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Test-Retest Reliability of MUNE and MUP Analysis from Decomposition-Based Quantitative Electromyography for the Flexor Carpi Radialis Muscle

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Graduate Program in Kinesiology
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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TEST-RETEST RELIABILITY OF MUNE AND MUP ANALYSIS FROM DECOMPOSITION-BASED
QUANTITATIVE ELECTROMYOGRAPHY FOR THE FLEXOR CARPI RADIALIS MUSCLE

(Integrated Article)

by

Saskia R. Knol

Graduate Program in Kinesiology

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

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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ABSTRACT

The purpose of this study was to establish a set of representative data from healthy subjects and determine the intra-rater reliability of decomposition-enhanced spike triggered averaging (DE-STA) motor unit number estimation (MUNE) and quantitative motor unit potential (MUP) analysis from D-QEMG for the flexor carpi radialis (FCR) muscle. Twenty subjects aged 21-51 were studied (9 females, 11 males). Trials A and B assessed test-retest reliability for FCR when the wrist was flexed only. The effects of finger flexion during wrist flexion were assessed in trial C. Results found high reliability for maximum CMAP (ICC = 0.92), moderate reliability for mean S-MUP (ICC = 0.63) and low reliability for MUNE (ICC = 0.39) between trials A and B. The SEMs and mean percent differences for maximum CMAP, mean S-MUP and MUNE were 0.84 mV and 4%, 11 μ V and 15%, and 87 MUs and 16%, respectively. There were no detected differences between trials A and B for any parameters. There was a significant difference in MUNE ($p = 0.035$) between trials A and C. Results are consistent with previous literature regarding the calculated MUNE, variability, and reliability. The importance of neutral finger position during wrist flexion contraction has been reiterated given the significant difference in MUNE between trials A and C. Overall, D-QEMG in FCR was shown to be reproducible in healthy subjects.

KEYWORDS: Decomposition-enhanced spike-triggered averaging (DE-STA);
electromyography (EMG); motor unit number estimation (MUNE); test-retest reliability;
flexor carpi radialis (FCR)

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LIST OF ABBREVIATIONS

ALS	Amyotrophic lateral sclerosis
AP	Adductor pollicis
BB	Biceps brachii
CMAP	Compound muscle action potential
DE-STA	Decomposition-enhanced spike triggered averaging
D-QEMG	Decomposition-based quantitative electromyography
FCR	Flexor carpi radialis
FDI	First dorsal interosseous muscle
ICC	Intraclass correlation coefficient
ICP	Intercarpal joint
IDI	Interdischarge interval
MCP	Metacarpophalangeal joint
MN	Motor neuron
MPS	Multiple point stimulation
MU	Motor unit
MUNE	Motor unit number estimation
MUP	Motor unit potential
NCS	Nerve conduction study
QEMG	Quantitative electromyography
S-MUP	Surface motor unit potential
STA	Spike-triggered averaging
TA	Tibialis anterior
UT	Upper trapezius

Chapter 1.0: General Introduction

1.0.1 Motor neurons and motor units

Neurons are electrically excitable cells that transmit information throughout the body by electrical and chemical signals. Cortical motor neurons (MNs) are derived from the motor cortex of the brain and project to the spinal cord. Lower MNs, also referred to as anterior horn cells, project from the spinal cord to skeletal muscle fibres. A single alpha motor neuron and all of the muscle fibres it innervates are known collectively as a motor unit (MU); this term was first defined by Liddell and Sherrington in 1925 (Doherty, Chan, & Brown, 2002; Liddell & Sherrington, 1925). Researchers have been able to determine how MUs are organized in the spinal cord. The distribution of MUs to various muscles can be mapped out in schemes called myotomes. There is considerable overlap in myotomes, as most muscles receive innervation from two to three spinal cord segments (Doherty et al., 2002). MUs can also be classified by type depending on their size and function. Slow oxidative MUs innervate small muscle fibres that contract slowly and generate relatively small forces. Slow MUs are resistant to fatigue and are important for activities that require sustained contractions (Clamann, 1993; Purves et al., 2001). Larger alpha motor neurons innervate larger muscle fibres. In larger muscle fibres mitochondria are less concentrated and it is more difficult to replenish energy, thus these larger MUs are known as fast fatigable MUs. Activation of fast fatigable MUs results in brief exertions of relatively large force production (Purves et al., 2001). Intermediate MU types have also been classified, including fast fatigue resistant and fast intermediate in fatiguability (Clamann, 1993). Generally, these MUs are more fatigue-

resistant than fast twitch MUs and they generate at least twice the force of slow twitch MUs (Purves et al., 2001). Knowledge regarding the organization and classification of MUs can aid clinicians in diagnosing various neuromuscular disorders. Researchers have long been interested in accurately estimating the number of functional motor neurons in humans. This would provide a quantifiable method in the study of healthy aging and diseases affecting the motor neuron or motor axon.

1.0.2 Collateral reinnervation

In normal healthy aging, various morphological changes to the neuromuscular system take place, leading to a significant loss of strength after the sixth decade of life (Doherty, 2003; McNeil et al., 2005; Power et al., 2010). One study suggests that beyond-middle age strength decreases by approximately 15% per decade (Vandervoort & McComas, 1986). The functional effects of aging can be attributed to many morphological changes, including a reduction in muscle cross-sectional area, reduction in the number of muscle fibres and reduction in MU number and size (Lexell & Vandervoort, 2002; Roos, Rice, & Vandervoort, 1997). Some processes thought to underlie the degenerative effects on peripheral nerves include loss of myelination, denervation from repeated trauma, programmed cell death, and muscle disuse (Conwit & Metter, 2002). Cell death also occurs in certain MN diseases such as amyotrophic lateral sclerosis (ALS). In both healthy aging and disease, MU loss leads to eventual muscle atrophy and weakness. When MUs are first lost, neighbouring healthy neurons compensate by sprouting new axons to regain input to the affected muscle fibres. This process is called collateral reinnervation (see Figure 1) (Stalberg & Falck, 1997). During

the initial period of MU loss degeneration occurs but collateral reinnervation counteracts loss of function. In fact, 50-90% of MU loss may occur with little or no apparent weakness (Doherty & Brown, 2002). In these cases, the compound muscle action potential (CMAP) may be normal or close to normal and routine electromyography (EMG) studies may not detect MU loss until later stages of degeneration. In order to detect MU loss with the occurrence of collateral reinnervation, quantitative EMG is needed to record amplitudes, durations and phases of detected motor unit potentials (MUPs). If abnormalities are observed along with reduced MU recruitment, clinicians can be confident that MU loss is occurring.

1.0.3 Motor unit number estimation and incremental stimulation

Motor unit number estimation (MUNE) was first described by Professor A.J. McComas. McComas and his colleagues studied findings from routine nerve conduction studies (NCS) (McComas, Fawcett, Campbell, & Sica, 1971). In NCS, the nerve supplying the muscle under study is stimulated, twitching the muscle and producing a measureable compound muscle action potential (CMAP). NCS are unable to determine the number of motor units/axons because of collateral innervation. That is, the size of the CMAP does not correlate well with the number of contributing MUs (Doherty & Stashuk, 2003; Doherty & Brown, 2002). McComas and colleagues observed that with progressive stimulation, the CMAPs increased incrementally with stronger stimuli, as single motor unit potentials (S-MUPs) were added to the waveform (Gooch et al., 2014). This meant that the mean S-MUP could be determined by dividing the size of the

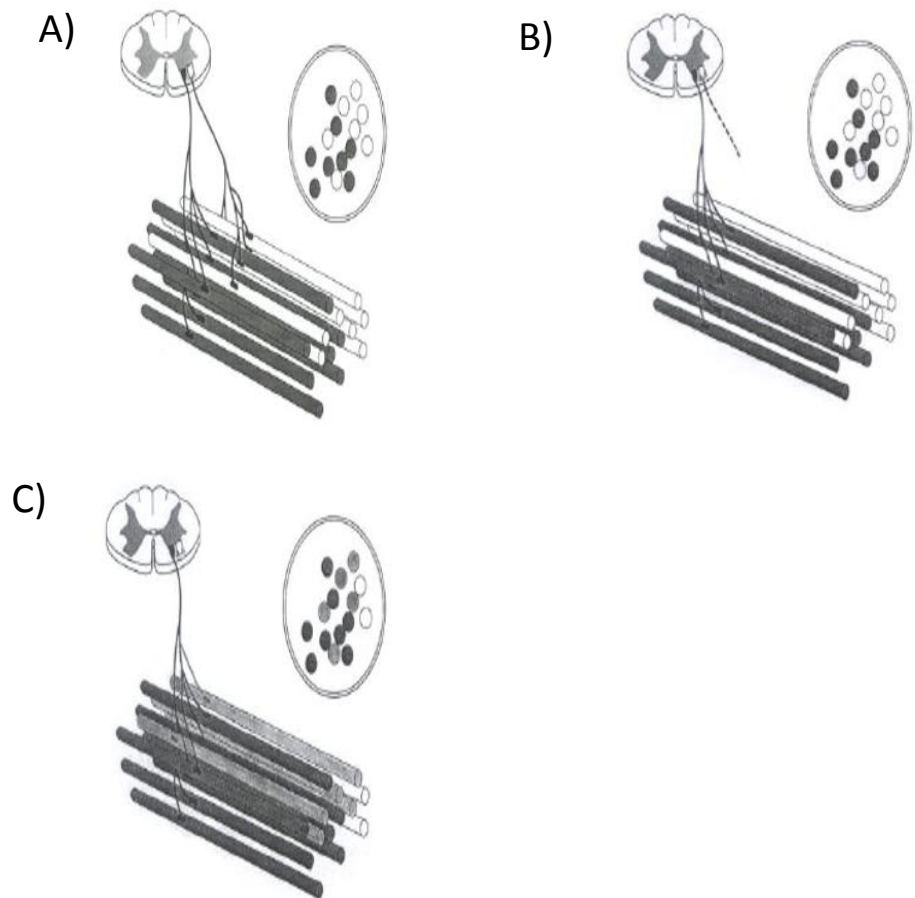


Figure 1: A) Two motor neurons (MNs) are depicted with origins from the anterior horn cross-section of the spinal cord. Their peripheral axons innervate specific fibres of a muscle, depicting two functioning motor units (MUs) [distinguished by black and white shading]. B) One of the MNs dies, leading to loss of innervation to muscle fibres. The second MU is unaffected, as the MN is functioning and the number of innervated fibres remains the same. C) The healthy MU sprouts axons to innervate the muscle fibres associated with the dead MU (grey shading). This increases the size of the healthy MU and preserves the unused muscle fibres. (Modified from Stalberg & Falck, 1997)

submaximal CMAP by the number of individual steps. The maximal CMAP represents the activation of the total motor unit pool. This measure divided by the average S-MUP size, would therefore estimate the number of functioning motor units. This is the premise on which MUNE is built; mathematically, MUNE is equal to the maximal CMAP amplitude divided by the average S-MUP amplitude.

From the paradigm described by McComas et al. arose the incremental stimulation method of MUNE. As of 2010, this was the most common technique used in MUNE papers (Gooch et al., 2014). The incremental stimulation method is based on the assumption that each increment represents the addition of a single MU. However, this has been challenged due to a phenomenon known as alternation (Gooch et al., 2014). Researchers became aware that the increments in a growing CMAP waveform could be the result of two different motor axons alternating in activation at similar depolarization thresholds (Gooch et al., 2014). In attempt to eliminate this phenomenon, other MUNE methods have been derived.

1.0.4 Motor unit number estimation techniques

Methods derived after the incremental stimulation method include multiple-point stimulation (MPS), the F wave response method, the statistical method, and spike triggered averaging (STA) [which includes decomposition-enhanced (DE) STA] (Doherty & Brown, 2002). The electrical activity of active MUs is recorded in all methods. The incremental stimulation method and MPS are based on electrical stimulation of motor nerves. However, these methods are limited to use in distal muscles because of the

need for an easily accessible nerve for percutaneous stimulation. STA and DE-STA are different from these methods because they draw on the sample of MUs collected through voluntary contraction, allowing proximal as well as distal muscles to be studied.

1.0.5 Spike-triggered averaging

During STA, an intramuscular electrode records isolated single motor unit discharges produced by voluntary contraction, while surface electrodes record the time-locked signal and average it over repeated discharges to extract the associated surface-recorded S-MUP (Doherty & Brown, 2002; Gooch et al., 2014). The intramuscular needle is then moved to sample MUPs from different muscle fibres. The average S-MUP is calculated from these recordings and used in the MUNE equation. Additional data from the quantitative electromyography (QEMG) recordings can give more information, including firing rates and the average motor unit action potential (MUP). From the MUP prototype, characteristics such as amplitude, duration, number of turns and phases can be assessed. Each characteristic has distinct implications to neuromuscular remodeling in aging and disease. For example, increased duration correlates to increased number of muscle fibres from collateral sprouting and/or hypertrophy of muscle fibres (Stashuk & Brown, 2002). Increased number of phases or turns correlates to loss of muscle fibres, increased variability among the diameters of muscle fibres of the MU and muscle fiber reinnervation (Stashuk & Brown, 2002).

While there is high test-retest reliability (Gooch et al., 2014), traditional STA is known for its sampling bias. Henneman's size principle states that in a voluntary

contraction, smaller MUs are recruited first, followed by larger MUs (Henneman, Somjen, & Carpenter, 1964). Since STA is employed only at lower voluntary contraction levels, the S-MUP size would be biased towards sampling from smaller MUs. Smaller S-MUPs would therefore give larger, overestimated MUNE values. Additionally, a considerable amount of time is needed to collect an adequate amount of MUs, with 15-20 MUs requiring more than one hour of collection.

1.0.6 Decomposition-enhanced spike triggered averaging

Decomposition-enhanced STA (DE-STA) was developed to sample a wider range of MU sizes at higher levels of voluntary contraction, up to 50% of maximum voluntary force (Doherty & Brown, 2002). A computer algorithm decomposes and extracts multiple MUPs from a moderate intensity interference pattern. This is collated with information from the surface EMG waveform to determine the S-MUP corresponding to each needle recorded MUP [See Figure 2 for sample output] (Gooch et al., 2014). Both STA and DE-STA methods are useful because they can sample from both proximal and distal muscles, as long as a valid CMAP can be obtained (Gooch et al., 2014). They also provide additional diagnostic and research data not available with other MUNE methods (i.e. MUP characteristics such as amplitude, duration, and firing pattern). Use of decomposition-based QEMG (D-QEMG) also makes the process of obtaining S-MUPs faster, requiring less patient cooperation (Doherty & Brown, 2002).

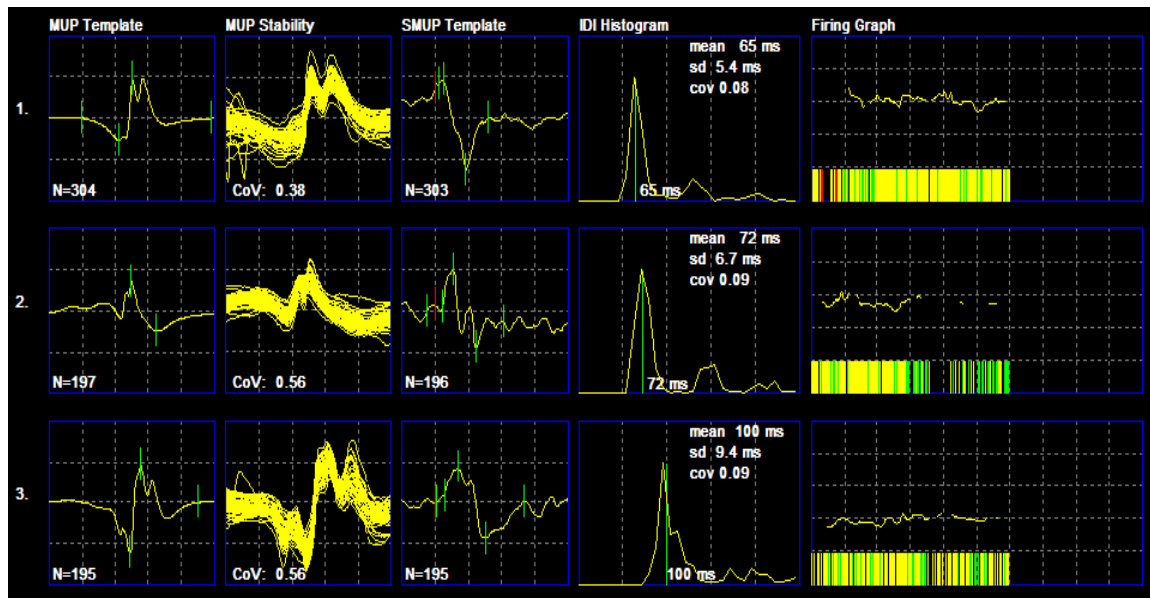


Figure 2: Decomposition summary of three MUP trains (horizontal, labelled 1-3), representing the decomposition of needle-detected EMG signal and analysis of needle- and surface-detected signals. From left to right, columns represent A) MUP prototype; B) individual MUPs superimposed on a shimmer-plot; C) mean S-MUP; D) inter-discharge interval histogram; E) firing rate versus time plot representing MUP train discharge times and instantaneous firing rate plots.

1.0.7 Conditions studied with motor unit number estimation

Aging has been extensively studied using MUNE in association with measures of strength to better understand when MU loss begins to affect functional output (Doherty, 2003; McNeil et al., 2005; Power et al., 2010; Roos et al., 1997). MUNE techniques have also been used to study MU loss, dysfunction and reinnervation in prior polio, spinal muscular atrophy, Charcot-Marie-Tooth disease, acquired polyneuropathies and entrapment neuropathies, among other clinical conditions (Gooch et al., 2014). One of the most extensively studied conditions has been ALS, since the disease is characterized primarily by MU loss. Upper neuron lesions have also been studied, with several researchers calculating MUNE of upper limb muscles.

Previous studies have examined reliability of upper limb muscles, including biceps brachii (BB), first dorsal interosseous (FDI), thenar and hypothenar muscles (Boe, Stashuk, & Doherty, 2006b; Bromberg, 1993; Doherty & Brown, 1993; Felice, 1995; Lomen-Hoerth & Olney, 2000; Shefner, Jilapalli, & Bradshaw, 1999). In the past decade, there has been a shift in how reliability is studied, moving away from the mere reproducibility of a method within a population, towards clinical reliability within subjects. Within-subject reliability of D-QEMG was conducted in proximal BB and distal FDI, with moderate-high intraclass correlation coefficients of 0.97 and 0.72, respectively (Boe et al., 2006b). Later in an inter-rater study, quantitative data was significantly different and likely correlated with variability in electrode placement during testing (Boe et al., 2010).

The current project therefore aimed to investigate a new muscle which would be anatomically easy to access both in terms of obtaining a maximum CMAP and the collection of intramuscular and surface EMG data. Flexor carpi radialis was selected as a new muscle with which to explore intra-rater reliability and generate representative data for a healthy group of subjects.

1.0.8 Flexor carpi radialis muscle

Flexor carpi radialis (FCR) is located in the anterior compartment of the forearm. It originates on the medial epicondyle of the humerus, travelling laterally to flexor digitorum superficialis and inserting at the base of the second metacarpal (Rohen, Yokochi, & Lutjen-Drecoll, 2011). When the wrist is brought into flexion, the most lateral tendon observed belongs to FCR. FCR receives blood supply from the radial artery and is innervated by the median nerve (Rohen et al., 2011). The median nerve has roots from C5, C6/C7 (lateral cord), and C8/T1 (medial cord), with the lateral cord supplying FCR. The median nerve travels along the arm between biceps brachii and brachialis, innervates the forearm muscles including FCR, then divides into anterior and posterior branches as it enters the hand (Rohen et al., 2011).

FCR is an appropriate muscle to study with D-QEMG because it is superficial and can be easily accessed with an intramuscular needle with minimal discomfort. The median nerve is also easy to stimulate to obtain a CMAP. By validating MUNE in the FCR of healthy individuals, this muscle can then be further explored in aging or neuromuscular disorders. FCR also has clinical relevance due to its common

involvement as an index C7 muscle in radiculopathy. No previous MUNE studies have examined this muscle.

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Chapter 2: Assessment of intra-rater reliability of decomposition-based quantitative electromyography (D-QEMG) in flexor carpi radialis (FCR) muscle.

2.0 Introduction

Motor unit (MU) loss is a characteristic observed in aging and many acute or progressive neuromuscular disorders. Collateral reinnervation is the process which attempts to counteract MU loss. In this process, healthy motor axons sprout new axons to reinnervate orphaned muscles fibres. Collateral reinnervation is able to preserve muscle function up until a critical threshold of MU loss (Doherty & Brown, 2002; McComas et al., 1971; Stalberg & Falck, 1997). Motor unit number estimation (MUNE) is a technique used to quantify the number of functioning motor units within a muscle using electrophysiological techniques (McComas et al., 1971). MUNE is dependent on determining the total electrical size of the muscle, by supramaximal stimulation to the nerve, resulting in the maximum compound action potential (CMAP). Then, the average surface motor unit potential (S-MUP) is calculated, representing the average size of a single MU. By dividing the maximum CMAP by the average S-MUP, an estimation of the number of functioning motor units can be obtained (Gooch et al., 2014). MUNE is a unique measurement because it takes into account the effects of collateral reinnervation by incorporating the mean S-MUP (McComas et al., 1971). This gives MUNE an advantage over traditional measures of EMG and nerve conduction, as well as strength and function at the whole muscle level.

Decomposition-based quantitative electromyography (D-QEMG) uses computer algorithms for MU analysis and decomposition-enhanced spike-triggered averaging (DE-STA) MUNE (Stashuk, 1999). D-QEMG not only provides estimates of MU number, but it measures physiological MU properties not assessed in other methods. Additionally, DE-STA MUNE can sample from distal and proximal muscles, as long as a valid CMAP can be obtained (Gooch et al., 2014).

Flexor carpi radialis (FCR) is a wrist flexor in the forearm which has not yet been studied in D-QEMG in the literature. FCR receives innervation from nerve roots C6-C7, and is therefore frequently implicated in radiculopathies. By establishing a set of representative data for FCR in healthy individuals, further studies may quantify FCR MUNE in individuals with clinical disorders affecting this muscle. Additionally, an important aspect of a measurement tool is that the results are reproducible by the same examiner at two different time points (Portney & Watkins, 2008). Therefore the intra-rater reliability of FCR must be studied in order to assess reproducibility and the inherent variability of the technique.

Intra-rater reliability of DE-STA MUNE has been established in thenar, first dorsal interosseous, biceps brachii, upper trapezius, and extensor carpi radialis muscles (Boe, Dalton, Harwood, Doherty, & Rice, 2009; Boe, Stashuk, & Doherty, 2004, 2006a; Calder, Agnew, Stashuk, & McLean, 2008; Ives & Doherty, 2012). The purpose of this study is to establish a set of representative data and determine the intra-rater reliability of DE-STA MUNE and quantitative MUP analysis from D-QEMG of FCR.

2.1 Methods

2.1.1 Subjects

Twenty subjects (9 females, 11 males) aged 21-51 (29 ± 11) with no self-reported neuromuscular or musculoskeletal disease volunteered to participate in the study. All 20 subjects successfully completed the test-retest portion of the study. Three subjects did not complete the third trial involving an altered contraction strategy. All subjects gave written, informed consent in accordance with The University of Western Ontario Health Sciences Research Ethics Board, which approved this study [see Appendix A].

2.1.2 Electromyographic data collection

EMG signals were collected using a Viking System (Natus Medical Incorporated, San Carlos, CA). Signals were then exported and analyzed with D-QEMG (Version 3.4). Self-adhering Silver Mactrode[®] electrodes (GE Medical Systems, Milwaukee, WI) were used to detect surface signals and 25mm x 30 gauge disposable concentric needle electrodes (TECA™ Elite, CareFusion, Middleton, WI) were used to detect intramuscular signals. Surface EMG was collected with a bandpass of 5 Hz by 5 KHz and needle EMG with a bandpass of 10Hz to 10 KHz.

Testing was conducted unilaterally in the subject's dominant forearm, which was the right forearm in every subject. Participants were seated upright on an examination table with their forearm relaxed and supine on their lap. The hand and forearm was strapped to a foam support to ensure that it was held still and straight during testing.

The foam support functioned to minimize movement of the hand. One strap secured the palm of each subject, and another strap was positioned across the distal forearm. The foam support did not function to completely immobilize the hand and forearm; it served as a reminder to each subject to contract isometrically and isolate the wrist flexor group as much as possible. Surface electrodes were cut in strips (1 cm x 3.5 cm) for active and reference electrodes. The ground electrode was full-sized (2 cm by 3.5 cm). Skin was cleansed with 70% isopropyl alcohol wipes prior to adherence of surface electrodes. The reference electrode was placed over the styloid process of the ulna; the ground electrode was placed distal to the anterior surface of the elbow joint; and the active electrode was placed transversally over the FCR muscle belly, approximately mid-forearm and medially.

A hand-held bipolar stimulator was used to elicit a maximum compound muscle action potential (CMAP), by exciting the median nerve on the medial arm at the antecubital fossa. The active electrode was repositioned over the belly of FCR in order to maximize the negative peak amplitude and minimize the rise time of the CMAP. The median nerve was gradually stimulated until the CMAP reached a plateau, then the electrodes were secured with surgical tape.

Next, a concentric needle electrode was inserted into the FCR muscle near the active surface electrode. Participants were asked to perform a series of 30-second isometric, submaximal wrist flexion contractions during which intramuscular needle and surface EMG data were collected simultaneously. Contractions were moderate intensity, generating needle detected EMG interference patterns of 40 to 60 pulses per

second (pps). Visual feedback from the computer screen allowed subjects to maintain the contraction at the appropriate intensity. The experimenter also gave verbal feedback to subjects, with cues to initiate a contraction, alter contraction strength, and terminate the contraction. Contractions were repeated 5-7 times with 30-60 second rest periods in between. The needle was removed and reinserted every 2-3 contractions in order to sample from different MUs. Depth and/or orientation was adjusted after each contraction. Contractions were performed until a minimum of 20 valid MUP trains were collected for each trial. In pilot studies, there was concern that active finger flexion during wrist flexion contraction may alter results. If the other forearm muscles were activated distant from the surface electrode, this could contaminate the recorded activity from FCR and decrease the ability to extract FCR S-MUPs. In order to test this theory, three trials were performed. Trial A and trial B occurred with the hand open and interphalangeal (IP) and metacarpophalangeal (MCP) joints held straight during wrist flexion. Trial C explored wrist flexion while fingers were flexed (with flexed IP and MCP joints).

2.1.3 Electromyographic signal decomposition and analysis

Upon completion of the data collection, the signals were analyzed using the D-QEMG software. The complex signal derived from the needle EMG was decomposed into its constituent MUP trains using computer algorithms described previously (Boe, Stashuk, & Doherty, 2004; Doherty & Stashuk, 2003; Stashuk, 1999). MUPs were first detected from the needle EMG signal based on amplitude and slope criteria (Stashuk, 1999). Next, unsupervised clustering algorithms identified MUPs belonging to particular

MUs based on their shape. Then, supervised clustering algorithms used information from the clustered MUPs to determine the identity of any MUPs left unclassified from the unsupervised clustering (Stashuk, 1999). Finally, the firing rates of the clustered MUs were assessed to ensure that MUPs belonging to different MUs fired at the same time occasionally, and MUPs belonging to the same MU never fired simultaneously (Stashuk, 1999). MUPs collected by the intramuscular needle were time-locked to the surface EMG signal, allowing the S-MUP to be extracted for each associated MUP through spike-triggered averaging.

Once extracted, MUPs were included or excluded based on specific criteria. Any MUPs failing to meet the criteria were excluded from further analysis (Boe, Stashuk, Brown, & Doherty, 2005; Boe et al., 2004). First, a minimum of 51 discharges were required for MUP trains. Second, MUPs were required to display consistent firing rates as expressed by Gaussian distribution of the main peak in the inter-discharge interval (IDI) histogram, and a coefficient of variation less than 0.3 (Fuglevand, Winter, & Patla, 1993; Stashuk, 1999). Assessment of the instantaneous firing rate plot also helped determine whether or not trains were consistent and within physiological range. Third, MUPs were assessed for the presence of cannula potentials, a mainly positive potential created by recording the cannula of the needle. Cannula potentials were excluded because they contain different detection characteristics from the core detection surface and have less high-frequency energy (Stashuk & Doherty, 2002). However, cannula potentials still serve as an accurate trigger-point for surface signals, so the associated S-MUPs for any detected MUP cannula potentials were retained. Fourth, MUP trains

which were labelled by the program as “disparate” were visually inspected. A pair of “disparate” trains were detected if they never fired simultaneously and were therefore potentially derived from the same MU. If the two trains were deemed very similar upon visual inspection, the MUP train with fewer discharges was excluded from further analysis. Upon meeting the necessary criteria the onset, positive peak, negative peak and end markers of the MUPs were visually inspected and repositioned if necessary. The same visual inspection was done for the negative onset, negative peak and positive peak S-MUP markers.

Automatic descriptive MUP and S-MUP statistics were generated by D-QEMG. The average S-MUPs were calculated by data-point averaging of accepted S-MUPs aligned by the onset markers. This negative peak amplitude of the average S-MUP was then divided into the negative peak amplitude of the maximal CMAP to obtain the MUNE.

2.1.4 Intra-rater reliability

The experimental protocol and data analysis was performed three times by the same evaluator (S.T.) for each subject. All tests occurred on the same day for each subject. Following completion of the first test (trial A), all electrodes were removed and, after a 5-10 minute break, a new set of electrodes was applied for the repeat test (trial B). After trial B, electrodes were removed and following a 5-10 minute break, a new set of electrodes was applied for trial C. This third trial involved flexion of interphalangeal and metacarpophalangeal joints along with wrist flexion (trial C). The electrode positions

were not marked for the first test, ensuring that the electrode placement for subsequent tests were independent of the first test. The experimenter was blinded to the results of all three tests until all data collection was complete (Boe et al., 2004, 2006b; Ives & Doherty, 2012).

2.1.5 Statistics

All statistics were analyzed using IBM® SPSS® Statistics (Version 22, SPSS Incorporated, Chicago, IL). Mean values and their standard deviations are presented throughout. Relative intra-rater reliability was assessed with a two-way mixed model of the single measures intraclass correlation coefficient (ICC), assessing for consistency. ICC was considered low if <0.50, moderate if between 0.50 and 0.75, and high if >0.75 (Portney & Watkins, 2008).

In addition to the ICC, the standard error of measurement (SEM) was calculated as a measure of absolute intra-rater reliability for maximum CMAP, mean S-MUP and MUNE values. The SEM represents the amount of variation expected if the same subject were tested numerous times in a single-testing session (Hopkins, 2000). The SEM calculation is depicted in equation 1:

$$\text{SEM} = \text{SD} / \sqrt{2} \quad (\text{Eq 1})$$

Where SEM, standard error of measurement; SD, standard deviation of the difference scores for the two ratings (Hopkins, 2000).

The mean percent difference was also calculated for intra-rater maximum CMAP, mean S-MUP, and MUNE values, depicted as equation 2 (Boe, Stashuk, & Doherty, 2006; Ives & Doherty, 2012, 2014).

$$\text{Mean \% difference} = \sum \{ |x_1 - x_2| / [|x_1 + x_2| / 2] \} / n * 100 \quad (\text{Eq 2})$$

Where x_1 , subject's observed value for test 1; x_2 , subject's observed value for test 2; n , number of subjects.

A repeated measures analysis of variance (ANOVA) was used to determine if there were significant differences in measurements within each subject between trials. Bonferroni post hoc tests were used to interpret any significant findings. An alpha level of $p < 0.05$ used to denote significance in all cases.

2.2 Results

2.2.1 Subjects

A summary of subject demographic data is found in Table 1.

2.2.2 Data collection results and S-MUP frequency distributions

On average, 25 ± 3 , 25 ± 3 and 24 ± 3 acceptable S-MUPs were obtained for each subject from 5 ± 1 , 5 ± 1 and 4 ± 1 contractions for trial A, B and C respectively.

Therefore each trial collected an average of 5 ± 1 acceptable S-MUPs per contraction.

Subjects 1, 3 and 4 did not undergo trial C. The frequency distributions of S-MUP data are illustrated in Figure 3. Mean MUNE values for trials A, B and C were 290 ± 97 , $302 \pm$

Table 1: Subject demographics

Variable	All subjects (n=20)
Age (years)	29 ± 11 (21, 51)
Sex	9 female, 11 male
Height (cm)	171.7 ± 9.0 (152, 191)
Weight (kg)	71.4 ± 14.4 (42.8, 104.7)
Side of muscle testing	Right

Values expressed as mean ± SD. Values in parentheses indicate range.

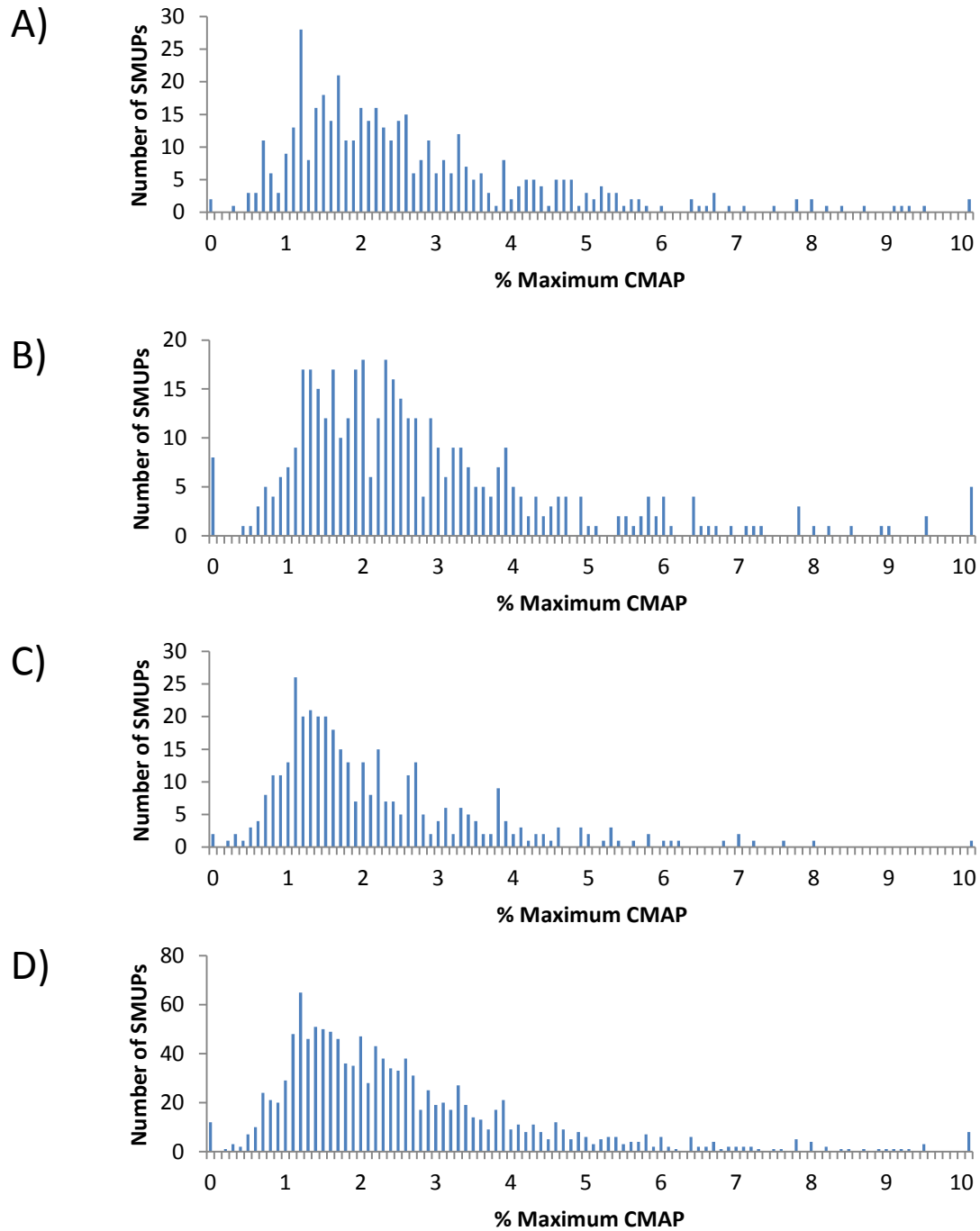


Figure 3: Frequency distributions of S-MUP data from all subjects for trial A (446 S-MUPs) (A), trial B (433 S-MUPS) (B), trial C (383 S-MUPS) (C), and pooled across all three trials (1262 S-MUPS) (D). The negative peak amplitudes of the S-MUPs have been normalized to the maximum CMAP for each subject.

124 and 376 ± 154 MUs, respectively. Values for the first two trials are presented in Table 2 for maximum CMAP, mean S-MUP and MUNE values, and in Table 3 for quantitative needle-detected MUP parameters.

2.2.3 Intra-rater reliability of maximum CMAP, mean S-MUP and MUNE

The single measures ICC was selected for analysis because a single rater (S.T.) performed all tests. Single measures ICC produces a slightly lower value than the average measures ICC, which is a model that attempts to average across multiple raters. Analysis using the single measures ICC revealed high reliability for maximum CMAP (ICC = 0.92), moderate reliability for mean S-MUP (ICC = 0.63) and low reliability for MUNE (ICC = 0.39) between trials A and B. The SEMs for maximum CMAP, mean S-MUP and MUNE were 0.84 mV, 11 μ V and 87 MUs, respectively. The mean percent differences were highest for MUNE and mean S-MUP (16% and 15%, respectively) and much lower for maximum CMAP (4%). Coefficients of variation are also presented in Table 2.

Repeated measures ANOVA for maximum CMAP in trials A, B and C assumed sphericity ($p = 0.367$) and found no significant differences ($p = 0.299$). The repeated measures one-way ANOVA test for MUNE met the assumption of sphericity ($p = 0.948$) and reported a significant difference between measures ($p = 0.018$). Bonferroni post-hoc tests showed a significant difference between trials A and C ($p = 0.035$), but no significant differences between trials B and C ($p = 0.139$) or trial A and B ($p = 1.00$). Repeated measures ANOVA for mean S-MUP in trials A, B and C assumed sphericity ($p = 0.579$) and was not significant ($p = 0.055$). These results are depicted in Figure 4.

Table 2: Maximum CMAP, mean S-MUP and MUNE values for trials A and B.

Subject	Maximum CMAP negative peak amplitude (mV)		Mean S-MUP negative peak amplitude (μ V)		MUNE (MUs)	
	Trial A	Trial B	Trial A	Trial B	Trial A	Trial B
1	8.5	7.3	44.6	43.1	190	169
2	11.0	10.8	35.8	23.1	308	466
3	11.3	9.6	34.0	57.1	333	168
4	11.5	11.4	30.3	31.9	378	356
5	20.1	20.1	53.5	59.2	375	339
6	12.9	12.4	33.8	39.0	381	316
7	12.8	14.2	46.5	64.6	275	220
8	10.1	10.1	40.7	30.6	249	329
9	11.9	11.0	48.5	46.2	245	237
10	8.1	9.1	62.8	48.3	129	221
11	15.1	16.5	64.9	80.2	232	205
12	10.1	10.5	28.0	42.6	360	245
13	14.4	14.7	30.4	26.2	473	561
14	11.6	13.4	47.3	31.6	244	423
15	8.5	8.0	27.3	37.4	312	212
16	10.1	10.8	40.2	19.4	250	558
17	12.1	13.5	97.0	84.6	124	159
18	12.8	13.0	77.6	42.1	164	307
19	9.1	11.4	21.3	32.4	427	353
20	13.2	10.9	41.5	66.5	348	186
Mean	11.8	11.9	45.3	45.3	290	302
SD	2.8	3.0	19.2	19.3	97	124
CV (%)	24.5		42.5		37.3	

^a Significantly different from Trial A ($p < 0.05$).

Abbreviations: CMAP, compound muscle action potential; CV, coefficient of variation; MU, motor unit; MUNE, motor unit number estimation; SD, standard deviation; S-MUP, surface-detected motor unit potential.

Table 3: Quantitative, needle-detected MUP parameter values for trials A and B

	Peak-to-peak voltage (μV)		Duration (ms)		Area (μVms)	
	Trial A	Trial B	Trial A	Trial B	Trial A	Trial B
Mean	287.7	308.4	9.6	10.4	439.2	513.9
SD	66.2	93.9	1.5	3.0	129.0	221.8
SEM	72.8		2.2		165.4	
Mean percent difference (%)	13.6		10.9		17.4	
CV (%)	26.9		22.5		36.8	

	AAR (ms)		Phases		Turns		Mean firing rate (Hz)	
	Trial A	Trial B	Trial A	Trial B	Trial A	Trial B	Trial A	Trial B
Mean	1.5	1.7	2.8	2.8	3.1	3.2	13.8	14.0
SD	0.2	0.4	0.3	0.4	0.5	0.8	1.5	1.8
SEM	0.3		0.2		0.4		0.7	
Mean percent difference (%)	8.4		5.2		6.6		2.7	
CV (%)	18.8		12.5		20.6		11.9	

Values expressed as means \pm SD. ^a Significantly different from Trial A ($p < 0.05$).

Abbreviations: AAR, area-to-amplitude ratio; CV, coefficient of variation; MUP, motor unit potential; SEM, standard error of measurement.

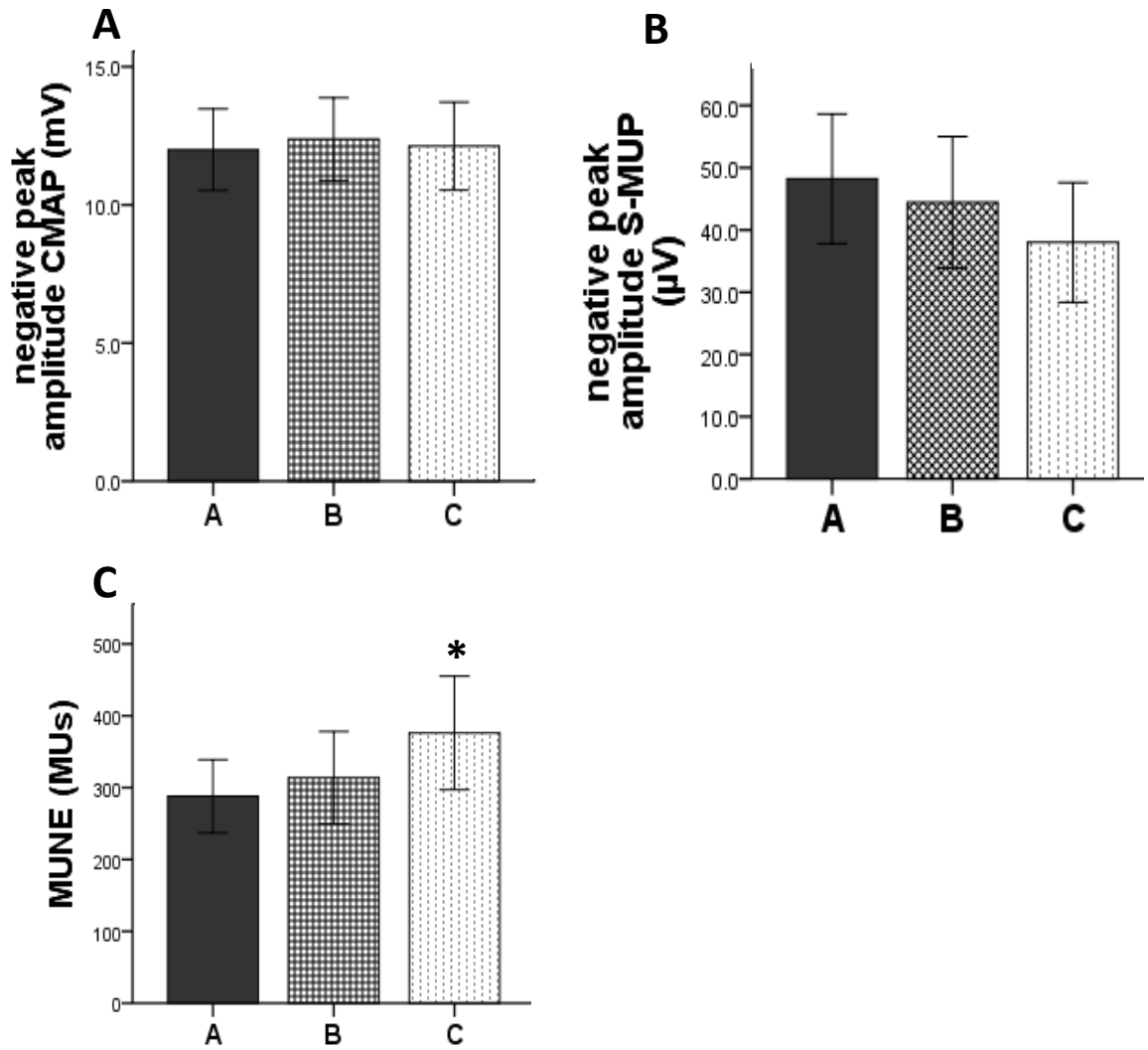


Figure 4: Comparison of maximum CMAP (A), mean S-MUP (B) and MUNE (C) values over the three trials. Error bars denote 95% confidence intervals. * denotes statistical significance from trial A ($p < 0.05$).

Abbreviations: CMAP, compound muscle action potential; MUNE, motor unit number estimation; S-MUP, surface-detected motor unit potential.

Analysis using the single measures ICC revealed high reliability for maximum CMAP (ICC = 0.92), and moderate reliability for mean S-MUP (ICC = 0.63) and MUNE (ICC = 0.39) between trials A and C. The SEMs for maximum CMAP, mean S-MUP and MUNE were 0.84 mV, 11 μ V and 87 MUs, respectively. The highest mean percent differences were MUNE and S-MUP (16% and 15%, respectively), and much lower for maximum CMAP (4%)

2.2.4 Intra-rater reliability of quantitative, needle-detected MUPs

Analysis using the single measures ICC revealed the highest level of reliability for mean firing rate in trials A and B (ICC = 0.84). The ICC values of the other MUP parameters were potentially inaccurate due to insufficient between-subject heterogeneity (Portney & Watkins, 2008). For example, the number of phases and turns would have inaccurate ICCs because all the data ranged between 2 and 6. This does not present enough variability to produce an accurate ICC which is dependent on a larger spread of data.

The SEMs, mean percent differences and coefficients of variation are presented in Table 3. The repeated measures one-way ANOVA found no significant findings for any of the MUP parameters ($p > 0.05$ for all parameters).

2.3 Discussion

The purpose of this study was to explore the use of DE-STA in FCR to establish test-retest intra-rater reliability and generate representative data in controls.

Electrophysiological properties of MUs and the size of the MU pool was established in FCR of healthy subjects aged 21-51 using DE-STA. When collected by the same examiner at two different time points, values for FCR exhibited high reliability for maximum CMAP (ICC = 0.92), moderate reliability for mean S-MUP (ICC = 0.63) and low reliability for MUNE (ICC = 0.39) (see Table 4). No differences in maximum CMAP, mean S-MUP, MUNE or MUP parameters were found between trials A and B ($p > 0.05$). There were however, differences in MUNE between trials A and C ($p = 0.035$), indicating that finger flexion during wrist contraction produced different results when compared to wrist flexion alone.

In order for DE-STA MUNE in FCR to be useful as a potential outcome measure, it must generate reliable results. The maximum CMAP values were very reliable, with a mean percent difference of just 4% between trials A and B and an ICC of 0.92. These values are consistent with test-retest reliability data from other muscles (see Table 5) (Boe et al., 2009; Boe et al., 2004, 2006; Ives & Doherty, 2012). Specifically, FCR CMAP of 11.8 ± 2.8 mV was very similar to other upper limb muscles, including first dorsal interosseous (13.7 ± 3.1 mV), thenar muscles (12.7 ± 2.0 mV) and biceps brachii (11.9 ± 2.4 mV) (Boe et al., 2009; Boe et al., 2004, 2006). Maximum CMAPs are not directly comparable between different muscles, due to differences in MU size and motor nerve stimulation. However, the observed similarities outlined in Table 5 serve to strengthen the results for this study. Studies in biceps brachii have documented difficulties in activation of all MUs and volume conduction of nearby muscles, potentially affecting the accuracy of obtained CMAPs (Bromberg, 1993). This did not appear to be an issue with

Table 4: Reliability of maximum CMAP, mean S-MUP and MUNE

	Intra-rater (1a vs 1b)		
	ICC	SEM	Mean % difference
Maximum CMAP (mV)	0.92	0.84	4
Mean S-MUP (μV)	0.63	11	15
MUNE (MUs)	0.39	87	16

Abbreviations: CMAP, compound muscle action potential; ICC, intra-class correlation coefficient; MU, motor unit; MUNE, motor unit number estimation; SEM, standard error of measurement; S-MUP, surface-detected motor unit potential.

Table 5: Test-retest data for DE-STA CMAP in FCR and other muscles

	Test CMAP (mV)	Retest CMAP (mV)
FCR	11.8 ± 2.8	11.9 ± 3.0
FDI	13.7 ± 3.1	14.2 ± 2.9
Thenar (FDI/AP)	12.7 ± 2.0	12.8 ± 1.1
BB	11.9 ± 2.4	12.2 ± 2.7
UT	8.5 ± 2.1	8.6 ± 1.9
TA	7.0 ± 1.7*	6.9 ± 1.6*

Values expressed as means ± SD. * depicts inter-rater reliability, all others are intra-rater reliability. Abbreviations: DE-STA, decomposition-enhanced spike triggered averaging; MU, motor unit; MUNE, motor unit number estimation. Information retrieved from Boe et al., 2009; Boe et al., 2004, 2006; Ives & Doherty, 2012.

Abbreviations: AP, adductor pollicis; BB, biceps brachii; CMAP, compound muscle action potential; DE-STA, decomposition-enhanced spike triggered averaging; FCR, flexor carpi radialis; FDI, first dorsal interosseous; TA, tibialis anterior; UT, upper trapezius.

CMAP in FCR, and consistent results were obtained from a technician with minimal training and experience.

Reliability of mean S-MUP data was found to be moderate (ICC = 0.63). The greater amount of variability within-subjects compared to maximum CMAP data may be a result of differences in needle data (i.e. depth and position) as well as contraction intensity between trials A and B. Based on Henneman's size principle, a consistent contraction intensity ensures that MUs of similar sizes are recruited for analysis (Doherty & Brown, 2002). If the average contraction intensity differed between trials, the size of S-MUPs sampled could be different between groups, potentially affecting the mean S-MUPs and contributing to decreased within-subject reliability. It is also possible that the quality of the averaging of the S-MUPs was not consistent. Despite the variability compared to maximum CMAP results, an ICC of 0.63 is within a moderate and acceptable range. At 15%, the mean percent difference for mean S-MUP was higher than maximum CMAP (see Table 4). This value is an appropriate result, as it lies between mean percent difference results for upper trapezius (31%) and biceps brachii (8%) in previous intra-rater reliability studies (Boe et al., 2006; Ives & Doherty, 2012). The large number of small S-MUPs seen in the frequency histograms (Figure 3) is consistent with previous findings in other muscles such as upper trapezius (UT) and hand muscles (Boe et al., 2004; Ives & Doherty, 2012) and in other MUNE techniques in various muscles (Bromberg & Abrams, 1995; Doherty & Brown, 1993). It appears that there may have been a slight shift to the left in Figure 3C indicating a greater proportion of small MUs in the third trial.

Mean MUNE values for FCR or more accurately, for the median innervated forearm muscles, were 290 ± 97 and 302 ± 124 MUs in trials A and B. Functionally speaking, these results are as expected, given the similar DE-STA MUNE values of 272 MUs in biceps brachii (BB), 167 MUs in first dorsal interosseous (FDI) and 153 MUs in tibialis anterior (TA) muscles (Gooch et al., 2014). BB is a more proximal muscle, functioning to flex and supinate the forearm, although it does not produce as much force as brachialis. BB is a larger muscle than FCR, but it is well known that a larger muscle does not correlate with a considerably larger MUNE (Doherty & Brown, 2002). This likely reflects the larger innervation ratio in larger, more proximal muscles (Doherty & Brown, 2002). It would therefore make sense that BB has a similar MUNE to the median forearm (i.e. FCR). FDI, while smaller than FCR, is needed for more precise movements to assist in thumb adduction and rotate the index finger slightly. Therefore it is logical that FDI would have a slightly smaller MUNE than FCR. TA is a lower limb muscle responsible for dorsiflexion and inversion of the foot. TA has a small innervation ratio of 329, compared to other distal lower limb muscles in its surroundings (e.g. gastrocnemius with an innervation ratio of 2000) (Campbell & DeJong, 2005). Given this information, it may make sense that TA MUNE is smaller than median forearm MUNE.

A great degree of variability between subjects was found for FCR MUNE values, ranging from 124 to 561 MUs. Anatomical estimates of the number of MUs in FCR could not be located in the literature for direct comparison, but considerable between-subject variability using DE-STA from D-QEMG has been reported previously in tibialis anterior (68-214 MUs), biceps brachii (159-547 MUs), and upper trapezius (172-586 MUs) (Boe,

Stashuk, & Doherty, 2007; Boe, Dalton, Harwood, Doherty, & Rice, 2009; Ives & Doherty, 2012). The data for FCR from DE-STA MUNE was comparable to results from within-subject reliability studies of other muscles (see Table 6). The low reliability measured in the ICC of MUNE could be a reflection of the lack of variability in the data. It is known that the ICC calculates values most accurately when there is adequate heterogeneity of data (Portney & Watkins, 2008). If a margin is too small, the ICC will project to a very low and sometimes even negative value. Too little variability is suspected in the case of MUNE, especially considering the high and moderate reliability of its constituents, CMAP and S-MUP (ICC = 0.92, 0.63, respectively). The mean percent difference for MUNE in FCR was 16% and similar to those found in upper trapezius (24%) and first dorsal interosseous (16%) muscles, and somewhat higher than biceps brachii (8%) (Boe et al., 2006; Ives & Doherty, 2012).

Furthermore, the significant difference in MUNE between trials A and C ($p = 0.035$) provides insight into the need for consistent study protocols which define the activation of muscles under study. Gehrman and colleagues measured wrist range of motion with fingers unconstrained compared to a closed-fist position. A 27% reduction in wrist range of motion was observed in the closed-fist group compared to the unconstrained group, indicating that finger position significantly affects wrist range of motion (Gehrman, Kaufmann, & Li, 2008). This study sought to determine if the reduction in wrist range of motion may be coupled with a reduction in activation of the wrist flexor group. Additional research demonstrated that the fingers flex the most in supine position, compared to pronation or neutral position (Lee & Jung, 2014).

Table 6: Test-retest reliability of DE-STA MUNE in FCR and other muscles

	Test MUNE (MUs)	Retest MUNE (MUs)	Mean percent difference (%)
FCR	290 ± 97	302 ± 124	16
FDI	134 ± 44	142 ± 38	16.1
Thenar	289 ± 115	248 ± 93	-
BB	272 ± 124	257 ± 125	7.1
UT	339 ± 121	320 ± 131	24
TA	118 ± 54*	126 ± 37*	19.1*

Values expressed as means ± SD. * from a study of inter-rater reliability, all others are intra-rater reliability. Information adapted from Boe et al., 2009; Boe et al., 2004, 2006; Ives & Doherty, 2012.

Abbreviations: BB, biceps brachii; DE-STA, decomposition-enhanced spike triggered averaging; FCR, flexor carpi radialis; FDI, first dorsal interosseous; MU, motor unit; MUNE, motor unit number estimation; TA, tibialis anterior; UT, upper trapezius.

Since the greatest finger flexion occurs in a supine position, this forearm position was chosen in the current study to make it easiest to detect any potential differences in DE-STA MUNE when the wrist was flexed with closed-fist versus open hand with neutral metacarpophalangeal (MCP) and interphalangeal joints (IP). Results determined significantly smaller S-MUPs in wrist flexion with flexed MCP and IP joints (i.e. a closed-fist) compared to wrist flexion alone. A lower mean S-MUP may not be surprising, given that activation of more distant muscles would take away from activity near the surface electrode located over FCR, reducing the ability to extract FCR S-MUPs. The lower mean S-MUP would bias results towards a higher MUNE. It is therefore important that researchers maintain strict study protocols and educate study participants in proper contraction positions in order to achieve consistent data collection and draw appropriate conclusions.

Certain limitations in this study include the small sample size, potential variation in contractions between subjects, needle position during data collection, and limited between-subject heterogeneity. First, there was a relatively small number of participants in this study ($n = 20$), making it difficult to observe normal distribution for DE-STA MUNE in FCR. More participants would be required to better understand the normal range of MUNE in this muscle. However, this study has a relatively large sample size compared to other reliability studies which used the DE-STA technique, often with 10 or fewer participants (Boe et al., 2006; Calder et al., 2008; Ives & Doherty, 2012). It is also important to note that smaller sample sizes are acceptable when studying neuromuscular properties. For example, the average age of participants was 28 years,

which may seem to bias results towards younger individuals. It is commonly known that neuromuscular changes associated with aging are not seen until the sixth decade of life (Doherty, 2003; McNeil et al., 2005; Power et al., 2012). Therefore a subject in their 30s or 40s should be expected to yield results which are comparable to a subject in their 20s.

Second, it is possible that certain subjects did not perform the ideal voluntary contraction to isolate the wrist flexors during data collection. Each subject was trained in how to flex the wrist with minimal contraction of other muscle groups such as the fingers (in trials A and B) or biceps brachii. The study protocol also attempted to control for levels of voluntary contraction through the use of a wrist and forearm brace and verbal cues from the technician. However, slight differences in muscle activation during voluntary contraction may have affected contraction intensity and the recording of S-MUP data, leading to moderate reliability for mean S-MUP (ICC = 0.63) in comparison to the high reliability of maximum CMAP (ICC = 0.92).

Third, variation in needle position and depth by the technician could have biased the collected S-MUPs between subjects (Ives & Doherty, 2014a). The technician had minimal training and experience. Since FCR is a relatively thin and superficial muscle, it was difficult to determine if the tip of the needle was located in the anterior, middle or posterior portion of the muscle for variety in data collection. By moving the needle to a slightly different depth and orientation for each contraction, the technician attempted to create heterogeneity in data to control for any potential bias towards a certain region of the muscle.

Finally, the limited variability between subjects made it difficult to calculate an accurate ICC for MUP parameters. If between-subject heterogeneity is low, the calculated ICC is often too low or produces negative values (Portney & Watkins, 2008). This limitation is consistent with other literature in the field. Insufficient heterogeneity appears to be an inherent property of MUP parameters in muscles previously tested using DE-STA MUNE (Boe et al., 2009; Calder et al., 2008; Ives & Doherty, 2012).

Future research into the causes of S-MUP variability in FCR could lead to improvements in reliability of this technique. Reliability could be assessed further through an inter-rater study. Additionally, studies examining FCR of elderly individuals could provide useful information regarding the changes in FCR and MUP parameters with aging. Since FCR is used as an index C7 muscle in radiculopathy, studies including C7 radiculopathy patients may be of benefit. Reporting the differences in MUNE between healthy subjects and C7 radiculopathy subjects could determine the extent of MU loss in FCR with this disease.

2.5 Conclusion

MUNE provides a unique approach to studying neuromuscular health at the whole muscle level, and it can detect MU loss well before other clinical measures. DE-STA is a technique that incorporates computer algorithms with conventional spike-triggered averaging of MUPs to determine MUNE and measure other quantitative MU properties. DE-STA has been used to study aging and neuromuscular disorders. The purpose of this study was to establish representative data in a healthy group of subjects

and discern within-subject reliability of the DE-STA MUNE in the FCR muscle. Twenty subjects completed three trials: trials A and B assessed test-retest reliability with wrist flexion and no finger flexion; trial C was completed with flexed MCP and IP joints (i.e. a closed fist) along with wrist flexion to test for differences. With no significant differences between trials A and B, a high ICC for maximum CMAP and moderate ICC for mean S-MUP, DE-STA has proven to be reliable in FCR. Data were consistent with within-subject reliability data from other muscles using the same method. The significant difference in MUNE between trials A and C reiterates the need for strict study protocols and proper participant training on the correct contraction techniques in order to obtain accurate results. Representative data of FCR in healthy subjects provides a basis for further research in FCR, perhaps in application to aging or clinical groups such as C7 radiculopathy patients.

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Appendix A: Ethics Approval



Use of Human Participants - Revision Ethics Approval Notice

Research Ethics

Principal Investigator: Dr. Tim Doherty
File Number:103980
Review Level:Delegated
Protocol Title:Comparing Neuromuscular Function in the Mobility Impaired and Healthy Older and Younger Adults
Department & Institution:Schulich School of Medicine and Dentistry/Clinical Neurological Sciences, St. Joseph's Health Care London
Sponsor:
Ethics Approval Date:April 17, 2014 **Expiry Date:**August 01, 2014
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Letter of Information & Consent		2014/04/11
Revised Western University Protocol	Received Mar 26, 2014	

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

 Erika Buslic (ebuslic@uwo.ca)	 Grace Kelly (grace.kelly@uwo.ca)	 Mira Mekhal (mmekhal@uwo.ca)	 Vikki Tran (vikki.tran@uwo.ca)
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This is an official document. Please retain the original in your files.

Appendix B: Letter of Information

Study Name: Comparing neuromuscular function in mobility impaired and healthy older adults.

Study investigators

Name	Title/Position	Degree	Role
Mr. Neal McKinnon	Graduate student	BSc (Hon.)	Data collection/analysis
Dr. Timothy Doherty	Physiatrist	MD, PhD, FRCPC	Principal investigator
Dr. Manuel Montero Odasso	Geriatrician	MD, PhD, AGSF, FRCPC	Co-investigator
Ms. Maddison Hourigan	Graduate Student	BSc	Data collection/analysis
Ms. Saskia Knol	Graduate Student	BSc (Hon.)	Data collection/analysis

Place of research:

Neuromuscular Performance Lab, Aging Rehabilitation and Geriatric Care Research Center (ARGC) B3041, Parkwood Hospital, St. Joseph's Health Care.

Introduction:

You are being invited to take part in a study that will examine muscle and nerve properties and strength measures of two leg muscles. This letter contains information about the study that will help you decide whether or not you would like to participate. Please read over this letter carefully and feel free to ask about any questions you may have.

Study Description:

This study will take place at the Neuromuscular Performance Laboratory, Aging Rehabilitation and Geriatric Care Research Center (ARGC) B3041, Parkwood Hospital, St. Joseph's Health Care.

For this project two groups will be studied; men and women with mobility impairment (slower than normal walking speed), and men and women with normal walking ability. An individual with mobility impairment in this study is defined as having a walking speed of less than 1 m/s,

which will be measured with a walking test. This walking test will take place on a GAITrite system (CIR Systems Inc., Sparta, NJ), which is a special mat connected to a computer software program that is able to track your step length and walking speed as you travel along it. Mobility impairment can make activities of daily living (ADLs) more difficult for these individuals, and can lead to the loss of independence.

Decomposition-based quantitative electromyography (D-QEMG) is a technique that can be used to detect and record the electrical activity of nerves and muscles. It can be used to track the changes in the health and number of nerves within a muscle. Previous research has shown that the health and number of nerves supplying a muscle decrease with age. This leads to a loss of strength and in turn mobility in these individuals. Thus, this study aims to learn if there is a difference in the properties and the number of nerves between individuals with mobility impairment compared to those with no mobility impairment.

Who is eligible?

You are eligible for this study if you are between the ages of 18 and 40 and have no evidence of neuromuscular or musculoskeletal disease, or any other serious medical problems that would limit you from performing moderate to strong muscle contractions with your legs. Study participants on blood thinners (e.g. Coumadin) will be excluded from the study due to increased risk of bruising associated with EMG needle insertion.

You must be able to contract and hold a mild to moderate contraction at the ankle (lifting the foot towards the ceiling), as well as a contraction at the knee (kicking the leg out to straighten the knee) for 30 seconds with one or both legs.

In order to be eligible for this study you must be able to walk 10 meters with or without a gait aid.

If you are participating in another study at this time, please inform the study investigator to determine if it is appropriate for you to participate in this study.

Study Procedure:

Investigator: Neal McKinnon

Duration: Two visits approximately 1 hour each

Note: If it is more convenient for you, the study may be condensed into 1 visit

Your age, height, and weight will be recorded at the first visit as well as any medications you may be taking.

Visit 1: D-QEMG

A. Tibialis Anterior (TA) D-QEMG

1) Positioning of surface electrodes

Surface EMG requires application of disposable, adhesive surface electrodes to the skin over your tibialis anterior (TA) muscle (the muscle that runs along the border of your shin). These electrodes record electrical activity of the nerves in the muscle. Your skin will be cleansed with rubbing alcohol in the areas where electrodes will be placed. Electrodes will be placed over the middle of the muscle (midway between the knee and ankle), down near the ankle joint, and over the patella (knee cap).

2) Electrical nerve stimulation

An electrical impulse will be delivered to the nerve that controls the TA muscle on the outside upper portion of the lower leg. Testing will begin at a low stimulus intensity, causing only a small muscle contraction. The stimulus intensity will then gradually be increased until there is no further increase in the recorded electrical signal.

3) Maximum voluntary contraction (MVC)

You will be comfortably seated on a Biodex System 3 Dynamometer (Biodex Medical Systems, Shirley, NY) which is a machine used to test and record muscle strength. Seatbelts will be fasted across your waist and chest to prevent any excess movement during the activities. You will then be asked to contract your foot strongly upward at the ankle joint against resistance provided by the machine. A computer program will measure how much force is produced by the contraction. Three to five contractions will be performed to make sure your best response has been measured.

4) Positioning of needle electrode

Needle EMG requires insertion of a disposable needle electrode (30 gauge, 25 mm concentric needle electrode) into the TA muscle. Following insertion, the needle remains inside the muscle until the contraction (see part 5) is completed.

5) Contractions

You will be asked to perform a series of 30 second, stationary mild to moderate (approximately 20% of maximum) contractions at the ankle. Contractions will be repeated 5-10 times, and the needle removed and reinserted every 2-3 contractions in order to collect adequate data. The needle will be inserted into the muscle no more than 3 times.

B. Vastus Medialis (VM) D-QEMG

Part A) will be performed on the vastus medialis (VM) muscle, which is a muscle in the thigh and is a part of the quadriceps muscle group. Changes to the protocol from Part A) are as follows:

- 1) The surface electrodes will be positioned over the middle of the VM muscle (inner middle portion of the thigh), just below the knee cap and on the knee cap.
- 2) There will be no nerve stimulation for the VM D-QEMG
- 3) You will be seated in a comfortable position on a Biodex System 3 Dynamometer (Biodex Medical Systems, Shirley, NY). You will then be asked to perform maximal knee extension stationary contractions at the knee against resistance provided by the machine.
- 4) The needle will be inserted into the VM muscle.
- 5) The series of mild to moderate contractions will be stationary knee contractions.

C. Flexor Carpi Radialis (FCR) D-QEMG (Investigator: Saskia Knol)

A series of tests will be performed on the flexor carpi radialis (FCR) muscle, which is a muscle in the front of the forearm and is a part of the wrist flexor muscle group.

Surface electrodes will be placed over the FCR muscle on the front of the forearm. The nerve to this muscle will be stimulated at the elbow obtain a maximal muscle EMG response.

The needle will be inserted into the FCR muscle and a series of 4 to 6, 30-second mild to moderate muscle contractions will be performed.

This process will be repeated on a second occasion after a brief 5 to 10 minute break.

Visit 2: Power output

We will be measuring the maximum power output of the TA and thigh muscles using the Biodex System 3 Dynamometer (Biodex Medical Systems, Shirley, NY). You will be seated comfortably in the dynamometer with hip and knee joint angles of 90°. Seatbelts will be fastened across your waist and chest to prevent any excess movement during activities. Before testing begins you will perform a few moderate intensity contractions in order to warm up and prevent any potential injuries. You will then be asked to perform a series of 3 maximal ankle contractions (raising your ankle up towards your shin) and 3 maximal knee extension contractions (kicking your lower leg out to straighten the knee) in order to determine the maximal voluntary contraction (MVC) of both the TA and quadriceps muscle groups. These contractions will be separated by at least 1 minute of rest in order to prevent fatigue. Once an adequate MVC has been calculated, you will be asked to perform a series of quick concentric (muscle shortening) contractions with mechanical resistance provided by the Biodex machine equal to 10, 20, 30, 40, and 50% of your previously determined MVC. You will be instructed to contract as quickly as possible against the resistance. You will perform 2 contractions of each of the stated MVC levels (i.e. 10, 20, 30, 40, 50%) for a total of 20 contractions (10 for TA and 10 for quadriceps).

Risks and Discomforts:

There may be some mild discomfort associated with electrical stimulation that will feel like a brief stinging or burning sensation. This sensation lasts less than a second and there are no lasting effects or associated risks.

There is mild to moderate discomfort associated with insertion of the needle electrode. This discomfort is generally considered less than that associated with having blood drawn and feels much like a pin prick.

Insertion of the needle electrode is associated with a low risk of muscle bruising and mild discomfort for 24 to 48 hours.

There is an extremely low risk of skin infection (less than 1 in 10,000) associated with the needle electrode insertion. The risk is greatly reduced by standard sterilization procedures and proper clinical practices including alcohol cleansing of the skin and use of latex gloves. Needle EMG electrodes are limited to one use. **If soreness or redness persists for an extended period of time at the insertion site following the testing session, you should contact the study investigators and your family physician immediately.**

Power testing may produce some mild muscle soreness 1-2 days after testing. However this soreness is typical of any unaccustomed muscle exercise and will resolve itself within a couple days.

If while taking part in this study you experience any adverse event or injury as a result of your participation, you will receive appropriate care for your injury.

Possible Benefits:

Benefit to you: There will be no direct benefit to you as a result of your participation in this research, other than receiving potentially interesting information regarding the function of your nerves and muscles.

Benefit to other people/science: This study may benefit society as a whole as it may present important findings about the physiology of aging, specifically, with respect to older adults with mobility impairments. Results of this study may help to determine possible mechanisms of the course of this disability and may be useful in future research to help designed exercise programs in order to improve mobility in frail older adults.

Voluntary participation:

Participation in this study is voluntary. You may refuse to participate, refuse to answer questions or withdraw your participation and/or your data from the study at any time with no effect on your future care. If, after reading this letter and discussing the study with the study investigator, you do not wish to participate, please inform us.

Reimbursement:

You will be compensated with \$25 at each visit for expenses such as parking, taxi fare, travel expenses, etc. that you may incur as a result of your participation. Participants who do not complete the study will still be compensated at each visit.

Confidentiality:

Any information identifying you as a research participant will be locked in a filing cabinet in a secure office. Only health information that is required for the study will be collected, no other personal health information will be recorded. You may request to have your data withdrawn from analysis at any point prior to publication. If the results of the study are published, your name will not be used. No information that discloses your identity will be released or published without your explicit consent to the disclosure, within the limits of the law.

Study data will remain in a locked filing cabinet in a secure office for 10 years, after which point they will be completely destroyed.

Representatives of The University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research.

Other information:

You do not waive any of your legal rights by signing the consent form.

You will receive a copy of this letter of information for future reference. If you choose to participate and sign the consent form, you will also receive a copy of your consent to retain in your personal records.

What to do if you have questions or problems:

If at any stage during the testing you have questions or problems you should address these to the study investigators (Dr. Timothy J. Doherty, Mr. Neal McKinnon or Ms. Saskia Knol, or Dr. Manuel Montero Odasso).

If you have any questions about your rights as a research participant and/or the conduct of the study you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute during regular office hours.

CONSENT DOCUMENTATION

Study name: Comparing neuromuscular function in mobility impaired and healthy older adults.

I, _____, have read the Information / Consent document, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Participant's signature: _____

Date: _____

Person responsible for obtaining informed consent:

Print name: _____

Signature: _____

Date: _____

Appendix C: Rights and Permissions

Permission for use of Figure 1:

License Details

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Miss Saskia Knol

EDUCATION

BScPA, Physician Assistant Education Program

McMaster University, Hamilton, ON

September 2015 – August 2017

- Accepted in to a 24-month program to become a certified Physician Assistant in Canada.
- Courses focus on the following four components: clinical sciences; interviewing, examining and reasoning (IER); professional competencies; longitudinal clinical experience program.
- Courses are followed by 48 weeks of supervised clinical placements in family medicine, surgery, pediatrics, medicine, emergency medicine and psychiatry.

MSc candidate, Exercise Physiology

Western University, London, ON

September 2013 – June 2015

- Studied in a two-year, thesis-based program through the School of Kinesiology and based at the Aging, Rehabilitation and Geriatric Care Research Centre at Parkwood Institute.
- Completed Exercise Physiology, Statistics, and Research and Seminar courses.
- Implemented a test-retest reliability study described in Research Experience below.
- Worked as a teaching assistant for three courses, marking, proctoring and teaching tutorial sessions, described below under Teaching Experience.

BScH, Biomedical Science (with distinction)

University of Guelph, Guelph, ON

September 2009 – April 2013

- Dean's Honours List student with a 90% cumulative GPA.
- Studied in a joint program offered between the Ontario Veterinary College and the Department of Human Health and Nutritional Sciences.
- Courses focused on the maintenance and promotion of human and animal health.
- Excelled in courses including Neuromuscular Physiology, Human Anatomy, Human Physiology, Endocrine Physiology, Biomedical Communications, Pharmacology, Epidemiology, Immunology, Fundamentals of Nutrition, Organic Chemistry, Biochemistry, and Cell Biology.

RESEARCH EXPERIENCE

Thesis: Test-Retest Reliability of MUNE and MUP Analysis with Decomposition-Based Quantitative Electromyography (D-QEMG) in Flexor Carpi Radialis Muscle

University of Western Ontario, London, ON

September 2013 – April 2015

- Completed a test-retest reliability study assessing the number of motor units and neuromuscular properties of the flexor carpi radialis muscle in the forearm.
- Findings established reliability in this muscle in healthy subjects.
- Future research may study patients with C7 radiculopathy, due to the large involvement of flexor carpi radialis muscle in this disease.

Poster and Seminar: D-QEMG in the Evaluation of Muscular Dystrophy Severity

University of Western Ontario, London, ON

April 2014

- Presented Dr. Doherty's research findings on decomposition-based quantitative electromyography (D-QEMG) as an indicator of disease severity in patients with three subtypes of muscular dystrophy.
- Findings showed measureable differences in MUP data when comparing more severe and less severe groups.

Seminar: Aerobic Exercise Protocols in Stroke Rehabilitation

University of Western Ontario, London, ON

December 2013

- This seminar was a requirement for the Exercise Physiology: Muscle Function and Metabolism course.
- Discussed the use of high-intensity interval training (HIIT) in functional recovery of stroke patients.
- Compared HIIT to moderate-intensity continuous aerobic exercise, demonstrating that HIIT leads to a greater improvement in gait speed, cadence, stride length, functional ambulation and VO₂ peak.

Thesis Proposal: Investigating the Influence of Lower Motor Neuron Performance on Functional Recovery of Stroke Patients

University of Western Ontario, London, ON

December 2013

- Presented a mock thesis proposal as part of the Research course. The material presented was different from the actual thesis completed under the supervision of Dr. Doherty.
- The study proposed an assessment of stroke survivors with low vs. high functional recovery and hypothesized that greater loss of functioning motor neurons would be exhibited in the low recovery group.

Undergraduate Research Assistant: NutriBiochem Mobile App

University of Guelph, Guelph, ON

May 2012 – August 2013

- Developed and submitted content for a free multi-platform Nutrition & Biochemistry Education app called NutriBiochem.
- Used graphic design skills to create images shown on review cards in modules. Wrote over one thousand multiple choice questions for the quizzing option.
- Promoted the app to undergraduate students at the University of Guelph and Guelph-Humber campuses. Students were surveyed upon completion of courses.
- Presented posters at the American Oil Chemists' Society 104th Annual Expo in April 2013 and the Western Conference on Science Education in July 2013. Presented findings at the Technology in Education Symposium at the University of Western Ontario in March 2014.
- Analyzed survey results to determine pedagogical impact of the app and wrote a research paper (currently under review).

Research in Human Health and Nutritional Sciences

University of Guelph, Guelph, ON

September 2012 – April 2013

- Investigated the effects of α -linolenic-rich oils on brain phospholipid fatty acid composition in delta-6 desaturase knockout mice, an extreme mouse model analogous to human delta-6 desaturase insufficiency.
- Delivered a seminar and wrote a research paper in April 2013 outlining results and relevance to the field of nutrition.
- WHMIS Safety Trained with knowledge of several lab techniques including PCR, gel electrophoresis, lipid extraction and esterification, and gas chromatography.
- Certified in Animal User Training Program at the University of Guelph Animal Care Services.

Seminar: Exploring the Functional Anatomy of the Gastrointestinal Tract

University of Guelph, Guelph, ON

April 2013

- Presented a seminar outlining the functional anatomy of the cadaver dissected in the Advanced Human Anatomy program from January-April 2013.
- Seminar featured photographs of the completed dissection which highlighted its unique anatomical features.
- Relevant clinical applications were discussed, based on the likely pathologies within the donor's gastrointestinal system.

Poster: Exercise & the Elderly

University of Guelph, Guelph, ON

March 2013

- Presented a poster with peers outlining the cardiovascular, neuromuscular, neurocognitive and psychosocial effects of exercise on older adults.
- Poster symposium was attended by students, professors and graduate teaching assistants from fourth year Biomedical Aspects of Aging and Endocrine Physiology classes.

Seminar: The Future of Stroke Therapy: A Continuum of Care

University of Guelph, Guelph, ON

February 2013

- Presented a seminar with peers reviewing acute and chronic treatment of stroke, rehabilitation, and issues specific to the aging population such as bedrest.
- Current advances in stroke rehabilitation along the continuum of care were reviewed. Topics included: human stem cell therapy, pharmacotherapy, physical therapy and lifestyle support.

Seminar: The Anatomy of Coronary Artery Bypass Grafting

University of Guelph, Guelph, ON

November 2012

- Presented an interactive seminar on the anatomy of the heart and its application to coronary artery bypass grafting, a common surgical procedure to bypass blocked coronary vessels in patients with cardiovascular disease.
- Educational specimens were prepared by the presenters, such as a heart with coronary arteries that had been bypassed. Photographs of the dissections were included in the presentation.

Seminar: Brain-Derived Neurotrophic Factor and a Personalized Approach to Stroke Recovery

University of Guelph, Guelph, ON

November 2012

- Presented current research on individualized stroke therapy based on single nucleotide polymorphisms in brain-derived neurotrophic factor (*BDNF*) gene.

Seminar: Flat Feet: Diagnosis, Treatment and Current Research

University of Guelph, Guelph, ON

April 2012

- Researched tendons and muscles affected by flat feet and summarized diagnosis and treatment of flat feet through an interactive seminar.
- Incorporated creative visual aids such as foot prosections at various tissue depths and molds of foot arches comparing flat feet, flexible flat feet, infant arches and a normal arch.

Seminar and Poster: Effects of the Senses on Oxytocin-Induced Lactation

University of Guelph, Guelph, ON

April 2012

- Conducted a comprehensive literature review on the relationship between maternal recognition sensory pathways and lactation.
- Determined how visual, auditory and olfactory stimuli alter oxytocin release and/or oxytocin receptor populations which then affect lactation. Compared differences in recognition pathways across species.
- Presented a seminar and poster with peers.

TEACHING EXPERIENCE & COMMUNITY OUTREACH

Graduate Teaching Assistant

University of Western Ontario, London, ON

September 2013 – December 2014

- Marked assignments and proctored for the Exercise Physiology (KIN 4430) class in Fall 2014. This course focused on the structure and function of skeletal muscle with an emphasis on muscle plasticity and the adaptive response to exercise.
- Taught interactive laboratory sessions in Systemic Approach to Functional Human Anatomy (KIN 222B) course in Winter 2014 semester. Students learned structure and function of the human body, emphasizing skeletal, muscular and cardiovascular systems.
- Assisted in marking laboratory assignments and examinations for the Physiology of Fitness Appraisal (KIN 3337) course in Fall 2013 semester. This course examined the scientific basis, construction and administration of physical fitness tests.

Personal Support Worker

Robertson Brown Health Services, London, ON

August 2014 – May 2015

- Provided in-home care to individuals requiring assistance with activities of daily living.
- Assisted with bathing, dressing, meal preparation, light housekeeping, and medication reminders.
- Fostered trust and a positive rapport with clients and learned how to work in a variety of settings.

Personal Attendant

Independent Living, London, ON

February 2014 – May 2015

- Provided home support, personal care and companionship to an individual with amyotrophic lateral sclerosis (ALS).
- Communicated with client through speech-reading and acted as an interpreter to those around him.
- Assisted with various activities of daily living including but not limited to hygiene, toileting, errands, nutrition, etc.
- Trained in two-person lifting transfers; comfortable operating client's feeding tube and Bipap.

Let's Talk Science: Department Representative and Instructor (Volunteer)

University of Western Ontario, London, ON

September 2013 – August 2014

- Affiliated with a national, non-profit organization that strives to improve scientific literacy by making science fun and interactive for youth in the community.
- Acted as the Kinesiology Department Representative, focusing on recruitment of graduate students.
- Partnered with an elementary public school teacher to engage students with interactive science projects throughout the school year. Participated in community events.

Anatomy Outreach Program: Instructor

University of Guelph, Guelph, ON

September 2011 – April 2013

- Privileged to be selected to work in one of only two Undergraduate Anatomy Dissection Labs in North America.
- Taught human anatomy concepts and applications to high school, college and university students, and health care professionals through the University of Guelph Human Anatomy Outreach Program.
- One of thirty students selected to participate in the highly competitive Advanced Studies in Human Anatomy Course from September 2012 to April 2013. Developed educational resources through traditional means (creating unique dissections and instructing students) and through multimedia (videos and photograph atlases).

Ms Infinity: Anatomy Workshop Coordinator (Volunteer)

University of Guelph, Guelph, ON

April – May 2013

- Planned and taught one of four workshops at Ontario's second annual Ms Infinity Conference. This free conference promoted Health Science and Engineering to girls in grades 9-11 and was funded in part by the Society for Canadian Women in Science and Technology.
- Created the "Anato(me): Getting to the Heart of the Matter" workshop. Participating youth learned the basic anatomy and physiology of the heart through a series of interactive stations taught by undergraduate Anatomy students.

First Response Team Member (Volunteer)

University of Guelph, Guelph, ON

September 2012 – April 2013

- Trained as an Advanced Medical First Responder with Health Care Provider CPR.
- A volunteer member of the University of Guelph student emergency response team, a student-run non-profit branch of St. John Ambulance.
- Delivered 379 hours of on-call and special event coverage to the campus community of over 18 000 people.

- Provided appropriate emergency medical procedures and high level of patient care on each shift. Ensured proper legal documentation guidelines were met when filing patient care reports.

College Idol United Way Fundraiser

University of Guelph, Guelph, ON

October 2012

- Won the 2012 College Idol talent show by raising the most funds for United Way.

Ms Infinity: Engineering Workshop Coordinator (Volunteer)

University of Guelph, Guelph, ON

May – June 2012

- Planned and taught one of four workshops at Ontario’s first annual Ms Infinity Conference.
- Attended weekly meetings and promoted the event to high school teachers and students.
- Created the “Medical Machines” workshop, where students were introduced to the field of Engineering with a focus on Biomedical Engineering. Youth engaged in a hands-on activity, designing and testing a model of a Dialysis Filter.

Creative Encounters with Science: Instructor

University of Guelph, Guelph, ON

May 2010 – June 2012

- Instructed Canadian youth throughout Ontario with Creative Encounters with Science, a member of a national non-profit educational organization called Actua. Organized in-school workshops, science camps and community events.
- Co-led the All Girls Science Club from September 2011 to June 2012. Planned and led monthly club meetings with hands-on, interactive science projects. Organized a community event where club members (ages 9-12) taught a science workshop to young children at the Guelph Public Library.
- Assisted in developing a short video about the activities of the Chair for Women in Science and Engineering of Ontario (CWSE-ON), funded by Research In Motion and featured at the 2011 TEDWomen Conference in Washington DC.
- Participated in filming an episode of the local television series “It’s a Kid’s World”, where children spent a day at Creative Encounters with Science camp. Featured projects taught children about Flight, Rocketry, Vision, Chemistry, and Human Kinetics.

PRESENTATIONS AND PUBLICATIONS

- Oral paper presentation of “Student Use and Pedagogical Impact of a Mobile Learning Application” at the Technology in Education Symposium at Western University on March 28, 2014.

- Teri, S., Acai, A., Griffith, D., Mahmoud, Q., Ma, D., Newton, G. Student Use and Pedagogical Impact of a Mobile Learning Application published March 2014 (doi: 10.1002/bmb.20771).
- Teri, S., Newton, G. Students Learn Biochemistry Better with Virtual Clinical Trial Lab (*currently unpublished*).
- “Use of NutriBiochem Mobile Application in Lipid Education” poster, American Oil Chemists’ Society 104th Annual Meeting & Expo in April 2013.
- “Student Use and Pedagogical Impact of a Mobile Application for Nutrition and Biochemistry Education” poster, Western Conference on Science Education in July 2013.
- Presented NutriBiochem app project to peers and professors at the 2012 and 2013 College of Biological Science Undergraduate Poster Days at the University of Guelph.
- Presented various posters and seminars to peers throughout undergraduate career.
- Presented many interactive science workshops to hundreds of Canadian youth.

AWARDS AND RECOGNITION

Ontario Graduate Scholarship, May 2014- April 2015

Western Graduate Research Scholarship, 2013-April 2015

College of Biological Science Dean’s Honours List, 2011-2013

Queen Elizabeth II Aiming for the Top Tuition Scholarship, 2009-2013

Tony & Anne Arrell Scholarship for academic excellence and financial need, 2011

University of Guelph Registrar’s Entrance Scholarship and Entrance Bursary, 2009

Groves Memorial Medical Society Chemistry Award, 2009

Groves Hospital Volunteer Association Bursary, 2009

Alexander T. Shaw Award for Math, Science & Technology, 2009

Lieutenant Governor’s Community Volunteer Award, 2009

Kin Canada Student Bursary, 2009