Motor unit activity during fatiguing isometric muscle contraction in hemispheric stroke survivors

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Keywords: motor unit$_1$, stroke$_2$, isometric fatigue$_3$, surface EMG decomposition$_4$, motor unit action potential$_5$, motor unit firing rate$_6$ (Min.5-Max. 8)

Number of text pages: 21, figures: 6, tables: 1

Number of words: abstract: 350, introduction: 760, discussion: 1710

Total number of words: 6268

Acknowledgements: The authors declare no competing financial interests.

Grants: Funding provided by the European Research Council (ERC-2014-CoG-646923_DBSModel), the Falk Trust (at the Rehabilitation Institute of Chicago) and the Irish Research Council.

Author contributions: L.M., M.M.L. and N.L.S. conception and design of research; L.M., X.H. and N.L.S. performed experiments; L.M., M.M.L. and N.L.S. analyzed data; L.M., M.M.L., W.Z.R. and N.L.S. interpreted results of experiments; L.M. prepared figures; L.M. and M.M.L. drafted manuscript; L.M., M.M.L., N.L.S. and W.Z.R. edited and revised manuscript; L.M., M.M.L., W.Z.R., X.H. and N.L.S. approved final version of manuscript.

Abstract

Enhanced muscle weakness is commonly experienced following stroke and may be accompanied by increased susceptibility to fatigue. To examine the contributions of central and peripheral factors to isometric muscle fatigue in stroke survivors, this study investigates changes in motor unit (MU) mean firing rate and action potential duration during, and directly following, a sustained submaximal fatiguing contraction at 30% maximum voluntary contraction (MVC). A series of short contractions of the first dorsal interosseous muscle were performed pre- and postfatigue at 20% MVC, and again following a 10-minute recovery period, by twelve chronic stroke survivors. Individual MU firing times were extracted using surface EMG decomposition and used to obtain the spike-triggered average MU action potential waveforms. During the sustained fatiguing contraction, the mean rate of change of the firing rate across all detected motor units was greater on the affected side (-0.02 ± 0.03 Hz/s) than on the less-affected side (-0.004 ± 0.003 Hz/s, $p = .045$). The change in firing rate immediately postfatigue was also greater on the affected side than less-affected side (-13.5 ± 20 % and 0.1 ± 19 %, $p = .04$). Mean MU firing rates increased following the recovery period on the less-affected side (19.3 ± 17 %), but not on the affected side (0.5 ± 20 %, $p = .03$). MU action potential duration increased postfatigue on both sides (10.3 ± 1.2 ms to 11.2 ± 1.3 ms on the affected side and 9.9 ± 1.7 ms to 11.2 ± 1.9 ms on the less-affected side, $p = .001$ and $p = .02$, respectively), and changes in MU action potential duration tended to be smaller in subjects with greater impairment ($p = .04$). This study presents evidence of both central and peripheral fatigue at the motor unit level during isometric fatiguing contraction for the first time in stroke survivors. Together, these preliminary observations indicate that the response to an isometric fatiguing contraction differs between the affected and less-affected side post-stroke, and may suggest that central mechanisms

observed here as changes in firing rate are the dominant processes leading to task failure on the affected side.

1 Introduction

Over the past decade, marked advancements in the acute management of stroke have led to an increase in the number of stroke survivors living with neurological disabilities (Feigin et al., 2014). One common limiting factor in the motor rehabilitation of stroke survivors is the prevalent loss of strength on the side of the body contralateral to the stroke lesion. This muscle weakness post-stroke has been attributed to alterations in the descending voluntary command, and to anatomical and physiological changes within the muscle (McComas et al., 1971;Bourbonnais and Noven, 1989;Dattola et al., 1993). Previous studies have identified impairments in voluntary muscle activation (Riley and Bilodeau, 2002;Knorr et al., 2011;Bowden et al., 2014;Hoffmann et al., 2016), altered motor unit firing rates (Rosenfalck and Andreassen, 1980;McNulty et al., 2014), a reduced ability to modulate motor unit firing (Gemperline et al., 1995;Mottram et al., 2014;Li et al., 2015) and abnormal motor unit recruitment patterns (Tang and Rymer, 1981;Hu et al., 2015;2016), all of which may contribute to muscle weakness post-stroke.

In addition to enduring muscle weakness, stroke survivors may experience increased susceptibility to muscle fatigue. Both central and peripheral factors can contribute to the overall manifestation of fatigue, which can be defined as a transient exercise-induced reduction in the force-generating capacity of muscle (Bigland-Ritchie and Woods, 1984). The few studies that have investigated fatigue in stroke survivors during voluntary contractions have reported relatively higher central fatigue on the affected side when compared to the less-affected side and healthy controls (Riley and Bilodeau, 2002;Knorr et al., 2011). Central fatigue encompasses both decreases in descending motor

commands to spinal motoneurons, and reduced excitatory afferent input, as well as decreases in motoneuron responsiveness due to changes in intrinsic properties or inhibitory afferent input (Gandevia, 2001). Conversely, in these studies stroke survivors showed lower levels of peripheral fatigue on the affected side. Peripheral fatigue refers to changes occurring beyond the motoneuron, including changes within the muscle fibers. Central fatigue was assessed in the stroke studies using twitch interpolation to quantify voluntary muscle activation (Riley and Bilodeau, 2002;Knorr et al., 2011), and peripheral fatigue was evaluated using the compression of the surface EMG power spectrum (Svantesson et al., 1999;Riley and Bilodeau, 2002) and changes in maximal twitch torque (Knorr et al., 2011).

Changes at the level of the single motor unit during muscle fatigue post-stroke have not yet been investigated. In the present study, we examine the hypothesis that there will be a greater loss in central activation during a sustained fatiguing contraction, and directly postfatigue, on the affected side in hemispheric stroke. If higher central fatigue is present on the affected side, subjects may experience greater difficulty maintaining motor unit firing during a fatiguing contraction, as well as a diminished capacity to regulate motor unit firing rate directly postfatigue. Changes in the excitability of the surface and tubular membranes of the muscle fiber on the affected side may also be lower postfatigue (i.e. a marker of lower peripheral fatigue) which would manifest as smaller increases in the motor unit action potential duration (Andreassen and Arendt-Nielsen, 1987;Houtman et al., 2003;Fortune and Lowery, 2009).

In the present study, surface EMG decomposition was used to identify individual motor unit activities from non-invasive surface recordings. This provides direct information on both the motor unit discharge rates and the action potential duration, which is more closely correlated with muscle

fiber conduction velocity and changes in muscle fiber excitability than indirect estimates from the surface EMG power spectrum. Samples of simultaneously active motor units were detected during short contractions (at 20% MVC) before and directly after a sustained isometric contraction of the first dorsal interosseous muscle in chronic stroke survivors. Motor units were also detected during the sustained contraction (at 30% MVC).

The results of this study show that in chronic stroke survivors, motor units on the affected side displayed a greater decline in firing rate during sustained, fatiguing isometric contractions, than on the less-affected side. Furthermore, a greater change in motor unit firing rate was observed on the affected side immediately postfatigue. Mean motor unit firing rates increased following the recovery period on the less-affected side but not on the affected side. A significant increase in action potential duration was observed on both sides postfatigue. On the affected side, the magnitude of the change tended to be lower in subjects with greater impairments post-stroke. In combination, these results suggest that during sustained isometric fatiguing contractions in stroke survivors, central mechanisms play a greater role on the affected side, when compared to the less-affected side, and likely contribute to difficulties maintaining force reported post-stroke.

2 Methods

2.1 Experimental Procedure

Written informed consent was obtained for twelve stroke survivors (7 female, age 60 ± 7 years) to participate in this study, and the experimental protocols were approved by the Institutional Review Board at Northwestern University, Table 1. The force and EMG activity of the first dorsal interosseous muscle was examined during isometric abduction of the index finger, on both the contralateral and affected sides. The proximal phalanx of the index finger was fixed to a ring-mount interface attached to a load cell (ATI, Inc., 3226), and forces were recorded from the x (abduction/adduction) and y (extension/flexion) directions, Figure 1 (a). Surface EMG was recorded from the FDI using a surface sensor array (Delsys, Inc.) that consisted of 5 cylindrical probes (0.5 mm diameter) located at the corners and at the center of a 5 × 5 mm square (Nawab et al., 2010), and a reference electrode on the skin surface of olecranon. Pairwise differential recordings of the 5 electrodes yielded 4 channels of surface EMG signals, which were amplified and filtered between 20 Hz and 2 kHz). The signals were sampled at 20 kHz and stored on a computer for further processing.

Figure 1

The experimental procedure was similar to that performed in healthy subjects, outlined in detail in McManus et al. (2015). Briefly, the maximal voluntary contraction (MVC) was determined as the highest force achieved during two or three short (3 s) maximum contractions, separated by a 1 min rest period, where the maximum force between trials lay within 10% of each other. Following the maximum voluntary contraction, subjects performed a series of four isometric prefatigue voluntary contractions. The force trajectory for each contraction consisted of a 3-s quiescent period for baseline noise calculation, an up-ramp increasing at 10% MVC per second, a constant force of 20% MVC for

10 s, a down-ramp decreasing at 10% MVC/s, and a final 3 s quiescent period. After the four prefatigue trials, a sustained isometric contraction was performed at 30% MVC until task failure, defined as the point at which the subject's force dropped 10% below the required output for 5 s or longer. Additional verbal encouragement was provided during the contraction to ensure that the force level was maintained for as long as possible. A single MVC was performed directly following task failure, and a series of four short duration contractions at 20 % MVC, identical to those performed prefatigue, were performed postfatigue with no rest period between trials to minimize recovery. Subjects were then allowed a 10-minute recovery period before a series of four more trapezoidal trajectories at 20% MVC. For each condition, the goal was for the subject to perform four 20% MVC trials both pre- and postfatigue. The number of trials completed, however, was higher on the affected side in some subjects in order to get the required number of trials with a steady force trace (4.8 ± 1 trials prefatigue and 4.4 ± 0.8 trials postfatigue). The trial with the highest combined ranking, in terms of the steadiness of the force trace (low standard deviation) and the number of accepted motor units, was chosen to represent each condition.

2.2 Data Analysis – Motor unit acceptance

Discriminable motor units (MUs) were extracted from the surface EMG signal using the decomposition EMG system (Delsys, version 4.1.1.0). The decomposition algorithm is outlined in detail in Nawab et al. (2010) and De Luca and Hostage (2010). For each detected MU, the output of the decomposition algorithm consisted of the MU firing times and 4 motor unit action potential (MUAP) waveforms corresponding to 4 pairs of bipolar electrode channels.

The identified firing times for each MU were used to spike triggered average (STA) the surface EMG signal on each channel, resulting in 4 representative STA MU action potential estimates for each

MU. MUAP duration was estimated as the time between the zero crossing before the first positive peak of the action potential and the zero crossing after the last positive peak. The variation of the spike triggered averaged MU action potential template over time was quantified using a moving average window. A spike triggered averaged MU action potential template estimate was calculated based on the firing events in each window and the window was shifted along the length of the surface EMG signal. The reliability of each detected MU was then assessed by comparing the STA template estimates across all windows, using two tests outlined in Hu et al. (2013). The first measure of reliability was obtained by calculating the coefficient of variation (CV) for the peak-to-peak amplitude of the MUAP templates detected in each window. For the second measure, the maximum linear correlation coefficient (CC) was computed between the STA MU action potential template estimate and the decomposition-estimated templates.

Motor units were required to have an average coefficient of variation in action potential amplitude < 0.3 and correlation coefficient (between the STA MUAP estimate and the decomposition MUAP template) > 0.7 across all four channels to be selected for further analysis. In addition, motor units were required to have a CC > 0.8 and CV < 0.2 (0.25 for the longer fatiguing contraction) on at least one of the two channels with the highest MU action potential amplitude. A moving average window of 2 s length and 0.5 s time step was used to obtain the MUAP template for the short contractions pre- and postfatigue and a window length of 4 s with a 1 s time step was used for the long fatiguing contraction. A minimum average of 5 MUs was required over the three trials (prefatigue, postfatigue and following the recovery period) for each subject. These units must also be recruited across a range of force levels, with a mean range of recruitment threshold defined as 5 %MVC (with force

normalized to subject MVC). Motor unit data from eleven of the twelve subjects satisfied both criteria and was used in further analysis.

Motor unit mean firing rates (MFR) were analyzed during the sustained fatiguing contraction and during the short duration contractions before and after fatigue. Firing rate analysis was restricted to periods of relatively steady force production (standard deviation ≤ 3 %MVC). Any overshoot during the initial increase to the required force level was excluded from the analysis and firing trains were truncated at the point where the mean force was below 10% of the desired force level for 5 consecutive seconds. The change in firing rate during the sustained fatiguing contraction was examined for each motor unit by fitting a least-squares regression line to the instantaneous firing rate data. For each accepted MU, the slope and intercept of the line was obtained, describing the initial MU firing rate and the change in mean firing rate over the course of the fatiguing contraction.

2.3 Data Analysis – Statistics

For each subject, the median motor unit mean firing rate and action potential duration was obtained in the prefatigue, postfatigue and recovery trials. To focus on the within-subject effect of fatigue and minimize the contribution of inter-subject variance to the visual representation of results, the median from the prefatigue, postfatigue and post-recovery contractions for a given subject were normalized by subtracting that subject's mean for the three contractions minus the grand mean of all subjects before generating the boxplot figures (Loftus and Masson, 1994).

A two-way within-subjects (or repeated measure) analysis of variance (ANOVA) was conducted to compare the change in each parameter across the prefatigue, postfatigue and recovery states, and on the affected and less-affected sides. Mauchly's Test of Sphericity was implemented to check the

assumption of sphericity, and if violated, a Greenhouse-Geisser correction was applied to the data. Pairwise differences between conditions were conducted using Fisher's Least Significant Difference test with Bonferroni correction for the affected and less-affected sides. The changes in median MU firing rate and action potential duration from pre- to postfatigue conditions, and from postfatigue to recovery, were compared between the two sides with a two-sided paired t-test.

The change in motor unit firing rate during the sustained fatiguing contraction was examined using linear regression, and the t-statistic was used to test for a significant increase or decrease in motor firing rate. The relationship between initial motor unit firing rate (the intercept of the regression line) and the change in firing rate (slope of the line) was examined using a Pearson product-moment correlation. For each subject, the root-mean-squared (RMS) value of the EMG signal was calculated during the fatiguing contraction on the highest amplitude channel, using a 2 second time window with a 1 second time-step. The percentage change in RMS-EMG amplitude was then calculated by fitting a least-squares regression line to the RMS value of the EMG signal over time. The percentage change in the median frequency of the surface EMG power spectrum and in the coefficient of variation of the force was obtained using the same window and timestep.

The relationships between Fugl-Meyer score and changes in median MU action potential duration, and between motor unit firing rates and action potential duration, were investigated with a Spearman's rank-order correlation. An alpha level of .05 was used for all statistical tests, and the effect size is reported as omega squared (ω^2) for the two-way ANOVA and as Hedges' G (g) for the paired t-tests.

3 Results

We first examined the properties of motor units detected on the more-affected and less-affected side in each stroke survivor. Motor unit mean firing rates were compared between the two sides, in addition to differences in the action potential duration. We then investigated the effect of fatigue on motor unit firing rate and action potential duration by comparing values recorded during the short trials conducted pre- and postfatigue. Changes in individual motor unit mean firing rates were also examined over the course of the sustained fatiguing contraction.

3.1 Motor unit properties on the affected and less-affected sides prefatigue

The average number of motor units detected prefatigue was 18.2 ± 7 and 22 ± 3.2 on the affected and less-affected sides. The corresponding averages postfatigue were 16.8 ± 7 and 22.6 ± 3.8, respectively. Out of the total number of motor units detected, 59% of MUs were accepted for further analysis on the affected side and 52% were accepted on the less-affected side during the short contractions at 20% MVC. During the fatiguing contraction at 30% MVC, 48% and 47% of MUs were accepted on the affected and less-affected side, respectively.

Motor unit action potential duration was not significantly different between the affected and less-affected side when examined across all subjects (10.3 ± 1.2 ms vs. 9.9 ± 1.7 ms, $p = .5$). Motor unit mean firing rates were similar on the affected and less-affected sides prefatigue (14 ± 4.4 Hz and 13.7 ± 3.6 Hz, $p = 0.70$, respectively), though the firing rate coefficient of variation was significantly higher on the affected side (0.09 ± 0.05 and 0.03 ± 0.01, respectively, $p < .01$, $g = 1.4$). A significant correlation was observed between the ratio of the mean firing rate on each side and the ratio of the MUAP duration ($r = 0.7$, $p = .01$), with subjects for whom MUAP durations were longer on the affected side tending to also have higher motor unit mean firing rates on the affected side.

3.2 MVC force, MU action potential duration and mean firing rate pre- and postfatigue

A two-way repeated measures ANOVA was used to compare maximum voluntary index finger abduction force in the prefatigue, postfatigue and post-recovery states. The results indicated a significant change in MVC across the three states ($F(1.3, 14.6) = 21.8$, $p < .001$, $\omega^2 = .62$), Figure 2. Lower MVC forces were recorded in each state on the affected side compared to the less-affected side ($F(1, 11) = 33.3$, $p < .001$, $\omega^2 = .7$). Post hoc tests revealed a significant decrease in maximum force postfatigue on both sides ($p < .01$, both). The time to task failure varied greatly among subjects (143 ± 160 s and 208 ± 73 s, on the affected and less-affected side respectively) and was not significantly different between sides ($p = 0.07$). After 10 minutes of rest, the MVC force increased but remained significantly lower than prefatigue values on both sides ($p = .036$ on the affected and $p = .01$ on the less-affected side), Figure 2.

Figure 2

Motor unit mean firing rates changed significantly across the prefatigue, postfatigue and recovery states ($F(2, 20) = 4.7$, $p = .02$, $\omega^2 = .24$), Figure 3. There was also a significant interaction between state and side (affected or less-affected) for MU firing rate ($F(2, 20) = 4.37$, $p < .05$, $\omega^2 = .23$), Figure 3. Post-hoc tests revealed that mean firing rates were significantly higher following the 10-minute recovery period than those reported prefatigue on the less-affected side (13.7 ± 3.6 Hz and 16.4 ± 5.6 Hz, $p = .03$, prefatigue and post-recovery respectively).

Figure 3

The percentage change in MU mean firing rate from the prefatigue to postfatigue trials was calculated to compare the response to the sustained fatiguing contraction on the affected and the less-

affected sides, Figure 4. The affected side exhibited a reduction in MU mean firing rates postfatigue that was not observed on the less-affected side (-13.5 ± 20 % on the affected and 0.1 ± 19 % on the less-affected side respectively, $p = .04$, $g = -0.67$). The percentage change in MU firing rate from prefatigue to post-recovery trials also differed between the affected (0.5 ± 20 %) and less-affected sides (19.3 ± 17 %, $p = .03$, $g = -1.1$), with higher MU firing rates observed on less-affected side following the recovery period.

Figure 4

Motor unit action potential duration also changed significantly over the three states ($F(1.34, 13.4) = 10.35$, $p < .01$, $\omega^2 = .44$). An increase in MU action potential duration was observed postfatigue on both the affected (10.3 ± 1.2 ms to 11.2 ± 1.3 ms, $p = .001$) and less-affected sides (9.9 ± 1.7 ms to 11.2 ± 1.9 ms, $p = .02$), Figure 5. Following the recovery period, MUAP duration recovered and did not differ significantly from prefatigue values (10.6 ± 1.2 ms, $p = .2$, on the affected side and 10.1 ± 1.2 ms, $p = .5$, on the less-affected side). Subjects that were more impaired post-stroke, as evidenced by their Upper Extremity Fugl-Meyer scores, showed smaller changes in MU action potential duration following the fatiguing contraction ($r = 0.6$, $p = .04$), Figure 6. The percentage change in MUAP duration from pre- to postfatigue did not differ significantly between the affected (8.2 ± 6 %) and less-affected sides (14.2 ± 17 %, $p = .19$), though there was a greater range of changes in MUAP duration on the less-affected side, Supplementary Figure 2.

Figure 5

Figure 6

3.3 Motor unit firing rate, surface EMG and force during the sustained fatiguing contraction

Motor unit firing times were obtained from the decomposed surface EMG signal during the fatiguing contraction at 30% MVC in 10 of 12 subjects, with data from an exemplar subject shown in Figure 1. A similar percentage of motor units exhibited a statistically significant decrease in mean firing rate over time on the affected and less-affected sides (28% and 30%, respectively). Only a small number of units exhibited a significant increase in firing rate (4% and 6%, respectively). Motor unit mean firing rates decayed faster on the affected side during the fatiguing contraction than on the less-affected side over all subjects (-0.02 ± 0.03 Hz/s and -0.004 ± 0.003 Hz/s, respectively, $p = .045$, $g = -0.94$), Figure 7. However there was no significant difference in the absolute decrease in MU firing rate (-0.85 ± 0.8 Hz on the affected side and -0.48 ± 0.36 Hz on the less-affected side, $p = .17$).When MUs were pooled over all subjects, lower threshold motor units with higher mean firing rates tended to show greater absolute decreases in firing rate during the fatiguing contraction on the affected side ($r = -0.18$, $p = .02$) and less-affected side ($r = -0.5$, $p < .001$), Figure 7.

The variability of the force (coefficient of variation) during the fatiguing contraction was higher on the affected side than on the less-affected side (0.1 ± 0.07 and 0.04 ± 0.02, $p < .001$, respectively), and increased on both sides as the contraction progressed (108 ± 121% on the affected side and 40 ± 72% on the less-affected side, no significant difference between sides, $p = .3$). Force variability was also higher on the affected side during the short contractions prefatigue (0.07 ± 0.05 and 0.03 ± 0.01, $p < .05$), and there was no significant change in force variability postfatigue on either the affected or less-affected side ($p = .4$ and $p = .7$, respectively). The RMS-EMG amplitude during the first quarter of the fatiguing contraction was lower on the affected side when compared to the less-affected side

297 (0.13 ± 0.1 mV and 0.28 ± 0.2 mV, $p < .01$), with no clear change as the contraction progressed on
298 either side (-1.6 ± 69 % and -13 ± 44 %, $p = .6$, respectively). There was no difference in the median
299 frequency of the surface EMG on the affected (146 ± 35 Hz) and less-affected sides (174 ± 61 Hz, p
300 = .3) during the first quarter of the fatiguing contraction. However, there was a greater decrease in
301 median frequency during the contraction on the less-affected side (-44 ± 15 %) when compared to the
302 affected side (-16 ± 19 %, $p < .01$).

303 *Figure 7*

304 **3.4 Motor unit properties in subjects with matched force levels**

305 As the majority of subjects had a large difference in MVC between the affected and less-affected
306 side, there is the additional confounding factor of different absolute force levels when comparing
307 changes in motor unit properties. However, in five subjects, the fatiguing contraction was performed
308 at similar absolute forces on the affected and less-affected sides (< 25% difference in MVC). In this
309 subset, two subjects were unable to sustain the fatiguing contraction on the affected side for more
310 than 25% of the time obtained on the less-affected side. These subjects had shorter MU action
311 potential durations and lower MU mean firing rates on the affected side compared to the less-affected
312 side. This could indicate recruitment of a greater proportion of the MU population, including higher
313 threshold motor units with higher muscle fiber conduction velocities and shorter duration action
314 potentials to achieve the target force on the affected side. The lack of reserve motor units available
315 for recruitment during the fatiguing contraction may have resulted in the early task failure. These
316 subjects exhibited small changes (< 10%) in MU action potential duration on the affected side
317 postfatigue, alongside a reduction in motor unit mean firing rate (-17%, -10%). Of the remaining
318 three subjects, two showed significant changes in MU action potential duration on the less-affected

side (> 25%), with smaller changes observed on the affected side (> 15%) and the third subject showed little change in MU action potential duration on the affected and less-affected side (< 5%). When changes in motor unit mean firing rate during the fatiguing contraction were examined, all subjects with matched force levels exhibited a significantly larger rate of decrease in motor unit mean firing rate on the affected side when compared to the less-affected side (-0.04 ± 0.02 Hz/s and -0.002 ± 0.003 Hz/s, respectively).

4 Discussion

In this study, changes in motor unit properties were investigated prior to, during and directly after a submaximal, isometric fatiguing contraction in chronic stroke survivors. The ability to investigate adaptations in motor unit firing rate of many motor units using surface EMG decomposition gives a unique insight into the regulation of motor unit behavior and how this contributes to the overall manifestation of fatigue in stroke survivors. During the sustained fatiguing contraction, motor units on the affected side displayed a greater decline in firing rate than those on the less-affected side. Furthermore, a greater change in motor unit firing rate was observed on the affected side immediately postfatigue. Mean motor unit firing rates increased following the recovery period on the less-affected side but not on the affected side. Changes in MUAP duration postfatigue tended to be smaller on the affected side in subjects with greater impairment, indicating lower levels of induced peripheral fatigue. These observations suggest that central fatigue was more dominant on the affected side when compared to the less-affected side, resulting in greater difficulty maintaining or augmenting motor unit firing rates during and directly postfatigue.

4.1 Comparison of MU properties on the affected and less-affected sides prefatigue

No significant difference was observed in either action potential duration or mean firing rate between sides prefatigue. Subjects with relatively longer MU action potential duration on the affected side tended to have higher MU mean firing rates on the affected side compared to the less-affected sides. Previous studies have reported slower muscle fiber conduction velocities in certain, but not all muscles (Yao et al., 2015;Conrad et al., 2017), and longer MUAP durations on the affected side post-stroke using intramuscular EMG (Lukács, 2005). Lower firing rates on the affected side have been reported when comparing firing rates recorded at the same absolute force on both sides, using

intramuscular (Gemperline et al., 1995;Chou et al., 2013) and surface EMG decomposition techniques (Suresh et al., 2011;Hu et al., 2012;Li et al., 2015). A tendency towards lower motor unit mean firing rates has also been observed on the affected side at the same relative force levels, similar to what was compared here, using intramuscular EMG (Rosenfalck and Andreassen, 1980;Hu et al., 2006) and surface EMG during low level contractions (McNulty et al., 2014).

4.2 Motor unit firing rate and action potential characteristics during the fatiguing contraction and directly postfatigue

During the fatiguing contraction, there was a significant decline in MU mean firing rate in approximately 30% of all accepted motor units, on both the affected and less-affected side, Figure 7. The average magnitude of this decline was greater on the affected side, even in subjects that performed the fatiguing contraction at similar force levels on both sides. The mean time to task failure was lower on the affected side, though did not reach statistical significance due to the large variability across subjects. This is similar to the findings of previous studies that have used forces at the same percentage of maximal effort on each side to examine fatigue in various muscles post-stroke, (Sunnerhagen et al., 1999;Svantesson et al., 1999;Riley and Bilodeau, 2002;Hyngstrom et al., 2012).

The change in MU firing rate from pre- to postfatigue contractions was also significantly larger on the affected side than the less-affected side, with lower MU firing rates observed postfatigue on the affected side, Figure 4. Failure to sustain steady motor unit discharge likely contributed to an inability to maintain force output on the affected side during the fatiguing contraction, particularly as recruitment often occurs over a compressed force range post-stroke and there may be few motor units available to recruit (Tang and Rymer, 1981;Hu et al., 2015). This decline in motor unit mean firing

rate may be mediated by the partial loss of excitatory efferent drive from the descending motor pathways to the segmental motoneurons and interneurons following stroke (McComas et al., 1973;Dattola et al., 1993;Lindberg et al., 2007), though impairments in descending corticospinal connections (Bowden et al., 2014), motor axons (Jankelowitz et al., 2007) and changes in intrinsic motoneuron properties could also play a role. Larger reductions in MU mean firing rate postfatigue were also associated with poorer recovery of muscle force capacity on the affected side following the rest period, Supplementary Figure 1 (c). On the affected side, the change in RMS-EMG amplitude was correlated with the change in MU mean firing rate during the fatiguing contraction, with little evidence of motor unit recruitment, Supplementary Figure 1 (a). Collectively, these observations provide evidence that changes in central mechanisms are the dominant processes contributing to fatigue on the affected side. This aligns with the findings of previous studies that have reported a greater reduction in voluntary muscle activation on the affected side during sustained submaximal and maximal contractions using twitch interpolation techniques (Riley and Bilodeau, 2002;Knorr et al., 2011).

Smaller changes in MU action potential duration postfatigue were observed on the affected side in subjects with greater impairment, Figure 6 (a). Consistent with this, the median frequency decreased by less during the fatiguing contraction on the affected side. Better muscle perfusion and lower intramuscular pressure at lower target forces on the affected side may have reduced metabolic accumulation (Hunter, 2009), which would present as smaller changes in MUAP duration. However, subjects who performed the fatiguing contraction at similar forces with comparable times to task failure on both sides also exhibited smaller changes in MUAP duration on the affected side (> 15%) than on the less-affected side (> 25%). There may also be a reduction in the proportion of the motor

391 unit pool capable of being recruited with the atrophy and/or functional loss of larger, high-threshold
392 motor units (Edström, 1970;Dattola et al., 1993;Lukács et al., 2008;Klein et al., 2013). A final
393 contributing factor may be the length of the fatiguing contraction, as subjects that held the
394 contraction for a very short amount of time on the affected side exhibited little change in MUAP
395 duration. Thus, lower peripheral fatigue on the affected side in the present study may arise as a result
396 of lower absolute force levels, the early cessation of the fatigue task due to higher central fatigue,
397 recruitment of a greater proportion of fatigue-resistant Type I fibers within the paretic muscle, or a
398 combination of these factors. Lower levels of peripheral fatigue on the affected side have been
399 reported in previous studies investigating peripheral fatigue using indices derived from surface EMG
400 during voluntary contractions in stroke survivors (Svantesson et al., 1999;Riley and Bilodeau, 2002).

401 The increase in MUAP duration reported on both the affected (8 ± 6 %) and less-affected side (14 ±
402 17 %) was considerably lower than that observed postfatigue in young, healthy subjects using a
403 similar protocol (25 ± 14 %) (McManus et al., 2015). Subject age is likely to have contributed to this
404 discrepancy, as a characteristic shift in muscle fiber-type distribution towards Type I fibers occurs
405 with ageing, with a denervation of fast-twitch fatigable fibers and a subsequent reinnervation of
406 adjacent slow-twitch fatigue resistant fibers.

407 In young subjects, lower MU mean firing rates were consistently observed postfatigue. However, on
408 the less-affected side, more than half the stroke survivors exhibited MU mean firing rates that were
409 higher or unchanged postfatigue. The reduction in MU firing rates and recruitment thresholds that
410 accompanies the shift towards Type I fibers and slowing contractile properties with age (Erim et al.,
411 1999) could account for the different response to fatigue on the less-affected side in stroke survivors.
412 In addition, the ability to voluntarily activate the muscle may be impaired on the less-affected side in

some subjects (Bowden et al., 2014). Subjects that were able to increase motor unit mean firing rates postfatigue on the less-affected side were more likely to exhibit greater changes in MUAP duration, suggesting the degree of peripheral fatigue experienced is related to the ability to voluntarily activate the muscle to its full capacity, Supplementary Figure 2 (c). The repeated short contractions prefatigue and long fatiguing contraction may have also increased motor unit mean firing rate postfatigue in some subjects, as repetitive muscle activation has also been shown to elicit improvements in motor performance and an increase in EMG in both stroke survivors and healthy subjects (Massie et al., 2016).

4.3 Limitations

The surface EMG decomposition method used in this study was chosen because its algorithm makes no assumptions about the characteristics of the MU action potential waveforms or the statistics of the motor unit firing instances (Kline and De Luca, 2014), both of which may be altered post-stroke. However, the decomposition method comes with certain caveats; the accuracy of the decomposition system for a particular MU can be influenced by the stability and the signal-to-noise ratio of its action potential waveform (Hu et al., 2014). In addition, the influence of MU synchronization on the algorithm's accuracy has not been quantitatively assessed. Smaller MUs, more instability in the MU action potential waveform or higher levels of broad band MU synchronization post-stroke could make the algorithms more susceptible to firing time inaccuracies during the decomposition of surface EMG signals in stroke survivors, when compared to healthy individuals. To minimize the contribution of falsely identified firing instances, the stability of each MU action potential waveform was assessed to select the most reliable MU firing trains for further analysis (Hu et al., 2013).

However, the contribution of firing instances missed by the decomposition system cannot be quantified and should be noted as a possible factor influencing MU mean firing rates in this study.

In the present study, the less-affected side was used as a control against the changes observed in MU firing rate and action potential duration on the affected side in stroke survivors. However, alterations in motor unit behavior are also observed on the less-affected side post-stroke, with higher mean firing rates reported when compared to healthy subjects (Hu et al., 2006;McNulty et al., 2014). Changes in motor unit contractile properties are also bilateral, and prolonged motor unit twitch contraction times (McComas et al., 1973;Young and Mayer, 1982;Frontera and Larsson, 1997) and longer muscle half relaxation times (Horstman et al., 2010) observed on both sides in stroke survivors when compared to data from age-matched controls. Thus, the response to fatigue on the less-affected side may differ from that of older, healthy controls due to bilateral changes occurring post-stroke. A final limitation of the study was the small sample size, which may have reduced the statistical power to detect some of the changes occurring postfatigue.

5 Conclusion

For the first time in stroke survivors, this study presents manifestations of both central and peripheral fatigue by examining the activity of a large number of simultaneously active motor units. Mean motor unit mean firing rates decreased more rapidly during the sustained contraction on the affected side when compared to the less-affected side. The change in motor unit mean firing rates from pre- to postfatigue trials was also greater on the affected side. Though the change in action potential duration was not significantly different between sides, changes in MU action potential duration tended to be smaller in subjects with greater impairment. These results suggest that central mechanisms are the dominant processes during fatigue on the affected side. The present study is the first to describe the specific changes in motor unit firing rates and action potential duration during a sustained fatiguing contraction to the endurance limit in chronic stroke survivors. These measures provide indices to assess the prevalence of central and peripheral fatigue from surface EMG recordings in stroke survivors. This opens-up the possibility of exploring fatigue in other pathological disorders using a non-invasive, stimulation-free protocol. These alterations in motor unit behavior provide insight into strategies employed by stroke survivors to compensate for impaired muscle force.

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7 Tables

Table 1. Clinical details on each stroke survivor, including time since stroke, location of brain lesion, the Upper-Extremity Fugl-Meyer Scale (FMUE) for the affected side and the MVC force ratio on the affected and less-affected sides. FMUE was assessed by a research physical therapist within 3-month period of the study. FMUE Scale scores < 31 correspond with 'no to poor' upper extremity capacity, 32 - 47 represent 'limited capacity', 48 - 52 represent 'notable capacity' and 53 - 66 represented 'full' upper extremity capacity (Hoonhorst et al., 2015).

Subject	Sex	Age	Years post-stroke	Type of stroke	Location	Fugl-Meyer Scale	MVC Ratio (affected/less-affected side)
1	F	61	8	haemorrhagic	cortical and subcortical	49	59 %
2	F	56	6	ischemic	cortical	51	75 %
3	M	69	11	uncertain	uncertain	18	31 %
4	M	50	5	ischemic	subcortical	54	91 %
5	M	58	3	ischemic	subcortical	53	68 %

6	F	70	7	ischemic	cortical and subcortical	52	23 %
7	M	59	11	ischemic	subcortical	52	67 %
8	F	62	9	haemorrhagic	cortical	53	92 %
9	M	48	7	ischemic	cortical and subcortical	60	90 %
10	F	55	14	haemorrhagic	cortical and subcortical	36	58 %
11	F	62	16	haemorrhagic	subcortical	19	27 %
12	F	69	15	uncertain	uncertain	28	75 %

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8 Figure Captions

Figure 1. (a) Experimental setup and sample motor unit action potentials (spike-triggered average) on each channel for the (b) affected side and (c) the less-affected side. The force trace, surface EMG signal (on the highest amplitude channel) and time-varying mean firing rate of MUs over the fatiguing contraction on the (e) affected and (f) less-affected side in a single subject (obtained by low-pass filtering the impulse train with 2 s and 5 s Hanning windows respectively).

Figure 2. Median and interquartile range of the maximum voluntary contraction force across all subjects tested prefatigue, postfatigue and after the recovery period, on the affected and less-affected sides (*p < .05, *p < .01).

Figure 3. Median and interquartile range of median MU firing rate across all subjects from motor units detected prefatigue, postfatigue and after the recovery period, on both the affected and less-affected sides (*p < .05).

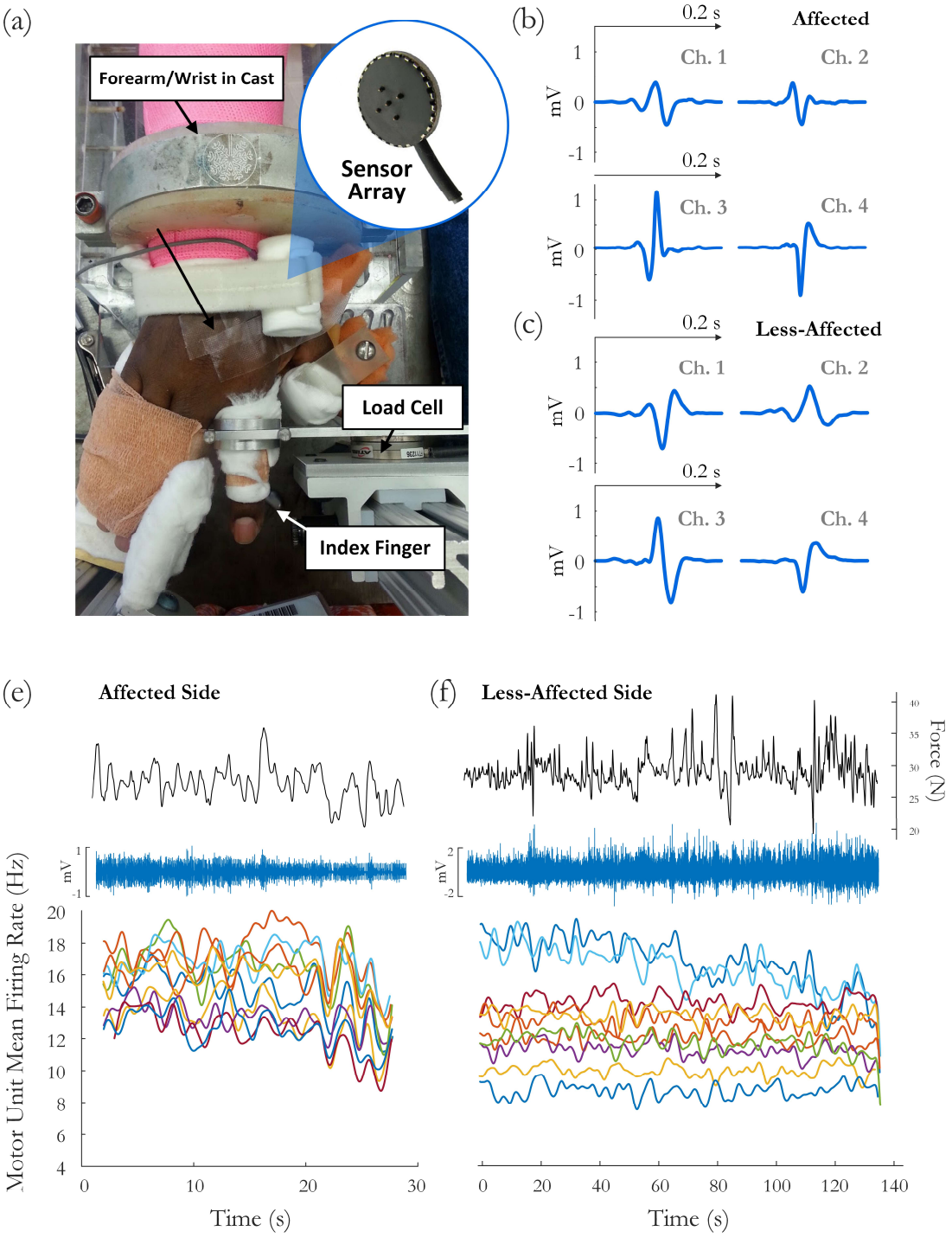
Figure 4. Median and interquartile range of the percentage change in MU firing rate on the affected and less-affected sides, comparing motor units detected prefatigue and postfatigue, and prefatigue with MUs detected after the recovery period (*p < .05).

Figure 5. Median and interquartile range of the median MU action potential duration across all subjects from motor units detected prefatigue, postfatigue and after the recovery period, on both the affected and less-affected sides (*p < .05, **p < .01).

Figure 6. The Wrist and Hand Upper Extremity Fugl-Meyer score for each subject is plotted against the percentage change in median MUAP duration from pre- to postfatigue observed for that subject (r

= 0.6, p = .04). Larger circles indicate longer times to task failure for the sustained fatiguing contraction.

Figure 7. The slope and intercept of the linear fit to the change in MU mean firing rate over the course of the sustained fatiguing contraction over all subjects on (a) the affected side and (b) the less-affected side, ** $p < .01$. Each data point represents an accepted MU; red points indicate MUs from the affected side of subjects with an endurance time for the fatigue task < 75% of the shortest time to task failure on the less-affected side.



652

653 Figure 1

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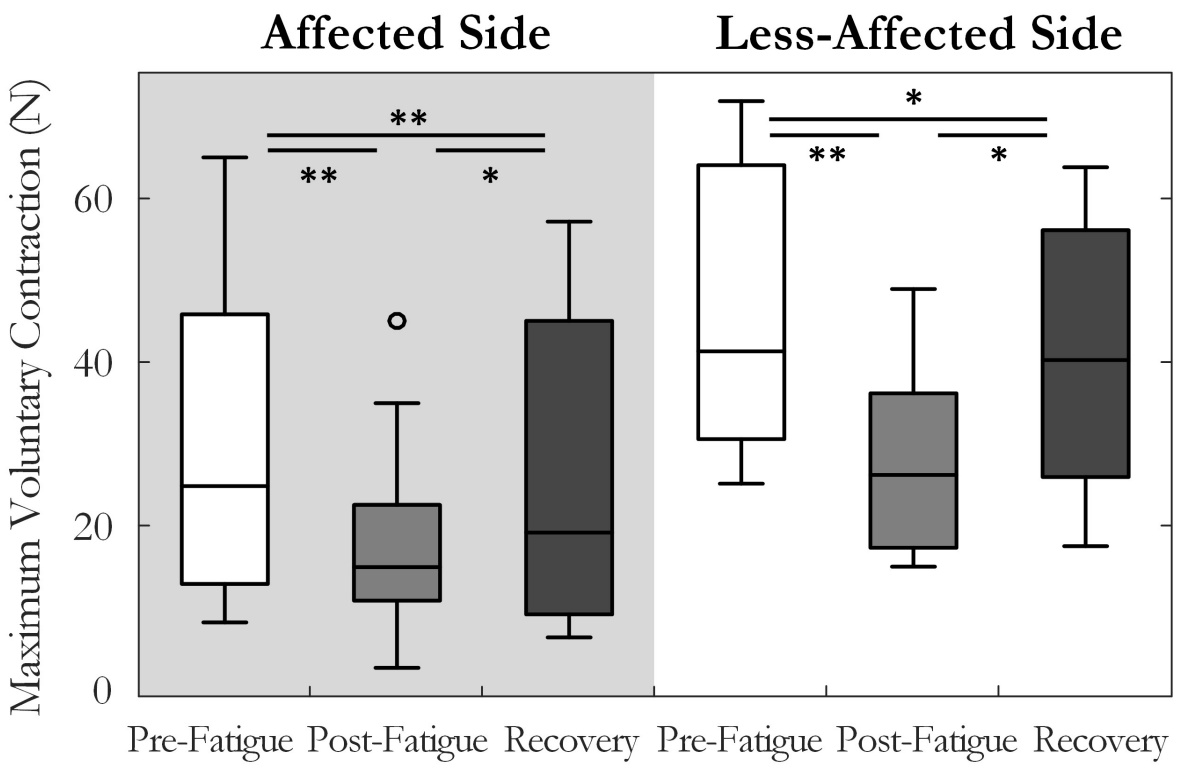
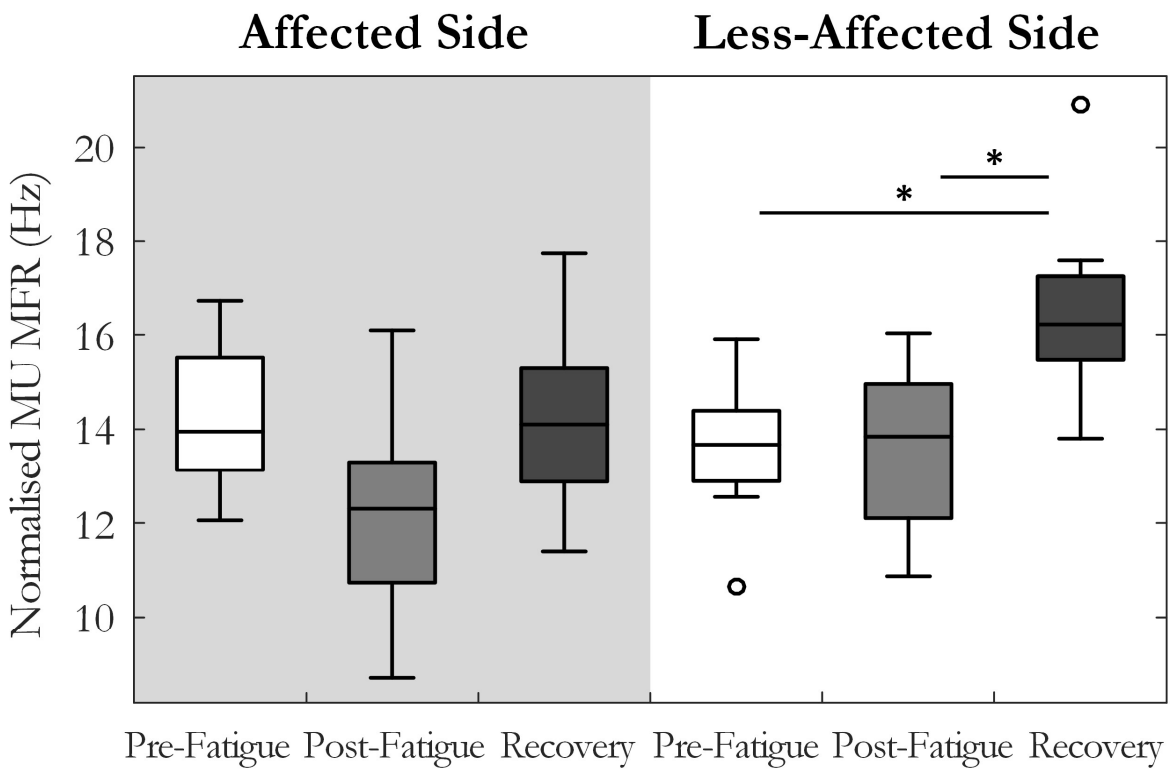

Affected Side
Less-Affected Side
Maximum Voluntary Contraction (N)
0
20
40
60
**
**
*
*
**
*
Pre-Fatigue
Post-Fatigue
Recovery
Pre-Fatigue
Post-Fatigue
Recovery

Figure 2



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660 Figure 3

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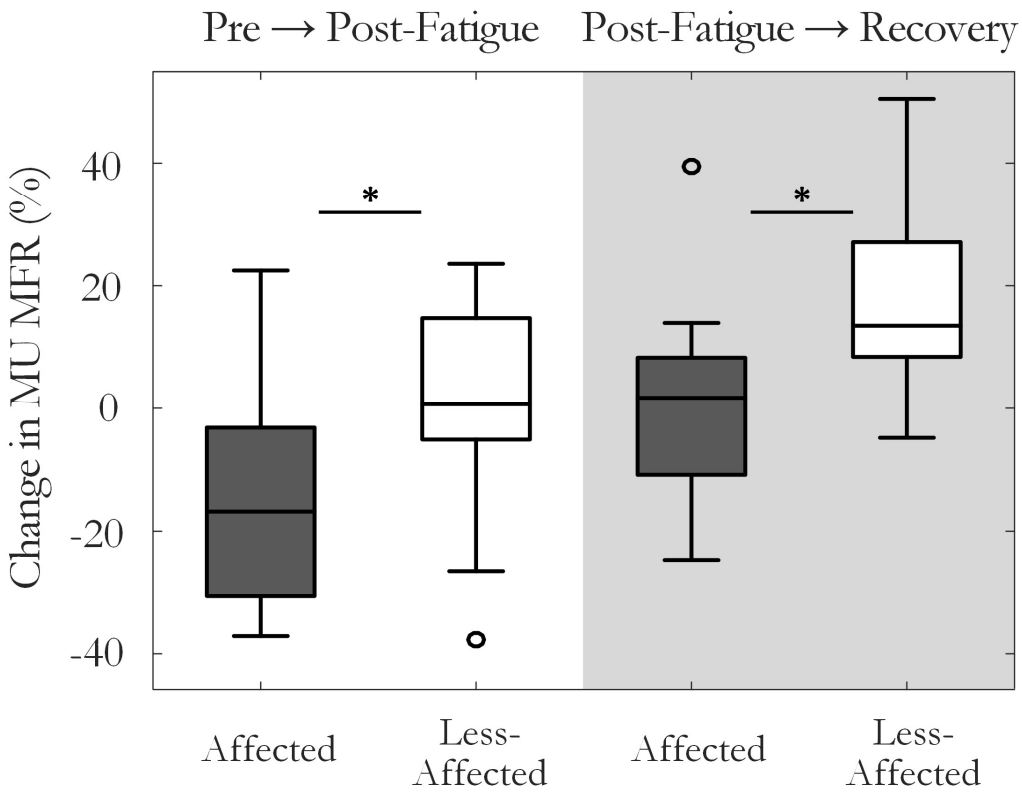

Pre → Post-Fatigue
Post-Fatigue → Recovery
Change in MU MFR (%)
40
20
0
-20
-40
*
*
Affected
Less-Affected
Affected
Less-Affected

Figure 4

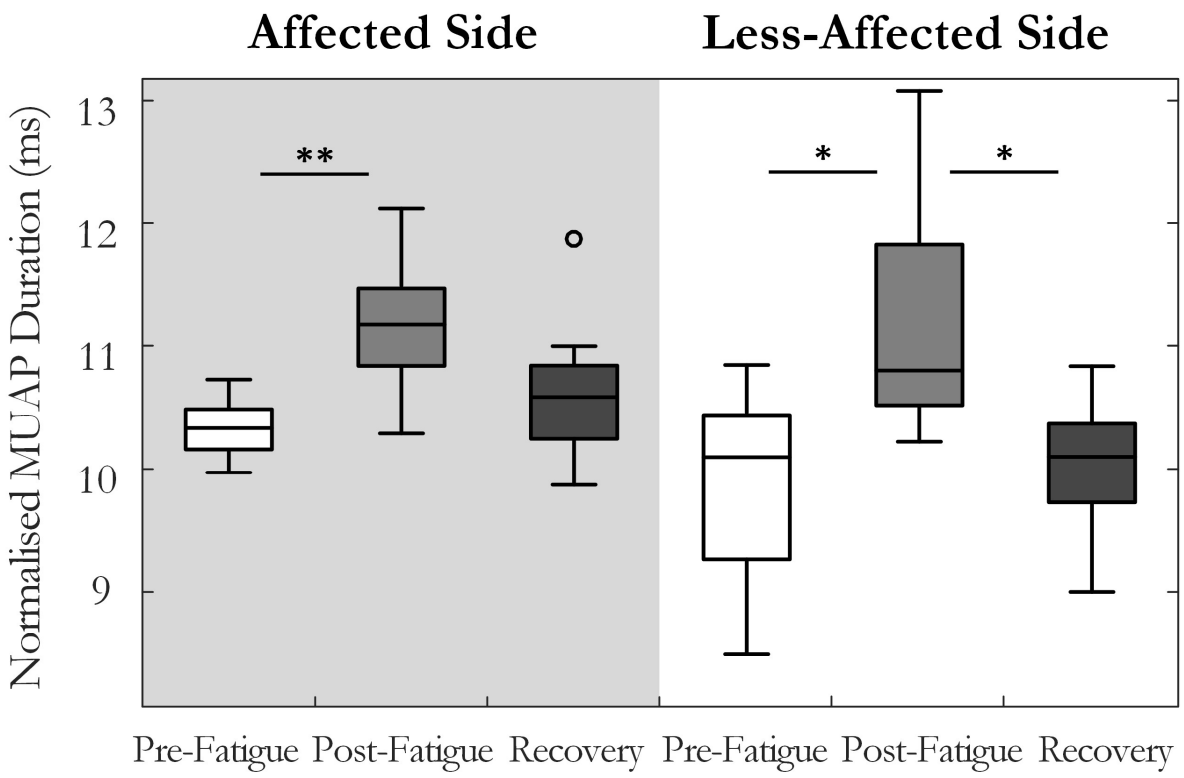
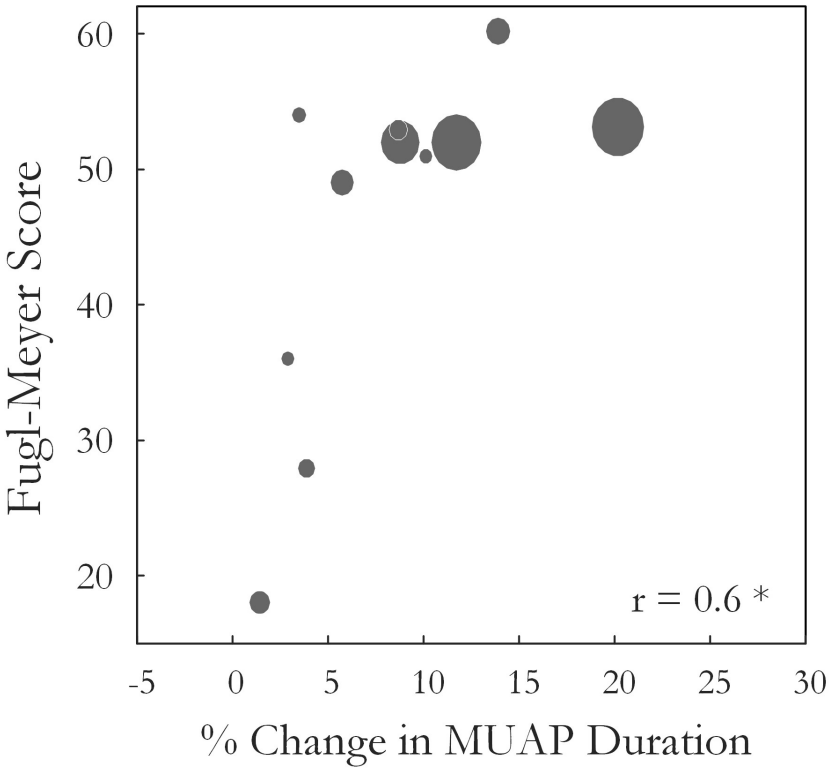

Affected Side
Less-Affected Side
Normalised MUAP Duration (ms)
13
12
11
10
9
**
*
*
Pre-Fatigue
Post-Fatigue
Recovery
Pre-Fatigue
Post-Fatigue
Recovery

Figure 5



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669 Figure 6

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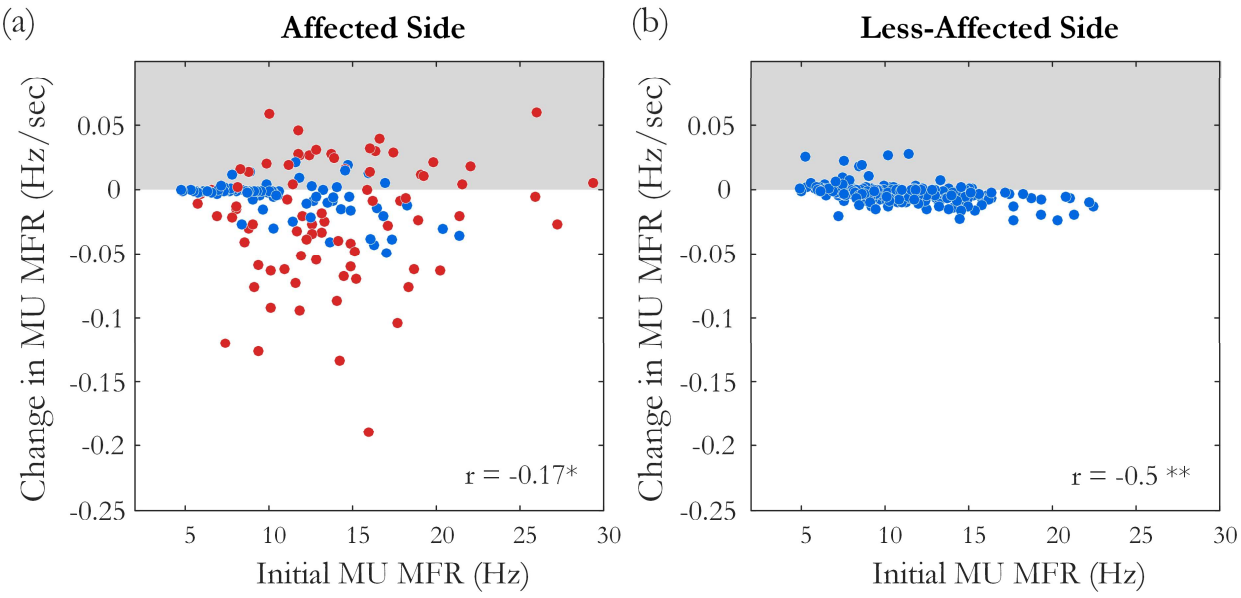

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672 Figure 7