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A Quantitative EMG Assessment of Motor Unit Recruitment in Patients with Ulnar Neuropathy

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

A QUANTITATIVE EMG ASSESSMENT OF MOTOR UNIT RECRUITMENT IN PATIENTS WITH ULNAR NEUROPATHY AT THE ELBOW

(Integrated Article)

by

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Abstract

The aim of the current study was to assess the test – retest reliability of motor unit firing rates with the use of decomposition based quantitative electromyography, and to quantify motor unit firing rates in the first dorsal interosseous of patients with ulnar neuropathy. 8 healthy subjects (mean age 35 ± 10 years) and 8 patients (mean age 48 ± 10 years) with ulnar neuropathy participated in the study. Following the acquisition of a maximum M wave, needle and surface detected EMGs were collected simultaneously during 30-second contractions performed at threshold (1-2% maximum voluntary contraction (MVC)) and 10% MVC- RMS (maximum voluntary contraction root mean square) to obtain motor unit potential (MUP) trains. From the data collected, motor unit amplitude, duration, area, firing rate, and motor unit number estimates (MUNE) were calculated. Test-retest reliability of MU firing rates in controls was high (ICC =0.85). Motor unit firing rates were found to be moderately correlated with recruitment as rated by experienced clinicians and the MU firing rates were increased in patients with ulnar neuropathy.

Keywords

Ulnar neuropathy, decomposition based quantitative electromyography (DQEMG), motor unit firing rates, reliability, first dorsal interosseous, motor unit recruitment

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EMG/DQEMG Patient Follow-up

Name:

Date:

FDI CMAP:

% Conduction Block

Area:

Amplitude:

Conduction Velocity Across Elbow:

Recruitment (circle appropriate):

Normal	Minimally Reduced	Mildly Reduced	Moderately Reduced	Severely Reduced
5	4	3	2	1

Indicate on the line the level of severity:

Normal _____ Severe

..... 38

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List of Abbreviations

FDI : first dorsal interosseous

MVC: maximum voluntary contraction

UNE: ulnar neuropathy at the elbow

EMG: electromyography

MU: motor unit

CB: conduction block

NCS: nerve conduction studies

CMAP: compound muscle action potential

DQEMG: decomposition based quantitative electromyography

MUNE: motor unit number estimation

MUP: motor unit potential

S-MUP: surface detected motor unit potential

AL: axonal loss

MVS-RMS: maximum voluntary contraction root mean square

IDI: inter-discharge interval

ICC: intra class correlation

1 Chapter 1

An Introduction to Peripheral Neuropathy and Associated Physiology

1.1 Anatomy and Physiology of Peripheral Nerves

The peripheral nervous system consists of spinal nerves, dorsal and ventral rami, plexuses, individual peripheral nerves and their associated branches. Peripheral nerves are comprised of both myelinated and unmyelinated fibres, both somatic and autonomic. Individual fibres are grouped in bundles called fascicles, which are in turn encased by the perineurium[1,2]. Peripheral nerves carry sensory and motor information to and from the brainstem, as well as from the spinal cord to the rest of the body.

1.2 Ulnar Nerve and First Dorsal Interosseous

The ulnar nerve originates from C8- T1 nerve roots, which descend to form part of the medial cord of the brachial plexus. The nerve continues to descend along the posteromedial aspect of the humerus. It enters the anterior compartment of the forearm, lying between the humeral and ulnar heads, where it then courses inferiorly down the ulna giving rise to the muscular, dorsal and palmar branches of the ulnar nerve [3]. Finally, it enters the hand through Guyon's Canal where it divides into the superficial and deep branches of the ulnar nerve. It is the deep branch of the ulnar nerve that innervates the first dorsal interosseous (FDI)[4]. FDI functions primarily in abduction of the index finger. It also plays a major role in the adduction of the thumb toward the index finger; these two actions occurring in synchronicity allow for the pinching function. Atrophy of the FDI leads to weakness and difficulty manipulating objects as a result of weak pinch strength. Because the FDI is a relatively small muscle, its increase in force production is primarily based on rate coding rather than recruitment of additional motor units. Most of the motor units of FDI are recruited by 50% MVC, and any further increases in force are dependent upon increasing firing rates[5]. This allows for precise control of the muscles in the hand, by allowing force to be increased by fractions of degrees.

Because peripheral nerves are not encased and protected by the skull or spinal column, as is the case for the central nervous system, peripheral nerves are more susceptible to injury by compression or trauma. A neuropathy occurs in any case of damage to the nerves, which then cause repercussions to the target cell (sensory, organ, muscle, etc.) that it innervates.

1.3 Ulnar Neuropathy

In areas where the nerve must pass through confined spaces, such as the median nerve through the carpal tunnel at the wrist, as well as the ulnar nerve at the elbow, the nerve is more susceptible to entrapment and compression. A compressed or entrapped nerve can lead to axonal damage and/or demyelination. With respect to the ulnar nerve, neuropathy is often caused by direct pressure on the nerve (eg from leaning on the elbow), strenuous activity of the arm at the elbow, or overuse of the arm causing pressure or entrapment of the nerve[6]. Compression of the ulnar nerve at the elbow can occur at one or more of four locations both proximal and distal to the elbow. These include: the medial intermuscular septum, the retroepicondylar groove, the humeroulnar arcade and at the point of exit of the nerve from the flexor carpi ulnari[4,7]. However, compression at the retroepicondylar groove is by far the most common site of focal ulnar neuropathy.

Ulnar neuropathy is the second most common focal neuropathy, next to carpal tunnel syndrome (CTS) [7]. In a study based in the United Kingdom, the annual incidence of ulnar neuropathy (at all anatomical locations) for men and women was 25.2 and 18.9 per 100 000 respectively[8]. Clinically, ulnar neuropathy at the elbow (UNE) typically presents with numbness or tingling of the fourth and fifth digits, elbow pain, deterioration of hand function and worsening of symptoms upon repeated elbow and wrist flexion[6,7]. Muscle weakness is most commonly present in the intrinsic hand muscles such as the first dorsal interosseous (FDI) and the abductor digiti minimi (ADM), which generate complaints of reduced grip strength and reduced ability to manipulate small objects[6]. Electrodiagnostic studies are completed in combination with the physical examination and comprise of motor and sensory conduction velocity measurements, and electromyography[7]. Electrodiagnostic studies are particularly helpful when diagnosis is

not straightforward, such as cases confounded with musculoskeletal pain, or radiculopathy[9]. Typically, motor nerve conduction studies record from either the hypothenar eminence or FDI with stimulation at the wrist, below the elbow and above the elbow. Focal slowing or conduction block across the elbow provides the most compelling evidence of a localized lesion[10]. In addition, needle electromyography (EMG) is often completed to determine the presence of axonal damage or conduction block that can lead to decreased recruitment. MU recruitment is also graded to determine the presence of conduction block (CB) or axonal loss. In most cases, an experienced electromyographer does this subjectively.

1.4 The Motor Unit

The motor unit is the most fundamental component of the peripheral motor system, as it serves to regulate our motor responses. A single motor unit (MU) is comprised of the alpha motor neuron, the motor axon and all the muscle fibres it innervates[11-13]. The nerve carries an impulse that is conducted along the axon and is transmitted along the muscle fibre via the neuromuscular junction. The communication between nerve and muscle is accomplished by a single neurotransmitter, acetylcholine (ACh). In a healthy system, this results in contraction of the muscle at the force desired. The control of force generated by a muscle contraction is accomplished by controlling the number of motor units activated and their firing rates[12]

1.5 Motor Unit Recruitment

Adrian and Bronk[14] stated there are two mechanisms by which force can be increased during a voluntary contraction. Either the number of motor units activated during the contraction can be increased, known as recruitment, or the firing rates of those motor units already activated can be increased, known as rate coding[5,14]. Motor units are recruited based on increasing size, such that smaller, low threshold motor units are recruited first, with the larger, higher threshold motor units recruited when contraction intensity increases[5,15]. It has been suggested that in small muscles of the hand, where precise motor control is needed, the excitability of motor neurons are such that all are

recruited at a relatively low force level, and further increases in force are achieved by rate coding[16]. Conversely, in large muscles, such as the quadriceps femoris, motor unit excitability is broadly distributed to allow for recruitment to be the primary method of increasing the force of contraction[13]. In healthy individuals, the first recruited motor unit fires at a stable rate of 5-7 Hz. When the force of contraction is gradually increased, the first motor unit increases its firing frequency to 8 -10 Hz. Upon any further increases in force, a second motor unit is recruited and so forth[17]. In cases of demyelination, resulting in conduction block or with a loss of motor axons and motor neurons, motor unit discharge rates of the normally conducting motor axons may increase to achieve a given desired contraction[18].

1.6 Conduction Block

Conduction block (CB) occurs when the nerve impulse is unable to propagate through a structurally intact axon. The most important form of CB is demyelinating conduction block, in which the insulating component of the axon, called myelin, has been compromised. Myelin enables the normal saltatory conduction of the nerve impulse, allowing for rapid conduction velocities along the nerve. In instances of nerve injury, demyelination may occur, resulting in lower conduction velocities or failure of conduction depending on severity[19]. Conduction block can be identified by nerve conduction studies (NCS), in which a nerve containing motor and sensory axons is stimulated at a given point along the nerve. The stimulus is a brief electrical pulse which generates an action potential. The action potential will travel distally toward the muscle innervated by that nerve and induce action potentials along the muscle fibres, which are recorded by surface electrodes. The summation of these muscle fibre action potentials is known as the compound muscle action potential (CMAP) [20]. By dividing the distance between two sites at each end of a nerve segment (ie. wrist and elbow) by the latency difference between the CMAPs induced at those sites, conduction velocity can be measured[20]. Conduction block is determined to be present by an amplitude reduction in comparing a distal with proximal stimulation site (eg. $>$ 20% reduction in amplitude across the elbow of the ulnar nerve), often combined with reduced conduction velocities

across the elbow of less than 50 m/s in the still conducting fibres[21]; see figure 1 for an example of conduction block.

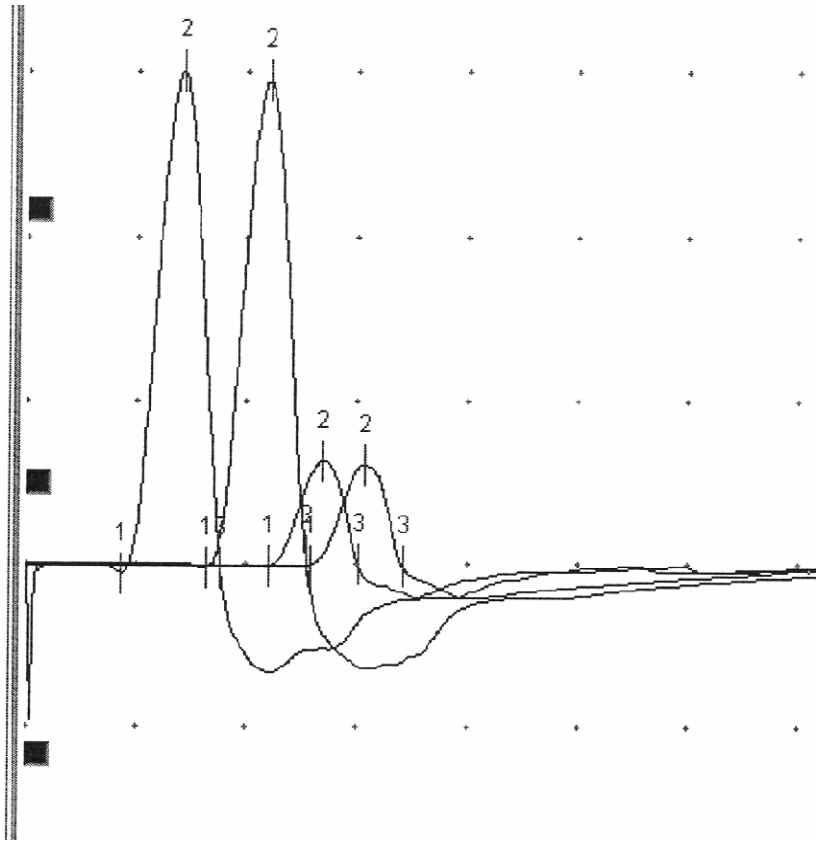

Figure 1. Conduction Block

Example of patient with 80% conduction block in the ulnar nerve segment across the elbow as recorded from the FDI muscle. The first two responses are from stimulation at the wrist and below the elbow, while the second pair of lower amplitude responses are from stimulation above the elbow and at the axilla. There is obvious conduction block from below to above the elbow. Each division vertically represents 2 mV, while each division horizontally represents 5 ms.

1.7 Axonal Loss

When a nerve becomes injured by inflammation, crush or ischemia, the integrity of the axon becomes compromised and degradation of the nerve fibres distal to the site of injury occurs in a process called Wallerian degeneration (WD). With axonal loss, there are a decreased number of nerve fibres innervating the target muscle, often resulting in some loss of muscle mass and subsequent decrease in force production in that muscle[20]. The presence and severity of axonal loss can be measured by routine nerve conduction studies in combination with needle EMG studies. Axonal loss can be measured by a reduction in amplitude of the CMAP; however, collateral reinnervation may result in a CMAP that appears normal in size. In this case, the still remaining MUs will have larger amplitudes and longer durations, as well as reduced recruitment on routine needle EMG studies. Although, such studies are subjective and lack the ability to quantify MU loss. Therefore, axonal loss can also be quantified by motor unit number estimation (MUNE) techniques such as decomposition-enhanced spike triggered averaging (DE-STA)[22,23] . MUNE was developed by McComas, et al[24] as a quantitative, electrophysiological method for estimating the number of functioning MUs within a muscle. MUNE is calculated through division of the CMAP, which represents the activation of all the motor axons in response to supramaximal electrical stimulation, by the mean surface detected motor unit potentials, representative of the average single MU size[25].

1.8 Collateral Reinnervation

In cases of peripheral nerve injury, where demyelination or axonal loss has occurred, muscles become weak and generation of force cannot be sustained. In these cases, normal orderly recruitment is disrupted and compensatory mechanisms may allow for relative preservation of contractile force[17]. In cases of neuronal loss, a compensatory mechanism occurs, termed collateral reinnervation. In collateral reinnervation, surviving neurons sprout new terminal processes that establish contact with abandoned muscle fibres. As a result of denervation and reinnervation, motor units enlarge. This can be detected with the use of needle electromyography[24]. Needle electrodes, when inserted into the belly of a given muscle can detect motor unit action potential (MUP see below)

amplitude. In healthy muscle, MUP amplitudes are less than 2 mV and have a duration of 10- 15 ms. In cases of axonal loss due to injury of the motor neuron, where reinnervation has occurred, amplitudes can reach 2-5 mV with durations of 20-30 ms[24]. Clinically, collateral reinnervation results in the slowing of the progression of weakness until a critical number of motor units are lost, perhaps as high as 70%[24]

1.9 Decomposition Based Quantitative Electromyography

Quantitative electromyography provides analysis of motor unit action potentials with the use of both surface and needle electrodes. Motor unit action potential exceeding a certain threshold that are detected and considered to represent a significant MUP occurrence are isolated and categorized into individual MUP trains. From this, features of the MUP such as size, shape, duration and firing patterns can be determined[25]. Filter and pattern recognition algorithms are applied to the needle detected EMG signals. Each motor unit action potential train (MUAPT) that is decomposed by the algorithm represents the activity of a single MU, which is then used to estimate the template or specific size and shape for the MU. Surface EMG signals are calculated concurrently with needle detected EMG signals, and are used to estimate the ensemble-averaged surface motor unit potential (S-MUP). This represents the contribution of the individual MU to the surface detected potential. The size of the S-MUP reflects the size of the underlying MUs[18]. This aspect of DQEMG allows for the estimation of motor unit number of the muscle under study. Quantitative MUP analysis involves the calculation of various parameters characterizing the MUP template, MUP shimmer plot, S-MUP template, and firing pattern associated with each MUP train using standard algorithms. Finally, descriptive statistics are calculated automatically for each parameter based on the entire sample of accepted MUPs and S-MUPs from the muscle under study[25].

2 Chapter 2

A Quantitative EMG Assessment of Motor Unit Recruitment in Patients with Ulnar Neuropathy at the Elbow

2.1 Introduction

Ulnar neuropathy is the second most common entrapment neuropathy next to carpal tunnel syndrome. Nerve injury is often attributed to prolonged and repetitive compression or stretch during elbow flexion[6]. Symptoms most commonly involve paraesthesia, muscle weakness and or sensory loss in the ulnar distribution. Injury to the nerve may cause focal demyelination and/or axonal loss. Demyelination of a nerve slows conduction velocity, and when severe enough can lead to conduction block (CB). The presence and severity of conduction block can be determined by routine nerve conduction studies (NCS) [4,26]. By providing an electrical impulse to the nerve at the wrist, below the elbow and above the elbow, compound muscle action potentials (CMAP) can be measured. Conduction block is diagnosed when the CMAP above the elbow is reduced by > 20% when compared to the CMAP below the elbow [21]. Needle electromyography can also be used in the diagnosis of UNE to determine if motor unit recruitment is reduced, indicating loss of axons or CB. Abnormalities such as positive sharp waves and fibrillations can be detected with needle EMG and can provide further evidence of axonal loss and denervation. Recruitment patterns can also be assessed during voluntary contraction of the muscle under study and examining the interference pattern[4]. Physicians and EMG technicians can determine if the recruitment pattern is normal, reduced, or if only a few motor units are firing rapidly.

Previous studies have used motor unit firing rates to assess neuropathic and myopathic conditions. Recruitment can be quantified by measuring the firing rate of the first recruited motor unit, and at the point when an additional motor unit is recruited [27]. In neuropathic conditions, such as focal neuropathy, both of these values are increased[27]. Recruitment can also be quantified by calculating the ratio between the number of active MUs and the firing rate of the most rapidly firing motor unit. In healthy muscle this

number is <5; however, in neuropathic muscle, this number is increased when axonal loss occurs[28]

When more than a few motor units are active at one time, the EMG signal becomes too complex to discern individual MUs. This complex signal became termed the interference pattern[29]. Sanders et al sought to objectively examine motor unit firing rates by examining the interference pattern during full, voluntary effort[29]. The EMG signal recorded at this level reflects the shape of individual MUPs, the size of active MUs and their individual firing rates. In pathological conditions, individual MUPs may be abnormal, the number of MUs active may be reduced, and their firing rates may increased. These pathological changes are notable in the interference pattern[29]. In neuropathic conditions such as generalized neuropathy, MUP size is increased and the number of MUPs that are available to be recruited at a given target force is reduced. The interference pattern is observed to be less full with larger MUP amplitudes. Reduced recruitment is apparent when areas of baseline are present, in spite of a maximum contraction.

Decomposition based quantitative electromyography provides clinically useful information pertaining to the physiological characteristics of individual motor units. It is a reliable and valid method for obtaining electrophysiological data in healthy subjects, as well as those with neuromuscular disease[22,23,30]. Along with providing measures of MUP size, duration and amplitude, DQEMG also provides information pertaining to the mean firing rates of individual motor units. Along with noting the number of MUP trains detected by the software in a given contraction, recruitment patterns can be assessed and analyzed.

The purpose of the current study is to determine the reliability of measuring motor unit firing rates with the use of decomposition based quantitative electromyography in the first dorsal interosseous muscle of healthy individuals, as well as to quantify motor unit firing rates in patients with ulnar neuropathy at the elbow. We would hypothesize that those with conduction block and axonal loss would have increased firing rates measured by DQEMG.

2.2 Methods

2.2.1 Subjects

Eight patients (7 men, 1 woman; age 48 ± 10) with clinically diagnosed ulnar neuropathy at the elbow were recruited from the EMG clinic at University Hospital, London Health Sciences Centre, and St Mary's Hospital, St Joseph's HealthCare to participate in this study. They were compared with 8 healthy controls with no known history of ulnar neuropathy or other known neuromuscular disorders (6 men, 2 women; age 35 ± 10). All subjects gave written, informed consent in accordance with Western University Health Sciences Research Ethics Board, which approved this study.

2.2.2 Physician Diagnosis of Ulnar Neuropathy at the Elbow

All patients had clinical features of ulnar neuropathy at the elbow (UNE) including numbness and paresthesiae in the fourth and fifth digit, weakness in grip and pinch and worsening with prolonged elbow flexion[7]. They were assessed by an experienced clinician who confirmed the clinical presence of an UNE through a typical history and physical examination. Standard motor nerve conduction studies recording from both the FDI and hypothenar eminence were completed. Sensory studies were completed for the radial, median and ulnar nerves. UNE was confirmed electrodiagnostically by the presence of conduction slowing across the elbow (less than 48 m/s and greater than 10 m/s less than the forearm conduction velocity) when recording from the FDI muscle, and for the CB group, amplitude reduction of greater than 20% when comparing the below to elbow stimulation sites. For the axonal loss (AL) group, the FDI CMAP amplitude with distal stimulation was required to be less than 10 mV with evidence of acute or chronic denervation on needle EMG studies. One patient met criteria for both groups but was classified as CB for the purposes of the study. Motor unit recruitment in the FDI, during standard needle EMG assessment, was then graded by the electromyographer on a 1 to 5 scale, with 1 denoting severely reduced recruitment and 5 considered normal.

2.2.3 Quantitative Electromyographic Data Collection

Quantitative electromyographic (EMG) signals were acquired using decomposition-based quantitative electromyography (DQEMG) (version 3.2) and Acquire EMG software on a Neuroscan Comperio (Neuroscan Medical Systems, El Paso, TX). Self-adhering Silver Mactrode® electrodes (GE Medical Systems, Milwaukee, WI) were used to detect surface signals, and 25 mm x 30 gauge TECA™ elite Disposable Concentric Needle Electrodes (CareFusion, Middleton, WI) were used to detect intramuscular signals, with bandpass settings of 5 Hz to 5 kHz and 10 Hz to 10 kHz, respectively[22,23]. Testing was conducted on the right arm of control individuals and the affected arm of the patients. Individuals were seated in an upright position with the tested arm resting on a table in the pronated position. Surface electrodes were cut in strips (1 cm x 3.5 cm) for use as the active and reference electrodes, with a full-sized electrode serving as a ground. The skin above the FDI was cleansed with isopropyl alcohol and surface electrodes were placed appropriately. The active electrode was positioned transversely over the belly of the muscle, with the reference electrode placed over the interphalangeal joint (IP) of the second digit (index finger), and the ground placed over the distal head of the radius.

A handheld bipolar stimulator was used to elicit a maximum compound muscle action potential (CMAP), with the ulnar nerve stimulated at the wrist. The active electrode was moved in small increments to a position that elicited the maximum negative peak amplitude and the smallest rise time of the CMAP. When optimal position of the active electrode was obtained, the surface electrodes were reinforced with surgical tape to ensure no movement occurred during the testing period. Stimulation was applied gradually until the CMAP negative peak amplitude reached a plateau. Markers indicating onset, negative peak, positive peak, and the end of maximum CMAP were automatically positioned and manually adjusted if necessary. Size related parameters of the maximum CMAP, including negative peak amplitude and duration, were calculated automatically.

Subjects were asked to perform a 3-4 second voluntary isometric contraction by way of abduction of the second digit. Subjects were encouraged to produce their

maximal effort, with the use of visual and auditory feedback from the EMG signal, as well as the investigator. The maximal root mean square value of the EMG signal over a 1 second interval was calculated automatically and the intensity of the subsequent sub-maximal contractions were graded as a percentage of this maximal voluntary contraction root mean square (% MVC-RMS)[31]

Next, the concentric needle electrode was inserted into the FDI, approximately 2-5 mm proximal or distal to the active surface electrode. Subjects were asked to perform minimal isometric contractions while an optimal needle position was located that minimized rise times of the MUPs of the first two to three MUs recruited. With the needle manually maintained in this position by the evaluator, the subject was asked to increase contraction force to 5% MVC-RMS, or threshold, where only the first few motor units were activated. Each submaximal isometric contraction was maintained for 30 seconds, during which the subject received visual and auditory feedback from the EMG signal and the % MVC-RMS information displayed on the screen. Contractions were performed until a minimum of 20 acceptable MUP trains were collected. The needle position was adjusted between contractions to ensure data was collected from different MUs, and if necessary, the needle was inserted at a new site to complete the collection of MUP trains[30,32]. This same procedure was completed a second time (with collection of 20 acceptable MU trains), with the MVC-RMS target being set at 10%.

2.2.4 Electromyographic Signal Decomposition and Analysis

DQEMG and its associated algorithms have been described in detail previously (Chapter 1.9) [23,25] . Briefly, DQEMG involves the decomposition of the composite intramuscular EMG signal into its constituent MUP trains. The individual MUP firings from each MUP train then serve as triggers to isolate the surface-detected motor unit potentials (S-MUP) from the surface-recorded EMG signal. The S-MUPs associated with each MUP firing are then ensemble-averaged to derive the S-MUP template associated with a given MU[25]

During offline analysis, the acceptability of acquired MUP template, S-MUP templates and MUP trains were reviewed based on specific criteria; those failing to meet the inclusion criteria were excluded from further analysis[22]. Accepted MUP trains demonstrated a consistent and physiological firing rate quantified by an interdischarge interval (IDI) histogram displaying a Gaussian shaped main peak, a coefficient of variation < 0.3, and by visual examination of the instantaneous firing rate plot[13,25]. Additionally, MUP trains were required to have MUP and S-MUP template derived from a minimum of 51 detected potentials each. When two MUP trains within a contraction were identified by the software as 'disparate' (i.e suspected to stem from the same MU), one of these MUP trains was excluded following confirmation based on visual inspection of their raster plots. The onset, positive peak, negative peak, and end markers of the MUP and S-MUP templates were visually analyzed and repositioned if necessary. Finally, the onsets of the MUP and S-MUP templates were required to occur within 10 ms of each other in order for the corresponding MUP train to be accepted. MUP templates consistent with cannula potentials (inverted MUPs as a result of a larger contribution from the cannula than from the core detection surface of the concentric needle electrode) were excluded, as they express different information than typical MUPs[33]. Although, their corresponding S-MUP templates from the same MUP trains were retained for further analysis, as the ability of cannula potentials to serve as accurate triggering source of spike-triggered averaging is not compromised. MUNE was calculated by dividing the mean S-MUP template amplitude from the 20 or more acceptable MUs into the maximum CMAP amplitude

2.2.5 Calculating Motor Unit Firing Rates

Motor unit firing rates were calculated with use of DQEMG software. For each acceptable MU train (MUAPT), the pattern of discharges was represented by a histogram and an estimation of the inter-discharge interval (IDI). Each MUs average firing rate was calculated as the inverse of its mean IDI[23]. Because there were missed and/or inaccurate motor unit firings that were present within the trains, an error filtering estimation (EFE) technique was used that recognized and ignored inaccurate firings (IDIs that are statistically too long or too short). The mean IDI, along with its inverse, in Hz, are

displayed as an output along with the MUP parameters. The motor unit firing rates of individual patients were derived from the average of the mean MUP firing rates of all accepted MUPTs.

2.2.6 Intra-rater reliability

In control subjects, after the attainment of 20 MUPs at both threshold and 10% MVC-RMS, subjects rested for a minimum of 15 minutes before completing the retest portion of the study. Data collection was executed by the same examiner (K.R) and tests took place on the same day for each subject. Following completion of the first test, all electrodes were removed and a new set of electrodes were applied for the repeat test. The electrode positions were not marked during the first assessment, and data analysis was completed only following collection of both sets of data so that the evaluator was blinded to the results of both assessments until data collection was complete.

2.2.7 Statistics

Mean values along with their standard deviations and ranges are presented throughout. Relative intra-rater reliability was assessed using a Model 3 (two way mixed, consistency) single measure intraclass correlation coefficient (ICC) (IBM® SPSS® Statistics 19, SPSS, Inc., Chicago, IL). ICC point estimates of <0.50 were considered poor, 0.50-0.75 considered moderate, and >0.75 considered good reliability[34]. Additionally, ICC point estimates >0.90 were classified as excellent reliability. If the *F*-test associated with between-subjects variance from the ICC output was not significant, the corresponding ICC value was deemed potentially inaccurate. This conclusion was made because between-subject heterogeneity is a necessary condition for reliability testing, without which the actual limits of the ICC may deviate from the theoretical limits of 0.00-1.00[34]. Pearson's correlation was computed for non-ordinal data, while Spearman's correlation was computed for ordinal data; correlation coefficients and p values are presented; *r* values of < 0.35 are considered to represent weak correlation, 0.36 to 0.67 represent moderate correlation, while values from 0.68 to 1 represent strong correlations[35].

A two tailed unpaired *t*-test was used to determine significant differences in firing rates, MUP and CMAP amplitudes between the control and patient populations, as well as between patient sub groups. An a priori alpha level of 0.05 was used to denote significance (IBM® SPSS® Statistics 19, SPSS, Inc., Chicago, IL). A paired t test was used to determine significant differences between MUNE values time 1 and time 2.

2.3 Results

2.3.1 Control Subjects Firing Rate and CMAP

In controls, FDI motor unit firing rates at threshold ranged from 8 – 12 Hz with a mean of 9.7 ± 0.9 and ranged from 10 -14 Hz with a mean of 11.7 ± 0.9 at 10% MVC-RMS. When stimulated at the wrist, normal ulnar CMAP values were also measured, with a range of 13 -20.7 mV and a mean of 16.2 mv ± 2.4.

2.3.2 Firing Rate Reliability in Controls

Motor unit firing rates were measured in controls at two time intervals, separated by at least 15 minutes. The reliability of mean MU firing rates was determined at threshold, as well as 10% MVC-RMS, and the values are presented in Table 1. Mean firing rates, measured at threshold, at time 1 and time 2 were 10 Hz and 10 Hz respectively. At 10% MVC-RMS mean firing rates increased to 12 and 12 Hz at time 1 and time 2. There was no significant difference between values at time 1 and time 2 at threshold or 10% MVC-RMS; analysis using ICC revealed excellent reliability for both threshold (ICC 0.83) and 10% MVC-RMS (ICC 0.85). There was a significant difference between firing rates at threshold and 10% MVC-RMS, $t(7) = 5.36$, $p < 0.05$(1.13, 2.9). MUNE values at time 1 and time 2 were not significantly different $t(7)=0.238$, $p < 0.05$ (-78.32 to 68.69). Mean value for MUNE at time 1 was 366 and 373 at time 2. ICC was not valid as there was insufficient heterogeneity of the data.

Table 1. Reliability of Mean Firing Rates

	Threshold Firing Rates	10% MVC-RMS Firing Rates
Test	10 Hz	12 Hz
Re-Test	10 Hz	12 Hz
ICC	0.83	0.85

Mean motor unit firing rates in healthy individuals showed high reliability at both threshold and 10% MVC-RMS

ICC, Intraclass Correlation; MVC-RMS, maximal voluntary contraction root mean squared

2.3.3 Effect of Force on Motor Unit Firing Rates

Motor unit firing rates increased with greater force production. Participants were asked to hold force levels at a threshold contraction and at 10% MVC-RMS. At threshold, few motor units are recruited and maintenance of force is dependent upon recruitment, less on firing rates. However, at higher levels of contraction, motor unit firing rates increase to sustain the level of contraction. In the present study, there was a significant difference between threshold and 10% MVC-RMS firing rates. This pattern of activation was seen in both healthy individuals, as well as those with ulnar neuropathy, see Table 2.

2.3.4 UNE and Nerve Conduction Studies

The mean duration of symptoms in the UNE patient group was 16.2 ± 21.5 weeks (range 3-52 weeks). Routine nerve conduction studies revealed a mean distal CMAP of 7.3 ± 3.2 mV (range, 1.9 – 10.05 mV). This was significantly reduced compared to healthy controls, $t(13) = 6.16$, $p < 0.05$ (5.82, 12.03). Results of nerve conduction studies differed depending on whether the primary pathology was axonal loss or conduction block. Those with axonal loss had increased MUP size, decreased motor unit number estimation (MUNE); however, MU firing rate remained normal, 1291.2 ± 689.1 μV, 53 ±27, and 8 ± 0.9 Hz respectively. MUP values between controls and UNE patients revealed a trend toward being significantly different, $t(13)=2.06$, $p=0.058$ (-14.64, 770.89). Alternatively, when a patient suffered primarily from conduction block, MUP size remained relatively normal, firing rates increased and MUNE remained relatively normal as well, with values of 655 ±98 μV, 14 ± 2.9 Hz, and 241.6 ± 134.5 respectively. Results of conduction and electromyography studies separated by diagnosis are displayed in Table 3. Mean patient and control data are presented in Table 4.

Table 2. Effect of Force on MU Firing Rates

Control Firing Rates		UNE Firing Rates	
Threshold	**10% MVC-RMS**	**Threshold**	**10% MVC-RMS**
9	13	7	7
9	12	11	17
9	12	8	9
10	11	16	18
9	10	13	14
9	11	9	11
9	11	8	9
12	13	11	11

Both control and UNE firing rates at threshold and 10% MVC-RMS significantly different, $p < 0.05$

Abbreviations: MVC-RMS, maximal voluntary contraction root mean square; UNE, ulnar neuropathy at the elbow; MU, motor unit

Table 3. Patient Data and Diagnosis

Firing	CMAP	MUP	MUNE	Diagnosis	%CB	Conduction

Rates (Hz)	(mV)	Amplitude (µV)				Velocity (m/s)
18	10.1	508	206	CB	80%	47.8
14	10.1	830	213	CB	65%	29.2
12	10	550	468	CB	70%	31.9
17	6.5	896	106	CB	75%	33.3
11	9.4	592	215	CB	85%	25.9
9	3.0	1859	63	AL	85%	14.2
7	7.8	1489	73	AL	15%	27.9
9	1.9	524	22	AL	30%	26.2

Values expressed as means. Firing rates, MUP amplitude and MUNE are taken at 10% MVC-RMS. Conduction Block was obtained by dividing the CMAP achieved above the elbow by the CMAP achieved below the elbow. Conduction velocity was measured from above elbow to below elbow segments.

Abbreviations: CMAP, Compound Muscle Action Potential; MUP, Motor Unit Potential; MUNE, Motor Unit Number Estimation; CB, Conduction Block; AL, Axonal Loss; CB, Conduction Block

Table 4. Comparison of Control and Patient Data

Control			UNE		
CMAP (mV)	S-MUP (μV)	MUP (μV)	CMAP (mV)	S-MUP (μV)	MUP (μV)
15	145	451	7.8	186	1489
15.4	162	658	6.5	197	896
16.5	166	444	1.9	198	524
13	187	679	10.1	215	508
14.3	147	663	10.1	119	830
16.9	159	430	10	180	549
20.8	195	463	2.95	328	1859
18.3	136	434	9.4	94	592

Statistical significance was reached between controls and UNE for CMAP values, and approaching significance for MUP values.

Abbreviations: UNE, ulnar neuropathy at the elbow; CMAP, compound muscle action potential; S-MUP, surface detected motor unit potential; MUP, motor unit potential

2.3.5 Firing Rates in Ulnar Neuropathy

Firing rates differed based on a diagnosis of conduction block or axonal loss. Mean firing rates for those with primarily conduction block were increased compared to controls, 14.2 Hz ±2.9, while firing rates for those with primarily axonal loss remained similar to controls, 8.3 Hz ±0.9. Mean firing rate values based on diagnosis are presented in Table 5. When separating conduction block from axonal loss patients, there is a statistically significant difference between normal, control firing rate values at 10% MVC-RMS and firing rates of UNE patients at 10%, $t(11) = 2.22$, $p < 0.05$ (0.026, 5.08). Greater conduction block was moderately correlated with increased motor unit firing rates, $r=0.56$, see figure 2.

Table 5. Ulnar Neuropathy Diagnosis and Firing Rates

Diagnosis	**N**	**Mean Firing Rate at Threshold (Hz)**	**Mean Firing Rate at 10% MVC-RMS (Hz)**
Conduction Block	5	12	14
Axonal Loss	3	8	8

Patients with conduction block displayed increased mean firing rates at both threshold, as well as 10% MVC-RMS.

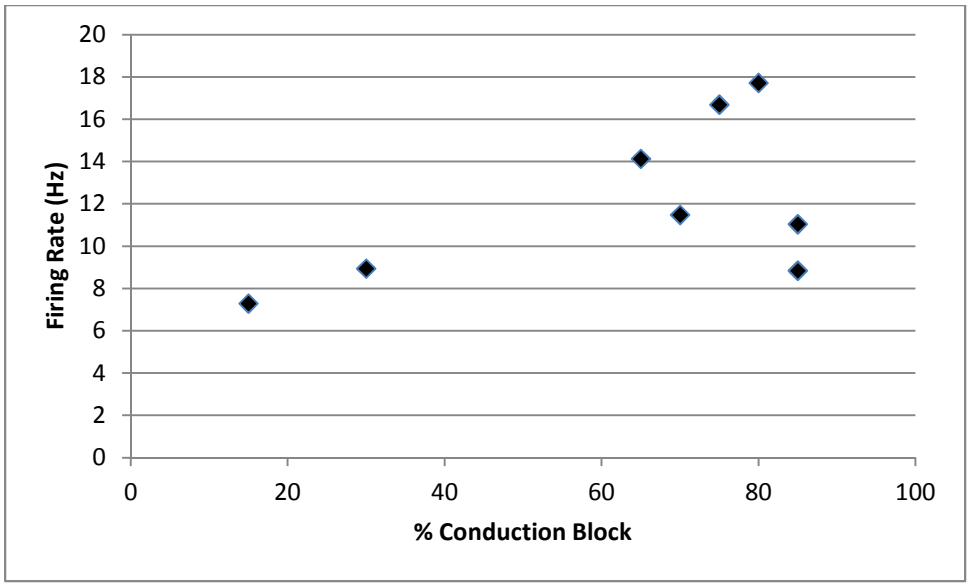

Figure 2. Firing Rates vs Conduction Block

Motor unit firing rates at 10% MVC RMS were moderately correlated to % conduction block, r = 0.57

2.3.6 UNE Firing Rates and Recruitment Severity Rating

To quantify motor unit firing rates and recruitment severity, clinicians provided a rating of each patient's recruitment severity on a 5 point scale; 1 denoting severely reduced recruitment and 5 symbolizing normal recruitment. The average rating for recruitment was 3.25 ±0.88. However, increased recruitment loss was skewed slightly toward conduction block, see Figure 3. Severity rating and firing rates were moderately correlated, r_s = -0.49.

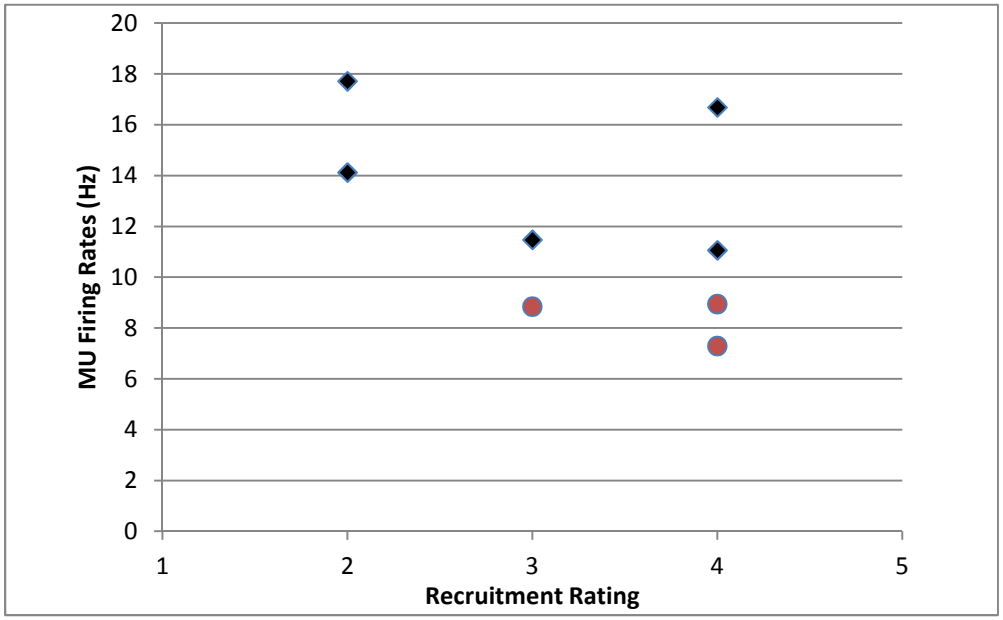

Figure 3. Motor Unit Recruitment Rating

Motor unit firing rates and recruitment severity rating are moderately correlated, r_s = -0.49. Circles represent axonal loss patients, while diamonds represent conduction block.

2.4 Discussion

This study examined the reliability of measuring motor unit firing rates with the use of DQEMG in healthy individuals, and quantified motor unit firing rates in patients with ulnar neuropathy, a focal neuropathy where altered MU recruitment would be expected. The main findings were: 1) FDI motor unit firing rates measured with DQEMG revealed high test –retest reliability (high ICCs); 2) motor unit firing rates differ significantly in ulnar neuropathy depending on the underlying pathophysiology, conduction block or axonal loss; 3) increased firing rates, due to CB, resulted in a more severe recruitment reduction rating from physicians.

Demonstrating reliability of a measure establishes that the values obtained from one measurement to the next are consistent. The current study demonstrated reliability with the use of intra class correlation (ICC). An ICC of > 0.75 is considered good reliability[34]. The present study demonstrated high reliability (0.85) in measuring motor unit firing rates with decomposition based quantitative electromyography (DQEMG). To our knowledge, this is the first study to determine reliability of measuring MU firing rates with DQEMG. Past studies have determined both the intra and inter -reliability of measuring motor unit number estimation (MUNE) using DQEMG[32,36]; additionally, it has been shown that contraction level can be estimated using root mean square (RMS) in DQEMG, and therefore the use of hand dynamometers and the biodex, tools that measure contraction level and strength, can be accurately supplemented using RMS[31]. Finally, DQEMG has been shown to reliably measure MUNE in neuromuscular disorders such as ALS[37]. With the many uses of DQEMG surfacing, the ability to reliably measure motor unit firing rates is of great importance and strengthens the use of DQEMG as both a diagnostic and research tool.

The mean motor unit firing rates reported for healthy controls are comparable to others stated in the literature[16,23,27,36]. Firing rates at threshold were significantly different from those at 10% MVC-RMS. This is to be expected, because as the level of contraction increases, two mechanisms are in place to ensure force can be sustained, recruitment of additional motor units, and increasing firing rates. As FDI is predominantly a muscle

dependent on rate coding for gradation of force, increased forced is produced primarily by increasing motor unit firing rates[16] . At threshold, a minimal amount of force is produced such that only the recruitment of the first few detectable motor units is required, and firing rates remain relatively stable. With an increase to 10% MVC-RMS, FDI has recruited a majority of its motor units and relies on the increase in firing rates to sustain contraction, see Table 2.

Individuals with UNE present with an underlying pathophysiology of axonal loss, conduction block, or a combination of the two. Consequently, motor unit firing rates differ, depending on the individual's primary pathology. The present study found significant differences in motor unit firing rates, CMAP amplitude and MUNE values between UNE patients suffering from conduction block, and those suffering from axonal loss. This is important, as although the diagnosis of ulnar neuropathy is assigned to both of these groups, their pathology as a result of entrapment differs. Those with axonal loss have more severe nerve injury and denervation as a result of entrapment, leading to muscle weakness and atrophy. To compensate for the loss of neurons, collateral reinnervation occurs, which increases MUP duration and amplitude; however, in the current study, the motor unit firing rates remained normal. On the other hand, those suffering from conduction block as a consequence of ulnar entrapment maintain the structural integrity of the axon, but have become demyelinated. As a result, the adaptive response observed in this study is in the form of increased firing frequency.

In the present study, patients afflicted with axonal loss suffered increased MUP size and decreased MUNE; however, firing rates remained normal. Collateral reinnervation results in the enlargement of motor units, which can be seen as an increase in motor unit potential amplitude and duration[31]. MUP amplitudes ranged from 524 – 1859 μV, with an average of 1291 μV; comparatively, normal MUP amplitudes ranged from 434 – 663 μV, with an average of 528 μV. Additionally, axonal loss was quantified with the use of motor unit number estimates. Normal motor unit number estimates in FDI ranged from 284 – 515 with an average of 374. These numbers are comparable to others found in the literature[36]. Those with axonal loss suffered from a diminished number of motor units, in the range of 22-73. Finally, axonal loss causes a decrease in CMAP

amplitude; the CMAP refers to the total number of motor units contributing to the muscle when stimulated at supramaximal stimulation. A lower CMAP indicates axonal damage, as there are less motor units to contribute to the action potential. Normal CMAP values ranged from 14.8 to 29.3 mV with an average of 21.6 mV. Those with axonal loss suffered from CMAP values that ranged from 2.9 to 10.1 mV, with an average of 7.3 mV (see table 5). Interestingly, motor unit firing rates remained normal (8.3 Hz @ 10% MVC-RMS). This was not expected, as previous studies have reported increased firing rates in cases where recruitment is altered as a result of chronic neuropathy[28,38]. With axonal loss, the number of available motor units for recruitment is reduced; therefore, sustained force is made possible by the increase in firing rates of available motor units[28]. A study by Reiners and colleagues studied motor unit firing rates in the first dorsal interosseous in patients with chronic neurogenic atrophy, which revealed an increase in firing rate[38]. In the present study, motor unit firing rates may not have increased due to the relatively low contraction level (10% MVC-RMS) reached by the participants, as recruitment has been shown to be normal at minimal to moderate levels of muscle contraction[39]. Such low levels of contraction are not high enough to activate the enlarged motor units that are now at a higher threshold[39]. It is possible that we may have revealed an increase in motor unit firing rates if the contraction level was increased to 30 – 50% MVC. However, decomposition techniques limit the level of contraction that can be analyzed, as in FDI, the interference pattern becomes too complex at 30% MVC as the majority of motor units are recruited at this point. At this level of contraction, the algorithms can no longer decompose motor units into individual trains. Secondly, using RMS-MVC as a means of measuring contraction, may have not equated the same contraction intensity for those with normal MU numbers compared to those with motor unit loss. This may have been resolved by using number of pulse per second instead, which is a more relative measure of contraction.

Conduction block inhibits the transmission of the electrical signal propagating the length of the axon to the target muscle. Therefore, the muscle does not have the entirety of its neurons creating synapses and aiding in generating force. To compensate for the reduction in available neurons propagating their signal down the length of the axon,

motor unit firing rates increase. In the present study, firing rates in those with CB increased to an average of 14.2 Hz. This is in accordance to earlier studies. Dietz et al reported increased firing rates in the FDI of patients with polyneuropathy[40]. Similar findings were reported by Petajan, who found increased firing rates in patients with neuropathies (21 Hz) compared to normal subjects (7.6 Hz)[27]. Halonen studied motor unit firing rates in the tibialis anterior muscle of patients with acute and chronic neuropathies and found significant increases in firing rate as well[41]. MUNE values and MUP amplitudes remained normal as the axons are still structurally intact, and motor units do not enlarge from collateral reinnervation; however CMAP values were slightly decreased, see Table 5 for comparison values between controls and UNE patients. In general, with greater conduction block (ie. 85% block vs 60% block); firing rates were increased to a greater extent compared to those with little to no block. Pearsons's correlation demonstrated moderate correlation, with an $r = 0.57$. With an increased sample size, perhaps the correlation would have been more formidable (refer to figure 2). Conduction block is diagnosed when velocity across the elbow is less than 50 m/s; all patients had some degree of conduction block, as all fell under this limit (range, 14.2 – 47.8 m/s).

The study incorporated the use of a recruitment severity scale to assess the subjective physician rating of motor unit recruitment. The scale was a 5 point scale; 1 demonstrating severely reduced recruitment, and 5 demonstrating normal recruitment. Those with increased firing rates had a lower subjective physician rating, indicating increased firing rates are associated with more severely reduced recruitment. It was also apparent that those who suffered from conduction block, had more severe recruitment reduction ratings (1s or 2s) in comparison to axonal loss, see figure 3. Spearman's correlation was computed and demonstrated a moderate correlation, $r_s = -0.49$. Those with axonal loss had lower firing rates and a less severe rating score, indicating more normal recruitment. Quantifying motor unit firing rates in this manner not only displays the accuracy of physician recruitment rating, but may also aid in the diagnosis of pathology of ulnar neuropathy. Understanding whether demyelination or axonal loss is causing the muscle weakness and atrophy may assist in early treatment methods.

2.5 Limitations

A noted limitation of the present study is the small sample size of the two pathologies. With only 5 conduction block and 3 axonal loss patients, it is difficult to make firm conclusions. With an increased sample size, it may have been easier to demonstrate the difference between the two groups, as well as make correlations between conduction block and firing rate, as well as firing rate and the recruitment severity index. Secondly, the present study did not account for strength of the FDI muscle. As electrodiagnostic studies are the gold standard for determining motor unit recruitment, we assessed recruitment severity with this method. It is also possible that by not accounting for strength or atrophy of the muscle, the level of activation at 10% MVC-RMS may not have been the same for all subjects. However, MVC-RMS has been shown to be a reliable and comparable tool for determining strength and was therefore the more preferable method[31].

2.6 Conclusion

This study has been the first to establish test – retest reliability of motor unit firing rates using DQEMG. DQEMG is already in use for the measurement of MUNE and other parameters of motor unit potentials. This finding builds to the utility of DQEMG in both a clinical and research aspect. Additionally, the study found that DQEMG was able to find a significant difference between motor unit firing rates in healthy individuals, as well as those with ulnar neuropathy. Lastly, the current study reported an increase in firing rates in those suffering from conduction block, but not those with axonal loss.

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2.8 Appendices

Appendix A

EMG/DQEMG Patient Follow-up

Name:

Date:

FDI CMAP:

% Conduction Block

Area:

Amplitude:

Conduction Velocity Across Elbow:

Recruitment (circle appropriate):

Normal	Minimally Reduced	Mildly Reduced	Moderately Reduced	Severely Reduced
5	4	3	2	1

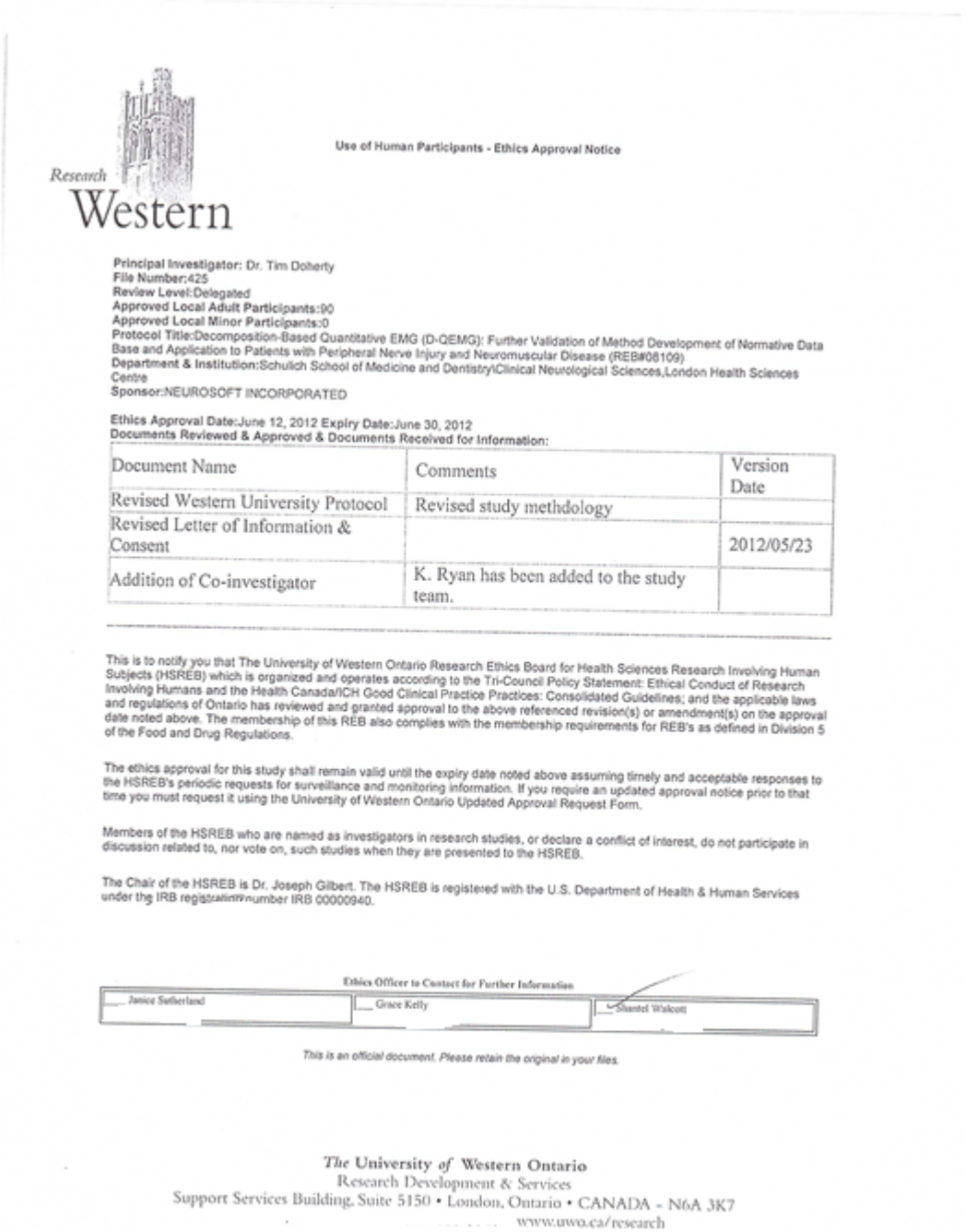
Indicate on the line the level of severity:

Normal Severe

_____

Appendix B

Appendix B Ethics



Research Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Tim Doherty
File Number:425
Review Level: Delegated
Approved Local Adult Participants:90
Approved Local Minor Participants:0
Protocol Title: Decomposition-Based Quantitative EMG (D-QEMG): Further Validation of Method Development of Normative Data Base and Application to Patients with Peripheral Nerve Injury and Neuromuscular Disease (REB#08109)
Department & Institution: Schulich School of Medicine and Dentistry\Clinical Neurological Sciences,London Health Sciences Centre
Sponsor:NEUROSOFT INCORPORATED

Ethics Approval Date: June 12, 2012 **Expiry Date:**June 30, 2012
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Revised study methdology	
Revised Letter of Information & Consent		2012/05/23
Addition of Co-investigator	K. Ryan has been added to the study team.	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

Janice Sutherland | Grace Kelly | Shantel Walcott

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2.9 Curriculum Vitae

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Abstracts/Presentations

K N Ryan, T J Doherty (2013). A Quantitative EMG Assessment of Motor Unit Recruitment in Patients with Ulnar Neuropathy at the Elbow. Aging Rehabilitation Geriatric Research Conference *Abstract*