimates were averaged. Furthermore, for each subject at least 50% of the CV values had to be between 2 and 8 m/s; otherwise, the CV data of the subject were excluded from the analysis.

For calculation of MUAP Rate, eight single differential signals with an IED of 10 mm were constructed from the two middle rows of monopolarly recorded signals (see Figure 5.3). This resulted in two sets of four unidirectionally propagating single differential signals. For both of these sets, cross-correlation between adjacent signals (in the direction parallel to the fibres) was calculated, resulting in three values from each set. The set with the highest average correlation coefficient was selected for further processing.

MUAPs were detected with a method that uses the Continuous Wavelet Transform to identify shapes that were similar to a mother wavelet (i.e. the first order Hermite-

Rodriguez function). The algorithm searched for candidate MUAPs on all channels. A candidate had to occur in at least three channels before being called a MUAP. The outcomes of the detection algorithm were the times of occurrence of the MUAPs detected, and the MUAP shapes on all channels. For more details, see Gazzoni et al. (2004) and Farina et al. (2000).

MUAP Rate (MR) was calculated for adjacent, non-overlapping epochs of one second throughout the duration of the tasks as the total number of detected MUAPs per second. MR reflects the sum of the firing rates of the active MUs and was shown to be strongly related to both the number of active MUs and their firing rate, especially for moderate force levels (Kallenberg and Hermens, 2006a). For higher force levels, MR is affected by overlappings of MUAPs, that are either detected as single MUAPs or not recognized. The applied force levels in the present study were moderate: the highest force level in the step contraction was 100 N, which corresponds to about 25 to 30% of maximal voluntary contraction (MVC), that was 357 N for healthy subjects in the same experimental setup (Schulte et al. 2006).

In addition, the RMS value (RMS_{MUAP}) and median power frequency ($FMED_{MUAP}$) were calculated from the MUAP shapes identified by the algorithm used for MR estimation (Kallenberg and Hermens, 2006b). The power density spectrum, from which $FMED_{MUAP}$ was extracted, was calculated using Fast Fourier Transformation and a rectangular window. The extracted MUAP shapes were zero-padded to obtain a frequency resolution of 1 Hz. The MUAP shape parameters RMS_{MUAP} and $FMED_{MUAP}$ were calculated separately from each of the four selected channels, and averaged across the channels afterwards. For each MUAP, RMS_{MUAP} was calculated from a window equal to the duration of the MUAP (on average 11.9 ms), which was determined by the detection algorithm based on the scale coefficient corresponding to the maximum of the scalogram.

For the step contractions, the outcome parameters (RMS_G, $FMED_G$, CV, MR, RMS_{MUAP} and $FMED_{MUAP}$) were averaged for each force level (resulting in five values per subject for each parameter). For the sustained contraction, averages were calculated per minute (resulting in 15 values per subject for each parameter).

Statistics

The VAS scores were statistically analysed with a two-way ANOVA with factors *VAS number* (1 to 4, referring to before and after the first step contraction, after the rest period and after the second step contraction) and *group* (case or control group). For statistical modelling of the EMG parameters, a mixed linear model was chosen. Mixed linear models are designed to handle correlated data, e.g. including multiple observations of each subject. The model enables the inclusion of two sources of noise: one noise term for each subject, and one noise term for each measurement within a subject. Restricted maximum

likelihood estimation was used for extraction of the significant factors. Quantitative changes in the EMG parameters were estimated by applying the mixed model again with only the significant factors included.

The two step contractions were compared with a linear mixed model with fixed factors *step contraction number* (1 or 2, corresponding to before and after the sustained contraction), *level* (1 to 5) and *group* (case or control group). *Level* was included as fixed factor because it was restricted to five values (20 to 100 N). The interaction between *group* and *level* was included in the model to examine differences between the groups in response to an increasing force level. The interaction between *group* and *step contraction number* was included to examine differences in the effect of the sustained contraction between the two groups. Since it is known that BMI can have an effect on EMG parameters (Nordander et al. 2003), BMI was included as covariate. Furthermore, a random intercept for each subject was taken into account.

To compare the data of the sustained contraction between the two groups, a mixed model with fixed factor *group* and covariates *minute* and *BMI* was used. *Minute* was included as a covariate since it represents a continuous parameter (time), that was arbitrarily quantified in minutes. The interaction between *group* and *minute* was included to examine differences in fatigue development between the two groups.

For both the step contractions and the sustained contraction, the residuals that the model generated were checked for normality with the one-sample Kolmogorov-Smirnov test. The only parameter for which the residual was not normally distributed was $FMED_G$ during the step contractions. Inspection of the data revealed one outlier. After removal of this data point, the residual was normally distributed.

The statistical tests were performed on six parameters, deduced from one EMG. The significance level should be corrected for this. For data with multivariate correlations, the modified Bonferroni correction can be applied (Simes, 1986). The p-values corresponding to the six parameters should be ordered such that $p(1) \leq p(2) \leq \ldots \leq p(6)$. The modified Bonferroni correction states that the significance level of the k^{th} parameter is equal to $k \cdot 0.05/6$. In the Results section is indicated whether differences were significant or not according to this criterion.

Results

The average distance between C7 and the acromion was 22.6, SD 1.62 cm.

The VAS scores of perceived fatigue are reported in Table 5.1. The VAS scores in the control group before the sustained contraction were low. The VAS scores after the sustained contraction are moderate in the control group and high in the case group. VAS scores were on average about two points higher in the case group than in the control

group, before the first contraction. An ANOVA with factors group (control or case) and VAS number (1 to 4) revealed a significant dependency on both factors ($p<0.01$).

Table 5.1 Visual Analogue Scales (mean and SD) of perceived fatigue

	Controls	Cases
VAS1	0.24 (0.28)	1.24 (1.77)
VAS2	0.95 (0.94)	3.39 (2.20)
VAS3	0.34 (0.40)	2.13 (2.13)
VAS4	4.32 (2.09)	6.17 (2.20)

VAS1 and VAS2 were measured before and after the first step contraction, VAS3 was measured before the sustained contraction and VAS4 was measured after the second step contraction.

In Figure 5.4, the mean force curves for both groups are shown. Linear regression analysis resulted in a slope of 0.020 N per minute in the control group (not significantly different from zero, $p>0.18$) and -0.14 N per minute (significantly different from zero, $p<0.001$) in the case group. Inspection of individual force curves revealed that the slight decrease in the case group is due to one subject that was not able to maintain the force level.

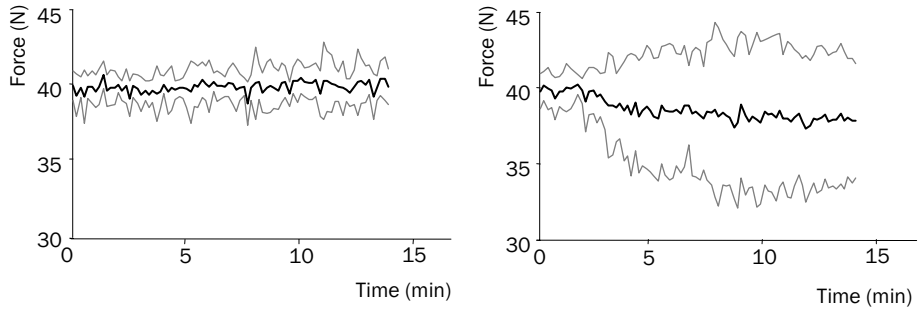

Figure 5.4 Average force curves during the sustained contraction (force values were averaged across ten second periods and across subjects). Right side: control group, left side: case group. Black lines: group mean, grey lines: standard deviation.

In Figure 5.5, RMS_G during both step contractions and the sustained contraction is shown. During the step contractions, RMS_G increased significantly with level ($p<0.001$, $F(4,154)=24.18$). RMS_G was significantly higher for the second than for the first step contraction ($p<0.001$, $F(1,154)=101.8$). No interaction between step contraction number and group was found.

During the sustained contraction, RMS_G increased significantly with time ($p<0.001$, $F(1,257)=207.4$) and there was a significant interaction between group and time ($p<0.001$, $F(1,257)=15.5$) with a stronger increase in the control group (control group: 3.9% per

minute, case group: 2.2% per minute). RMS_{MUAP} showed a similar behaviour. The correlation between RMS_{MUAP} and RMS_G was very high (step contractions: r^2=0.91, sustained contraction r^2=0.90).

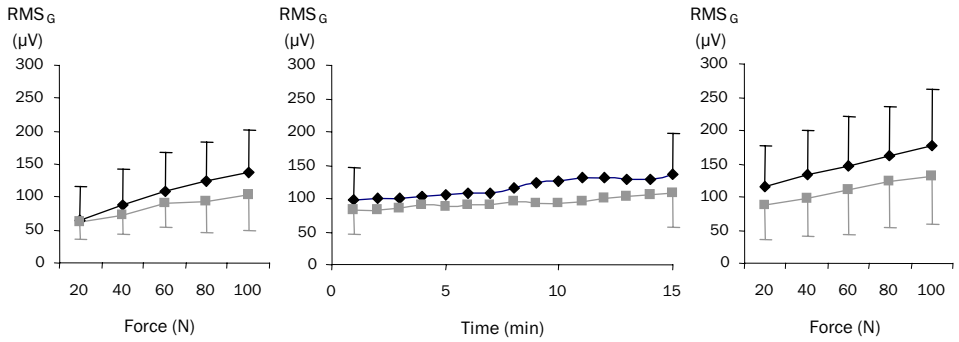

Figure 5.5 RMS_G during both step contractions (left and right) and sustained contraction (middle). Black diamonds: controls (n=10), grey squares: cases (n=10). Note that the x-axis is different for the step contractions and the sustained contraction. Bars indicate standard deviations.

In Figure 5.6, $FMED_G$ during both step contractions and the sustained contraction is shown. For the step contractions, there was a significant interaction between group and step contraction number ($p<0.001$, $F(1,155)=11.86$) with the case group showing an increase (4.7%) and the control group a decrease (-1.7%) from the first to the second step contraction. There was a trend for an increase of $FMED_G$ with level ($p<0.08$, corrected significance level 0.04, $F(4,154)=2.13$). There was a significant dependence of $FMED_G$ on BMI (2.0% per kg/m^2). For the sustained contraction, there was a significant dependence of $FMED_G$ on time ($p<0.001$, $F(1,257)=11.19$) and a significant interaction between group and time ($p<0.001$, $F(1,257)=21.31$). $FMED_G$ decreased with time in the control group and stayed constant in the case group (control group: -0.42% per minute, case group: 0.069% per minute, not significantly different from zero). For $FMED_{MUAP}$, results were similar. The correlation between $FMED_G$ and $FMED_{MUAP}$ was moderate (r^2=0.66 for the step contraction and r^2=0.72 for the sustained contraction).

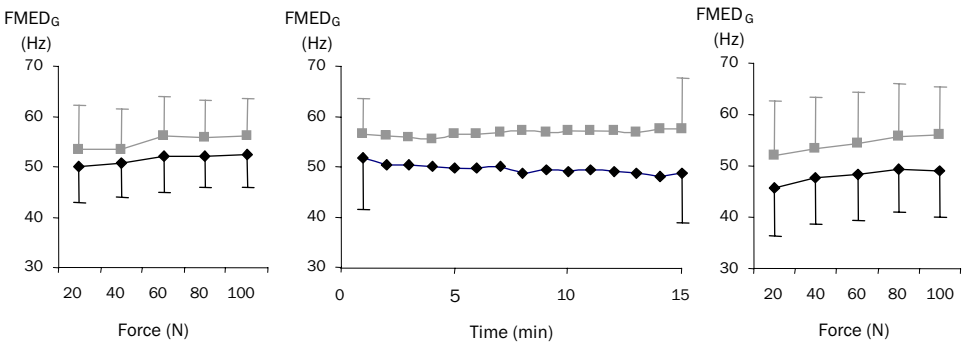

Figure 5.6 FMED$_G$ during both step contractions (left and right) and sustained contraction (middle). Black diamonds: controls (n=10), grey squares: cases (n=10). Note that the x-axis is different for the step contractions and the sustained contraction. Bars indicate standard deviations.

In Figure 5.7, CV during both step contractions and the sustained contraction is shown. For the step contractions, two subjects showed extreme values (higher or lower than the mean value ± three times the interquartile range). For the sustained contraction, three subjects showed extreme values and for two subjects more than 50% of the CV values were lower than 2 m/s. Data of these subjects were excluded from the analysis. CV was significantly higher during the second step contraction than during the first step contraction ($p<0.001$, $F(1,120)=31.96$). No interaction between step contraction number and group was found. There was a dependence on BMI ($p<0.001$, $F(1,27)=18.7$). A trend for a dependence of CV on level was found ($p<0.10$, corrected level 0.05, $F(4,115)=1.99$). During the sustained contraction, there was a significant interaction between group and time ($p<0.001$, $F(1,216)=47.5$). CV decreased in controls and increased slightly in cases (control group: -0.35% per minute, case group: 0.21% per minute).

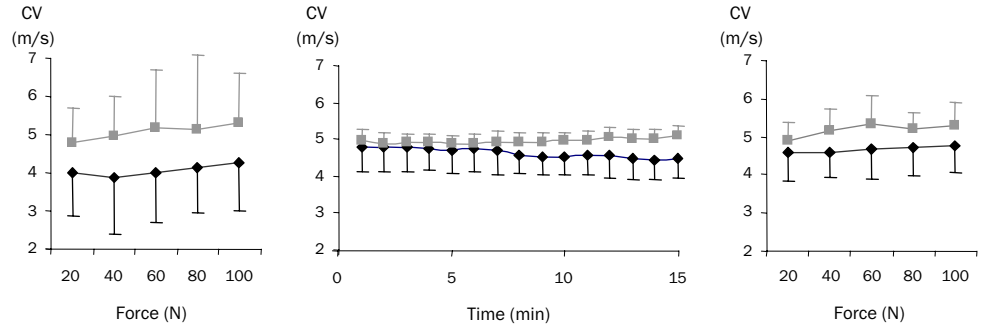

Figure 5.7 CV during both step contractions (left and right) and sustained contraction (middle). Black diamonds: controls (n=8), grey squares: cases (n=8). Note that the x-axis is different for the step contractions and the sustained contraction. Bars indicate standard deviations.

In Figure 5.8, MR during both step contractions and the sustained contraction is shown. For the step contractions, MR increased significantly with level ($p<0.001$, $F(4,153)=86.5$). There was a significant relation between MR and step contraction number ($p<0.026$, corrected significance level 0.033, $F(1,155)=5.04$) and a trend for dependence on the interaction of group and step contraction number ($p<0.039$, corrected significance level 0.025, $F(1,155)=4.33$). MR increased in the control group (12.6%) while in the case group it stayed constant (0.27%, not significantly different from zero) from the first to the second step contraction. Figure 5.8 shows that this is largely caused by differences at the lower force levels. A significant negative association of MR with BMI was found ($p<0.014$, corrected significance level 0.025, $F(1,23)=7.15$).

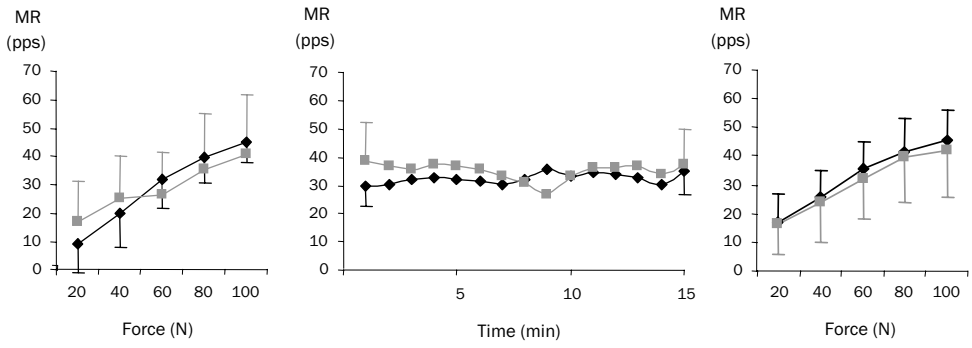

Figure 5.8 MR during both step contractions (left and right) and sustained contraction (middle). Black diamonds: controls (n=10), grey squares: cases (n=10). Note that the x-axis is different for the step contractions and the sustained contraction. Bars indicate standard deviations.

For the sustained contraction, a significant negative association with BMI was found (2.9% per kg/m^2, $p<0.002$, corrected significance level 0.008, $F(1,15)=13.3$). Furthermore, there was a trend for interaction between time and group ($p<0.06$, $F(1,244)=3.54$, corrected significance level 0.05), with increasing MR in the control group and decreasing MR in the case group (control group: 0.40% per minute, case group: -0.25% per minute).

Discussion

The objective of this study was to investigate differences in myoelectric manifestations of fatigue development at low force levels between healthy subjects (controls) and subjects with chronic neck-shoulder pain (cases). It was hypothesized that part of the MUs would already be chronically fatigued before the start of the experiment in the case group. The early decrease in force production of these MUs would be compensated for by recruitment of higher-threshold MUs, which in turn would result in a less pronounced

response in terms of myoelectric changes to a low-level fatiguing contraction in the case group. To generate fatigue, subjects were asked to perform a 15 minute sustained contraction at a force level of 40 N.

Myoelectric signs of fatigue consist of an increase of RMS_G and a decrease of global CV (conventionally measured with two surface electrodes) and $FMED_G$ (Merletti et al. 1990, 2002; Madeleine et al. 2002). For a single MU, a decrease in muscle fibre CV induces an increase in MUAP duration (Lindstrom and Magnusson, 1977) and a decrease in $FMED_{MUAP}$ (Seki and Naruwasa, 1998). Fatigue also leads to additional MU recruitment (Olsen et al. 2001, Jensen et al. 2000, Enoka et al. 1989, Maton and Gamet 1989, Moritani et al. 1986), which would induce an increase in MR with fatigue. Furthermore, according to the size principle (Henneman et al. 1965), additionally recruited MUs are higher-threshold MUs with in general a higher muscle fibre CV (Andreassen and Arendt-Nielsen, 1987) and a larger size. This would result in an increase in RMS_{MUAP} (Roeleveld et al. 1997).

Several results indicate that the sustained contraction was indeed fatiguing. Firstly, the VAS scores after the sustained contraction were much higher than the VAS scores before. Secondly, in the control group myoelectric manifestations of fatigue were found: during the sustained contraction, RMS_G, RMS_{MUAP} and MR increased significantly, while CV and $FMED_G$ decreased. It was hypothesized that cases would show less myoelectric signs of fatigue than controls. Indeed, the results indicate that cases do not respond as much as controls to a fatiguing task. During the sustained contraction, myoelectric manifestations of fatigue were smaller in the case group. Cases showed a less steep increase in RMS_G and RMS_{MUAP}. Additionally, controls showed a decrease in $FMED_G$, $FMED_{MUAP}$ and CV whereas in the case group these variables stayed constant or increased slightly with time. In addition, there was a trend for a difference in MR slope: in the control group MR increased with time and in the case group MR decreased with time. Further evidence to support the hypothesis that cases show less signs of fatigue is demonstrated when comparing the two step contractions. Similar to the results of the sustained contraction, controls showed a decrease in $FMED_G$ and $FMED_{MUAP}$ from the first to the second step contraction, whereas these variables increased in cases.

These results are in line with the hypothesis that part of the MUs is chronically fatigued in the case group. The higher VAS scores in the case group, already before the contractions started are in agreement with the hypothesis as well. Furthermore, the VAS scores did not return to baseline during a 15 min rest period in the case group, in contrast to the control group.

A confounding factor might be the slight decrease in force level in the case group, although visual inspection of individual data revealed that this is due to only one subject. Another confounding factor might be the development of pain during the contraction.

This might cause a decrease of the activation level of the trapezius that is compensated for by synergistic muscles. However, no evidence for such a mechanism was found; global RMS did not decrease in the case group.
The finding that cases show less signs of fatigue is in line with a study that compared secretaries with work-related bilateral chronic muscle pain with healthy controls (Schulte et al. 2006). In this study, changes in CV during an isometric endurance task were more pronounced in the control group than in the case group. The present results are also in line with previous findings reported by Öberg et al. (1992). They demonstrated a smaller increase in RMS and a smaller decrease in mean power frequency on the affected side than on the healthy side in cases with unilateral myalgia. A lower response to a fatiguing task in cases has been demonstrated as well for cases with low back pain (Oddsson and De Luca, 2003; Lariviere et al. 2003).
Underlying the hypothesis that cases would show less signs of fatigue than controls, it was assumed that the painful muscles of cases are chronically fatigued. This would imply that peripheral muscle fibre properties (e.g. muscle fibre CV, cell membrane properties etc.) are changed in cases. This should then be reflected in the EMG parameters already at the beginning of the tasks. For the case group, MR seems to be somewhat higher for the low force levels of the first step contraction (20 and 40 N). Although not significant, this increase might give some indication that the force output of the low-threshold MUs is decreased in cases. To investigate this further, a study with a larger sample size should be performed.

During the sustained contraction, there was a significant but slight increase of CV in the case group. Since CV of higher threshold MUs is generally higher (Masuda and De Luca, 1991; Andreassen and Arendt-Nielsen 1987; Hogrel 2003), this may indicate additional recruitment of higher-threshold MUs. Such additional recruitment would lead to an increase in MR. However, the results also show that MR does not increase in the case group, which seems to be in contrast. A possible explanation is that part of the low-threshold MUs are de-recruited due to fatigue. To compensate for this, less high-threshold MUs are needed because of their larger force output (Feiereisen et al. 1997), which results in a lower MR.
In the control group, $FMED_G$ decreased from the first to the second step contraction, whereas CV did not. Although the frequency content of the signal is largely determined by CV (Lindstrom and Magnusson, 1977, Dumitru, 1999), Merletti et al. (1990) showed that changes in spectral variables due to fatigue are larger than those in CV. Furthermore, they concluded that CV is not the only physiological factor affecting spectral variables. Another study showed that $FMED_G$ is affected by shape and duration of the MUAPs (Hermens et al. 1992).

In the present study, the placement of the force sensors was adjusted to body size, such that the sensor was located slightly above the acromion. Thus, the subjects applied the force in the same way; i.e. the contact with the sensor occurred at a bony point. Since the required force was constant, differences in the distance between C7 and acromion might lead to differences in applied torque. However, since the differences in distance between C7 and acromion were rather small (SD was 7% of the mean value) the effect on the results can be expected to be limited.

Many authors have used relative force levels, related to MVC for investigating the relation between EMG parameters and force (e.g. Conwit et al. 1999, Bilodeau et al. 2003, Queisser et al. 1994). One of the reasons for using relative force levels is that inter-subject variability is assumed to be decreased. We used absolute force levels (in N) rather than relative force levels for several reasons. First, since MVC is probably different between the two groups, relative force levels might mask the differences between the groups. Second, the assessment of MVC is difficult, especially in people with pain or fear of pain, since the measured MVC might not be the maximal force, but the force that is acceptable in terms of pain. Third, the force levels that are needed in daily life activities are also absolute levels independent of a subject's muscle capacity. Schulte et al. (2006) reported lower MVC values for cases than for controls. The force level during the sustained contraction would thus be relatively higher for cases than for controls. Thus, it would be expected that cases encounter more fatigue than controls. However, the results of our study indicate that cases show *l*ess myoelectric signs of fatigue. When relative force levels would have been used, this effect might have been even stronger.

Conclusion

The aim of the present work was to investigate differences in myoelectric manifestations of fatigue development between cases and controls during a low force level sustained contraction. Cases showed a less pronounced myoelectric response to the fatiguing task than controls, suggesting that additional higher-threshold MUs are recruited. The results are in line with the hypothesis that part of the MUs in cases was already (chronically) fatigued at the start of the experiment.

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Chapter 6

Distinction between computer workers with and without work-related neck-shoulder complaints based on multiple surface EMG parameters

Laura A.C. Kallenberg, Hermie J. Hermens, Miriam M.R. Vollenbroek-Hutten
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Abstract

The aim of this study was to investigate whether it is possible to distinguish between computer workers with (cases) and without (controls) work-related neck-shoulder complaints by combining multiple surface electromyography (EMG) parameters in a logistic regression model. Fourteen controls and thirteen cases performed five tasks: a unilateral dynamic hand task, a typing task, an editing task, a mouse task and a stress task. EMG of the trapezius muscle was measured using multi-channel electrode arrays. Root-mean-square value and median power frequency, the number of motor unit action potentials (MUAPs) per second and MUAP shape properties were assessed. Logistic regression models were developed for each task with data from ten controls and nine cases. The mouse task resulted in the most discriminative model with correct classification of 89% (jack knife evaluation). MUAP-related parameters were selected as most discriminative. Explorative evaluation with the remaining subjects resulted in a sensitivity and specificity of 3 out of 4 in both groups. In conclusion, a combination of multiple surface EMG parameters was capable of distinguishing computer workers with and without neck-shoulder complaints in a small pilot sample.

Relevance to industry The results are promising for development of an objective assessment method that can identify workers who are at risk to develop chronic neck-shoulder complaints.

Introduction

In western countries, the prevalence of work-related neck-shoulder complaints is significant. In the Netherlands, 22% of the working population reported work-related complaints in the neck, shoulders, arms or hands (Hupkens 2002). Despite the low force levels required, computer workers are at a considerable risk to develop neck-shoulder complaints (Bongers et al. 2002, Jensen 2003). Many computer workers may develop chronic complaints that eventually result in absenteeism from work, leading to high costs for society. If workers who are at risk to develop chronic neck-shoulder complaints could be identified, early application of ergonomic interventions might help to reduce absenteeism from work.

Conventional diagnostic tools such as medical imaging or neurography largely fail to discriminate cases with neck-shoulder complaints from control subjects. During the past decades, extensive research has been directed at investigating the possibility of using deviations in muscle activation patterns to discriminate between case and controls. Muscle activation patterns can be assessed objectively with parameters extracted from surface electromyography (EMG). Several authors found that EMG activity of the shoulder muscles during work-related tasks was increased in subjects with neck-shoulder complaints (Lundberg et al. 2002, Madeleine et al. 2003, Veiersted et al. 1990, Veiersted 1994, Westgaard et al. 2001). Contrary to this, in a recent large field study lower EMG activity was found in subjects with neck-shoulder pain during an isometric contraction at 30% of the maximum voluntary contraction (MVC) (Sjøgaard et al. 2006). Another study demonstrated an inability to relax in trapezius myalgia patients in between dynamic maximal shoulder flexion contractions (Elert et al. 1992). In agreement with this, a recent study found a lower rest time during a cognitive stress task in chronic pain cases (Thorn et al. in press).

Other authors investigated the development of muscle fatigue in neck-shoulder pain cases. In a study with patients with unilateral myalgia the affected side showed less EMG signs of fatigue (Öberg et al. 1992). In agreement with this, a recent study showed that chronic pain cases show less signs of fatigue than healthy controls during a low-level isometric contraction (Kallenberg et al. in press). Other studies of fatigue in relation to chronic pain did not reveal differences in EMG parameters, but showed that endurance time was shorter for chronic pain cases (Hagberg and Kvarnström 1984, Hansson et al. 1992, Larsson et al. 2000).

During the past decades, the use of multi-channel surface electrode arrays that provide a spatially more selective view of the muscle has been investigated (Merletti et al. 2003, Disselhorst-Klug et al. 2000, Stegeman et al. 2000). This promising technique provides

more detailed information about superficially located motor units (MUs). A recent study investigated properties of motor unit action potentials (MUAPs) as well as the number of MUAPs per second (MUAP Rate) in cases with chronic neck-shoulder pain (Kallenberg and Hermens 2006a). They found a significantly increased MUAP Rate in cases compared to controls during work-related tasks. Furthermore both the root-mean-square value of the MUAPs and their median power frequency were increased in cases. These findings may indicate an increased contribution of higher-threshold MUs to the EMG signal. Further was found that MUAP-related parameters show larger differences between the two groups better than global parameters.

Although several of these studies were able to show differences between subjects with and without neck-shoulder complaints, in general the differences are rather small compared to the inter-subject variability in the groups. Therefore, it seems complicated to distinguish between the two groups with a single parameter. A recent study investigated the possibility of using a combination of multiple EMG parameters to discriminate between computer workers with and without trapezius myalgia (Goudy and McLean, 2006). A logistic regression model based on a combination of global EMG parameters obtained from isometric shoulder flexion contractions resulted in a high sensitivity (86%), but an inadequate specificity (43%). Since our previous work indicated that MUAP-related parameters showed larger between-group differences than global EMG parameters, the aim of the present study was to investigate whether discrimination between subjects with and without work-related neck-shoulder pain can be achieved by using parameters obtained with multi-channel surface EMG recordings. Global as well as MUAP-related parameters were obtained from multi-channel surface EMG recordings of the upper trapezius muscle of both groups during representative computer work-related tasks. Logistic regression models were developed for each task, and an explorative evaluation of the best model was performed.

Materials and methods

Subjects

Twenty-seven subjects participated in this study. All subjects were computer workers with an age between 18 and 60 years that worked at least 20 hours/week. Subjects were recruited from a local university and a local library. Their history of neck-shoulder complaints was assessed by means of a questionnaire (an adapted version of the Standardized Nordic Questionnaire, Kuorinka et al. 1987). The questionnaire was used to assess if subjects experienced pain in the shoulders, arms (both left and right separately), neck and upper back. Subjects were included in the control group if they did not have any

self-reported complaints in the neck and/or shoulders region during the last year and if they did not have any complaints for longer than 30 days in more than two other body parts. Subjects were included in the case group if they reported work-related neck-shoulder complaints (either in the dominant shoulder, in both shoulders and/or in the neck) for more than 30 days during the last year without complaints in more than two other body parts. Furthermore, to be included cases had to report that their complaints restricted them in their working abilities.

Exclusion criteria were the presence of any neck-shoulder complaints that were not work-related, use of muscle relaxants, structural deviations of the spine and tumours or inflammatory diseases. Because of the confounding influence of body mass index (BMI) on EMG (Nordander et al. 2003), subjects with a BMI of more than 30 kg/m^2 were excluded. Colour blindness was an exclusion criterion as well because of the importance of colour in one of the tasks of the protocol.

Table 6.1 Demographic characteristics of the subjects

	First data set		Second data set	
	Cases	Controls	Cases	Controls
Gender	4 m, 5 f	1 m, 9 f	4 f	4 f
Age (yrs)	36.1 (24-51)	40.7 (21-53)	46.0 (39-51)	51.8 (50-54)
Height (cm)	176.2 (164-195)	172.3 (158-183)	166.3 (157-174)	186.5 (163-175)
Weight (kg)	71.2 (57-86)	68.8 (56-80)	58.5 (55-62)	63.5 (56-71)
BMI (kg/m^2)	23.0 (19.4-28.3)	23.1 (20.9-25.8)	21.2 (19.8-22.3)	22.4 (20.6-24.3)

Mean values and ranges are reported. The first data set was used for development of logistic regression models for each task; the second data set was used for an explorative evaluation of the performance of the best model. There are no significant differences between cases and controls in both data sets. BMI: body mass index

Demographic characteristics of the subjects are summarized in Table 6.1. The first data set, used to build a logistic regression model, was obtained from ten randomly selected controls and nine randomly selected cases. The second data set, used for an explorative evaluation of the performance of the model, consisted of data from the remaining four controls and four cases. Of the first data set, 7 cases reported pain at both shoulders and/or neck, and 2 cases reported pain at their right shoulder and/or neck. Of the second data set, 3 reported pain at both shoulders and/or neck and 1 reported pain at the right shoulder and/or neck. All cases except one in the first data set used their right hand for operating the mouse. The left-handed subject reported pain in both left and right shoulder.

The study was approved by the local medical ethics committee. All subjects gave their written informed consent. Data of part of the subjects has been reported previously (Kallenberg and Hermens 2006a).

General procedures

Five different tasks were performed. Three of these were work related; a typing task, an editing task and a mouse task. Because of the importance of stress for neck-shoulder complaints (Lundberg et al. 2002) a cognitive stress task was included in the protocol. In addition to these tasks, requiring relatively low physical demands, a unilateral dynamic hand task (referred to as the dots task) that required a higher activity level was included. The duration of each task was set to five minutes.

During the *dots task*, subjects were asked to continuously move the dominant arm between three target areas by putting marks in small circles (diameter 12 mm) with a pencil. The targets were positioned in a triangle with 22.5 cm in between. The pace was held constant at 88 marks/min by a metronome. The direction of the movement was counter-clockwise for left-handed and clockwise for right-handed subjects.

The *typing task* consisted of re-typing a standard text that was shown in front of the subject on a document holder.

During the *editing task*, subjects had to make the first word with five characters or more bold and capitalise the first character of the next word with five characters or more. This had to be repeated throughout the whole text or until time was finished. Subjects were allowed to perform the type and editing tasks in their own preferred way (e.g. with the wrists rested on the desk or not). The typing and editing tasks were performed with both hands.

The *mouse task* was performed using a drawing program on the PC, where subjects had to draw a pattern by mouse clicking on small circles (7 mm diameter). The mouse task was performed with the hand that the subject preferred.

The three computer work-related tasks were performed in a self-determined pace at an ergonomic work place, consisting of an in height adjustable table and an office chair with adjustable height, back rest, and arm supports. Chair height, table height and position of the computer screen were adjusted to the subject, according to the guidelines of Verbeek (1990).

During the *stress task* (STROOP colour word test, Faucett and Rempel 1994), the Dutch words for 'blue', 'yellow', 'green' and 'red' were shown in different colours. Subjects had to point the mouse to an icon showing the colour of the word in black characters as quickly as possible. If a mistake was made or if a time limit was passed, a beep sounded.

Subjects were instructed not to speak and keep their head straight during the tasks.

Before the first task, perceived pain intensity in arms, shoulders, neck and upper back were measured with a 10-point Likert scale with written anchors at the two extremes: "no pain" and "the worst pain ever experienced". A lower score was associated with less pain intensity.

EMG recordings

EMG of the trapezius muscles at the dominant side was recorded during the tasks. In all cases, this was the side that was used to operate the mouse. For the cases, this corresponded to their painful side, if the pain was not bilateral. The trapezius muscle was selected because of its involvement in neck-shoulder complaints, its sensitivity to stress (Lundberg et al. 2002, Urquhart and McLean 2001) and its superficial location, which makes it suitable for surface EMG recordings. EMG was recorded with linear 8-channel electrode arrays (LISiN – SPES Medica, S. Pedrino di Vignate, Milano, Italy) with an inter-electrode distance (IED) of 5 mm. See Figure 6.1.

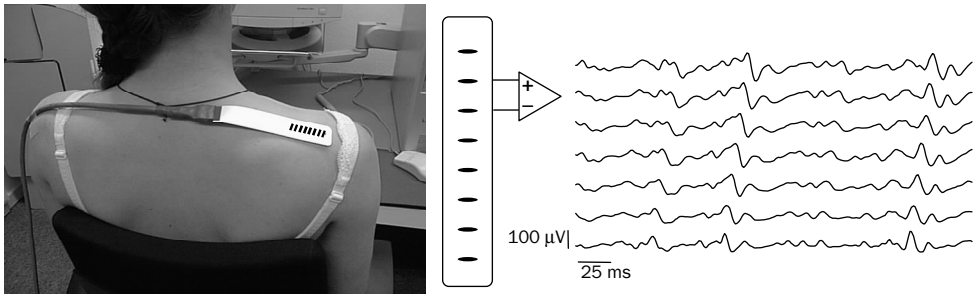

Figure 6.1 Measurement setup. Left: the eight-channel linear electrode array is placed at the trapezius of the dominant side. Middle: schematic representation of the electrode array. An example of a differential amplifier to obtain the bipolar signals is shown. Right: bipolar signals derived from adjacent electrodes. Propagating motor unit action potentials can clearly be recognised.

The arrays were placed on the upper trapezius muscle of the dominant side, on the line from the spinous process of the 7th cervical vertebra to the acromion. The most medial electrode was placed 5-10 mm lateral from the midpoint, such that unidirectionally propagating signals were recorded (Farina et al. 2003). The part of the skin where the electrode arrays were placed was cleaned with alcohol. Conductive gel (20-30 μl for each electrode of the array) was used to assure proper electrode-skin contact and was inserted with a gel dispenser (model Eppendorf AG – Multipette plus, Hamburg, Germany) into the cavities of the adhesive electrode array. A ground electrode was wrapped around the wrist. The signals were bipolarly amplified 3500 times, analogue band-pass filtered (cut-off frequencies 6-500 Hz) and sampled at 2048 Hz. The signals were digitised using a 12 bit A/D-converter and stored on a data logger (LISiN – Sirio Automazione, Rivoli, Turin, Italy). Before the measurement started and in between the recordings, the signal quality was inspected visually. When excessive noise was present, a small amount of gel was added to the electrodes or they were repositioned until signals with good quality were obtained.

Signal processing

Global EMG parameters, MUAP Rate and MUAP shape properties were extracted from the EMG data. The global parameters consisted of the commonly used root-mean-square value (RMS_G) and median frequency of the power spectrum ($FMED_G$). Central aspects of motor control were investigated by assessing MUAP Rate (MR); i.e. the number of MUAPs per second. Furthermore, MUAP shape properties (amplitude and characteristic frequencies of the power spectrum) were assessed. MUAP Rate and MUAP shape parameters were included since in a previous study was found that they show larger differences between cases with neck-shoulder complaints and controls on a group level than the global EMG parameters (Kallenberg and Hermens 2006a).

The *global parameters* were calculated for adjacent non-overlapping epochs of 1 s from a bipolar signal with an IED of 2 cm, in accordance with the recommendations by Mathiassen et al. (1995) and Hermens et al. (2000). The four channels that were used to construct this bipolar signal were selected from all available channels (with 5 mm IED) using a previously described method that minimises the sensitivity to changes in electrode position (Farina et al. 2002a).

Öberg et al. (1992) reported differences in myoelectric signs of fatigue development for the affected and unaffected side in patients with unilateral myalgia. Therefore, possible fatigue-related changes during the tasks were identified by fitting a linear regression line through the RMS and FMED values of the one second epochs (Farina et al. 2000). RMS_G_init and $FMED_G$_init were defined as the intercepts of the respective regression lines. The rate of change over time of RMS (RMS_G_slope) and FMED ($FMED_G$_slope) were defined as the slopes of the regression lines.

The EMG signal consists of the summed contribution of MUAP trains originating from many MUs. Each MUAP train is characterised by the firing rate of the MU, and the shape of its corresponding MUAP. *MUAP Rate* was obtained by an algorithm that counts the total number of MUAPs in the EMG signal, which corresponds to the sum of the firing rates of the contributing MUs. MUAP Rate was shown to be strongly related to the number of MUs in the signal as well as to their average firing rate (Kallenberg and Hermens 2006b). For calculation of MR, MUAPs were detected with a method that used the Continuous Wavelet Transform. For a detailed description of this method, see Gazzoni et al. (2004) and Kallenberg and Hermens (2006a). In summary, the algorithm separated MUAPs from background activity by identifying shapes that were similar to a mother wavelet (i.e. the first order Hermite-Rodriguez function, selected because of its similarity with the MUAPs). At least five bipolar signals that showed propagating MUAPs with high quality were selected manually. The algorithm searched for candidate MUAPs on all channels. A candidate had to occur in at least three channels before being called a MUAP. Outcome of

the detection algorithm were the times of occurrence of the MUAPs detected, and the MUAP shapes on all channels.

MUAP Rate (MR) was calculated for adjacent, non-overlapping epochs of 1 s throughout the duration of the tasks as the number of detected MUAPs per second from the middle one of the selected signals. Mean, median and standard deviation (SD) of MR within each subject (across time) were calculated (MR_mean, MR_median and MR_sd). Additionally, analogue to the global analysis, to identify possible fatigue-related changes over time in MR, a linear regression line was fitted through the MR values of the 1 s epochs. The rate of change of MR over time was defined as the slope of the regression line (MR_slope). The intercept of the regression line was extracted as well (MR_init).

Furthermore, *MUAP shape properties* of each detected MUAP were extracted. RMS (RMS_{MUAP}), peak-to-peak voltage (VPP_{MUAP}), median frequency of the power spectrum ($FMED_{MUAP}$) and mean frequency of the power spectrum ($FMEAN_{MUAP}$) of all detected MUAP shape properties were calculated from the same signal as was used for MR estimation. Mean values and SDs of these parameters were calculated per subject.

Logistic Regression Analysis

Based on this data set, logistic regression analysis was used to build a model with the most discriminative set of parameters. Logistic regression analysis was selected rather than e.g. discriminant analysis because it does not require normally distributed input variables. The dependent variable was group (case or control). The logistic regression model predicted the probability P (case) that a subject belonged to the case group:

$$P\,(\text{case}) = \frac{1}{1+ e^{-z}}$$

with

$$Z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n$$

The model estimated the coefficients β_i using the input parameters X_i (i.e. the EMG parameters). The predicted probabilities should be higher for cases than for controls. Ideally, the probability would be equal to 1 for cases and 0 for controls.

The coefficients β_i indicate the importance of each input parameter for the model. However, since the input ranges of the parameters X_i might be different, the coefficients need to be normalized to determine the relative importance of each input parameter. This was performed by multiplying the coefficients β_i with the average input values X_i of the first data set (ten controls and nine cases).

Logistic regression analysis performs better when there is no multicollinearity. Therefore, before building the model, correlations between all input parameters were calculated for each task separately. When the average Spearman correlation coefficient between two parameters was higher than 0.85, one parameter was omitted. Of the closely correlated parameters, the one with the lowest within-group variability (expressed as coefficient of variation, i.e. SD/mean) was selected. For both cases and controls, this resulted in selection of the same parameters. The omitted parameters are MR_median, MR_init, RMS_{MUAP}_std, VPP_{MUAP}_std, VPP_{MUAP}_mean, $FMEAN_{MUAP}$_mean, and $FMEAN_{MUAP}$_std.
A logistic regression model was built for each task separately using the selected parameters. A stepwise forward method, based on the probability of the likelihood ratio statistic was used. The likelihood is a measure for how well the model fits the data. The likelihood ratio is the ratio between the likelihood for the model including an input parameter and the likelihood for the model without that parameter. The likelihood ratio statistic reflects the probability that a parameter does not change the likelihood of the model (Norušis 1994). At each step, the parameter showing the smallest p-value (with a maximum of 0.05) was included in the model. Next, all previously included parameters were examined for removal: if the significance level for a parameter became higher than 0.10, it was removed. After the model was built, the residuals were checked for normality as well as for outliers. Sensitivity, defined as the number of correctly classified cases divided by the total number of cases, as well as specificity, defined as the number of correctly classified controls divided by the total number of controls, were calculated.

From the five models (one for each task), the one that resulted in the best prediction was selected for an explorative evaluation of its performance. Two procedures were used. The first procedure was the so-called jack knife method which is a statistical cross-validation method that can be employed in studies with limited sample size (Wasson et al. 1985). One subject at a time was left out from the data set and a test model was built from the data of the remaining 18 subjects. For generation of these test models, only the parameters that were included in the original model were used. The generated test model was then used to predict to which group the subject that was left out belonged. This procedure was repeated so that each subject was left out once.
The second procedure to explore the performance of the model was its application to the second data set. This was a new data set that was not used for building the model. The researcher who built the model was blind to the group (case or control) to which the subjects of this second set belonged.

Results

Due to technical problems the typing task data from one case, the mouse task from one case and the stress task data from three controls and one case were missing in the first data set.

Cases and controls were not different with respect to age, height, weight or body-mass index in both data sets (Student's t-test, first data set: $0.19<p<0.97$, second data set: $0.11<p<0.64$).

The Likert scale scores of both groups for perceived pain and discomfort in arms, shoulders, neck and upper back are reported in Table 6.2. For the first data set, the scores for shoulders, neck and upper back were significantly higher in the case group than in the control group (Mann-Whitney-U test, $p<0.002$) and there was a trend for a higher value for the arms ($p<0.09$). For the second data set, cases had significantly higher scores on all items ($p<0.008$). As expected, the values for the control group were low. The values in the case group were moderate (on average around 4).

Table 6.2 Likert scales of case and control group for perceived pain and discomfort in arms, shoulders, neck and upper back

Item	First data set		Second data set	
	Control group (n=10)	Case group (n=9)	Control group (n=4)	Case group (n=4)
Pain/discomfort in arms	0.40 (0.67)	1.72 (1.71)	0.25 (0.50)	3.00 (2.45)
Pain/discomfort in shoulders	0.18 (0.37)	4.59 (2.56)	0.50 (0.58)	4.50 (1.91)
Pain/discomfort in neck	0.10 (0.30)	4.36 (2.85)	0.00 (0.00)	3.50 (1.73)
Pain/discomfort in upper back	0.14 (0.42)	3.04 (2.70)	0.00 (0.00)	4.25 (1.50)

Group standard deviations are reported between parentheses. First data set: cases had significantly higher scores for shoulders, neck, and upper back ($p<0.002$) while there was a trend for higher scores in the arms ($p<0.09$). Second data set: cases had significantly higher scores for all items ($p<0.007$).

To indicate the activity levels of the five different tasks, RMS_G_init values for both groups of the first data set are shown in Table 6.3. The highest values of RMS_G_init occurred during the dots task, that was included because of its higher activity level.

Table 6.3 Initial global root-mean-square (RMS_G_init) values of both groups for all tasks (first data set, controls: n=10, cases: n=9)

	Control group	Case group
Dots	45.4 (26.0)	47.4 (24.0)
Typing	32.4 (18.3)	33.1 (22.2)
Editing	29.5 (13.5)	25.2 (16.2)
Mouse	17.1 (7.42)	22.9 (14.5)
Stress	16.9 (5.15)	23.3 (14.3)

Group standard deviations are reported between parentheses

The models that were created from the first data set (n=19) for each task and their classification results are shown in Table 6.4. The residuals of the models were normally distributed and there were no outliers.

Table 6.4 Models created from the first data set for each task separately

	Model (Z)	-2 log likelihood	Specificity	Sensitivity
Dots	72 + 1.6 FMED – 0.62 $FMEAN_{MUAP}$_SD	7.01	90.0	88.9
Typing	---	---	---	---
Editing	-0.71 + 85 $FMED_{SLOPE}$	19.3	90.0	66.7
Mouse	168 -5.9 $FMEAN_{MUAP}$_SD + 10 MR_SD +504 RMS_{SLOPE}	0.00	100	100
Stress	2.1 + 0.52 MR_SD	14.1	71.4	75.0

The performance of each model in terms of its log likelihood a well as its sensitivity and specificity are shown. For the typing task, no model could be generated.
Abbreviations: FMED: Median frequency of the power spectrum, FMEAN: mean frequency of the power spectrum, MR: Motor unit action potential rate, SD: Standard deviation, MUAP: Motor unit action potential, G: Global

The model based on the mouse task was the most discriminative. This model predicted a probability of 1.000 for all cases and a probability of 0.000 for all controls in the first data set (from which the model was built).

For the typing task, none of the parameters could be included in the model. The models for the dots, editing and stress task misclassified 2, 4 and 4 subjects respectively. One case was misclassified by all these three models. This case showed lower values for the predictor parameters than all other cases for all three tasks.

For the mouse task, the normalized β_i coefficients (normalized to the average value of each parameter), indicating the relative importance of each parameter, were: MR_sd: 54.3, RMS_slope: 13.5, $FMEAN_{MUAP}$_sd: -235.2. The low absolute value of the coefficient for RMS_slope indicates that this parameter is of minor importance.

In Figure 6.2, the distributions of the predictor parameters of the mouse task (MR_sd, RMS_slope, $FMEAN_{MUAP}$_sd) in both groups of the first data set are shown. A general linear model with fixed factor group and covariate BMI showed trends for higher MR_sd and RMS_slope in cases ($p=0.096$ and 0.056) and significantly lower $FMEAN_{MUAP}$_sd values in cases ($p<0.044$).

An explorative evaluation of the model of the mouse task was performed. The jack knife method resulted in a correct classification of 89%. Out of the 10 controls and 9 cases, 1 control and 1 case were misclassified.

Application of the model to the second data set resulted in a correct prediction of the group in 3 out of 4 cases and 3 out of 4 controls, resulting in a sensitivity and specificity of 3 out of 4.

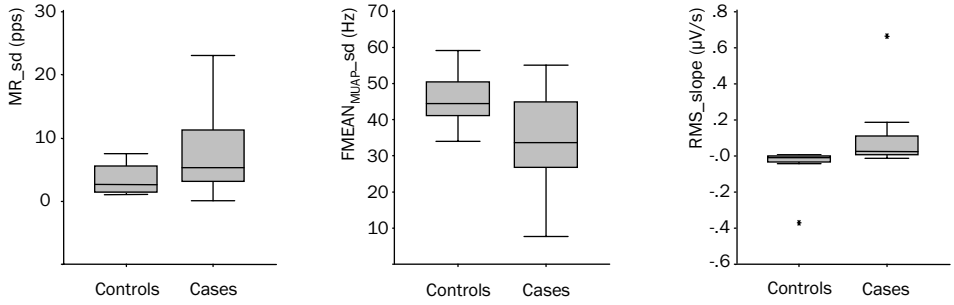

Figure 6.2 Distribution of the predictor variables in both subject groups of the first data set. Data from the mouse task.

Discussion

The aim of the present study was to investigate whether it is possible to objectively distinguish between subjects with and without neck-shoulder complaints by combining several EMG parameters in a logistic regression model. Conventional diagnostic tools largely fail to discriminate cases with neck-shoulder complaints from control subjects, whereas several EMG studies have shown that muscle activation patterns differ between these two groups and might offer possibilities for diagnosis (Elert et al. 1992, Kallenberg and Hermens 2006a, Lundberg et al. 2002, Madeleine et al. 2003, Veiersted et al. 1990, Veiersted 1994). However, the differences between cases and controls are small compared to the inter-subject variability. The present study explored the possibility to distinguish cases from controls by combining multiple EMG parameters. Logistic regression analysis was applied to select the most discriminating parameters and to subsequently combine them in a model for each of five work-related tasks. An explorative evaluation of the best model was performed with the jack knife method and by applying it to a second data set. The mouse task resulted in the best model; evaluation of this model with the jack knife method resulted in a sensitivity of 89% and specificity of 90%.

The logistic regression analysis selected FMEAN$_{MUAP}$_sd, MR_sd and RMS_slope as the most discriminative parameters. In general, the selected parameters were the most discriminative at an individual level. This does not necessarily imply that these parameters also show the greatest between-groups differences.
FMEAN$_{MUAP}$_sd reflects the variability in the mean power frequency of detected MUAPs within a subject. The frequency content of the signal is mainly determined by muscle fibre conduction velocity (Lindstrom and Magnusson 1977, Dumitru et al. 1999) and by the duration of the MUAPs (Hermens et al. 1992). Since conduction velocity of a motor unit

is correlated with its recruitment threshold (Andreassen and Arendt-Nielsen 1987) the lower values of $FMEAN_{MUAP}$_sd in the case group indicate a more homogeneous MU population. The cause of this homogeneity remains speculative. A possible explanation could be that it is related to a drop-out of low-threshold MUs, due to long term selective over-exertion as described by the Cinderella hypothesis (Hägg 1991).
The second parameter that was included in the model is the standard deviation of the MUAP Rate (MR_sd). The higher values of MR_sd in the case group indicate an increased variability in the number of MUAPs per second during the task. The number of MUAPs per second reflects the sum of the firing rates of the contributing MUs and is thus related to the motor drive from the central nervous system (CNS). The increased MR_sd indicates a more variable central drive from the CNS to the motor unit pool in cases. This may also be related to more variable behaviour of the cases: postural changes are likely to have contributed to the variability in MR_sd as well.
The last parameter that was included in the model was RMS_slope. From the normalized β_i coefficients it becomes clear that the influence of this parameter on the model is rather limited. RMS_slope reflects the rate of change of RMS over time, which is related to fatigue development (De Luca 1984, Merletti et al. 1990, Merletti et al. 2002).The higher values in the case group may indicate that cases are more sensitive to fatigue compared to the controls. Conflicting results concerning fatigue development in subjects with chronic neck-shoulder pain have been reported. Some studies found that cases show less signs of fatigue (Öberg et al. 1992, Kallenberg et al. in press). Other studies did not show differences in fatigue development between cases and controls (Hagberg and Kvarnström 1984, Hansson et al. 1992, Larsson et al. 2000).

In principle, the most discriminative task would be the task involving the highest contrast between the two groups and the lowest variability within the groups. With respect to contrast, the Cinderella hypothesis (Hägg 1991) suggests that differences between cases and controls are largely related to the low-threshold MUs. Differences in muscle activation patterns might therefore be most distinguishable at low contraction levels, when higher-threshold MUs are not yet recruited to a large extent. With respect to variability, a highly standardized task would be optimal in decreasing inter-subject variability. This applies especially to the dots task and the mouse task, whereas the typing and editing task allowed more freedom in performing the task. As the dots task requires a higher contraction level, it could be expected that the mouse task would result in the best performance of the model.
Amplitude-related parameters apparently were less discriminative than frequency content-related parameters. Probably this is caused by their higher inter-subject variability. Signal amplitude depends on many factors, not only related to physiological phenomena but also

to the detection system (Farina et al. 2002a, Farina et al. 2002b). Especially RMS_{MUAP}_sd and RMS_{MUAP}_mean are strongly influenced by inter-subject variability in geometrical distance between the muscle fibres and the skin.

MUAP Rate and MUAP shape parameters can only be assessed from EMG recordings, performed with multi-channel array electrodes. The used configuration, with small contact points and an IED of 10 mm results in a high spatial selectivity: only superficially located MUs that are located underneath the array contribute to the signal. By limiting the number of MUs, individual MUAPs can be detected. The choice of the spatial selectivity of the measurement system involves a trade-off between a good representation of the MU population and the performance of the detection algorithm. Thus, the electrode configuration and especially IED should be adapted to the activity level and the muscle under investigation.
Some methodological comments regarding the development of the model can be made. Before the logistic regression analysis was applied, the data set was reduced by selecting parameters based on correlation coefficients and within-group variability. This may have contributed to exclusion of discriminative parameters. Furthermore, the size of the second data set, used for an explorative evaluation of the model was rather limited. The groups consisted of both male and female cases in the present study. Possible gender differences and their effect on the model may be subject of further research. The inclusion criteria for the cases (pain in the neck/shoulder region for more than three months, that restricted them in their working abilities) resulted in selection of cases that have severe complaints. For cases in other stadia of pain development, the performance of the present model remains to be investigated.
A possible direction for further improvement of the model may be the additional inclusion of parameters that are not related to EMG in the model. For example, several research groups have investigated cognitive-behavioural characteristics to explain the development of chronic pain (Hasenbring et al. 2001, Vlaeyen and Linton 2000).

The aim of this study was to investigate whether a combination of multiple EMG parameters is able to discriminate between computer workers with and without work-related neck-shoulder complaints. Both the present results and the study of Goudy and McLean (2006) indicate that a combination of parameters can discriminate cases and controls to some extent, even though the distributions of the individual parameters showed considerable overlap between the groups. Although studies with a larger sample size are needed to confirm the findings, these results are promising for the development of an objective assessment method for the identification of subjects with work-related neck-shoulder complaints.

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Chapter 7

General discussion

Introduction

The aims of this thesis were twofold:

1. To develop and evaluate a non-invasive method to enable assessment of motor control at the motor unit level;
2. To investigate whether there are differences in motor control between chronic pain cases and healthy subjects and to what extent these differences can be used to distinguish these groups in an objective way.

Chapters 2 and 3 dealt with the first aim. MUAP Rate was proposed as a new measure for motor control, since it reflects the two parameters that are used by the CNS for this purpose: the number of MUs and their average firing rate. Although the developed method does not result in complete firing patterns of individual MUs, MUAP Rate appropriately reflects motor control. A simulation study (Chapter 2) showed that MUAP Rate was strongly related to both number of MUs and firing rate. In contrast to RMS, MR was insensitive to changes in MU size, which is a peripheral parameter. Experimental research (Chapter 3) showed that MUAP Rate increases approximately linear with force, and that the sensitivity of MUAP Rate to changes in force is higher than that of global RMS. Further, during a sustained fatiguing contraction, MUAP Rate showed a slight increase while global RMS increased strongly. This underlines that MUAP Rate is determined by motor control properties, whereas RMS is also strongly influenced by MUAP properties.

The second aim was investigated in three experimental studies. The first study was focused on computer work (Chapter 4). MUAP Rate was higher in the case group than in the control group. This indicates a greater contribution of higher-threshold MUs to the contraction in cases. The MUAP shape properties (higher RMS_{MUAP} and $FMED_{MUAP}$ in cases) supported this.

In the second study, differences between cases and controls in development of muscle fatigue during an isometric low force contraction were investigated (Chapter 5). It was assumed that the process of developing chronic muscle pain includes a stage of chronic fatigue of the low-threshold MUs. Based on this, it was hypothesized that in the case group part of the MUs would already be fatigued at the beginning of the contractions. In accordance with this, the response to a fatiguing task was less pronounced in cases than in healthy subjects. The results further indicated that during the sustained contraction, higher-threshold MUs were recruited in the case group.

Chapter 6 presents a pilot study showing that a combination of three surface EMG parameters, obtained during a computer mouse task, could distinguish between chronic

pain cases and healthy controls. Parameters related to MUAP Rate and MUAP shape properties were more discriminative than conventional EMG parameters. The results of this pilot study are encouraging for the development of a clinical test that is able to objectively diagnose (part of) the chronic pain cases as subjects with specific deviations in motor control and/or motor unit properties.
In the next sections, the obtained results will be discussed in more detail in the context of the existing literature and the objectives of this thesis.

Assessing motor control with surface EMG

The new method to assess motor control that was developed and evaluated in the first part of this thesis is based on array EMG recordings. Assessment of muscle activity with electrode arrays has a number of advantages when compared to conventional bipolar EMG. Recordings with an array in general can provide a more complete view of muscle activity because not only temporal, but also spatial information becomes available. Array recordings enable investigation of anatomical properties of the muscle fibres, e.g. muscle fibre length, location of the innervation zone, pennation angle etc. The combination of array recordings with decomposition algorithms allows the investigation of MU territories (Blok et al. 2002). Array recordings also enable examination of the spatial distribution of muscular activity, which may be applied in e.g. studies of intra-muscular coordination. Changes in spatial distribution of muscle activity may also provide new insights in diseases of the central nervous system. For example, Drost et al. (2001) used array recordings to show that the propagation of MUAPs is disturbed in patients with generalized myotonia.
Inherent to the use of array recordings, there is a trade-off between view of the electrode configuration, i.e. the part of the muscle and the proportion of MUs that contribute to the signal, and spatial selectivity, i.e. the extent to which different individual MUs can be distinguished. The spatial selectivity of the recording depends on the inter-electrode distance and on the spatial filter that is applied. The minimal inter-electrode distance that is required to appropriately sample fast spatial changes is determined by the spatial equivalent of the Nyquist criterion. In the direction parallel to the muscle fibres, the maximum temporal components of the frequency spectrum are about 400 Hz for superficial muscles with short muscle fibres (Blok et al. 2002). This requires a temporal sample frequency of at least 800 Hz, which means a maximum sample interval of 1.25 ms. With a conduction velocity of 4 m/s, this corresponds to an inter-electrode distance of 5 mm. Other considerations for the choice of the inter-electrode distance are related to the surface that is covered by the array. Arrays with 5 mm inter-electrode distance and e.g. 64 channels arranged in a square would cover 35 x 35 mm, which is a rather small area for large limb muscles. Increasing the surface of the array by increasing the number of

channels would lead to more expensive equipment and to vast amounts of data, that would require huge efforts for analysis. Furthermore, the SNR also plays a role. The shorter the inter-electrode distance, the lower the SNR because the filtering of the signal is stronger, while the noise remains the same. This is particularly important because the noise level for array electrodes is larger than for conventional electrodes due to the larger impedances (typically 50-200 kΩ) that are related to the smaller electrode diameter. Because of its influence on the SNR, the thickness of the subcutaneous layer between the muscle and electrode is relevant as well when selecting the appropriate inter-electrode distance.

Besides the inter-electrode distance, the order of the applied spatial filter also determines the spatial selectivity. Higher-order spatial filters limit the view of the electrodes to superficially located MUs. As for the choice of the inter-electrode distance, an important consideration for the choice of the spatial filter is the signal quality. Because the variance of the noise increases linearly with the number of channels that are added to create the spatial filter, higher-order filters result in a lower SNR. Since the selection of the spatial filter depends on many factors that are not a priori known, it is advisable to record the EMG signals in a monopolar fashion, thereby enabling offline application of different spatial filters.

A key advantage of array recordings in comparison to conventional bipolar recordings is the availability of spatial information, in particular the possibility of CV estimation. CV is an important parameter reflecting muscle fatigue, which is valuable in clinical diagnosis (Farina et al. 2001). CV estimations are often biased towards higher values by the presence of non-propagating components reflecting end-of-fibre effects (Farina et al. 2002). Optimal suppression of these components can be obtained with higher-order spatial filters, but especially for low force levels this might compromise the SNR.

The results from the simulation and experimental studies described in Chapter 2 and 3 show that array recordings provide the opportunity to extract information at the level of MUAPs. Instead of a stochastic description of the EMG signal, array recordings provide deterministic information about MU behaviour. Different research groups are working on decomposition algorithms that can unravel firing patterns of individual MUs (De Luca et al. 2006, Holobar & Zazula 2004, Gazzoni et al. 2004, Kleine et al. 2000). These algorithms use the differences between MUs in MUAP shape and in topography to distinguish between them. To date, these algorithms are able to extract "fingerprints" of individual active MUs (i.e. the electrical activity related to a firing of one MU at all channels of the array). Full decomposition in terms of the complete firing patterns remains yet unsolved, especially for high force levels, due to the large number of superimposed MUAPs, that increases linearly with the number of MUs and mean firing rate. Recently, statistical techniques such as blind source separation and independent

component analysis have been applied for EMG decomposition. These techniques do not rely on the occurrence of isolated MUAPs and might therefore be more successful in decomposing superimposed MUAPs (Holobar & Zazula 2003, Nakamura et al. 2004). However, future research has to prove whether the extraction of reliable, complete firing patterns from surface EMG for a large number of MUs, particularly during dynamic contractions, is possible.

EMG characteristics in chronic pain

The Cinderella hypothesis is probably the most widely used hypothesis to explain the development of chronic pain in work requiring rather low force levels. It is hypothesized that particularly the low-threshold MUs are getting damaged due to continuous activation without sufficient rest. However, the Cinderella hypothesis does not explain how the development of muscle pain proceeds. It might be that muscle fibres or whole MUs first become chronically fatigued before they get damaged. Such a dynamic adaptation of the Cinderella model, reflecting the process of development of chronic pain, is presented in Figure 7.1.

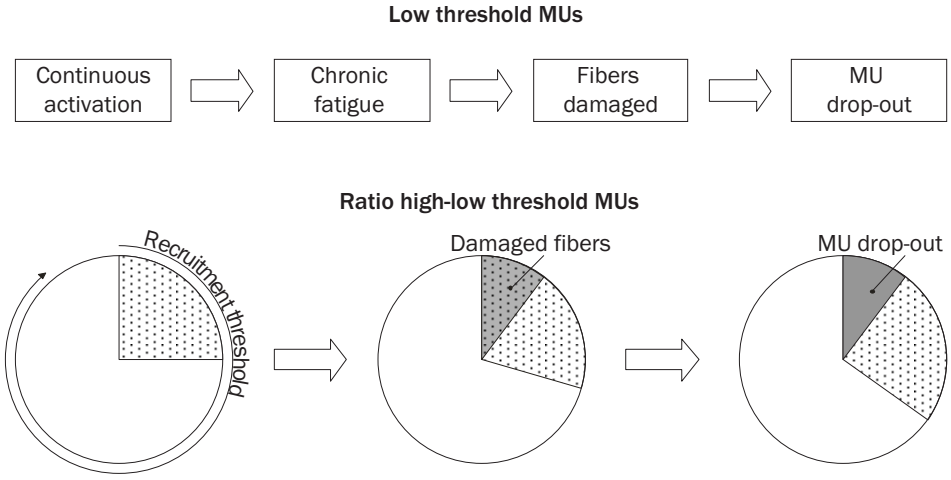

Figure 7.1 Dynamic Cinderella model. The upper part illustrates that low-threshold MUs first become chronically fatigued before they get damaged and eventually drop out. The lower part shows the impact of the drop-out of MUs on the ratio between high- and low threshold MUs that contribute to a contraction. The circle represents the total MU pool; the dotted area represents the active part of the MU pool. The grey part indicates the damaged fibres (middle) and the dropped-out MUs (right). The loss of force of low-threshold MUs will be compensated by additional recruitment of higher-threshold MUs.

In line with this model, the results of the computer task study (Chapter 4) suggest a greater contribution of higher-threshold MUs in cases. However, the results of Chapter 4 do not specifically reveal the process of development of chronic pain. During a fatiguing contraction, cases showed a less pronounced response (Chapter 5). In agreement with the proposed adaptation, this might indicate that part of the muscle fibres or MUs was already fatigued before the contraction started.

The vicious circle model, suggesting that muscle pain leads to muscle activation that in turn leads to more pain, is not necessarily contradictory to the Cinderella hypothesis. It might be that the over-activation of the low-threshold MUs that is described by the Cinderella hypothesis is caused by the underlying mechanisms that the vicious circle model proposes. There is some evidence that especially low-threshold MUs are affected by the positive feedback loop that is proposed in the vicious circle, because group I afferents mainly project to small α-motor neurons (Burke 1981).

In general, the present findings are in line with both the Cinderella hypothesis and the vicious circle. The increased drive from the CNS to the muscle and the greater contribution of higher-threshold MUs in cases during computer tasks may be related to compensation of the loss of force of low-threshold MUs, in line with the Cinderella hypothesis. Alternatively, these findings might also be related to the exertion of higher force levels than biomechanically demanded, or to stiffening of the shoulder. In the fatigue study comparable results were found: there was a trend for higher MUAP Rate values in cases at the lowest force levels. However, since in this study the force levels were imposed and force feedback was provided, the increased activity is more likely to be related to loss of force output for the low-threshold MUs. Future research specifically aimed at this finding is needed before firm conclusions can be drawn.

The Cinderella model is based on the assumption that low-threshold MUs remain continuously activated for long periods of time. This suggests that central processes rather than peripheral changes play an important role. There is evidence in the literature for deviations in central processes in chronic pain cases from various perspectives. Backman et al. (1988) found a lower MVC in subjects with fibromyalgia. However, when the muscles were electrically stimulated, there was no difference in force output. Schwoebel et al. (2002) showed longer response times for imagined movements in subjects with unilateral arm pain. In another study was found that in these cases the response time for laterality determination of pictured hands in different positions was longer for the affected arm (Schwoebel et al. 2001). This was interpreted as a change in mental representation of movement, caused by nociceptive stimuli. Other authors (Hudson et al. 2006, Moseley et al. 2005) found that both experimental muscle pain, evoked by insertion of hypertonic saline, and the expectation of muscle pain, evoked by insertion of isotonic saline, resulted in a decrease of reaction time for laterality tasks concerning the non-painful side, while the

reaction time at the painful side did not change. They suggested that this is due to the focus of attention towards the painful side. Furthermore, changes in cortical organization have been found in both low back pain cases and in cases with fibromyalgia (Flor 2003). The amount of reorganization was found to increase with chronicity. Finally, changes in propriocepsis were found in relation to chronic pain (Revel et al. 1991, Sarnoch 1995).

In summary, the present findings are in line with both the Cinderella hypothesis and the vicious circle model. Evidence for the pain adaptation model (Lund et al. 1991), that suggests a limitation of the activity of the painful muscle to prevent it from more pain, was not found. Central processes related to motor control, pain and fear of pain, and propriocepsis play an important role in the development of chronic pain complaints. Changes in central processes might be the cause of peripheral changes, but stimuli resulting from peripheral receptors might also lead to changes in central processes. An interaction between central and peripheral factors seems likely. Investigation of such a complex interaction is not straightforward. The majority of the studies, including the studies presented in this thesis, is focusing on one isolated aspect.

Apart from this complexity, research is hampered by the characteristics of the study population. Firstly, the heterogeneity is rather large, partly due to the lack of clear diagnostic criteria, which hampers the definition of appropriate inclusion criteria. A second source of variability consists of the large differences in the duration of the complaints as well as in treatment that subjects with chronic pain receive. This compromises the comparability of different studies and complicates the interpretation of the results.

To overcome these limitations, there is a strong need for large, longitudinal studies. To bring research in the field of chronic pain a step further, a multidisciplinary approach including muscle activity recordings both during daily life and in well-controlled lab conditions, biopsies as well as psychosocial measures is advisable. Only a large longitudinal study can clarify the causality of the relations between work-related risk factors, individual factors, deviations in motor control, peripheral changes at the muscle cell level, and pain, which is essential for our understanding of the chronification process.

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Summary

Chronic muscular pain has become an important problem, affecting a considerable part of the working population in the industrialised countries. Chronic muscular pain is a multifactorial problem and comprises a range of conditions that are not all clinically well-defined. Subjective symptoms include constant muscle pain, muscle fatigue and/or stiffness, and radiating pain. Identified risk factors for the development of chronic pain in the neck-shoulder region include exposure to awkward posture, repetitious movements, low level static contractions and high force demands. Beside these physical factors, psychosocial risk factors such as stress, high job demands and low vocational satisfaction play an important role. A variety of individual factors such as age, body mass index and perception of work load can contribute to the development of chronic pain as well.

Several pathophysiological models, explaining the mechanisms that underlie the development of chronic pain, have been proposed. The vicious circle model predicts a positive feedback loop consisting of muscle pain that via nociceptors activates the γ-motoneuron system that projects to the α-motoneuron, thereby activating the muscle, which in turn leads to increased muscle pain. The pain adaptation model suggests a task-dependent increased antagonist activity and decreased agonist activity, thereby reducing painful movements. The Cinderella hypothesis suggests that muscle fibres of low-threshold motor units (MUs) are getting damaged in chronic pain cases because of continuous activation and lack of sufficient muscle relaxation.

These models have in common that they predict changes in motor control. However, the models propose different working mechanisms and consensus on the nature of the changes in motor control is lacking. A better understanding of the underlying mechanisms is an important prerequisite for development of effective treatment methods. Model-based experimental studies assessing motor control in chronic pain cases may provide more insight into these mechanisms.

Motor control can be investigated non-invasively with electromyography (EMG). Conventional surface EMG recordings obtained with two electrodes, placed on the skin above the muscle under investigation, reflect the summation of the spatial and temporal electrical activity of all active MUs. This results in a signal with a stochastic nature in which action potentials of individual MUs cannot be distinguished. With multiple electrodes, arranged in an array with short inter-electrode distances, the spatial selectivity of the recording can be enhanced. In combination with spatial filters that further enhance the selectivity, motor unit action potentials (MUAPs) can be extracted from the EMG signals. This may create new possibilities for assessment of motor control at a more

detailed level, which may clarify the nature of changes in motor control in chronic pain cases. Therefore, the two main objectives of this thesis were:

1. To develop and evaluate a non-invasive method to enable assessment of motor control at the motor unit level;
2. To investigate whether there are differences in motor control between chronic pain cases and healthy subjects and to what extent these differences can be used to distinguish these groups in an objective way.

Chapter 2 and 3 describe the evaluation of a new method for non-invasive assessment of motor control in simulated as well as experimental conditions. For quantification of muscle activity, the root-mean-square (RMS) value of the EMG signal is often used. This variable is affected by central motor control parameters (number of MUs and firing rate) as well as by peripheral muscle properties such as MU size. In contrast, the number of MUAPs per second (MUAP Rate) would reflect the summed firing rates of the active MUs. MUAP Rate is thus a combination of the two parameters that the Central Nervous System adapts in performing motor control, and would therefore solely reflect motor control. A simulation study was performed to explore the relation between MUAP Rate and both number of MUs and firing rate (Chapter 2). This study showed strong, monotonously increasing relations of MUAP Rate with both parameters. In contrast to RMS, MUAP Rate was not affected by MU size.
In Chapter 3 an experimental evaluation of MUAP Rate behaviour is presented. MUAP Rate was compared to the commonly used parameters RMS and median frequency of the power spectrum (FMED) during a step contraction with different force levels and during a fatiguing contraction. This study showed a strong, linear relation between MUAP Rate and force. MUAP Rate increased less than RMS during the fatiguing contraction, suggesting that MUAP Rate selectively reflects central motor control whereas RMS also reflects peripheral changes.
Several research groups are working on decomposition algorithms that can unravel firing patterns of individual MUs based on the differences between MUs in MUAP shape and in topography. To date, these algorithms are able to extract "fingerprints" of individual active MUs (i.e. the electrical activity related to a firing of one MU at all channels of the array). Full decomposition in terms of the complete firing patterns remains yet unsolved, especially for high force levels, due to the large number of superimposed MUAPs. However, the results of Chapter 2 and 3 show that the detection of MUAPs without their classification already results in useful information that cannot be obtained with conventional EMG recordings.
Following the evaluation of the proposed measure for motor control by means of simulation and experiments, it was applied to investigate motor control in subjects with

chronic pain in comparison with healthy controls (Chapters 4 to 6). Because of the work-related character of the pain, Chapter 4 presents a study investigating motor control in pain cases during computer tasks. The results suggested a greater contribution of high-threshold MUs to the contraction in chronic pain cases. It was concluded that this might be a compensation for a lowered force output of the low-threshold MUs, possibly due to damage, which would be in accordance with the Cinderella hypothesis.

Although the Cinderella hypothesis states that low-threshold MUs get damaged, it does not explain how development of damaged MUs proceeds. We assumed that before a MU gets damaged, there might be a stage in which it gets chronically fatigued. Therefore, the next study was directed towards the investigation of muscle fatigue development in the two groups (Chapter 5). It was hypothesized that cases would show a less pronounced myoelectric response to the fatiguing task than controls, because part of their MUs would already be chronically fatigued before the experiment started. The results were in accordance with the hypothesis, and furthermore, indications for the additional recruitment of higher-threshold MUs in the case group were found.

Both studies showed differences in EMG parameters between the two groups. Since clinical diagnostic tools generally do not reveal deviations in chronic pain cases, the next study investigated the discriminating ability of the EMG parameters. Chapter 6 presents a pilot study investigating if a combination of multiple EMG parameters can objectively distinguish between chronic pain cases and controls at the level of individual subjects. Classification with a sensitivity of 89% and specificity of 90% was obtained with a logistic regression model based on three EMG parameters extracted from array EMG recordings during a mouse task. Application of the obtained model to a second data set resulted in correct classification of 6 out of 8 subjects.

The findings presented in this thesis are in line with both the Cinderella hypothesis and the vicious circle model. Evidence for the pain adaptation model, that suggests a task-dependent limitation of the activity of the painful muscle to prevent it from painful movements, was not found. Although the present results contribute to the understanding of the development of chronic pain, the causality of the relation between deviations in motor control and chronic pain development remains unclear, due to the cross-sectional study design. To bring research in the field of chronic pain a step further, a multidisciplinary approach including muscle activity recordings during daily life and in well-controlled lab conditions, biopsies as well as psychosocial measures is advisable. Only a large longitudinal study can clarify the causality of the relations between work-related risk factors, individual factors, deviations in motor control, peripheral changes at the muscle cell level, and pain, which is essential for our understanding of the chronification process.

Samenvatting

Chronische pijn is een belangrijk probleem dat voorkomt bij een substantieel deel van de werkende populatie in de geïndustrialiseerde landen. Het is een multifactoriaal probleem dat een verzameling van condities omvat, die niet allemaal klinisch duidelijk gedefinieerd zijn. Subjectieve symptomen zijn onder meer: constante spierpijn, vermoeidheid van de spieren en/of stijfheid en uitstralende pijn. Tot de risicofactoren voor het ontwikkelen van chronische pijn in de nek-schouderregio behoren blootstelling aan ongebruikelijke houdingen, herhaalde bewegingen, lage statische contractieniveaus en hoge krachtniveaus. Naast deze werkgerelateerde fysieke factoren spelen psychosociale risicofactoren zoals stress, veeleisend werk en een lage arbeidssatisfactie een belangrijke rol. Ook individuele factoren zoals leeftijd, body-mass index en perceptie van werkbelasting kunnen bijdragen aan het ontwikkelen van chronische pijn.

Er zijn verschillende pathofysiologische modellen die de onderliggende mechanismen voor het ontwikkelen van chronische pijn verklaren. Het vicieuze cirkel-model voorspelt een positieve feedback-loop bestaande uit spierpijn die via nociceptoren het γ-motorneuronsysteem activeert, dat vervolgens projecteert op het α-motorneuron, waardoor de spier geactiveerd wordt, wat weer leidt tot toegenomen pijn. Het pijn-adaptatiemodel suggereert een taakafhankelijke toename van antagonist-activiteit en een afname van agonist-activiteit waardoor de spier wordt beschermd tegen pijnlijke bewegingen. De Cinderella-hypothese suggereert dat spiervezels van laagdrempelige motor units (MUs) beschadigd raken bij chronische pijn door continue activatie en gebrek aan voldoende spierontspanning.

Deze modellen hebben met elkaar gemeen dat ze veranderingen in bewegingssturing en/of spiersamenstelling en membraaneigenschappen voorspellen. De modellen beschrijven echter verschillende werkingsmechanismen en consensus omtrent de aard van de veranderingen in bewegingssturing ontbreekt. Een beter begrip van de onderliggende werkingsmechanismen is een belangrijke voorwaarde voor het ontwikkelen van effectieve behandelmethoden. Model-gebaseerde experimentele studies gericht op bewegingssturing bij mensen met chronische pijn kunnen tot meer inzicht in deze mechanismen leiden.

Bewegingssturing kan niet-invasief worden onderzocht met behulp van electromyografie (EMG). Met conventionele oppervlakte-EMG metingen, verkregen met twee electrodes geplaatst op de huid boven de betreffende spier, wordt de sommatie van de spatiële en temporele electrische activiteit van alle actieve MUs gemeten. Dit resulteert in een signaal met een stochastisch karakter, waarin actiepotentialen van individuele MUs niet onderscheiden kunnen worden. Met verscheidene electroden geplaatst in een array met kleine inter-electrode afstanden kan de spatiële selectiviteit van de meting worden

bevorderd. In combinatie met spatiële filters die de selectiviteit verder verhogen kunnen motor unit actiepotentialen (MUAPs) worden verkregen uit de EMG-signalen. Dit kan nieuwe mogelijkheden creëren voor het meten van bewegingssturing op een gedetailleerd niveau, wat tot nieuwe inzichten kan leiden in de bewegingssturing bij mensen met chronische pijn. Daarom zijn de twee doelstellingen van dit proefschrift als volgt geformuleerd:

1. Het ontwikkelen en evalueren van een niet-invasieve methode voor het meten van bewegingssturing op motor unit niveau;
2. Het onderzoeken of er verschillen in bewegingssturing zijn tussen mensen met chronische pijn en gezonde personen en in welke mate deze verschillen kunnen worden gebruikt om een objectief onderscheid te maken tussen deze twee groepen.

Hoofdstuk 2 en 3 beschrijven de evaluatie van een nieuwe methode voor het niet-invasief meten van bewegingssturing in zowel gesimuleerde als experimentele condities. Voor kwantificatie van spieractiviteit wordt veelvuldig de root-mean-square-waarde (RMS) gebruikt. Deze variabele wordt zowel door centrale parameters (aantal MUs en vuurfrequentie) als door perifere spiereigenschappen (zoals de grootte van de MUs) beïnvloed. Het aantal MUAPs per seconde (MUAP Rate) daarentegen vertegenwoordigt de gesommeerde vuurfrequenties van de actieve MUs. MUAP Rate is dus een combinatie van de twee parameters die het centraal zenuwstelsel gebruikt voor bewegingssturing (aantal MUs en vuurfrequentie), en zou daarom een selectieve maat zijn voor bewegingssturing.
Een simulatiestudie is uitgevoerd om de relatie tussen MUAP Rate en zowel aantal MUs als vuurfrequentie te onderzoeken (Hoofdstuk 2). Deze studie laat sterke, monotoon stijgende relaties zien van MUAP Rate met beide parameters. In tegenstelling tot RMS werd MUAP Rate niet beïnvloed door de grootte van de MU.
In Hoofdstuk 3 wordt een experimentele evaluatie van het gedrag van MUAP Rate gepresenteerd. MUAP Rate wordt daarin vergeleken met de gangbare parameters RMS en mediaanfrequentie van het vermogensspectrum (FMED) tijdens een stapcontractie met verschillende krachtsniveaus en tijdens een vermoeiende contractie. Deze studie laat een sterk verband zien tussen MUAP Rate en kracht. MUAP Rate nam minder toe dan RMS tijdens de vermoeiende contractie, wat suggereert dat MUAP Rate selectief bewegingssturing meet, terwijl RMS ook beïnvloed wordt door perifere veranderingen.
Verschillende onderzoeksgroepen werken aan decompositie-algoritmen die vuurpatronen van individuele MUs kunnen ontrafelen, daarbij gebruik makend van verschillen tussen MUs in MUAP vorm en topografie. Met deze algoritmen kunnen op dit moment "vingerafdrukken" van individuele MUs (i.e. de actiepotentiaal van één MU zoals gemeten

op alle kanalen van het array) worden verkregen. Volledige decompositie in de zin van het complete vuurpatroon blijft nog onopgelost, in het bijzonder voor hoge krachtniveaus, vanwege het grote aantal gesuperponeerde MUAPs. De resultaten van hoofdstukken 2 en 3 demonstreren echter dat de detectie van MUAPs ook zonder classificatie al in bruikbare informatie resulteert, die niet verkregen kan worden met conventionele EMG-metingen.
Volgend op de evaluatie van de voorgestelde maat voor bewegingssturing met behulp van simulaties en experimenten is de methode toegepast om bewegingssturing bij mensen met chronische pijn in vergelijking met gezonde mensen te onderzoeken (hoofdstuk 4 t/m 6). In verband met het werkgerelateerde karakter van de pijn wordt in hoofdstuk 4 een studie naar bewegingssturing tijdens computertaken bij mensen met chronische pijn beschreven. De resultaten suggereren dat het aandeel van hoogdrempelige MUs in de contractie groter is bij mensen met chronische pijn. Dit is mogelijk een compensatie van een verminderd vermogen van de laagdrempelige MUs om kracht te genereren, potentieel veroorzaakt door beschadiging, wat in overeenstemming met de Cinderella-hypothese zou zijn.
Hoewel de Cinderella-hypothese stelt dat de laagdrempelige MUs beschadigd raken, verklaart ze niet hoe deze beschadiging zich ontwikkelt. Een mogelijkheid is dat een MU eerst chronisch vermoeid raakt voordat deze beschadigt. Daarom was de volgende studie (hoofdstuk 5) gericht op het ontstaan van vermoeidheid in de spieren in beide groepen. De hypothese was dat mensen met chronische pijn een minder geprononceerde myoelectrische respons op de vermoeidheidstaak zouden laten zien dan gezonden mensen omdat een deel van hun MUs al chronisch vermoeid zouden zijn voordat het experiment begon. De resultaten waren in overeenstemming met de hypothese, en daarnaast waren er indicaties voor additionele recrutering van hoogdrempelige MUs bij mensen met chronische pijn.
Beide studies lieten verschillen in EMG parameters zien tussen de twee groepen. Omdat klinische diagnostische instrumenten vaak geen afwijkingen laten zien bij mensen met chronische pijn werd in de volgende studie het discriminerend vermogen van de EMG-parameters onderzocht. Hoofdstuk 6 beschrijft een pilotstudie, waarin onderzocht werd of een combinatie van enkele EMG-parameters een objectief onderscheid kan maken tussen mensen met chronische pijn en gezonde mensen op het niveau van individuele proefpersonen. Classificatie met een sensitiviteit van 89% en een specificiteit van 90% werd verkregen met een logistisch regressiemodel gebaseerd op drie EMG-parameters uit array EMG-metingen tijdens een muistaak. Toepassing van het model op een tweede dataset resulteerde in correcte classificatie van 6 van de 8 proefpersonen.
De bevindingen beschreven in dit proefschrift zijn in lijn met de Cinderella-hypothese en het vicieuze cirkel-model. Er is geen bewijs gevonden voor het pijn-adaptiemodel, dat een taakafhankelijke beperking van de activiteit van de pijnlijke spier suggereert als bescherming tegen pijnlijke bewegingen. Hoewel de huidige resultaten bijdragen aan het

inzicht in het ontwikkelen van chronische pijn kan ten gevolge van de cross-sectionele opzet van het onderzoek geen uitspraak worden gedaan omtrent de causaliteit van de relatie tussen afwijkingen in bewegingssturing en ontwikkeling van chronische pijn. Om het onderzoek in het veld van chronische pijn een stap verder te brengen is een multidisciplinaire benadering wenselijk waarbij spieractiviteit, zowel tijdens het dagelijks leven als in goed gecontroleerde lab-omstandigheden, biopsieën en psychosociale maten met elkaar in verband worden gebracht. Slechts een grootschalige longitudinale studie kan de causaliteit van de relaties tussen werkgerelateerde risicofactoren, individuele factoren, afwijkingen in bewegingssturing, perifere veranderingen op het niveau van spiercellen en chronische pijn verklaren. Dit is essentieel voor ons begrip van het chronificatieproces.

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Curriculum vitae

Laura Kallenberg was born in Amsterdam, the Netherlands, in 1978. After her graduation from the Carmellyceum (Oldenzaal) in 1996 she enrolled at the University of Twente, Enschede, where she studied Electrical Engineering. She graduated cum laude in 2002. She performed the research for her MSc thesis on motor unit activation patterns in people with chronic pain at the Roessingh Research and Development in Enschede. After her graduation she was subsequently employed as a PhD student at Roessingh Research and Development, where she has been working on the application of multi-channel surface EMG techniques to investigate mechanisms underlying work-related chronic pain. The present thesis is the result of her PhD research. Her research interest is in the area of biomedical signal processing for investigation of neuromuscular disorders.

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